Understanding sex disparities in tuberculosis and assessing the potential impact of strategies to improve men's access to care

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Thesis submitted in accordance with the requirements for the degree of Doctor of Philosophy of the University of London

2021

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No funding was received

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Acknowledgments

To my supervisors, Prof. Liz Corbett, Dr. Richard White, and Rein Houben,
for guiding me through this work, for facilitating my growth as a researcher,
and for your understanding as I have navigated the balance
of academic research and family responsibilities.

To members of my advisory committee,
members of the TB Modelling Group, colleagues, and friends,
for your assistance and encouragement over the past seven years.

To Susan Chisholm, Judith Prior, Alice dePuit, Aliaa el Shabrawy,
and the teams at Eveline Day Nursery and St. Faith's After School Club,
for looking after my boys and giving me space to pursue this work.

To Guy Horton,
for all of your support throughout the course of this degree.

This work is dedicated to Thomas, Henry, and William.

Declaration of own work

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

K. Horton

November 2020

Abstract

Background: Tuberculosis (TB) case notifications among men outnumber those among women, yet sex disparities in TB burden and access to care are not well-understood.

Methods: Systematic reviews, meta-analyses, and mathematical modelling were utilised to estimate sex disparities in TB burden and access to care, to identify drivers of those disparities in Viet Nam and Malawi, to explore sex-specific factors underlying those drivers, and to quantify the potential epidemiological impact of sex-specific strategies to further improve access to care in Viet Nam.

Results: The prevalence of bacteriologically positive TB was twice as high in men as in women in low- and middle-income countries, and gaps in detection and reporting were 50% higher among men. Sex disparities in Viet Nam and Malawi were attributable to higher TB incidence and untreated disease duration in men, the latter being a year longer than in women. Sex-assortative mixing patterns that emerge in adulthood likely contribute to men's higher incidence. Future interventions to improve access to diagnosis and treatment were projected to be most effective at reducing the epidemiological burden of TB in men, women, and children when rates of access to TB care improved in both men and women as a result of those interventions.

Conclusion: Men have a higher epidemiological burden of TB and less access to care than women due to a complex nexus of biological and socio-cultural factors. Global strategies and national TB programmes should recognise men as a key affected population and prioritise men's access to care in order to reduce TB morbidity and mortality in men, women, and children.

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List of abbreviations

ABC	Approximate Bayesian computation
AIM	AIDS Impact Model
AMR	Antimicrobial resistance
ARTI	Annual risk of *Mycobacterium tuberculosis* infection
AXIS	Appraisal tool for cross-sectional studies
BCG	Bacillus Calmette-Guérin vaccine
CDR	Case detection rate
CI	Confidence interval
CrI	Credible interval
DOTS	Directly observed treatment short course
HIV	Human immunodeficiency virus
IHME	Institute for Health Metrics and Evaluation
IQR	Inter-quartile range
LMICs	Low- and middle-income countries
MCMC	Markov chain Monte Carlo
MDR	Multidrug-resistant
M:F	Male-to-female (ratio)
MOOSE	Meta-analyses of observational studies in epidemiology
Mtb	*Mycobacterium tuberculosis*
OR	Odds ratio
NTP	National tuberculosis programme
PAF	Population attributable factor
PDR	Patient diagnostic rate
P:N	Prevalence-to-notification (ratio)
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
RR	Relative risk
SDGs	Sustainable development goals
TB	Tuberculosis
UI	Uncertainty interval
UN	United Nations
WHO	World Health Organization

Chapter 1 Introduction

1.1 Aims

This research aims to estimate sex disparities in TB burden and access to care, to identify drivers of those disparities in Viet Nam and Malawi, to explore sex-specific specific factors underlying those drivers, and to quantify the potential epidemiological impact of sex-specific strategies to further improve access to care in Viet Nam.

1.2 Objectives

This research has four primary objectives:

1. To estimate male-to-female (M:F) ratios in TB prevalence and prevalence-to-notification (P:N) ratios through a systematic review of national and sub-national TB prevalence surveys in low- and middle-income countries,
2. To identify drivers of sex disparities in TB burden in two exemplar settings – Viet Nam and Malawi – utilising a Bayesian approach to analyse a simple, compartmental model of TB,
3. To explore sex-specific factors likely underlying drivers of sex disparities in TB burden and care through a systematic review of sex differences in social contact patterns, and
4. To quantify the potential epidemiological impact of future sex-specific strategies to further improve access to diagnosis and treatment in a single setting – Viet Nam – utilising a dynamic transmission model of TB.

1.3 Thesis structure

This doctoral thesis is submitted in the research paper style according to regulations of the London School of Hygiene and Tropical Medicine. Four research papers are included, each with a brief introduction, and supplemental materials for these papers are included in the appendices. Each research paper stands alone as an independent manuscript, so there is some repetition through the thesis, and formatting for each research paper follows the guidelines of the journal to which the paper was (or will be) submitted.

The thesis includes six chapters:

Chapter 1 introduces the aims and objectives of the research. This chapter also outlines the structure of the thesis and provides details related to the author's contributions, ethical considerations, and funding.

Chapter 2 serves as a background to the thesis. The chapter first discusses sex and gender as determinants of health and provides an outline of TB natural history and overview of the global

burden of TB. This chapter then discusses sex disparities in TB burden and evidence of sex disparities in TB natural history and access to treatment that may explain observed disparities in disease burden. Explanations of factors that contribute to sex disparities in TB natural history and access to treatment are then summarised. The chapter closes with a discussion of the importance of sex disparities within the wider movement to end TB.

Chapter 3 presents a systematic review and meta-analysis of sex differences in TB prevalence and notifications in low- and middle-income countries to address Objective 1. This research paper was published in Plos Medicine in 2016 [1].

Chapter 4 describes Bayesian analyses using a simple compartmental model of disease incidence, treatment access, self-cure, and untreated-TB mortality rates to identify which of these factors most likely explain the sex differences in the epidemiologic burden of disease in two settings, Viet Nam and Malawi, to address Objective 2. This research paper was published in the American Journal of Epidemiology in 2018 [2].

Chapter 5 presents a systematic review and meta-analysis of sex differences in social contact patterns relevant to TB transmission at a global level to address Objective 3. This research paper was published in Emerging Infectious Diseases in 2020 [3].

Chapter 6 presents a dynamic compartmental transmission model and associated analyses to address Objective 4. The sex-stratified dynamic compartmental TB transmission model incorporates sex-specific risk factors for *Mtb* infection and TB disease identified in Chapters 4 and 5 and was fitted to population and TB burden estimates for Viet Nam including sex disparities identified in Chapter 3. Analyses examined the historical impact of sex disparities in access to TB diagnosis and treatment and explored the potential impact of future sex-specific strategies to further improve access to diagnosis and treatment. This research paper will be submitted for publication in 2021.

Chapter 7 summarises and discusses findings presented throughout the thesis. The chapter also assesses the strengths and limitations of the research as an overall body of work and provides recommendations for policy makers and researchers.

1.4 Contributions of the author

The subject of sex disparities in TB burden and care was conceived and proposed by Prof. Liz Corbett. I developed the approach and methodologies for each research paper in coordination with Prof. Liz Corbett, Prof. Richard White, Dr. Rein Houben, and other advisory committee members and co-authors.

I conducted the literature review and drafted the text for the background presented in Chapter 2.

For the systematic review and meta-analysis of sex differences in TB prevalence and notifications in low- and middle-income countries presented in Chapter 3, I developed the overall aim of this manuscript, originally conceived by Prof. Liz Corbett, and wrote the protocol for the study, which details the methodology for both the systematic review and meta-analyses. I then conducted the systematic review, searching the literature, maintaining search records, reviewing titles/abstracts, reviewing full-text manuscripts, and extracting relevant data, with second review and support from Dr. Peter MacPherson. I contacted authors, where necessary, and collated the final dataset for analysis. I conducted all analyses and produced tables and figures to summarise results. I drafted the manuscript and then incorporated feedback from co-authors. I oversaw the manuscript submission process and revised the manuscript, as necessary, to respond to input from peer review.

For the modelling analysis to identify drivers of sex differences in the epidemiologic burden of disease presented in Chapter 4, I developed the overall aim and approach of this manuscript with Prof. Richard White. I worked with Dr. Tom Sumner to develop the model structure. I then conducted the necessary literature reviews, gathered data for prior estimates, coded the model, conducted analyses, and produced tables and figures to summarise results. I drafted the manuscript and then incorporated feedback from co-authors. I oversaw the manuscript submission process and revised the manuscript, as necessary, to respond to input from peer review.

For the systematic review and meta-analysis of social contact patterns presented in Chapter 5, I developed the overall aim for this manuscript with Prof. Richard White. I designed the methodology for both the systematic review and meta-analyses. I then conducted the systematic review, searching the literature, maintaining search records, reviewing titles/abstracts, reviewing full-text manuscripts, and extracting relevant data, with second review and support from Dr. Anne Hoey. I contacted authors, where necessary, and collated the final dataset for analysis. I conducted all analyses and produced tables and figures to summarise results. I drafted the manuscript and then incorporated feedback from co-authors. I oversaw the manuscript submission process and revised the manuscript, as necessary, to respond to input from peer review.

For the dynamic compartmental transmission modelling to quantify the potential epidemiological impact of future sex-specific strategies to further improve access to diagnosis and treatment in Viet Nam presented in Chapter 6, I developed the overall aim and approach of this manuscript with Dr. Rein Houben and Prof. Richard White. Building off previous work by Dr. Rein Houben and Dr. Tom Sumner, I reviewed literature to identify sex-specific risks of *Mtb* infection and TB disease for inclusion in the model and developed the structure for the sex-

stratified model. The model was coded by Dr. Roel Bakker and edited by myself. I calibrated the model, conducted analyses, and produced tables and figures to summarise results. I drafted the manuscript and then incorporated feedback from co-authors. I will oversee the manuscript submission process and revise the manuscript, as necessary, to respond to input from peer review.

I summarised the findings, limitations, strengths and recommendations presented in Chapter 7.

1.5 Ethical considerations

No ethical approvals were necessary for the research undertaken for this thesis. All analyses were based on publicly-available de-identified estimates and datasets.

1.6 Funding

This research was unfunded. Publication costs were supported by Prof. Liz Corbett (Wellcome Trust Senior Research Fellowship in Clinical Science, grant number WT091769) and Dr. Rein Houben (European Research Council Starting Grant, action number 757699).

1.7 References

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2. Horton KC, Sumner T, Houben RM, Corbett EL, White RG. A Bayesian approach to understanding sex differences in tuberculosis disease burden. Am J Epidemiol. 2018;187(11):2431-8.

3. Horton KC, Hoey AL, Béraud G, Corbett EL, White RG. Systematic Review and Meta-Analysis of Sex Differences in Social Contact Patterns and Implications for Tuberculosis Transmission and Control. Emerging Infectious Diseases. 2020;26(5):910.

Chapter 2 Background

2.1 Sex and gender as determinants of health

Sex and gender are together considered one of the most important determinants of health [1]. Sex, a biological classification distinguishing males and females based on genetic, epigenetic and hormonal differences [2], interacts with gender, a social construction that refers to "the roles, behaviours, activities, and attributes that a given society at a given time considers appropriate for men and women and people with non-binary gender identities" [3], and with other social factors to influence biological, socio-behavioural, and institutional determinants of health [4].

2.2 Tuberculosis

Tuberculosis disease (TB) is caused by infection with the *Mycobacterium tuberculosis* complex (*Mtb*) [5] and manifests as pulmonary disease within the lungs or extra-pulmonary disease disseminated to other organs. The former is classified as smear-positive when *Mtb* is observed through microscopic examination of sputum samples and smear-negative when no acid-fast bacilli are observed. The bacterium is spread through the air-borne transmission of infectious droplet nuclei [5], which are expelled by affected individuals with pulmonary TB and then inhaled by susceptible individuals [6]. The likelihood of a transmission event depends on the individual characteristics of infected and susceptible individuals, as well as social and environmental conditions [7].

The innate immune system provides the first line of defence against *Mtb* infection following introduction to respiratory mucosa [8]. Bacilli are phagocytosed by alveolar macrophages [9] and destroyed through autophagy [10,11] or apoptosis [12], while antigen-presenting dendritic cells [13] migrate to the lymph node to initiate T cell differentiation [14,15]. The adaptive immune system responds with Th1-phenotype CD4+ and CD8+ T cells [16-23] which secrete key cytokines interferon gamma, interleukin 12, and tumour necrosis factor alpha to facilitate interactions between the innate and adaptive immune response cells [24-29]. Following activation of the adaptive immune response, macrophages, neutrophils and lymphocytes physically contain Mtb in the lungs within granuloma [30] to encourage a state of dormancy in the bacteria.

Exposure to *Mtb* may result in presentation across a spectrum of infection and disease [31,32], with progression and possible regression between states of infection and minimal, subclinical, and clinical, or symptomatic, disease. However this complex process is often simplified to a binary differentiation between latent *Mtb* infection and active TB. The majority of individuals exposed to *Mtb* will remain in an asymptomatic, non-infectious state of latent infection, though

with risk of progressing to active TB through distal progression to reactivated disease or through subsequent exposure and reinfection. Only 5-10% of individuals infected with *Mtb* will progress to active TB during their lifetime [33,34], either by rapid progression to primary disease within approximately two years of infection or by distal progression to reactivated disease following a longer period of latency. Individuals with TB disease typically present with symptoms including prolonged cough, haemoptysis, fever, fatigue, lack of appetite, and weight loss [5], although recent prevalence surveys suggest the burden of subclinical active TB disease may be substantial [35].

Diagnosis of TB often relies on symptom screening and/or chest x-ray, followed by sputum analysis using smear microscopy, bacteriological culture, and/or molecular tests such as the Xpert MTB/RIF assay [33,34]. Active TB is further differentiated into smear-positive and smear-negative disease, based on the presence or absence of bacteria in smear microscopy examination.

Individuals with active TB may recover through natural self-cure or through treatment following diagnosis, though neither provides lasting immunity, and recovered individuals remain at risk of relapse or reinfection. The current treatment regimen for drug-susceptible TB involves six months of treatment involving four first-line drugs: isoniazid, rifampicin, ethambutol, and pyrazinamide [33,34]. Longer treatment regimens with second-line drugs are required for rifampicin-resistant and multidrug-resistant (MDR) TB [33,34].

In the absence of treatment, the case fatality rate for TB is high. A recent review found that 70% of individuals with smear-positive pulmonary TB and 20% of individuals with smear-negative pulmonary TB died within 10 years of diagnosis [36].

2.3 Global tuberculosis epidemic

In 2018, 7.0 million cases of TB were reported to the World Health Organization (WHO). An estimated 10 million people developed TB in the same year, leaving 3 million individuals with TB “missing” due to under-diagnosis and underreporting [33,34]. An estimated 1.5 million people died from TB in 2018, including 251,000 co-infected with human immunodeficiency virus (HIV) and 214,000 with drug resistant TB. TB has been the leading infectious cause of death globally since 2007 [33,34] and is the source of a third of all antimicrobial resistance (AMR) deaths [37].

The global burden of TB is inequitably distributed with most cases and deaths occurring in low- and middle-income countries [34]. In 2018, 44% of estimated incident cases occurred in the WHO South East Asia region, 24% in the WHO Africa region, and 18% in the Western Pacific region [34]. While annual incidence was less than 10 per 100,000 in most high-income

countries, incidence ranged from 150 to 400 per 100,000 in most of the 30 high TB burden countries[1] and was over 500 per 100,000 in a handful of settings [34]. Regional disparities extend to TB mortality estimates, with the WHO South East Asia and Africa regions together accounting for 85% of TB deaths [34].

These distributions highlight TB as a disease of poverty but also reflect other inequities between geographic regions. In the WHO Africa region, coinfection with human immunodeficiency virus (HIV) contributes substantially to TB incidence and mortality. The region also has one of the highest prevalences of harmful alcohol consumption globally. In the WHO South East Asia and Western Pacific regions, high TB burden can be attributed to additional factors including crowded living conditions in megacities, high prevalence of tobacco smoking, and fragmented health systems.

2.4 Sex differences in global tuberculosis epidemic

TB case notifications, which are counts of individuals with TB detected by national TB programmes (NTPs) and reported to WHO, have been higher among men than women since WHO began collecting and reporting these data in the early 1990s [34]. Of the 7.0 million TB case notifications in 2018, 58% were men, 34% women, and 8% children under 15 years of age [38]. The male-to-female (M:F) ratio in adult case notifications was 1.7, ranging from 1.1 in the WHO Eastern Mediterranean region to 2.1 in the WHO Western Pacific region [38]. Among case notifications in children, the M:F ratio ranged from 1.0 in the WHO Region of the Americas and Eastern Mediterranean region to 1.2 in the WHO Western Pacific region, with a global estimate of 1.1 [38], suggesting the possibility that sex disparities emerge during or after adolescence. The M:F ratio in adult extra-pulmonary TB case notifications was 1.1 among the 149 countries reporting at least one case of extra-pulmonary TB in 2012 (the last year these data were reported) [38].

Although case notification data may give a biased estimate of sex disparities in disease burden due to differential access to TB treatment by the sexes, the stark difference in the number of cases reported among men and those reported among women invites further examination. Sex disparities in the number of cases reported could be attributed to sex differences in TB natural history that affect the sex distribution of individuals with TB and/or sex differences in access to TB treatment that affect the number of cases detected and reported by NTPs.

2.5 Sex differences in tuberculosis natural history

[1] The 30 high TB burden countries include the 20 countries with the highest absolute number of estimated incident cases, plus the 10 countries with the highest incidence rates per capita, provided those countries are not already included in the 20 aforementioned countries and are estimated to have at least 10,000 incident cases.

TB natural history describes the cycle from *Mtb* infection, through progression to TB disease, and on to recovery or death, as illustrated below in Figure 1. Sex disparities in transition rates through any step in the natural history cycle could result in sex-based differences in the burden of disease that underlies the number of case notifications for each sex. Men's excess case notifications could be the result of, for example, increased rates of infection and/or development of disease, and/or lower rates of self-cure and/or TB-associated mortality. I review evidence of the impact of sex on TB natural history below.

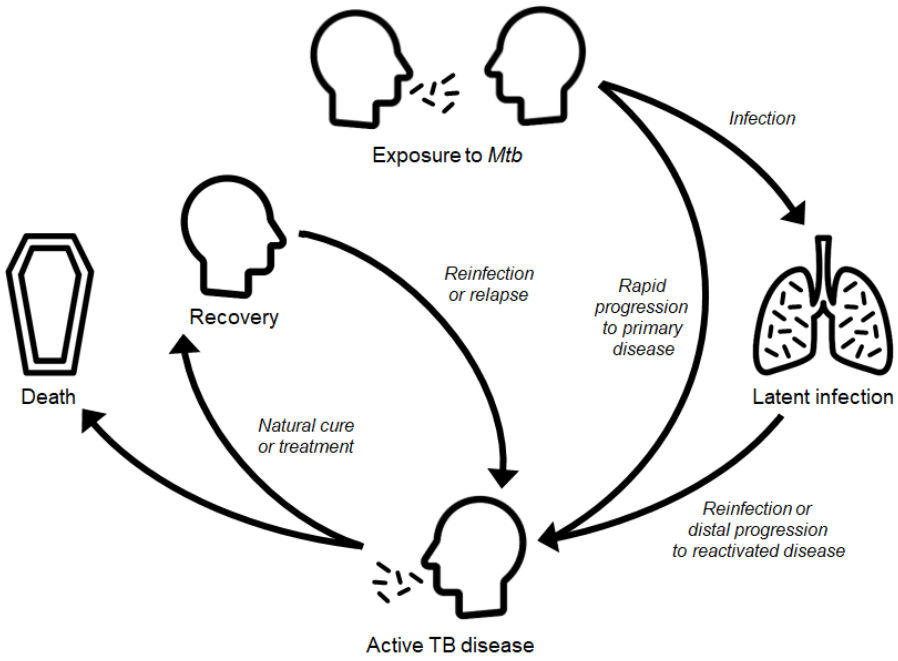

Figure 1: TB natural history. Exposure to *Mtb* may result in rapid progression to primary TB or in latent infection, which may then progress to active disease through reinfection or distal progression to reactivated disease. Individuals with active TB may die or may recover through treatment or natural self-cure, though recovered individuals remain at risk of returning to active TB due to relapse or reinfection. [39-41]

Data on TB natural history primarily relies on studies from the early twentieth century prior to the availability of chemoprophylactic or therapeutic intervention. During this time, the sex- and age-based patterns observed in case notifications were often different than those reported over the last three decades. Data from Denmark, Norway, Wales, and England present case notification rates that were similar for boys and girls, 10-35% higher in women among adults from adolescence to age 40 years, and higher in men among adults over age 40 years [42-44]. As TB incidence decreased in these industrialised countries, the sex- and age-based pattern of case notifications shifted such that notification rates were slightly higher among men in all adult age groups [42, 44-46]. Notably, as shown above, more recent case notification data from high TB incidence settings in low- and middle-income countries have not reflected these earlier sex-

and age-based patterns and have instead reported consistently higher case notifications among men [47].

2.5.1 *Mycobacterium tuberculosis* transmission

Limited data are available to assess differences in infectiousness or transmission by patient sex. Studies that exposed guinea pigs to air from TB patient wards have either pooled air from patients of different sexes or not reported results by sex [48-50]. Studies of transmission clusters, either among household contacts or by molecular sequencing, have yielded conflicting results on sex differences in transmission. Neither a household contact study in Peru [51] nor whole genome sequencing in Malawi [52] identified any difference in transmission by index case sex. However, two studies of transmission clusters in the Netherlands found that male index cases generated more secondary cases than female index cases [53,54], and a household contact study in Malawi found more paediatric *Mtb* infections among household contacts of male index cases than female index cases [55].

2.5.2 *Mycobacterium tuberculosis* infection

Tuberculin surveys present a consistent picture of sex- and age-based patterns in the prevalence of *Mtb* infection, despite methodological limitations related to their conduct and interpretation, as well as cross-reactivity with the bacillus Calmette Guérin (BCG) vaccine [56]. Results from mass BCG campaigns in 17 countries across Europe, the Eastern Mediterranean, and South America between 1948 and 1951 show nearly equal prevalence of *Mtb* infection among boys and girls, with male prevalence surpassing female prevalence between ages 10 and 16 years [57]. Prevalence surveys of *Mtb* infection conducted in Africa between 1955 and 1961 [58,59] and in Asia between 1953 and 1997 [60-67] show similar patterns, with male and female prevalence diverging to show a clear male excess after adolescence. In two studies in Asia, *Mtb* infection prevalence was slightly higher in females up to ages 20 to 25 years, after which prevalence among men surpassed that among women [68,69].

Higher prevalence of *Mtb* infection in young men implies a higher annual risk of *Mtb* infection (ARTI) from adolescence [70]. Comparisons of the prevalence of *Mtb* infection in cohorts of children and young adults and repeat testing for *Mtb* infection in children also imply higher ARTI among males from adolescence. Surveys of male army recruits aged 19 years and schoolchildren aged 12 to 18 years in the Netherlands indicate that ARTI was 9% higher among males than females each year from 1910 to 1966 [71]. Further tuberculin prevalence surveys among Dutch schoolchildren between 1966 and 1979 found no difference in ARTI between boys and girls aged 6 to 12 years, but among those aged 12 to 18 years, ARTI was 10.2% higher among boys than girls (2.0 vs. 1.9) [72].

2.5.3 Rapid progression to primary tuberculosis disease

Most studies of rapid progression from *Mtb* infection to primary TB disease report higher rates of progression among women at younger ages and among men at older ages [42,73-77], though consistently higher rates of progression among women [47,78] or men [74] have also been observed (Figure 2).

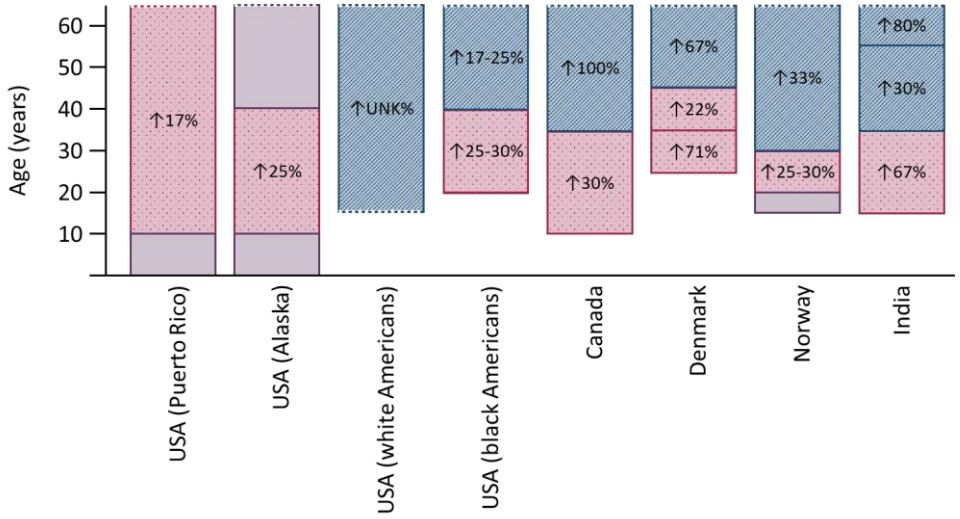

Figure 2: Sex differences in rates of progression by age group Shading indicates group with higher rate of progression (men in striped blue, women in dotted red, neither sex in plain purple). Percentages indicate how much higher progression was in that group (UNK indicates unknown). Dashed lines indicate uncertainty in upper or lower limit for age group indicated.

It is notable that six of the seven studies referenced above included participants who were tuberculin-positive with normal chest x-ray or with healed lesions, so cases attributed to recent progression from *Mtb* infection may actually reflect reactivation. Only the Norwegian study limited participation to tuberculin-negative individuals at enrolment and therefore avoided this risk [47]. The 30% higher progression among men in older ages in this study [76] is low relative to the increased rates reported elsewhere, although the age grouping of individuals age 30 years and older is less granular than groupings used elsewhere. While the passive follow-up methodology most of the studies may have introduced bias due to sex differences in care-seeking behaviours, a similar sex- and age-based pattern in progression was observed in the Indian study which utilised active follow-up [77].

Although it has been hypothesised that higher rates of progression from *Mtb* infection to TB disease observed in women during reproductive years is due to the impact of pregnancy on the immune system [47], evidence of any association between pregnancy (during antenatal or postnatal periods) is inconclusive and thus the relationship remains unclear [47,79].

2.5.4 Distal progression to reactivation tuberculosis disease

Many studies of reactivation of latent *Mtb* infection have failed to report results by sex [80-82] or have included participants of only a single sex [83]. Those that do report results by sex draw disparate conclusions, ranging from there being little difference between the sexes in reactivation rates to substantially higher rates among men than women. Sex differences in progression discussed above in section 2.5.3 may also in part reflect sex differences in reactivation.

In the United States [84], reactivation rates among participants aged 15 to 65 years with untreated inactive TB were reported to have been slightly higher among men than women over 2.5 to 12.5 years of follow-up. In a Canadian study with up to 20 years of follow-up of individuals with untreated inactive TB, rates of reactivation were similar among men and women less than 40 years of age (2.5% for men and 2.1% for women) and 2.7 times higher among men ages 40 years and older [85]. Criteria for inactive disease varied substantially between these two studies with direct patient observation. While the American study required two years of inactivity prior to the development of disease being considered reactivation, the Canadian study considered reactivation after only six months. More extreme results were reported in the Netherlands, where among participants ages 15 to 69 years, the risk of developing TB after five years of infection, in the absence of reinfection, was estimated to be 12 times higher among men than women [86]. Analysis of birth cohort data from Norway also show greater declines in TB rates over time for women (59%) than men (55%), likely reflecting a greater decline in progression over time for women and therefore a higher reactivation rate among men [87].

2.5.5 Reinfection

Limited evidence is available on the degree to which previous *Mtb* infection may protect against the development of TB disease following reinfection in men and women. A single study was identified that reported on the risk of reinfection by sex. In this study from the Netherlands, analyses indicate that protection is greater in women than men, with an 81% reduction in incidence following reinfection in women, compared to a 63% reduction for men [86].

2.5.6 Case fatality

A recent systematic review of case fatality in untreated pulmonary TB reported no difference by sex [36]. Indeed, the majority of retrospective cohort studies from the pre-chemotherapy era, including studies in the United Kingdom [88-90], Sweden [91], and Denmark [92], found no substantial differences in case fatality by sex.

Studies that found a difference in case fatality rates by sex differ in their conclusions. A cohort study of individuals ages 20 to 55 years in the United Kingdom suggests worse outcomes

among men, particularly in older ages [93]. In contrast, in a Norwegian study, mortality was higher among women for the first four years after diagnosis, after which no differences were observed by sex [94], and in another study in Denmark, higher mortality was reported in women [95].

Box 1: Evaluation of sex differences in TB natural history

- *Mtb* infection rates are similar among boys and girls, but higher among men than women.
- Rates of progression from *Mtb* infection to TB disease are similar for boys and girls, higher among women from adolescence until around 40 years of age, and higher for men over 40 years of age.
- Reactivation rates are likely similar among men and women, or perhaps higher among men, particularly at older ages.
- Rates of reinfection may be higher in men due to more limited protection due to previous infection.
- Case fatality rates are similar for men and women.

2.6 Sex differences in access to tuberculosis treatment

Sex differences in case notifications may also arise due to sex disparities in case detection rates (CDRs) for men and women. In order to be counted in case notification numbers, individuals with active TB disease must access TB treatment, which requires obtaining care from an appropriate provider, receiving a TB diagnosis and initiating treatment, as illustrated in Figure 3, and providers must then report cases to the NTP. Excess case notifications among men could arise if women are relatively disadvantaged in their progression through this pathway.

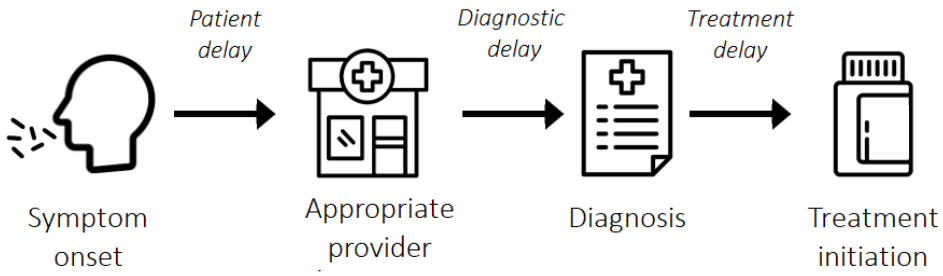

Figure 3: Pathway from symptom onset to TB treatment. Patients must progress from symptom onset to an appropriate provider to TB diagnosis to treatment initiation. Patients may experience delays at any stage of this path. [39,96-98]

While sex-specific CDRs measuring the ratio of notified cases to incident cases in a given year could summarise overall sex disparities in progression through these steps in the pathway to

treatment, TB incidence is not directly measured and therefore estimates of CDR are often uncertain [99]. An alternate indicator, the patient diagnostic rate (PDR), measures the ratio of notified cases to prevalent cases in a given year using prevalence survey data [99]. Sex-specific PDRs provide directly-measured estimates of gaps in detection and reporting, which can indicate sex disparities in access to treatment. A 2000 review calculated PDRs for 29 prevalence surveys conducted in 14 countries across the WHO Africa, Eastern Mediterranean, South East Asia, and Western Pacific regions between 1950 and 1997 and suggested that female cases are more likely to be notified than male cases, except in some African settings [99].

Numerous recent studies have attempted to quantify progression through various steps of the pathway to TB treatment, despite potential recall and reporting biases. Studies that describe self-reported delays or document loss to follow-up in access to appropriate care, diagnosis, and treatment initiation are summarised below. Studies that report different intervals in the care cascade (for example, from symptom onset to diagnosis or from sputum sample provision to diagnosis) have been excluded from this summary for clarity and consistency.

2.6.1 Patient delay

In order to access TB treatment, and therefore be included in case notifications, individuals with TB must first access care from an appropriate provider. This requires that individuals recognise the onset of TB symptoms, overcome barriers related to seeking care, seek external care, and, if necessary, self-refer or be referred to an appropriate provider who can diagnose TB. While it is not feasible to break down quantitative sex differences in each of these steps, a number of studies have examined self-reported patient delay, defined as the time interval from symptom onset to first care-seeking from a formal healthcare provider (ranging from primary care to hospital), among individuals recently diagnosed with TB.

The majority of studies identified no difference in the duration of patient delay reported by men and women [100-125]. Some surveys report longer patient delay among women than men [102,126-131], while others found longer patient delay among men than women [132-136]. Most of these studies did not report results with sufficient detail to allow rigorous comparison of diagnostic delays reported by men and women (some did not even report delay values); assessments presented here rely on authors' reports. Diagnostic delays in men and women for those studies that report mean or median values are reported in Table 1.

Table 1: Patient delays in men and women. Includes only studies that report mean or median delays. Blue shading indicates longer delays for men; red shading indicates longer delays for women; no shading indicates no sex difference in delay.

Region	Country	Measure	Patient delay (days)			Ref.
			Male	Female	Total	
AFR	Ethiopia	median			45	[100]
	Gambia	median			60	[101]
	Malawi	mean	33	35		[102]
	Nigeria	median			56	[103]
	Rwanda	median			25	[104]
	South Africa	median	30	14		[132]
	South Africa	median			28	[106]
	South Africa	median			8	[105]
AMR	Peru	median			61	[107]
EMR	Egypt	mean	153	132		[108]
	Syria	mean	64	40		[134]
EUR	Norway	median			28	[110]
	Spain	median			22	[111]
	Tajikistan	median			22	[112]
	Turkey	median			18	[113]
	United Kingdom	median	32	23		[135]
SEAR	India	median			14	[114]
	India	median			26	[115]
	India	mean	68	66		[102]
	Nepal	median			42	[116]
	Thailand	median	28	22		[133]
WPR	Bangladesh	median	42	50		[126]
	Bangladesh	mean	49	52		[102]
	China	median			10	[117]
	Malaysia	median			14	[118]
	Mongolia	median	35.3	30		[119]
	Viet Nam	mean	31	29		[127]
	Viet Nam	median	53	55		[120]
	Viet Nam	median			7	[121]
	Viet Nam	mean	27	41		[128]

2.6.2 Diagnostic delay

Individuals with TB who seek care from an appropriate provider must then rely on providers to suspect TB and order appropriate diagnostics. Those individuals must then provide at least one sputum specimen of adequate quality for diagnosis, test positive by the available diagnostic algorithm, and receive diagnostic results from their provider. Quantifying these individual steps is difficult and therefore the period from seeking care from an appropriate provider to diagnosis, referred to as diagnostic delay, is considered.

Most studies have found no difference between men and women in the time to TB diagnosis after seeking care from an appropriate provider [102-104,108,110,126,130,132,137]. Several studies report longer diagnostic delay among women, compared to men [115,120,121,129,138]. Only one study reports a longer diagnostic delay for men compared to women [113]. Most of these studies did not report results with sufficient detail to allow rigorous comparison of diagnostic delays reported by men and women (some did not even report delay values); assessments presented here rely on authors' reports. Diagnostic delays in men and women for those studies that report mean or median values are reported in Table 2.

Table 2: Diagnostic delays in men and women. Includes only studies that report mean or median delays. Blue shading indicates longer delays for men; red shading indicates longer delays for women; no shading indicates no sex difference in delay.

Region	Country	Measure	Diagnostic delay (days)			Ref.
			Male	Female	Total	
AFR	Malawi	mean	27	32		[102]
	Nigeria	median			7	[103]
	Rwanda	median			28	[104]
	South Africa	median			30	[132]
EMR	Egypt	mean	66	63		[112]
	Iran	mean			59	[138]
EUR	Norway	median	22	35		[110]
	Turkey	mean	4	2		[113]
SEAR	India	mean	4	7		[102]
	India	median			5	[115]
	Nepal	median	69	99		[137]
WPR	Bangladesh	mean	10	9		[102]
	Bangladesh	median	3	2		[126]
	Malaysia	median			22	[130]
	Viet Nam	mean	27	38		[120]
	Viet Nam	mean			49	[121]

2.6.3 Treatment delay

The final step towards case notification is treatment initiation. After receiving a TB diagnosis, individuals with TB must return to their providers to initiate treatment. A 2014 review found that pre-treatment loss to follow-up is significant: 38% in sub-Saharan Africa and 13% in Asia [139]. Studies summarised below present either pre-treatment loss to follow-up or time intervals from TB diagnosis to treatment initiation by sex.

There was no difference between the sexes in the proportion of pre-treatment loss to follow-up in several studies [114,140], nor was there any significant sex difference in the time interval from diagnosis to treatment initiation [103,126,141]. A single study in Tanzania reported that a higher proportion of women experienced longer treatment delay than men [129]. Treatment delay or pre-treatment loss to follow-up was greater among men than women in a few studies [108,142,143]. Most of these studies did not report results with sufficient detail to allow rigorous comparison of diagnostic delays reported by men and women (some did not even report delay values); assessments presented here rely on authors' reports. Treatment delays in men and women for those studies that report mean or median values are reported in Table 3, and pre-treatment loss to follow-up in men and women for those studies that report values are reported in Table 4.

Table 3: Treatment delays in men and women. Includes only studies that report mean or median delays. Blue shading indicates longer delays for men; red shading indicates longer delays for women; no shading indicates no sex difference in delay.

Region	Country	Measure	Treatment delay (days)			Ref.
			Male	Female	Total	
AFR	Nigeria	median			7	[103]
EMR	Egypt	mean	1.4	1.2		[108]
WPR	Bangladesh	median	1.0	1.0		[126]

Table 4: Pre-treatment loss to follow-up in men and women. Includes only studies that report values. Blue shading indicates longer delays for men; red shading indicates longer delays for women; no shading indicates no sex difference in delay.

Region	Country	Pre-treatment loss to follow-up			Ref.
		Male	Female	Total	
AFR	South Africa	18	17		[140]
AFR	Zimbabwe	23.9	17.5		[142]
SEAR	India	17	8.4		[143]
SEAR	India	29	29		[114]

Box 2: Evaluation of sex differences in TB care cascade

- There is little evidence of sex differences in access to qualified care, diagnosis, or treatment initiation in most settings.
- Limited evidence suggests women may be more likely to experience diagnostic delay in some settings.
- Limited evidence suggests men may be more likely to experience treatment delay or pre-treatment loss to follow-up in some settings.

2.7 Explanations for sex differences in TB natural history and case detection

Evidence of sex differences in TB natural history and in the TB care cascade indicate that higher case notifications among men may reflect higher TB burden among men.

2.7.1 Conceptual framework

A male disadvantage in TB burden and case detection has been attributed to a number of biological, socio-behavioural, and health systems factors. The distribution of these factors across realms of influence in individuals' lives is illustrated in the conceptual framework in Figure 4. This framework, built on Dahlgren and Whitehead's Main Determinants of Health [144], illustrates sex and gender factors that disadvantage men in TB burden and case detection by increasing risk men's risk of *Mtb* infection and/or TB and discouraging men from accessing TB diagnosis and treatment.

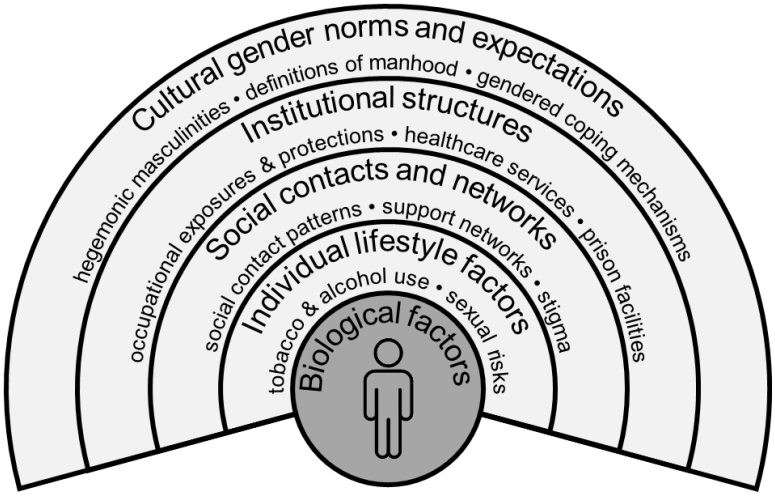

Figure 4: Conceptual framework of factors that disadvantage men with regard to TB burden and access to care. Light grey indicates gender-based risk factors; dark grey indicates sex-based factors. [145]

The framework emphasises how sex and gender factors associated with TB burden and case detection are nested within one another. Men's risk of TB is influenced by biological sex

factors, which are generally fixed and are identified at the centre of the framework. Men's risk of TB is then affected by individual lifestyle factors, which are nested within social contacts and networks and institutional structures, both of which affect men's risk of disease and access to treatment. Cultural gender norms and expectations form an overarching layer, influencing institutional structures, social contacts and networks, and individual lifestyle factors and thereby affecting TB risk and access to treatment across. Risks highlighted in this framework are detailed below.

2.7.2 Biological factors

Biological differences in anatomy, genetic susceptibility, sex hormones, nutrition, and reproduction may contribute to sex differences in *Mtb* infection and TB [146,147].

2.7.2.1 Anatomy

There are notable sex differences in the structure and function of the respiratory system [148]. The larger airway flow and calibre and larger lungs of a more pyramidal shape in men [148] have been hypothesised to contribute to sex disparities in TB by affecting susceptibility to *Mtb*. However the impact of these physiological differences has yet to be quantified [146].

2.7.2.2 Genetic susceptibility

Several genes associated with TB susceptibility have been identified through studies of specific candidate genes and genome-wide linkage analyses [146]. Several of these, including the Toll-like receptor 8 gene polymorphisms and Mendelian susceptibility to mycobacteria disease, are located on the X chromosome and therefore are observed nearly exclusively in men and boys [147]. While these polymorphisms are rare and therefore unlikely to explain sex differences in TB burden, the X chromosome contains over 10 times as many immunomodulatory genes as the Y chromosome, indicating potential for X-linked polymorphisms to play some role in population level sex disparities [147].

2.7.2.3 Sex hormones

The appearance of sex differences in TB burden during adolescence suggests the emergence of sex hormones during puberty may play a role in sex-specific susceptibility.

Animal studies have found a higher risk of mycobacterial infection and disease among males than females in mice [149, 150] and brushtail possums [151], though not in all studies [152]. Castration of male animals was found to reduce disease severity and improve TB survival [149-151, 153]. Conversely, treatment of female mice and castrated male mice with testosterone increased TB risk, further implicating testosterone in the association between sex and TB severity [149]. A unique study from a mental institution in the United States found similar

reductions in TB risk among castrated men, among whom 8% died from TB, compared to 21% of non-castrated men [154].

While the specific role of sex hormones in immune response is complex, it is thought that testosterone down-regulates the Th1 immune response, which is essential for TB control, while oestrogen may enhance that response [147]. Similarly, macrophage activation is enhanced by oestradiol and inhibited by testosterone [147]. Further research is needed to evaluate the impact of these associations on TB burden and transmission dynamics.

2.7.2.4 Nutrition

Malnutrition and undernutrition, as indicated by body mass index, are associated with increased TB risk [155, 156] and may be responsible for a quarter of TB cases [157]. However nutrition indicators are reported at similar levels for men and women globally [158], suggesting overall nutrition status may not impact sex differences in TB.

Sex differences in more nuanced nutritional factors, such as fat metabolism [159] and micronutrient levels, however, may play some role. Experimental data from animal studies suggest that iron overload, more common in men than women, significantly increases susceptibility to *Mtb* [146], perhaps by raising concentrations of the hormone hepcidin, which encourages pathogen growth within macrophages [160]. A study in the United Kingdom found higher incidence of TB in a vegetarian population with cobalamin (vitamin B_{12}) deficiency, which limits phagocytotic function, than in a population with a mixed diet [161]. Sex differences in other nutrients relevant to mycobacterial immunity, such as vitamin D, may also influence *Mtb* infection and TB outcomes [146, 147].

Diabetes, the increase of which has been fuelled by rising obesity, increases TB risk and complicates diagnosis and treatment [162, 163]. Case-control studies have identified odds of developing TB disease 2.4 to 8.3 times higher among diabetics, compared to non-diabetics [162]. However, there is no evidence that the prevalence of diabetes differs between men and women [164, 165].

2.7.3 Individual lifestyle factors

Men are generally more likely to engage in risky behaviours than women [166], often to prove their manhood [167]. Risk behaviours such as tobacco smoking, alcohol consumption, illicit drug use, and risky sexual behaviours are all associated with increased TB risk and are more prevalent in men who may demonstrate dominance and independence through these behaviours [168]. Not only do these behaviours increase risk of TB, but they may also mask symptoms among those affected by the disease. TB symptoms, specifically cough and night sweats, may

be attributed mistakenly to tobacco smoking and excessive alcohol consumption, respectively, further complicating access to TB care, particularly among men.

2.7.3.1 Tobacco smoking

Globally, 1.12 billion (33%) men and 279 million (6%) women were tobacco smokers in 2018 [168]. Although the prevalence of tobacco smoking is declining in both men and women, declines are expected to plateau around 30% for men and around 4% for women over the next ten years [168].

Tobacco smoking is associated with 1.7-1.9 times higher risk of *Mtb* infection and 2.0-2.7 times higher risk of TB disease, compared to non-smokers [169, 170]. Smoking-associated TB risks increase with increased number of cigarettes smoked per day and number of years smoking [171]. Mathematical modelling has indicated that smoking account for an excess 18 million TB cases and 40 million TB deaths between 2010 and 2050 [172], and regression analysis found that one-third of the variance in sex differences in TB case notifications could be explained by sex differences in smoking prevalence [173].

2.7.3.2 Alcohol consumption

In all WHO regions, men consume alcohol more often and in greater quantity than women [174]. In 2016, global estimates indicate that 54% of men were currently drinkers, compared to 32% of women, though prevalence decreasing for both men and women. Across WHO regions, the adult prevalence of alcohol consumption is 1.3 to 3.8 times higher in men than women, total alcohol per capita consumption is 2.7 to 2.8 times higher in men than women, and the prevalence of heavy episodic drinking is 2.1 to 4.2 times higher in men than women [174]. Globally an estimated 237 million men and 46 million women have alcohol use disorders.

Studies since the mid-twentieth century have shown an association between alcohol consumption and TB [176, 177]. More recent studies have shown that heavy alcohol consumption significantly increases the risk of TB disease, with a relative risk of 2.94 (95% CI: 1.89–4.59) for individuals with alcohol use disorder. However, it is not clear whether this link is biological due to alcohol's effects on the immune system or social due to mixing patterns associated with regular drinking in a public venue or associations with alcohol consumption among individuals in homeless shelters, prisons, or other social institutions [177].

2.7.3.3 Illicit drug use

Two thirds of drug users globally are men [178], but global data do not report the sex distribution of drug users by type of drug use. Data from South Africa show the prevalence of smoked drug use shows use among men is 50% higher among men (72% of study participants)

than women (48% of study participants), and smoked drug users in that study had a two-fold higher risk of smear-positive TB [179]. Similarly, a study in London found crack cocaine users and other hard drug users were 2.4 times and 1.6 times, respectively, more likely to be diagnosed with smear-positive TB than non-drug users [180].

2.7.3.4 Sexual behaviours

While sexual behaviours are not directly associated to TB risk, the two are indirectly linked through HIV infection, which is considered the most potent risk factor for TB [181]. There is evidence of some sex difference in HIV prevalence at a global level: 48% of adults living with HIV are men, and men make up 53% of new HIV infections among adults [182].

While men's risky sexual behaviours, including multiple partners and inconsistent condom use [183], may not have resulted in a higher risk of HIV infection, men are substantially less likely than women to access timely treatment for their HIV infections. An analysis of antiretroviral treatment (ART) enrolment in 12 countries – 10 in the WHO Africa region, one in the WHO region of the Americas, and one in the WHO Western Pacific region – found strong evidence that in 11 countries, ART enrolment was disproportionately higher among women with HIV than men with HIV, and in most countries, this disparity is increasing [184]. A systematic review and meta-analysis of 23 cohorts in the WHO Africa region similarly found that ART enrolment was lower among men than women, and also that men were at significantly greater risk of death once enrolled, suggesting that men delay care for HIV and seek treatment with more advanced disease than women [185].

2.7.4 Social contacts and networks

2.7.4.1 Social contact patterns

Social and community networks play important roles in *Mtb* transmission by influencing the number and type of contacts by an individual. It has been suggested that sex differences in TB emerge after adolescence due to cultural gender roles that place greater restrictions on women's socialization patterns after puberty [186]. As children mature during adolescence, social contact patterns within and outside the household may shift such that males have greater numbers of contacts outside the household and therefore increased risk of exposure to *Mtb* [187]. The few social contact surveys that have reported results by sex and age suggest that contact patterns differ by sex, but these results are limited to settings in southern Africa [188] and Europe [189, 190].

2.7.4.2 Stigma and social support

TB stigma affects both men and women. Although it has often been reported that stigma may be harsher for women than men [186], some tools used to measure stigma may underestimate stigma in men by ignoring gendered dimensions of power in relationships [191].

For men, the social impact of TB often focuses on the financial and occupational consequences of TB disease and treatment, as highlighted by qualitative studies in Malawi [192, 193], India [193-195], Bangladesh [193], Vietnam [196], and Colombia [193]. In these and other studies, men express concerns about loss of income and job opportunities as a result of TB; these fears are particularly strong in settings where men are reliant on informal work and lack social protections [192]. Men's financial and work-related concerns about TB link to their social status within the community. Any loss of employment or reduction in income affects a man's standing within his family and his family's standing within the community, particularly in settings where a man is expected to be a provider for both his immediate family and more distant relatives [192, 197, 198]. Men who do not live up to these standards report being shunned, humiliated, and devalued by both men and women in the community [192].

Feelings of shame and social isolation relating to TB have also been reported by men across settings. Men's reports of stigma particularly highlight the ways in which TB disease threatens men's perceptions of masculinity and manhood, limiting their independence and control [198, 199]. In Egypt, men report stronger feelings of shame associated with TB than women [200], and in India and Viet Nam, men tend to conceal their disease and refrain from discussing their diagnosis or treatment with friends and family [201, 202]. Stigma is further compounded in settings with high HIV burden, such as Malawi, where chronic cough, TB and HIV are often considered interchangeable and thus TB stigma is compounded by HIV stigma [199].

2.7.5 Institutional structures

Gender norms and expectations are embedded into societal structures [203] and thus affect living and working conditions. Institutional structures, including, but not limited to, government, industry, and health care systems, generally "foster unhealthy beliefs and behaviours among men, and undermine men's attempts to adopt healthier habits" [166].

2.7.5.1 Occupational risks

Men's traditional role of provider has put them at increased risk of occupational accidents and exposures [167]. A particular hazard is silicosis, one of the most prevalent industrial lung diseases [204], which develops from the inhalation of crystalline silica dust. In a study among miners in South Africa, the risk of incident TB was 1.4 times higher among those with possible silicosis and 2.5 times higher among those with advanced silicosis, both compared to miners with no evidence of silicosis [204]. Though the disease is preventable, workers, primarily young

men in low- and middle-income countries, often lack the legal protections and workplace regulations to ensure protective measures are taken [205].

Occupational risks extend beyond those associated with specific occupations. Economic pressures, again associated with traditional gender roles, prevent men from prioritising their health at the expense of work, particularly when doing so may result in a loss of livelihood. Many men also migrate for work, particularly from rural to urban areas, which increases TB risk as workers reside in crowded, poorly ventilated, polluted environments. Migration also interrupts access to health care through factors such as lack of familiarity with available services, language barriers, ineligibility for public health services, and disruptions to continuity of care [206].

2.7.5.2 Health care facilities

Men engage in fewer health-promoting behaviours than women [166], and have fewer opportunities than women to engage with health institutions [207]. Gendered barriers to men's utilisation of health services are institutionalised in organisational policy and practice [207]. Institutional factors that discourage men's utilisation of health services include inconvenient clinic hours, long travel or wait times, lack of privacy, or perceptions of rudeness from health care providers [207, 208]. Inconvenient clinic hours have been cited as having particular impact on men's lack of engagement with care in settings where income relies on informal work with no social protections [199].

2.7.6 Gender norms and expectations

Gender norms provide references for daily life and constrain psychological and material freedoms for both men and women [209]. Hegemonic masculinity represents a culturally dominant, idealised form of masculinity [209], often based on traditional beliefs about manhood [166]. Although gender roles and norms are fluid over time and differ across settings [183] and even within populations [210], studies have identified common themes associated with hegemonic masculinities.

Research among young men in the United States, United Kingdom, and Mexico identifies overarching themes used to define manhood, including self-sufficiency, acting tough, physical attractiveness, rigid masculine gender roles, heterosexuality and homophobia, hyper-sexuality, and aggression and control [211]. These characteristics are often emphasised in the "reputation-based" form of hegemonic masculinity and have been reported across geographic and cultural settings [212]. Qualitative research in Botswana, Nigeria, South Africa, and Uganda emphasises the corresponding "respectability-based" form of hegemonic masculinity, with key determinants of manhood requiring financial independence and, subsequently, starting and supporting a

family [183]. Few men fully achieve the respectability-based ideal of hegemonic masculinity or practice the reputation-based concept of hegemonic masculinity in its entirety, yet this does not diminish the influence of these dominant cultural norms [209].

Gender norms and expectations have important implications for health and health behaviours [166] and underly most, if not all, of the TB-associated risks discussed in the previous sections. Health beliefs that men are "independent, self-reliant, strong, robust and tough" often dissuade men from pursuing health services [166] and have been cited as deterrents for men in seeking care for TB [198,213].

2.8 Global relevance of sex disparities in tuberculosis

Through the End TB Strategy [214], adopted in 2014, and the Sustainable Development Goals (SDGs) [215], adopted in 2015, member states of the WHO and the United Nations (UN) committed to ending the TB epidemic by 2030. Specific targets include reducing TB incidence by 80-90% and TB mortality by 90-95%, both compared to 2015 estimates, and ensuring that no one faces catastrophic costs due to TB [214,215]. UN member states affirmed their commitment to ending TB at the first UN high-level meeting on TB in 2018 [216].

Despite substantial investment in prevention and treatment efforts since TB was declared a global health emergency in 1993, progress in reducing TB incidence and mortality is slower than required to meet the ambitious targets of the End TB Strategy and SDGs. The annual decline in TB incidence, currently approximately 1.5%, must accelerate to 10% by 2025 in order to meet global targets [11]. The global case fatality rate must fall to 6.5% by 2025 [11]. Historical data and mathematical modelling suggest these milestones can be achieved by scaling and optimising current strategies and tools, though novel technologies will be required for the further accelerations needed after 2025 to meet 2035 targets [217].

The need to optimise current strategies has renewed focus on key affected populations, including those with increased risk of exposure to TB due to where they live or work, increased risk of TB due to biological or behavioural factors, and/or limited access to TB services [214]. If the sex disparities reported in case notifications reflect true disparities in the underlying burden of TB disease and/or access to TB treatment, there may be a need to recognise men or women as a key affected population and follow that recognition with a redirection of resources and efforts, both to reduce the epidemiological burden of TB and to ensure equity and human rights are respected in the global TB response.

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Chapter 3 Sex differences in tuberculosis burden

3.1 Introduction

I conducted a systematic review and meta-analysis to quantify sex differences in adult TB prevalence and P:N ratios in national and sub-national TB prevalence surveys conducted in low- and middle-income countries between 1993 and 2016. Prevalence surveys are cross-sectional, population-based studies in which the number of people with TB within the study population is measured. Briefly, the population within the study area is enumerated, the study population is selected, individuals who consent to participate are screened by symptom interview and/or chest X-ray, sputum samples are collected from individuals with symptoms suggestive of TB and/or abnormal chest X-ray, and samples are analysed to identify bacteriologically positive and/or smear-positive TB. Surveys typically focus on pulmonary TB within adult populations, due to difficulty diagnosing extra-pulmonary and paediatric disease within a community setting. The exclusion of extra-pulmonary and paediatric disease is not expected to impact the results of this analysis substantially, as both occur less frequently than adult pulmonary disease.

This research paper was published in Plos Medicine in 2016 and is reproduced as follows with no revision or adaptation from the published manuscript. Supplemental materials are provided in Appendix A.

3.2 Cover sheet

The Research Paper Cover Sheet is enclosed on the following pages.

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Student ID Number	429972	**Title**	Mrs
First Name(s)	Katherine Chisholm		
Surname/Family Name	Horton		
Thesis Title	Understanding sex disparities in tuberculosis and assessing the potential impact of strategies to improve men's access to care		
Primary Supervisor	Elizabeth L. Corbett		

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

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For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I developed the overall aim of this manuscript, originally conceived by Prof. Liz Corbett, and wrote the protocol for the study, which details the methodology for both the systematic review and meta-analyses. I then conducted the systematic review, searching the literature, maintaining search records, reviewing titles/abstracts, reviewing full-text manuscripts, and extracting relevant data, with second review and support from Dr. Peter MacPherson. I contacted authors, where necessary, and collated the final dataset for analysis. I conducted all analyses and produced tables and figures to summarise results. I drafted the manuscript and then incorporated feedback from coauthors. I oversaw the manuscript submission process and revised the manuscript, as necessary, to respond to input from peer review.

SECTION E

Student Signature	K. Horton
Date	

Supervisor Signature	E. Corbett
Date	

Citation: Horton KC, MacPherson P, Houben RMGJ, White RG, Corbett EL (2016) Sex Differences in Tuberculosis Burden and Notifications in Low- and Middle-Income Countries: A Systematic Review and Meta-analysis. PLoS Med 13(9): e1002119. doi:10.1371/journal.pmed.1002119

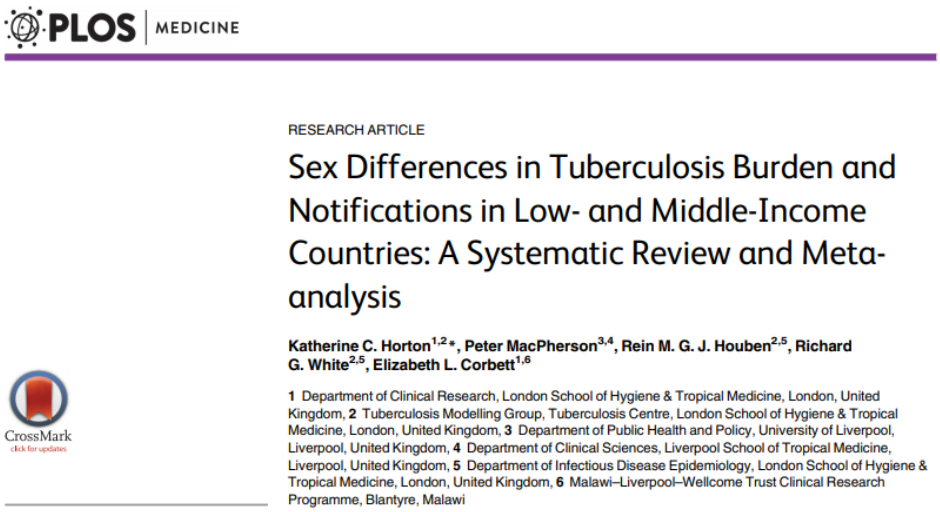
Academic Editor: John Z Metcalfe, University of California San Francisco, UNITED STATES

Received: December 17, 2015

Accepted: July 29, 2016

Published: September 6, 2016

3.3 Title and authors



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RESEARCH ARTICLE

Sex Differences in Tuberculosis Burden and Notifications in Low- and Middle-Income Countries: A Systematic Review and Meta-analysis

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3.4 Abstract

Background: Tuberculosis (TB) case notification rates are usually higher in men than in women, but notification data are insufficient to measure sex differences in disease burden. This review set out to systematically investigate whether sex ratios in case notifications reflect differences in disease prevalence and to identify gaps in access to and/or utilisation of diagnostic services.

Methods and Findings: In accordance with the published protocol (CRD42015022163), TB prevalence surveys in nationally representative and sub-national adult populations (age ≥ 15 y) in low- and middle-income countries published between 1 January 1993 and 15 March 2016 were identified through searches of PubMed, Embase, Global Health, and the Cochrane Database of Systematic Reviews; review of abstracts; and correspondence with the World Health Organization. Random-effects meta-analyses examined male-to-female (M:F) ratios in TB prevalence and prevalence-to-notification (P:N) ratios for smear-positive TB. Meta-regression was done to identify factors associated with higher M:F ratios in prevalence and higher P:N ratios. Eighty-three publications describing 88 surveys with over 3.1 million participants in 28 countries were identified (36 surveys in Africa, three in the Americas, four in the Eastern Mediterranean, 28 in South-East Asia and 17 in the Western Pacific). Fifty-six surveys reported in 53 publications were included in quantitative analyses. Overall random-effects weighted M:F prevalence ratios were 2.21 (95% CI 1.92–2.54; 56 surveys) for bacteriologically positive TB and 2.51 (95% CI 2.07–3.04; 40 surveys) for smear-positive TB. M:F prevalence ratios were highest in South-East Asia and in surveys that did not require self-report of signs/symptoms in initial screening procedures. The summary random-effects weighted M:F ratio for P:N ratios was 1.55 (95% CI 1.25–1.91; 34 surveys). We intended to

stratify the analyses by age, HIV status, and rural or urban setting; however, few studies reported such data.

Conclusions: TB prevalence is significantly higher among men than women in low- and middle-income countries, with strong evidence that men are disadvantaged in seeking and/or accessing TB care in many settings. Global strategies and national TB programmes should recognise men as an underserved high-risk group and improve men's access to diagnostic and screening services to reduce the overall burden of TB more effectively and ensure gender equity in TB care.

3.5 Author Summary

Why Was This Study Done?

- Global health initiatives have tended to treat "gender" issues in health as being synonymous with women's health. However, for infectious diseases, policy and practice need to be guided by epidemiological data and consideration of transmission dynamics.
- Many more men than women are diagnosed with, and die from, tuberculosis (TB) globally.
- Data from population-level surveys for undiagnosed TB, carried out in a number of countries during the last two decades, can be combined with data on diagnosed (notified) cases to provide more complete insight into the magnitude and nature of sex differences in TB.

What Did the Researchers Do and Find?

- Surveys conducted to identify adult cases of TB in communities in low- and middle-income countries between 1993 and 2016 were analysed by sex.
- TB prevalence among men was over twice as high as among women and was substantially higher even in settings with high HIV prevalence.
- Case notification rates were also higher for men, and the ratio of prevalent-to-notified cases of TB – an indication of how long patients take to be diagnosed, on average – was 1.5 times higher among men than women, suggesting that men are less likely than women to achieve a timely diagnosis.

What Do These Findings Mean?

- Given that undiagnosed TB is the key driver for transmission in communities, our data show that greater effort and investment are needed to improve awareness of TB in men as an individual and public health issue.

- Policies on gender and TB should place greater emphasis on the high burden of disease in men and the need to invest in male-friendly diagnostic and screening services, with the aim of reducing undiagnosed TB.

3.6 Manuscript

3.6.1 Introduction

Over the past twenty years, tuberculosis (TB) case notifications among men have exceeded those among women in most settings [1]. In 2014, the male-to-female (M:F) ratio in smear-positive pulmonary TB case notification was 1.7 globally and ranged from 1.0 in the Eastern Mediterranean Region to 2.1 in the Western Pacific Region [2]. The excess of notified cases among men has often been explained as a result of barriers faced by women in seeking care for and being diagnosed with TB [3,4]. However, notification data alone are insufficient to determine whether this is true, or whether sex differences in case notifications reflect an excess in the burden of disease among men and even a disadvantage among men in seeking and accessing TB care.

Prevalence surveys offer a robust measure of disease burden in the community, reducing or eliminating the care-seeking biases that affect case notifications: a higher proportion of men in case notifications could reflect either higher incidence of TB disease or more complete registration for treatment by men. Prevalence surveys predominantly identify infectious TB patients with previously undiagnosed TB disease who have, therefore, not contributed to routine notification data before participation in the survey. As such, comparison of the characteristics of diagnosed TB patients (notification data) with those of undiagnosed TB patients (prevalence survey data) provides a unique insight into diagnosis and treatment access barriers. For example, finding a similar male predominance in undiagnosed TB (prevalence surveys) patients as in notified TB cases would support the hypothesis that men genuinely have a higher burden of TB disease, while finding a greater male predominance in undiagnosed TB patients than in notified TB cases would suggest male-specific access barriers or male sex being a risk factor for TB disease.

A previous analysis in 2000 found that male TB prevalence exceeded female TB prevalence in 27 (93%) of 29 prevalence surveys conducted in 14 countries between 1953 and 1997 [5]. The same analysis calculated the patient diagnostic rate (the inverse of the prevalence-to-notification ratio) and found that female cases were more likely to be notified than male cases in 21 (72%) surveys.

Despite these findings, men are often overlooked in discussions of gender and TB. While global TB reports and meetings on gender acknowledge the fact that the majority of TB cases and TB-

associated deaths occur among men, greater focus is usually placed on women. More broadly in global health discussions, there is a tendency to use the word "gender" when really "women" is meant, as exemplified by the Millennium Development Goals [6] and Sustainable Development Goals [7]. Subsequently, an emphasis on men runs contrary to global norms [8], and strategies to assess and address men's barriers to TB care are notably absent from the global research agenda.

The World Health Organization's End TB Strategy emphasises the importance of equity in access to diagnosis and treatment [9]; men should not be excluded from this target. The End TB Strategy has also prioritised systematic screening of high-risk groups to ensure early diagnosis of individuals with TB [10]. If TB prevalence remains higher among men than women, as in previous analysis [5], men should be considered a high-risk group for TB [11], and national TB programmes should more actively target men with routine diagnostic and/or screening services. This action is necessary to reduce the burden of TB in the whole population more effectively [12] and to ensure that principles of gender equity are upheld.

This review set out to systematically investigate sex differences in the prevalence of bacteriologically positive TB and smear-positive TB in adult participants in cross-sectional surveys conducted in low- and middle-income countries to determine whether sex ratios in adult case notifications reflect population sex differences in disease and to compare prevalence-to-notification (P:N) ratios for men and women. The current study adds to previous analysis [5] by including surveys conducted since the widespread availability of anti-TB chemotherapy in low-resource settings and the implementation of the directly observed treatment short course (DOTS) strategy, as well as the rise of the HIV/AIDS pandemic and the implementation of interventions against it—all factors that may have different effects on TB in men and women. The current study also provides more detailed meta-analyses of sex differences in TB prevalence and P:N ratios.

3.6.2 Methods

Search Strategy

In accordance with the published protocol [13], studies describing national and sub-national TB prevalence surveys in adult populations (age ≥ 15 y) in low- and middle-income countries published between 1 January 1993 and 15 March 2016 were identified through searches of PubMed, Embase, Global Health, and the Cochrane Database of Systematic Reviews (Table 1). The WHO *Global Tuberculosis Report 2015* [2] and abstract books from the Union World Conference on Lung Health (2012–2015) were also searched by hand, as were the reference lists of included studies. Researchers in the field and at WHO were contacted to assist with identification of relevant studies.

Table 1: Search strategy

Set	Search Algorithm		
	PubMed	**Embase/Global Health**	**Cochrane Library**
1	(("tuberculosis"[MeSH terms] OR "tuberculosis" OR "Tuberculoses") OR ("Mycobacterium tuberculosis"[MeSH terms])) NOT (("animals"[MeSH terms] NOT ("humans"[MeSH terms] AND "animals"[MeSH terms])))	((tuberculos* or Mycobacterium tuberculosis) NOT (animals not (humans and animals))).hw,ti.	(tuberculos* or "Mycobacterium tuberculosis"): ti,kw
2	(cross-sectional[MeSH terms] OR mass screening[MeSH terms] OR prevalence[MeSH terms] OR (prevalence[tw] AND study[tw]) OR (prevalence[tw] AND studies[tw]))	(cross-sectional or mass screening or prevalence).hw,ti.	(cross-sectional or "mass screening" or prevalence):ti,kw
3	Cochrane LMIC search terms [14]	Cochrane LMIC search terms [14]	Cochrane LMIC search terms [14]
4	"1993/01/01"[Date—Publication]: "3000"[Date—Publication]	1 and 2 and 3	(#1 AND #2 AND #3)
5	English [la]	Limit 4 to time period from 1993–present	Limit 4 to time period 1993–present
6	1 AND 2 AND 3 AND 4 AND 5	Limit 5 to English language	

Two authors (K. C. H. and P. M.) independently reviewed titles and abstracts in parallel to identify relevant studies for full-text review. A third author (E. L. C.) resolved any discrepancies. The same authors reviewed full texts to determine whether studies met inclusion criteria and then extracted data on study methodology and TB prevalence in parallel using piloted electronic forms.

Study authors were contacted for additional information if studies did not report the number of participants and the number of bacteriologically positive and/or smear-positive TB cases by sex for adult participants. Authors were also contacted if sex-specific prevalence data were not available by age group.

Inclusion and Exclusion Criteria

The review included cross-sectional prevalence surveys conducted in low- and middle-income countries [15]. Studies conducted among symptomatic or care-seeking individuals, children, individuals of a single sex, occupational settings, or other sub-populations (e.g., only HIV-positive individuals) were excluded. Studies reporting prevalence of *Mycobacterium tuberculosis* infection but not TB disease were excluded. Individuals under 15 y of age were excluded since diagnosis of childhood TB is more complicated than diagnosis of adult disease, especially within the context of community-based surveys [16]. Studies including both adults and children were included in the qualitative review but were excluded from quantitative analyses unless the study reported participation and prevalence for adults. Studies published in languages other than English were excluded due to limited resources for translation. Where more than one report was identified for a single survey, the most complete source was included and the others were excluded.

Study Quality

The risk of bias in included studies was assessed in parallel by K. C. H. and P. M. Each study was ranked on eight criteria from a tool developed to assess the risk of bias in prevalence surveys [17]. These criteria assessed factors related to the selection of the study population, the

risk of nonresponse bias, data collection methods, and case definitions. The eight criteria were summarised to give an assessment of the overall risk of bias.

Definitions

Study participants were defined as individuals who were interviewed and/or underwent initial screening procedures, according to study-specific procedures. Participation was defined as the number of participants divided by the number of individuals who were eligible or invited to participate. High relative male participation was defined as a M:F ratio in participation ≥ 0.90.

Case definitions for TB were based on internationally recognised terminology, where available, and study-specific definitions otherwise. Bacteriologically positive TB was defined as positive smear microscopy, culture, or WHO-approved rapid diagnostic results (such as from Xpert MTB/RIF) [18].

Sex-specific prevalence of bacteriologically and smear-positive TB was defined as the number of individuals with bacteriologically or smear-positive TB divided by the number of study participants, by sex. Reported prevalence was used to estimate the number of cases or the number of participants where one of these values was missing. No adjustments were made for nonparticipation or nonsampling.

Sex-specific P:N ratios were calculated as the ratio of smear-positive TB prevalence per 100,000 individuals to smear-positive TB case notifications per 100,000 individuals among adults [5,19]. WHO case notification data [20] and United Nations population estimates [21] were matched to each prevalence survey by country and year. For surveys that took place over more than one calendar year, the annual case notification rate was averaged over all survey years (excluding years with no reported data). No adjustments were made for sub-national surveys.

National estimates of TB and HIV burden were matched to each prevalence survey by country and year. For surveys that took place over more than one calendar year, estimates were averaged over all survey years (excluding years with no reported data). High TB prevalence was defined using the median value for included studies, which was an estimated national TB prevalence ≥ 300 per 100,000 individuals [22]. High HIV prevalence was defined as estimated national HIV prevalence ≥ 1% in the general population [23,24], and high HIV prevalence in incident TB was defined as estimated HIV prevalence ≥ 20% in new and relapse TB cases [22,25].

Data Analysis

Prevalence of bacteriologically positive TB and smear-positive TB was calculated for included studies by sex. Prevalence of bacteriologically positive TB by sex and age was also calculated,

where possible. Sub-group prevalence was estimated for sub-groups based on survey characteristics including WHO geographical region, survey setting (national versus sub-national), national estimates of TB and HIV burden (both in the general population; the latter also in incident TB), study quality, initial screening procedures, case definitions, and relative male participation. Clopper-Pearson confidence intervals [26] and M:F ratios were calculated for all prevalence estimates. P:N ratios for smear-positive TB were estimated with confidence intervals based on the estimated variance using a continuity correction of 0.5 in the corresponding prevalence estimates.

Heterogeneity was assessed using the I^2 statistic [27]. Due to substantial heterogeneity between studies, random-effects models were used for meta-analyses, weighting for the inverse of the variance. Random-effects weighted summary M:F ratios were calculated for participation, prevalence of bacteriologically positive TB and smear-positive TB, age-specific prevalence of bacteriologically positive TB, and P:N ratios.

Meta-regression was performed for M:F ratios in prevalence and M:F ratios in P:N ratios to examine associations with the survey characteristics mentioned above, plus the starting year of each survey. Univariate meta-regression of M:F ratios in prevalence was conducted separately for bacteriologically positive TB and smear-positive TB. If either univariate meta-regression suggested evidence of an association with a particular characteristic, that characteristic was included as a variable in the multivariate meta-regression models for both bacteriologically positive and smear-positive TB. Similarly, multivariate meta-regression of M:F ratios in P:N ratios was based on evidence of associations in univariate analysis.

All analyses were performed using R version 3.2.2 [28] (S1 Data; S1 Analysis).

3.6.3 Results

Study Characteristics

Of 7,502 potentially relevant English-language studies screened by title and abstract, 148 were reviewed in full; of these, 65 were excluded after full-text review (S1 Table) and 83 were eligible for inclusion (Fig. 1; S2 Table) [29–111]. Included studies describe 88 surveys in 28 countries: 36 surveys in 13 countries in the African Region, three surveys in two countries in the Region of the Americas, four surveys in two countries in the Eastern Mediterranean Region, 28 surveys in five countries in the South-East Asia Region, and 17 surveys in six countries in the Western Pacific Region (Fig. 2). There were 22 nationally representative surveys and 66 sub-national surveys, with at least 20 of the latter conducted in urban settings and eight among tribal populations. Over 3.1 million adult participants were included; 16 surveys did not report the number of adult participants.

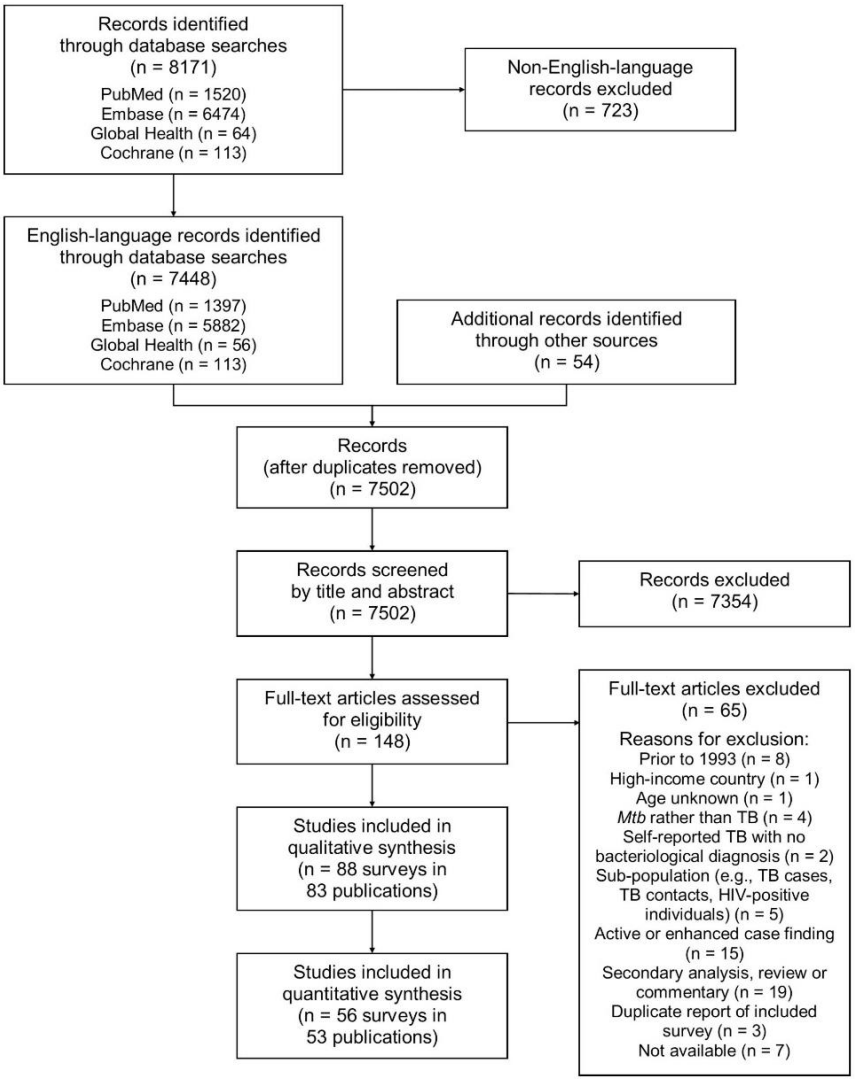

Figure 1: PRISMA flow diagram. *Mtb, Mycobacterium tuberculosis*

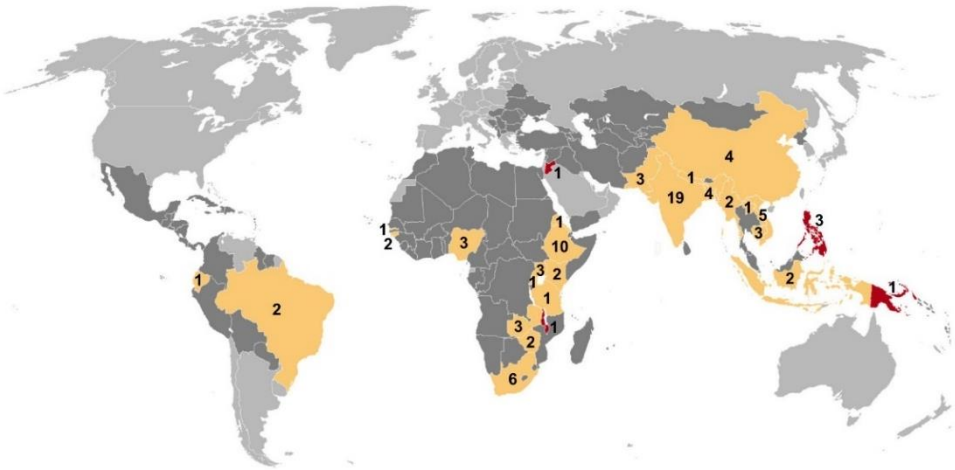

Figure 2: Global map showing countries in which prevalence surveys have been conducted. Yellow indicates low- and middle-income countries for which sex-disaggregated data are available from at least one prevalence survey (n=24). Red indicates low- and middle-income countries in which at least one prevalence survey has been conducted but sex-disaggregated data are not available (n=4). Dark gray indicates low- and middle-income countries where no prevalence survey has been identified

(n=107). Labels show the total number of surveys identified within each country for which at least one prevalence survey was identified (n=88).

Study Quality

The risk of bias assessment identified 33 (43%) surveys with low risk of bias, 32 (42%) with moderate risk of bias, and 12 (16%) with high risk of bias (S1 Fig.). Eleven surveys for which only an abstract was available were characterised as unknown risk of bias due to limited information on study methodology [34,57,62,63,75,76,80,95,104]. The quantitative analyses included a slightly higher proportion of surveys with low risk of bias than the qualitative summary. In all, 84% to 94% of the surveys in the quantitative analyses had low to moderate risk of bias (S2 Fig.).

Participation by Sex

Female participation equalled or exceeded male participation in all of the 28 surveys for which participation was reported by sex (Fig. 3). Of 687,926 men eligible or invited to participate, 521,934 (75.9%) participated, while 611,901 (82.5%) of 741,705 eligible or invited women participated. The overall random-effects weighted M:F ratio in participation was 0.90 (95% CI 0.86–0.93; range 0.50 to 1.00).

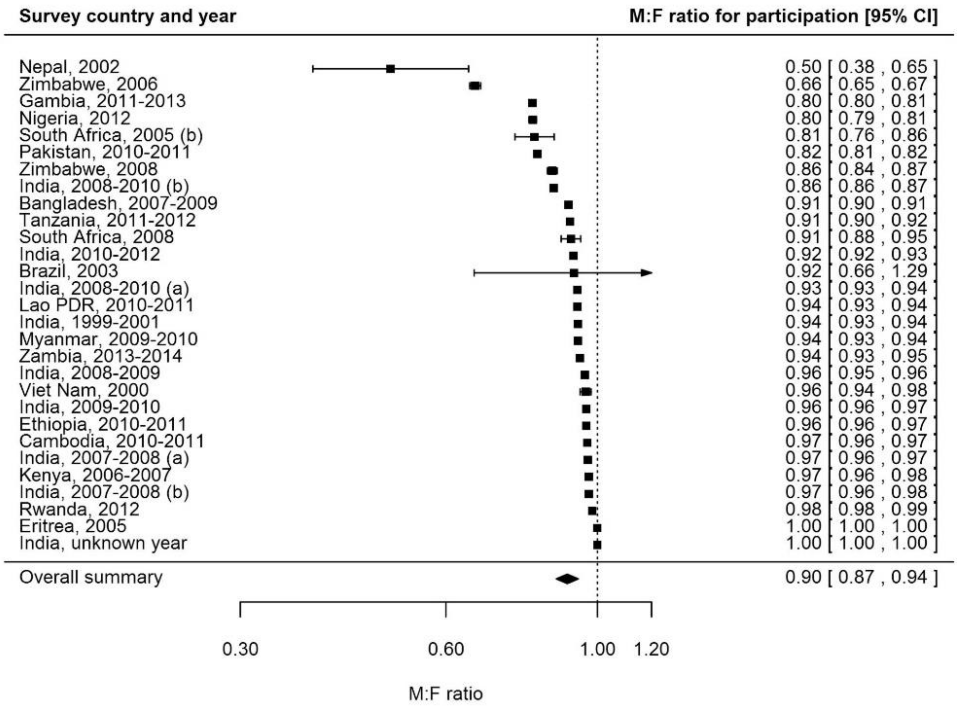

Figure 3: Male-to-female ratios of participation among eligible or invited individuals (n=29). Analysis includes surveys that report the number of individuals who were eligible for screening and the number of individuals screened by sex. See S2 Table for survey details and references. Lao PDR, Lao People's Democratic Republic.

TB Prevalence by Sex

The prevalence of bacteriologically positive TB was reported by sex in 56 surveys with 2.2 million participants in 24 countries [29,30,32,33,35,36,38–44,47–51,53,55,56,58–60,65–67,69–74,82,84,85,87,89–94,97,101,102,104,105,107,110–112]. Forty surveys with 1.7 million participants in 22 countries reported the prevalence of smear-positive TB by sex [35,40,43,44,48–51,53,55,56,58–60,65–67,69–71,73,74,85,87,89,90,92,94,97,101,102,105,107,110,111]. The overall random-effects weighted prevalence per 100,000 individuals was 488 (95% CI 382–623) among men and 231 (95% CI 166–321) among women for bacteriologically positive TB and 314 (95% CI 245–403) among men and 129 (95% CI 89–189) among women for smear-positive TB (S3 Table).

Excluding the Region of the Americas – because it had only two small sub-national surveys included in the quantitative analysis – the prevalence of bacteriologically positive TB and smear-positive TB was highest in the African Region. There was strong evidence that male and female prevalence of bacteriologically positive TB per 100,000 individuals was higher in settings with high HIV prevalence in the general population (high versus low HIV prevalence settings: for men, 1,162, 95% CI 735–1,834, versus 360, 95% CI 275–471, $p < 0.01$; for women, 735, 95% CI 448–1202, versus 157, 95% CI 110–223, $p < 0.01$). This same relationship (higher prevalence of undiagnosed TB in settings with high HIV prevalence) was also apparent when HIV data from diagnosed TB patients, rather than the general population, were used (for men: 907, 95% CI 582–1,413, versus 359, 95% CI 270–477, $p < 0.01$; for women: 553, 95% CI 341–896, versus 153, 95% CI 105–224, $p < 0.01$) (S4 Table). Prevalence of smear-positive TB per 100,000 individuals was also higher in settings with high HIV prevalence in the general population (high versus low HIV prevalence settings: for men, 548, 95% CI 303–990, versus 275, 95% CI 208–364, $p = 0.04$; for women, 273, 95% CI 131–568, versus 110, 95% CI 71–169, $p = 0.04$) and in settings with high HIV prevalence in diagnosed TB patients for women (229, 95% CI 126–416, versus 103, 95% CI 64–165, $p = 0.04$) but not for men (459, 95% CI 289–727, versus 270, 95% CI 200–366, $p = 0.06$) (S4 Table).

Male-to Female Ratios in TB Prevalence

The overall random-effects weighted M:F prevalence ratio was 2.21 for bacteriologically positive TB (95% CI 1.92–2.54; range 0.62 to 6.18; 56 surveys in 24 countries) and 2.51 for smear-positive TB (95% CI 2.07–3.04; range 0.25 to 5.91; 40 surveys in 22 countries). Random-effects weighted M:F prevalence ratios for bacteriologically positive TB and smear-positive TB were significantly greater than one in all regions except the Region of the Americas, where analyses included only two small sub-national surveys (Fig. 4).

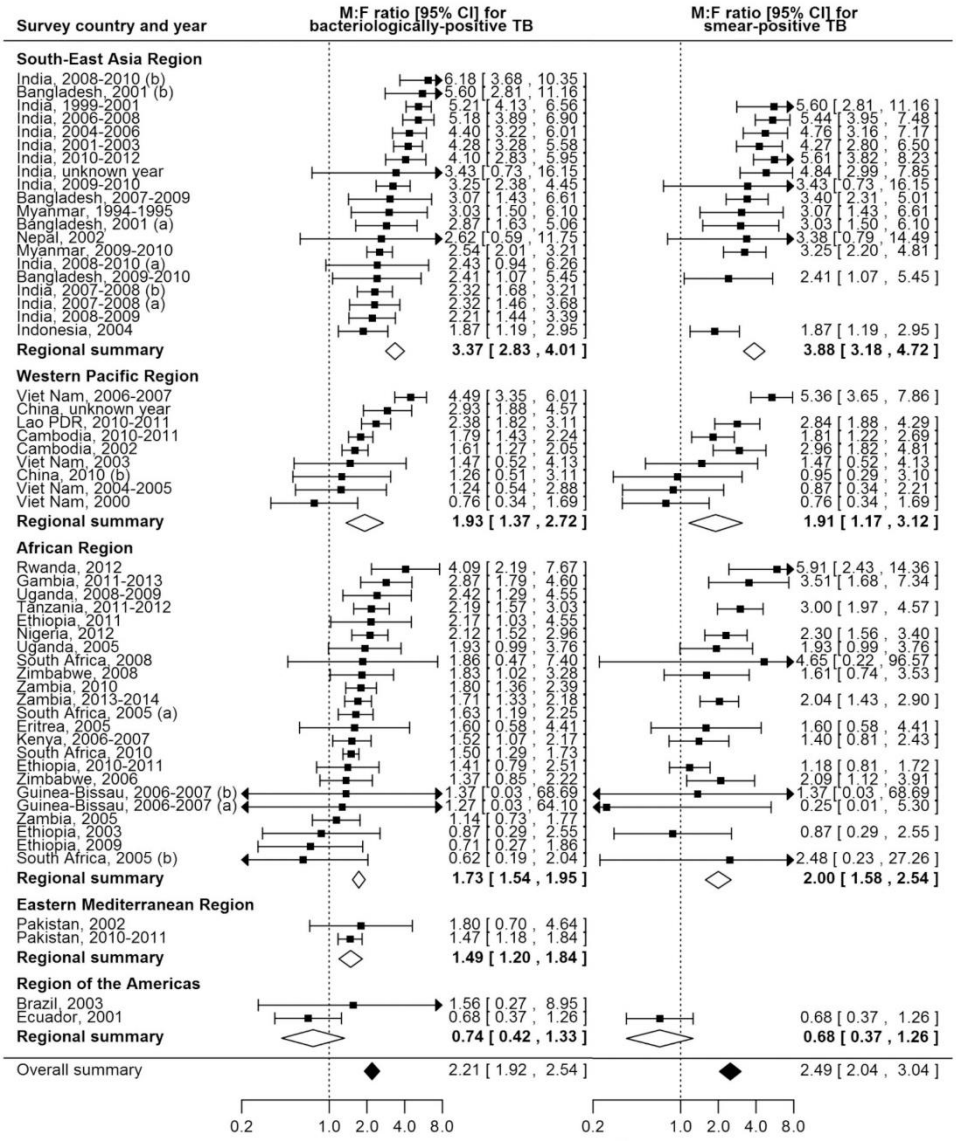

Figure 4: Male-to-female ratios in bacteriologically positive (n=56) and smear-positive (n=40) TB prevalence by WHO region. Regional and overall summaries from random-effects models for bacteriologically positive and smear-positive TB. See S2 Table for survey details and references. Lao PDR, Lao People's Democratic Republic.

Among countries with multiple surveys, an excess of male TB cases was observed in all studies in eight (73%) of 11 countries. Exceptions with inconsistent results were Ethiopia, South Africa, and Viet Nam, although overall random-effects weighted M:F prevalence ratios exceeded one for each of these countries.

Univariate Meta-regression of Male-to-Female Ratios in Prevalence

In univariate meta-regression of M:F ratios in bacteriologically positive TB (Table 2), there was strong evidence that M:F prevalence ratios were 1.95 times higher in the South-East Asia Region than in the African Region (95% CI 1.54–2.48; 56 surveys). M:F prevalence ratios were lower in settings with high HIV prevalence in the general population (0.67, 95% CI 0.49–0.90; 54 surveys) or in incident TB (0.69, 95% CI 0.53–0.93; 54 surveys).

Table 2: Univariate and multivariate random-effects meta-regression results for male-to-female ratios in bacteriologically positive TB and smear-positive TB.

Analysis	Bacteriologically Positive TB			Smear-Positive TB		
	N	Relative M:F Ratio (95% CI)	*p*-Value	*N*	Relative M:F Ratio (95% CI)	*p*-Value
Univariate analysis						
AMR versus AFR	56	0.45 (0.21–0.99)	0.047	39	0.34 (0.13–0.89)	0.029
EMR versus AFR		0.89 (0.51–1.56)	0.692		n/a	
SEAR versus AFR		1.95 (1.54–2.48)	<0.001		1.91 (1.33–2.75)	<0.001
WPR versus AFR		1.17 (0.87–1.59)	0.302		1.05 (0.68–1.61)	0.838
National versus sub-national	56	1.01 (0.75–1.37)	0.927	39	1.11 (0.74–1.67)	0.610
Survey starting year	54	0.99 (0.96–1.03)	0.697	38	1.00 (0.96–1.05)	0.976
High versus low TB prevalence	54	0.97 (0.72–1.32)	0.864	38	1.12 (0.73–1.70)	0.605
High versus low HIV prevalence in general population	54	0.67 (0.49–0.90)	0.008	38	0.78 (0.47–1.29)	0.334
High versus low HIV prevalence in incident TB	54	0.69 (0.52–0.93)	0.014	38	0.77 (0.49–1.21)	0.254
Low versus moderate/high risk of bias	55	0.85 (0.63–1.10)	0.266	39	1.07 (0.71–1.63)	0.739
Initial screening procedures requiring self-report of signs/symptoms versus broader initial screening procedures	56	0.80 (0.58–1.10)	0.170	39	0.63 (0.42–0.96)	0.031
Diagnosis by smear microscopy versus other diagnostic measures	53	0.93 (0.68–1.28)	0.660	36	0.72 (0.45–1.14)	0.159
Low versus high relative male participation	29	0.89 (0.60–1.32)	0.553	22	0.93 (0.53–1.62)	0.789
Multivariate analysis						
AMR versus AFR	54	0.46 (0.19–1.10)	0.080	38	0.53 (0.18–1.56)	0.250
EMR versus AFR		0.82 (0.41–1.61)	0.557		n/a	
SEAR versus AFR		1.78 (1.13–2.80)	0.013		2.21 (1.23–3.97)	0.008
WPR versus AFR		1.01 (0.61–1.67)	0.971		1.19 (0.63–2.22)	0.590
High versus low HIV prevalence in general population		0.72 (0.43–1.20)	0.210		0.87 (0.46–1.66)	0.676
High versus low HIV prevalence in incident TB		1.18 (0.62–2.22)	0.617		1.26 (0.59–2.71)	0.555
Initial screening procedures requiring self-report of signs/symptoms versus broader initial screening procedures		0.83 (0.63–1.10)	0.190		0.65 (0.45–0.93)	0.020

AFR, African Region; AMR, Region of the Americas; EMR, Eastern Mediterranean Region; n/a, not applicable; SEAR, South-East Asia Region; WPR, Western Pacific Region.

doi:10.1371/journal.pmed.1002119.t002

M:F prevalence ratios were also higher in the South-East Asia Region than in the African Region in univariate meta-regression of smear-positive TB (1.91, 95% CI 1.33–2.75; 39 surveys). In this analysis there was also evidence that M:F prevalence ratios were lower in surveys that required individuals to report signs or symptoms of TB during initial screening procedures (0.63, 95% CI 0.42–0.96; 39 surveys) compared to surveys within which initial screening procedures included criteria such as chest X-ray, self-reported history of TB, or self-reported contact with a TB case, instead of or in addition to self-reported signs or symptoms.

In univariate meta-regression models for M:F ratios in bacteriologically positive TB and M:F ratios in smear-positive TB, none of the following survey characteristics were associated with differences in M:F ratios in TB prevalence: survey setting (national versus sub-national), survey starting year, TB prevalence, risk of bias, case definitions, or relative sex ratios in participation.

Multivariate Meta-regression of Male-to-Female Ratios in Prevalence

In multivariate meta-regression of M:F ratios in bacteriologically positive TB, there was evidence that M:F ratios remained higher in the South-East Asia Region than in the African Region after adjusting for HIV prevalence and initial screening procedures, although the relative M:F ratio between these two regions was slightly lower than in univariate analysis (1.78, 95% CI 1.13–2.80; 54 surveys).

There was evidence in the multivariate meta-regression of M:F ratios in smear-positive TB that M:F ratios were 2.21 times higher in the South-East Asia Region than in the African region

(95% CI 1.23–4.04; 38 surveys). There was also evidence in the multivariate meta-regression that M:F ratios in surveys that required individuals to self-report signs or symptoms of TB in initial screening procedures were lower than those in surveys with broader initial screening procedures (0.65, 95% CI 0.45–0.93; 38 surveys).

TB Prevalence by Sex and Age

Data on the prevalence of bacteriologically positive TB by sex and age were available for 19 surveys in 13 countries [32,33,35,36,43,44,50,51,53,58,60,65–67,70,71,97,101,107]. Random-effects weighted M:F ratios in prevalence appear to increase with age from 1.28 (95% CI 0.85–1.92; range 0.29 to 5.06) among individuals aged 15–24 y to 3.18 (95% CI 2.24–4.53; range 0.57 to 11.34) among individuals aged 45–54 y (Fig. 5).

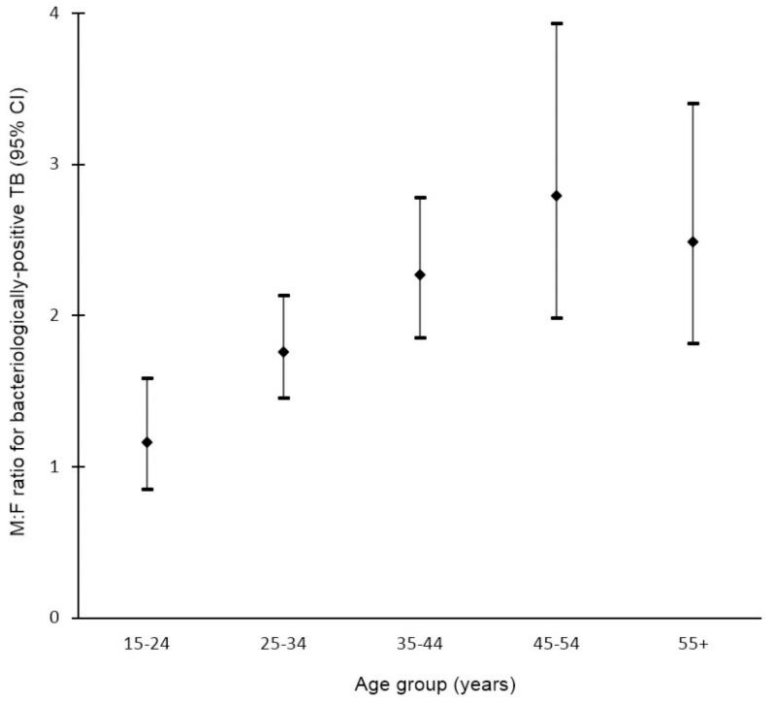

Figure 5: Random-effects weighted male-to-female prevalence ratios for bacteriologically positive TB by age group (n=19). Analysis includes surveys that report the number of individuals screened and the number of bacteriologically positive TB cases by sex and age. Horizontal axis shows age groups in years. Vertical axis shows random-effects weighted M:F ratios in prevalence of bacteriologically positive TB per 100,000 individuals with 95% confidence intervals.

Prevalence-to-Notification Ratios by Sex

P:N ratios for smear-positive TB exceeded one for both men and women in 25 (74%) of 34 surveys in 20 countries with available data (Fig. 6). The median number of prevalent cases per notified case was 2.6 (interquartile range 1.3–3.4) for men and 1.6 (interquartile range 1.2–2.7) for women, and the overall random-effects weighted M:F ratio for P:N ratios was 1.55 (95% CI 1.25–1.91).

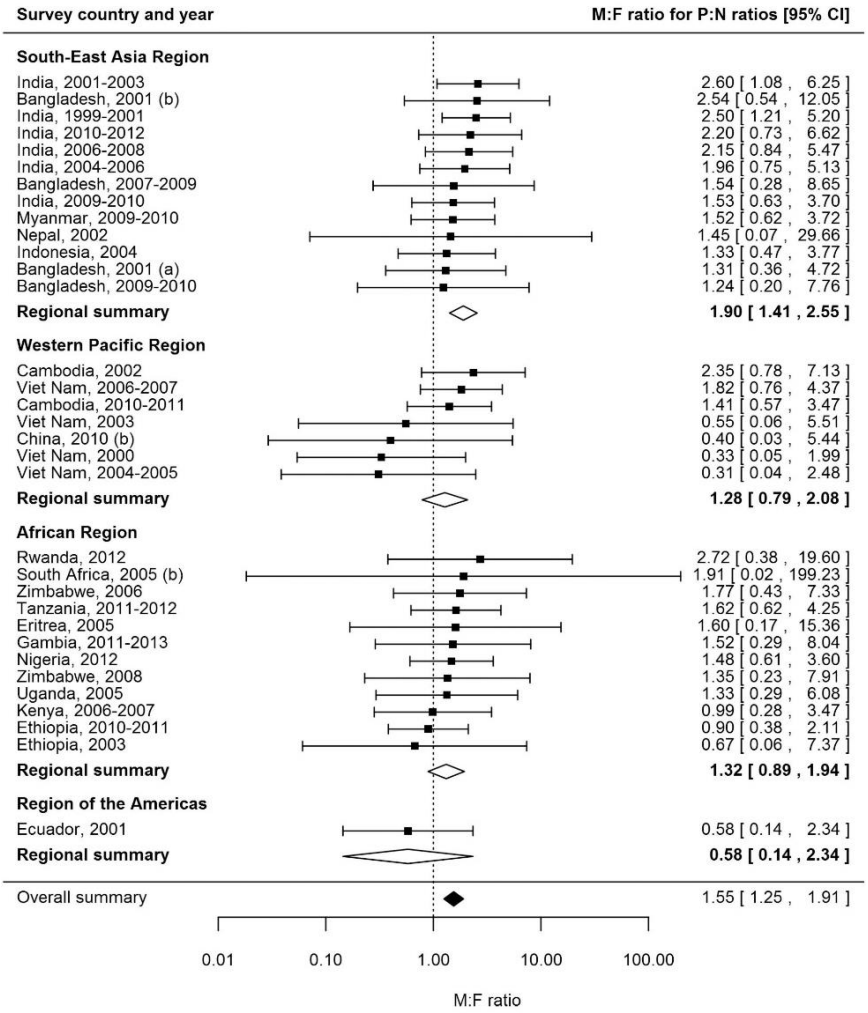

Figure 6: Male-to-female ratios in prevalence-to-notification ratios (n=34). Analysis includes surveys that report the prevalence of smear-positive TB by sex and for which corresponding national notification and population data are available. See S2 Table for survey details and references.

Univariate Meta-regression for Male-to-Female Ratios in Prevalence-to-Notification Ratios

There was no evidence in univariate meta-regression that any of the study or setting characteristics examined were associated with M:F ratios in P:N ratios (S5 Table). Due to the lack of evidence of associations in univariate analyses, multivariate meta-regression was not performed for M:F ratios in P:N ratios.

3.6.4 Discussion

Meta-analysis of 56 TB prevalence surveys including 2.2 million participants in 28 countries provides strong evidence that TB prevalence is higher among men than women, with a higher M:F ratio than that reported for case notification data. The number of prevalent cases per notified case of smear-positive TB was also higher among men than women, adding evidence that men may be less likely than women to seek or access care in many settings. Further evidence of men's barriers to seeking or accessing care is provided by results showing that men

were less likely than women to participate in prevalence surveys and that relatively fewer prevalent cases were found among men in surveys that required participants to self-report signs or symptoms in initial screening procedures.

The excess male prevalence observed in surveys conducted between 1953 and 1997 [5] persists in more recent surveys, despite widespread implementation of the DOTS strategy and interventions against the HIV pandemic that have decreased overall TB prevalence. Regional summary M:F ratios in the current study were similar to those previously reported for South-East Asia (3.8 versus 3.2), where sex differences were greatest, and the Western Pacific (1.9 versus 2.0). However, in the current study, the summary M:F ratio for the African Region was twice that previously reported (2.0 versus 1.0), suggesting that sex disparities in TB prevalence in this region have increased over the past fifty years. The emergence of HIV during this time has had a substantial impact on TB epidemiology, especially in the African Region. However, while the prevalence of HIV is slightly higher among women than men [113], this study shows that the prevalence of TB is higher among men, even in countries with generalised HIV epidemics. Men also face a relative disadvantage in accessing and remaining in HIV care [114–117], and so men's risk of TB is likely to be further increased as a result of undiagnosed and untreated HIV co-infection and missed opportunities for TB screening within HIV care.

Comparisons of sex ratios in TB prevalence and notification highlight sex differences in time to diagnosis and imply that in many settings women are more likely than men to have a timely TB diagnosis. While these results could be attributed to men seeking care in private facilities and therefore being less likely to be included in case notification numbers, this explanation would require that the proportion of men who seek care in the public sector be only two-thirds the proportion of women who seek care in that sector. Instead, there is wider evidence that men are less well-served than women by health services [118,119]. Within the context of HIV, which has a similarly lengthy pathway to diagnosis, there is also substantial evidence that men experience greater attrition and worse outcomes [114–117]. Men are less likely than women to access antiretroviral therapy, and in many countries this disparity has increased over time [114]. Similar evidence showing men's disadvantage in the TB care pathway is building [120–122]. Focusing specifically on access to diagnosis, male TB patients often delay care-seeking longer than female TB patients [123], and this review adds support that timely entry into the TB care pathway may be more difficult for men than women in many settings.

Lower prevalence survey participation among men and evidence of lower M:F prevalence ratios in studies that require individuals to self-report signs or symptoms of TB in initial screening procedures imply that symptom screening in community-based active case finding may be a less effective tool for identifying TB disease in men than women. It is not known whether this is due

to men refusing to report symptoms or whether the sub-clinical phase of disease may be longer for men [124]. Further investigation is needed to examine men's acceptance of screening and reporting of symptoms, even when barriers related to visiting a healthcare facility are removed.

Findings from this review suggest that case detection efforts, whilst not ignoring women, should be greatly strengthened for men. This will require a detailed understanding of the barriers that men face in accessing care. Previous studies have highlighted factors such as loss of income and financial barriers, as well as stigma, that affect men's healthcare decisions [125,126]. Care-seeking decisions are further influenced by perceptions of masculinity that discourage admission of illness, and systems of care that take away men's sense of control and leave feelings of inadequacy [127,128]. Interventions to improve case detection among men must recognise and address these barriers. Healthcare providers should be sensitive to men's needs and consider offering dedicated clinic times and outreach services for men. TB diagnostic services that incorporate men's peer networks or workplaces to promote wellness and reduce stigma may also be effective. In South Africa, a men-only after-hours clinic situated close to a transport hub has been effective in improving men's uptake of HIV testing and adherence to antiretroviral therapy [129]. Comparable opportunities for TB strategies that offer convenient access to care while maintaining men's sense of control should be explored.

This review summarises evidence on sex ratios in TB prevalence from a large number of prevalence surveys across geographic regions, an approach which introduces a number of potential sources of bias. Surveys varied greatly in their methodology, particularly in screening criteria and case definitions, and levels of participation varied within and between studies. However, over 84% of the surveys in the analyses had low to moderate risk of bias.

Prevalence as a measure of disease burden has limitations as it provides an estimate at a single point in time and cannot distinguish between disease as a result of recent infection and disease from reactivation, limiting understanding of current transmission. Comparing the rate of prevalent cases to notified cases is a crude measurement, especially comparing all surveys to national case notification rates, regardless of study setting. Stratifying by age and rural or urban setting would improve P:N ratios; however, data on these characteristics were not available at the time of analysis. Prevalence data by sex and HIV status were too infrequently available to be reported here. To our knowledge, no surveys that conducted drug susceptibility testing reported the results of those analyses by sex, so it is not possible to comment on whether the sex differences reported here are also relevant to drug-resistant TB. Given the significant sex differences reported in prevalence, future surveys should analyse and report all results by sex to facilitate greater understanding of the relationship between gender and TB.

Men have a higher prevalence of TB and, in many settings, remain infectious in the community for a longer period of time than women. Men are therefore likely to generate a greater number of secondary infections than women, and social mixing patterns have suggested that, as a result, men are responsible for the majority of infections in men, women, and children [12]. Addressing men's burden of disease and disadvantage in TB care is therefore an issue not only for men's health but for broader TB prevention and care. Given the compelling evidence presented here, global discourse and policy on key underserved populations need to include a focus on men. Recommendations to address issues of gender and TB cannot continue to insist on addressing the needs of women and girls [130] while ignoring the inequity faced by men and boys, who carry the higher burden of disease, often with less access to timely diagnosis and treatment. With a clear need and high burden, improving diagnosis and treatment among men is essential to achieving the ambitious targets of the End TB Strategy.

3.6.5 Acknowledgments

Authors acknowledge support from the London School of Hygiene & Tropical Medicine TB Centre. Authors also appreciate support from Irwin Law (World Health Organization, Geneva, Switzerland) in identifying and gathering national prevalence surveys for inclusion in this review.

The contents of this document are the sole responsibility of the authors and can under no circumstances be regarded as reflecting the positions of the International Union Against Tuberculosis and Lung Disease nor those of its donors.

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Chapter 4 Drivers of sex differences in tuberculosis burden

4.1 Introduction

The systematic review and meta-analysis presented in Chapter 3 highlighted men's higher epidemiological burden of TB, as evidenced by prevalence survey results and comparisons of those results with case notifications. I then developed a simple compartmental model of disease incidence, treatment access, self-cure, and untreated-TB mortality rates and utilised a Bayesian approach to identify drivers of men's higher burden of TB in two settings: Viet Nam and Malawi. This analysis was limited to smear-positive TB to ensure alignment between case definitions used in prevalence surveys and those used for case notification data during corresponding years. Smear-positive TB can be either subclinical (asymptomatic) or clinical (symptomatic), so the durations of untreated disease presented here do not correspond to symptom presentation and likely include periods of symptom fluctuation between subclinical and clinical states.

This research paper was published in the American Journal of Epidemiology in 2018 and is reproduced as follows with minor revision or adaptation from the published manuscript. The web appendix is provided in Appendix B.

4.2 Cover sheet

The Research Paper Cover Sheet is enclosed on the following pages.

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RESEARCH PAPER COVER SHEET

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SECTION A – Student Details

Student ID Number	429972	**Title**	Mrs
First Name(s)	Katherine Chisholm		
Surname/Family Name	Horton		
Thesis Title	Understanding sex disparities in tuberculosis and assessing the potential impact of strategies to improve men's access to care		
Primary Supervisor	Elizabeth L. Corbett		

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

SECTION B – Paper already published

Where was the work published?	American Journal of Epidemiology		
When was the work published?	27 June 2018		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	n/a		
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SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I developed the overall aim and approach of this manuscript with Prof. Richard White. I worked with Dr. Tom Sumner to develop the model structure. I then conducted the necessary literature reviews, gathered data for prior estimates, coded the model, conducted analyses, and produced tables and figures to summarise results. I drafted the manuscript and then incorporated feedback from coauthors. I oversaw the manuscript submission process and revised the manuscript, as necessary, to respond to input from peer review.

SECTION E

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4.3 Title and authors

American Journal of Epidemiology

Vol. 187, No. 11
DOI: 10.1093/aje/kwy131
Advance Access publication:
June 27, 2018

Practice of Epidemiology

A Bayesian Approach to Understanding Sex Differences in Tuberculosis Disease Burden

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Initially submitted June 9, 2017; accepted for publication June 22, 2018.

4.4 Abstract

Globally, men have a higher epidemiological burden of tuberculosis (incidence, prevalence, mortality) than women, possibly due to differences in disease incidence, treatment access, self-cure and/or untreated-tuberculosis mortality rates. Using a simple, gender-stratified compartmental model, we employed a Bayesian approach to explore which factors most likely explain men's higher burden. We applied the model to smear-positive pulmonary tuberculosis in Viet Nam (2006-07) and Malawi (2013-14). Posterior estimates were consistent with gender-specific prevalence and notifications in both countries. Results supported higher incidence in men and showed that both genders faced longer durations of untreated disease than estimated by self-reports. Prior untreated disease durations were revised upwards 8- to 24-fold, to 2.2 (95% credible interval: 1.7, 2.9) and 2.8 (1.8, 4.1) years for men in Viet Nam and Malawi, respectively, approximately a year longer than for women in each country. Results imply that substantial gender differences in tuberculosis burden are almost solely attributable to men's disadvantages in disease incidence and untreated disease duration. The latter, for which self-reports provide a poor proxy, implies inadequate coverage of case finding strategies. These results highlight an urgent need for better understanding of gender-specific barriers faced by men and support the systematic targeting of men for screening.

4.5 Manuscript

4.5.1 Introduction

Substantial gender disparity exists in the burden of tuberculosis, as indicated by incidence, prevalence and mortality estimates. Each year, more tuberculosis cases are reported among men than women globally and in most countries (1). Prevalence surveys, which provide the most

reliable source of data on tuberculosis burden (2), show even greater gender disparity, with a two-fold higher underlying burden of undiagnosed disease among men than among women in low- and middle-income countries (3). Comparisons of these two measures using prevalence-to-notification ratios (4) imply that gaps in the detection and reporting of new cases are greater for men than for women (3, 5). Yet discussions of gender and tuberculosis tend to focus on and prioritize the needs of women (6-9), often highlighting women as a key population with need for improved access to tuberculosis services (6-8).

Gender disparities in the epidemiological burden of tuberculosis could be explained by gender differences in four factors: disease incidence, treatment access, self-cure and/or untreated-tuberculosis mortality rates. Individuals are added to the pool of prevalent cases upon development of incident disease, and disease incidence rates could differ between men and women due to gender differences in exposure to infection and/or susceptibility to disease. Diseased individuals are then removed from the prevalent pool by successfully initiating treatment, naturally clearing themselves of disease ("self-cure") or dying (10), rates of which may differ by gender due to biological and/or socio-behavioral factors. Existing evidence suggests that there may be gender differences in disease incidence and treatment access rates, while there is no evidence to support differences in self-cure or untreated-tuberculosis mortality rates (11).

Using a simple compartmental model (12) of tuberculosis incidence, prevalence and case notification rates, we employed a Bayesian approach to explore which factors most likely explain the higher epidemiological burden of disease in men. A better understanding of gender differences in the burden of tuberculosis is imperative for the formulation of evidence-based gender-sensitive policies and programs. Implementing such programs at both the global and national level will improve gender equity in access to diagnosis and treatment, as prioritized in the End Tuberculosis Strategy (13) and Sustainable Development Goals (14). Although little attention is placed on men's burden of disease in current gender policies and programs (6-9), addressing gender imbalances in tuberculosis will ultimately benefit men, women and children.

4.5.2 Methods

Data

We conducted analyses for smear-positive pulmonary tuberculosis in two settings: Viet Nam, where the male-to-female ratio in smear-positive tuberculosis prevalence is one of the highest in the world at 5.1:1 (15), and Malawi, where the corresponding gender disparity is less extreme, with a male-to-female prevalence ratio of 2.0:1 (16).

Gender-specific tuberculosis incidence rates were based on 2015 World Health Organization (WHO) estimates of incident cases (age ≥ 15 years) (17) and population estimates from the United Nations Department of Economic and Social Affairs (18, 19). Treatment access rates for men and women were calculated as the inverse of untreated disease duration based on self-reported time from disease onset to treatment access (20, 21), as extracted from literature reviews (Web Appendix 1, Web Tables 1-3). Self-cure and untreated-tuberculosis-specific mortality rates were gathered from sources used in previous modelling studies (22-24). Untreated-tuberculosis-specific mortality and background mortality (25) rates were combined to give an overall untreated-tuberculosis mortality rate. Log-normal distributions, which provided the best fit to the data, were used to describe disease incidence, treatment access, self-cure and untreated-tuberculosis mortality rates. Informative priors were chosen so that the middle 95% of expected values fell within the 95% confidence interval or the middle 50% of expected values fell within the interquartile range, as appropriate to available data. Distributions were fitted using Parameter Solver, version 3.0, a software application that solves for the distribution parameters of a random variable given user-defined quantiles (26).

Gender-specific smear-positive tuberculosis prevalence data were collated from national prevalence surveys conducted in Viet Nam in 2006-07 (15) and in Malawi in 2013-14 (16). Case notification rates for smear-positive tuberculosis in men and women were calculated using case notification numbers reported to WHO (1) and population estimates from the United Nations Department of Economic and Social Affairs (18, 19) with a 10% uncertainty interval to account for over- or under-diagnosis or -reporting. Confidence intervals for prevalence and case notification rates were based on the normal approximation to the binomial distribution.

Full details of prior specification and data are provided in the Web Appendices 1 and 2 and Web Tables 4-6, and data on prevalence and case notification rates are shown in Figure 1.

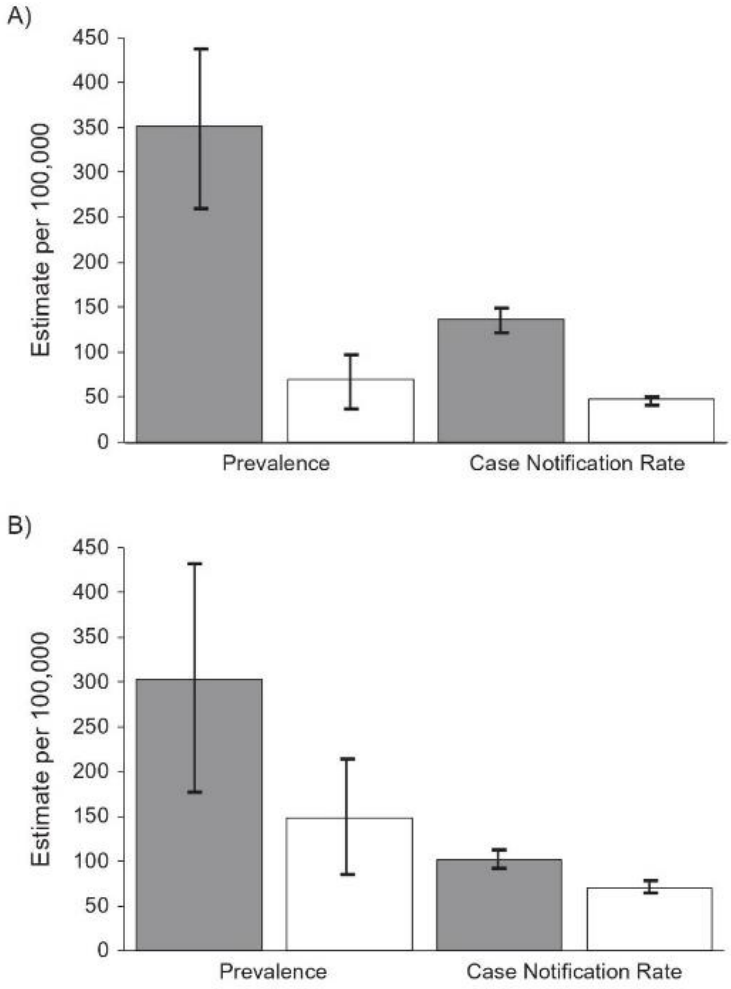

Figure 1: Prevalence and case notification rates for tuberculosis, according to sex, in Vietnam (2006-2007) (A) and Malawi (2013-2014) (B). Male-to-female ratios in prevalence-to-notification ratios: 1.75 (95% credible interval 1.21,2.58) in Vietnam and 1.41 (95% credible interval: 0.91, 2.20) in Malawi. Dark gray bars indicate distributions for men, white bars indicate distribution for women, and lines indicate 95% confidence intervals.

Model

We developed a simple gender-stratified (male and female) model of disease incidence, prevalence and case notification rates for adult (age ≥ 15 years) smear-positive tuberculosis, as shown in Figure 2. (Directed acyclic graphs are provided in Web Figures 1 and 2 in Web Appendix 3.) Transition rates for disease incidence, treatment access, self-cure and untreated-tuberculosis mortality were used to calculate expected prevalence and case notification rates under an assumption of epidemic equilibrium, which is presumed valid given the slow decline in estimated incidence in each country. Gendered risk factors for infection with *Mycobacterium tuberculosis*, progression to tuberculosis disease and death following infection, notably tobacco smoking in Viet Nam and HIV in Malawi, were not explicitly modelled, instead being captured as part of overall gender differences in disease incidence and untreated-tuberculosis mortality rates.

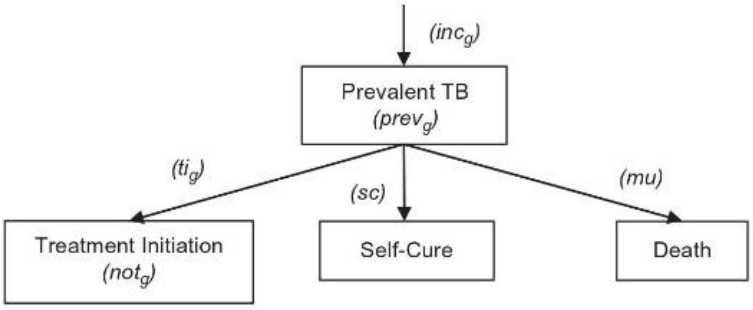

Figure 2: A sex-stratified (male and female) model of disease incidence, prevalence, and case notification rates for adult (age ≥ 15 years) smear-positive tuberculosis. In this model, $prev_g$ is the tuberculosis prevalence in sex *g*, not_g is the case notification rate in sex *g*, inc_g is the disease incidence rate in sex *g*, ti_g is the treatment access rate (inverse of untreated disease duration) in sex *g*, *sc* is the self-cure rate, and *mu* is the untreated-tuberculosis mortality rate.

The expected prevalence of smear-positive tuberculosis in gender *g*, $prev_g$, was calculated as $prev_g = inc_g / (ti_g + sc + mu)$ where inc_g is the disease incidence rate in gender *g*, ti_g is the treatment access rate in gender *g*, *sc* is the self-cure rate, and *mu* is the untreated-tuberculosis mortality rate. The expected case notification rate for smear-positive tuberculosis in gender *g*, not_g, was calculated as $not_g = prev_g \times ti_g$. Male-to-female ratios in expected prevalence-to-notification ratios were calculated.

Statistical analysis

The evidence described above was used to specify model priors for disease incidence, treatment access, self-cure and untreated-tuberculosis mortality for each gender in each country (Table 1 and Table 2 "Model priors"). The model was then confronted with gender-specific data on prevalence and case notification rates (Table 1 and Table 2 "Empirical data") in a Bayesian framework (27). Posterior model estimates (Table 1 and Table 2 "Model posteriors") show how prior beliefs about disease incidence, treatment access, self-cure and untreated-tuberculosis mortality should be modified in light of the empirical prevalence and notification data. Posterior estimates were examined for consistency with empirical data on gender-specific prevalence and case notification rate, as well as male-to-female ratios in prevalence-to-notification ratios. The model was considered consistent with empirical data if empirical point estimates were within the 95% credible intervals of posterior model estimates.

Table 1: Model priors, epidemiological data, and model posteriors for a Bayesian analysis of sex disparities in the epidemiological burden of tuberculosis, Vietnam, 2006-2007

Parameter	Model Priors[a]		Empirical Data		Model Posteriors[a]	
	Median	95% CrI	Estimate	95% CI	Median	95% CrI
Incidence rate, annual per 100,000[b]						
Male	245	192, 312			258	216, 314
Female	58	27, 124			67	56, 83
Untreated disease duration, years[c]						
Male	0.09	0.02, 0.39			2.20	1.65, 2.89
Female	0.11	0.03, 0.38			1.01	0.60, 1.59
Self-cure rate, annual						
Male and female	0.19	0.09, 0.41			0.17	0.09, 0.31
Untreated-TB mortality rate, annual						
Male and female	0.29	0.11, 0.77			0.21	0.10, 0.41
Prevalence, per 100,000[b]						
Male			351	262, 440	305	234, 389
Female			69	39, 99	48	29, 75
Notification, per 100,000[b]						
Male			137	123, 151	138	125, 153
Female			47	42, 52	48	43, 53
Prevalence-to-notification ratio						
Male-to-female ratio			1.75	1.21, 2.58	2.18	1.28, 3.90

Abbreviations: CI, confidence interval; CrI, credible interval; TB, tuberculosis.
[a] All potential scale reduction factors, which equal 1 at convergence, were between 1.001 and 1.003.
[b] Modeled as proportion but shown as number per 100,000 population.
[c] Untreated disease duration is the inverse of treatment initiation rate.

Table 2: Model priors, epidemiological data, and model posteriors for a Bayesian analysis of sex disparities in the epidemiological burden of tuberculosis, Malawi, 2013-2014

Parameter	Model Priors[a]		Empirical Data		Model Posteriors[a]	
	Median	95% CrI	Estimate	95% CI	Median	95% CrI
Incidence rate, annual per 100,000[b]						
Male	354	235, 534			295	218, 410
Female	151	57, 402			161	118, 235
Untreated disease duration, years[c]						
Male	0.22	0.07, 1.03			2.77	1.83, 4.06
Female	0.23	0.06, 1.86			1.88	1.17, 2.86
Self-cure rate, annual						
Male and female	0.19	0.09, 0.41			0.22	0.10, 0.47
Untreated-TB mortality rate, annual						
Male and female	0.30	0.12, 0.78			0.43	0.18, 0.87
Prevalence, per 100,000[b]						
Male			303	176, 431	286	191, 413
Female			149	85, 213	134	84, 201
Notification, per 100,000[b]						
Male			102	91, 112	103	93, 113
Female			71	64, 78	71	65, 78
Prevalence-to-notification ratio						
Male-to-female ratio			1.42	0.91, 2.20	1.48	0.83, 2.73

Abbreviations: CI, confidence interval; CrI, credible interval; TB, tuberculosis.
[a] All potential scale reduction factors, which equal 1 at convergence, were between 1.001 and 1.003.
[b] Modeled as proportion but shown as number per 100,000 population.
[c] Untreated disease duration is the inverse of treatment initiation rate.

Posterior model estimates were calculated using Markov chain Monte Carlo algorithm in WinBUGS (28) via R (29) according to code included in Web Appendix 4. Results were based on three Markov chains of 21,000 iterations; the first 1,000 samples of each chain were discarded as burn-in. Convergence was assessed visually and using potential scale reduction factors (30).

Sensitivity analyses

We conducted extensive sensitivity analyses, which are described in detail in Web Appendices 5, 6, and 7. We explored our choice of model structure by examining all combinations of fixing individual parameters by gender and allowing individual parameters to differ by gender. We also explored our choice of incidence rate priors using incidence rate priors based on estimates from the Institute for Health Metrics and Evaluation (IHME) (31). Finally, we explored the implications of assuming self-reports of symptom duration prior to treatment accurately describe untreated disease duration.

4.5.3 Results

Prior model estimates accurately represented evidence on disease incidence, treatment access, self-cure rate and untreated-tuberculosis mortality rates.

Posterior model estimates were consistent with empirical data on gender-specific prevalence and case notification rates, as well as male-to-female ratios in prevalence-to-notification ratios, in both countries (Table 1 and Table 2).

In both countries, posterior incidence rate estimates were consistent with empirical data. In Viet Nam, incidence was estimated as (posterior median) 258 (95% credible interval, CrI: 216, 314) per 100,000 men and 67 (95% CrI: 56, 83) per 100,000 women. In Malawi, incidence was estimated as (posterior median) 295 (95% CrI: 218, 410) per 100,000 men and 161 (95% CrI: 118, 235) per 100,000 women.

Posterior estimates for treatment access rate showed that both men and women faced much longer time between onset of disease and initiation of treatment than estimated from self-reports of symptom duration prior to treatment (Figure 3). Prior untreated disease durations were revised upwards 8- to 24-fold, to posterior median estimates of 2.2 (95% CrI: 1.7, 2.9) and 2.8 (95% CrI: 1.8, 4.1) years for men in Viet Nam and Malawi, respectively, and 1.0 (95% CrI: 0.6, 1.6) and 1.9 (95% CrI: 1.2, 2.9) years for women, respectively.

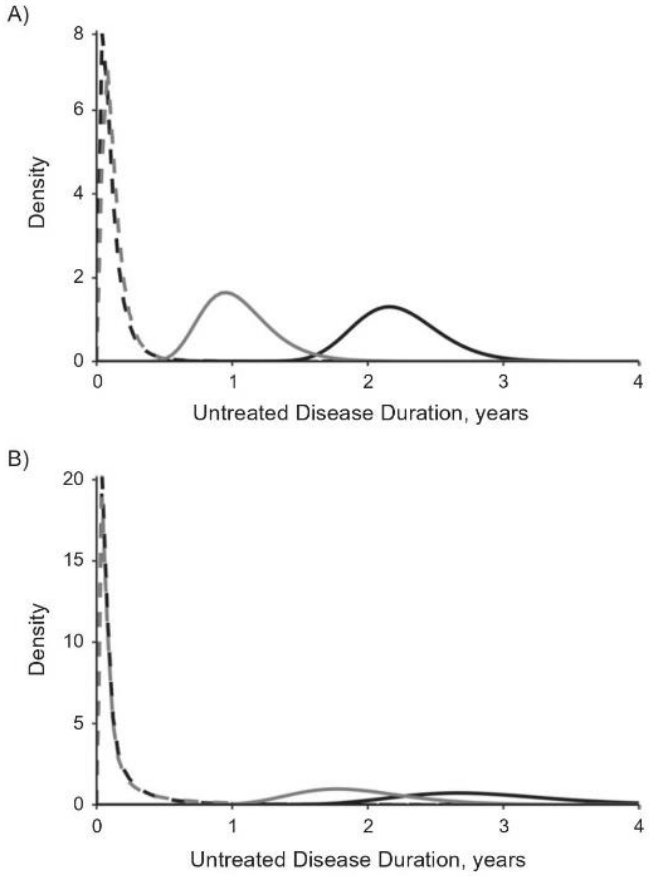

Figure 3: Density plots for prior and posterior distributions for untreated tuberculosis disease duration, according to sex, in Vietnam (2006-2007) (A) and Malawi (2013-2014) (B). Prior distributions are shown as dashed lines, and posterior distributions are shown as solid lines. Dark gray lines indicate distributions for men; light gray lines indicate distributions for women.

In both countries, sensitivity analyses around model structure (Web Table 7) supported our decision to allow only disease incidence and treatment access rates to differ by gender (Web Tables 8-22). In these analyses, all scenarios that allowed rates of disease incidence and treatment access to differ by gender (regardless of restrictions on self-cure and untreated-tuberculosis mortality rates) were consistent with empirical data (Web Tables 18, 19, 22). When self-cure and/or untreated-tuberculosis mortality rates, in addition to disease incidence and treatment access rates, were allowed to differ by gender, posterior estimates were not substantially different from the main analysis (Web Tables 18, 19, 22). In Malawi, posterior estimates from two additional scenarios were also consistent with empirical data (Web Tables 16 and 21). However posterior estimates for untreated-tuberculosis mortality rates among women in these scenarios were over twice those estimated among men, which evidence suggests is unlikely (11). No other scenarios produced posterior estimates consistent with empirical data.

Sensitivity analyses were also conducted using incidence estimates from IHME rather than WHO (Web Table 23). Posterior estimates for Viet Nam were not consistent with empirical data

on gender-specific prevalence or male-to-female ratios in prevalence-to-notification ratios. This is likely a result of IHME underestimating gender disparity in disease incidence in Viet Nam. While WHO estimates that incidence is over four times higher in men than in women, IHME estimates that incidence in men is only 50% higher than in women (Web Figure 3). In contrast, in Malawi, where both WHO and IHME estimate that incidence among men is approximately twice that among women (Web Figure 4), posterior estimates were consistent with empirical data on gender-specific prevalence and case notification rates, as well as male-to-female ratios in prevalence-to-notification ratios (Web Table 24).

Final sensitivity analyses assumed self-reports of symptom duration prior to treatment accurately described untreated disease duration and examined the impact of this assumption on disease burden estimates. Posterior prevalence estimates from these analyses were only 4 to 12 percent those reported in recent prevalence surveys (for example, 13 (95% CrI: 12, 15) per 100,000 men in Viet Nam) and male-to-female ratios in prevalence-to-notification ratios significantly less than one (Web Table 25). These results illustrate how unlikely it is that self-reports of symptom duration are accurate measures of untreated disease duration in light of recent prevalence surveys.

4.5.4 Discussion

Our results imply that the substantial gender differences in the epidemiological burden of tuberculosis are almost solely attributable to gender differences in disease incidence and treatment access rates, both of which disadvantage men. Although differences between self-reported symptom duration prior to treatment and our model posteriors indicate that both men and women face long periods of undiagnosed tuberculosis disease prior to treatment, men face substantially longer durations of untreated disease. Improved access to tuberculosis diagnostic and treatment services is needed for all individuals, but with more pressing need to better understand and address men's barriers to care.

Our model confirms gender differences in tuberculosis incidence that have already been acknowledged to some extent in estimates from WHO (17) and IHME (31). Men's higher incidence of disease may be a result of a number of factors including biological susceptibility (32, 33), social contact patterns (34, 35), tobacco smoking (36), alcohol consumption (37) and/or undiagnosed or untreated HIV infection (38, 39). While the relative contribution of these different factors is not well-understood, it is clear that there are more new cases of tuberculosis among men than women in both Viet Nam and Malawi, and likely other countries where similar gender differences in prevalence are found (3).

We also found that prevalence and case notification data are simply not consistent with a longer untreated disease duration in women than in men, despite the widespread recognition of women

as a key population with need for improved access to tuberculosis services (6-8). Our results imply that men either have lower symptom awareness or face greater barriers in accessing tuberculosis care than women. Men tend to present with more advanced disease and show lower health utilization for tuberculosis (40), like many infectious and non-infectious conditions (38, 39, 41, 42). Men's healthcare decisions are rooted in societal constructs of masculinity, including concepts that lead to societal pressure to neglect symptoms in order to be physically strong and to fulfill roles as the leader and provider for their immediate and extended family (43-48). Although women with tuberculosis may face greater delays in receiving appropriate medical attention after seeking care (40), our findings suggest that, on average, men's delays in seeking healthcare far outweigh any delays women face after seeking care in these two countries.

Timely access to tuberculosis care is essential for successful patient outcomes and for the prevention of transmission, yet current evidence points to considerable delays between the onset of disease and treatment access (49-52). Our findings urge caution in the interpretation of self-reports as a measure of untreated disease duration, as these estimates appear to substantially underestimate time to treatment for both genders. Patients usually report the time from symptom onset to treatment access in terms of weeks (49-52), yet our results and those of others (4, 11, 24, 49-54) suggest instead that years pass between the development of disease and treatment access. Self-reports may be limited by recall accuracy and different perceptions of disease. They may also fail to capture the full duration of long-term illness characterized by remissions and relapses along a continuum (55) rather than unrelenting progression of symptom severity (10, 55, 56). It is likely that patients report only the duration of the most recent episode of "acute-on-chronic" symptom deterioration that has led directly to care-seeking and diagnosis, rather than the full duration of untreated disease. The marked differences between self-reported time to treatment and our posterior estimates may explain in part why current passive case finding strategies have not been as successful as initially projected, despite global implementation (57).

There are several limitations to the results presented here. The model chosen for this analysis was deliberately simple to clearly define and examine the overall impact of each parameter within the model. As such, results provided here describe median untreated disease duration and do not take into account heterogeneity within the populations of interest. Furthermore, we cannot assess the relative contribution of specific biological and socio-cultural factors to increased disease incidence and untreated disease duration among men. In addition, we have not included any consideration of smear-negative and extra-pulmonary tuberculosis disease, for which untreated disease duration is likely even longer than described here, although it seems unlikely that the gender differences found here would disappear when other disease types are considered.

Our results imply that the substantial gender differences in the epidemiological burden of tuberculosis are almost solely attributable to gender differences in disease incidence and treatment access rates, both of which disadvantage men. Our results add weight to the growing body of evidence that men have a higher incidence of tuberculosis disease (17, 31) and also often face longer delays than women in accessing treatment (3-5). Self-reported symptom duration prior to treatment provides a poor proxy for untreated disease duration for both genders, especially for men. In both Viet Nam and Malawi our posterior median estimates suggest that men spent over a year longer than women prior to initiating treatment for tuberculosis disease.

Despite male disadvantage in accessing care and strong evidence that men have a higher epidemiological burden of disease, discussions of gender and tuberculosis tend to focus on and prioritize the needs of women. There is little consideration that men face substantial gendered barriers of their own when accessing tuberculosis diagnosis and treatment. National and international tuberculosis programs need to reconsider gender disparity as a barrier to achieving the ambitious elimination goals set for tuberculosis under the End Tuberculosis Strategy (13) and the Sustainable Development Goals (14), from the perspective of men.

Acknowledging men as a disadvantaged group with limited access to timely diagnosis and treatment is only a first step. The long duration of untreated disease estimated here, particularly among men, implies inadequate coverage of current case finding strategies. Action is needed to ensure that men are not being unduly disadvantaged by the prominent focus on maternal and child health that characterizes primary care in many countries. Steps must be taken to acknowledge and address the ways in which constructions of masculinity add to and interact with health system barriers that affect men's health seeking behaviors. Systematic screening offers an opportunity to expedite diagnosis with less reliance on severe symptoms (58): the consideration of screening programs predominately aimed at men is supported by our data showing them to be a high prevalence, high incidence sub-group with longer untreated disease duration than women.

4.5.5 Acknowledgements

Authors appreciate input from Dr. Emily Webb, who provided statistical support in early phases of this work, and Dr. Ben Cooper, who provided support in responding to reviewers' comments. Authors also acknowledge support from the London School of Hygiene and Tropical Medicine TB Centre.

The contents of this document are the sole responsibility of the authors and can under no circumstances be regarded as reflecting the positions of the International Union Against Tuberculosis and Lung Disease (The Union North America) nor those of the Donors.

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Chapter 5 Factors underlying drivers of sex differences in tuberculosis burden

5.1 Introduction

Analyses presented in Chapter 4 showed incidence to be a driver of sex differences in TB burden. The literature review presented in Chapter 2 highlighted social contact patterns as a potential contributor to sex disparities in TB incidence, yet relatively few studies have reported detailed results by sex. To gain further insight into the potential role of social contact patterns in driving sex differences in TB incidence, I conducted a systematic review and meta-analysis to examine sex differences in social contact patterns reported by children and adults in surveys of social contacts relevant to airborne disease transmission between 1997 and 2018. This research paper was published in Emerging Infectious Diseases in 2020 and is reproduced as follows with minor revision from the published manuscript. Supplemental materials are provided in Appendix C.

5.2 Cover sheet

The Research Paper Cover Sheet is enclosed on the following pages.

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SECTION A – Student Details

Student ID Number	429972	**Title**	Mrs
First Name(s)	Katherine Chisholm		
Surname/Family Name	Horton		
Thesis Title	Systematic review and meta-analysis of sex differences in social contact patterns and implications for tuberculosis transmission and control		
Primary Supervisor	Elizabeth L. Corbett		

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

SECTION B – Paper already published

Where was the work published?	Emerging Infectious Diseases		
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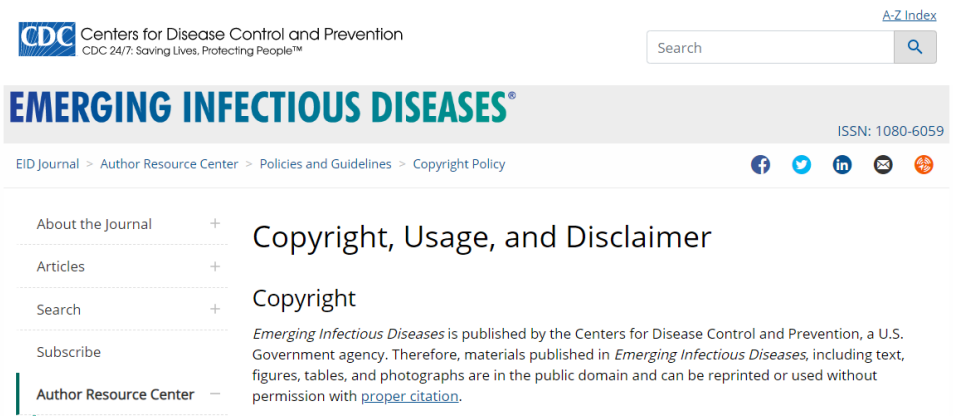
SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I developed the overall aim for this manuscript with Prof. Richard White. I designed the methodology for both the systematic review and meta-analyses. I then conducted the systematic review, searching the literature, maintaining search records, reviewing titles/abstracts, reviewing full-text manuscripts, and extracting relevant data, with second review and support from Dr. Anne Hoey. I contacted authors, where necessary, and collated the final dataset for analysis. I conducted all analyses and produced tables and figures to summarise results. I drafted the manuscript and then incorporated feedback from coauthors. I oversaw the manuscript submission process and revised the manuscript, as necessary, to respond to input from peer review.

SECTION E

Student Signature	K. Horton
Date	

Supervisor Signature	E. Corbett
Date	18 November 2020



5.3 Title and authors

RESEARCH

Systematic Review and Meta-Analysis of Sex Differences in Social Contact Patterns and Implications for Tuberculosis Transmission and Control

Katherine C. Horton, Anne L. Hoey, Guillaume Béraud, Elizabeth L. Corbett, Richard G. White

5.4 Abstract

Social contact patterns may contribute to men's excess burden of tuberculosis. We conducted a systematic review and meta-analysis of social contact surveys to evaluate contact patterns relevant to tuberculosis transmission. Available data describe 21 surveys in 17 countries and show profound differences in sex- and age-based patterns of contact. Adults reported more adult contacts than children. Children of both sexes preferentially mixed with women in all surveys (median sex-assortativity 58%, interquartile range, IQR, 57-59%, for boys; 61%, IQR 60-63%, for girls), while men and women reported sex-assortative mixing in 80% and 95% of surveys (median sex-assortativity 56%, IQR 54-58%, for men; 59%, IQR 57-63% for women). Sex-specific patterns of contact with adults were similar at home and outside the home for children; adults reported greater sex-assortativity outside the home in most surveys. Sex-assortativity in adult contacts likely contributes to sex disparities in adult tuberculosis burden by amplifying incidence among men.

5.5 Manuscript

5.5.1 Introduction

Tuberculosis (TB) is the leading infectious cause of death worldwide, with an estimated 1.3 million deaths in 2017 (1). Approximately a quarter of the world's population is infected with *Mycobacterium tuberculosis* (*Mtb*) (2), the bacteria that causes TB disease (3). Of the 1.7 billion people infected with *Mtb*, 10 million developed TB disease in 2017 (1, 4). Despite major investment in disease control efforts since the 1990s, progress has been slow with incidence currently declining at only 1.5% per year (3).

TB predominantly affects adult men, who make up 60% of notified cases and 65% of reported deaths, globally (1). Men are less likely than women to access timely TB diagnosis and treatment (5, 6), remaining infectious in the community for a much longer period of time (5, 7).

The impact is apparent from recent prevalence surveys of undiagnosed TB disease, which offer the most accurate measure of disease burden (1) and confirm pronounced sex disparity, with men accounting for 70% of infectious cases in the community (5).

Critically, *Mtb* is spread person-to-person by airborne transmission, with undiagnosed infectious TB the key driver of ongoing transmission and most TB disease episodes reflecting recent transmission from adult contacts (3). It has been hypothesized that men's excess burden of TB disease is a result of broader socialization patterns that emerge during adolescence (8, 9). We have previously hypothesized that men's risk of TB may be amplified if sex-assortative ("like-with-like" by sex, male or female) mixing is prevalent, such that men have greater contact with other men than with women (5). Sex-specific social contact patterns may also be important to understanding TB disease in women and children, as illustrated by analytical results suggesting most new *Mtb* infections among men, women, and children in South Africa and Zambia can be attributed to contact with men (10).

Data from social contact surveys provide insight into how individual behaviours drive disease dynamics at population level (11), providing better predictions of patterns of infection for respiratory pathogens (12, 13) than can be made from assumptions of homogenous or proportionate mixing (14). Several analyses have examined sex differences in social contact patterns, although most report sex differences in the number of reported contacts. Only a few analyses have assessed the sex-assortativity of contacts in sufficient detail to provide important insight into the transmission potential for diseases with significant sex disparities, such as TB (10, 15, 16).

This systematic review and meta-analysis examined sex differences in the number, sex-assortativity and location of social contacts reported by children and adults. Our main aims were to evaluate (1) sex-based social contact patterns in children and adults, (2) sex-assortative mixing among adults, and (3) the frequency of contact between men and boys, men and girls, and men and women.

5.5.2 Methods

The systematic review was conducted following PRISMA and MOOSE guidelines (Web Checklist 1, Web Checklist 2) in accordance with the published protocol (17).

Search strategy

Publications describing social contact surveys conducted between 1 January 1997 and 5 August 2018 were identified through searches of PubMed, Embase, Global Health, and the Cochrane Database of Systematic Reviews (Web Table 1). Reference lists from included publications were searched by hand, and researchers with expertise in these surveys, particularly authors of a

recent systematic review (18), were contacted to assist with the identification of relevant publications.

Two authors (KCH and ALH) independently reviewed titles and then abstracts, in parallel, for relevance. Publications identified by either author were included for full-text review. The same authors reviewed full texts to determine which publications met inclusion criteria and then reviewed texts and supplemental materials to determine whether data on sex were recorded for both participants and contacts. Authors were contacted if it was unclear whether these data had been collected.

KCH extracted data on methodology from included surveys using a piloted electronic form. Datasets were gathered from supplemental materials or a social contact data repository (www.socialcontactdata.org) if results were not reported in a format necessary for meta-analyses. When datasets were not publicly available, authors were contacted and asked to share relevant results and/or data.

Inclusion and exclusion criteria

The review included cross-sectional surveys conducted to assess social contact patterns relevant to airborne disease transmission that recorded both participant sex and contact sex. Only surveys that recorded all contacts over the survey period were included; surveys that examined only a subset of participants' contacts (e.g., only those within a work place or with other participants) were excluded. Surveys that included only participants or contacts of a single sex were excluded. Publications in languages other than English were excluded due to limited resources for translation. When more than one report was identified for a single survey, the earliest source or most complete dataset was included; other records were excluded.

Survey quality

Each survey was assessed using the Appraisal Tool for Cross-sectional Studies (AXIS tool) to evaluate survey design, reporting quality, and risk of bias (19).

Definitions

Participation was considered equitable by sex if each sex made up 45 to 55% of the survey population. Numbers of participants were adjusted for analyses of physical and location-based contacts to exclude participants who did not report this information.

Participants and contacts were stratified by age, as children (boys and girls) and adults (men and women). For most surveys, adults were defined as individuals age 15 years and older (1); where aggregate age categories did not allow disaggregation at this cut-off point, the nearest possible value was used.

Close contacts, including both physical and non-physical contacts, were defined according to survey-specific definitions, typically by a conversation longer than a greeting or more than three words.

Preferential mixing was defined as significantly more mixing with one sex/age group than another. Sex-assortative mixing was defined as "like-with-like" contacts according to sex (male or female), either within age groups (e.g., men-with-men) or between age groups (e.g., men-with-boys).

Data analysis

For each survey, the average number of contacts over a 24-hour period was calculated for each sex/age category of participant with each sex/age category of contact. For surveys in which data were collected over a 48- or 72-hour period, the number of contacts was divided by 2 or 3, respectively. The average number of contacts was compared across sex and age groups using the Mann-Whitney-Wilcoxon Test.

The percentage of sex-assortative mixing was calculated with 95% Clopper-Pearson confidence intervals as contacts with the same sex divided by total contacts. Sex-assortative mixing was assessed in children's contacts with children and adults and in adults' contacts with children and adults. The proportion of sex-assortative mixing was also compared by contact location: contacts within the home and contacts outside the home and, among contacts outside the home, contacts at work (for adults), school (for children) and elsewhere. Heterogeneity was assessed using the I2 statistic (20). Findings across surveys were summarised using the median and interquartile range (IQR).

The percentage of boys', girls', men's and women's adult contacts with men was estimated for subgroups based on survey setting characteristics (region, setting and TB burden) and survey methodology (sampling methods, reporting duration, age cut-off values for adults, and participation by sex).

Contact events for which the participant's sex or age or the contact's sex or age was missing were excluded from analyses. No adjustments were made for non-participation or non-sampling. No weighting was used.

All analyses were performed using R version 3.2.2 (21).

5.5.3 Results

Of 124 full-text publications reviewed for eligibility, 76 were excluded (Web Table 2), and 48 publications with eligible methodology were identified (Figure 1). Twenty-three publications described surveys that did not, to our knowledge, record sex and age for both participants and

contacts (Web Table 3); 25 publications described surveys that were known to have recorded sex and age for both participants and contacts (Web Table 4);. Data were available for meta-analysis from 14 publications describing 21 surveys (10, 13-16, 22-30) (Table 1, Web Appendix 2).

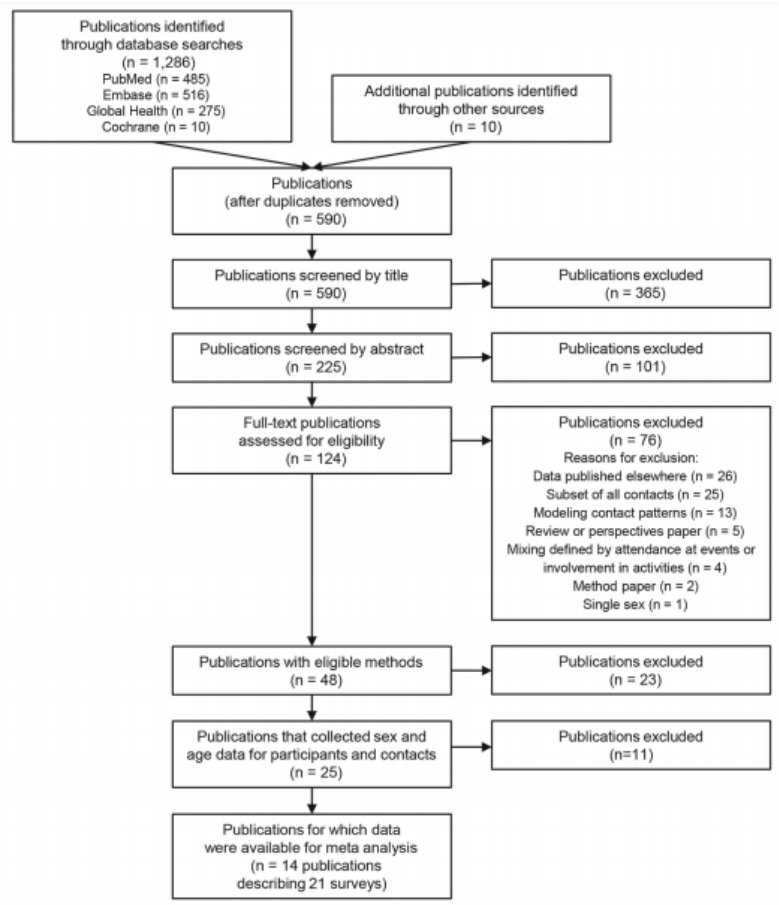


Figure 1: Preferred reporting items for systematic reviews and meta-analyses flowchart used for analysis of sex differences in social contact patterns and tuberculosis transmission and control.

Included surveys had over 22,146 participants and 270,308 sex-/age-specific contacts. Surveys were conducted in 17 different countries: 4 surveys with 5,085 participants in Africa, 1 survey with 558 participants in the Americas, 11 surveys with 11,260 participants in Europe, and 5 surveys with 5,243 participants in the Western Pacific. Thirteen surveys were conducted in high-income countries, 5 in upper-middle-income countries, 2 in lower-middle-income countries, and one in a low-income country. Ten surveys were conducted at a national scale; 11 were sub-national. All surveys were conducted between 2005 and 2016. Seventeen surveys included child participants; 20 surveys included adult participants. Sixteen surveys included both children and adults.

Participation by sex

Children's participation was considered equitable by sex in 15/17 (88%) surveys. In two (12%) surveys, boys' participation substantially exceeded that of girls, with boys making up 56% and 57% of each survey's population. Adults' participation was considered equitable by sex in 11/20 (55%) surveys. In 8/20 (40%) surveys, women's participation substantially exceeded that of men, with women making up 56% to 83% of each survey's population; in one (5%) survey, men's participation substantially exceeded that of women, with men making up 60% of the survey population.

Social contacts by boys and girls

The median number of contacts reported over a 24-hour period was 12.9 (IQR 9.3-15.9) for boys and 13.5 (IQR 9.5-15.9) for girls (Web Table 5). There was no difference between the number of contacts reported by boys and by girls (p=0.92). Approximately half of contacts reported by boys (median 53%, IQR 43-55%) and girls (median 51%, IQR 45-56%) were with other children.

Among children's contacts with other children, there was strong evidence of sex-assortative mixing reported by boys in 15/17 (88%) surveys and by girls in 15/17 (88%) surveys (Figure 2 A and C, Web Table 6). The median percentage of sex-assortative mixing in contacts with children was 62% (IQR 59-63%) among boys and 59% (IQR 59-65%) among girls. Summary measures are not reported due to substantial heterogeneity between surveys (I^2=96.3% for boys, I^2=95.6% for girls).

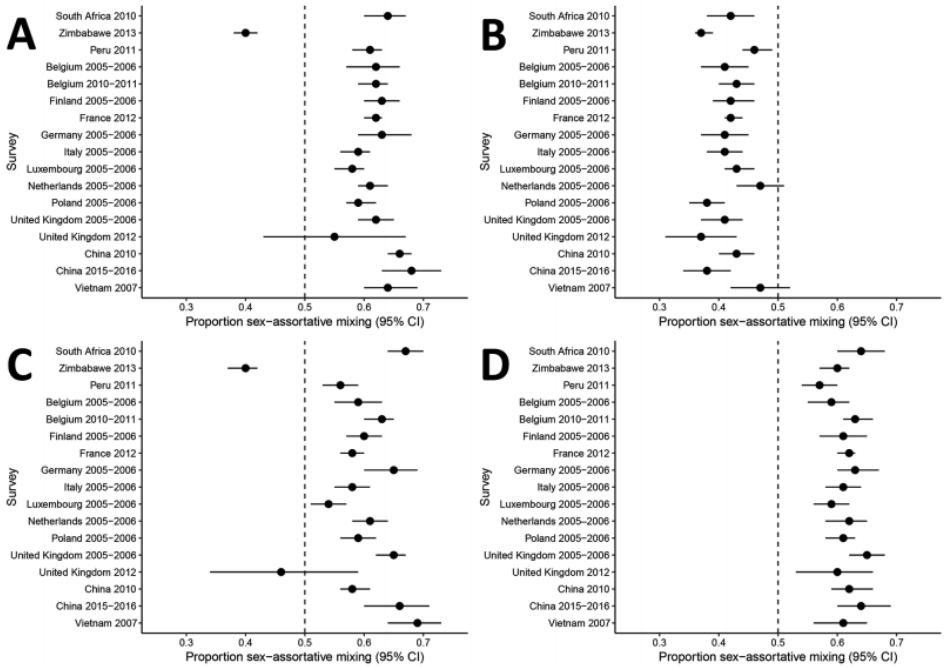


Figure 2: Analysis of sex differences in social contact patterns and tuberculosis transmission and control showing proportion of contacts with the same sex as reported for A) boys with boys, B) boys with men, C) girls with girls, and D) girls with women. Forest plots of sex-assortative mixing in contacts show contacts (black dots) and 95% CIs (error bars) reported by boys (A, B) and girls (C, D) with children (A, C) and with adults (B, D).

Among children's contacts with adults, there was no evidence of sex-assortative mixing reported by boys, and strong evidence reported by girls in 17/17 (100%) surveys (Figure 2 B and D, Web Table 6). The median percentage of sex-assortative mixing was 42% (IQR 41-43%) among boys and 61% (IQR 60-63%) among girls. Boys reported preferential mixing with women in 15/17 (88%) surveys. Summary measures are not reported due to substantial heterogeneity between surveys (I2=73.8% for boys, I2=44.3% for girls).

The majority of contacts reported by children took place outside the home (median 65%, IQR 62-72%, for boys; median 67%, IQR 56-73%, for girls) (Web Table 7). The sex-assortativity of children's contacts outside the home was similar to that at home. Among contacts with children, boys and girls reported significantly more sex-assortative mixing in contacts outside the home than at home in 6/14 (43%) and 5/14 (36%) surveys, respectively (Figure 3 A and C, Web Table 8). Among contacts with adults, boys reported no more sex-assortative mixing in adult contacts outside the home than at home in all 14/14 (100%) surveys, while girls reported more sex-assortative mixing outside the home than at home in 6/14 (42%) surveys (Figure 3 B and D, Web Table 8). Summary measures are not reported due to substantial heterogeneity between surveys (I2=88.4% for boys, I2=83.0% for girls).

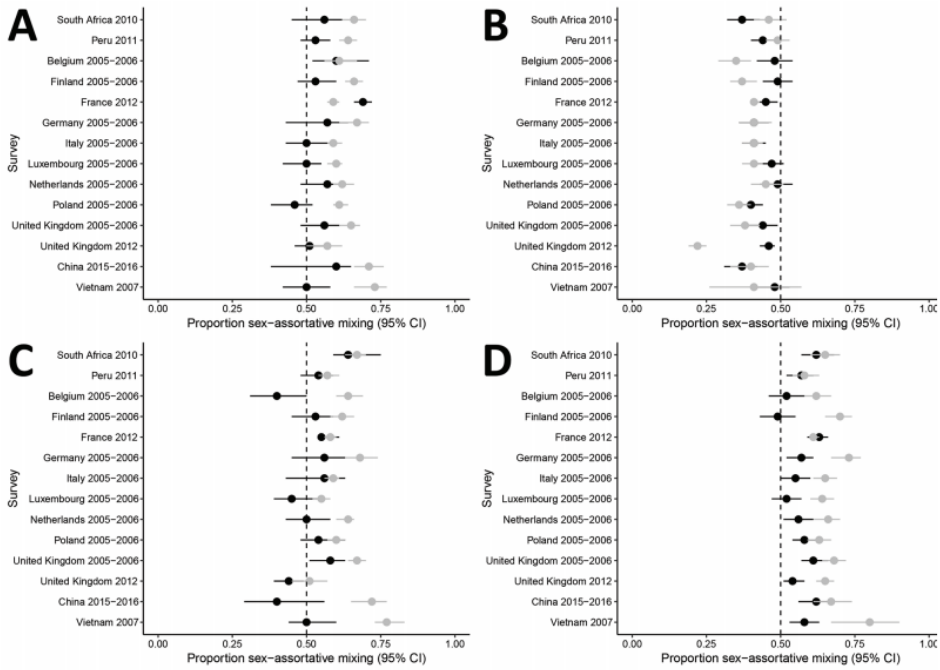


Figure 3: Analysis of sex differences in social contact patterns and tuberculosis transmission and control showing proportion of contacts with the same sex, disaggregated by location, as reported for A) boys with boys, B) boys with men, C) girls with girls, and D) girls with women. Forest plots of sex-assortative mixing show contacts at home (black dots) and outside the home (gray dots) with 95% CIs (error bars) reported by boys (A, B) and girls (C, D) with children (A, C) and with adults (B, D).

Among children's contacts outside the home, approximately half of boys' and girls' respective contacts (median 56%, IQR 39-62%, for boys; median 55%, IQR 38-63%, for girls) took place at school (Web Table 9). There were few differences in the sex-assortativity of contacts at school, compared to those at other locations outside the home (Web Table 10, Web Figure 1). Summary measures are not reported due to substantial heterogeneity between surveys (I2=84.7% for boys, I2=74.1% for girls).

Social contacts by men and women

The median number of contacts reported over a 24-hour period was 11.1 (IQR 8.1-15.3) for men and 11.6 (IQR 7.8-14.3) for women (Web Table 11). There was no difference between the number of contacts reported by men and by women (p=0.88), nor did the total number of contacts reported by adults differ from the total number of contacts reported by children (p=0.26). The vast majority of contacts reported by men (median 91%, IQR 88-93%) and women (median 87%, IQR 83-90%) were with other adults, significantly more than the number of adult contacts reported by children (p=0.01).

Among adults' contacts with children, there was strong evidence of sex-assortative mixing reported by men in 4/20 (20%) surveys and by women in 4/20 (20%) surveys (Figure 4 A and C, Web Table 12). In 15/20 (75%) surveys, there was no significant evidence of preferential

mixing by sex reported by men or women in contacts with children. The median percentage of sex-assortative mixing was 53% (IQR 50-57%) among men and 52% (IQR 50-54%) among women. Summary measures are not reported due to substantial heterogeneity between surveys (I2=76.3% for boys, I2=81.6% for girls).

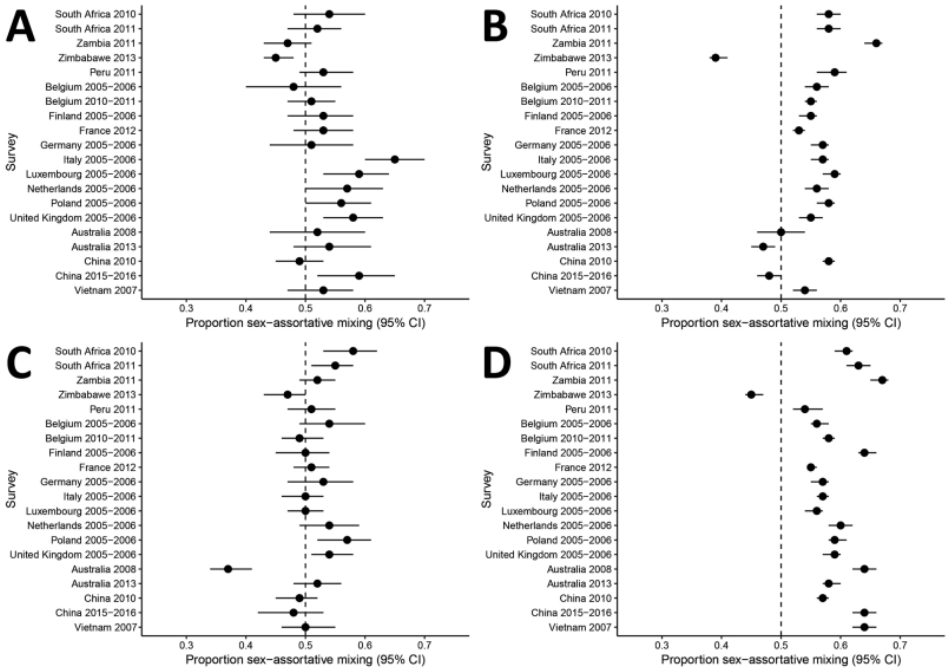


Figure 4: Analysis of sex differences in social contact patterns and tuberculosis transmission and control showing proportion of contacts with the same sex as reported for A) men with boys, B) men with men, C) women with girls, and D) women with women. Forest plots of sex-assortative mixing in contacts show contacts (black dots) and 95% CIs (error bars) reported by men (A, B) and women (C, D) with children (A, C) and with adults (B, D).

Among adult contacts with other adults, there was strong evidence of sex-assortative mixing reported by men in 16/20 (80%) surveys and by women in 19/20 (95%) surveys (Figure 4 B and D, Web Table 12). The median percentage of sex-assortative mixing was 56% (IQR 54-58%) among men and 59 (IQR 57-63%) among women. Summary measures are not reported due to substantial heterogeneity between surveys (I2=98.1% for men, I2=97.0% for women).

The majority of contacts reported by adults took place outside the home (median 74%, IQR 62-77%, for men; median 70%, IQR 54-76%, for women) (Web Table 13). Adults' contacts with children showed similar sex-assortativity at home and outside the home (Figure 5 A and C, Web Table 14). Among adults' contacts with adults, there was significantly more sex-assortative mixing by men and women in contacts outside the home than in contacts within the home in 14/15 (93%) surveys (Figure 5 B and D, Web Table 14). Summary measures are not reported due to substantial heterogeneity between surveys (I2=63.1% for men, I2=28.6% for women).

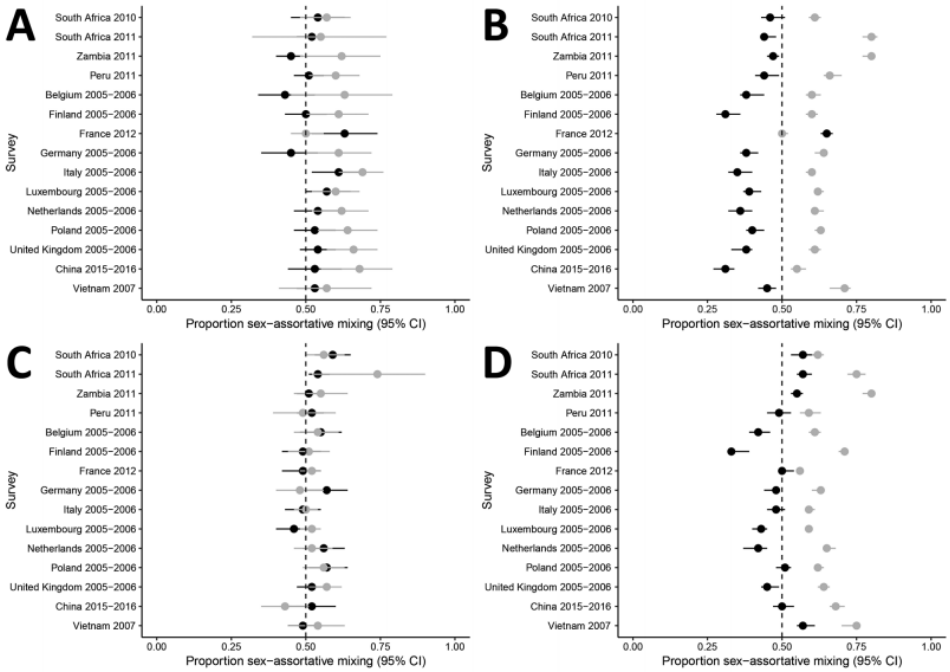


Figure 5: Analysis of sex differences in social contact patterns and tuberculosis transmission and control showing proportion of contacts with the same sex, disaggregated by location, as reported for A) men with boys, B) men with men, C) women with girls, and D) women with women. Forest plots of sex-assortative show mixing in contacts at home (black dots) and outside the home (gray dots) with 95% CIs (error bars) reported by men (A, B) and women (C, D) with children (A, C) and with adults (B, D) at home (black dots) and outside the home (gray dots).

Among adult contacts outside the home, approximately a third of men's and women's respective contacts (median 35%, IQR 28-39%, for men; median 29%, IQR 26-34%, for women) took place at work (Web Table 15). Adults reported few contacts with children at work, so confidence intervals are wide for sex-assortative mixing estimates for both men and women in most surveys (Web Table 16, Web Figure 2 A and C). Men reported significantly more sex-assortative mixing in contacts with other adults at work, compared to contacts elsewhere outside the home, in 12/15 (80%) surveys and elsewhere in 1/15 (7%) survey (Web Table 16, Web Figure 2 B and D). Women reported significantly more sex-assortative mixing at work, compared to contacts elsewhere outside the home, in only 2/15 (13%) surveys and elsewhere in 1/15 (7%) survey. Summary measures are not reported due to substantial heterogeneity between surveys (I2=32.3% for men, I2=87.0% for women).

Subgroup analyses

Subgroup analyses did not reveal clear differences in the frequency of contact with men by survey setting or methodology. There was little variation in the survey characteristics measured by the AXIS tool (Web Table 17). There remained substantial heterogeneity in summary measures for subgroups examined (Web Table 18).

5.5.4 Discussion

The main findings of this systematic review and meta-analysis of 21 social contact surveys in 17 countries are that sex differences in social contact patterns are profound, to an extent likely to be amplifying sex disparities in the adult burden of TB in many settings. Differences in sex- and age-specific social contact patterns between children and adults suggest a behavioral shift during adolescence, potentially driving the emergence of sex difference in TB epidemiology in adults. Sex-assortative mixing in adult contacts was reported by men and women in 80% and 95% of surveys. These findings have critical implications for men's health and for broader TB prevention efforts, as half of men's contacts, a third of women's contacts and a fifth of children's contacts were with adult men.

Social contact patterns clearly differ for children and adults. There was no significant difference in the total number of contacts reported by children and by adults. However, half of children's contacts were with other children, who are significantly less likely than adults either to have TB or to transmit *Mtb* (31), while most adult contacts were with other adults. Children of both sexes frequently reported preferential mixing with women in adult contacts, while men and women both reported sex-assortativity in contacts with other adults.

Among children, sex-specific patterns of contact with adults were similar at home and outside the home, with preferential mixing with women reported across locations. While many contacts were reported at school and while substantial child contact time occurs at school (25), those contacts include few adult contacts and therefore limited opportunity for exposure to *Mtb*. These differences in contact patterns among children and adults support recent genetic epidemiology studies suggesting that a small proportion of all adult infections occur within the household (32, 33) but that the odds of household transmission of *Mtb* are much higher among children (34). The relative risk of infection is high for household contacts of TB cases, regardless of their age, yet the higher number of adult contacts outside the home and greater sex-assortativity of those contacts, relative to children, increase opportunities for adults to be infected elsewhere, perhaps partially explaining the emergence of sex differences in TB epidemiology in adults.

In nearly all of the surveys examined, strong sex-assortative mixing in adult contacts was reported by both men and women, as noted in previous studies that have examined sex-assortativity (10, 15, 16). Results from this review indicate that in many settings, sex-assortative mixing may exacerbate men's disproportionate burden of disease by amplifying risk of infection in a population already at greater risk of disease due to a nexus of biological, socio-behavioral and health systems factors (5). Further research is needed to determine the relative contribution of sex-assortative mixing amongst these factors.

Among adults, reports of sex-assortative mixing were not symmetrical, with men reporting less sex-assortative mixing than women in nearly half of surveys conducted among adults. In three surveys in which men did not report strong sex-assortative mixing, women did (13, 29, 30), raising questions of reporting bias. Previous studies using wireless sensor devices have shown greater concordance between sensor and self-report methods for women than men (35), suggesting that inconsistencies may in part reflect less accurate reporting by men.

Only one survey, from rural and peri-urban Zimbabwe, reported no assortative mixing by either male or female adult respondents (26). This survey provided strong evidence of true negative sex-assortativity among boys, girls, men, and women, suggesting underlying differences in social behaviour that affect social interactions may indeed pertain in some settings. This survey was similar in design to others, but also reported a young age-structure and substantial intergenerational mixing with extremes of age (26). Interestingly, sex differences were less pronounced in the 2014 national TB survey in Zimbabwe than in other African countries (1).

Our analysis of social contact patterns across sex and age groups has implications for *Mtb* transmission beyond understanding men's excess burden of TB. While sex-assortative mixing among adults to some extent protects women from exposure to *Mtb* transmission, a third of women's contacts and a fifth of children's contacts were with men. The excess burden of TB disease among men therefore has implications for *Mtb* transmission across the population, making strategies to provide early diagnosis of TB for men of potentially high public health value.

There are several limitations to our analyses. Less than half of eligible publications collected data on sex and age for both participants and contacts, limiting the number of surveys included in analyses. We recommend future social contact surveys collect and report these data, ideally using standardised tools to try to reduce high inter-survey heterogeneity that prevented us from reporting summary measures. Additionally, our focus on close contacts will have excluded some contacts relevant to the spread of *Mtb* (36) and to the sex disparities in TB burden due to sex differences in the number and assortativity of contacts in congregate settings (e.g., occupational and social settings), but this was dictated by data availability as no surveys reported casual contacts by sex. We also did not assess the intimacy or duration of contacts by sex. Because contacts were reported over a 24 hour period, we were unable to assess any sex differences in the cumulative number of contacts over a longer period of time. Our analysis in just two age categories (children and adults) also reflects the nature of available data but may have led us to overlook more nuanced age differences in sex-based social contact patterns. Some surveys deliberately oversampled certain age groups, and we made no adjustments in our analyses for sampling bias and used no weighting, due to a lack of data on which to weight.

Response bias may also have affected results, but few surveys reported the response rate, and none distinguished the response rate by sex.

Men are often overlooked in discussions of gender and TB, and strategies to assess and address men's excess burden of disease and barriers to TB care are notably absent from the global research agenda. However, because men comprise the majority of TB cases and remain untreated, and therefore infectious, longer than women, a better understanding of the factors that drive their disproportionate burden of disease is essential to appropriately direct resources to address these disparities. Our results here show that social contact patterns likely contribute to the emergence of sex disparities in the adult burden of TB by amplifying men's burden of disease. Men's contacts with women, boys, and girls show that the excess burden of TB disease among men also has important implications for *Mtb* transmission across sex and age groups. Addressing men's excess burden of TB is essential to improve men's health and to meet the ambitious targets for reducing TB incidence and deaths (37, 38).

5.5.5 Acknowledgements

Authors appreciate support from the TB Centre at the London School of Hygiene and Tropical Medicine. Authors also acknowledge Pietro Coletti (Hasselt University) for assistance in identifying and gathering datasets for inclusion in this review and authors of included studies who shared their datasets for meta-analysis.

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Chapter 6 Potential impact of sex-specific intervention strategies

6.1 Introduction

Chapters 4 and 5 identified drivers of men's higher epidemiological burden of TB, and factors underlying those drivers, building on evidence of higher prevalence, case notifications, and P:N ratios among men, as presented in Chapter 3. A dynamic compartmental transmission model of *Mtb* infection and TB disease was then developed, incorporating factors which likely contribute to men's excess incidence and limited access to diagnosis and treatment. This model was used to explore drivers of sex differences in TB epidemiology and estimate trends in TB epidemiology by sex in Viet Nam, to examine the historical impact of sex disparities in access to TB diagnosis and treatment, and assess the potential impact of future sex-specific strategies to further improve access to diagnosis and treatment. This research paper will be submitted for publication in 2021. Supplemental materials are provided in Appendix D.

6.2 Cover sheet

The Research Paper Cover Sheet is enclosed on the following pages.

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First Name(s)	Katherine Chisholm		
Surname/Family Name	Horton		
Thesis Title	Understanding sex disparities in tuberculosis and assessing the potential impact of strategies to improve men's access to care		
Primary Supervisor	Elizabeth L. Corbett		

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SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I developed the overall aim and approach of this manuscript with Dr. Rein Houben and Prof. Richard White. Building off previous work by Dr. Rein Houben and Dr. Tom Sumner, I reviewed literature to identify sex-specific risks of Mtb infection and TB disease for inclusion in the model and developed the structure for the sex-stratified model. The model was coded by Dr. Roel Bakker and edited by myself. I calibrated the model, conducted analyses, and produced tables and figures to summarise results. I drafted the manuscript and then incorporated feedback from co-authors. I will oversee the manuscript submission process and revise the manuscript, as necessary, to respond to input from peer review.

SECTION E

Student Signature	K. Horton
Date	18 November 2020

Supervisor Signature	E. Corbett
Date	18 November 2020

6.3 Title and authors

The epidemiological impact of sex disparities in access to TB diagnosis and treatment in Viet Nam: a modelling study

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6.4 Abstract

Background: Men have higher TB morbidity and mortality than women and children. Their high prevalence of undiagnosed infectious TB suggests improving diagnosis and treatment for men would likely benefit women and children too.

Methods: We developed a sex-stratified dynamic compartmental transmission model to explore drivers of sex differences in TB epidemiology and estimate trends in disease burden by sex in Viet Nam. We examined the historical impact of sex disparities in access to TB care, and we assessed the potential impact of future strategies to improve access to diagnosis and treatment by evaluating five scenarios representing different degrees of sex equity in improvements in access to TB care.

Findings: We estimate that TB incidence, mortality, and prevalence remain three times higher in men than women and that without further action, men's burden of disease in 2035 will remain as high as women's burden in 2000. Between 2000 and 2020, improvements in access to TB care among men were responsible for median 61%, 37%, and 41% of declines in, respectively, incidence, mortality, and prevalence. Future sex-specific interventions that double the rate of access to TB care in both men and women by 2025 are projected to result in median 40%, 59%, and 58% declines in, respectively, incidence, mortality, and prevalence in 2035; these declines are three times greater than those projected for interventions that only double the rate of access to TB care in women.

Interpretation: Better inclusion of men in strategies to improve access to TB diagnosis and treatment is essential for gender equity and will have the greatest impact on reducing disease burden in men, women, and children.

6.5 Manuscript

6.5.1 Introduction

Nearly twice as many cases of tuberculosis (TB) are reported among men as among women each year [1]. Prevalence surveys indicate even greater disparity in the underlying burden of disease, with men accounting for 70% of adults with undiagnosed TB in low- and middle-income settings [2]. Comparisons of these two data sources indicate that men's disadvantage extends to TB care, with substantially greater gaps in disease detection and reporting for men than women [2]. As a result of these disparities, over 60% of adults dying from TB each year are men [1], and most new infections among men, women, and children are likely attributable to contact with men [3].

Sex disparities in TB burden are driven by factors that increase men's incidence of disease and limit men's access to timely diagnosis and treatment [4]. Socio-behavioural risks, such as tobacco smoking, alcohol consumption, and social contact patterns [5-9], and institutional risks including occupational hazards [10, 11], are rooted in cultural gender norms and expectations [12] and place men at greater risk of infection with *Mycobacterium tuberculosis* (*Mtb*) and progression to TB disease. Biological sex differences in anatomy and immune response may further increase men's risk of infection and disease [13, 14]. Men are also limited by societal structures and expectations that impair their ability to recognise illness and access appropriate and timely care [15-17].

The impact of these inequities is clear in the setting of Viet Nam. The country has a high TB burden, with an estimated incidence of 182 per 100,000 in 2018 [1]. The first national TB prevalence survey in 2007 identified one of the highest male-to-female ratios in TB prevalence globally, with four male cases of undiagnosed TB for every female case [18]. Prevalence-to-notification ratios, which indicate gaps in disease detection and reporting, were 72% higher among men than women [19], and modelling indicate that men with smear-positive TB remained undiagnosed for one year longer than women [4]. While overall prevalence and sex disparities in prevalence-to-notification ratios had fallen by the second national prevalence survey in 2017, TB prevalence remained four times higher among men than women, and over 80% of individuals with prevalent TB were not yet on treatment, highlighting a need to further improve access to diagnosis and treatment [20]. The direct impact of these inequities is clear in data on disease burden [1], but broader implications of men's disadvantages in TB burden and care are not well-documented in Viet Nam or elsewhere.

We therefore use dynamic compartmental transmission modelling to explore drivers of sex differences in TB epidemiology and estimate trends in TB epidemiology by sex in Viet Nam, to examine the historical impact of sex disparities in access to TB diagnosis and treatment, and to

assess the potential impact of future sex-specific strategies to further improve access to diagnosis and treatment. In each of these analyses, we considered the epidemiological impact of sex disparities in TB burden and care on men, women, and children. While our analyses focus on Viet Nam as an exemplar setting, we expect lessons on the impact of sex disparities in access to TB diagnosis and treatment in this setting will have wider relevance across high TB burden settings with sex disparities in TB burden and access to timely diagnosis and treatment.

6.5.2 Methods

Data

We developed a sex-stratified dynamic compartmental model of *Mtb* transmission and TB disease incorporating sex-specific demographics and TB-associated risks where data indicate different relative risks for men and women in Viet Nam. The sex ratio at birth in Viet Nam is skewed towards an excess of male births [21], and life expectancy has been 8-10 years longer for women than men for the past 50 years [22]. Two-thirds of HIV infections occur among men, and fewer men living with HIV are on treatment relative to women living with HIV [23]. Social contact patterns show a high proportion of sex-assortative mixing [24]. In 2020, 40% of men and less than 2% of women were current tobacco smokers [25]. In the same year, the proportion of current alcohol drinkers was 48% in men and 10% in women, and men who were current alcohol drinkers consumed over five times as many standard drinks daily as women (51 grams vs. 8 grams) [26]. The adult prevalence of diabetes is similar in men and women (1% in 2000 projected to rise to 2% by 2030) [27], as is the proportion of the population that is underweight, as indicated by body mass index less than 18.5 (25% in 2002) [28], so neither of these risks was explicitly considered in our model. Gaps in detection and reporting have been greater among men than women in Viet Nam [4, 20].

Model structure

Our model is based on a model previously published by Houben et al. [29] (Appendix). The core model has four states related to *Mtb* infection and TB disease: susceptible (uninfected), latent *Mtb* infection, active smear-positive TB disease, and active smear-negative TB disease. States of infection and disease are stratified by treatment history (treatment-naïve or previously-treated) and drug resistance (drug susceptible or multidrug-resistant, MDR), and the entire model is stratified by sex (male or female), age (five year age groups), and HIV and antiretroviral treatment (ART) status (based on CD4 cell count and duration of ART).

Sex-specific risks of *Mtb* infection and progression to active disease are incorporated in the model (Appendix). Demographic data and data on HIV incidence, HIV progression, and ART uptake are sex-specific. Heterogeneous mixing reflects age- and sex-assortative mixing patterns

between men (males age ≥ 15 years), women (females age ≥ 15 years), and children (both sexes age < 15 years). Increased risks of *Mtb* infection and progression to active disease as a result of tobacco smoking are applied to the proportion of men and women who are current smokers, based on time trends in the prevalence of tobacco smoking for each sex. Increased risk of progression to active disease is raised further for the proportion of men and women who consume alcohol, based on time trends in alcohol consumption by sex. Additional sex-based risks are represented by a constant relative risk term applied to the risk of infection to reflect residual effects not otherwise specified. Sex differences in access to diagnosis and treatment are represented by separate rates of access to TB care for men and women.

Model calibration

We calibrated the model to population size estimates and projections [30, 31] and 37 epidemiological data points. Calibration targets included total incidence and mortality estimates for 2000, 2010, and 2018 [32]; total case notification rates for 2000, 2010, and 2018 [33]; bacteriologically positive prevalence for 2007 and 2017 [18, 20]; smear-positive prevalence for 2017 [20]; and proportion of MDR in new and retreatment cases in 2005 and 2011 [34]. HIV-positive calibration targets include incidence and mortality in 2018 [32] and proportion of HIV-positive case notifications in 2015 [33]. Sex-specific calibration targets for men and women include new smear-positive case notification rate for 2000 and 2010 [33]; new and relapse case notification rate in 2018 [33]; bacteriologically positive prevalence for 2007 and 2017 [18, 20]; smear-positive prevalence for 2017 [20]; and male-to-female ratios in total prevalence in 2007 and 2017 [18, 20], smear-positive prevalence in 2017 [20], and *Mtb* infection prevalence in 2015 [35]. Paediatric calibration targets include proportion of incidence in 2018 [32] and proportion of case notifications in 2015 [33].

We first selected 2 million random parameter sets, based on uniform distributions for all parameters, none of which fit all calibration targets. The 14 best-fitting parameter sets (3 sets fitting 29 targets and 11 sets fitting 28 targets) were used as seed values with an adaptive approximate Bayesian computation (ABC) Markov chain Monte Carlo (MCMC) method [36, 37], using a modified version of the easyABC package that accepts seed parameter values [38] in R [39], until we sampled from a posterior distribution consistent with all 37 epidemiological targets. A final set of acceptances was thinned to select 1,000 parameter sets that fit all calibration targets. Results for the calibrated model present median values, with uncertainty intervals (UIs) based on minimum and maximum values, from these runs.

Examining the historical impact of sex differences in access to diagnosis and treatment

We examined the contribution of improvements in men's access to diagnosis and treatment between 2000 and 2020 to declines in TB burden during this period. To do so, we fixed the

male-to-female ratio in rates of access to TB care from 2000 onwards. We compared TB burden estimates (incidence, mortality, and prevalence) in 2020 between the calibrated model and the historical impact model and calculated the percent decline in TB burden between 2000 and 2020 that could be attributed to improvements in men's access to diagnosis treatment during this time. We also calculated the number of incident TB cases and deaths averted over the period 2000-2020 by improvements in men's access to diagnosis and treatment by subtracting the numbers projected in the calibrated model from the numbers projected in the historical impact model. We report the impact of each analysis on men, women, and children, presenting median values, with UIs based on minimum and maximum values, for each of the final 1,000 parameter sets.

Estimating the impact of future interventions to further improve access to diagnosis and treatment

We assessed the potential impact of future interventions to further improve access to diagnosis and treatment, as indicated in the model by the rate of access to TB care parameter. We assessed five scenarios representing interventions that aim to double the adult rate of access to TB care over the five-year period 2021-2025; in all scenarios, adult rates of access to TB care are assumed constant from 2025, and paediatric rates of access to TB care are assumed constant from 2020. Scenarios differ in the distribution of improvements by sex, as shown in Box 1.

Box 1: Future intervention scenarios

Scenario 1: Rate of access to TB care doubles in women and remains constant in men

Scenario 2: Rate of access to TB care doubles in women and increases by 50% in men

Scenario 3: Rate of access to TB care doubles in men and women

Scenario 4: Rate of access to TB care doubles in men and increases by 50% in women

Scenario 5: Rate of access to TB care doubles in men and remains constant in women

We compared TB burden projections (incidence, mortality, and prevalence) for 2035 between the calibrated model and each intervention scenario, calculating the expected percent decline in each measure for each scenario relative to the calibrated model. We also projected the number of incident TB cases and deaths averted over the period 2021-2035 in each scenario relative to the calibrated model. We report the impact of each analysis on men, women, and children, presenting median values, with UIs based on minimum and maximum values, for each of the final 1,000 parameter sets.

6.5.3 Results

Calibrated model

The calibrated model fits population size estimates and projections and epidemiological calibration targets (Appendix). Model estimates reflect substantial declines in TB burden in recent decades. Between 2000 and 2020, modelled incidence fell by a fifth in men, from 379 (UI 350-475) to 241 (UI 213-281), and nearly a third in women, from 135 (UI 117-162) to 72 (UI 61-86). Mortality fell by half, from 108 (UI 92-121) to 42 (UI 377-46) in men and from 34 (UI 25-44) to 13 (UI 10-15) in women, as did prevalence, from 1,056 (UI 951-1,172) to 403 (UI 367-467) in men and from 340 (UI 258-456) to 125 (UI 98-151) in women (Figure 1).

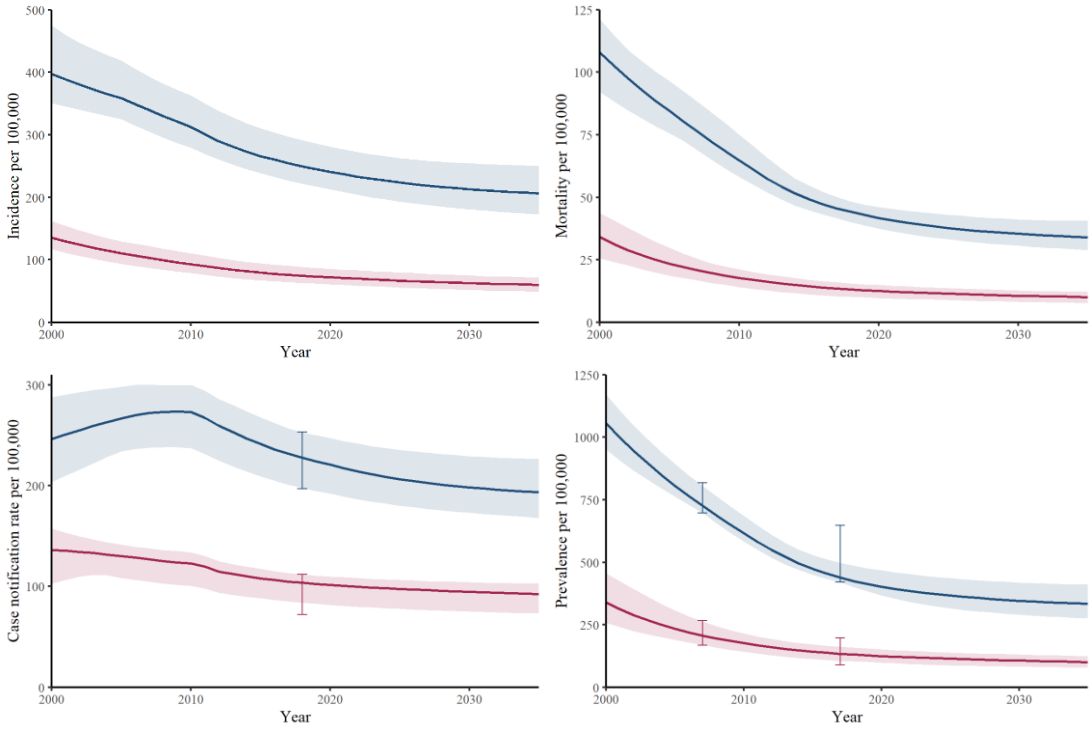

Figure 1: Epidemiological estimates and projections for men (blue) and women (red) for incidence (upper left), mortality (upper right), case notification rate (lower left), and prevalence (lower right) for the calibrated model. Figures show median model estimates (line), model uncertainty (shaded area), and calibration targets (error bars).

Sex disparities in TB burden changed little between 2000 and 2020 in our model (Appendix). Incidence was three times higher in men than in women (median 3.0, UI 2.6-3.5, in 2000; 3.4, UI 2.7-4.0, in 2020), as was mortality (median 3.2, UI 2.3-4.5, in 2000; 3.3, UI 2.8-4.4, in 2020) and prevalence (median 3.1, UI 2.2-4.3, in 2000; 3.2, UI 2.7-4.2, in 2020). Case notification rates were approximately twice as high in men as in women throughout this period (1.8, UI 1.4-2.5, in 2000; 2.2, UI 1.8-2.8, in 2020). The shift in the trajectory of case notification rates, particularly among men, in 2010 reflects a dramatic increase in linkage to care and treatment

success, particularly for individuals diagnosed with MDR-TB, who account for median 3% of new cases and median 22% of retreatment cases in that year.

Drivers of sex disparities

Posterior estimates from the calibrated model indicate relative risks attributable to tobacco smoking in current smokers of 2.19 (range 1.69-2.30) for *Mtb* infection and 1.21 (range 1.14-1.58) for progression to TB disease. The posterior relative risk of progression to TB disease attributable to alcohol consumption was median 0.014 (range 0.008-0.020) per gram alcohol consumption by current drinkers. The posterior residual relative risk of *Mtb* infection in men was median 1.57 (range 1.35-1.94).

Annual rates of access to TB care, which indicate access to diagnosis and treatment, increased substantially between 2000 and 2020 in men, from 0.76 (range 0.59-0.94) to 1.43 (range 1.18-1.74); rates of access to TB care in women were constant over the same time period: 1.13 (range 0.67-1.55) in 2000 and 1.37 (range 1.01-1.63) in 2020 (Figure 2). Male-to-female ratios in rates of access to TB care increased from 0.67 (range 0.43-1.26) in 2000 to 1.05 (range 0.96-1.45) in 2020 (Appendix).

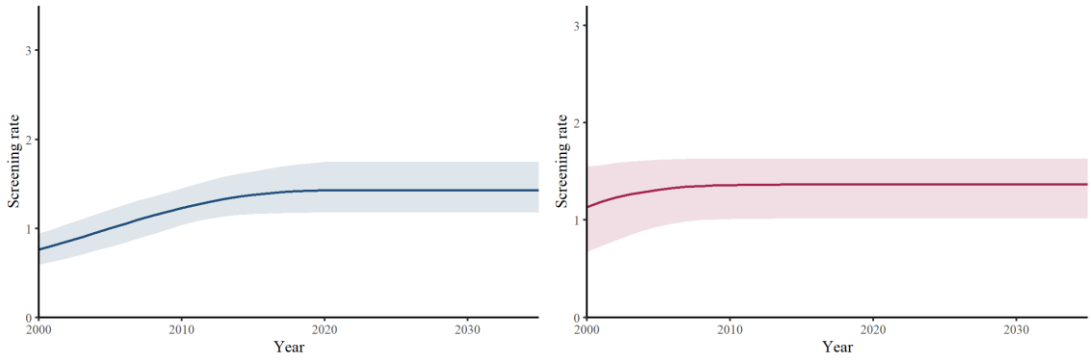

Figure 2: Rates of access to TB care for men (left in blue) and women (right in red) for the calibrated model. Figures show median model estimates (line) and range (shaded area).

Estimating the impact of future interventions to further improve access to diagnosis and treatment

In the historical impact model (Appendix), projections for incidence, mortality, and prevalence in 2020 were 27% (UI -27-49%), 36% (UI -41-57%), and 36% (-41-57%), respectively, lower in the calibrated model than in the historical impact model (Figure 3, Appendix). [Negative values reflect parameter sets for which the historical impact model projected increased incidence, mortality, and prevalence, relative to the calibrated model. These projections come from a small subset of parameter sets in which women experienced greater improvements in the rate of access to TB care, relative to men, after 2000.]

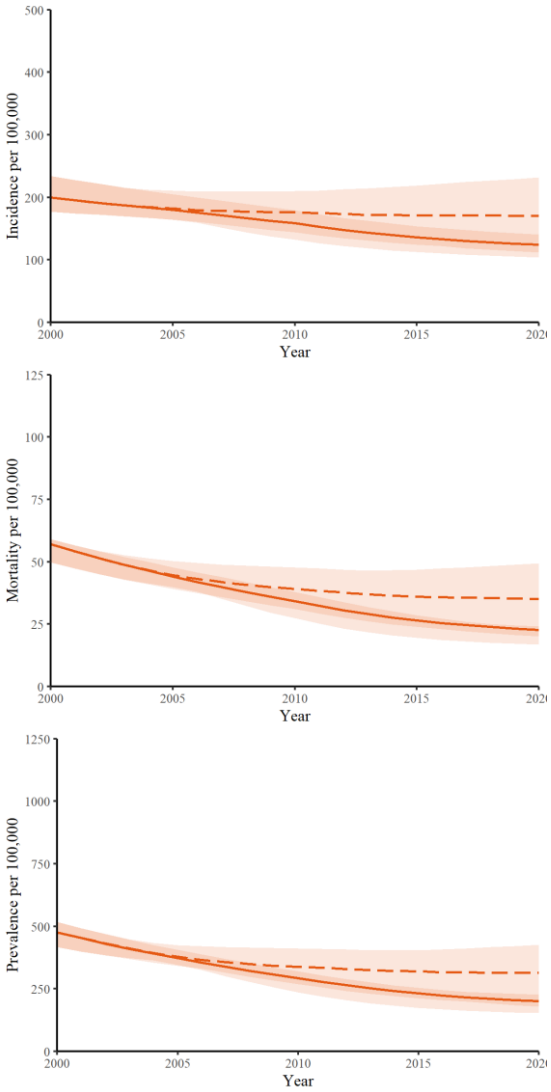

Figure 3: Epidemiological estimates for total population incidence (upper), mortality (middle), and prevalence (lower) for the calibrated model (solid line) and the historical impact model (dashed line). Figures show median model estimates (line) and model uncertainty (shaded area).

Between 2000 and 2020, 61% (UI -35-145%) of the decline in incidence, 37% (UI -20-82%) of the decline in mortality, and 41% (UI -22-92%) of the decline in prevalence in the calibrated model can be attributed to closing the gender gap in access to diagnosis and treatment by improvements in men's access to diagnosis and treatment (Figure 4, Appendix). Closing this gap averted 383,00 (UI -363,000-871,000) incident cases, representing 13% (UI -15-25%) of cases in men, 9% (UI -10-19%) of cases in women, and 12% (UI -14-24%) of cases in children, and 104,000 (UI -89,000-216,000) deaths, representing 17% (UI -20-29%) of deaths in men, 7% (UI -7-14%) of deaths in women, and 8% (UI -9-17%) of deaths in children (Appendix).

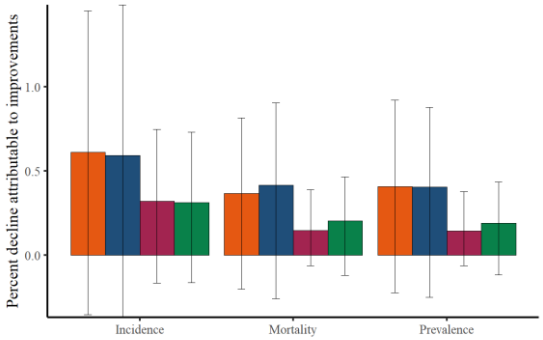

Figure 4: Percent decline in TB incidence, mortality, and prevalence from 2000 to 2020 attributable to improvements in men's access to diagnosis and treatment in the total population (orange), men (blue), women (red), and children (green). Figure shows median model estimates (bar) and model uncertainty (error bars).

Future interventions to improve access to diagnosis and treatment

Future intervention scenario models (Appendix) project declines in 2035 population incidence, mortality, and prevalence. The greatest epidemiological impact – 40% (UI 32-53%) decline in incidence, 59% (UI 53-68%) decline in mortality, and 58% (UI 53-68%) decline in prevalence – is projected for interventions which double the rate of access to TB care for both men and women (Scenario 3) (Figure 5, Appendix). Projections indicate the least epidemiological impact – 13% (UI 10-17%) decline in incidence, 19% (UI 16-22%) decline in mortality, and 19% (UI 16-22%) decline in prevalence – for interventions which only double the rate of access to TB care for women (Scenario 1).

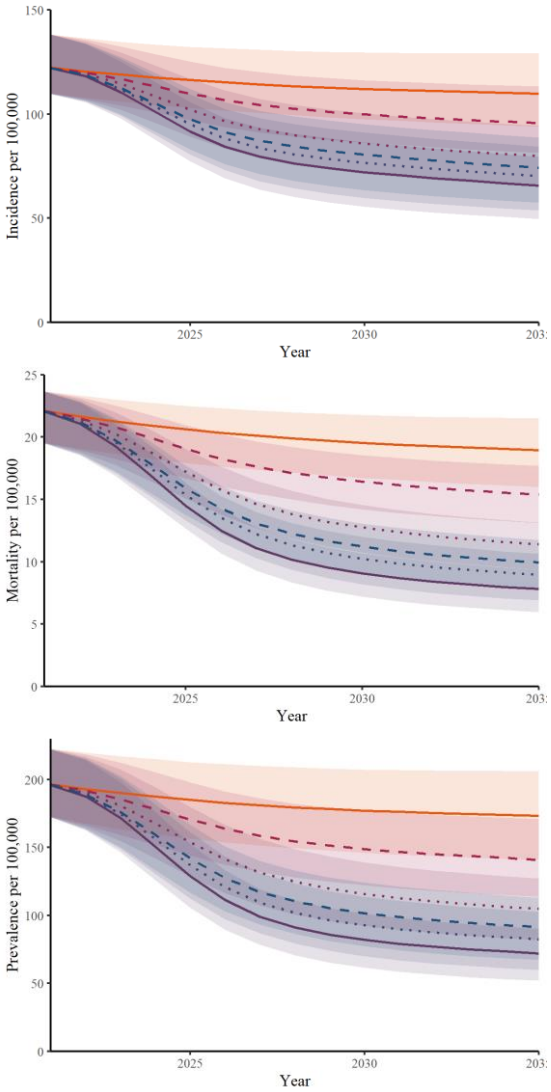

Figure 5: Projections for total population incidence (upper), mortality (middle), and prevalence (lower) for the calibrated model (solid orange line) and each intervention scenario: 1 (dashed red line), 2 (dotted red line), 3 (solid purple line), 4 (dotted blue line), 5 (dashed blue line). Figures show median model estimates (lines) and model uncertainty (shaded area).

Projected declines in incidence are highest for men, women, and children in scenarios which double the rate of access to TB care in men (Scenario 3-5) and lowest in the scenario which only doubles the rate of access to TB care in women with no change in men (Scenario 1) (Figure 6). Across all scenarios, projected declines in incidence in 2035 are higher for children than for men or women. Scenarios which double the rate of access to TB care in men project the greatest declines in mortality and prevalence in men (Scenarios 3-5); likewise, scenarios which double the rate of access to TB care in women project the greatest declines in mortality and prevalence in women (Scenarios 1-3). The greatest declines in mortality and prevalence in children are projected by scenarios which double the rate of access to TB care in men (Scenarios 3-5).

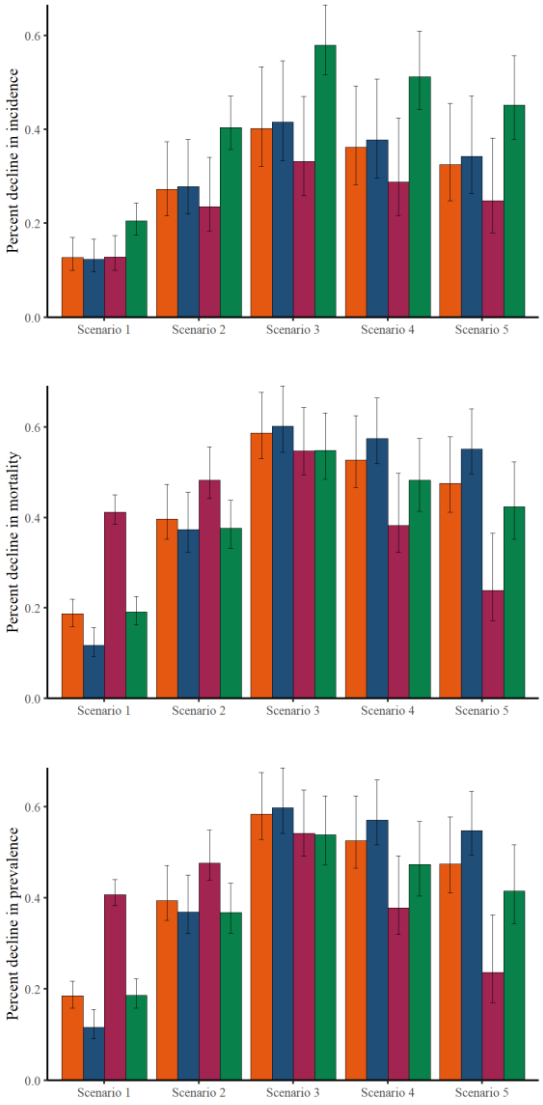

Figure 6: Percent decline in 2035 incidence (upper), mortality (middle), and prevalence (lower) attributable to interventions to further improve access to diagnosis and treatment (Scenarios 1-5) in the total population (orange), men (blue), women (red), and children (green). Figures show median model estimates (bar) and model uncertainty (error bars).

Between 2021 and 2035, intervention scenarios are projected to avert between 8% (UI 6-10%, Scenario 1) and 26% (UI 21-35%, Scenario 3) of incident cases and between 11% (UI 10-13%, Scenario 1) and 38% (UI 35-44%, Scenario 3) of deaths. More incident cases and deaths are projected to be averted by scenarios with greater improvements to men's rates of access to TB care (Appendix).

Intervention scenarios are projected to substantially increase annual numbers of case notifications (Appendix). The peak in additional annual case notifications is projected in 2024 with between 24,000 (UI 19,000-26,000, Scenario 1) and 61,000 (UI 55,000-67,000, Scenario 3) additional annual case notifications. Additional annual case notifications are projected to

settle to between 8,000 (UI -3,000-16,000, Scenario 5) and 26,000 (UI 16,000-35,000, Scenario 3) by 2035.

6.5.4 Discussion

Our mathematical modelling study of TB epidemiology in Viet Nam indicates that sex disparities in the burden of TB are pronounced and enduring. Without further action, we project men's burden of disease in 2035 will remain as high as women's burden of disease in 2000. Despite substantial improvements to close the gender gap in access to diagnosis and treatment between 2000 and 2020, we estimate that incidence, mortality, and prevalence remain three times higher in men than in women. Future interventions to improve access to diagnosis and treatment are projected to be most effective when both sexes benefit equally from those interventions: sex-specific interventions that double the rate of access to TB care in both men and women are projected to result in declines in incidence, mortality, and prevalence that are three times greater than those projected for interventions that only double rate of access to TB care in women.

Our analyses indicate that the gender gap in access to diagnosis and treatment in Viet Nam has closed due to substantial improvements in men's access to diagnosis and treatment between 2000 and 2020. Active case finding activities scaled up during this time may have contributed to these improvements, as a particular focus was placed on screening high risk populations including prison inmates and coal miners [20], both populations that are predominantly male. However, these declines have not been enough to eliminate or even substantially reduce disparities in TB burden. Little progress has been made to address socio-behavioural factors that increase men's risk of *Mtb* infection and progression to TB disease. Tobacco smoking among men has declined only slightly [40], and alcohol consumption among men has increased substantially [26]. The contribution of these and other gendered risk factors, particularly those that may contribute to high rates of reactivation among men, should be investigated more thoroughly to identify strategies that may further reduce men's burden of TB.

Men's access to TB diagnosis and treatment has important implications for men's health and for broader TB prevention efforts. We project the greatest epidemiological impact for future interventions that effectively increase access to diagnosis and treatment for both men and women, emphasising the importance of gender equity in active case finding strategies. Improvements in men's access to diagnosis and treatment resulted in the greatest declines in incidence among men, women, and children, illustrating that most new infections are attributable to contact with adult men, as previously shown in South Africa and Zambia [3]. Across all scenarios, declines in incidence were greatest for children, among whom most incident disease is attributable to recent infection and therefore averted by reduced transmission,

especially from men. Improved access to diagnosis and treatment reduced mortality and prevalence, primarily in the population that benefited directly from improved access. Improved access to diagnosis and treatment among men provided greater additional benefit to women in terms of mortality and prevalence than vice versa, due to the greater reduction in incidence resulting from men's improved access to diagnosis and treatment. For similar reasons, declines in mortality and prevalence among children were greatest in scenarios with the greatest improvements in men's access to care.

Future active case finding interventions, whilst not ignoring women, should focus efforts on men to most effectively reduce TB morbidity and mortality in men, women, and children. Appropriately, the National Strategic Plan for the National TB Programme in Viet Nam highlights vulnerable, predominantly male populations including tobacco smokers, alcohol consumers, those with silicosis, inmates and staff in correctional facilities, and migrants. Active case finding strategies to reach these and other hard-to-reach male populations must consider gendered barriers that disadvantage men in access TB care in Viet Nam. To overcome financial and work-related concerns, stigma, and negative masculinities, active case finding strategies should offer gender-sensitive, convenient access to diagnosis and treatment without detracting from perceptions of masculinity.

As countries around the world strive to reduce TB incidence and mortality in line with the End TB Strategy and Sustainable Development Goals [41, 42], improving access to TB diagnosis and treatment is essential. Our work shows clear population-wide benefits of improving access to diagnosis and treatment, particularly among men. However men are routinely underrepresented in community- and household-based systematic screening [2, 43-45], and efforts to incorporate TB care into health services often fail to engage men. Strategies to improve access to TB care must ensure gender equity. While the TB community can draw on lessons from men's engagement in the HIV care cascade [46, 47], research is urgently needed to identify feasible and acceptable strategies tailored specifically to engage men with TB diagnosis and treatment.

We have not specified intervention strategies in this analysis given the lack of available evidence on feasible and acceptable strategies to reach men. For the same reason, we have considered neither the economic costs nor operational feasibility of the future intervention scenarios modelled here. We recognise that the scenarios presented here are ambitious and would require substantial effort and resources to increase case notifications to the extent shown under each scenario. However, our aim was to examine the potential benefits, focusing primarily on the relative impact of strategies with different degrees of equity by sex, in order to guide the development of future intervention strategies.

Our work has several additional limitations. Few sex-stratified data points were available for model calibration, emphasising the need for further disaggregation of routine surveillance data and TB burden estimates by sex. Similarly, we were not able to examine more nuanced age-sex interactions in natural history and gendered risks due to the lack of available data. The sex-specific risks we have included in the model are not comprehensive, and we have not explored their interactions. We also have not considered the role of subclinical TB in our analyses, despite the fact that a third of individuals with bacteriologically confirmed TB did not report any symptoms in the most recent national prevalence survey in Viet Nam [20].

To our knowledge, this study presents the first sex-stratified dynamic transmission model of TB. Given the substantial and consistent sex disparities in TB burden across low- and middle-income countries [1, 2], such modelling is essential to better understand factors that contribute to these disparities and to identify areas of potential intervention for further study. By incorporating sex-specific socio-behavioural and biological factors associated with increased risk of *Mtb* infection and TB disease, such as tobacco smoking and alcohol consumption, future research can identify context-specific drivers of sex disparities in TB burden, as we have done here, as well as generate TB burden estimates and trends not currently available with sex disaggregation.

Despite substantial improvements in men's access to diagnosis and treatment in recent decades, incidence, mortality, and prevalence remain three times higher in men than in women. Addressing men's excess epidemiological burden of TB in Viet Nam and ensuring equitable inclusion in future active case finding strategies is essential for men's health outcomes and for reducing disease burden in women and children.

6.5.5 Acknowledgements

Authors acknowledge support from the London School of Hygiene and Tropical Medicine TB Centre.

The contents of this document are the sole responsibility of the authors and can under no circumstances be regarded as reflecting the positions of the International Union Against Tuberculosis and Lung Disease (The Union North America) nor those of the Donors.

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Chapter 7 Summary, recommendations, and conclusion

7.1 Summary of findings

The research presented within this thesis provides strong evidence that the epidemiological burden of TB is higher in men than in women and that men have more limited access to timely diagnosis and treatment. These disparities are driven by men's disadvantages in TB incidence and access to diagnosis and treatment, which may be attributable to biological factors, individual lifestyle factors, social contacts and networks, institutional structures, and cultural gender norms and expectations. Future interventions to improve access to diagnosis and treatment are projected to be most effective at reducing TB morbidity and mortality in men, women, and children when rates of access to TB care improve in both men and women as a result of those interventions.

Chapter 2: Background

I summarised evidence of sex differences in case notification data, which have been higher among men than women since the early 1990s. I evaluated evidence of sex differences in TB natural history to show that *Mtb* infection rates are similar among boys and girls, but higher among men than women; rates of progression from *Mtb* infection to TB disease are similar for boys and girls, higher among women from adolescence until around 40 years of age, and higher for men over 40 years of age; reactivation rates are likely similar among men and women, or perhaps higher among men, particularly at older ages; rates of reinfection may be higher in men due to more limited protection due to previous infection; and case fatality rates are similar for men and women. I also examined evidence of sex differences in the TB care cascade and found little evidence of sex differences in access to appropriate care, diagnosis, or treatment access in most settings, though limited evidence suggests women may be more likely to experience diagnostic delay in some settings and men may be more likely to experience treatment delay or pre-treatment loss to follow-up in some settings. I presented a conceptual framework based on Dahlgren and Whitehead's Main Determinants of Health to consider factors underlying men's disadvantages with regard to TB burden and access to care. I showed that sex differences in biological factors, individual lifestyle factors, social contacts and networks, institutional structures, and cultural gender norms and expectations may result in sex disparities in TB incidence and access to diagnosis and treatment.

Chapter 3: Sex differences in tuberculosis burden

Objective 1: To estimate male-to-female ratios in TB prevalence and prevalence-to-notification ratios through a systematic review of national and sub-national TB prevalence surveys in low- and middle-income countries

I presented strong evidence from my systematic review and meta-analysis of 56 TB prevalence surveys that TB prevalence in low- and middle-income countries is over twice as high among men as among women, with summary random-effects weighted M:F prevalence ratios of 2.21 (95% CI 1.92–2.54) for bacteriologically positive TB and 2.51 (95% CI 2.07–3.04) for smear-positive TB. The summary random-effects weighted M:F ratio for P:N ratios was 1.55 (95% CI 1.25–1.91), indicating that men may be less likely than women to seek or access care in many settings. In this analysis I also found that men were less likely than women to participate in prevalence surveys and that relatively fewer prevalent cases were found among men in surveys that required participants to self-report signs or symptoms in initial screening procedures. These findings provide further evidence that men face barriers in seeking and/or accessing timely TB diagnosis and treatment.

Chapter 4: Drivers of sex differences in tuberculosis burden

Objective 2: To identify drivers of sex disparities in TB burden in two exemplar settings – Viet Nam and Malawi – utilising a Bayesian approach to analyse a simple, compartmental model of TB

I determined that sex differences in the epidemiological burden of TB can be attributed to sex differences in disease incidence and treatment access rates, both of which disadvantage men. Using a Bayesian approach with a simple sex-stratified compartmental model for the exemplar settings of Viet Nam and Malawi, I showed that self-reports underestimate time to treatment 8- to 24-fold for both sexes and that men face substantially longer durations of untreated disease than women (median 2.2, 95% CrI 1.7-2.9, years for men and median 1.0, 95% CrI 0.6-1.6, years for women in Viet Nam; median 2.8, 95% CrI 1.8-4.1, years for men and median 1.9, 95% CrI 1.2-2.9, years for women in Malawi).

Chapter 5: Factors underlying drivers of sex differences in tuberculosis burden

Objective 3: To explore sex-specific factors likely underlying drivers of sex disparities in TB burden and care through a systematic review of sex differences in social contact patterns

I presented results from my systematic review and meta-analysis of 21 social contact surveys in 17 countries. These results indicate that sex-assortative mixing among adults likely amplifies sex disparities in the adult burden of TB in many settings. Differences in social contact patterns between children and adults suggest a behavioural shift during adolescence, potentially contributing to the emergence of sex difference in TB epidemiology in adults. I also suggested that men's excess burden of TB may have implications beyond men's health, as a third of women's social contacts and a fifth of children's contacts were with adult men.

Chapter 6: Potential impact of sex-specific intervention strategies

Objective 4: To quantify the potential epidemiological impact of future sex-specific strategies to further improve access to diagnosis and treatment in a single setting – Viet Nam – utilising a dynamic transmission model of TB

I developed a sex-stratified dynamic compartmental transmission model of TB and showed that sex disparities in the burden of TB in Viet Nam are pronounced and enduring such that men's burden of disease is projected to remain as high in 2035 as women's burden of disease in 2000. Substantial improvements were made between 2000 and 2020 to close the gender gap in access to timely diagnosis and treatment, yet incidence, mortality, and prevalence remain three times higher in men than in women. I projected the impact of sex-specific interventions to show that future interventions to improve access to diagnosis and treatment will be most effective at reducing the epidemiological burden of TB in men, women, and children when rates of access to TB care improve in both men and women as a result of those interventions.

7.2 Strengths

7.2.1 Public health relevance

The work presented within this thesis addresses a subject with significant public health relevance and strong policy implications. Independently, both TB and gender equity are global priorities: TB is the leading cause of death from an infectious disease worldwide and remains a major public health priority [1], and gender inequities and restrictive gender norms are no longer considered acceptable [2, 3]. The importance of gender as a social determinant of health is receiving greater attention [3] with the recognition that "rigid gender norms undermine the health and wellbeing of all people – girls and women, boys and men, and gender minorities" [4]. However, the intersection of these two priorities has received little attention from global policy makers, funding agencies, and researchers, particularly within the global TB community, prior to dissemination of the work presented in this thesis. This work is therefore highly relevant, providing strong quantitative evidence with implications at the intersection of these two priorities: TB elimination and gender equity.

7.2.2 Global and country-level analyses

The thesis benefits from a combination of global and country-level analyses. Systematic reviews and meta-analyses presented in Chapter 3 and Chapter 5 utilise data from geographically-diverse and globally-representative settings (as available) in order to answer broad questions about sex differences in TB burden and social contact patterns. Chapter 4 and Chapter 6 then focus on country-level modelling analyses in order to explore drivers and implications of those sex differences with greater detail and specificity than would be possible

at a global level due to heterogeneity in TB burden and associated risks across settings. This combination of global and country-level analyses gives the thesis both breadth and depth.

7.2.3 Range of quantitative methods

The work presented within this thesis utilises a range of quantitative and mathematical modelling methodologies in novel analyses. These approaches provide a framework to answer research questions that are not currently prioritised by funding agencies and, if they were, would require vast and challenging field studies. The range of quantitative methods used in this body of work brings together evidence from disparate studies and effectively generates strong evidence that can be used to guide future research and programmatic actions.

The systematic review of TB burden presented in Chapter 3 is, to my knowledge, the first meta-analysis to take advantage of the wealth of data provided by recent national TB prevalence surveys [1]. The systematic review of social contact patterns presented in Chapter 5, while not the first systematic review of such studies [5], is the first to include a quantitative meta-analysis of these data.

Chapter 4 provides an excellent example of the utility of a deliberately simple model, in contrast to the more complex modelling presented in Chapter 6. The latter represents, to my knowledge, the first sex-stratified dynamic transmission model of TB calibrated to country-level data. This model allows analyses to identify drivers of sex disparities in TB burden by incorporating sex-specific socio-behavioural and biological factors associated with increased risk of *Mtb* infection and TB disease, and model stratifications allow the generation of TB burden estimates and trends not otherwise available by sex.

7.2.4 Use of a conceptual framework

Quantitative analyses within this thesis have been conducted within a conceptual framework that brings together quantitative, qualitative, and theoretical evidence relating to sex/gender and TB. As I have shown in Chapter 5, the biological and socio-behavioural factors that are most often associated with men's increased risk of TB fit within institutional and cultural norms that are shaped by gender norms and societal expectations. Framing analyses and results within this bigger picture provides greater context to understand the complex causal pathways leading to sex disparities in TB.

7.2.5 Broad impact considerations

I have considered the impact of men's excess burden of TB and limited access to timely diagnosis and treatment, and potential interventions to address these disparities, not only for men, but also for women and children, in order to understand how sex disparities impact across the population.

7.3 Limitations

7.3.1 Limited data availability

Analyses within this thesis were often limited by data availability. While many studies report their main findings by sex, few stratify all results by sex or provide further disaggregation by both sex and other factors such as age, urban or rural setting, or HIV status.

In Chapter 3, few studies included in my systematic review and meta-analysis reported prevalence data by age and sex, so the analysis of the intersection of those factors is limited, and prevalence data were too infrequently reported by sex and HIV status to be analysed. No surveys that conducted drug susceptibility testing reported the results of those analyses by sex, so it is not possible to comment on whether the sex differences reported here are also relevant to drug-resistant TB[2]. P:N ratios could have been improved by stratifying by these factors, particularly by age and rural or urban setting, but data on these characteristics were not available at the time of analysis.

In Chapter 5, less than half of the publications eligible for my systematic review and meta-analysis collected data on sex and age for both participants and contacts, which limited the number of surveys that could be included in analyses. The use of two age categories (children and adults) also reflects limitations in data availability and may have obscured more nuanced age differences in sex-based social contact patterns. Similarly, few surveys reported the response rate, and none distinguished the response rate by sex, so I could not assess the presence or absence of sex differences in response bias.

In Chapter 6, few sex-specific estimates of TB burden were available for model calibration, so only prevalence and case notification rates could be directly fitted to data. (Incidence estimates are now available by sex but were not at the time when this work began.)

[2] Although it was not possible to utilise prevalence survey data to comment on sex differences in drug resistant TB, I have elsewhere contributed to an analysis that found no evidence that the risk of drug resistant TB among those with TB differs by sex, as indicated by periodic, nationally representative drug-resistance surveys of a sample of patients, or through continuous surveillance by the routine collection of DST results [6].

7.3.2 Focus on epidemiological burden of TB

This study focused solely on the epidemiological burden of TB. I was not able to consider sex differences in broader aspects of the considerable impact of TB, including social impact, economic costs, and health service operations.

7.3.3 Focus on limited spectrum of TB

Several analyses focused solely on smear-positive TB, despite recognition that individuals with TB present across a spectrum of disease [7]. Comparisons of prevalence and notification data in Chapter 3 and mathematical modelling in Chapter 4 considered only smear-positive disease in order to ensure consistency across data points since, at the time, sex-specific case notification numbers were reported only for smear-positive TB. As such, it is not possible to comment on gaps in detection and reporting and untreated disease duration for smear-negative and extra-pulmonary TB, both of which are likely greater than for smear-positive TB.

Subclinical TB was not explicitly considered in this work. Findings in Chapter 3 that relatively fewer men with prevalent TB were identified in prevalence surveys that required symptom screening and inconsistencies between self-reported and modelled duration of untreated TB in Chapter 4 suggest sex differences in presentation may exist. Given the high prevalence of asymptomatic prevalent TB [8] and unknown contribution to transmission [9], there could be benefit in assessing whether the sex differences in prevalent TB and gaps in detection and reporting reported in Chapter 3 are consistent across symptomatic and asymptomatic disease.

7.3.4 Reliance on prevalence data

Throughout the thesis, I relied heavily on prevalence data and P:N ratios. Recent national prevalence surveys provide estimates that are considered the most accurate measure of TB burden [10], yet limitations remain. These estimates provide an estimate at a single point in time and cannot distinguish between disease as a result of recent infection and disease from reactivation, limiting understanding of current transmission. Furthermore, P:N ratios provide a crude indicator of gaps in detection and reporting, particularly when subnational prevalence data are compared to national notification data.

7.3.5 Lack of heterogeneity

Considerations of the gendered epidemiological burden of TB were limited to binary distinctions between men and women due to data limitations. I was not able to consider the impact of heterogeneity that may result from intersections of sex and gender with other social factors such as age, race, and social class, nor assess TB burden and access to diagnosis and treatment among transgender or individuals with non-binary gender identities.

My limited approach to considerations of heterogeneity are apparent in Chapter 4, where results describe median untreated disease duration and do not take into account heterogeneity within the populations of interest. Similarly, posterior parameter values from transmission modelling in Chapter 6 represent population averages, and I was not able to examine more nuanced age-sex interactions in natural history and gendered risks.

7.4 Recommendations

7.4.1 Sex-disaggregated data

Gender data, defined as "data disaggregated by sex and analysed to understand the differential outcomes for women, men, girls, and boys" [11], is key to understanding sex disparities in disease burden and care. Given the significant sex differences reported in TB prevalence and access to care, future prevalence surveys, modelling analyses, research studies, and programmatic reports should analyse and report all results by sex to facilitate greater understanding of the relationship between sex/gender and TB. Results from my systematic review on sex differences in TB burden, presented in Chapter 3, have been used to revise the methodology used by WHO to calculate sex-specific TB incidence [10]; methodologies used for other national and global burden estimates, particularly mortality, should also be disaggregated by sex. Where possible, results should be further disaggregated by both sex and other relevant factors, such as age, urban or rural setting, or HIV status, as appropriate, in order to allow more nuanced analyses.

7.4.2 Global recognition and policy shift

Given the compelling evidence presented within this thesis, global discourse and policy on key affected populations need to include a focus on men. Key affected populations include "people at increased risk of TB because of biological or behavioural factors" and "people who have limited access to quality TB services" [12]. Men clearly meet both of these definitions.

Recommendations to address issues of gender and TB cannot insist on addressing the needs of women and girls [13] while ignoring the inequity affecting men and boys, who carry the higher burden of disease, often with more limited access to timely diagnosis and treatment. My systematic review on sex differences in TB burden, presented in Chapter 3, has been cited as the impetus for a shift in understanding gender issues in TB and as key evidence for strategies to improve men's access and utilization of health services for tuberculosis by the World Health Organization [10], USAID [14], and UK Academics and Professionals to End TB [15]. However, while many other organisations acknowledge the relative burden of disease in men, most continue to focus gender-specific recommendations on women [13]. Global and national TB programs should reconsider the significance of sex disparities in TB in order to drive policy

and resources appropriately towards men and to mandate efforts to successfully reach men with TB services.

7.4.3 Research to address knowledge gaps

Strategies to assess and address men's excess TB morbidity and barriers to TB diagnosis and treatment are notably absent from the global research agenda, with the exception of the UK Foreign, Commonwealth & Development Office [16]. Research funding is needed across a range of fields to address remaining knowledge gaps relating to men's higher incidence of TB, barriers faced in accessing diagnosis and treatment, and strategies to address both.

Further research is needed to evaluate the contribution of different biological and socio-behavioural factors to men's excess incidence across geographic settings. More detailed studies on social contact patterns that include detail on contact age, sex, location, and context could provide data for a more nuanced understanding of sex-assortative mixing patterns. Additional studies should examine the impact of alcohol consumption and undiagnosed or untreated HIV infection, particularly in the African region. A better understanding of the intersection of risks such as tobacco smoking and alcohol consumption would also be useful to clarify the contribution of these factors to sex disparities in TB. Strategies on tobacco smoking cessation and alcohol consumption reduction should be evaluated to estimate their direct impact on TB morbidity and mortality, and evaluations must include a gender lens to determine the impact of these programmes on sex disparities in TB.

Gender analyses must be incorporated into research on patient pathways and care cascades to better understand delays and loss to follow up by identifying barriers and facilitators that influence men's engagement with TB care. Steps much be taken to acknowledge and address the ways in which constructions of masculinity add to and interact with health system barriers that affect men's health seeking behaviours. Gender-transformative interventions that not only consider gender but seek to challenge gender norms and expectations should be implemented and evaluated within the context of TB-associated risks and care pathways.

Urgent research is needed to identify strategies to improve men's engagement with TB diagnostic and treatment services. While current gender-specific strategies focused on improving access to TB diagnosis in women [13] may provide an entry point to care for men within women's households, strategies with tailored interventions and messaging for men are urgently needed. Systematic screening offers an opportunity to expedite diagnosis with less reliance on severe symptoms [17], which evidence presented in Chapter 3 suggests is particularly relevant for men. A range of strategies should be developed across community [20], health care [21], occupational [22, 23], transport [24], and leisure settings, with the recognition that different strategies will be needed to reach men in different geographic settings, age groups,

and socioeconomic strata. Research studies should rigorously evaluate the acceptability and feasibility of identified strategies, as well as the potential impact on morbidity and mortality and patient and health systems costs. Parallel research is needed to identify effective research uptake approaches through which results from studies described above may inform and influence global and national policy and programmes.

Funding agencies should broaden their mandates for gender research and support social research, mathematical modelling, intervention trials, and economic analyses, as appropriate, in each of these areas.

7.4.4 Strategies to engage men in TB diagnosis and treatment

Remaining knowledge gaps described above should not prohibit immediate action to develop and implement strategies to improve men's access to TB diagnosis and treatment. The excess disease burden and long duration of untreated TB among men identified within this thesis implies inadequate coverage of current case finding strategies. While studies are conducted to identify the most effective strategies to reach men with TB services, the TB community should draw on lessons from men's engagement in the HIV care cascade [18] and evidence showing community-based screening programmes are more effective in reaching men for HIV testing than facility-based strategies [18, 19].

7.4.5 Strategies to reduce gender disparities in TB burden

Improving men's access to TB services will not be sufficient to reduce gender disparities in TB burden. Efforts are also needed to address the social determinants of gender disparities in TB that contribute to men's disproportionate incidence of disease. Individual lifestyle factors that increase TB risk, including tobacco smoking, alcohol consumption, illicit drug use, and risky sexual behaviours, must be addressed through gender-responsive approaches. In high TB burden regions, tobacco smoking and alcohol consumption are highly prevalent, particularly among men, with male-to-female ratios in tobacco smoking prevalence ranging from 8:1 in the African region to 20:1 in the South East Asia region and comparable ratios in alcohol consumption ranging from 2:1 in the African and South East Asia regions to 9:1 in the Western Pacific region. In addition, poverty reduction measures, expected to reduce TB burden across the population, may also contribute to reductions in gender disparities by easing the economic pressures that drive men into risky occupations and work-related migration.

Underlying these and other factors that increase men's burden of TB, as well as those factors that limit their access to TB services, are gender norms and expectations. Efforts to achieve gender equality must engage men and boys in order to shift these societal norms. Empowering men and boys to move away from traditional hegemonic masculinities and transform their

relationships with gendered social, economic, and societal structures is expected to have broad impact which includes reducing gender disparities in TB burden.

7.5 Conclusions

Men have higher TB morbidity and mortality than women and children and more limited access to timely diagnosis and treatment due to a complex nexus of biological and socio-cultural factors. These inequities have consequences for men, women, and children. The work presented within this thesis provides strong evidence for an imperative to formulate evidence-based gender-sensitive policies and programs to better engage men in TB services. Implementing such priorities at both the global and national level will improve gender equity in access to diagnosis and treatment, and addressing gender imbalances in TB will ultimately benefit men, women and children. Without extending the benefits of TB care and prevention to men, the TB community is unlikely to achieve its ambitious targets under the End TB Strategy and the Sustainable Development Goals [2, 12].

7.6 References

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Appendix A Supplemental materials for Chapter 3 manuscript "Sex differences in tuberculosis burden and notifications in low- and middle-income countries: A systematic review and meta-analysis"

S1 Checklist: PRISMA Checklist

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported in section and paragraph
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Introduction par. 1-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Introduction par. 6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Methods par. 1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Methods par. 1
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Methods par. 1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Table 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Methods par. 2-4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Methods par. 6-10

S1 Checklist: PRISMA Checklist

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Methods par. 5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Methods par. 11-13
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Methods par. 12
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	S1 Analysis
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Methods par. 13
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Results par. 1, Fig 1, S1 Table
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	S2 Table
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Results par. 2, S1 Figure, S2 Figure
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Results par. 3-15, Fig 3-6, S3 Table

S1 Checklist: PRISMA Checklist

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Results par. 3-15, Fig 3-6, S4 Table, S5 Table
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	S1 Analysis
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Results par. 3-15, Fig 3-6, S4 Table, S5 Table
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion par. 1-4
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Discussion par. 7
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Discussion par. 8
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Financial statement

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

S2 Checklist: MOOSE Checklist

From: Donna F. Stroup, PhD, MSc; Jesse A. Berlin, ScD; Sally C. Morton, PhD; Ingram Olkin, PhD; G. David Williamson, PhD; Drummond Rennie, MD; David Moher, MSc; Betsy J. Becker, PhD; Theresa Ann Sipe, PhD; Stephen B. Thacker, MD, MSc; for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. **Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting** JAMA. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008

	Reported in section and paragraph	Comments
Reporting of background should include		
Problem definition	Introduction par. 1, 4-5	Tuberculosis (TB) case notifications among men have exceeded those among women in most settings, but due to care-seeking and access biases, notification data alone are insufficient to measure sex differences in TB burden.
Hypothesis statement	Introduction par. 5	TB prevalence remains higher among men than women.
Description of study outcomes	Introduction par. 6	Outcomes include sex ratios in TB prevalence and prevalence-to-notification (P:N) ratios.
Type of exposure or intervention used	Introduction par. 6	No exposure or intervention was examined, as such; the outcome of interest was sex ratios in prevalence surveys.
Type of study designs used	Introduction par. 6	A systematic review was conducted to examine prevalence surveys.
Study population	Introduction par. 6	The study population included adults in low- and middle-income countries.
Reporting of search strategy should include		
Qualifications of searchers (eg librarians and investigators)	Methods par. 2	Searches were designed by investigators.
Search strategy, including time period used in the synthesis and key words	Methods par. 1, 4, Table 1	Studies describing national and sub-national TB prevalence surveys in adult populations (age ≥ 15 years) in low- and middle-income countries published between 1 January 1993 and 31 May 2015. Specific search strategies are shown in Table 1.
Effort to include all available studies, including contact with authors	Methods par. 3	Study authors were contacted for additional information if studies did not report the number of participants and the number of

S2 Checklist: MOOSE Checklist

		bacteriologically-positive and/or smear-positive TB cases by sex for adult participants. Authors were also contacted if sex-specific prevalence data were not available by age group.
Databases and registries searched	Methods par. 1	The following databases were searched: PubMed, Embase, Global Health and the Cochrane Database of Systematic Reviews.
Search software used, name and version, including special features used (eg explosion)	Methods par. 1	Searches were performed using online PubMed, Embase, Global Health and the Cochrane Database of Systematic Reviews databases. No additional search software was used.
Use of hand searching (eg reference lists of obtained articles)	Methods par. 1	Abstract books from the Union World Conference on Lung Health (2012-2014) and the World Health Organization (WHO) Global TB Report 2014 were also searched by hand, as were reference lists from included studies. Researchers in the field and at WHO were contacted to assist with identification of relevant studies.
List of citations located and those excluded, including justification	Fig 1, S1 Table, S2 Table	S2 Table summarises included surveys; S1 Table shows excluded studies that underwent full-text review with the reason for exclusion.
Method of addressing articles published in languages other than English	Methods par. 4, Fig 1	Studies published in languages other than English were excluded due to limited resources for translation.
Method of handling abstracts and unpublished studies	Methods par. 1-4	Abstracts and unpublished studies were reviewed in the same method as published studies.
Description of any contact with authors	Methods par. 3	Study authors were contacted for additional information if studies did not report the number of participants and the number of bacteriologically-positive and/or smear-positive TB cases by sex for adult participants. Authors were also contacted if sex-specific prevalence data were not available by age group.

S2 Checklist: MOOSE Checklist

Reporting of methods should include		
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Methods par. 4	Cross-sectional prevalence surveys were used to measure prevalence.
Rationale for the selection and coding of data (eg sound clinical principles or convenience)	Methods par. 6-10	Case definitions and definitions of all measures are included.
Documentation of how data were classified and coded (eg multiple raters, blinding and interrater reliability)	Methods par. 6-10	Case definitions and definitions of all measures are included.
Assessment of confounding (eg comparability of cases and controls in studies where appropriate)	Methods par. 11-13	Univariate and multivariate meta-regression were performed, the latter to account for confounding between variables assessed.
Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	Methods par. 5	The risk of bias in included studies was assessed in parallel. Each study was ranked on eight criteria from a tool developed by Hoy and colleagues to assess the risk of bias in prevalence surveys. These criteria assessed factors related to selection of the study population, risk of non-response bias, data collection methods and case definitions. The eight criteria were summarised to give an assessment of the overall risk of bias.
Assessment of heterogeneity	Methods par. 12	Heterogeneity was assessed using the I^2 statistic.
Description of statistical methods (eg complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Methods par. 12-13	Due to substantial heterogeneity between studies, random-effects models were used for meta-analyses, weighting for the inverse of the variance. Random-effects weighted summary M:F ratios were calculated for participation, bacteriologically-positive and smear-positive TB and bacteriologically-positive TB for each age group. Meta-regression was performed to examine associations between M:F ratios and WHO geographical region, survey setting (national vs. sub-national), national estimates of TB and HIV burden (both in the general

S2 Checklist: MOOSE Checklist

		population; the latter also in incident TB), study quality, initial screening procedures and case definitions. Univariate meta-regression was conducted separately for bacteriologically-positive TB and smear-positive TB. If either univariate meta-regression suggested evidence of an association for a particular variable, that variable was included in multivariate meta-regression models for both bacteriologically-positive and smear-positive TB. All analyses were performed using R version 3.2.2
Provision of appropriate tables and graphics	Tables 1-2, Fig 1-6, S1-5 Table, S1-2 Figure	Key data and graphics are provided in tables and figures.
Reporting of results should include		
Graphic summarizing individual study estimates and overall estimate	Fig 3-6	Figures show individual study and overall estimates for male-to-female ratios in bacteriologically-positive and smear-positive TB prevalence; individual study estimates for male-to-female ratios in prevalence-to-notification ratios; and individual and overall estimates for male and female prevalence for bacteriologically-positive and smear-positive TB.
Table giving descriptive information for each study included	S2 Table	S2 Table shows descriptive information for each study included, including survey country and year, setting, initial screening procedures, case definitions and participant numbers.
Results of sensitivity testing (eg subgroup analysis)	Results par. 5, 8-15	Due to substantial heterogeneity between studies, random-effects models were used for meta-analyses, weighting for the inverse of the variance. Subgroup analyses were also conducted and reported.
Indication of statistical uncertainty of findings	Results par. 3-15	Confidence intervals are included for all measures.
Reporting of discussion should include		

S2 Checklist: MOOSE Checklist

Quantitative assessment of bias (eg publication bias)	S1 Analysis	Results shown in S1 Analysis.
Justification for exclusion (eg exclusion of non-English language citations)	Methods par. 4	Studies conducted among symptomatic or care-seeking individuals, children, single sex, occupational settings or other sub-populations (e.g., only HIV-positive individuals) were excluded. Studies reporting prevalence of *Mycobacterium tuberculosis* infection but not TB disease were excluded. Individuals under 15 years of age were excluded since diagnosis of childhood TB is more complicated than adult disease, especially within the context of community-based surveys. Studies including both adults and children were included in the qualitative review but were included in quantitative analyses only if the study reported the participation and prevalence for adults. Studies published in languages other than English were excluded due to limited resources for translation.
Assessment of quality of included studies	Results par. 2, S1 Figure, S2 Figure	S1 Figure shows the distribution of risk of bias classification by response to each assessment criteria; S2 Figure shows the distribution of risk of bias classification for each analysis.
Reporting of conclusions should include		
Consideration of alternative explanations for observed results	Discussion par. 3-4	Sex differences in prevalence-to-notification ratios could be attributed to men seeking care in private facilities and therefore being less likely to be included in case notification numbers.
Generalization of the conclusions (eg appropriate for the data presented and within the domain of the literature review)	Discussion par. 5, 8	Authors recommend that given the compelling evidence presented on burden and access to care, global discourse and policy on key underserved populations needs to include a focus on men. With a clear need and high burden, improving diagnosis and treatment

S2 Checklist: MOOSE Checklist

		among men is essential to achieve the ambitious targets of the post-2015 End TB Strategy.
Guidelines for future research	Discussion par. 7-8	Several recommendations for future research are made, including examining whether men may be less likely than women to accept TB screening and report symptoms, and analysing prevalence survey results by sex and age, rural or urban setting and HIV status.
Disclosure of funding source	Financial statement	PM was supported by the Wellcome Trust (grant number: WT089673). RMGJH was funded by the Bill and Melinda Gates Foundation. RGW is funded the Medical Research Council (UK) (MR/J005088/1), the Bill and Melinda Gates Foundation (TB Modelling and Analysis Consortium: OPP1084276), and USAID/IUTLD/The Union North America (TREAT TB: Technology, Research, Education, and Technical Assistance for Tuberculosis; GHN-A-OO-08-00004-00). ELC was funded by a Wellcome Trust Senior Research Fellowship in Clinical Science (grant number: WT091769).

Transcribed from the original paper within the Support Unit for Research Evidence (SURE), Cardiff University, United Kingdom. February 2011.

S1 Table: Reasons for exclusion of studies with full-text review (n=65)

Reference	Reason for exclusion
(2004) TB prevalence down 30% in China after DOTS. Bulletin of the World Health Organization 82: 716.	Commentary on results from 2000 prevalence survey reported in Wang et al. (2014).
(2005) Short-course chemotherapy significantly reduces the prevalence of tuberculosis in China. Evidence-Based Healthcare and Public Health 9: 71-72.	Abstract on results from 2000 prevalence survey reported in Wang et al. (2014).
Ahuja S, Batra S, Chen J (2014) Higher yield for tuberculosis cases using enhanced case finding compared to passive case finding in Cambodia. International Journal of Tuberculosis and Lung Disease 18: S332.	Abstract describes ongoing active case finding rather than a survey conducted at a single point in time.
Alavi SM, Bakhtiyariniya P, Eghtesad M, Salmanzadeh S (2014) Prevalence of pulmonary tuberculosis before and after soil dust in Khuzestan, southwest Iran. Caspian Journal of Internal Medicine 5: 190-195.	Article describes a register review of TB patients.
al-Kassimi FA, Abdullah AK, al-Hajjaj MS, al-Orainey IO, Bamgboye EA, et al. (1993) Nationwide community survey of tuberculosis epidemiology in Saudi Arabia. Tubercle and Lung Disease 74: 254-260.	Date of survey is not reported, but article was published in 1993 so survey must have been conducted prior to 1993 and is therefore ineligible.
Balasubramanian R, Garg R, Santha T, Gopi PG, Subramani R, et al. (2004) Gender disparities in tuberculosis: report from a rural DOTS programme in south India. International Journal of Tuberculosis and Lung Disease 8: 323-332.	Analysis to examine gender differences using data from the 1999-2001 prevalence survey reported in Gopi et al. (2003)
Banda R, Mpunga J, Munthali A (2014). Results from the national TB prevalence survey of Malawi. International Journal of Tuberculosis and Lung Disease 18(11 Suppl 1): S44.	Duplicate report of the 2013-2014 prevalence survey reported in Banda et al. (2015).
Baral, S., et al. (2015). Effectiveness of innovative TB case finding strategies to reach the unreached slum population in the urban areas in Nepal. Union World Conference on Lung Health. Cape Town, South Africa.	Age of study population is unknown.
Basta PC, Coimbra CE, Jr., Camacho LA, Santos RV (2006) Risk of tuberculous infection in an indigenous population from Amazonia, Brazil. International Journal of Tuberculosis and Lung Disease 10: 1354-1359.	Article discusses prevalence of *Mtb* infection and annual risk of *Mtb* infection rather than prevalence of TB.
Borgdorff MW, Nagelkerke NJ, Dye C, Nunn P (2000) Gender and tuberculosis: a comparison of prevalence surveys with notification data to explore sex differences in case detection. International Journal of Tuberculosis and Lung Disease 4: 123-132.	Review of prevalence surveys including Tupasi et al. (1999).
Chadha VK (2003) Epidemiological situation of tuberculosis in India. Journal of the Indian Medical Association 101: 144-147.	Full text not available. Based on the abstract, article is a review of data reported elsewhere.
Chadha VK (2005) Tuberculosis epidemiology in India: a review. International Journal of Tuberculosis and Lung Disease 9: 1072-1082.	Review of TB in India including prevalence data reported in Gopi et al. (2003) and Murhekar et al. (2004).

S1 Table: Reasons for exclusion of studies with full-text review (n=65)

Reference	Reason for exclusion
Chakma T, Vinay Rao P, Pall S, Kaushal L, Datta M, et al. (1996) Survey of pulmonary tuberculosis in a primitive tribe of Madhya Pradesh. Indian Journal of Tuberculosis 43: 85-90.	Survey was conducted between 1991 and 1992 and is therefore ineligible.
Chakraborty AK, Suryanarayana HV, Murthy VV, Murthy MS, Shashidhara AN (1995) Prevalence of tuberculosis in a rural area by an alternative survey method without prior radiographic screening of the population. Tubercle and Lung Disease 76: 20-24.	Survey was conducted between 1984 and 1986 and is therefore ineligible.
Choko A, Chavula K, Thindwa D, Macpherson P, Mdolo A, et al. (2013) Periodic active case finding for tuberculosis in Blantyre Malawi: a follow-on experience from active case finding in Harare, Zimbabwe. International Journal of Tuberculosis and Lung Disease 17: S460.	Abstract describes ongoing active case finding rather than a survey conducted at a single point in time.
Choko A, Corbett E (2014) Characteristics of undiagnosed tuberculosis cases identified through periodic intensified case finding in Blantyre, Malawi. International Journal of Tuberculosis and Lung Disease 18: S333.	Abstract describes ongoing active case finding rather than a survey conducted at a single point in time.
Datiko DG, Lindtjørn B (2009) Health extension workers improve tuberculosis case detection and treatment success in southern Ethiopia: a community randomized trial. PloS One 4: e5443.	Article describes community health worker education aimed at improving participant presentation at health centres for TB screening, rather than community-level survey.
Datta M, Radhamani MP, Sadacharam K, Selvaraj R, Rao DL, et al. (2001) Survey for tuberculosis in a tribal population in North Arcot District. International Journal of Tuberculosis and Lung Disease 5: 240-249.	Survey was conducted in 1989 and is therefore ineligible.
Doocy SC, Todd CS, Llainez YB, Ahmadzai A, Burnham GM (2008) Population-based tuberculin skin testing and prevalence of tuberculosis infection in Afghanistan. World Health & Population 10: 44-53.	Article discusses prevalence of *Mtb* infection rather than prevalence of TB.
Dye C (2004) Epidemiology and control of tuberculosis in Malaysia: A provisional analysis of survey and surveillance data. Geneva, Switzerland: World Health Organization.	Report does not provide sufficient information on study methodology and results.
Elink Schuurman MW, Srisaenpang S, Pinitsoontorn S, Bijleveld I, Vaeteewoothacharn K, et al. (1996) The rapid village survey in tuberculosis control. Tubercle and Lung Disease 77: 549-554.	Date of survey is not reported, but article references Pinitsoontom et al. (1996) for additional detail on survey methodology. This article states that the survey was conducted between 1990 and 1991 and is therefore ineligible.
Fatima R, Qadeer E, Enarson D, Hinderaker S (2014) Active case finding: a much needed strategy to increase TB case detection in unreached areas. International Journal of Tuberculosis and Lung Disease 18: S379.	Abstract describes ongoing active case finding rather than a survey conducted at a single point in time.

S1 Table: Reasons for exclusion of studies with full-text review (n=65)

Reference	Reason for exclusion
Gopali R, Ishikawa N, Shimouchi A, Pant R (2013) Urban volunteers can play a vital role in identifying hidden tuberculosis cases in a slum population, Nepal. Int J Tuberc Lung Dis 17: S343.	Abstract describes ongoing enhanced case finding to promote attendance at health care facilities rather than a survey conducted at a single point in time.
Gopi P, Vallishayee R, Appe Gowda B, Paramasivan C, Ranganatha S, et al. (1997) A tuberculosis prevalence survey based on symptoms questioning and sputum examination. Indian Journal of Tuberculosis 44: 171-180.	Survey was conducted between 1988 and 1989 and is therefore ineligible.
Gopi PG, Subramani R, Narayanan PR (2008) Evaluation of different types of chest symptoms for diagnosing pulmonary tuberculosis cases in community surveys. Indian Journal of Tuberculosis 55: 116-121.	Analysis to examine case definitions used for screening in the 1999-2001 prevalence survey reported in Gopi et al. (2003) and in the 2001-2003 and 2004-2006 prevalence surveys reported in Kolappan et al. (2013).
Gopi PG, Subramani R, Sadacharam K, Narayanan PR (2006) Yield of pulmonary tuberculosis cases by employing two screening methods in a community survey. International Journal of Tuberculosis and Lung Disease 10: 343-345.	Analysis to examine screening methods used in the 1999-2001 prevalence survey reported in Gopi et al. (2003) and in the 2001-2003 prevalence survey reported in Kolappan et al. (2013).
Gopi PG, Subramani R, Santha T, Kumaran PP, Kumaraswami V, et al. (2006) Relationship of ARTI to incidence and prevalence of tuberculosis in a district of south India. International Journal of Tuberculosis and Lung Disease 10: 115-117.	Analysis to examine the relationship between prevalence and annual risk of *Mtb* infection using data from the 1999-2001 prevalence survey reported in Gopi et al. (2003) and the 2001-2003 prevalence survey reported in Kolappan et al. (2013).
Hill PC, Whalen CC (2015) Prevalence of tuberculosis in China. The Lancet 385: 773.	Commentary on results from 2010 prevalence survey reported in Wang et al. (2014).
Hoa NB, Tiemersma EW, Sy DN, Nhung NV, Gebhard A, et al. (2011) Household expenditure and tuberculosis prevalence in VietNam: prediction by a set of household indicators. International Journal of Tuberculosis and Lung Diseases 15: 32-37.	Analysis to examine the association between household expenditures and TB using data from the 2006 prevalence survey reported in Hoa et al. (2010).
Hoa NB, Tiemersma EW, Sy DN, Nhung NV, Vree M, et al. (2011) Health-seeking behaviour among adults with prolonged cough in Vietnam. Tropical Medicine and International Health 16: 1260-1267.	Analysis to examine health-seeking behaviour using data from the 2006 prevalence survey reported in Hoa et al. (2010).
Hong YP, Kim SJ, Lew WJ, Lee EK, Han YC (1998) The seventh nationwide tuberculosis prevalence survey in Korea, 1995. International Journal of Tuberculosis and Lung Disease 2: 27-36.	The Republic of Korea is a high-income country and therefore ineligible.
Hossain S, Huq N, Haque N, Gazi R, Iqbal M, et al. (2014) Active and semi-active case finding to increase tuberculosis case identification in rural Bangladesh: a cluster randomised trial. International Journal of Tuberculosis and Lung Disease 18: S353.	Article describes active or semi-active case finding conducted at 90-day intervals, rather than a survey conducted at a single time point, and is therefore ineligible.
International Institute for Population Sciences and ORC Macro (2000) India National Family Health Survey (NFHS-2) 1998-1999. Mumbai, India: International Institute for Population Sciences.	Survey reports self-reported TB rather than bacteriologically-confirmed TB.

S1 Table: Reasons for exclusion of studies with full-text review (n=65)

Reference	Reason for exclusion
International Institute for Population Sciences and Macro International (2007) India National Family Health Survey (NFHS-3) 2005-2006. Mumbai, India: International Institute for Population Sciences.	Survey reports self-reported TB rather than bacteriologically-confirmed TB.
Kapata N, Chanda-Kapata P, Ngosa W, Metitiri M, Klinkenberg E, et al. (2016) The prevalence of tuberculosis in Zambia: Results from the first national TB prevalence survey, 2013-2014. PLoS ONE 11 (1).	Duplicate report of the 2013-2014 prevalence survey reported in Ministry of Health – Zambia (2015).
Kebede AH, Alebachew Wagaw Z, Tsegaye F, Lemma E, Abebe A, et al. (2014) The first population-based national tuberculosis prevalence survey in Ethiopia, 2010-2011. International Journal of Tuberculosis and Lung Disease 18: 635-639.	Duplicate report of the 2010-2011 prevalence survey reported in Ministry of Health – Ethiopia (2011).
Khaint T, Naing K, Lwin T (2014) TB case finding using mobile team in two selected peri-urban townships of Yangon region. International Journal of Tuberculosis and Lung Disease 18: S459.	Abstract describes ongoing active case finding rather than a survey conducted at a single point in time.
Koenig SP, Rouzier V, Vilbrun SC, Morose W, Collins SE, et al. (2015) Tuberculosis in the aftermath of the 2010 earthquake in Haiti. Bulletin of the World Health Organization 93: 498-502.	Paper describes ongoing active case finding rather than a survey conducted at a single point in time.
Lorent N, Choun K, Thai S, Rigouts L, Lynen L (2014) Active tuberculosis screening of close contacts among the urban poor: A Cambodian experience. International Journal of Tuberculosis and Lung Disease 18: 1259-1260.	Report describes screening among contacts rather than within the general population.
Mahomed H, Ehrlich R, Hawkridge T, Hatherill M, Geiter L, et al. (2013) Screening for TB in high school adolescents in a high burden setting in South Africa. Tuberculosis 93: 357-362.	Study targets high school students rather than general adolescent population.
Ministry of Health - Thailand. National prevalence survey 2012-2013.	Report not available.
Ministry of Health - Ethiopia. National prevalence survey 2010-11.	Report not available.
Ministry of Health - Ghana. National prevalence survey 2013.	Report not available.
Ministry of Health - Sudan. National prevalence survey 2013-2014.	Report not available.
Narang P, Tyagi NK, Mendiratta DK, Jajoo UN, Bharambhe MS, et al. (1999) Prevalence of sputum-positive pulmonary tuberculosis in tribal and non-tribal populations of the Ashti and Karanja tahsils in Wardha district, Maharashtra State, India. International Journal of Tuberculosis and Lung Disease 3: 478-482.	Survey was conducted between 1989 and 1990 and is therefore ineligible.

S1 Table: Reasons for exclusion of studies with full-text review (n=65)

Reference	Reason for exclusion
Nguyen T, Marks G, Fox G, Nguyen V, Nguyen P, et al. (2014) Will centralised community screening or home-based visit result in high participation rate of TB screening among general population? Int J Tuberc Lung Dis 18: S458-459.	Abstract describes ongoing active case finding rather than a survey conducted at a single point in time.
Ogbudebe C, Chukwa J, Ekeke N, Meka A, Oshi D, et al. (2013) Reaching the underserved: active tuberculosis case finding among urban slum populations in south-east Nigeria. Int J Tuberc Lung Dis 17: S345.	Abstract describes ongoing active case finding rather than a survey conducted at a single point in time.
Okada K, Onozaki I, Yamada N, Yoshiyama T, Miura T, et al. (2012) Epidemiological impact of mass tuberculosis screening: a 2-year follow-up after a national prevalence survey. International Journal of Tuberculosis and Lung Disease 16: 1619-1624.	Article describes a follow-up study to the 2002 survey reported in Ministry of Health - Cambodia. The follow-up study does not assess TB prevalence.
Onozaki I, Law I, Sismanidis C, Zignol M, Glaziou P, et al. (2015) National tuberculosis prevalence surveys in Asia, 1990-2012: An overview of results and lessons learned. Tropical Medicine and International Health 20: 1128-1145.	Review of prevalence surveys including those described in Qadeer, Zaman (2012), Soemantri (2007), Ministry of Health – Myanmar (1994), Ministry of Health – Myanmar, Ministry of Heatlh – Cambodia (2005), Mao (2014), Wang (2014), Law (2015), Tupasi (1999), Tupasi (2009), Hoa (2010)
Onyango PN (2012) Prevalence of tuberculosis (TB) infection and disease among adolescents in western Kenya, in preparation for future TB vaccine trials. Tropical Medicine and International Health 17: 35-36.	Full text not available. Based on the abstract, article reports the same study described by Nduba et al. (2015).
Parija D, Patra T, Oeltmann J, Swain B, Satyanarayana S, et al. (2013) Innovative community-based approach to increase detection of sputum smear positive tuberculosis cases in the low case notification districts in Odisha, India. International Journal of Tuberculosis and Lung Disease 17: S144-145.	Abstract describes ongoing active case finding rather than a survey conducted at a single point in time.
Pe R, Choun K, Thai S, Lorent N, Van Griensven J (2014) Role of community TB officers for screening and improve TB case finding in the community. International Journal of Tuberculosis and Lung Disease 18: S463-464.	Abstract describes ongoing active case finding rather than a survey conducted at a single point in time.
Pretorius C, Bacaer N, Williams B, Wood R, Ouifki R (2009) On the relationship between age, annual rate of infection, and prevalence of mycobacterium tuberculosis in a South African township. Clinical Infectious Diseases 48: 994-996; author reply 996.	Article discusses prevalence of *Mtb* infection and annual risk of *Mtb* infection rather than prevalence of TB.
Rao VG, Gopi PG, Bhat J, Yadav R, Selvakumar N, et al. (2012) Selected risk factors associated with pulmonary tuberculosis among Saharia tribe of Madhya Pradesh, central India. European Journal of Public Health 22: 271-273.	Analysis to examine risk factors using data from the 2007-2008 survey reported in Rao et al. (2010).

S1 Table: Reasons for exclusion of studies with full-text review (n=65)

Reference	Reason for exclusion
Santha T, Renu G, Frieden TR, Subramani R, Gopi PG, et al. (2003) Are community surveys to detect tuberculosis in high prevalence areas useful? Results of a comparative study from Tiruvallur District, South India. International Journal of Tuberculosis and Lung Disease 7: 258-265.	Analysis to compare cases identified through passive case finding to those identified through the 1999-2001 prevalence survey reported in Gopi et al. (2003).
Sharma PP, Kumar A, Singh P (2010) A study of gender differentials in the prevalence of tuberculosis based on NFHS-2 and NFHS-3 data. Indian Journal of Community Medicine 35: 230-237.	Paper examines gender differences using data from the India National Family Health Survey 1998-1999 and the India National Family Health Survey 2005-2006, which include data on self-reported TB, but no clear measurement of bacteriologically-positive TB.
Subramani R, Radhakrishna S, Frieden TR, Kolappan C, Gopi PG, et al. (2008) Rapid decline in prevalence of pulmonary tuberculosis after DOTS implementation in a rural area of South India. International Journal of Tuberculosis and Lung Disease 12: 916-920.	Analysis of results from 2004-2006 prevalence survey reported in Kolappan et al. (2013).
Subramani R, Santha T, Frieden T, Radhakrishna S, Gopi P, et al. (2007) Active community surveillance of the impact of different tuberculosis control measures, Tiruvallur, South India, 1968-2001. International Journal of Epidemiology 36: 387-393.	Analysis of results from 2001-2003 prevalence survey reported in Kolappan et al. (2013).
Tadesse T, Demissie M, Berhane Y, Kebede Y, Abebe M (2013) The clustering of smear-positive tuberculosis in Dabat, Ethiopia: a population based cross sectional study. PLoS One 8: e65022.	Spatial analysis of results from 2010 prevalence survey reported in Tadesse et al. (2011).
Thein S, Nu G, Nishiyama H, Yamada N, Okada K, et al. (2014) Effectiveness of active-case detection using mobile team in selected township in Myanmar. International Journal of Tuberculosis and Lung Disease 18: S459-460.	Abstract describes ongoing active case finding rather than a survey conducted at a single point in time.
Tuberculosis Research Centre (2001) Trends in the prevalence and incidence of tuberculosis in south India. International Journal of Tuberculosis and Lung Disease 5: 142-157.	Time trend analysis of prevalence surveys conducted between 1968 and 1986.
van der Werf MJ, Sebhatu M, Borgdorff MW (2007) Evaluating tuberculosis case detection in Eritrea. Emerging Infectious Diseases 13: 1497-1499.	Analysis of case detection rate using data from the 2005 survey reported in Sebhatu et al. (2007).
Waako J, Verver S, Wajja A, Ssengooba W, Joloba ML, et al. (2013) Burden of tuberculosis disease among adolescents in a rural cohort in Eastern Uganda. BMC Infectious Diseases 13: 349.	Article describes ongoing active case finding rather than a survey conducted at a single point in time.
Wood R, Liang H, Wu H, Middelkoop K, Oni T, et al. (2010) Changing prevalence of tuberculosis infection with increasing age in high-burden townships in South Africa. International Journal of Tuberculosis and Lung Disease 14: 406-412.	Article discusses prevalence of *Mtb* infection and annual risk of *Mtb* infection rather than prevalence of TB.

S1 Table: Reasons for exclusion of studies with full-text review (n=65)

Reference	Reason for exclusion
Zaman K, Rahim Z, Yunus M, Arifeen S, Baqui A, et al. (2005) Drug resistance of Mycobacterium tuberculosis in selected urban and rural areas in Bangladesh. Scandinavian Journal of Infectious Diseases 37: 21-26.	Study of drug resistance among TB cases rather than TB among the general population.

S2 Table: Characteristics of included surveys (n=88) Survey country and year, setting, initial screening procedures, case definitions for smear-positive TB and bacteriologically-positive TB, number of participants ≥ 15 years and percent of participants who were male for all included surveys.

Survey country and year	Setting	Initial screening procedures	Case definition for smear-positive TB	Case definition for bacteriologically-positive TB	No. participants ≥ 15 years	% male participants	Ref.
AFRICAN REGION							
Eritrea, 2005	National	None (all participants undergo diagnostic procedures)	At least two smear-positive samples, or or at least one smear-positive sample and CXR consistent with active TB	At least two smear-positive samples, or or at least one smear-positive sample and CXR consistent with active TB	19 185	35.4%	[1]
Ethiopia, 2001	4 kebeles in Addis Ababa	Persistent cough, breathing difficulty or chest pain > 2 weeks	Smear-positive	Smear-positive	Not reported	Not reported	[2]
Ethiopia, 2003	Lemo district in Hadiya zone in Southern Nations, Nationalities and Peoples' region	Cough ≥ 2 weeks	Smear-positive	Smear-positive	872	49.8%	[3]
Ethiopia, 2008	Mecha district in West Gojam zone in Amhara region	Cough, chest pain or difficulty breathing > 2 weeks, as reported by head of household	Smear-positive	Smear-positive	47 478	Not reported	[4]
Ethiopia, 2009	10 kebeles in Gilgel Gibe in Jimma zone in Oromia region	Cough ≥ 2 weeks	Smear-positive	Culture-positive	27 597	49.7%	[5]
Ethiopia, 2010 (a)	Amibara district in Afar region	Cough ≥ 2 weeks	At least two smear-positive samples	Culture-positive	18 192	Not reported	[6]
Ethiopia, 2010 (b)	Dabat district in Amhara region	Cough > 2 weeks	Two smear-positive samples, one smear-positive sample with abnormal CXR or one smear-positive sample if HIV-positive	Two smear-positive samples, one smear-positive sample with abnormal CXR or one smear-positive sample if HIV-positive	Not reported	Not reported	[7]

CXR: chest x-ray; HIV: human immunodeficiency virus; MGIT: mycobacteria growth indicator tube; MOTT: mycobacteria other than tuberculosis; NAAT: nucleic acid amplification test; NTM: non-tuberculous mycobacteria; PTB: pulmonary tuberculosis; TB: tuberculosis; TST: tuberculin skin test

S2 Table: Characteristics of included surveys (n=88) Survey country and year, setting, initial screening procedures, case definitions for smear-positive TB and bacteriologically-positive TB, number of participants ≥ 15 years and percent of participants who were male for all included surveys.

Survey country and year	Setting	Initial screening procedures	Case definition for smear-positive TB	Case definition for bacteriologically-positive TB	No. participants ≥ 15 years	% male participants	Ref.
Ethiopia, 2010-2011	National	Cough ≥ 2 weeks or abnormal CXR	One smear-positive sample and one culture-positive sample	One culture-positive sample with at least one smear-positive or culture-positive sample or abnormal CXR	46 697	46.7%	[8]
Ethiopia, 2011	16 districts in Tigray region	Cough ≥ 2 weeks	Smear-positive	Smear- and/or culture-positive pooled sample	12 175	44.4%	[9]
Ethiopia, 2011-2012	Dale district in Sidama zone in Southern Nations, Nationalities and Peoples' region	Cough ≥ 2 weeks	At least one smear-positive sample	At least one smear-positive sample	Not reported	Not reported	[10]
Ethiopia, unknown year	Hetosa district in Oromiya region	Cough > 2 weeks	Smear-positive	Culture-positive	33 073	Not reported	[11]
Gambia, 2011-2013	National	Cough ≥ 2 weeks, or cough < 2 weeks with at least two of the following: chest pain, night sweats, shortness of breath, loss of appetite, weight loss, or any three of the following: chest pain, night sweats, shortness of breath, loss of appetite, weight loss	One smear-positive sample and one culture-positive sample	One culture-positive sample and at least one of the following: a second culture-positive sample, a smear-positive sample, CXR abnormalities suggestive of TB	43 100	40.6%	[12]

CXR: chest x-ray; HIV: human immunodeficiency virus; MGIT: mycobacteria growth indicator tube; MOTT: mycobacteria other than tuberculosis; NAAT: nucleic acid amplification test; NTM: non-tuberculous mycobacteria; PTB: pulmonary tuberculosis; TB: tuberculosis; TST: tuberculin skin test

S2 Table: Characteristics of included surveys (n=88) Survey country and year, setting, initial screening procedures, case definitions for smear-positive TB and bacteriologically-positive TB, number of participants ≥ 15 years and percent of participants who were male for all included surveys.

Survey country and year	Setting	Initial screening procedures	Case definition for smear-positive TB	Case definition for bacteriologically-positive TB	No. participants ≥ 15 years	% male participants	Ref.
Guinea-Bissau, 2006-2007 (a)	6 suburban districts in Bissau	Cough, haemoptysis or two other symptoms (expectorate, breathlessness, chest pain, fever, night sweats, fatigue, weight loss, loss of appetite) with clinical evaluation OR any 1 symptom with clinical evaluation if HIV-positive	At least two smear-positive samples	At least two smear-positive samples	2 989	44.0%	[13]
Guinea-Bissau, 2006-2007 (b)	6 suburban districts in Bissau	Cough, haemoptysis or two other symptoms (expectorate, breathlessness, chest pain, fever, night sweats, fatigue, weight loss, loss of appetite) with clinical evaluation OR any 1 symptom with clinical evaluation if HIV-positive	At least two smear-positive samples	At least two smear-positive samples	571	42.2%	[13]
Kenya, 2006-2007	Asembo area of Rarieda district and Gem district in Nyanza province	None (all participants undergo diagnostic procedures)	Two smear-positive samples (without culture for MOTT), or one smear-positive sample and one culture-positive sample	One culture-positive sample, or two smear-positive samples (without culture for MOTT)	20 710	37.0%	[14]
Kenya, 2008-2009	Karemo division in Siaya district in Nyanza province	Cough ≥ 2 weeks, weight loss ≥ 2 weeks, fever ≥ 2 weeks, night sweats ≥ 2 weeks, hemoptysis, household contact with known TB case within 2 years or positive TST	Undefined	At least two smear-positive samples and/or one culture-positive sample	2 195	Not reported	[15]

CXR: chest x-ray; HIV: human immunodeficiency virus; MGIT: mycobacteria growth indicator tube; MOTT: mycobacteria other than tuberculosis; NAAT: nucleic acid amplification test; NTM: non-tuberculous mycobacteria; PTB: pulmonary tuberculosis; TB: tuberculosis; TST: tuberculin skin test

S2 Table: Characteristics of included surveys (n=88) Survey country and year, setting, initial screening procedures, case definitions for smear-positive TB and bacteriologically-positive TB, number of participants ≥ 15 years and percent of participants who were male for all included surveys.

Survey country and year	Setting	Initial screening procedures	Case definition for smear-positive TB	Case definition for bacteriologically-positive TB	No. participants ≥ 15 years	% male participants	Ref.
Malawi, 2013-2014	National	Cough ≥ 2 weeks or abnormal CXR	Smear-positive	Xpert MTB/RIF- or culture-positive	31 579	Not reported	[16]
Nigeria, 2011-2012	Nomadic communities in Adamawa state	"Symptomatic checklist"	Smear-positive	Smear-positive and/or Xpert MTB/RIF-positive	Not reported	Not reported	[17]
Nigeria, 2012	National	Cough ≥ 2 weeks or abnormal CXR	Smear-positive	Smear- and/or culture-positive	44 186	41.1%	[18]
Nigeria, 2013-2014	3 local government areas	"Symptomatic TB"	Undefined	n/a	Not reported	Not reported	[19]
Rwanda, 2012	National	Cough, abnormal CXR, or refused CXR	One smear-positive sample and at least one of the following: a culture-positive sample, another smear-positive sample, abnormal CXR	One culture-positive sample and at least one of the following: a second culture-positive sample, a smear-positive sample, CXR abnormalities suggestive of TB	43 779	42.3%	[20]
South Africa, 1999	Agincourt sub-district in Bushbuckridge region in Limpopo province	Cough ≥ 3 weeks	Smear-positive	Smear-positive	Not reported	Not reported	[21]
South Africa, 2002	2 urban communities in Cape Town	None (all participants undergo diagnostic procedures)	Not used in study	At least one smear-positive and/or one culture-positive sample	2 608	40.5%	[22]
South Africa, 2005 (a)	2 urban communities in Cape Town	None (all participants undergo diagnostic procedures)	One smear-positive sample and one culture-positive sample	One culture-positive sample	6 262	39.3%	[23]

CXR: chest x-ray; HIV: human immunodeficiency virus; MGIT: mycobacteria growth indicator tube; MOTT: mycobacteria other than tuberculosis; NAAT: nucleic acid amplification test; NTM: non-tuberculous mycobacteria; PTB: pulmonary tuberculosis; TB: tuberculosis; TST: tuberculin skin test

S2 Table: Characteristics of included surveys (n=88) Survey country and year, setting, initial screening procedures, case definitions for smear-positive TB and bacteriologically-positive TB, number of participants ≥ 15 years and percent of participants who were male for all included surveys.

Survey country and year	Setting	Initial screening procedures	Case definition for smear-positive TB	Case definition for bacteriologically-positive TB	No. participants ≥ 15 years	% male participants	Ref.
South Africa, 2005 (b)	High-density residential area	None (all participants undergo diagnostic procedures)	Two smear-positive samples, or one smear-positive and one culture-positive sample	Two smear-positive samples, one smear-positive and one culture-positive sample or two culture-positive samples with identical spoligotype patterns	762	44.6%	[24]
South Africa, 2008	High-density residential area	None (all participants undergo diagnostic procedures)	One smear-positive sample with a second smear-positive or a culture-positive sample	Two smear-positive samples, or two culture-positive samples, or one smear-positive sample with a separate culture-positive sample	1 250	51.8%	[25]
South Africa, 2010	Enumeration areas	None (all participants undergo diagnostic procedures)	Not used in study	One culture-positive sample	30 017	Not reported	[26]
Tanzania, 2011-2012	National	Cough > 2 weeks, haemoptysis, fever > 2 weeks, weight loss, excessive sweating or abnormal CXR	At least two smear-positive samples, or one smear-positive sample with abnormal CXR	One culture-positive sample and/or at least two smear-positive samples, or one smear-positive sample with abnormal CXR	50 436	41.1%	[27]
Uganda, 2001-2002	Kawempe division of Kampala	Haemoptysis within 3 weeks or 2 other symptoms (cough ≥ 2 weeks, weight loss, loss of appetite, swelling of glands, night fevers, night sweats) within 3 weeks	Not used in study	Culture-positive	Not reported	Not reported	[28]
Uganda, 2005	Kisenyi slum in Kampala	"Chronic cough"	At least two smear-positive samples	At least two smear-positive samples	930	32.8%	[29]

CXR: chest x-ray; HIV: human immunodeficiency virus; MGIT: mycobacteria growth indicator tube; MOTT: mycobacteria other than tuberculosis; NAAT: nucleic acid amplification test; NTM: non-tuberculous mycobacteria; PTB: pulmonary tuberculosis; TB: tuberculosis; TST: tuberculin skin test

S2 Table: Characteristics of included surveys (n=88) Survey country and year, setting, initial screening procedures, case definitions for smear-positive TB and bacteriologically-positive TB, number of participants ≥ 15 years and percent of participants who were male for all included surveys.

Survey country and year	Setting	Initial screening procedures	Case definition for smear-positive TB	Case definition for bacteriologically-positive TB	No. participants ≥ 15 years	% male participants	Ref.
Uganda, 2008-2009	Rubaga community in Kampala	Cough ≥ 2 weeks	Not used in study	At least one smear- and/or culture-positive sample	5 102	24.2%	[30]
Zambia, 2005	2 wards of Lusaka	None (all participants undergo diagnostic procedures)	Not used in study	One culture-positive sample with at least one smear-positive or another culture-positive sample	8 043	46.1%	[31]
Zambia, 2010	Enumeration areas	None (all participants undergo diagnostic procedures)	Not used in study	One culture-positive sample	34 446	Not reported	[26]
Zambia, 2013-2014	National	Cough ≥ 2 weeks, fever ≥ 2 weeks, chest pain ≥ 2 weeks, abnormal CXR or indeterminate CXR	At least one smear-positive sample confirmed by culture and/or Xpert MTB/RIF	Smear-positive and/or MGIT culture-positive	40 189	42.2%	[32]
Zimbabwe, 2006	46 neighbourhoods in Harare	None (all participants undergo diagnostic procedures)	Not used in study	One culture-positive sample with positive culture or radiological or progressive clinical disease with response to TB treatment (or only one culture-positive if died before follow-up)	10 235	39.3%	[33]
Zimbabwe, 2008	46 neighbourhoods in Harare	None (all participants undergo diagnostic procedures)	Not used in study	One culture-positive sample with positive culture or radiological or progressive clinical disease with response to TB treatment (or only one culture-positive if died before follow-up)	11 211	36.8%	[34]

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S2 Table: Characteristics of included surveys (n=88) Survey country and year, setting, initial screening procedures, case definitions for smear-positive TB and bacteriologically-positive TB, number of participants ≥ 15 years and percent of participants who were male for all included surveys.

Survey country and year	Setting	Initial screening procedures	Case definition for smear-positive TB	Case definition for bacteriologically-positive TB	No. participants ≥ 15 years	% male participants	Ref.
REGION OF THE AMERICAS							
Brazil, 2003	Suruí indigenous community in Rondônia state	Cough ≥ 3 weeks with fever and/or weight loss or weakness, or household contacts of known TB cases	Smear-positive	Culture-positive	106	49.1%	[35]
Brazil, 2006	Xavante indigenous community in Mato Grosso state	Fever, prolonged cough, weight loss, chest pain and/or enlarged lymph nodes	Smear-positive	Smear- and/or culture-positive	Not reported	Not reported	[36]
Ecuador, 2001	Indigenous community in Cotopaxi province	Cough > 2 weeks	Smear-positive	Smear-positive	335	49.0%	[37]
EASTERN MEDITERRANEAN REGION							
Jordan, 2005	Balqa governorate in Central region and Ma'an and Karak governorates in South region	Cough ≥ 3 weeks	One smear-positive sample	One smear-positive sample	61 730	Not reported	[38]
Pakistan, 1996	Shimshal Valley in Gilgit-Baltistan region	Cough ≥ 3 weeks, history of haemoptysis, history of TB or close contact with TB patient	One smear-positive sample	One smear-positive sample	213	Not reported	[39]
Pakistan, 2002	2 low-income peri-urban neighbourhoods of Karachi	Productive cough ≥ 2 weeks	At least one smear-positive sample	At least one smear-positive and/or culture-positive sample	5 479	46.6%	[40]

CXR: chest x-ray; HIV: human immunodeficiency virus; MGIT: mycobacteria growth indicator tube; MOTT: mycobacteria other than tuberculosis; NAAT: nucleic acid amplification test; NTM: non-tuberculous mycobacteria; PTB: pulmonary tuberculosis; TB: tuberculosis; TST: tuberculin skin test

S2 Table: Characteristics of included surveys (n=88) Survey country and year, setting, initial screening procedures, case definitions for smear-positive TB and bacteriologically-positive TB, number of participants ≥ 15 years and percent of participants who were male for all included surveys.

Survey country and year	Setting	Initial screening procedures	Case definition for smear-positive TB	Case definition for bacteriologically-positive TB	No. participants ≥ 15 years	% male participants	Ref.
Pakistan, 2010-2011	National	Cough ≥ 2 weeks, abnormal CXR, current TB treatment or cough of any duration without CXR results	Two smear-positive samples but no culture-positive or NAAT-positive sample, or one smear-positive sample and CXR consistent with TB but no culture-positive or NAAT-positive, or one positive smear with culture-positive or NAAT-positive result	Culture-positive with ≥ 5 colonies, culture-positive with < 5 colonies with at least one smear-positive or abnormal CXR, or smear-positive with NAAT- or Xpert MTB/RIF-positive and no isolation of NTM	105 853	42.3%	[41]
SOUTH-EAST ASIA REGION							
Bangladesh, 2001 (a)	23 sub-districts	Cough ≥ 3 weeks	At least two smear-positive samples or at least one smear-positive sample with ≥ 4 bacilli per 100 fields	At least two smear-positive samples or at least one smear-positive sample with ≥ 4 bacilli per 100 fields	236 920	51.1%	[42]
Bangladesh, 2001 (b)	Matlab in Chandpur district in Chittagong division	Cough > 3 weeks	Two smear-positive samples or one smear-positive sample with abnormal CXR	Two smear-positive samples or one smear-positive sample with abnormal CXR	59 395	42.9%	[43]
Bangladesh, 2007-2009	National	None (all participants undergo diagnostic procedures)	Two smear-positive samples or one smear-positive sample with abnormal CXR	Two smear-positive samples or one smear-positive sample with abnormal CXR	52 098	46.5%	[44]

CXR: chest x-ray; HIV: human immunodeficiency virus; MGIT: mycobacteria growth indicator tube; MOTT: mycobacteria other than tuberculosis; NAAT: nucleic acid amplification test; NTM: non-tuberculous mycobacteria; PTB: pulmonary tuberculosis; TB: tuberculosis; TST: tuberculin skin test

S2 Table: Characteristics of included surveys (n=88) Survey country and year, setting, initial screening procedures, case definitions for smear-positive TB and bacteriologically-positive TB, number of participants ≥ 15 years and percent of participants who were male for all included surveys.

Survey country and year	Setting	Initial screening procedures	Case definition for smear-positive TB	Case definition for bacteriologically-positive TB	No. participants ≥ 15 years	% male participants	Ref.
Bangladesh, 2009-2010	1 section of Mirpur slum in Dhaka	Cough ≥ 3 weeks or BMI ≤ 17 kg/m2	One smear-positive sample with a second smear-positive sample, a culture-positive sample or CXR with abnormalities consistent with TB	One smear-positive sample with a second smear-positive sample, a culture-positive sample or CXR with abnormalities consistent with TB	9 873	42.4%	[45]
India, 1999-2001	5 blocks in Tiruvallur district in Tamil Nadu state	"Chest symptoms" or abnormal CXR	One smear-positive sample	One culture-positive sample	83 390	49.0%	[46]
India, 2001-2002	Car Nicobar tribal district in Andaman and Nicobar Islands territory	Cough, chest pain, unexplained fever ≥ 2 weeks or haemoptysis	Smear-positive	Smear-positive	10 570	Not reported	[47]
India, 2001-2003	5 blocks in Tiruvallur district in Tamil Nadu state	"Chest symptoms", abnormal CXR or known TB cases from previous surveys	Smear-positive	Culture-positive	85 474	48.7%	[48]
India, 2004-2006	5 blocks in Tiruvallur district in Tamil Nadu state	"Chest symptoms", abnormal CXR or known TB cases from previous surveys	Smear-positive	Culture-positive	89 413	48.6%	[48]
India, 2006-2008	5 blocks in Tiruvallur district in Tamil Nadu state	"Chest symptoms", abnormal CXR or known TB cases from previous surveys	Smear-positive	Culture-positive	92 255	48.8%	[48]
India, 2007-2008 (a)	Tribal population in Madhya Pradesh state	Cough ≥ 2 weeks, chest pain ≥ 1 month, fever ≥ 1 month, haemoptysis or history of TB treatment	Smear-positive	Smear- and/or culture-positive	22 270	48.6%	[49]

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S2 Table: Characteristics of included surveys (n=88) Survey country and year, setting, initial screening procedures, case definitions for smear-positive TB and bacteriologically-positive TB, number of participants ≥ 15 years and percent of participants who were male for all included surveys.

Survey country and year	Setting	Initial screening procedures	Case definition for smear-positive TB	Case definition for bacteriologically-positive TB	No. participants ≥ 15 years	% male participants	Ref.
India, 2007-2008 (b)	Saharia tribe in Karhal block in Sheopur district in Madhya Pradesh state	Cough ≥ 2 weeks, haemoptysis, chest pain ≥ 1 month, fever ≥ 1 month, of all individuals or history of TB treatment	Not used in study	Smear- and/or culture-positive	11 116	47.9%	[50]
India, 2008 (a)	Bharia tribal villages in Chhindwara District in Madhya Pradesh state	"Chest symptoms"	Not used in study	At least one smear- and/or culture-positive sample	Not reported	Not reported	[51]
India, 2008 (b)	Baiga Chak tribal community in Madhya Pradesh state	"Symptoms suggestive of PTB"	Smear-positive	Smear- and/or culture-positive	1 374	Not reported	[52]
India, 2008-2009	Faridabad district in Haryana state	Cough ≥ 2 weeks, fever ≥ 1 month, chest pain ≥ 1 month, haemoptysis within 6 months or history of TB treatment	At least one smear-positive sample	At least one smear-positive sample and/or undefined culture-positive	98 599	51.3%	[53]
India, 2008-2010 (a)	Sahibzada Ajit Singh Nagar in Mohali district in Punjab state	Cough ≥ 2 weeks, haemoptysis within 6 months, chest pain ≥ 1 month, fever ≥ 1 month or history of TB treatment	At least one smear-positive sample	At least one smear-positive and/or culture-positive sample	85 770	50.7%	[54]
India, 2008-2010 (b)	Nelamangala in Bangalore rural district in Karnataka state	Cough for ≥ 2 weeks, fever ≥ 1 month, chest pain ≥ 1 month, haemoptysis within 6 months, history of TB treatment or abnormal CXR (Note: CXR only available in 6 clusters)	At least one smear-positive sample	At least one smear-positive and/or culture-positive sample	63 362	47.0%	[55]

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S2 Table: Characteristics of included surveys (n=88) Survey country and year, setting, initial screening procedures, case definitions for smear-positive TB and bacteriologically-positive TB, number of participants ≥ 15 years and percent of participants who were male for all included surveys.

Survey country and year	Setting	Initial screening procedures	Case definition for smear-positive TB	Case definition for bacteriologically-positive TB	No. participants ≥ 15 years	% male participants	Ref.
India, 2008-2010 (c)	6 districts in Arunachal Pradesh state and 2 districts in Assam state	Cough ≥ 1 week	At least one smear-positive sample	At least one smear-positive sample	Not reported	Not reported	[56]
India, 2009-2010	Jabalpur district in Madhya Pradesh state	Cough ≥ 2 weeks, chest pain ≥ 1 month, fever ≥ 1 month, haemoptysis within 6 months or history of TB treatment	Smear-positive	At least one smear- and/or culture-positive sample	95 071	50.6%	[57]
India, 2010-2012	100 wards in Chennai	"Chest symptoms" or abnormal CXR	At least one smear-positive sample	At least one smear-positive and/or culture-positive sample	55 617	48.4%	[58]
India, 2012-13	3 districts in Chhattisgarh state and 4 districts in Madhya Pradesh state	Cough > 2 weeks	Undefined	Undefined	93 825	Not reported	[59]
India, 2013	Sonepat district in Haryana state and Banda district in Uttar Pradesh state	Cough > 2 weeks	Smear-positive	Undefined	Not reported	Not reported	[60]
India, 2014	4 urban slums in Thiruvananthapuram in Kerala	Cough ≥ 2 weeks or haemoptysis	Smear-positive	Smear-positive	Not reported	Not reported	[61]
India, unknown year	7 villages in block R.S. Pura in Jammu district in Jammu and Kashmir state	Cough, fever or chest pain ≥ 2 weeks	Sputum-positive	Sputum-positive	5 000	53.8%	[62]
Indonesia, 2004	National	Productive cough within 1 month	At least two smear-positive samples	At least two smear-positive samples	50 154	48.4%	[63]
Indonesia, 2013-2014	National	"TB symptoms" or abnormal CXR	Smear-positive	Bacteriologically-positive	67 915	Not reported	[64]

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S2 Table: Characteristics of included surveys (n=88) Survey country and year, setting, initial screening procedures, case definitions for smear-positive TB and bacteriologically-positive TB, number of participants ≥ 15 years and percent of participants who were male for all included surveys.

Survey country and year	Setting	Initial screening procedures	Case definition for smear-positive TB	Case definition for bacteriologically-positive TB	No. participants ≥ 15 years	% male participants	Ref.
Myanmar, 1994-1995	National	Cough ≥ 2 weeks	At least two smear-positive samples	At least two smear-positive samples	25 178	44.8%	[65]
Myanmar, 2009-2010	National	Cough ≥ 3 weeks, haemoptysis or abnormal CXR	Two sputum smear-positive sample, or one smear-positive sample with CXR consistent with active TB or with a culture-positive sample	Two smear-negative samples with at least one culture-positive sample, two sputum smear-positive sample, or one smear-positive sample with CXR consistent with active TB or with a culture-positive sample	51 367	43.6%	[66]
Nepal, 2002	Ward 13 in Mahendra Nagar municipality of Kanchanpur district in Mahakali zone	Cough ≥ 2 weeks, chest pain, fever or haemoptysis	Smear-positive	Smear-positive	70	57.1%	[67]
WESTERN PACIFIC REGION							
Cambodia, 2002	National	Cough ≥ 3 weeks, haemoptysis or abnormal CXR	Two positive smear results, or one positive smear result with an X-ray result consistent with active tuberculosis, or one positive smear slide with a culture confirmation	Two smear results were negative with at least 1 culture confirmation of *M. tuberculosis* excluding the following cases: two positive smear results, or one positive smear result with an X-ray result consistent with active tuberculosis, or one positive smear slide with a culture confirmation	17 641	44.7%	[68]

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Survey country and year	Setting	Initial screening procedures	Case definition for smear-positive TB	Case definition for bacteriologically-positive TB	No. participants ≥ 15 years	% male participants	Ref.
Cambodia, 2010-2011	National	Cough ≥ 2 weeks, haemoptysis or abnormal CXR	Two smear-positive samples and a culture-negative for MOTT, or one smear-positive sample with one culture-positive or CXR consistent with tuberculosis	Smear-negative with at least one culture-positive for five or more colonies, or smear-negative with one culture-positive for four or fewer colonies and CXR consistent with TB, or two smear-positive samples and a culture-negative for MOTT, or one smear-positive sample with one culture-positive or CXR consistent with TB	37 417	45.5%	[69]
Cambodia, 2012-2013	"Poor urban settlements of Phnom Penh"	Cough, unintentional weight loss, fever or night sweats or haemoptysis	At least one smear-positive sample	At least one smear-positive, culture-positive or Xpert MTB/RIF-positive sample	253 094	Not reported	[70]
China, 2000	National	Cough ≥ 2 weeks, haemoptysis, abnormal CXR or previous TB diagnosis AND pregnant women or persons with restricted mobility not examined by CXR	At least one smear-positive sample	At least one smear-positive or culture-positive sample	Not reported	Not reported	[71]
China, 2010 (a)	National	Cough ≥ 2 weeks, haemoptysis, abnormal CXR or previous TB diagnosis AND pregnant women or persons with restricted mobility not examined by CXR	At least one smear-positive sample	At least one smear-positive or culture-positive sample	252 940	Not reported	[71]

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S2 Table: Characteristics of included surveys (n=88) Survey country and year, setting, initial screening procedures, case definitions for smear-positive TB and bacteriologically-positive TB, number of participants ≥ 15 years and percent of participants who were male for all included surveys.

Survey country and year	Setting	Initial screening procedures	Case definition for smear-positive TB	Case definition for bacteriologically-positive TB	No. participants ≥ 15 years	% male participants	Ref.
China, 2010 (b)	Shandong province	Cough ≥ 2 weeks, haemoptysis, fever, weight loss or abnormal CXR	Smear-positive	Smear- and/or culture-positive	54 279	46.8%	[72]
China, unknown year	6 villages in Yunnan province	None (all participants undergo diagnostic procedures)	Smear-positive	Smear-positive	9 305	49.6%	[73]
Lao PDR, 2010-2011	National	Cough ≥ 2 weeks within 1 month, haemoptysis within 1 month or abnormal CXR	At least one smear-positive sample with one culture-positive sample or CXR consistent with TB	Two positive cultures, or one positive culture with greater than four colonies with CXR consistent with TB, or one positive culture with greater than four colonies, or one positive culture less than five colonies with CXR consistent with TB, or at least one smear-positive sample with one culture-positive sample, or CXR consistent with TB	39 212	45.2%	[74]
Papua New Guinea, unknown year	Usino Bundi district in Madang province and Alotau district in Milne Bay province	"Chronic cough"	Smear-positive	Smear-positive	5 038	Not reported	[75]
Philippines, 1997 (a)	National	Abnormal CXR	Smear-positive	Culture-positive	Not reported	Not reported	[76]
Philippines, 1997 (b)	Manila, Cebu and Cagayan de Oro	Abnormal CXR	Smear-positive	Culture-positive	Not reported	Not reported	[77]

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S2 Table: Characteristics of included surveys (n=88) Survey country and year, setting, initial screening procedures, case definitions for smear-positive TB and bacteriologically-positive TB, number of participants ≥ 15 years and percent of participants who were male for all included surveys.

Survey country and year	Setting	Initial screening procedures	Case definition for smear-positive TB	Case definition for bacteriologically-positive TB	No. participants ≥ 15 years	% male participants	Ref.
Philippines, 2007	National	Cough ≥ 2 weeks and/or haemoptysis	At least two smear-positive samples, or at least one smear-positive sample with abnormal CXR	At least one culture-positive sample, or at least two smear-positive samples, or at least one smear-positive sample with abnormal CXR	Not reported	Not reported	[78]
Viet Nam, 2000	Bavi district in Hà Tây province	Cough ≥ 3 weeks	At least two smear-positive samples, or at least one smear-positive sample with abnormal CXR	At least two smear-positive samples, or at least one smear-positive sample with abnormal CXR	35 832	46.7%	[79]
Viet Nam, 2003	12 districts in Tây Nguyên region	Cough ≥ 3 weeks	At least two smear-positive sputum samples	At least two smear-positive sputum samples	68 944	50.5%	[80]
Viet Nam, 2004-2005	20 communes in Hanoi	"Symptoms such as cough ≥ 3 weeks, sputum or fever" or abnormal CXR	Smear-positive	Smear- and/or culture-positive	10 818	40.1%	[81]
Viet Nam, 2006-2007	National	Productive cough ≥ 2 weeks, abnormal CXR, current TB treatment, history of TB treatment within 2 years	At least two smear-positive samples, or one smear-positive sample with abnormal CXR or a positive culture	One culture-positive sample, or at least two smear-positive samples, or one smear-positive sample with abnormal CXR	94 179	45.3%	[82]
Viet Nam, unknown year	Cà Mau region	None (all participants undergo diagnostic procedures)	Not used in study	Xpert MTB/RIF-positive	39 403	Not reported	[83]

CXR: chest x-ray; HIV: human immunodeficiency virus; MGIT: mycobacteria growth indicator tube; MOTT: mycobacteria other than tuberculosis; NAAT: nucleic acid amplification test; NTM: non-tuberculous mycobacteria; PTB: pulmonary tuberculosis; TB: tuberculosis; TST: tuberculin skin test

S3 Table: Male and female prevalence of bacteriologically-positive TB (n=56) and smear-positive TB (n=40) per 100,000 Random-effects weighted prevalence estimates are shown for each region and overall. 95% confidence intervals are included in parentheses.

Survey country and year	Prevalence of bacteriologically-positive TB (95% CI) Male	Female	Prevalence of smear-positive TB (95% CI) Male	Female
AFRICAN REGION	597 (384-928)	365 (226-589)	364 (244-545)	185 (112-306)
Eritrea, 2005	103 (41-212)	65 (28-127)	103 (41-212)	65 (28-127)
Ethiopia, 2003	1382 (509-2985)	1598 (645-3265)	1382 (509-2985)	1598 (645-3265)
Ethiopia, 2009	51 (21-105)	72 (35-132)	-	-
Ethiopia, 2010-2011	119 (78-175)	84 (52-129)	257 (194-333)	217 (163-283)
Ethiopia, 2011	352 (212-549)	162 (81-290)	-	-
Gambia, 2011-2013	291 (217-383)	102 (66-149)	137 (88-204)	39 (19-72)
Guinea-Bissau, 2006-2007 (a)	0 (0-280)	0 (0-220)	0 (0-280)	119 (14-431)
Guinea-Bissau, 2006-2007 (b)	0 (0-1519)	0 (0-1112)	0 (0-1519)	0 (0-1112)
Kenya, 2006-2007	758 (576-978)	498 (384-634)	300 (191-450)	214 (143-310)
Nigeria, 2012	473 (379-584)	223 (169-288)	363 (281-462)	158 (113-214)
Rwanda, 2012	211 (150-288)	51 (27-88)	140 (92-206)	24 (9-52)
South Africa, 2005 (a)	3050 (2406-3808)	1867 (1461-2349)	-	-
South Africa, 2005 (b)	1176 (321-2985)	1896 (822-3701)	588 (71-2109)	237 (6-1313)
South Africa, 2008	926 (341-2004)	498 (103-1449)	309 (37-1110)	0 (0-611)
South Africa, 2010	2948 (2644-3276)	1971 (1777-2181)	-	-
Tanzania, 2011-2012	434 (349-533)	199 (151-256)	323 (251-410)	108 (74-152)
Uganda, 2005	5246 (3028-8379)	2720 (1592-4319)	5246 (3028-8379)	2720 (1592-4319)
Uganda, 2008-2009	1378 (805-2197)	569 (357-860)	-	-
Zambia, 2005	1051 (749-1435)	923 (660-1255)	-	-
Zambia, 2010	791 (638-969)	438 (357-533)	-	-
Zambia, 2013-2014	831 (700-979)	487 (401-585)	448 (353-560)	220 (164-289)
Zimbabwe, 2006	771 (524-1092)	563 (393-783)	572 (363-857)	274 (159-438)
Zimbabwe, 2008	557 (354-835)	305 (191-461)	291 (150-507)	180 (96-308)
REGION OF THE AMERICAS	8461 (5394-13032)	8379 (2366-25660)	9146 (5589-14617)	13450 (9104-19428)
Brazil, 2003	5769 (1206-15947)	3704 (452-12747)	-	-
Ecuador, 2001	9146 (5210-14637)	13450 (8721-19496)	9146 (5210-14637)	13450 (8721-19496)
EASTERN MEDITERRANEAN REGION	368 (317-427)	247 (211-289)	-	-
Pakistan, 2002	431 (215-770)	239 (96-492)	-	-
Pakistan, 2010-2011	364 (310-424)	247 (209-290)	-	-
SOUTH-EAST ASIA REGION	375 (260-540)	112 (73-170)	311 (215-449)	77 (54-110)
Bangladesh, 2001 (a)	40 (29-53)	14 (8-22)	40 (29-53)	14 (8-22)
Bangladesh, 2001 (b)	165 (119-223)	29 (14-54)	165 (119-223)	29 (14-54)
Bangladesh, 2007-2009	99 (64-148)	32 (15-61)	99 (64-148)	32 (15-61)
Bangladesh, 2009-2010	382 (218-619)	158 (72-300)	382 (218-619)	158 (72-300)
India, 1999-2001	1053 (956-1156)	202 (162-250)	575 (504-653)	106 (77-142)
India, 2001-2003	663 (588-746)	155 (120-196)	397 (338-462)	71 (48-100)
India, 2004-2006	469 (407-538)	107 (79-141)	251 (206-302)	59 (39-86)
India, 2006-2008	613 (543-690)	118 (90-154)	282 (235-336)	59 (39-86)
India, 2007-2008 (a)	526 (399-681)	227 (149-333)	-	-
India, 2007-2008 (b)	2124 (1753-2548)	915 (686-1195)	-	-
India, 2008-2009	138 (108-175)	63 (42-89)	-	-
India, 2008-2010 (a)	34 (19-57)	14 (5-31)	-	-
India, 2008-2010 (b)	312 (252-383)	51 (29-81)	-	-
India, 2009-2010	353 (302-411)	109 (81-143)	239 (197-287)	70 (48-99)
India, 2010-2012	501 (420-593)	122 (85-170)	338 (272-415)	70 (43-108)

S3 Table: Male and female prevalence of bacteriologically-positive TB (n=56) and smear-positive TB (n=40) per 100,000 Random-effects weighted prevalence estimates are shown for each region and overall. 95% confidence intervals are included in parentheses.

Survey country and year	Prevalence of bacteriologically-positive TB (95% CI)		Prevalence of smear-positive TB (95% CI)	
	Male	Female	Male	Female
India, unknown year	297 (128-585)	87 (10-313)	297 (128-585)	87 (10-313)
Indonesia, 2004	210 (156-276)	112 (75-161)	210 (156-276)	112 (75-161)
Myanmar, 1994-1995	240 (158-348)	79 (39-141)	240 (158-348)	79 (39-141)
Myanmar, 2009-2010	920 (799-1054)	362 (297-439)	393 (315-484)	121 (84-168)
Nepal, 2002	17500 (7338-32779)	6667 (818-22074)	22500 (10840-38451)	6667 (818-22074)
WESTERN PACIFIC REGION	330 (184-591)	181 (88-372)	160 (91-279)	89 (52-153)
Cambodia, 2002	1916 (1624-2243)	1189 (983-1424)	698 (526-907)	236 (149-353)
Cambodia, 2010-2011	1105 (954-1274)	617 (515-735)	365 (280-467)	201 (144-272)
China, 2010 (b)	39 (19-72)	31 (14-59)	20 (6-46)	21 (8-45)
China, unknown year	1626 (1281-2034)	554 (362-811)	-	-
Lao PDR, 2010-2011	885 (753-1034)	373 (296-463)	423 (333-530)	149 (102-210)
Viet Nam, 2000	60 (29-110)	79 (44-130)	60 (29-110)	79 (44-130)
Viet Nam, 2003	26 (12-49)	18 (6-38)	26 (12-49)	18 (6-38)
Viet Nam, 2004-2005	230 (111-423)	185 (96-323)	161 (65-332)	185 (96-323)
Viet Nam, 2006-2007	497 (432-568)	111 (84-143)	333 (280-392)	62 (42-88)
OVERALL SUMMARY	**488 (382-623)**	**231 (166-321)**	**314 (245-403)**	**129 (89-189)**

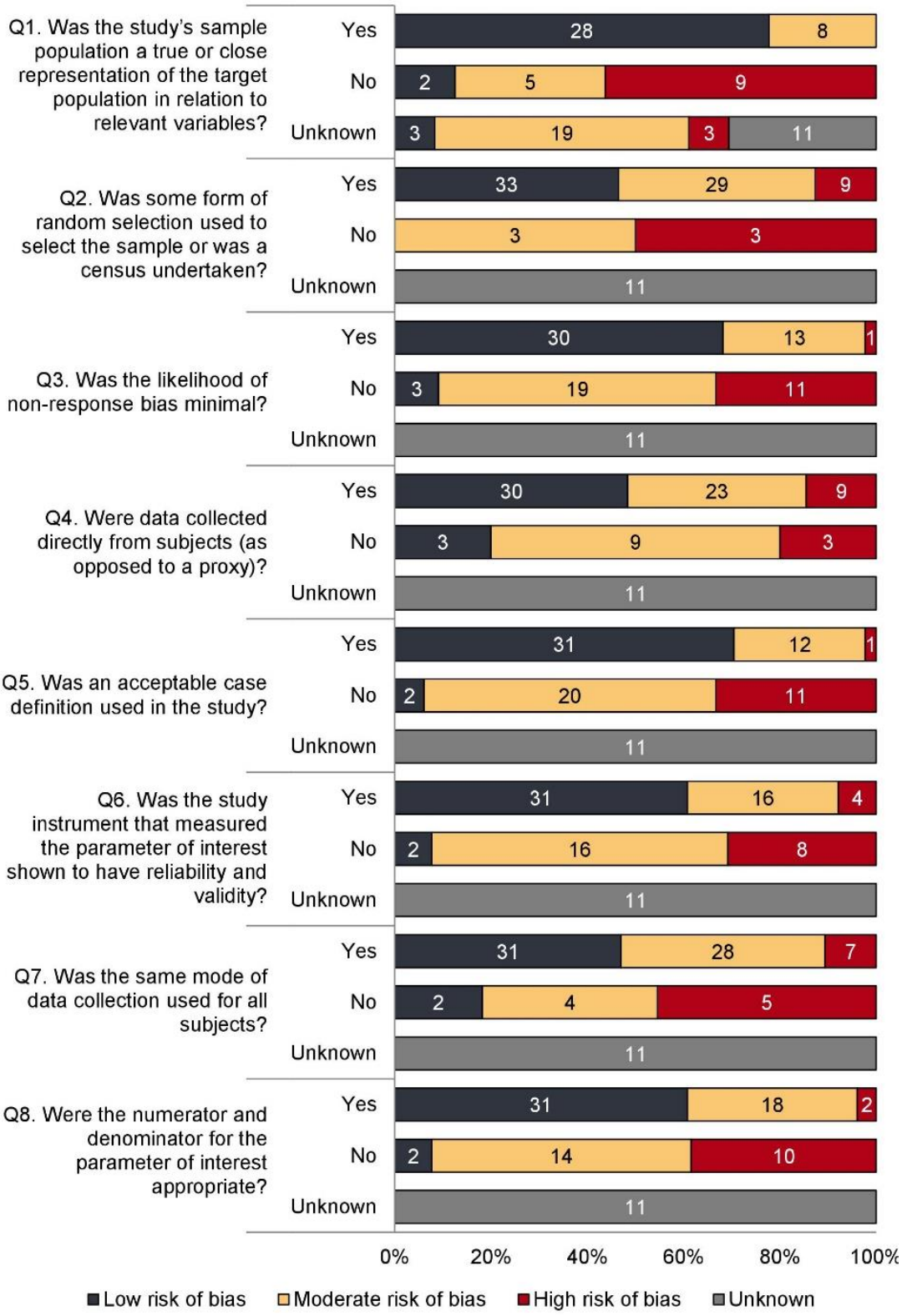
S4 Table: Subgroup analysis of male and female prevalence of bacteriologically-positive TB and smear-positive TB Random-effects weighted prevalence shown for each subgroup. 95% confidence intervals are included in parentheses. P-values indicate differences within subgroups.

	Bacteriologically-positive TB (95% CI)					Smear-positive TB (95% CI)				
	N	Male prevalence	p-value	Female prevalence	p-value	N	Male prevalence	p-value	Female prevalence	p-value
WHO region			<0.001		<0.001			<0.001		<0.001
AFR	23	597 (384-928)		365 (226-589)		16	364 (244-545)		185 (112-306)	
AMR	2	8461 (5394-13032)		8379 (2366-25660)		1	9146 (5589-14617)		13450 (9104-19428)	
EMR	2	368 (317-427)		247 (211-289)		0	n/a		n/a	
SEAR	20	375 (260-540)		112 (73-170)		15	311 (215-449)		77 (54-110)	
WPR	9	330 (184-591)		181 (88-372)		8	160 (91-279)		89 (52-153)	
Setting			0.210		0.221			0.308		0.295
National	40	536 (386-744)		261 (164-414)		15	275 (220-344)		105 (78-141)	
Sub-national	16	395 (278-560)		177 (117-267)		25	350 (233-524)		155 (80-301)	
TB prevalence			0.192		0.342			0.434		0.572
High	32	546 (402-742)		265 (178-395)		24	289 (212-393)		118 (80-176)	
Low	22	399 (279-571)		190 (110-330)		15	361 (226-576)		154 (68-350)	
HIV prevalence in general population			<0.001		<0.001			0.039		0.036
High	13	1162 (735-1834)		735 (448-1202)		8	548 (303-990)		273 (131-568)	
Low	41	360 (275-471)		157 (110-223)		31	275 (208-364)		110 (71-169)	
HIV prevalence in incident TB			0.001		<0.001			0.060		0.040
High	18	907 (582-1413)		553 (341-896)		13	459 (289-727)		229 (126-416)	
Low	36	359 (270-477)		153 (105-224)		26	270 (200-366)		103 (64-165)	
Risk of bias			0.686		0.931			0.112		0.235
Low	29	457 (336-621)		225 (151-335)		21	263 (209-329)		104 (80-135)	
Moderate or high	26	508 (337-764)		232 (126-428)		19	428 (247-713)		184 (74-454)	
Initial screening procedures			0.134		0.443			0.954		0.504
Requires self-report of signs/symptoms	20	331 (164-666)		179 (73-437)		16	308 (126-750)		169 (52-549)	
Broader criteria	36	585 (453-754)		261 (182-375)		24	316 (269-372)		112 (88-142)	
Case definition			0.810		0.533			0.853		0.472
Smear microscopy	17	524 (323-849)		288 (152-544)		13	307 (178-527)		176 (67-458)	
Other diagnostic measures	36	488 (356-669)		226 (150-340)		24	326 (235-450)		120 (80-180)	
Relative male participation			0.063		0.075			0.083		0.068
Low (M:F ratio < 0.90)	8	679 (441-1043)		331 (187-585)		6	700 (239-2037)		234 (104-527)	
High (M:F ratio ≥ 0.90)	21	403 (286-567)		178 (122-259)		16	264 (206-338)		105 (79-139)	

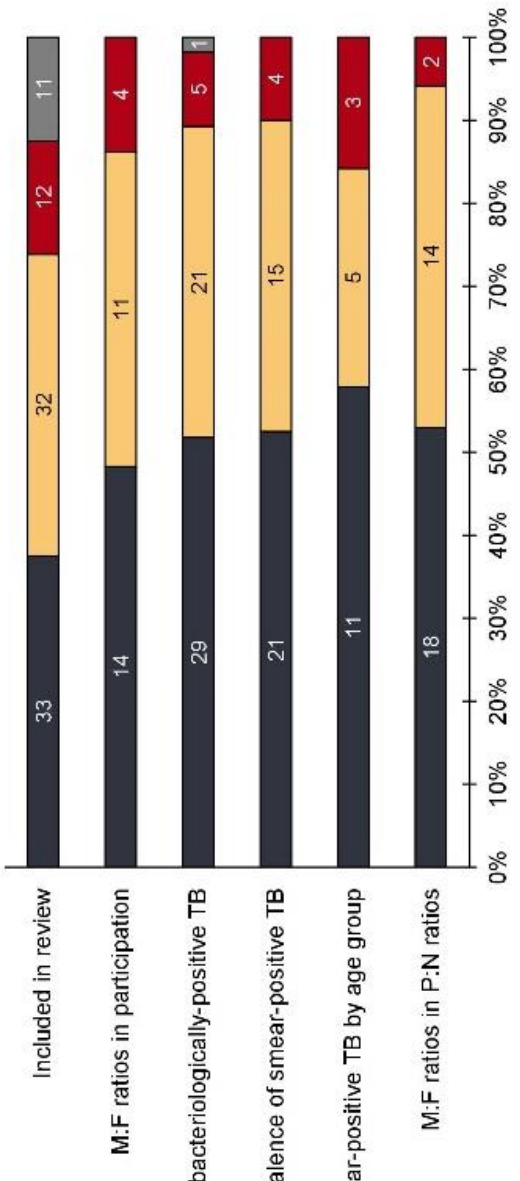
S5 Table: Univariate random-effects meta-regression results for M:F ratios in P:N ratios (n=33)

	Relative M:F ratio (95% CI)	p-value
AMR vs. AFR	0.44 (0.10-1.87)	0.267
SEAR vs. AFR	1.44 (0.86-2.35)	0.141
WPR vs. AFR	0.97 (0.52-1.81)	0.927
National vs. sub-national	0.95 (0.62-1.44)	0.794
Survey starting year	0.98 (0.93-1.03)	0.460
High vs. low TB prevalence	1.23 (0.80-1.90)	0.344
High vs. low HIV prevalence in general population	0.90 (0.49-1.68)	0.751
High vs. low HIV prevalence in incident TB	0.92 (0.55-1.54)	0.746
Low vs. moderate or high risk of bias	1.03 (0.66-1.59)	0.905
Initial screening procedures requiring self-report of signs/symptoms vs. broader initial screening procedures	0.62 (0.37-1.06)	0.080
Diagnosis by smear microscopy vs. other diagnostic measures	0.95 (0.60-1.52)	0.832
Low vs. high relative male participation	1.01 (0.50-2.02)	0.979

S1 Figure: Distribution of overall risk of bias by response to each assessment criteria Labels within each bar indicate the number of studies with each classification of overall risk of bias.



S2 Figure: Distribution of overall risk of bias for each analysis Labels in each bar indicate the number of studies with each classification of overall risk of bias.



Appendix B Web appendix for Chapter 4 manuscript "A Bayesian approach to understanding sex differences in tuberculosis disease burden"

Web Appendix 1: Priors

All priors, model estimates and data on which priors are based are summarised at the end of this section in Web Table 4 and Web Table 5.

Disease incidence rate

Disease incidence estimates were calculated from World Health Organization (WHO) tuberculosis (TB) country profile estimates of the number of incident cases in men and women ≥ 15 years of age in 2015 [1] combined with 2015 national population estimate for individuals ≥ 15 years of age from the United Nations World Population Prospect [2,3]. Although we would have preferred to match the year of disease incidence estimates to that of other data sources (e.g., prevalence, case notification rate), 2015 was the only year for which gender-specific incidence estimates were available from WHO. Similarly, only overall disease incidence estimates for all forms of TB were available, rather than estimates for smear-positive TB alone.

Overall TB disease estimates are derived from prevalence survey results, combined with estimates of disease duration. To calculate gender-specific disease incidence, WHO applies the male-to-female (M:F) ratio in case notifications to overall disease incidence estimates, assuming no gender differential in detection of incident cases and acknowledging that the proportion of disease incidence among men is likely underestimated due to this assumption [4].

In Viet Nam, there were an estimated 88,000 (95% CI 67,000-109,000) incident cases of TB among men and 28,000 (95% CI 10,000-46,000) incident cases among women in 2015 [1]. Given 2015 population estimates of 34,964,611 men and 36,906,231 women [2,3], the corresponding disease incidence rate is estimated at 252 (95% CI 192-312) per 100,000 men and 76 (95% CI 27-125) per 100,000 women. Overall estimates suggest there were 116,000 (95% CI 101,000-131,000) total incident cases of TB in 2015 [1], which corresponds to an overall disease incidence rate of 161 (95% CI 141-182) per 100,000 population.

In Malawi, there were an estimated 18,000 (95% CI 11,000-25,000) incident cases of TB among men and 11,000 (95% CI 2,700-19,000) incident cases among women in 2015 [1]. Given population estimates of 4,679,650 men and 4,761,703 women [2,3], the corresponding disease incidence rate is estimated at 385 (95% CI 235-534) per 100,000 men and 231 (95% CI 57-399) per 100,000 women. Overall estimates suggest there were 29,000 (95% CI 19,000-39,000) total incident cases of TB in 2015 [1], which corresponds to an overall disease incidence rate of 307 (95% CI 201-413) per 100,000 population.

Disease incidence estimates were fitted to log-normal distributions with the middle 95% of probabilities falling within the 95% confidence interval.

Treatment access rate

A literature review was conducted to identify studies describing the progression of smear-positive TB patients through the TB care pathway. Studies conducted in Viet Nam or Malawi were identified through searches of PubMed, Embase, Global Health and the Cochrane Library using standardised search terms (Web Table 1). Searches were last updated 26 April 2017.

Web Table 1: Database search terms

Database	Country	
	Viet Nam	Malawi
PubMed	viet* AND ("chronic cough" OR tubercul*) AND (seek* OR access* OR utilis* OR utiliz* OR delay* OR los* OR default* OR adher* OR complet* OR outcome)	malawi* AND ("chronic cough" OR tubercul*) AND (seek* OR access* OR utilis* OR utiliz* OR delay* OR los* OR default* OR adher* OR complet* OR outcome)
Embase/ Global Health	(viet* and ("chronic cough" or tubercul*) and (seek* or access* or utilis* or utiliz* or delay* or los* or default* or adher* or complet* or outcome)).af	(malawi* and ("chronic cough" or tubercul*) and (seek* or access* or utilis* or utiliz* or delay* or los* or default* or adher* or complet* or outcome)).af
Cochrane	(viet* and ("chronic cough" or tubercul*) and (seek* or access* or utilis* or utiliz* or delay* or los* or default* or adher* or complet* or outcome)) in Title, Abstract, Keywords in Trials	(malawi* and ("chronic cough" or tubercul*) and (seek* or access* or utilis* or utiliz* or delay* or los* or default* or adher* or complet* or outcome)) in Title, Abstract, Keywords in Trials

For Viet Nam, 377 records were screened by title and abstract; 19 full-text articles were assessed for eligibility; 10 relevant studies were identified, of which four reported results by gender [5-8].

For Malawi, 452 records were screened by title and abstract; 48 full-text articles were assessed for eligibility; 18 relevant studies were identified, of which five reported results by gender [9-13].

Studies reporting results by gender were evaluated for their ability to form a complete path from onset of symptoms to treatment access (alone or in combination with data from another study) and whether reported results included estimates of uncertainty in addition to point estimates. Selected studies are described below. Studies reporting results by gender but not selected for inclusion are described in Web Table 2.

Web Table 2: Studies reporting results by gender but not included in final prior estimates

Viet Nam			
Study description	Results	Reason for exclusion	Reference
National survey of 4381 TB suspects (2006-07)	Mean time from onset of cough to first attendance at a health care facility was 4.4 weeks (95% CI 4.1-4.7) for men and 3.6 (95% CI 3.3-4.0) weeks for women.	Cannot be combined with another data source to form complete path from onset to treatment access.	Hoa 2011 [5]

Outpatient survey of 1027 TB patients in 23 districts in four provinces (1996)	Mean time from symptom onset to TB diagnosis was 13.3 weeks (95% CI 11.5-15.1) for women and 11.4 weeks (95% CI 10.6-12.2) for men.	Cannot be combined with another data source to form complete path from onset to treatment access.	Long 1999 [6]
Community-based survey of 492 chronic coughers in Ha Tay province (pre-2000)	Mean time from onset of symptoms to hospital treatment was longer for women (41 days) than men (19 days).	Cannot be combined with another data source to form complete path from onset to treatment access.	Thorson 2000 [7]
Malawi			
Study description	Results	Reason for exclusion	Reference
Outpatient survey of 290 men and 257 women with TB in six districts in three regions (pre-2006)	Mean time from symptom onset to sputum examination was 58.1 days for men and 64.6 days for women. No difference between men and women.	No estimate of uncertainty around mean reported.	Weiss 2006 [9]
Appx. 100 TB patients in Lilongwe (pre-2008)	58% of men and 42% of women diagnosed within 30 days of symptom onset; 18% of men and 30% of women diagnosed after delay of more than 90 days.	Cannot be combined with another data source to form complete path from onset to treatment access.	Gosoniu 2008 [10]
Interview of 598 TB patients in Karonga district (1996-2001)	Median duration from onset of cough to treatment access was appx. 2 months. No difference between men and women.	Results shown graphically but not reported numerically for men and women.	Crampin 2004 [11]
Comparison of programme registers in rural Ntcheu district (2000)	Appx. 15% of men and women lost to follow-up between diagnosis and treatment access.	Results report proportion progressing through care pathway rather than duration of progression.	Squire 2005 [12]

Appx.: approximately; CI: confidence interval

In Viet Nam, a cross-sectional survey of consecutively-enrolled new TB patients treated by the National TB Control Programme in 70 randomly selected districts in one quarter of 2002 stated that men (n=1491) reported a median of 4 (inter-quartile range, IQR, 3-8) weeks interval from cough onset to treatment access, while women (n=596) reported a median of 5 (IQR 4-9) weeks interval [8]. Among all study participants (n=2093), the median reported time from cough onset to treatment access was 4 (IQR 3-8) weeks [8].

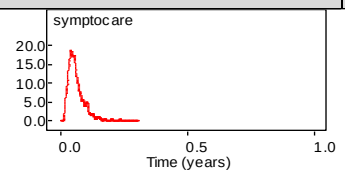
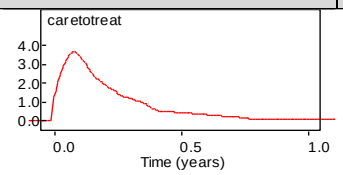
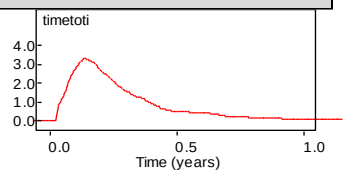
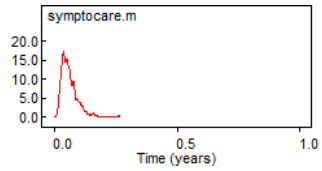
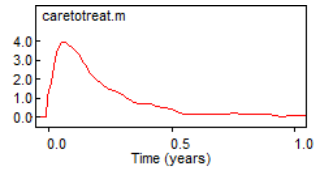
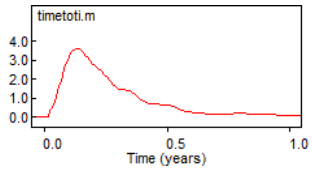
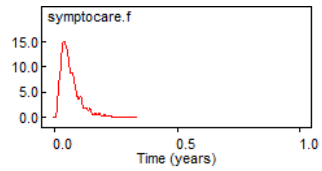
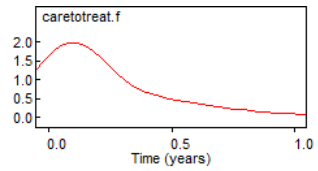
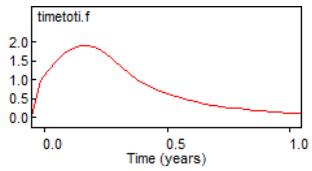
In Malawi, a cross-sectional survey of 588 pulmonary TB patients conducted in three TB centres in Blantyre, Lilongwe, and Mzuzu between July and December 2011 stated that men (n=304) reported a median of 14 (IQR 14-28) days from onset of TB symptoms to visiting any healthcare provider; men then reported a median of 59 (IQR 28-99) days from visiting any healthcare provider to initiating treatment [13]. Women (n=156) reported a median of 21 (IQR 14-30) days from onset of TB symptoms to visiting any healthcare provider and a median of 64 (IQR 24-125) days from visiting any healthcare provider to initiating treatment [13]. Among all

study participants (n=460), the median reported time from onset of TB symptoms to visiting any healthcare provider was 14 (IQR 14-28) days, and the median reported time from visiting any healthcare provider to initiating treatment was 59 (IQR 27-108) days [13].

For each time interval of interest, data reported in days or weeks were converted to years (assuming 52 weeks or 365 days in a year) and fitted to a log-normal distribution with the middle 50% of probabilities falling within the IQR.

In Malawi, log-normal distributions for estimates of time from onset of TB symptoms to visiting any healthcare provider and time from visiting any healthcare provider to initiating treatment were summed to give a log-normal distribution of time from onset of TB symptoms to treatment access. The derivation of priors for self-reported symptom duration prior to treatment in Malawi is shown in Web Table 3.

Web Table 3: Derivation of priors for self-reported symptom duration prior to treatment based on self-reports in Malawi

Gender	A. Time from symptom onset to visiting any healthcare provider	B. Time from visiting any care provider to treatment access	C. Time from symptom onset to treatment access (A+B)
M & F			
M			
F			

M: male; F: female

Self-cure rate

The annual self-cure rate was taken from previous studies modelling TB transmission that have assumed this rate to be between 0.15 and 0.25 [14-16]. A log-normal distribution was fitted to these data assuming the middle 50% of probabilities fall between 0.15 and 0.25. The range

assumed by previous studies was treated as an IQR in fitting to reflect uncertainty around estimates for self-cure rate.

Untreated-TB mortality rate

Annual untreated-TB mortality rate estimates combine background mortality in the population and excess untreated-TB mortality attributable to smear-positive TB.

Background mortality was based on 2015 WHO estimates of life expectancy at birth, 71.3 years for men (annual rate of 0.014) and 80.7 years for women (annual rate of 0.012) in Viet Nam and 59.9 years for men (annual rate of 0.017) and 56.7 years for women (annual rate of 0.018) in Malawi [17]. Excess mortality for untreated smear-positive TB has been assumed between 0.20 and 0.40 in previous modelling studies [14-16].

A log-normal distribution was fitted to the sum of these rates assuming the middle 50% of probabilities between 0.21 and 0.41 for Viet Nam and the middle 50% of probabilities between 0.22 and 0.42 for Malawi. Ranges were treated as IQRs in fitting to reflect uncertainty around estimates for excess untreated smear-positive TB mortality rate.

Web Table 4: Data, model estimates and prior distributions for Viet Nam

Viet Nam					
Parameter	Gender	Data estimate (95% CI or range or IQR)	Model median (95% CrI)	Distribution in WinBUGS
Incidence rate (annual per 100,000*)	M & F	161 (95% CI 141-182)	161 (95% CrI 141-183)	dlnorm(-6.4365422,235.8498345)
	M	252 (95% CI 192-312)	245 (95% CrI 192-312)	dlnorm(-6.0126762,65.1874099)
	F	76 (95% CI 27-125)	58 (95% CrI 27-125)	dlnorm(-7.4508502,6.5428704)
Untreated disease duration (years)	M & F	0.08 (IQR 0.06-0.15)	0.09 (95% CrI 0.02-0.40 IQR 0.05-0.15)	dlnorm(-2.4474648,1.6973627)
	M	0.08 (IQR 0.06-0.15)	0.09 (95% CrI 0.02-0.40 IQR 0.05-0.15)	dlnorm(-2.4474648,1.6973627)
	F	0.10 (IQR 0.08-0.17)	0.11 (95% CrI 0.03-0.38 IQR 0.07-0.16)	dlnorm(-2.2355818,2.4323685)
Self-cure rate (annual)	M & F	0.20 (range 0.15-0.25)	0.19 (95% CrI 0.09-0.41 IQR 0.15-0.26)	dlnorm(-1.6417072,6.973734)
Untreated-TB mortality rate (annual)	M & F	0.31 (range 0.21-0.41)	0.29 (95% CrI 0.11-0.77 IQR 0.20-0.39)	dlnorm(-1.2261229,4.065313436)

M: male; F: female; CI: confidence interval; CrI: credible interval; IQR: inter-quartile range; Untreated disease duration: inverse of treatment initiation rate
* Modelled as proportion but shown as number per 100,000 population

Web Table 5: Data, model estimates and prior distributions for Malawi

Malawi					
Parameter	Gender	Data estimate (95% CI or range or IQR)	Model median (95% CrI)	Distribution in WinBUGS
Incidence rate (annual per 100,000*)	M & F	307 (95% CI 201-413)	288 (95% CrI 200-410)	dlnorm(-5.8495492,29.6291428)
	M	385 (95% CI 235-534)	354 (95% CrI 234-533)	dlnorm(-5.6429348,22.8071247)
	F	231 (95% CI 57-399)	152 (95% CrI 57-401)	dlnorm(-6.4969191,4.0579866)
Untreated disease duration (years)	M & F	0.04 (IQR 0.04-0.08) + 0.16 (0.07-0.30)	0.22 (95% 0.06-1.25 IQR 0.14-0.37)	dlnorm(-2.914242,3.788399) + dlnorm(-1.872126,0.937561)
	M	0.04 (IQR 0.04-0.08) + 0.16 (IQR 0.08-0.27)	0.22 (95% 0.07-1.03 IQR 0.15-0.36)	dlnorm(-2.914242,3.788399) + dlnorm(-1.8864809,1.117929)
	F	0.06 (IQR 0.04-0.08) + 0.18 (IQR 0.07-0.34)	0.23 (95% 0.06-1.86 IQR 0.14-0.45)	dlnorm(-2.8690639,3.124268) + dlnorm(-1.828793,0.653974)
Self-cure rate (annual)	M & F	0.20 (range 0.15-0.25)	0.19 (95% CrI 0.09-0.41 IQR 0.15-0.25)	dlnorm(-1.6417072,6.973734)
Untreated-TB mortality rate (annual)	M & F	0.32 (range 0.22-0.42)	0.30 (95% CrI 0.12-0.78 IQR 0.22-0.43)	dlnorm(-1.1908142,4.352139601)

M: male; F: female; CI: confidence interval; CrI: credible interval; IQR: inter-quartile range; Untreated disease duration: inverse of treatment initiation rate
* Modelled as proportion but shown as number per 100,000 population

Web Appendix 2: Data

Data for prevalence and case notification rates are summarised at the end of this section in Web Table 6.

Prevalence

Prevalence estimates for smear-positive TB were taken from the most recent national prevalence survey conducted in each country. Weighted estimates were used to account for stratification by area, differential population growth prior to the survey and different cluster sizes.

In Viet Nam, a 2006-07 national prevalence survey reported weighted prevalence estimates for smear-positive TB of 351 (95% CI 262-440) per 100,000 men and 69 (95% CI 39-99) per 100,000 women [18]. Treating uncertainty estimates as confidence intervals for a population mean, these data are approximated in the model by 59 cases per 16,809 male population and 20 cases per 28,986 female population, with a corresponding M:F ratio of 5.09 (95% CI 3.61-7.41).

In Malawi, a 2013-14 national prevalence survey reported weighted prevalence estimates for smear-positive TB of 303 (95% CI 176-431) per 100,000 men and 149 (95% CI 85-213) per 100,000 women [19]. Treating uncertainty estimates as confidence intervals for a population mean, these data are approximated in the model by 21 cases per 6,931 male population and 21 cases per 14,094 female population, with a corresponding M:F ratio of 2.03 (95% CI 1.33-1.59).

The normal approximation to the binomial distribution was used to estimate the number of prevalent cases based on calculated prevalence and prevalence survey participants.

Case notification rate

Case notification counts for new cases of smear-positive TB in individuals ≥ 15 years of age were taken from data routinely reported by National TB Programmes to WHO [20]. These data were matched to the nearest five-year national population estimate for individuals ≥ 15 years of age from the United Nations World Population Prospect [2,3] to calculate annual case notification rates by gender.

In Viet Nam, the average number of annual case notifications reported over 2006-07 (the years of the prevalence survey) was 40,668 for men and 14,672 for women. The nearest population estimates from 2005 report a male population of 29,742,533 and a female population of 31,595,138. This gives a case notification rate (with confidence intervals ± 10% of the point estimate) of 137 (95% CI 123-151) per 100,000 men and 47 (95% CI 42-52) per 100,000 women. Treating uncertainty estimates as confidence intervals for a population mean, these data

are approximated in the model by 350 cases in a male population of 255,474 and 300 cases in a female population of 638,298, with a corresponding M:F ratio of 2.92 (95% CI 2.61-3.26).

In Malawi, the average number of annual case notifications over 2011-12 (the last years in which case notifications for smear-positive TB were reported by gender) was 3,992 for men and 2,849 for women. The nearest population estimates from 2010 report a male population of 3,932,713 and a female population of 4,015,137. This gives a case notification rate (with confidence intervals ± 10% of the point estimate) of 102 (95% CI 91-112) per 100,000 men and 71 (95% CI 64-78) per 100,000 women. Treating uncertainty estimates as confidence intervals for a population mean, these data are approximated in the model by 400 cases in a male population of 392,157 and 400 cases in a female population of 563,380, with a corresponding M:F ratio of 2.03 (95% CI 1.30-1.59).

The normal approximation to the binomial distribution was used to estimate the number of notified cases based on calculated case notification rate and population.

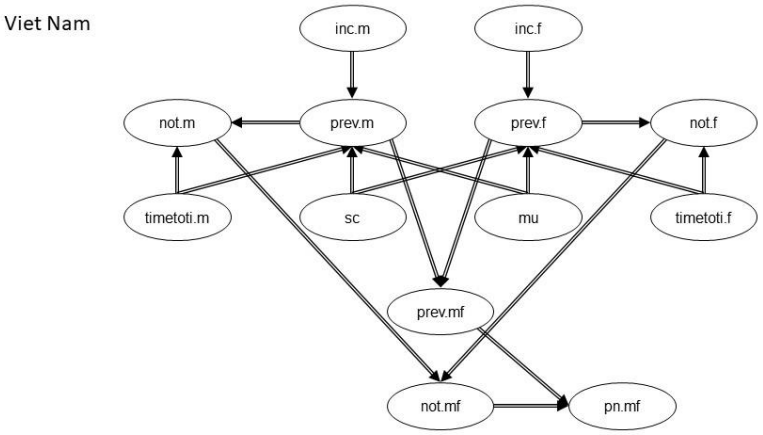
Web Table 6: Data for prevalence and case notification rates for Viet Nam and Malawi

Viet Nam			
Parameter	Gender	Data estimate (95% CI)	Data used in model numerator / denominator
Prevalence (per 100,000*)	M	351 (262-440)	59 / 16,809
	F	69 (39-99)	20 / 28,986
	M:F	5.09 (3.61-7.41)	-
Case notification rate (per 100,000*)	M	137 (123-151)	350 / 255,474
	F	47 (42-52)	300 / 638,298
	M:F	2.03 (1.33-1.59)	-
Malawi			
Parameter	Gender	Data estimate (95% CI)	Data used in model numerator / denominator
Prevalence (per 100,000*)	M	303 (176-431)	21 / 6,931
	F	149 (85-213)	21 / 14,094
	M:F	2.92 (2.61-3.26)	-
Case notification rate (per 100,000*)	M	102 (91-112)	400 / 392,157
	F	71 (64-78)	400 / 563,380
	M:F	2.03 (1.30-1.59)	-

M: male; F: female; M:F: male-to-female ratio
* Modelled as proportion but shown as number per 100,000 population

Web Appendix 3: Directed Acyclic Graphs

Model structure and corresponding equations are shown below in Web Figure 1 and Web Figure 2.

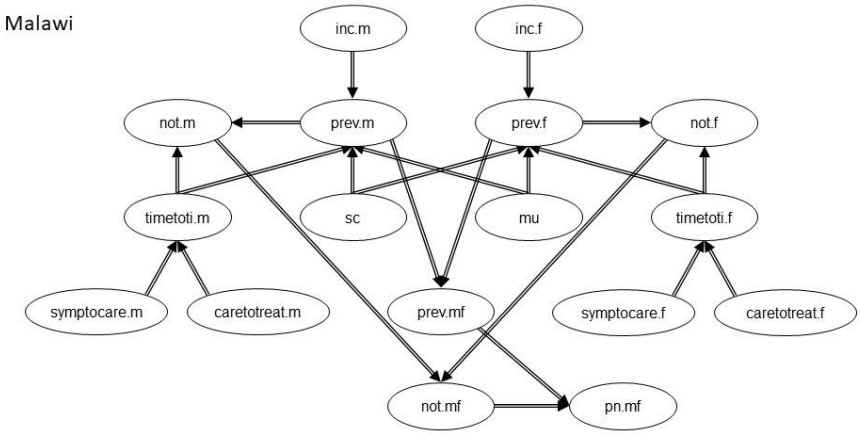


inc.m ~ dlnorm(-6.0126762,65.1874099)
inc.f ~ dlnorm(-7.4508502,6.5428704)
timetoti.m ~ dlnorm(-2.4474648,1.6973627)
timetoti.f ~ dlnorm(-2.2355818,2.4323685)
sc ~ dlnorm(-1.6417072,6.973734)
mu ~ dlnorm(-1.2261229,4.065313436)

prev.m = inc.m/((1/timetoti.m)+sc+mu)
prev.f = inc.f/((1/timetoti.f)+sc+mu)
not.m = (1/timetoti.m)*prev.m
not.f = (1/timetoti.f)*prev.f

prev.mf = prev.m/prev.f
not.mf = not.m/not.f
pn.mf = prev.mf/not.mf

Web Figure 1: Directed acyclic graph with corresponding equations for Viet Nam



inc.m ~ dlnorm(-5.6429348,22.8071247)
inc.f ~ dlnorm(-6.4969191,4.0579866)
symptocare.m ~ dlnorm(-2.914242,3.788399)
caretotreat.m ~ dlnorm(-1.8864809,1.117929)
timetoti.m = symptocare.m + caretotreat.m
symptocare.f ~ dlnorm(-2.8690639,3.124268)
caretotreat.f ~ dlnorm(-1.828793,0.653974)
timetoti.f = symptocare.f + caretotreat.f
sc ~ dlnorm(-1.6417072,6.973734)
mu ~ dlnorm(-1.1908142,4.352139601)

prev.m = inc.m/((1/timetoti.m)+sc+mu)
prev.f = inc.f/((1/timetoti.f)+sc+mu)
not.m = (1/timetoti.m)*prev.m
not.f = (1/timetoti.f)*prev.f

prev.mf = prev.m/prev.f
not.mf = not.m/not.f
pn.mf = prev.mf/not.mf

Web Figure 2: Directed acyclic graph with corresponding equations for Malawi

Web Appendix 4: Code

The model is run using R [21], which calls WinBUGS [22] and associated data files. All files used in the main analysis and in sensitivity analyses are available at http://bit.ly/2HAKyon. A sample of the code used in the main analysis is included below for reference.

```
R code
## INSTALL PACKAGES ##

library(R2WinBUGS)
library(coda)

## PREPARE DATA AND PARAMETER LISTS ##

# Set working directory
setwd("C:/WinBUGSModel")

# Import data files
Data_VPr <- read.csv("C:/WinBUGSModel/Data_VPr.csv")
Data_VPo <- read.csv("C:/WinBUGSModel/Data_VPo.csv")
Data_MPr <- read.csv("C:/WinBUGSModel/Data_MPr.csv")
Data_MPo <- read.csv("C:/WinBUGSModel/Data_MPo.csv")

# List parameters
Params <-
c("inc.m","inc.f","timetoti.m","timetoti.f","sc","mu","prev.m","prev.f
","not.m","not.f","prev.mf","not.mf","pn.mf")

## RUN MODEL FOR VIET NAM ##

 # Priors (no confrontation)
 Model_V1PrW2A <- bugs(data=Data_VPr, inits=NULL, Params,
model.file="C:/WinBUGSModel/Model_VPr.txt", n.chains=3, n.iter=21000,
n.burnin=1000, n.thin=1, digits=5, bugs.directory="c:/WinBUGS14",
DIC=FALSE)
 print(Model_V1PrW2A$summary,digits=5)
 gelman.diag(Model_V1PrW2A, confidence = 0.95, transform=FALSE,
autoburnin=TRUE, multivariate=TRUE)
 gelman.plot(Model_V1PrW2A)

 # Posteriors (after confrontation)
 Model_V1PoW2A <- bugs(data=Data_VPo, inits=NULL, Params,
model.file="C:/WinBUGSModel/Model_VPo.txt", n.chains=3, n.iter=21000,
n.burnin=1000, n.thin=1, digits=5, bugs.directory="c:/WinBUGS14",
DIC=FALSE)
 print(Model_V1PoW2A$summary,digits=5)
 gelman.diag(Model_V1PoW2A, confidence = 0.95, transform=FALSE,
autoburnin=TRUE, multivariate=TRUE)
 gelman.plot(Model_V1PoW2A)

## RUN MODEL FOR MALAWI ##

 # Priors (no confrontation)
 Model_M1PrW2A <- bugs(data=Data_MPr, inits=NULL, Params,
model.file="C:/WinBUGSModel/Model_MPr.txt", n.chains=3, n.iter=21000,
n.burnin=1000, n.thin=1, digits=5, bugs.directory="c:/WinBUGS14",
DIC=FALSE)
 print(Model_M1PrW2A$summary,digits=5)
```

```
 gelman.diag(Model_M1PrW2A, confidence = 0.95, transform=FALSE,
autoburnin=TRUE, multivariate=TRUE)
 gelman.plot(Model_M1PrW2A)

 # Posteriors (after confrontation)
 Model_M1PoW2A <- bugs(data=Data_MPo, inits=NULL, Params,
model.file="C:/WinBUGSModel/Model_MPo.txt", n.chains=3, n.iter=21000,
n.burnin=1000, n.thin=1, digits=5, bugs.directory="c:/WinBUGS14",
DIC=FALSE)
 print(Model_M1PoW2A$summary,digits=5)
 gelman.diag(Model_M1PoW2A, confidence = 0.95, transform=FALSE,
autoburnin=TRUE, multivariate=TRUE)
 gelman.plot(Model_M1PoW2A)

sink()

WINBUGS code (Model_VPr.txt)
model{

# Incidence

inc.m ~ dlnorm(-6.0126762,65.1874099)
inc.f ~ dlnorm(-7.4508502,6.5428704)

# Time to treatment

timetoti.m ~ dlnorm(-2.4474648,1.6973627)
timetoti.f ~ dlnorm(-2.2355818,2.4323685)

# Self-cure

sc ~ dlnorm(-1.6417072,6.973734)

# Mortality

mu ~ dlnorm(-1.2261229,4.065313436)

# Calculate prevalence, case notification rate and M:F ratios

prev.m <- inc.m/((1/timetoti.m)+sc+mu)
prev.f <- inc.f/((1/timetoti.f)+sc+mu)

not.m <- (1/timetoti.m)*prev.m
not.f <- (1/timetoti.f)*prev.f

prev.mf <- prev.m/prev.f
not.mf <- not.m/not.f
pn.mf <- prev.mf/not.mf

# Calculate model priors

prevcasemodelprior.m ~ dbin(prev.m,prevpop.m)
notcasemodelprior.m ~ dbin(not.m,notpop.m)
prevcasemodelprior.f ~ dbin(prev.f,prevpop.f)
notcasemodelprior.f ~ dbin(not.f,notpop.f)

}

WINBUGS code (Model_VPO.txt)
model{
```

```
# Incidence

inc.m ~ dlnorm(-6.0126762,65.1874099)
inc.f ~ dlnorm(-7.4508502,6.5428704)

# Time to treatment

timetoti.m ~ dlnorm(-2.4474648,1.6973627)
timetoti.f ~ dlnorm(-2.2355818,2.4323685)

# Self-cure

sc ~ dlnorm(-1.6417072,6.973734)

# Mortality

mu ~ dlnorm(-1.2261229,4.065313436)

# Calculate prevalence, case notification rate and M:F ratios

prev.m <- inc.m/((1/timetoti.m)+sc+mu)
prev.f <- inc.f/((1/timetoti.f)+sc+mu)

not.m <- (1/timetoti.m)*prev.m
not.f <- (1/timetoti.f)*prev.f

prev.mf <- prev.m/prev.f
not.mf <- not.m/not.f
pn.mf <- prev.mf/not.mf

# Confront model with data on prevalence and case notification rate

prevcase.m ~ dbin(prev.m,prevpop.m)
prevcasemodelpost.m ~ dbin(prev.m,prevpop.m)
notcase.m ~ dbin(not.m,notpop.m)
notcasemodelpost.m ~ dbin(not.m,notpop.m)
prevcase.f ~ dbin(prev.f,prevpop.f)
prevcasemodelpost.f ~ dbin(prev.f,prevpop.f)
notcase.f ~ dbin(not.f,notpop.f)
notcasemodelpost.f ~ dbin(not.f,notpop.f)

}

WINBUGS code (Model_MPr.txt)
model{

# Incidence

inc.m ~ dlnorm(-5.6429348,22.8071247)
inc.f ~ dlnorm(-6.4969191,4.0579866)

# Time to treatment

symptocare.m ~ dlnorm(-2.914242,3.788399)
caretotreat.m ~ dlnorm(-1.8864809,1.117929)
timetoti.m <- symptocare.m + caretotreat.m
symptocare.f ~ dlnorm(-2.8690639,3.124268)
caretotreat.f ~ dlnorm(-1.828793,0.653974)
timetoti.f <- symptocare.f + caretotreat.f

# Self-cure
```

```
sc ~ dlnorm(-1.6417072,6.973734)

# Mortality

mu ~ dlnorm(-1.1908142,4.352139601)

# Calculate prevalence, case notification rate and M:F ratios

prev.m <- inc.m/((1/timetoti.m)+sc+mu)
prev.f <- inc.f/((1/timetoti.f)+sc+mu)

not.m <- (1/timetoti.m)*prev.m
not.f <- (1/timetoti.f)*prev.f

prev.mf <- prev.m/prev.f
not.mf <- not.m/not.f
pn.mf <- prev.mf/not.mf

# Calculate model priors

prevcasemodelprior.m ~ dbin(prev.m,prevpop.m)
notcasemodelprior.m ~ dbin(not.m,notpop.m)
prevcasemodelprior.f ~ dbin(prev.f,prevpop.f)
notcasemodelprior.f ~ dbin(not.f,notpop.f)

}

WINBUGS code (Model_MPO.txt)
model{

# Incidence

inc.m ~ dlnorm(-5.6429348,22.8071247)
inc.f ~ dlnorm(-6.4969191,4.0579866)

# Time to treatment

symptocare.m ~ dlnorm(-2.914242,3.788399)
caretotreat.m ~ dlnorm(-1.8864809,1.117929)
timetoti.m <- symptocare.m + caretotreat.m
symptocare.f ~ dlnorm(-2.8690639,3.124268)
caretotreat.f ~ dlnorm(-1.828793,0.653974)
timetoti.f <- symptocare.f + caretotreat.f

# Self-cure

sc ~ dlnorm(-1.6417072,6.973734)

# Mortality

mu ~ dlnorm(-1.1908142,4.352139601)

# Calculate prevalence, case notification rate and M:F ratios

prev.m <- inc.m/((1/timetoti.m)+sc+mu)
prev.f <- inc.f/((1/timetoti.f)+sc+mu)

not.m <- (1/timetoti.m)*prev.m
not.f <- (1/timetoti.f)*prev.f
```

```
prev.mf <- prev.m/prev.f
not.mf <- not.m/not.f
pn.mf <- prev.mf/not.mf

# Confront model with data on prevalence and case notification rate

prevcase.m ~ dbin(prev.m,prevpop.m)
prevcasemodelpost.m ~ dbin(prev.m,prevpop.m)
notcase.m ~ dbin(not.m,notpop.m)
notcasemodelpost.m ~ dbin(not.m,notpop.m)
prevcase.f ~ dbin(prev.f,prevpop.f)
prevcasemodelpost.f ~ dbin(prev.f,prevpop.f)
notcase.f ~ dbin(not.f,notpop.f)
notcasemodelpost.f ~ dbin(not.f,notpop.f)

}

Data file (Data_VPr.csv)
prevpop.m,notpop.m,prevpop.f,notpop.f
16809,255474,28986,638298

Data file (Data_VPo.csv)
prevcase.m,prevpop.m,notcase.m,notpop.m,prevcase.f,prevpop.f,notcase.f
,notpop.f
59,16809,350,255474,20,28986,300,638298

Data file (Data_mPr.csv)
prevpop.m,notpop.m,prevpop.f,notpop.f
6931,392157,14094,563380

Data file (Data_mPo.csv)
prevcase.m,prevpop.m,notcase.m,notpop.m,prevcase.f,prevpop.f,notcase.f
,notpop.f
21,6931,400,392157,21,14094,400,563380
```

Web Appendix 5: Sensitivity Analyses – Model Structure

We examined additional scenarios reflecting all combinations of fixing individual parameters by gender and allowing individual parameters to differ by gender, as shown in Web Table 7.

Web Table 7: Scenarios

Scenario	Incidence rate	Treatment access rate	Self-cure rate	Untreated-TB mortality rate
0	M=F	M=F	M=F	M=F
1A	M≠F	M=F	M=F	M=F
1B	M=F	M≠F	M=F	M=F
1C	M=F	M=F	M≠F	M=F
1D	M=F	M=F	M=F	M≠F
MAIN	**M≠F**	**M≠F**	**M=F**	**M=F**
2B	M≠F	M=F	M≠F	M=F
2C	M≠F	M=F	M=F	M≠F
2D	M=F	M≠F	M≠F	M=F
2E	M=F	M≠F	M=F	M≠F
2F	M=F	M=F	M≠F	M≠F
3A	M≠F	M≠F	M≠F	M=F
3B	M≠F	M≠F	M=F	M≠F
3C	M≠F	M=F	M≠F	M≠F
3D	M=F	M≠F	M≠F	M≠F
4	M≠F	M≠F	M≠F	M≠F

Only scenarios that allowed both disease incidence and treatment access rate to differ by gender were consistent with empirical data on gender-specific prevalence and case notification rates and M:F ratios in prevalence-to-notification ratios in both countries (Scenarios 3A, 3B, 4). Posterior estimates for incidence, treatment access, self-cure and untreated-TB mortality rates (and therefore prevalence and case notification rate) did not differ substantially between the main model and those that also allowed self-cure and/or untreated-TB mortality to differ by gender (Scenarios 3A, 3B, 4) in either country.

In Malawi, scenarios that allowed treatment access and untreated-TB mortality rates (Scenario 2E) or treatment access, self-cure and untreated-TB mortality rates to differ by gender (Scenario 3D) also were consistent with empirical data on gender-specific prevalence and case notification rates and M:F ratios in prevalence-to-notification ratios. In each of these models, posterior estimates for untreated-TB mortality rate among women were over twice those estimated among men. These differences were considered too extreme to be feasible in light of previous studies that have found no evidence of a gender difference in TB mortality [23].

Remaining scenarios did not generate posterior estimates consistent with observed gender-specific prevalence, case notification rates and/or with M:F ratios in prevalence or case notification rates.

Scenario 0

Scenario 0 examined the scenario in which no parameters were allowed to differ by gender. Modelled gender-specific prevalence and case notification rates were calculated as:

$$prev_g = \frac{inc}{ti + sc + mu}$$

$$not_g = prev_g * ti$$

The model could not generate posterior estimates consistent with empirical data on gender-specific prevalence and case notification rates, nor M:F ratios in prevalence-to-notification ratios, for either country (except female prevalence in Malawi). Results are shown below in Web Table 8.

Web Table 8: Prior and posterior estimates for Scenario 0

Viet Nam				
Parameter	Gender	Model priors median (95% CrI)	Empirical data estimate (95% CI)	Model posteriors median (95% CrI)
Incidence rate (annual per 100,000*)	M & F	160 (141-182)		159 (141-180)
Untreated disease duration (years)	M & F	0.09 (0.02-0.40)		2.19 (1.73-2.75)
Self-cure rate (annual)	M & F	0.19 (0.09-0.41)		0.21 (0.10-0.38)
Untreated-TB mortality rate (annual)	M & F	0.29 (0.11-0.77)		0.32 (0.15-0.52)
Prevalence (per 100,000*)	M		351 (262-440)	161 (129-198)
	F		69 (39-99)	161 (129-198)
Notification (per 100,000*)	M		137 (123-151)	73 (68-79)
	F		47 (42-52)	73 (68-79)
Prevalence-to-notification ratio	M:F		1.75 (1.21-2.58)	1.00 (1.00-1.00)
Malawi				
Parameter	Gender	Model priors median (95% CrI)	Empirical data estimate (95% CI)	Model posteriors median (95% CrI)
Incidence rate (annual per 100,000*)	M & F	288 (201-413)		239 (177-328)
Untreated disease duration (years)	M & F	0.22 (0.06-1.25)		2.39 (1.75-3.18)
Self-cure rate (annual)	M & F	0.19 (0.09-0.41)		0.23 (0.11-0.49)
Untreated-TB mortality rate (annual)	M & F	0.30 (0.12-0.78)		0.51 (0.21-1.03)
Prevalence (per 100,000*)	M		303 (176-431)	201 (149-265)
	F		149 (85-213)	201 (149-265)
Notification (per 100,000*)	M		102 (91-112)	84 (78-90)
	F		71 (64-78)	84 (78-90)
Prevalence-to-notification ratio	M:F		1.42 (0.91-2.20)	1.00 (1.00-1.00)

M: male; F: female; M:F: male-to-female ratio; CI: confidence interval; CrI: credible interval; Untreated disease duration: inverse of treatment access rate
*Modelled as proportion but shown as number per 100,000 population
All potential scale reduction factors, which equal one at convergence, were between 1.001 and 1.002.

Scenario 1A

In Scenario 1A, incidence rate was the only parameter allowed to differ by gender. Modelled gender-specific prevalence and case notification rates were calculated as:

$$prev_g = \frac{inc_g}{ti + sc + mu}$$

$$not_g = prev_g * ti$$

Results in Web Table 9 show that the model could not generate posterior estimates consistent with empirical data on M:F ratios in prevalence-to-notification ratios in either country, nor with male prevalence in Viet Nam.

Web Table 9: Prior and posterior estimates for Scenario 1A

Viet Nam				
Parameter	Gender	Model priors median (95% CrI)	Empirical data estimate (95% CI)	Model posteriors median (95% CrI)
Incidence rate (annual per 100,000*)	M	245 (192-312)		251 (211-304)
	F	58 (27-125)		81 (66-101)
Untreated disease duration (years)	M & F	0.09 (0.02-0.39)		1.93 (1.51-2.42)
Self-cure rate (annual)	M & F	0.19 (0.09-0.41)		0.17 (0.09-0.32)
Untreated-TB mortality rate (annual)	M & F	0.29 (0.11-0.77)		0.22 (0.10-0.42)
Prevalence (per 100,000*)	M		351 (262-440)	272 (216-338)
	F		69 (39-99)	88 (69-111)
Notification (per 100,000*)	M		137 (123-151)	141 (128-156)
	F		47 (42-52)	46 (41-51)
Prevalence-to-notification ratio	M:F		1.75 (1.21-2.58)	1.00 (1.00-1.00)
Malawi				
Parameter	Gender	Model priors median (95% CrI)	Empirical data estimate (95% CI)	Model posteriors median (95% CrI)
Incidence rate (annual per 100,000*)	M	354 (234-533)		277 (208-386)
	F	152 (57-401)		186 (139-264)
Untreated disease duration (years)	M & F	0.22 (0.06-1.22)		2.44 (1.79-3.23)
Self-cure rate (annual)	M & F	0.19 (0.09-0.41)		0.22 (0.10-0.46)
Untreated-TB mortality rate (annual)	M & F	0.30 (0.12-0.78)		0.44 (0.19-0.90)
Prevalence (per 100,000*)	M		303 (176-431)	254 (186-336)
	F		149 (85-213)	171 (126-226)
Notification (per 100,000*)	M		102 (91-112)	104 (95-115)
	F		71 (64-78)	70 (64-77)
Prevalence-to-notification ratio	M:F		1.42 (0.91-2.20)	1.00 (1.00-1.00)

M: male; F: female; M:F: male-to-female ratio; CI: confidence interval; CrI: credible interval; Untreated disease duration: inverse of treatment access rate
*Modelled as proportion but shown as number per 100,000 population
All potential scale reduction factors, which equal one at convergence, were between 1.000 and 1.003.

Scenario 1B

In Scenario 1B, treatment access rate was the only parameter allowed to differ by gender. Modelled gender-specific prevalence and case notification rates were calculated as:

$$prev_g = \frac{inc}{ti_g + sc + mu}$$

$$not_g = prev_g * ti_g$$

Results in Web Table 10 show that the model could not generate posterior estimates consistent with empirical data on prevalence, nor M:F ratios in prevalence-to-notification ratios, in either country.

Web Table 10: Prior and posterior estimates for Scenario 1B

Viet Nam				
Parameter	Gender	Model priors median (95% CrI)	Empirical data estimate (95% CI)	Model posteriors median (95% CrI)
Incidence rate (annual per 100,000*)	M & F	160 (141-182)		190 (171-212)
Untreated disease duration (years)	M	0.09 (0.02-0.39)		0.85 (0.63-1.13)
	F	0.11 (0.03-0.38)		3.62 (2.79-4.62)
Self-cure rate (annual)	M & F	0.19 (0.09-0.41)		0.24 (0.11-0.49)
Untreated-TB mortality rate (annual)	M & F	0.30 (0.11-0.78)		0.51 (0.24-0.80)
Prevalence (per 100,000*)	M		351 (262-440)	98 (75-125)
	F		69 (39-99)	183 (146-227)
Notification (per 100,000*)	M		137 (123-151)	115 (104-127)
	F		47 (42-52)	51 (45-57)
Prevalence-to-notification ratio	M:F		1.75 (1.21-2.58)	0.24 (0.18-0.31)
Malawi				
Parameter	Gender	Model priors median (95% CrI)	Empirical data estimate (95% CI)	Model posteriors median (95% CrI)
Incidence rate (annual per 100,000*)	M & F	288 (201-414)		244 (185-331)
Untreated disease duration (years)	M	0.22 (0.07-1.03)		1.68 (1.18-2.32)
	F	0.23 (0.06-1.86)		2.86 (2.08-3.84)
Self-cure rate (annual)	M & F	0.19 (0.09-0.41)		0.24 (0.11-0.52)
Untreated-TB mortality rate (annual)	M & F	0.30 (0.12-0.77)		0.58 (0.24-1.12)
Prevalence (per 100,000*)	M		303 (176-431)	171 (123-229)
	F		149 (85-213)	207 (154-271)
Notification (per 100,000*)	M		102 (91-112)	102 (92-112)
	F		71 (64-78)	72 (65-79)
Prevalence-to-notification ratio	M:F		1.42 (0.91-2.20)	0.59 (0.46-0.73)

M: male; F: female; M:F: male-to-female ratio; CI: confidence interval; CrI: credible interval; Untreated disease duration: inverse of treatment access rate
*Modelled as proportion but shown as number per 100,000 population
All potential scale reduction factors, which equal one at convergence, were between 1.001 and 1.002.

Scenario 1C

In Scenario 1C, self-cure rate was the only parameter allowed to differ by gender. Modelled gender-specific prevalence and case notification rates were calculated as:

$$prev_g = \frac{inc}{ti + sc_g + mu}$$

$$not_g = prev_g * ti$$

Results in Web Table 11 show that the model could not generate posterior estimates consistent with empirical data on M:F ratios in prevalence-to-notification ratios in either country, nor female prevalence in Viet Nam.

Web Table 11: Prior and posterior estimates for Scenario 1C

Viet Nam				
Parameter	Gender	Model priors median (95% CrI)	Empirical data estimate (95% CI)	Model posteriors median (95% CrI)
Incidence rate (annual per 100,000*)	M & F	160 (141-182)		175 (159-194)
Untreated disease duration (years)	M & F	0.09 (0.02-0.39)		2.13 (1.7-2.65)
Self-cure rate (annual)	M	0.19 (0.09-0.41)		0.09 (0.05-0.14)
	F	0.19 (0.09-0.41)		1.14 (0.87-1.50)
Untreated-TB mortality rate (annual)	M & F	0.30 (0.11-0.78)		0.09 (0.05-0.16)
Prevalence (per 100,000*)	M		351 (262-440)	269 (216-332)
	F		69 (39-99)	103 (82-128)
Notification (per 100,000*)	M		137 (123-151)	126 (115-139)
	F		47 (42-52)	48 (43-54)
Prevalence-to-notification ratio	M:F		1.75 (1.21-2.58)	1.00 (1.00-1.00)
Malawi				
Parameter	Gender	Model priors median (95% CrI)	Empirical data estimate (95% CI)	Model posteriors median (95% CrI)
Incidence rate (annual per 100,000*)	M & F	289 (201-414)		232 (179-308)
Untreated disease duration (years)	M & F	0.22 (0.06-1.22)		2.55 (1.89-3.35)
Self-cure rate (annual)	M	0.19 (0.09-0.41)		0.15 (0.08-0.27)
	F	0.19 (0.09-0.41)		0.48 (0.31-0.72)
Untreated-TB mortality rate (annual)	M & F	0.30 (0.12-0.78)		0.36 (0.16-0.70)
Prevalence (per 100,000*)	M		303 (176-431)	254 (187-335)
	F		149 (85-213)	187 (139-243)
Notification (per 100,000*)	M		102 (91-112)	100 (90-110)
	F		71 (64-78)	73 (66-80)
Prevalence-to-notification ratio	M:F		1.42 (0.91-2.20)	1.00 (1.00-1.00)

M: male; F: female; M:F: male-to-female ratio; CI: confidence interval; CrI: credible interval; Untreated disease duration: inverse of treatment access rate
*Modelled as proportion but shown as number per 100,000 population
All potential scale reduction factors, which equal one at convergence, were between 1.000 and 1.002.

Scenario 1D

In Scenario 1D, untreated-TB mortality rate was the only parameter allowed to differ by gender. Modelled gender-specific prevalence and case notification rates were calculated as:

$$prev_g = \frac{inc}{ti + sc + mu_g}$$

$$not_g = prev_g * ti$$

Results in Web Table 12 show that the model could not generate posterior estimates consistent with empirical data on M:F ratios in prevalence-to-notification ratios in either country, nor male or female prevalence in Viet Nam.

Web Table 12: Prior and posterior estimates for Scenario 1D

Viet Nam				
Parameter	Gender	Model priors median (95% CrI)	Empirical data estimate (95% CI)	Model posteriors median (95% CrI)
Incidence rate (annual per 100,000*)	M & F	160 (141-182)		179 (162-198)
Untreated disease duration (years)	M & F	0.09 (0.02-0.39)		1.98 (1.56-2.47)
Self-cure rate (annual)	M & F	0.19 (0.09-0.41)		0.10 (0.06-0.17)
Untreated-TB mortality rate (annual)	M	0.29 (0.11-0.77)		0.09 (0.05-0.16)
	F	0.30 (0.11-0.78)		1.31 (0.98-1.74)
Prevalence (per 100,000*)	M		351 (262-440)	255 (204-317)
	F		69 (39-99)	93 (74-117)
Notification (per 100,000*)	M		137 (123-151)	129 (117-142)
	F		47 (42-52)	47 (42-53)
Prevalence-to-notification ratio	M:F		1.75 (1.21-2.58)	1.00 (1.00-1.00)
Malawi				
Parameter	Gender	Model priors median (95% CrI)	Empirical data estimate (95% CI)	Model posteriors median (95% CrI)
Incidence rate (annual per 100,000*)	M & F	289 (201-414)		234 (182-306)
Untreated disease duration (years)	M & F	0.22 (0.06-1.22)		2.5 (1.86-3.3)
Self-cure rate (annual)	M & F	0.19 (0.09-0.41)		0.23 (0.11-0.46)
Untreated-TB mortality rate (annual)	M	0.30 (0.12-0.78)		0.27 (0.12-0.52)
	F	0.30 (0.12-0.78)		0.67 (0.41-1.05)
Prevalence (per 100,000*)	M		303 (176-431)	256 (190-338)
	F		149 (85-213)	179 (134-235)
Notification (per 100,000*)	M		102 (91-112)	102 (93-112)
	F		71 (64-78)	72 (65-79)
Prevalence-to-notification ratio	M:F		1.42 (0.91-2.20)	1.00 (1.00-1.00)

M: male; F: female; M:F: male-to-female ratio; CI: confidence interval; CrI: credible interval; Untreated disease duration: inverse of treatment access rate
*Modelled as proportion but shown as number per 100,000 population
All potential scale reduction factors, which equal one at convergence, were between 1.000 and 1.002.

Scenario 2B

In Scenario 2B, incidence and self-cure rates were allowed to differ by gender. Modelled gender-specific prevalence and case notification rates were calculated as:

$$prev_g = \frac{inc_g}{ti + sc_g + mu}$$

$$not_g = prev_g * ti$$

Results in Web Table 13 show that the model could not generate posterior estimates consistent with empirical data on M:F ratios in prevalence-to-notification ratios in either country, nor male prevalence in Viet Nam.

Web Table 13: Prior and posterior estimates for Scenario 2B

Viet Nam				
Parameter	Gender	Model priors median (95% CrI)	Empirical data estimate (95% CI)	Model posteriors median (95% CrI)
Incidence rate (annual per 100,000*)	M	245 (192-312)		253 (212-307)
	F	58 (27-124)		82 (65-106)
Untreated disease duration (years)	M & F	0.09 (0.02-0.39)		1.92 (1.51-2.42)
Self-cure rate (annual)	M	0.19 (0.09-0.41)		0.18 (0.09-0.34)
	F	0.19 (0.09-0.41)		0.18 (0.09-0.36)
Untreated-TB mortality rate (annual)	M & F	0.29 (0.11-0.77)		0.22 (0.10-0.41)
Prevalence (per 100,000*)	M		351 (262-440)	271 (215-338)
	F		69 (39-99)	88 (68-112)
Notification (per 100,000*)	M		137 (123-151)	141 (128-155)
	F		47 (42-52)	46 (41-51)
Prevalence-to-notification ratio	M:F		1.75 (1.21-2.58)	1.00 (1.00-1.00)
Malawi				
Parameter	Gender	Model priors median (95% CrI)	Empirical data estimate (95% CI)	Model posteriors median (95% CrI)
Incidence rate (annual per 100,000*)	M	355 (235-536)		279 (207-387)
	F	150 (57-400)		180 (128-260)
Untreated disease duration (years)	M & F	0.22 (0.06-1.22)		2.43 (1.79-3.21)
Self-cure rate (annual)	M	0.19 (0.09-0.40)		0.23 (0.11-0.49)
	F	0.19 (0.09-0.41)		0.19 (0.09-0.39)
Untreated-TB mortality rate (annual)	M & F	0.30 (0.12-0.77)		0.44 (0.18-0.90)
Prevalence (per 100,000*)	M		303 (176-431)	253 (187-335)
	F		149 (85-213)	171 (126-225)
Notification (per 100,000*)	M		102 (91-112)	104 (95-114)

	F		71 (64-78)	70 (64-77)
Prevalence-to-notification ratio	M:F		1.42 (0.91-2.20)	1.00 (1.00-1.00)

M: male; F: female; M:F: male-to-female ratio; CI: confidence interval; CrI: credible interval; Untreated disease duration: inverse of treatment access rate
*Modelled as proportion but shown as number per 100,000 population
All potential scale reduction factors, which equal one at convergence, were between 1.000 and 1.002.

Scenario 2C

In Scenario 2C, incidence and untreated-TB mortality rates were allowed to differ by gender. Modelled gender-specific prevalence and case notification rates were calculated as:

$$prev_g = \frac{inc_g}{ti + sc + mu_g}$$

$$not_g = prev_g * ti$$

Results in Web Table 14 show that the model could not generate posterior estimates consistent with empirical data on M:F ratios in prevalence-to-notification ratios in either country, nor male prevalence in Viet Nam.

Web Table 14: Prior and posterior estimates for Scenario 2C

Viet Nam				
Parameter	Gender	Model priors median (95% CrI)	Empirical data estimate (95% CI)	Model posteriors median (95% CrI)
Incidence rate (annual per 100,000*)	M	245 (192-312)		255 (213-309)
	F	58 (27-124)		83 (65-115)
Untreated disease duration (years)	M & F	0.09 (0.02-0.39)		1.92 (1.51-2.40)
Self-cure rate (annual)	M & F	0.19 (0.09-0.41)		0.17 (0.09-0.32)
Untreated-TB mortality rate (annual)	M	0.29 (0.11-0.78)		0.24 (0.11-0.45)
	F	0.29 (0.11-0.77)		0.25 (0.10-0.57)
Prevalence (per 100,000*)	M		351 (262-440)	270 (214-336)
	F		69 (39-99)	88 (68-110)
Notification (per 100,000*)	M		137 (123-151)	141 (128-156)
	F		47 (42-52)	46 (41-51)
Prevalence-to-notification ratio	M:F		1.75 (1.21-2.58)	1.00 (1.00-1.00)
Malawi				
Parameter	Gender	Model priors median (95% CrI)	Empirical data estimate (95% CI)	Model posteriors median (95% CrI)
Incidence rate (annual per 100,000*)	M	355 (235-536)		285 (209-398)
	F	150 (57-400)		162 (117-242)
Untreated disease duration (years)	M & F	0.22 (0.06-1.22)		2.44 (1.80-3.22)
Self-cure rate (annual)	M & F	0.19 (0.09-0.40)		0.22 (0.10-0.46)
Untreated-TB mortality rate (annual)	M	0.30 (0.12-0.78)		0.47 (0.20-0.96)
	F	0.30 (0.12-0.77)		0.29 (0.12-0.69)
Prevalence (per 100,000*)	M		303 (176-431)	253 (187-334)

	F		149 (85-213)	171 (126-226)
Notification (per 100,000*)	M		102 (91-112)	104 (94-114)
	F		71 (64-78)	70 (64-77)
Prevalence-to-notification ratio	M:F		1.42 (0.91-2.20)	1.00 (1.00-1.00)

M: male; F: female; M:F: male-to-female ratio; CI: confidence interval; CrI: credible interval; Untreated disease duration: inverse of treatment access rate
*Modelled as proportion but shown as number per 100,000 population
All potential scale reduction factors, which equal one at convergence, were between 1.000 and 1.003.

Scenario 2D

In Scenario 2D, treatment access and self-cure rates were allowed to differ by gender. Modelled gender-specific prevalence and case notification rates were calculated as:

$$prev_g = \frac{inc}{ti_g + sc_g + mu}$$

$$not_g = prev_g * ti$$

Results in Web Table 15 show that the model could not generate posterior estimates consistent with empirical data on male prevalence or M:F ratios in prevalence-to-notification ratios in either country.

Web Table 15: Prior and posterior estimates for Scenario 2D

Viet Nam				
Parameter	Gender	Model priors median (95% CrI)	Empirical data estimate (95% CI)	Model posteriors median (95% CrI)
Incidence rate (annual per 100,000*)	M & F	160 (141-182)		175 (159-193)
Untreated disease duration (years)	M	0.09 (0.02-0.39)		1.97 (1.45-2.63)
	F	0.11 (0.03-0.38)		1.90 (1.32-2.66)
Self-cure rate (annual)	M	0.19 (0.09-0.41)		0.09 (0.05-0.15)
	F	0.19 (0.09-0.41)		1.26 (0.87-1.85)
Untreated-TB mortality rate (annual)	M & F	0.29 (0.11-0.78)		0.09 (0.05-0.17)
Prevalence (per 100,000*)	M		351 (262-440)	251 (188-328)
	F		69 (39-99)	93 (66-127)
Notification (per 100,000*)	M		137 (123-151)	128 (116-140)
	F		47 (42-52)	49 (44-55)
Prevalence-to-notification ratio	M:F		1.75 (1.21-2.58)	1.04 (0.66-1.66)
Malawi				
Parameter	Gender	Model priors median (95% CrI)	Empirical data estimate (95% CI)	Model posteriors median (95% CrI)
Incidence rate (annual per 100,000*)	M & F	288 (201-414)		235 (178-320)
Untreated disease duration (years)	M	0.22 (0.07-1.03)		1.93 (1.27-2.93)
	F	0.23 (0.06-1.86)		2.70 (1.93-3.68)
Self-cure rate (annual)	M	0.19 (0.09-0.41)		0.17 (0.08-0.32)
	F	0.19 (0.09-0.41)		0.32 (0.14-0.65)

Untreated-TB mortality rate (annual)	M & F	0.30 (0.12-0.78)		0.50 (0.20-1.01)
Prevalence (per 100,000*)	M		303 (176-431)	197 (132-294)
	F		149 (85-213)	195 (142-259)
Notification (per 100,000*)	M		102 (91-112)	102 (92-112)
	F		71 (64-78)	72 (65-79)
Prevalence-to-notification ratio	M:F		1.42 (0.91-2.20)	0.71 (0.49-1.14)

M: male; F: female; M:F: male-to-female ratio; CI: confidence interval; CrI: credible interval; Untreated disease duration: inverse of treatment access rate
*Modelled as proportion but shown as number per 100,000 population
All potential scale reduction factors, which equal one at convergence, were between 1.001 and 1.004.

Scenario 2E

In Scenario 2E, treatment access and untreated-TB mortality rates were allowed to differ by gender. Modelled gender-specific prevalence and case notification rates were calculated as:

$$prev_g = \frac{inc}{ti_g + sc + mu_g}$$

$$not_g = prev_g * ti_g$$

Results in Web Table 16 show that the model could not generate posterior estimates consistent with empirical data on male prevalence in Viet Nam. The model produced posterior estimates that were consistent with empirical data on gender-specific prevalence and case notification rates and M:F ratios in prevalence-to-notification ratios in Malawi. However, posterior estimates for untreated-TB mortality rate among women were over twice those estimated among men, which is inconsistent with available evidence [23].

Web Table 16: Prior and posterior estimates for Scenario 2E

Viet Nam				
Parameter	Gender	Model priors median (95% CrI)	Empirical data estimate (95% CI)	Model posteriors median (95% CrI)
Incidence rate (annual per 100,000*)	M & F	160 (141-182)		178 (162-197)
Untreated disease duration (years)	M	0.09 (0.02-0.39)		1.99 (1.47-2.65)
	F	0.11 (0.03-0.38)		1.49 (0.99-2.17)
Self-cure rate (annual)	M & F	0.19 (0.09-0.41)		0.10 (0.06-0.16)
Untreated-TB mortality rate (annual)	M	0.29 (0.11-0.77)		0.09 (0.05-0.16)
	F	0.29 (0.11-0.78)		1.70 (1.13-2.60)
Prevalence (per 100,000*)	M		351 (262-440)	257 (193-334)
	F		69 (39-99)	72 (49-103)
Notification (per 100,000*)	M		137 (123-151)	129 (117-142)
	F		47 (42-52)	48 (43-54)
Prevalence-to-notification ratio	M:F		1.75 (1.21-2.58)	1.34 (0.82-2.21)
Malawi				
Parameter	Gender	Model priors	Empirical data	Model posteriors

		median (95% CrI)	estimate (95% CI)	median (95% CrI)
Incidence rate (annual per 100,000*)	M & F	288 (201-414)		229 (178-301)
Untreated disease duration (years)	M	0.22 (0.07-1.03)		2.35 (1.52-3.5)
	F	0.23 (0.06-1.86)		2.36 (1.59-3.39)
Self-cure rate (annual)	M & F	0.19 (0.09-0.41)		0.23 (0.11-0.47)
Untreated-TB mortality rate (annual)	M	0.30 (0.12-0.78)		0.27 (0.12-0.57)
	F	0.30 (0.12-0.78)		0.68 (0.34-1.24)
Prevalence (per 100,000*)	M		303 (176-431)	241 (158-355)
	F		149 (85-213)	169 (115-239)
Notification (per 100,000*)	M		102 (91-112)	103 (93-113)
	F		71 (64-78)	72 (65-79)
Prevalence-to-notification ratio	M:F		1.42 (0.91-2.20)	0.99 (0.58-1.71)

M: male; F: female; M:F: male-to-female ratio; CI: confidence interval; CrI: credible interval; Untreated disease duration: inverse of treatment access rate
*Modelled as proportion but shown as number per 100,000 population
All potential scale reduction factors, which equal one at convergence, were between 1.001 and 1.004.

Scenario 2F

In Scenario 2F, self-cure and untreated-TB mortality rates were allowed to differ by gender. Modelled gender-specific prevalence and case notification rates were calculated as:

$$prev_g = \frac{inc}{ti + sc_g + mu_g}$$

$$not_g = prev_g * ti$$

Results in Web Table 17 show that the model could not generate posterior estimates consistent with empirical data on M:F ratios in prevalence-to-notification ratios in either country, nor male or female prevalence in Viet Nam.

Web Table 17: Prior and posterior estimates for Scenario 2F

Viet Nam				
Parameter	Gender	Model priors median (95% CrI)	Empirical data estimate (95% CI)	Model posteriors median (95% CrI)
Incidence rate (annual per 100,000*)	M & F	160 (141-182)		178 (162-197)
Untreated disease duration (years)	M & F	0.09 (0.02-0.39)		1.98 (1.57-2.48)
Self-cure rate (annual)	M	0.19 (0.09-0.41)		0.10 (0.05-0.16)
	F	0.19 (0.09-0.41)		0.24 (0.11-0.57)
Untreated-TB mortality rate (annual)	M	0.29 (0.11-0.77)		0.09 (0.05-0.16)
	F	0.29 (0.11-0.78)		1.14 (0.69-1.62)
Prevalence (per 100,000*)	M		351 (262-440)	257 (205-318)
	F		69 (39-99)	94 (74-118)
Notification (per 100,000*)	M		137 (123-151)	129 (118-142)
	F		47 (42-52)	47 (42-53)
Prevalence-to-notification ratio	M:F		1.75 (1.21-2.58)	1.00 (1.00-1.00)

Malawi				
Parameter	Gender	Model priors median (95% CrI)	Empirical data estimate (95% CI)	Model posteriors median (95% CrI)
Incidence rate (annual per 100,000*)	M & F	288 (201-413)		231 (180-300)
Untreated disease duration (years)	M & F	0.22 (0.06-1.22)		2.52 (1.86-3.31)
Self-cure rate (annual)	M	0.19 (0.09-0.40)		0.19 (0.09-0.37)
	F	0.19 (0.09-0.41)		0.24 (0.11-0.54)
Untreated-TB mortality rate (annual)	M	0.29 (0.11-0.77)		0.29 (0.13-0.55)
	F	0.29 (0.11-0.78)		0.62 (0.29-1.07)
Prevalence (per 100,000*)	M		303 (176-431)	258 (190-339)
	F		149 (85-213)	180 (133-235)
Notification (per 100,000*)	M		102 (91-112)	103 (93-113)
	F		71 (64-78)	71 (65-78)
Prevalence-to-notification ratio	M:F		1.42 (0.91-2.20)	1.00 (1.00-1.00)

M: male; F: female; M:F: male-to-female ratio; CI: confidence interval; CrI: credible interval; Untreated disease duration: inverse of treatment access rate
*Modelled as proportion but shown as number per 100,000 population
All potential scale reduction factors, which equal one at convergence, were between 1.000 and 1.002.

Scenario 3A

In Scenario 3A, incidence, treatment access and self-cure rates were allowed to differ by gender. Modelled gender-specific prevalence and case notification rates were calculated as:

$$prev_g = \frac{inc_g}{ti_g + sc_g + mu}$$

$$not_g = prev_g * ti_g$$

Results in Web Table 18 show that the model produced posterior estimates that were consistent with empirical data on gender-specific prevalence and case notification rates and M:F ratios in prevalence-to-notification ratios in both countries. Posterior estimates for transition rates, and therefore prevalence and case notification rate, do not differ substantially from the main model.

Web Table 18: Prior and posterior estimates for Scenario 3A

Viet Nam				
Parameter	Gender	Model priors median (95% CrI)	Empirical data estimate (95% CI)	Model posteriors median (95% CrI)
Incidence rate (annual per 100,000*)	M	245 (192-313)		259 (216-314)
	F	58 (27-125)		68 (56-86)
Untreated disease duration (years)	M	0.09 (0.02-0.39)		2.20 (1.65-2.89)
	F	0.11 (0.03-0.38)		1.01 (0.60-1.59)
Self-cure rate (annual)	M	0.19 (0.09-0.40)		0.17 (0.09-0.32)
	F	0.19 (0.09-0.41)		0.19 (0.09-0.39)
Untreated-TB mortality rate (annual)	M & F	0.30 (0.11-0.78)		0.21 (0.10-0.40)

Prevalence (per 100,000*)	M		351 (262-440)	305 (234-390)
	F		69 (39-99)	48 (29-75)
Notification (per 100,000*)	M		137 (123-151)	138 (125-153)
	F		47 (42-52)	48 (43-53)
Prevalence-to-notification ratio	M:F		1.75 (1.21-2.58)	2.19 (1.28-3.90)
Malawi				
Parameter	Gender	Model priors median (95% CrI)	Empirical data estimate (95% CI)	Model posteriors median (95% CrI)
Incidence rate (annual per 100,000*)	M	355 (235-536)		295 (215-415)
	F	152 (57-396)		155 (112-232)
Untreated disease duration (years)	M	0.22 (0.07-1.03)		2.78 (1.82-4.08)
	F	0.23 (0.06-1.89)		1.88 (1.17-2.85)
Self-cure rate (annual)	M	0.19 (0.09-0.41)		0.22 (0.10-0.47)
	F	0.19 (0.09-0.41)		0.19 (0.09-0.39)
Untreated-TB mortality rate (annual)	M & F	0.30 (0.12-0.78)		0.42 (0.18-0.86)
Prevalence (per 100,000*)	M		303 (176-431)	287 (190-415)
	F		149 (85-213)	134 (84-200)
Notification (per 100,000*)	M		102 (91-112)	103 (93-114)
	F		71 (64-78)	71 (65-78)
Prevalence-to-notification ratio	M:F		1.42 (0.91-2.20)	1.49 (0.82-2.69)

M: male; F: female; M:F: male-to-female ratio; CI: confidence interval; CrI: credible interval; Untreated disease duration: inverse of treatment access rate
*Modelled as proportion but shown as number per 100,000 population
All potential scale reduction factors, which equal one at convergence, were between 1.001 and 1.003.

Scenario 3B

In Scenario 3B, incidence, treatment access and untreated-TB mortality rates were allowed to differ by gender. Modelled gender-specific prevalence and case notification rates were calculated as:

$$prev_g = \frac{inc_g}{ti_g + sc + mu_g}$$

$$not_g = prev_g * ti_g$$

Results in Web Table 19 show that the model produced posterior estimates that were consistent with empirical data on gender-specific prevalence and case notification rates and M:F ratios in prevalence-to-notification ratios in both countries. Posterior estimates for transition rates, and therefore prevalence and case notification rate, do not differ substantially from the main model.

Web Table 19: Prior and posterior estimates for Scenario 3B

Viet Nam				
Parameter	Gender	Model priors median (95% CrI)	Empirical data estimate (95% CI)	Model posteriors median (95% CrI)

Incidence rate (annual per 100,000*)	M	245 (192-313)		259 (215-315)
	F	58 (27-125)		69 (57-93)
Untreated disease duration (years)	M	0.09 (0.02-0.39)		2.19 (1.65-2.88)
	F	0.11 (0.03-0.38)		1.00 (0.60-1.58)
Self-cure rate (annual)	M & F	0.19 (0.09-0.40)		0.17 (0.09-0.31)
Untreated-TB mortality rate (annual)	M	0.29 (0.11-0.77)		0.22 (0.10-0.42)
	F	0.30 (0.11-0.78)		0.27 (0.11-0.67)
Prevalence (per 100,000*)	M		351 (262-440)	304 (233-389)
	F		69 (39-99)	48 (29-74)
Notification (per 100,000*)	M		137 (123-151)	138 (125-153)
	F		47 (42-52)	48 (43-53)
Prevalence-to-notification ratio	M:F		1.75 (1.21-2.58)	2.19 (1.28-3.92)
Malawi				
Parameter	Gender	Model priors median (95% CrI)	Empirical data estimate (95% CI)	Model posteriors median (95% CrI)
Incidence rate (annual per 100,000*)	M	355 (235-536)		297 (216-420)
	F	151 (57-396)		145 (106-218)
Untreated disease duration (years)	M	0.22 (0.07-1.03)		2.76 (1.80-4.06)
	F	0.23 (0.06-1.89)		1.89 (1.18-2.84)
Self-cure rate (annual)	M & F	0.19 (0.09-0.41)		0.22 (0.10-0.46)
Untreated-TB mortality rate (annual)	M	0.30 (0.12-0.78)		0.44 (0.18-0.92)
	F	0.30 (0.12-0.78)		0.31 (0.12-0.73)
Prevalence (per 100,000*)	M		303 (176-431)	284 (188-414)
	F		149 (85-213)	135 (85-200)
Notification (per 100,000*)	M		102 (91-112)	103 (94-114)
	F		71 (64-78)	71 (65-78)
Prevalence-to-notification ratio	M:F		1.42 (0.91-2.20)	1.46 (0.81-2.68)

M: male; F: female; M:F: male-to-female ratio; CI: confidence interval; CrI: credible interval; Untreated disease duration: inverse of treatment access rate
*Modelled as proportion but shown as number per 100,000 population
All potential scale reduction factors, which equal one at convergence, were between 1.001 and 1.004.

Scenario 3C

In Scenario 3C, incidence, self-cure and untreated-TB mortality rates were allowed to differ by gender. Modelled gender-specific prevalence and case notification rates were calculated as:

$$prev_g = \frac{inc_g}{ti + sc_g + mu_g}$$

$$not_g = prev_g * t$$

Results in Web Table 20 show that the model could not generate posterior estimates consistent with empirical data on M:F ratios in prevalence-to-notification ratios in either country, nor male prevalence in Viet Nam.

Web Table 20: Prior and posterior estimates for Scenario 3C

Viet Nam				
Parameter	Gender	Model priors median (95% CrI)	Empirical data estimate (95% CI)	Model posteriors median (95% CrI)
Incidence rate (annual per 100,000*)	M	245 (192-313)		256 (214-311)
	F	58 (27-125)		85 (65-118)
Untreated disease duration (years)	M & F	0.09 (0.02-0.39)		1.91 (1.50-2.40)
Self-cure rate (annual)	M	0.19 (0.09-0.41)		0.18 (0.09-0.33)
	F	0.19 (0.09-0.40)		0.18 (0.09-0.37)
Untreated-TB mortality rate (annual)	M	0.29 (0.11-0.77)		0.23 (0.11-0.45)
	F	0.30 (0.11-0.78)		0.25 (0.10-0.58)
Prevalence (per 100,000*)	M		351 (262-440)	269 (214-334)
	F		69 (39-99)	87 (68-110)
Notification (per 100,000*)	M		137 (123-151)	141 (128-155)
	F		47 (42-52)	46 (41-51)
Prevalence-to-notification ratio	M:F		1.75 (1.21-2.58)	1.00 (1.00-1.00)
Malawi				
Parameter	Gender	Model priors median (95% CrI)	Empirical data estimate (95% CI)	Model posteriors median (95% CrI)
Incidence rate (annual per 100,000*)	M	354 (234-536)		286 (210-402)
	F	151 (58-398)		157 (114-236)
Untreated disease duration (years)	M & F	0.22 (0.06-1.22)		2.44 (1.80-3.22)
Self-cure rate (annual)	M	0.19 (0.09-0.41)		0.23 (0.11-0.48)
	F	0.19 (0.09-0.41)		0.19 (0.09-0.40)
Untreated-TB mortality rate (annual)	M	0.30 (0.12-0.78)		0.47 (0.19-0.96)
	F	0.30 (0.12-0.78)		0.30 (0.12-0.70)
Prevalence (per 100,000*)	M		303 (176-431)	253 (187-334)
	F		149 (85-213)	171 (127-226)
Notification (per 100,000*)	M		102 (91-112)	104 (94-114)
	F		71 (64-78)	70 (64-77)
Prevalence-to-notification ratio	M:F		1.42 (0.91-2.20)	1.00 (1.00-1.00)

M: male; F: female; M:F: male-to-female ratio; CI: confidence interval; CrI: credible interval; Untreated disease duration: inverse of treatment access rate
*Modelled as proportion but shown as number per 100,000 population
All potential scale reduction factors, which equal one at convergence, were between 1.000 and 1.002.

Scenario 3D

In Scenario 3D, treatment access, self-cure and untreated-TB mortality rates were allowed to differ by gender. Modelled gender-specific prevalence and case notification rates were calculated as:

$$prev_g = \frac{inc}{ti_g + sc_g + mu_g}$$

$$not_g = prev_g * ti_g$$

Results in Web Table 21 show that the model could not generate posterior estimates consistent with empirical data on male prevalence in Viet Nam. The model produced posterior estimates that were consistent with empirical data on gender-specific prevalence and case notification rates and M:F ratios in prevalence-to-notification ratios in Malawi. However, posterior estimates for untreated-TB mortality rate among women were over twice those estimated among men, which is inconsistent with available evidence [23].

Web Table 21: Prior and posterior estimates for Scenario 3D

Viet Nam				
Parameter	Gender	Model priors median (95% CrI)	Empirical data estimate (95% CI)	Model posteriors median (95% CrI)
Incidence rate (annual per 100,000*)	M & F	160 (141-182)		178 (161-197)
Untreated disease duration (years)	M	0.09 (0.02-0.39)		2 (1.48-2.66)
	F	0.11 (0.03-0.38)		1.51 (1.01-2.20)
Self-cure rate (annual)	M	0.19 (0.09-0.40)		0.09 (0.05-0.16)
	F	0.19 (0.09-0.41)		0.23 (0.10-0.56)
Untreated-TB mortality rate (annual)	M	0.30 (0.11-0.78)		0.09 (0.05-0.16)
	F	0.29 (0.11-0.78)		1.52 (0.86-2.43)
Prevalence (per 100,000*)	M		351 (262-440)	258 (195-335)
	F		69 (39-99)	73 (50-105)
Notification (per 100,000*)	M		137 (123-151)	129 (117-142)
	F		47 (42-52)	48 (43-54)
Prevalence-to-notification ratio	M:F		1.75 (1.21-2.58)	1.33 (0.82-2.17)
Malawi				
Parameter	Gender	Model priors median (95% CrI)	Empirical data estimate (95% CI)	Model posteriors median (95% CrI)
Incidence rate (annual per 100,000*)	M & F	289 (202-412)		226 (178-295)
Untreated disease duration (years)	M	0.22 (0.07-1.03)		2.42 (1.54-3.60)
	F	0.23 (0.06-1.89)		2.36 (1.58-3.36)
Self-cure rate (annual)	M	0.19 (0.09-0.41)		0.19 (0.09-0.38)
	F	0.19 (0.09-0.41)		0.24 (0.11-0.53)
Untreated-TB mortality rate (annual)	M	0.30 (0.12-0.78)		0.29 (0.13-0.60)
	F	0.30 (0.12-0.78)		0.65 (0.29-1.25)
Prevalence (per 100,000*)	M		303 (176-431)	249 (161-364)
	F		149 (85-213)	169 (115-237)
Notification (per 100,000*)	M		102 (91-112)	103 (93-113)
	F		71 (64-78)	72 (65-79)
Prevalence-to-notification ratio	M:F		1.42 (0.91-2.20)	1.03 (0.59-1.77)

M: male; F: female; M:F: male-to-female ratio; CI: confidence interval; CrI: credible interval; Untreated disease duration: inverse of treatment access rate
*Modelled as proportion but shown as number per 100,000 population
All potential scale reduction factors, which equal one at convergence, were between 1.001 and 1.002.

Scenario 4

In Scenario 4, incidence, treatment access, self-cure and untreated-TB mortality rates were allowed to differ by gender. Modelled gender-specific prevalence and case notification rates were calculated as:

$$prev_g = \frac{inc_g}{ti_g + sc_g + mu_g}$$

$$not_g = prev_g * ti_g$$

Results in Web Table 22 show that the model produced posterior estimates that were consistent with empirical data on gender-specific prevalence and case notification rates and M:F ratios in prevalence-to-notification ratios in both countries. Posterior estimates for transition rates, and therefore prevalence and case notification rate, do not differ substantially from the main model.

Web Table 22: Prior and posterior estimates for Scenario 4

Viet Nam				
Parameter	Gender	Model priors median (95% CrI)	Empirical data estimate (95% CI)	Model posteriors median (95% CrI)
Incidence rate (annual per 100,000*)	M	245 (192-312)		260 (217-317)
	F	58 (27-125)		71 (57-95)
Untreated disease duration (years)	M	0.09 (0.02-0.39)		2.20 (1.65-2.88)
	F	0.11 (0.03-0.37)		1.00 (0.59-1.58)
Self-cure rate (annual)	M	0.19 (0.09-0.41)		0.17 (0.09-0.32)
	F	0.19 (0.09-0.41)		0.19 (0.09-0.39)
Untreated-TB mortality rate (annual)	M	0.29 (0.11-0.78)		0.22 (0.10-0.42)
	F	0.29 (0.11-0.77)		0.27 (0.11-0.68)
Prevalence (per 100,000*)	M		351 (262-440)	304 (233-389)
	F		69 (39-99)	48 (29-74)
Notification (per 100,000*)	M		137 (123-151)	138 (125-153)
	F		47 (42-52)	48 (43-53)
Prevalence-to-notification ratio	M:F		1.75 (1.21-2.58)	2.21 (1.29-3.93)
Malawi				
Parameter	Gender	Model priors median (95% CrI)	Empirical data estimate (95% CI)	Model posteriors median (95% CrI)
Incidence rate (annual per 100,000*)	M	354 (236-533)		296 (216-417)
	F	151 (57-396)		141 (104-214)
Untreated disease duration (years)	M	0.22 (0.07-1.02)		2.78 (1.80-4.06)
	F	0.23 (0.06-1.87)		1.89 (1.18-2.88)
Self-cure rate (annual)	M	0.19 (0.09-0.41)		0.22 (0.10-0.46)
	F	0.19 (0.09-0.41)		0.19 (0.09-0.40)
Untreated-TB mortality rate (annual)	M	0.30 (0.12-0.78)		0.43 (0.18-0.91)
	F	0.30 (0.12-0.77)		0.31 (0.12-0.73)
Prevalence (per 100,000*)	M		303 (176-431)	287 (188-413)
	F		149 (85-213)	135 (85-203)

Notification (per 100,000*)	M		102 (91-112)	103 (93-114)
	F		71 (64-78)	71 (65-78)
Prevalence-to-notification ratio	M:F		1.42 (0.91-2.20)	1.47 (0.80-2.70)

M: male; F: female; M:F: male-to-female ratio; CI: confidence interval; CrI: credible interval; Untreated disease duration: inverse of treatment access rate
*Modelled as proportion but shown as number per 100,000 population
All potential scale reduction factors, which equal one at convergence, were between 1.001 and 1.002.

Web Appendix 6: Sensitivity Analyses – Incidence Rate

We conducted sensitivity analyses to explore the impact of different disease incidence estimates on model results. Our main analyses, described in the main text and above, relied on disease incidence estimates from WHO. We also examined disease incidence estimates from the Institute for Health Metrics and Evaluation (IHME) [24] for each of the scenarios shown in Web Table 7.

IHME disease incidence estimates were calculated from IHME estimates of the number of incident cases (all forms) in men and women ≥ 15 years of age [24]. These data were matched to the nearest five-year national population estimate for individuals ≥ 15 years of age from the United Nations World Population Prospect [2,3]. Only overall disease incidence estimates for all forms of TB were available, rather than estimates for smear-positive TB alone.

In Viet Nam, the average annual number of incident TB cases over 2006-07 (the years of the prevalence survey) was estimated as 75,987 (95% CI 58,918-95,913) for men and 52,653 (95% CI 41,102-65,680) for women. The nearest population estimates from 2005 report a male population of 29,742,533 and a female population of 31,595,138. The corresponding disease incidence rate is estimated at 255 (95% CI 198-322) per 100,000 men and 167 (95% CI 130-208) per 100,000 women. These estimates given an overall disease incidence rate of 210 (95% CI 163-263) per 100,000 population.

In Malawi, the average annual number of incident TB cases over 2013-14 (the years of the prevalence survey) was estimated as 15,028 (95% CI 11,148-20,310) for men and 7,386 (95% CI 5,287-9,704) for women. The nearest population estimates from 2015 report a male population of 4,679,650 and a female population of 4,761,703. The corresponding disease incidence rate is estimated at 321 (95% CI 238-434) per 100,000 men and 155 (95% CI 111-204) per 100,000 women. These estimates given an overall disease incidence rate of 237 (95% CI 174-318) per 100,000 population.

Disease incidence estimates were fitted to log-normal distributions with the middle 95% of probabilities falling within the 95% confidence interval, as shown in Web Table 23.

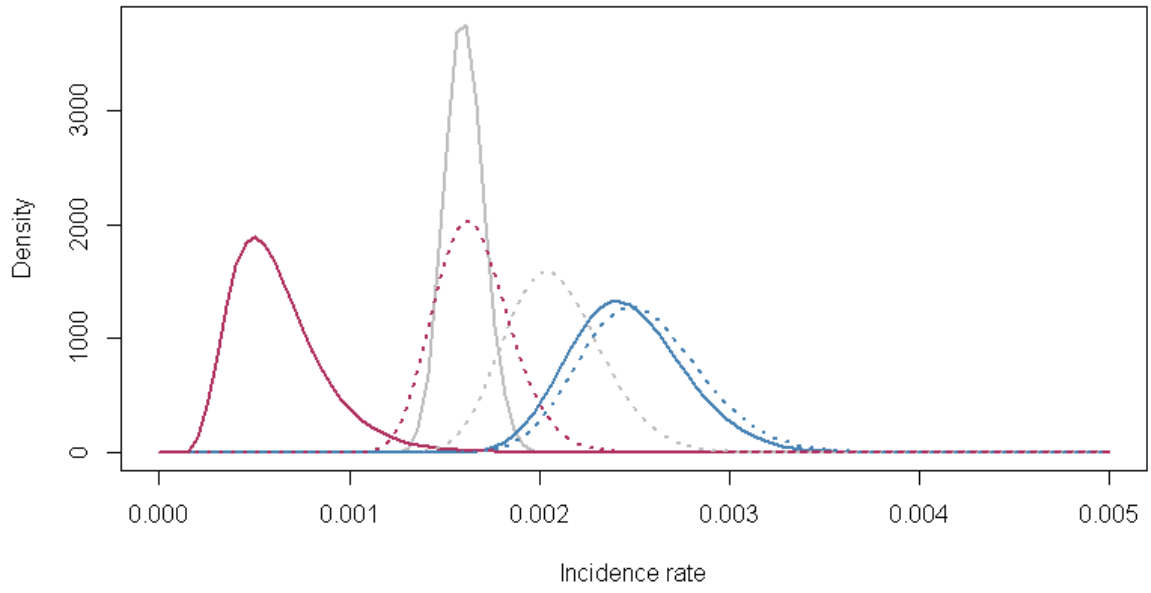
Web Table 23: Data, model estimates and prior distributions for disease incidence (per 100,000) based on IHME estimates

Country	Gender	Data point estimate (95% CI)	Model median (95% CrI)	Distribution in WinBUGS
Viet Nam	M & F	210 (163-263)	207 (163-263)	dlnorm(-6.1799733,67.13776025)
	M	255 (198-322)	253 (198-322)	dlnorm(-5.9815162,64.97934133)
	F	167 (130-208)	164 (130-208)	dlnorm(-6.4103892,69.55906531)
Malawi	M & F	237 (174-318)	235 (174-318)	dlnorm(-6.0523721,42.25977497)
	M	321 (238-434)	321 (238-434)	dlnorm(-5.7402679,42.57298873)
	F	155 (111-204)	151 (111-204)	dlnorm(-6.4991004,41.48650512)

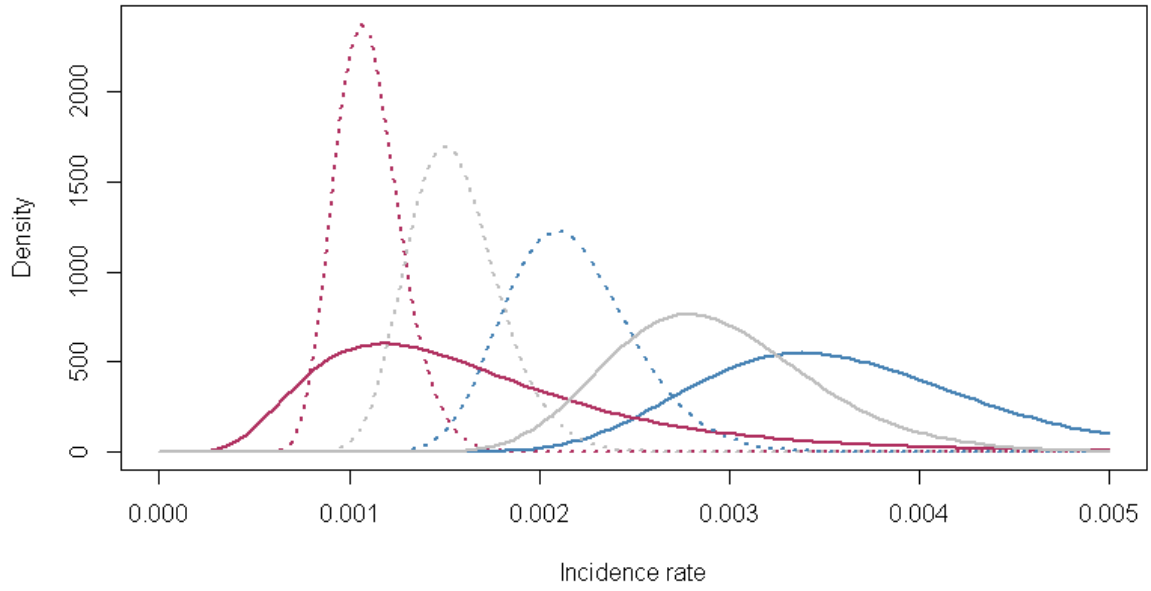
M: male; F: female; CI: confidence interval; CrI: credible interval

*Modelled as proportion but shown as number per 100,000 population

WHO and IHME disease incidence priors are compared below in Web Figure 3 for Viet Nam and Web Figure 4 for Malawi.



Web Figure 3: Comparison of WHO and IHME disease incidence distributions for Viet Nam Solid lines: WHO; dashed lines: IHME; grey: overall estimates; light red: female estimates; blue: male estimates



Web Figure 4: Comparison of WHO and IHME incidence distributions for Malawi Solid lines: WHO; dashed lines: IHME; grey: overall estimates; light red: female estimates; blue: male estimates.

Results from the main model using incidence rate priors based on IHME estimates are shown below in Web Table 24. While posterior estimates for Malawi were consistent with empirical data on prevalence, case notification rate and M:F ratios in prevalence-to-notification ratios, posterior estimates for Viet Nam were not consistent with empirical data on male prevalence or M:F ratios in prevalence-to-notification ratios. This is likely a result of IHME underestimating gender disparity in disease incidence in the country, where WHO estimates that incidence is over four times higher in men than in women, while IHME estimates that incidence among men is only 50% higher than among women.

Web Table 24: Model priors, empirical data and model posteriors for sensitivity analyses using IHME estimates for disease incidence priors in Viet Nam and Malawi

Viet Nam				
Parameter	Gender	Model priors median (95% CrI)	Empirical data estimate (95% CI)	Model posteriors median (95% CrI)
Incidence rate (annual per 100,000*)	M	253 (198-322)		327 (273-395)
	F	164 (130-208)		117 (95-144)
Untreated disease duration (years)	M	0.09 (0.02-0.39)		1.89 (1.41-2.50)
	F	0.11 (0.03-0.38)		1.82 (1.26-2.54)
Self-cure rate (annual)	M & F	0.19 (0.09-0.41)		0.23 (0.11-0.48)
Untreated-TB mortality rate (annual)	M & F	0.29 (0.11-0.77)		0.49 (0.23-0.83)
Prevalence (per 100,000*)	M		351 (262-440)	258 (196-333)
	F		69 (39-99)	90 (64-122)
Notification (per 100,000*)	M		137 (123-151)	136 (123-151)

	F		47 (42-52)	50 (44-55)
Prevalence-to-notification ratio	M:F		1.75 (1.21-2.58)	1.04 (0.69-1.60)
Malawi				
Parameter	Gender	Model priors median (95% CrI)	Empirical data estimate (95% CI)	Model posteriors median (95% CrI)
Incidence rate (annual per 100,000*)	M	321 (238-434)		288 (224-370)
	F	151 (111-204)		154 (124-195)
Untreated disease duration (years)	M	0.22 (0.07-1.03)		2.81 (1.89-4.02)
	F	0.23 (0.06-1.86)		1.83 (1.20-2.67)
Self-cure rate (annual)	M & F	0.19 (0.09-0.41)		0.22 (0.10-0.43)
Untreated-TB mortality rate (annual)	M & F	0.30 (0.12-0.78)		0.40 (0.18-0.73)
Prevalence (per 100,000*)	M		303 (176-431)	290 (198-407)
	F		149 (85-213)	130 (87-187)
Notification (per 100,000*)	M		102 (91-112)	103 (94-114)
	F		71 (64-78)	71 (64-78)
Prevalence-to-notification ratio	M:F		1.42 (0.91-2.20)	1.53 (0.92-2.55)

M: male; F: female; M:F: male-to-female ratio; CI: confidence interval; CrI: credible interval; Untreated disease duration: inverse of treatment access rate
*Modelled as proportion but shown as number per 100,000 population
All potential scale reduction factors, which equal one at convergence, were between 1.000 and 1.003.

We also examined additional model structure scenarios described in Web Table 7 using disease incidence priors based on estimates from IHME. (Results from additional scenarios are not shown.)

For both countries, scenarios that allowed both disease incidence and treatment access rate to differ by gender (Scenarios 3A, 3B, 4), that allowed treatment access and untreated-TB mortality rates to differ by gender (Scenario 2E), and that allowed treatment access, self-cure and untreated-TB mortality rates to differ by gender (Scenario 3D) were consistent with empirical data on gender-specific prevalence and case notification rates and M:F ratios in prevalence-to-notification ratios. In each of these models – with the exception of Scenario 3A in Malawi – posterior estimates for untreated-TB mortality rate among women showed extreme gender differences that are not considered feasible in light of previous studies showing no evidence of a gender difference in untreated-TB mortality [23]. For Scenario 3A in Malawi, posterior estimates in incidence, treatment access, self-cure and untreated-TB mortality rates (and therefore prevalence and case notification rate) did not differ substantially from posterior estimates using the main model.

Web Appendix 7: Sensitivity Analyses – Treatment access Rate

We conducted sensitivity analyses to explore the implications of the assumption that self-reported symptom duration prior to treatment accurately describes untreated disease duration by setting model priors for untreated disease duration equal to the median self-reported symptom duration prior to treatment for each gender in each country.

Results in Web Table 25 show the model could not generate posterior estimates consistent with empirical data on prevalence in either gender nor case notification rate in men nor M:F ratios in prevalence-to-notification ratios. In both countries, posterior prevalence estimates were substantially lower than estimates from recent prevalence surveys.

In Viet Nam, posterior prevalence estimates were 4% of those reported in survey results for men and 7% those for women. In Malawi, posterior prevalence estimates were 7% of those reported in survey results for men and 12% those for women.

Web Table 25: Model priors, empirical data and model posteriors for sensitivity analyses assuming self-reported symptom duration prior to treatment accurately describes untreated disease duration in Viet Nam and Malawi

Viet Nam				
Parameter	Gender	Model priors median (95% CrI)	Empirical data estimate (95% CI)	Model posteriors median (95% CrI)
Incidence rate (annual per 100,000*)	M	245 (192-312)		176 (160-193)
	F	58 (27-125)		53 (47-60)
Untreated disease duration (years)	M	0.09 (0.09-0.09)		0.09 (0.09-0.09)
	F	0.10 (0.10-0.10)		0.10 (0.10-0.10)
Self-cure rate (annual)	M & F	0.19 (0.09-0.41)		0.20 (0.10-0.44)
Untreated-TB mortality rate (annual)	M & F	0.29 (0.11-0.78)		0.35 (0.12-0.99)
Prevalence (per 100,000*)	M		351 (262-440)	13 (12-15)
	F		69 (39-99)	5 (4-6)
Notification (per 100,000*)	M		137 (123-151)	168 (153-183)
	F		47 (42-52)	50 (45-56)
Prevalence-to-notification ratio	M:F		1.75 (1.21-2.58)	0.80 (0.80-0.80)
Malawi				
Parameter	Gender	Model priors median (95% CrI)	Empirical data estimate (95% CI)	Model posteriors median (95% CrI)
Incidence rate (annual per 100,000*)	M	354 (236-533)		131 (116-164)
	F	151 (57-396)		89 (78-116)
Untreated disease duration (years)	M	0.20 (0.20-0.20)		0.20 (0.20-0.20)
	F	0.24 (0.24-0.24)		0.24 (0.24-0.24)
Self-cure rate (annual)	M & F	0.19 (0.09-0.41)		0.22 (0.10-0.50)
Untreated-TB mortality rate (annual)	M & F	0.30 (0.12-0.77)		0.54 (0.17-2.01)
Prevalence (per 100,000*)	M		303 (176-431)	23 (21-25)
	F		149 (85-213)	18 (16-20)

Notification (per 100,000*)	M		102 (91-112)	113 (103-123)
	F		71 (64-78)	75 (68-82)
Prevalence-to-notification ratio	M:F		1.42 (0.91-2.20)	0.83 (0.83-0.83)

M: male; F: female; M:F: male-to-female ratio; CI: confidence interval; CrI: credible interval; Untreated disease duration: inverse of treatment access rate

*Modelled as proportion but shown as number per 100,000 population

All potential scale reduction factors, which equal one at convergence, were between 1.000 and 1.002.

Web References

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3. United Nations Department of Economic and Social Affairs Population Division (2017) File POP/8-3: Female population by broad age group, major area, region and country, 1950-2100 (thousands). World Population Prospects: The 2015 Revision.

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Appendix C Technical appendix for Chapter 5 manuscript "Systematic review and meta-analysis of sex differences in social contact patterns and implications for tuberculosis transmission and control"

Appendix 1 Checklist 1: PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2 (as possible with journal word limits)
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Appendix 1 address), and, if available, provide registration information including registration number.	n/a
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4, Table 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6-7

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Appendix 1 Table 14
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figures 2-5, Appendix 1 Tables 2-13, Appendix 1 Figures 1-2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	n/a
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Appendix 1 Table 15
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12, 14-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12-14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Title page

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7) e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Appendix 1 Checklist 2: MOOSE Checklist

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	3
2	Hypothesis statement	3-4
3	Description of study outcome(s)	4
4	Type of exposure or intervention used	n/a
5	Type of study designs used	4
6	Study population	4
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	4-5
8	Search strategy, including time period included in the synthesis and key words	4, Table 1
9	Effort to include all available studies, including contact with authors	4-5
10	Databases and registries searched	4
11	Search software used, name and version, including special features used (eg, explosion)	4
12	Use of hand searching (e.g., reference lists of obtained articles)	4-5
13	List of citations located and those excluded, including justification	Appendix 1 Table 1
14	Method of addressing articles published in languages other than English	n/a
15	Method of handling abstracts and unpublished studies	n/a
16	Description of any contact with authors	5
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	6-7
18	Rationale for the selection and coding of data (e.g., sound clinical principles or convenience)	6
19	Documentation of how data were classified and coded (e.g., multiple raters, blinding and interrater reliability)	6
20	Assessment of confounding (e.g., comparability of cases and controls in studies where appropriate)	n/a
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	6
22	Assessment of heterogeneity	7
23	Description of statistical methods (e.g., complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	6-7
24	Provision of appropriate tables and graphics	Figures 2-5, Appendix 1 Tables 2-13, Appendix 1 Figures 1-2
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figures 2-5, Appendix 1 Figures 1-2
26	Table giving descriptive information for each study included	Table 2
27	Results of sensitivity testing (e.g., subgroup analysis)	Appendix 1 Table 15
28	Indication of statistical uncertainty of findings	8-11, Figures 2-5, Appendix 1 Figures 1-2

Appendix 1 Table 1: Search Strategy

Set	PubMed	Embase/Global Health	Cochrane Library
1	(social contact*[Title/Abstract] OR contact pattern*[Title/Abstract] OR social mixing[Title/Abstract])	(social contact* or contact pattern* or social mixing).ab,ti.	(social contact* or contact pattern* or social mixing):ti,kw
2	(infectious disease*[Title/Abstract] OR respiratory[Title/Abstract] OR tuberculosis[Title/Abstract] OR influenza[Title/Abstract] OR transmission[Title/Abstract])	(infectious disease* or respiratory or tuberculosis or influenza or transmission).ab,ti.	(infectious disease* or respiratory or tuberculosis or influenza or transmission):ti,kw
3	“1997/01/01”[Date - Publication] : “3000”[Date - Publication]	1 and 2	(#1 AND #2)
4	English [la]	limit 3 to (English language and yr="1997 - Current")	Limit 3 to time period 1997-present
5	1 AND 2 AND 3 AND 4		

Appendix 1 Table 2: Reasons for Exclusion of Publications After Full-text Review

Reference	Reason for Exclusion
Aiello AE, Simanek AM, Eisenberg MC, Walsh AR, Davis B, Volz E, et al. Design and methods of a social network isolation study for reducing respiratory infection transmission: The eX-FLU cluster randomized trial. Epidemics. 2016;15:38-55. doi: http://dx.doi.org/10.1016/j.epidem.2016.01.001. PubMed PMID: 608374678.	Participants report contacts only with other study participants
Alexander ME, Kobes R. Effects of vaccination and population structure on influenza epidemic spread in the presence of two circulating strains. BMC public health. 2011;11 Suppl 1:S8. PubMed PMID: 560051654.	Modelling study
Amaku M, Coutinho FA, Azevedo RS, Burattini MN, Lopez LF, Massad E. Vaccination against rubella: analysis of the temporal evolution of the age-dependent force of infection and the effects of different contact patterns. Physical review. 2003;E, Statistical, nonlinear, and soft matter physics. 67(5 Pt 1):051907. PubMed PMID: 137611835.	Modelling study
Andrews JR, Morrow C, Walensky RP, Wood R. Integrating social contact and environmental data in evaluating tuberculosis transmission in a South African township. Journal of Infectious Diseases. 2014;210(4):597-603. doi: http://dx.doi.org/10.1093/infdis/jiu138. PubMed PMID: 373710043.	Data published elsewhere (Johnstone Robertson 2011)
Apolloni A, Poletto C, Colizza V. Age-specific contacts and travel patterns in the spatial spread of 2009 H1N1 influenza pandemic. BMC Infectious Diseases. 2013;13 (1) (no pagination)(176). doi: http://dx.doi.org/10.1186/1471-2334-13-176. PubMed PMID: 52541688.	Data published elsewhere (Mossong 2008)
Bansal S, Read J, Pourbohloul B, Meyers LA. The dynamic nature of contact networks in infectious disease epidemiology. Journal of Biological Dynamics. 2010;4(5):478-89. doi: http://dx.doi.org/10.1080/17513758.2010.503376. PubMed PMID: 362174279.	Review or perspectives piece
Barrat A, Cattuto C, Tozzi AE, Vanhems P, Voirin N. Measuring contact patterns with wearable sensors: Methods, data characteristics and applications to data-driven simulations of infectious diseases. Clinical Microbiology and Infection. 2014;20(1):10-6. doi: http://dx.doi.org/10.1111/1469-0691.12472. PubMed PMID: 370529746.	Participants report contacts only with other study participants
Benavides J, Demianyk BCP, Mukhi SN, Laskowski M, Friesen M, McLeod RD. Smartphone technologies for social network data generation and infectious disease modeling. Journal of Medical and Biological Engineering. 2012;32(4):235-44. doi: http://dx.doi.org/10.5405/jmbe.974. PubMed PMID: 365841598.	Methodology paper
Blaser N, Zahnd C, Hermans S, Salazar-Vizcaya L, Estill J, Morrow C, et al. Tuberculosis in Cape Town: An age-structured transmission model. Epidemics. 2016;14:54-61. doi: http://dx.doi.org/10.1016/j.epidem.2015.10.001. PubMed PMID: 607220757.	Data published elsewhere (Johnstone Robertson 2011)
Campbell PT, McVernon J, Shrestha N, Nathan PM, Geard N. Who's holding the baby? A prospective diary study of the contact patterns of mothers with an infant. BMC Infectious Diseases. 2017;17 (1) (no pagination)(634). doi: http://dx.doi.org/10.1186/s12879-017-2735-8. PubMed PMID: 618339477.	Single sex participants (women)
Cauchemez S, Valleron AJ, Boelle PY, Flahault A, Ferguson NM. Estimating the impact of school closure on influenza transmission from Sentinel data. Nature. 2008;452(7188):750-4. doi: http://dx.doi.org/10.1038/nature06732. PubMed PMID: 351521077.	Modelling study
Chan TC, Fu YC, Hwang JS. Changing social contact patterns under tropical weather conditions relevant for the spread of infectious diseases. Epidemiology and Infection. 2015;143(2):440-51. doi: http://dx.doi.org/10.1017/S0950268814000843. PubMed PMID: 53155073.	Data published elsewhere (Fu 2012)
Chen SC, Chang CF, Jou LJ, Liao CM. Modelling vaccination programmes against measles in Taiwan. Epidemiology and Infection. 2007;135(5):775-86. doi: http://dx.doi.org/10.1017/S0950268806007369. PubMed PMID: 47161661.	Modelling study
Conlan AJK, Eames KTD, Gage JA, von Kirchbach JC, Ross JV, Saenz RA, et al. Measuring social networks in british primary schools through scientific engagement. Proceedings of the Royal Society B: Biological Sciences. 2011;278(1711):1467-75. doi: http://dx.doi.org/10.1098/rspb.2010.1807. PubMed PMID: 361607401.	Participants report contacts only within school
Cornforth DM, Reluga TC, Shim E, Bauch CT, Galvani AP, Meyers LA. Erratic flu vaccination emerges from short-sighted behavior in contact networks. PLoS Computational Biology. 2011;7 (1) (no pagination)(e1001062). doi: http://dx.doi.org/10.1371/journal.pcbi.1001062. PubMed PMID: 361204748.	Modelling study
Danon L, Read JM, House TA, Vernon MC, Keeling MJ. Social encounter networks: characterizing Great Britain. Proceedings. 2013;Biological sciences / The Royal Society. 280(1765):20131037. PubMed PMID: 563039898.	Data published elsewhere (Danon 2012)
De Cao E, Zagheni E, Manfredi P, Melegaro A. The relative importance of frequency of contacts and duration of exposure for the spread of directly transmitted infections. Biostatistics (Oxford, England). 2014;15(3):470-83. doi: http://dx.doi.org/10.1093/biostatistics/kxu008. PubMed PMID: 605882135.	Data published elsewhere (Mossong 2008)

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Reference	Reason for Exclusion
Eames K, Bansal S, Frost S, Riley S. Six challenges in measuring contact networks for use in modelling. Epidemics. 2015;10:72-7. Epub 2015/04/07. doi: 10.1016/j.epidem.2014.08.006. PubMed PMID: 25843388.	Review or perspectives piece
Eames KTD, Tilston NL, Edmunds WJ. The impact of school holidays on the social mixing patterns of school children. Epidemics. 2011;3(2):103-8. doi: http://dx.doi.org/10.1016/j.epidem.2011.03.003. PubMed PMID: 361842166.	Data published elsewhere (Eames 2010)
Eames KTD. The influence of school holiday timing on epidemic impact. Epidemiology and Infection. 2014;142(9):1963-71. doi: http://dx.doi.org/10.1017/S0950268813002884. PubMed PMID: 373586411.	Modelling study
Edwards CH, Tomba GS, Blasio BFd. Influenza in workplaces: transmission, workers' adherence to sick leave advice and European sick leave recommendations. European Journal of Public Health. 2016;26(3):478-85. doi: http://dx.doi.org/10.1093/eurpub/ckw031. PubMed PMID: 20163190224.	Review or perspectives piece
Ewing A, Lee EC, Viboud C, Bansal S. Contact, travel, and transmission: The impact of winter holidays on influenza dynamics in the United States. Journal of Infectious Diseases. 2017;215(5):732-9. doi: http://dx.doi.org/10.1093/infdis/jiw642. PubMed PMID: 616354022.	Modelling study
Ferraro CF, Trotter CL, Nascimento MC, Jusot JF, Omotara BA, Hodgson A, et al. Household crowding, social mixing patterns and respiratory symptoms in seven countries of the African meningitis belt. PLoS ONE. 2014;9 (7) (no pagination)(e101129). doi: http://dx.doi.org/10.1371/journal.pone.0101129. PubMed PMID: 373459847.	Social contacts defined by attendance at events or involvement in activities
Fournet J, Barrat A. Contact patterns among high school students. PLoS ONE. 2014;9 (9) (no pagination)(e107878). doi: http://dx.doi.org/10.1371/journal.pone.0107878. PubMed PMID: 600033432.	Participants report contacts only with other study participants
Gerlier L, Weil-Olivier C, Carrat F, Lenne X, Lamotte M, Greneche S, et al. Public health and economic impact of vaccinating children with a quadrivalent live attenuated influenza vaccine in France using a dynamic transmission model. Value in Health. 2014;17 (7):A674. doi: http://dx.doi.org/10.1016/j.jval.2014.08.2502. PubMed PMID: 71674377.	Data published elsewhere (Mossong 2008)
Goeyvaerts N, Hens N, Ogunjimi B, Aerts M, Shkedy Z, Damme Pv, et al. Estimating infectious disease parameters from data on social contacts and serological status. Journal of the Royal Statistical Society : Series C. 2010;59(2):255-77. doi: http://dx.doi.org/10.1111/j.1467-9876.2009.00693.x. PubMed PMID: 20103088230.	Data published elsewhere (Mossong 2008)
Guclu H, Read J, Vukotich CJ, Galloway DD, Gao H, Rainey JJ, et al. Social contact networks and mixing among students in K-12 Schools in Pittsburgh, PA. PLoS ONE. 2016;11 (3) (no pagination)(e0151139). doi: http://dx.doi.org/10.1371/journal.pone.0151139. PubMed PMID: 609076919.	Participants report contacts only within school
Hens N, Ayele GM, Goeyvaerts N, Aerts M, Mossong J, Edmunds JW, et al. Estimating the impact of school closure on social mixing behaviour and the transmission of close contact infections in eight European countries. BMC Infectious Diseases. 2009;9 (no pagination)(187). doi: http://dx.doi.org/10.1186/1471-2334-9-187. PubMed PMID: 358047454.	Data published elsewhere (Mossong 2008)
Hens N, Goeyvaerts N, Aerts M, Shkedy Z, Van Damme P, Beutels P. Mining social mixing patterns for infectious disease models based on a two-day population survey in Belgium. BMC Infectious Diseases. 2009;9 (no pagination)(5). doi: http://dx.doi.org/10.1186/1471-2334-9-5. PubMed PMID: 354371756.	Data published elsewhere (Mossong 2008)
Huang C, Liu X, Sun S, Li SC, Deng M, He G, et al. Insights into the transmission of respiratory infectious diseases through empirical human contact networks. Sci Rep. 2016;6:31484. Epub 2016/08/17. doi: 10.1038/srep31484. PubMed PMID: 27526868; PubMed Central PMCID: PMCPMC4985757.	Participants report contacts only with other study participants
Kifle YW, Goeyvaerts N, Van Kerckhove K, Willem L, Faes C, Leirs H, et al. Animal ownership and touching enrich the context of social contacts relevant to the spread of human infectious diseases. PLoS ONE. 2015;10 (7) (no pagination)(e0133461). doi: http://dx.doi.org/10.1371/journal.pone.0133461. PubMed PMID: 606006430.	Data published elsewhere (Willem 2012)
Kiti MC, Tizzoni M, Kinyanjui TM, Koech DC, Munywoki PK, Meriac M, et al. Quantifying social contacts in a household setting of rural Kenya using wearable proximity sensors. EPJ data science. 2016;5:21. Epub 2016/07/30. doi: 10.1140/epjds/s13688-016-0084-2. PubMed PMID: 27471661; PubMed Central PMCID: PMCPMC4944592.	Participants report contacts only with other study participants
Kretzschmar M, Mikolajczyk RT. Contact profiles in eight European countries and implications for modelling the spread of airborne infectious diseases. PLoS ONE. 2009;4 (6) (no pagination)(e5931). doi: http://dx.doi.org/10.1371/journal.pone.0005931. PubMed PMID: 354877141.	Data published elsewhere (Mossong 2008)
Kretzschmar M, Teunis PFM, Pebody RG. Incidence and reproduction numbers of pertussis: Estimates from Serological and Social Contact Data in Five European Countries. PLoS Medicine. 2010;7(6). doi: http://dx.doi.org/10.1371/journal.pmed.1000291. PubMed PMID: 359258160.	Data published elsewhere (Mossong 2008)

Continued on following page

Reference	Reason for Exclusion
Kucharski AJ, Gog JR. The Role of Social Contacts and Original Antigenic Sin in Shaping the Age Pattern of Immunity to Seasonal Influenza. PLoS Computational Biology. 2012;8 (10) (no pagination)(e1002741). doi: http://dx.doi.org/10.1371/journal.pcbi.1002741. PubMed PMID: 365953585.	Data published elsewhere (Mossong 2008)
Kucharski AJ, Wenham C, Brownlee P, Racon L, Widmer N, Eames KTD, et al. Structure and consistency of self-reported social contact networks in British secondary schools. PLoS ONE. 2018;13(7):e0200090. doi: 10.1371/journal.pone.0200090.	Participants report contacts only within school
le Polain de Waroux O, Flasche S, Kucharski AJ, Langendorf C, Ndazima D, Mwanga-Amumpaire J, et al. Identifying human encounters that shape the transmission of Streptococcus pneumoniae and other acute respiratory infections. Epidemics. 2018.	Data published elsewhere (le Polain de Waroux 2018)
Leecaster M, Pettey W, Toth D, Rainey J, Uzicanin A, Samore M. Heterogeneity in social contact among school-age children and implications for influenza transmission. American Journal of Epidemiology. 2013;11):S151. doi: http://dx.doi.org/10.1093/aje/kwt103. PubMed PMID: 71079718.	Participants report contacts only with other study participants
Leecaster M, Toth DJA, Pettey WBP, Rainey JJ, Gao H, Uzicanin A, et al. Estimates of social contact in a middle school based on self-report and wireless sensor data. PLoS ONE. 2016;11 (4) (no pagination)(e0153690). doi: http://dx.doi.org/10.1371/journal.pone.0153690. PubMed PMID: 610063709.	Participants report contacts only with other study participants
Liccardo A, Fierro A. A Lattice Model for Influenza Spreading. PLoS ONE. 2013;8 (5) (no pagination)(e63935). doi: http://dx.doi.org/10.1371/journal.pone.0063935. PubMed PMID: 368973605.	Data published elsewhere (Mossong 2008)
Lowery-North DW, Hertzberg VS, Elon L, Cotsonis G, Hilton SA, Vaughns ICF, et al. Measuring Social Contacts in the Emergency Department. PLoS ONE. 2013;8 (8) (no pagination)(e70854). doi: http://dx.doi.org/10.1371/journal.pone.0070854. PubMed PMID: 369619793.	Participants report contacts only with emergency room patients and staff
Luca GD, Kerckhove KV, Coletti P, Poletto C, Bossuyt N, Hens N, et al. The impact of regular school closure on seasonal influenza epidemics: A data-driven spatial transmission model for Belgium. BMC Infectious Diseases. 2018;18 (1) (no pagination)(29). doi: http://dx.doi.org/10.1186/s12879-017-2934-3. PubMed PMID: 620158016.	Modelling study
Machens A, Gesualdo F, Rizzo C, Tozzi AE, Barrat A, Cattuto C. An infectious disease model on empirical networks of human contact: bridging the gap between dynamic network data and contact matrices. BMC Infectious Diseases. 2013;13 (1) (no pagination)(185). doi: http://dx.doi.org/10.1186/1471-2334-13-185. PubMed PMID: 52561646.	Participants report contacts only with other study participants
Melegaro A, Jit M, Gay N, Zagheni E, Edmunds WJ. What types of contacts are important for the spread of infections? Using contact survey data to explore European mixing patterns. Epidemics. 2011;3(3-4):143-51. doi: http://dx.doi.org/10.1016/j.epidem.2011.04.001. PubMed PMID: 51485516.	Data published elsewhere (Mossong 2008)
Meyer S, Held L. Incorporating social contact data in spatio-temporal models for infectious disease spread. Biostatistics (Oxford, England). 2017;18(2):338-51. doi: http://dx.doi.org/10.1093/biostatistics/kxw051. PubMed PMID: 617575085.	Data published elsewhere (Mossong 2008)
Milne GJ, Kelso JK, Kelly HA, Huband ST, McVernon J. A small community model for the transmission of infectious diseases: Comparison of School closure as an intervention in individual-based models of an influenza pandemic. PLoS ONE. 2008;3 (12) (no pagination)(e4005). doi: http://dx.doi.org/10.1371/journal.pone.0004005. PubMed PMID: 354011933.	Modelling study
Nguyen VK, Mikolajczyk R, Hernandez-Vargas EA. High-resolution epidemic simulation using within-host infection and contact data. BMC Public Health. 2018;18(1):886. doi: 10.1186/s12889-018-5709-x.	Modelling study
Ogunjimi B, Hens N, Goeyvaerts N, Aerts M, Damme Pv, Beutels P. Using empirical social contact data to model person to person infectious disease transmission: an illustration for varicella. Mathematical Biosciences. 2009;218(2):80-7. doi: http://dx.doi.org/10.1016/j.mbs.2008.12.009. PubMed PMID: 20093104437.	Data published elsewhere (Mossong 2008)
Oussaid N, Voirin N, Regis C, Khanafer N, Martin-Gaujard G, Vincent A, et al. Contacts between health care workers and patients in a short-stay geriatric unit during the peak of a seasonal influenza epidemic compared with a nonepidemic period. American Journal of Infection Control. 2016;44(8):905-9. doi: http://dx.doi.org/10.1016/j.ajic.2016.02.002. PubMed PMID: 609465419.	Participants report contacts only with other study participants
Ozella L, Gesualdo F, Tizzoni M, Rizzo C, Pandolfi E, Campagna I, et al. Close encounters between infants and household members measured through wearable proximity sensors. PLoS ONE. 2018;13 (6) (no pagination)(e0198733).	Participants report contacts only with other study participants

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Reference	Reason for Exclusion
Potter GE, Handcock MS, Longini IM, Jr., Halloran ME. ESTIMATING WITHIN-HOUSEHOLD CONTACT NETWORKS FROM EGOCENTRIC DATA. The annals of applied statistics. 2011;5(3):1816-38. Epub 2011/01/01. PubMed PMID: 22427793; PubMed Central PMCID: PMCPMC3306235.	Participants report contacts only within school
Potter GE, Handcock MS, Longini IM, Jr., Halloran ME. ESTIMATING WITHIN-SCHOOL CONTACT NETWORKS TO UNDERSTAND INFLUENZA TRANSMISSION. The annals of applied statistics. 2012;6(1):1-26. Epub 2012/05/29. doi: 10.1214/11-aoas505. PubMed PMID: 22639701; PubMed Central PMCID: PMCPMC3359895.	Modelling study
Potter GE, Hens N. A penalized likelihood approach to estimate within-household contact networks from egocentric data. Journal of the Royal Statistical Society Series C, Applied statistics. 2013;62(4):629-48. Epub 2013/08/13. doi: 10.1111/rssc.12011. PubMed PMID: 23935218; PubMed Central PMCID: PMCPMC3736605.	Data published elsewhere (Mossong 2008)
Potter GE, Smieszek T, Sailer K. Modeling workplace contact networks: The effects of organizational structure, architecture, and reporting errors on epidemic predictions. Network science (Cambridge University Press). 2015;3(3):298-325. Epub 2015/12/04. doi: 10.1017/nws.2015.22. PubMed PMID: 26634122; PubMed Central PMCID: PMCPMC4663701.	Participants report contacts only with other study participants
Prem K, Cook AR, Jit M. Projecting social contact matrices in 152 countries using contact surveys and demographic data. PLoS Computational Biology. 2017;13 (9) (no pagination)(e1005697). doi: http://dx.doi.org/10.1371/journal.pcbi.1005697. PubMed PMID: 618570555.	Data published elsewhere (Mossong 2008)
Rainey JJ, Cheriyadat A, Radke RJ, Suzuki Crumly J, Koch DB. Estimating contact rates at a mass gathering by using video analysis: a proof-of-concept project. BMC public health. 2014;14:1101. doi: http://dx.doi.org/10.1186/1471-2458-14-1101. PubMed PMID: 605896131.	Methodology paper
Read JM, Edmunds WJ, Riley S, Lessler J, Cummings DAT. Close encounters of the infectious kind: Methods to measure social mixing behaviour. Epidemiology and Infection. 2012;140(12):2117-30. doi: http://dx.doi.org/10.1017/S0950268812000842. PubMed PMID: 366086476.	Review or perspectives piece
Salt P, Banner C, Oh S, Yu LM, Lewis S, Pan D, et al. Social mixing with other children during infancy enhances antibody response to a pneumococcal conjugate vaccine in early childhood. Clinical and Vaccine Immunology. 2007;14(5):593-9. doi: http://dx.doi.org/10.1128/CVI.00344-06. PubMed PMID: 352278830.	Social contacts defined by attendance at events or involvement in activities
Schmidt-Ott R, Schwehm M, Eichner M. Influence of social contact patterns and demographic factors on influenza simulation results. BMC Infectious Diseases. 2016;16 (1) (no pagination)(646). doi: http://dx.doi.org/10.1186/s12879-016-1981-5. PubMed PMID: 613266742.	Data published elsewhere (Mossong 2008)
Segerstrom SC. Social networks and immunosuppression during stress: Relationship conflict or energy conservation? Brain, Behavior, and Immunity. 2008;22(3):279-84. doi: http://dx.doi.org/10.1016/j.bbi.2007.10.011. PubMed PMID: 351172712.	Social contacts defined by attendance at events or involvement in activities
Smieszek T, Balmer M, Hattendorf J, Axhausen KW, Zinsstag J, Scholz RW. Reconstructing the 2003/2004 H3N2 influenza epidemic in Switzerland with a spatially explicit, individual-based model. BMC Infectious Diseases. 2011;11 (no pagination)(115). doi: http://dx.doi.org/10.1186/1471-2334-11-115. PubMed PMID: 51418223.	Modelling study
Smieszek T, Barclay VC, Seeni I, Rainey JJ, Gao H, Uzicanin A, et al. How should social mixing be measured: Comparing Appendix 1-based survey and sensor-based methods. BMC Infectious Diseases. 2014;14 (1) (no pagination)(136). doi: http://dx.doi.org/10.1186/1471-2334-14-136. PubMed PMID: 372943011.	Participants report contacts only within school
Smieszek T, Burri EU, Scherzinger R, Scholz RW. Collecting close-contact social mixing data with contact diaries: reporting errors and biases. Epidemiology & Infection. 2012;140(4):744-52.	Participants report contacts only with other study participants
Smieszek T, Castell S, Barrat A, Cattuto C, White PJ, Krause G. Contact diaries versus wearable proximity sensors in measuring contact patterns at a conference: Method comparison and participants' attitudes. BMC Infectious Diseases. 2016;16 (1) (no pagination)(341). doi: http://dx.doi.org/10.1186/s12879-016-1676-y. PubMed PMID: 611305281.	Participants report contacts only with other study participants
Stehle J, Voirin N, Barrat A, Cattuto C, Colizza V, Isella L, et al. Simulation of an SEIR infectious disease model on the dynamic contact network of conference attendees. BMC Medicine. 2011;9 (no pagination)(87). doi: http://dx.doi.org/10.1186/1741-7015-9-87. PubMed PMID: 51541345.	Participants report contacts only with other study participants
Stehle J, Voirin N, Barrat A, Cattuto C, Isella L, Pinton JF, et al. High-resolution measurements of face-to-face contact patterns in a primary school. PLoS ONE. 2011;6 (8) (no pagination)(e23176). doi: http://dx.doi.org/10.1371/journal.pone.0023176. PubMed PMID: 362343935.	Participants report contacts only with other study participants

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Reference	Reason for Exclusion
Towers S, Feng Z. Social contact patterns and control strategies for influenza in the elderly. Mathematical Biosciences. 2012;240(2):241-9. doi: http://dx.doi.org/10.1016/j.mbs.2012.07.007. PubMed PMID: 52173631.	Data published elsewhere (Mossong 2008)
Vino T, Singh GR, Davison B, Campbell PT, Lydeamore MJ, Robinson A, et al. Indigenous Australian household structure: A simple data collection tool and implications for close contact transmission of communicable diseases. PeerJ. 2017;2017 (10) (no pagination)(e3958). doi: http://dx.doi.org/10.7717/peerj.3958. PubMed PMID: 618894679.	Participants report contacts only within household
Voirin N, Payet C, Barrat A, Cattuto C, Khanafer N, Regis C, et al. Combining high-resolution contact data with virological data to investigate influenza transmission in a tertiary care hospital. Infection Control and Hospital Epidemiology. 2015;36(3):254-60. doi: http://dx.doi.org/10.1017/ice.2014.53. PubMed PMID: 602525419.	Participants report contacts only with other study participants
Voirin N, Stehle J, Barrat A, Cattuto C, Isella L, Pinton JF, et al. Using wearable electronic sensors for assessing contacts between individuals in various environments. BMC Proceedings Conference: International Conference on Prevention and Infection Control, ICPIC. 2011;5(SUPPL. 6). PubMed PMID: 70730204.	Participants report contacts only with other study participants
Volz EM, Miller JC, Galvani A, Meyers L. Effects of heterogeneous and clustered contact patterns on infectious disease dynamics. PLoS Computational Biology. 2011;7 (6) (no pagination)(e1002042). doi: http://dx.doi.org/10.1371/journal.pcbi.1002042. PubMed PMID: 362058323.	Modelling study
Wallinga J, Edmunds WJ, Kretzschmar M. Perspective: Human contact patterns and the spread of airborne infectious diseases. Trends in Microbiology. 1999;7(9):372-7. doi: http://dx.doi.org/10.1016/S0966-842X%2899%2901546-2. PubMed PMID: 29421663.	Review or perspectives piece
Watson CH, Coriakula J, Ngoc DTT, Flasche S, Kucharski AJ, Lau CL, et al. Social mixing in Fiji: Who-eats-with-whom contact patterns and the implications of age and ethnic heterogeneity for disease dynamics in the Pacific Islands. PLoS ONE. 2017;12 (12) (no pagination)(e0186911). doi: http://dx.doi.org/10.1371/journal.pone.0186911. PubMed PMID: 619533637.	Participants report contacts only during meals
Willem L, Verelst F, Kuylen E, Abboud LA, Bicke J, Hens N, et al. Catching the risk of measles outbreaks in a clustered society. Tropical Medicine and International Health. 2017;22 (Supplement 1):52. doi: http://dx.doi.org/10.1111/%28ISSN%291365-3156. PubMed PMID: 618977811.	Data published elsewhere (Willem 2012)
Wood R, Racow K, Bekker LG, Morrow C, Middelkoop K, Mark D, et al. Indoor social networks in a south african township: Potential contribution of location to tuberculosis transmission. PLoS ONE. 2012;7 (6) (no pagination)(e39246). doi: http://dx.doi.org/10.1371/journal.pone.0039246. PubMed PMID: 365133365.	Data published elsewhere (Johnstone Robertson 2011)
Zagheni E, Billari FC, Manfredi P, Melegaro A, Mossong J, Edmunds WJ. Using time-use data to parameterize models for the spread of close-contact infectious diseases. American Journal of Epidemiology. 2008;168(9):1082-90. doi: http://dx.doi.org/10.1093/aje/kwn220. PubMed PMID: 352577381.	Social contacts defined by time use data

Appendix 1 Table 3: Publications Eligible for Inclusion That Did Not Collect (To Our Knowledge) Sex and Age Data for Participants and Contacts

Reference
Ajelli M, Litvinova M. Estimating contact patterns relevant to the spread of infectious diseases in Russia. Journal of Theoretical Biology. 2017 21 Apr;419:1-7.
Chan TC, Hu TH, Hwang JS. Estimating the Risk of Influenza-Like Illness Transmission Through Social Contacts: Appendix 1-Based Participatory Cohort Study. JMIR public health and surveillance. 2018 Apr 9;4(2):e40.
Chen S-C, You S-H, Ling M-P, Chio C-P, Liao C-M. Use of seasonal influenza virus titer and respiratory symptom score to estimate effective human contact rates. Journal of epidemiology. 2012;22(4):353-63.
Danon L, House TA, Read JM, Keeling MJ. Social encounter networks: Collective properties and disease transmission. Journal of the Royal Society Interface. 2012 07 Nov;9(76):2826-33.
Destefano F, Haber M, Currivan D, Farris T, Burrus B, Stone-Wiggins B, et al. Factors associated with social contacts in four communities during the 2007-2008 influenza season. Epidemiology and Infection. 2011 August;139(8):1181-90.
Eames KTD, Tilston NL, Brooks-Pollock E, Edmunds WJ. Measured dynamic social contact patterns explain the spread of H1N1v influenza. PLoS Computational Biology. 2012 March;8 (3) (no pagination)(e1002425).
Edmunds WJ, O'Callaghan CJ, Nokes DJ. Who mixes with whom? A method to determine the contact patterns of adults that may lead to the spread of airborne infections. Proceedings of the Royal Society B: Biological Sciences. 1997;264(1384):949-57.
Glass LM, Glass RJ. Social contact networks for the spread of pandemic influenza in children and teenagers. BMC Public Health. 2008;8 (no pagination)(61).
Ibuka Y, Ohkusa Y, Sugawara T, Chapman GB, Yamin D, Atkins KE, et al. Social contacts, vaccination decisions and influenza in Japan. Journal of epidemiology and community health. 2016 01 Feb;70(2):162-7.
Jackson C, Mangtani P, Vynnycky E, Fielding K, Kitching A, Mohamed H, et al. School closures and student contact patterns. Emerging infectious diseases. 2011;17(2):245.
Kiti MC, Kinyanjui TM, Koech DC, Munywoki PK, Medley GF, Nokes DJ. Quantifying age-related rates of social contact using diaries in a rural coastal population of Kenya. PLoS ONE. 2014 15 Aug;9 (8) (no pagination)(e104786).
Kucharski AJ, Kwok KO, Wei VWI, Cowling BJ, Read JM, Lessler J, et al. The Contribution of Social Behaviour to the Transmission of Influenza A in a Human Population. PLoS Pathogens. 2014 June;10 (6) (no pagination)(e1004206).
Kwok KO, Cowling B, Wei V, Riley S, Read JM. Temporal variation of human encounters and the number of locations in which they occur: a longitudinal study of Hong Kong residents. Journal of the Royal Society, Interface. 2018 Jan;15(138).
Kwok KO, Cowling BJ, Wei VW, Wu KM, Read JM, Lessler J, et al. Social contacts and the locations in which they occur as risk factors for influenza infection. Proceedings. 2014 22 Aug;Biological sciences / The Royal Society. 281(1789):20140709.
Lapidus N, De Lamballerie X, Salez N, Setbon M, Delabre RM, Ferrari P, et al. Factors associated with post-seasonal serological titer and risk factors for infection with the pandemic A/H1N1 virus in the French general population. PloS one. 2013;8(4):e60127.
Read JM, Eames KTD, Edmunds WJ. Dynamic social networks and the implications for the spread of infectious disease. Journal of the Royal Society Interface. 2008 06 Sep;5(26):1001-7.
Read JM, Lessler J, Riley S, Wang S, Tan LJ, Kwok KO, et al. Social mixing patterns in rural and urban areas of southern China. Proceedings. 2014 22 Jun;Biological sciences / The Royal Society. 281(1785):20140268.
Smieszek T. A mechanistic model of infection: why duration and intensity of contacts should be included in models of disease spread. Theoretical Biology and Medical Modelling. 2009;6(1):25.
Stein ML, van der Heijden PGM, Buskens V, van Steenbergen JE, Bengtsson L, Koppeschaar CE, et al. Tracking social contact networks with online respondent-driven detection: Who recruits whom? BMC Infectious Diseases. 2015;15 (1) (no pagination)(522).
Stein ML, Van Steenbergen JE, Buskens V, Van Der Heijden PGM, Chanyasanha C, Tipayamongkholgul M, et al. Comparison of contact patterns relevant for transmission of respiratory pathogens in Thailand and The Netherlands using respondent-driven sampling. PLoS ONE. 2014 25 Nov;9 (11) (no pagination)(e113711).
Stein ML, Van Steenbergen JE, Chanyasanha C, Tipayamongkholgul M, Buskens V, Van Der Heijden PGM, et al. Online respondent-driven sampling for studying contact patterns relevant for the spread of close-contact pathogens: A pilot study in Thailand. PLoS ONE. 2014 08 Jan;9 (1) (no pagination)(e85256).
Stromgren M, Holm E, Dahlstrom O, Ekberg J, Eriksson H, Spreco A, et al. Place-based social contact and mixing: A typology of generic meeting places of relevance for infectious disease transmission. Epidemiology and Infection. 2017 01 Sep;145(12):2582-93.
Wallinga J, Teunis P, Kretzschmar M. Using data on social contacts to estimate age-specific transmission parameters for respiratory-spread infectious agents. American Journal of Epidemiology. 2006 November;164(10):936-44.

Appendix 1 Table 4: Publications Eligible for Inclusion Known to Have Collected Sex and Age Data for Participants and Contacts

Reference
Beraud G, Kazmercziak S, Beutels P, Levy-Bruhl D, Lenne X, Mielcarek N, et al. The French connection: The first large population-based contact survey in France relevant for the spread of infectious diseases. PLoS ONE. 2015 15 Jul;10 (7) (no pagination)(e0133203).
Bernard H, Fischer R, Mikolajczyk RT, Kretzschmar M, Wildner M. Nurses' contacts and potential for infectious disease transmission. Emerging infectious diseases. 2009;15(9):1438.
Beutels P, Shkedy Z, Aerts M, Van Damme P. Social mixing patterns for transmission models of close contact infections: Exploring self-evaluation and diary-based data collection through a Appendix 1-based interface. Epidemiology and Infection. 2006 December;134(6):1158-66.
Chen SC, You ZS. Social contact patterns of school-age children in Taiwan: Comparison of the term time and holiday periods. Epidemiology and Infection. 2015 15 Apr;143(6):1139-47.
Dodd PJ, Looker C, Plumb ID, Bond V, Schaap A, Shanaube K, et al. Age- and Sex-Specific Social Contact Patterns and Incidence of Mycobacterium tuberculosis Infection. American Journal of Epidemiology. 2016 15 Jan;183(2):156-66.
Eames KTD, Tilston NL, White PJ, Adams E, Edmunds WJ. The impact of illness and the impact of school closure on social contact patterns. Health Technology Assessment. 2010;14(34):267-312.
Edmunds W, Kafatos G, Wallinga J, Mossong J. Mixing patterns and the spread of close-contact infectious diseases. Emerging themes in epidemiology. 2006;3(1):10.
Fu Yc, Wang DW, Chuang JH. Representative Contact Diaries for Modeling the Spread of Infectious Diseases in Taiwan. PLoS ONE. 2012 03 Oct;7 (10) (no pagination)(e45113).
Grijalva CG, Goeyvaerts N, Verastegui H, Edwards KM, Gil AI, Lanata CF, et al. A household-based study of contact networks relevant for the spread of infectious diseases in the highlands of peru. PLoS ONE. 2015 03 Mar;10 (3) (no pagination)(e0118457).
Horby P, Thai PQ, Hens N, Yen NTT, Mai LQ, Thoang DD, et al. Social contact patterns in vietnam and implications for the control of infectious diseases. PLoS ONE. 2011;6 (2) (no pagination)(e16965).
Johnstone-Robertson SP, Mark D, Morrow C, Middelkoop K, Chiswell M, Aquino LDH, et al. Social mixing patterns within a South African township community: Implications for respiratory disease transmission and control. American Journal of Epidemiology. 2011 01 Dec;174(11):1246-55.
Kerckhove KV, Hens N, Edmunds WJ, Eames KTD. The impact of illness on social networks: Implications for transmission and control of influenza. American Journal of Epidemiology. 2013 01 Dec;178(11):1655-62.
Kumar S, Amarchand R, Gosain M, Sharma H, Dawood F, Jain S, et al. Design of a study to examine contact mixing and acute respiratory infection in Ballabgarh, Haryana. International Journal of Infectious Diseases. 2016 April;1):282.
le Polain de Waroux O, Cohuet S, Ndazima D, Kucharski AJ, Juan-Giner A, Flasche S, et al. Characteristics of human encounters and social mixing patterns relevant to infectious diseases spread by close contact: A survey in Southwest Uganda. BMC Infectious Diseases. 2018 11 Apr;18 (1) (no pagination)(172).
Leung K, Jit M, Lau EHY, Wu JT. Social contact patterns relevant to the spread of respiratory infectious diseases in Hong Kong. Sci Rep. 2017 Aug 11;7(1):7974.
Luh DL, You ZS, Chen SC. Comparison of the social contact patterns among school-age children in specific seasons, locations, and times. Epidemics. 2016 March 01;14:36-44.
McCaw JM, Forbes K, Nathan PM, Pattison PE, Robins GL, Nolan TM, et al. Comparison of three methods for ascertainment of contact information relevant to respiratory pathogen transmission in encounter networks. BMC infectious diseases. 2010;10(1):166.
Melegaro A, Fava ED, Poletti P, Merler S, Nyamukapa C, Williams J, et al. Social contact structures and time use patterns in the manicaland province of Zimbabwe. PLoS ONE. 2017 January;12 (1) (no pagination)(e0170459).
Mikolajczyk RT, Akmatov MK, Rastin S, Kretzschmar M. Social contacts of school children and the transmission of respiratory-spread pathogens. Epidemiology and Infection. 2008 June;136(6):813-22.
Mossong J, Hens N, Jit M, Beutels P, Auranen K, Mikolajczyk R, et al. Social contacts and mixing patterns relevant to the spread of infectious diseases. PLoS Medicine. 2008 March;5(3):0381-91.
Oguz MM, Camurdan AD, Aksakal FN, Akcaboy M, Altinel Acoglu E. Social contact patterns of infants in deciding vaccination strategy: A prospective, cross-sectional, single-centre study. Epidemiology and Infection. 2018 01 Jul;146(9):1157-66.
Rolls DA, Geard NL, Warr DJ, Nathan PM, Robins GL, Pattison PE, et al. Social encounter profiles of greater Melbourne residents, by location–a telephone survey. BMC infectious diseases. 2015;15(1):494.
van de Kassteele J, van Eijkeren J, Wallinga J. Efficient estimation of age-specific social contact rates between men and women. The annals of applied statistics. 2017;11(1):320-39.

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van Hoek AJ, Andrews N, Campbell H, Amirthalingam G, Edmunds WJ, Miller E. The Social Life of Infants in the Context of Infectious Disease Transmission; Social Contacts and Mixing Patterns of the Very Young. PLoS ONE. 2013 16 Oct;8 (10) (no pagination)(e76180).
Willem L, van Kerckhove K, Chao DL, Hens N, Beutels P. A Nice Day for an Infection? Weather Conditions and Social Contact Patterns Relevant to Influenza Transmission. PLoS ONE. 2012 14 Nov;7 (11) (no pagination)(e48695).

Appendix 1 Table 5: Contacts Reported by Boys and Girls with Boys, Girls, Men, and Women

Region	Survey	Partici-pants	Contacts													
			Children						Adults						Total	
			Boys		Girls		Total		Men		Women		Total			
			n	%	n	%	n	%	n	%	n	%	n	%	n	
AFR	South Africa 2010	Boys	5.0	34	2.8	19	7.8	52	3.0	20	4.1	28	7.1	48	15.0	
		Girls	3.1	19	6.2	39	9.2	58	2.4	15	4.3	27	6.7	42	15.9	
	Zimbabwe 2013	Boys	1.6	17	2.4	26	4.0	43	2.0	22	3.3	36	5.3	57	9.3	
		Girls	2.3	27	1.5	18	3.8	45	1.9	22	2.8	33	4.7	55	8.5	
AMR	Peru 2011	Boys	6.2	32	4.0	21	10.2	53	4.2	22	4.9	25	9.1	47	19.3	
		Girls	3.5	23	4.5	29	8.0	51	3.2	20	4.4	28	7.6	49	15.6	
EUR	Belgium 2005-06	Boys	2.6	26	1.6	16	4.2	43	2.3	23	3.4	34	5.7	57	9.9	
		Girls	1.9	16	2.8	24	4.7	40	2.9	25	4.1	35	7.0	60	11.7	
	Belgium 2010-11	Boys	5.4	34	3.4	21	8.7	56	3.0	19	4.0	25	6.9	44	15.7	
		Girls	3.6	20	6.1	34	9.7	55	2.9	17	5.1	29	8.0	45	17.7	
	Finland 2005-06	Boys	4.5	35	2.6	20	7.2	56	2.4	19	3.3	26	5.7	45	12.9	
		Girls	2.7	22	4.0	32	6.7	54	2.2	18	3.5	28	5.8	46	12.5	
	France 2012	Boys	3.1	28	1.9	17	5.0	46	2.5	23	3.5	32	6.0	55	11.0	
		Girls	2.3	19	3.2	26	5.5	45	2.6	21	4.2	34	6.8	55	12.3	
	Germany 2005-06	Boys	2.0	24	1.1	13	3.1	38	2.1	26	3.0	37	5.1	62	8.2	
		Girls	1.1	14	1.9	23	3.0	37	1.9	23	3.3	40	5.1	63	8.1	
	Italy 2005-06	Boys	6.6	32	4.7	23	11.3	55	3.9	19	5.6	27	9.4	45	20.7	
		Girls	5.0	24	7.0	34	12.0	58	3.4	16	5.4	26	8.8	42	20.7	
	Luxembourg 2005-06	Boys	5.7	32	4.1	23	9.8	55	3.5	19	4.5	26	8.0	45	17.8	
		Girls	4.2	26	4.9	30	9.1	56	3.0	18	4.3	26	7.3	45	16.4	
	Netherlands 2005-06	Boys	6.2	39	3.9	25	10.1	64	2.7	17	3.1	19	5.8	36	15.9	
		Girls	3.4	22	5.4	35	8.8	57	2.6	17	4.2	27	6.8	44	15.6	
	Poland 2005-06	Boys	5.2	32	3.6	22	8.8	54	2.9	18	4.7	29	7.6	46	16.3	
		Girls	3.3	20	4.7	29	8.0	49	3.3	20	5.1	31	8.4	51	16.3	
	United Kingdom 2005-06	Boys	3.8	32	2.4	20	6.2	53	2.3	19	3.3	28	5.6	47	11.8	
		Girls	2.6	19	4.7	35	7.2	54	2.2	16	4.0	30	6.2	46	13.5	

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Region	Survey	Partici-pants	Contacts													
			Children						Adults						Total	
			Boys		Girls		Total		Men		Women		Total			
			n	%	n	%	n	%	n	%	n	%	n	%	n	
EUR	United Kingdom 2012	Boys	0.7	12	0.5	9	1.2	21	1.7	29	2.9	50	4.6	79	5.8	
		Girls	0.7	13	0.6	11	1.3	24	1.7	31	2.5	46	4.2	76	5.5	
WPR	China 2010	Boys	6.3	40	3.3	21	9.6	60	2.7	17	3.6	23	6.3	40	15.8	
		Girls	3.6	24	5.0	34	8.6	58	2.3	16	3.9	26	6.2	42	14.8	
	China 2015-16	Boys	2.2	28	1.1	14	3.3	42	1.8	22	2.9	36	4.6	58	7.9	
		Girls	0.8	12	1.5	24	2.3	36	1.4	22	2.6	42	4.0	64	6.3	
	Viet Nam 2007	Boys	2.2	33	1.2	18	3.5	51	1.6	23	1.8	26	3.3	49	6.8	
		Girls	1.1	16	2.4	35	3.4	50	1.3	20	2.1	30	3.4	50	6.8	

Appendix 1 Table 6: Sex-Assortative Mixing Reported by Boys and Girls in Contacts with Children and Adults

Region	Survey	Partici-pants	Contacts			
			Children		Adults	
			%	95% CI	%	95% CI
AFR	South Africa 2010	Boys	64	(60-67)	42	(38-46)
		Girls	67	(64-70)	64	(60-68)
	Zimbabwe 2013	Boys	40	(38-42)	37	(36-39)
		Girls	40	(37-42)	60	(57-62)
AMR	Peru 2011	Boys	61	(58-63)	46	(44-49)
		Girls	56	(53-59)	57	(54-60)
EUR	Belgium 2005-06	Boys	62	(57-66)	41	(37-45)
		Girls	59	(55-63)	59	(55-62)
	Belgium 2010-11	Boys	62	(59-64)	43	(40-46)
		Girls	63	(60-65)	63	(61-66)
	Finland 2005-06	Boys	63	(60-66)	42	(39-46)
		Girls	60	(57-63)	61	(57-65)
	France 2012	Boys	62	(60-63)	42	(41-44)
		Girls	58	(56-60)	62	(60-63)
	Germany 2005-06	Boys	63	(59-68)	41	(37-45)
		Girls	65	(60-69)	63	(60-67)
	Italy 2005-06	Boys	59	(56-61)	41	(38-44)
		Girls	58	(55-61)	61	(58-64)
	Luxembourg 2005-06	Boys	58	(55-60)	43	(41-46)
		Girls	54	(51-57)	59	(56-62)
	Netherlands 2005-06	Boys	61	(59-64)	47	(43-51)
		Girls	61	(58-64)	62	(58-65)
	Poland 2005-06	Boys	59	(57-62)	38	(35-41)
		Girls	59	(56-62)	61	(58-63)
	United Kingdom 2005-06	Boys	62	(59-65)	41	(37-44)
		Girls	65	(62-67)	65	(62-68)
	United Kingdom 2012	Boys	55	(43-67)	37	(31-43)
		Girls	46	(34-59)	60	(53-66)
WPR	China 2010	Boys	66	(64-68)	43	(40-46)
		Girls	58	(56-61)	62	(59-66)
	China 2015-16	Boys	68	(63-73)	38	(34-42)
		Girls	66	(60-71)	64	(60-69)
	Viet Nam 2007	Boys	64	(60-69)	47	(42-52)
		Girls	69	(64-73)	61	(56-65)

Appendix 1 Table 7: Contacts Reported by Boys and Girls with Boys, Girls, Men, and Women at Home and Outside the Home

Region	Survey	Partici-pants	At Home										Outside the Home									
			Children				Adults				Total		Children				Adults				Total	
			Boys		Girls		Men		Women				Boys		Girls		Men		Women			
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
AFR	South Africa 2010	Boys	0.9	6	0.7	5	1.3	9	2.2	15	5.1	34	4.1	27	2.1	14	1.7	11	2.0	13	9.9	66
		Girls	0.5	3	0.9	6	1.1	7	1.8	11	4.3	27	2.6	16	5.2	33	1.3	8	2.5	16	11.6	73
AMR	Peru 2011	Boys	1.6	8	1.4	7	1.9	10	2.4	13	7.3	38	4.6	24	2.6	14	2.3	12	2.4	13	11.9	62
		Girls	1.3	8	1.5	9	1.8	11	2.4	15	7.0	44	2.3	14	3.1	19	1.5	9	2.1	13	9.0	56
EUR	Belgium 2005-06	Boys	0.6	6	0.4	4	1.3	13	1.4	14	3.7	37	2.0	20	1.3	13	1.0	10	1.9	19	6.2	63
		Girls	0.6	5	0.4	3	1.3	11	1.4	12	3.7	32	1.3	11	2.3	20	1.6	14	2.7	23	7.9	68
	Finland 2005-06	Boys	0.8	6	0.7	5	1.2	9	1.2	9	3.9	30	3.7	29	1.9	15	1.2	9	2.1	16	8.9	70
		Girls	0.7	6	0.8	6	1.2	10	1.2	10	3.9	31	2.0	16	3.3	26	1.0	8	2.3	18	8.6	69
	France 2012	Boys	0.9	8	0.4	4	0.5	5	0.6	5	2.4	22	2.3	21	1.6	14	2.0	18	2.8	25	8.7	78
		Girls	0.5	4	0.6	5	0.4	3	0.7	6	2.2	18	1.9	15	2.6	21	2.2	18	3.5	28	10.2	82
	Germany 2005-06	Boys	0.4	5	0.3	4	1.2	15	1.7	21	3.6	44	1.6	20	0.8	10	0.9	11	1.3	16	4.6	56
		Girls	0.4	5	0.5	6	1.3	16	1.7	20	3.9	47	0.7	8	1.5	18	0.6	7	1.6	19	4.4	53
	Italy 2005-06	Boys	0.5	2	0.5	2	1.6	8	2.2	11	4.8	23	6.1	29	4.2	20	2.3	11	3.3	16	15.9	77
		Girls	0.4	2	0.5	2	1.5	7	1.9	9	4.3	21	4.6	22	6.5	31	1.9	9	3.6	17	16.6	79
	Luxembourg 2005-06	Boys	0.7	4	0.7	4	1.6	9	1.8	10	4.8	27	5.0	28	3.4	19	1.9	11	2.7	15	13.0	73
		Girls	0.6	4	0.5	3	1.4	9	1.5	9	4.0	24	3.6	22	4.4	27	1.6	10	2.8	17	12.4	76
	Netherlands 2005-06	Boys	0.8	5	0.6	4	1.3	8	1.3	8	4.0	25	5.3	33	3.3	21	1.5	9	1.8	11	11.9	75
		Girls	0.8	5	0.8	5	1.3	8	1.7	11	4.6	29	2.6	17	4.6	29	1.3	8	2.5	16	11.0	71
	Poland 2005-06	Boys	0.6	4	0.7	4	1.7	10	2.4	15	5.4	33	4.6	28	2.9	18	1.2	7	2.2	13	10.9	67
		Girls	0.6	4	0.7	4	1.8	11	2.5	15	5.6	34	2.7	16	4.0	24	1.5	9	2.6	16	10.8	66
	United Kingdom 2005-06	Boys	0.9	8	0.7	6	1.3	11	1.6	14	4.5	38	3.0	25	1.6	14	1.0	8	1.7	14	7.3	62
		Girls	0.8	6	1.1	8	1.2	9	1.8	13	4.9	36	1.8	13	3.6	27	1.0	7	2.2	16	8.6	64
	United Kingdom 2012	Boys	3.8	8	3.7	8	10.3	21	12.2	25	30.0	61	2.4	5	1.8	4	3.2	7	11.6	24	19.0	39
		Girls	4.1	9	3.2	7	8.5	18	10.1	22	25.9	55	2.8	6	2.9	6	5.3	11	10.0	21	21.0	45
WPR	China 2015-16	Boys	0.3	4	0.2	3	0.9	11	1.6	20	3.0	38	2.0	25	0.8	10	0.8	10	1.3	16	4.9	62
		Girls	0.3	5	0.2	3	0.9	14	1.4	22	2.8	44	0.5	8	1.3	20	0.6	9	1.2	19	3.6	56

Continued on following page

Region	Survey	Partici-pants	At Home										Outside the Home									
			Children				Adults				Total		Children				Adults				Total	
			Boys		Girls		Men		Women				Boys		Girls		Men		Women			
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
WPR	Viet Nam 2007	Boys	0.6	9	0.6	9	1.4	21	1.6	24	4.2	63	1.6	24	0.6	9	0.1	1	0.2	3	2.5	37
		Girls	0.6	9	0.6	9	1.3	19	1.7	25	4.2	62	0.5	7	1.7	25	0.1	1	0.3	4	2.6	38

Appendix 1 Table 8: Sex-Assortative Mixing Reported by Boys and Girls in Contacts with Children and Adults at Home and Outside the Home

Region	Survey	Partici-pants	At Home				Outside the Home			
			Children		Adults		Children		Adults	
			%	95% CI	%	95% CI	%	95% CI	%	95% CI
AFR	South Africa 2010	Boys	54	(45-62)	37	(32-43)	66	(62-70)	46	(41-52)
		Girls	67	(59-75)	62	(57-68)	67	(63-70)	65	(60-70)
AMR	Peru 2011	Boys	53	(48-58)	44	(40-48)	64	(61-67)	49	(45-53)
		Girls	53	(48-59)	57	(52-61)	57	(54-61)	58	(54-63)
EUR	Belgium 2005-06	Boys	62	(52-71)	48	(42-54)	61	(56-67)	35	(29-40)
		Girls	40	(31-50)	52	(46-58)	65	(60-69)	62	(58-67)
	Finland 2005-06	Boys	54	(47-60)	49	(44-54)	66	(63-69)	37	(33-42)
		Girls	52	(45-59)	49	(43-55)	62	(58-66)	70	(65-74)
	France 2012	Boys	69	(66-72)	45	(41-49)	59	(57-61)	41	(40-43)
		Girls	57	(54-61)	63	(59-66)	58	(56-60)	61	(60-63)
	Germany 2005-06	Boys	54	(43-64)	41	(36-46)	66	(61-71)	41	(36-47)
		Girls	54	(45-63)	57	(52-61)	69	(63-74)	73	(67-77)
	Italy 2005-06	Boys	52	(43-60)	41	(37-45)	59	(57-62)	41	(37-44)
		Girls	53	(43-63)	55	(50-60)	59	(56-61)	65	(61-69)
	Luxembourg 2005-06	Boys	49	(42-55)	47	(42-51)	59	(57-62)	41	(37-44)
		Girls	47	(39-55)	52	(47-57)	55	(52-58)	64	(60-68)
	Netherlands 2005-06	Boys	55	(48-63)	49	(43-54)	62	(59-66)	45	(40-51)
		Girls	50	(43-58)	56	(51-51)	63	(60-66)	66	(61-70)
	Poland 2005-06	Boys	45	(38-52)	40	(37-44)	62	(59-64)	36	(32-40)
		Girls	55	(48-63)	58	(54-52)	60	(57-63)	63	(59-67)
	United Kingdom 2005-06	Boys	55	(48-61)	44	(39-49)	64	(61-68)	38	(33-43)
		Girls	57	(51-63)	61	(57-66)	67	(64-70)	68	(64-72)
	United Kingdom 2012	Boys	51	(46-56)	46	(43-48)	56	(50-62)	22	(19-25)
		Girls	44	(39-49)	54	(51-58)	51	(45-57)	65	(62-68)
WPR	China 2015-16	Boys	52	(38-65)	37	(31-42)	71	(66-76)	40	(33-46)
		Girls	42	(29-56)	62	(56-68)	72	(64-77)	67	(61-74)
	Viet Nam 2007	Boys	50	(42-58)	48	(42-53)	72	(66-77)	41	(26-57)
		Girls	52	(44-60)	58	(53-63)	78	(73-83)	80	(67-90)

Appendix 1 Table 9: Contacts Reported by Boys and Girls with Boys, Girls, Men, and Women at School and Elsewhere Outside the Home

Region	Survey	Partici-pants	At School										Elsewhere Outside the Home									
			Children				Adults				Total		Children				Adults				Total	
			Boys		Girls		Men		Women				Boys		Girls		Men		Women			
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
AFR	South Africa 2010	Boys	1.2	12	0.7	7	0.2	2	0.2	2	2.3	23	3.1	31	1.4	14	1.5	15	1.8	18	7.8	77
		Girls	1.3	11	2.2	18	0.2	2	0.5	4	4.2	35	1.4	12	3.2	26	1.2	10	2.1	17	7.9	65
AMR	Peru 2011	Boys	4.3	29	2.6	17	1.2	8	1.3	9	9.4	63	1.4	9	0.7	5	1.8	12	1.7	11	5.6	37
		Girls	2.5	21	3.5	29	1.0	8	1.2	10	8.2	68	0.6	5	0.6	5	1.1	9	1.6	13	3.9	32
EUR	Belgium 2005-06	Boys	1.2	17	0.8	11	0.1	1	0.4	6	2.5	36	1.1	16	0.6	9	1.0	14	1.8	26	4.5	64
		Girls	0.8	9	1.2	13	0.2	2	0.4	4	2.6	29	0.6	7	1.5	17	1.7	19	2.6	29	6.4	71
	Finland 2005-06	Boys	3.1	30	1.6	15	0.3	3	1.0	10	6.0	57	1.3	12	0.7	7	1.1	10	1.4	13	4.5	43
		Girls	1.7	16	2.6	25	0.3	3	1.0	9	5.6	53	0.7	7	1.4	13	1.0	9	1.9	18	5.0	47
	France 2012	Boys	0.1	1	0.0	0	0.0	0	0.0	0	0.1	1	2.2	26	1.5	17	2.0	23	2.8	33	8.5	99
		Girls	0.1	1	0.1	1	0.0	0	0.0	0	0.2	2	1.8	18	2.5	25	2.2	22	3.5	34	10.0	98
	Germany 2005-06	Boys	1.1	19	0.7	12	0.2	4	0.7	12	2.7	47	0.9	16	0.3	5	0.9	16	0.9	16	3.0	53
		Girls	0.6	11	1.1	20	0.1	2	0.8	15	2.6	47	0.3	5	0.8	15	0.6	11	1.2	22	2.9	53
	Italy 2005-06	Boys	4.4	26	3.7	22	0.7	4	1.7	10	10.5	62	2.1	12	0.8	5	1.7	10	1.9	11	6.5	38
		Girls	3.7	22	4.7	28	0.6	4	1.6	9	10.6	62	1.0	6	2.0	12	1.4	8	2.0	12	6.4	38
	Luxembourg 2005-06	Boys	3.7	26	2.7	19	0.7	5	1.2	8	8.3	58	1.9	13	1.1	8	1.3	9	1.8	13	6.1	42
		Girls	3.0	22	3.5	26	0.6	4	1.2	9	8.3	61	1.0	7	1.3	10	1.1	8	1.9	14	5.3	39
	Netherlands 2005-06	Boys	4.2	35	0.9	8	0.5	4	0.9	8	6.5	54	2.2	18	0.9	8	1.2	10	1.2	10	5.5	46
		Girls	2.0	16	3.3	27	0.5	4	1.0	8	6.8	56	0.9	7	1.8	15	1.0	8	1.7	14	5.4	44
	Poland 2005-06	Boys	4.5	33	2.8	21	0.2	1	1.0	7	8.5	63	1.2	9	0.8	6	1.3	10	1.7	13	5.0	37
		Girls	2.7	21	3.8	29	0.5	4	1.1	9	8.1	63	0.5	4	1.1	9	1.3	10	1.9	15	4.8	37
	United Kingdom 2005-06	Boys	2.8	32	1.4	16	0.3	3	0.8	9	5.3	60	0.8	9	0.5	6	0.9	10	1.3	15	3.5	40
		Girls	1.6	16	3.4	34	0.4	4	1.3	13	6.7	67	0.4	4	0.8	8	0.8	8	1.3	13	3.3	33
	United Kingdom 2012	Boys	0.0	0	0.0	0	0.1	3	0.2	7	0.3	10	0.3	10	0.2	7	0.5	17	1.7	57	2.7	90
		Girls	0.0	0	0.0	0	0.0	0	0.1	3	0.1	3	0.4	10	0.4	10	1.1	28	1.9	49	3.8	97
WPR	China 2015-16	Boys	1.9	28	0.8	12	0.3	4	0.6	9	3.6	53	0.8	12	0.4	6	0.9	13	1.1	16	3.2	47
		Girls	0.4	8	1.2	23	0.2	4	0.7	13	2.5	48	0.4	8	0.7	13	0.6	12	1.0	19	2.7	52

Continued on following page

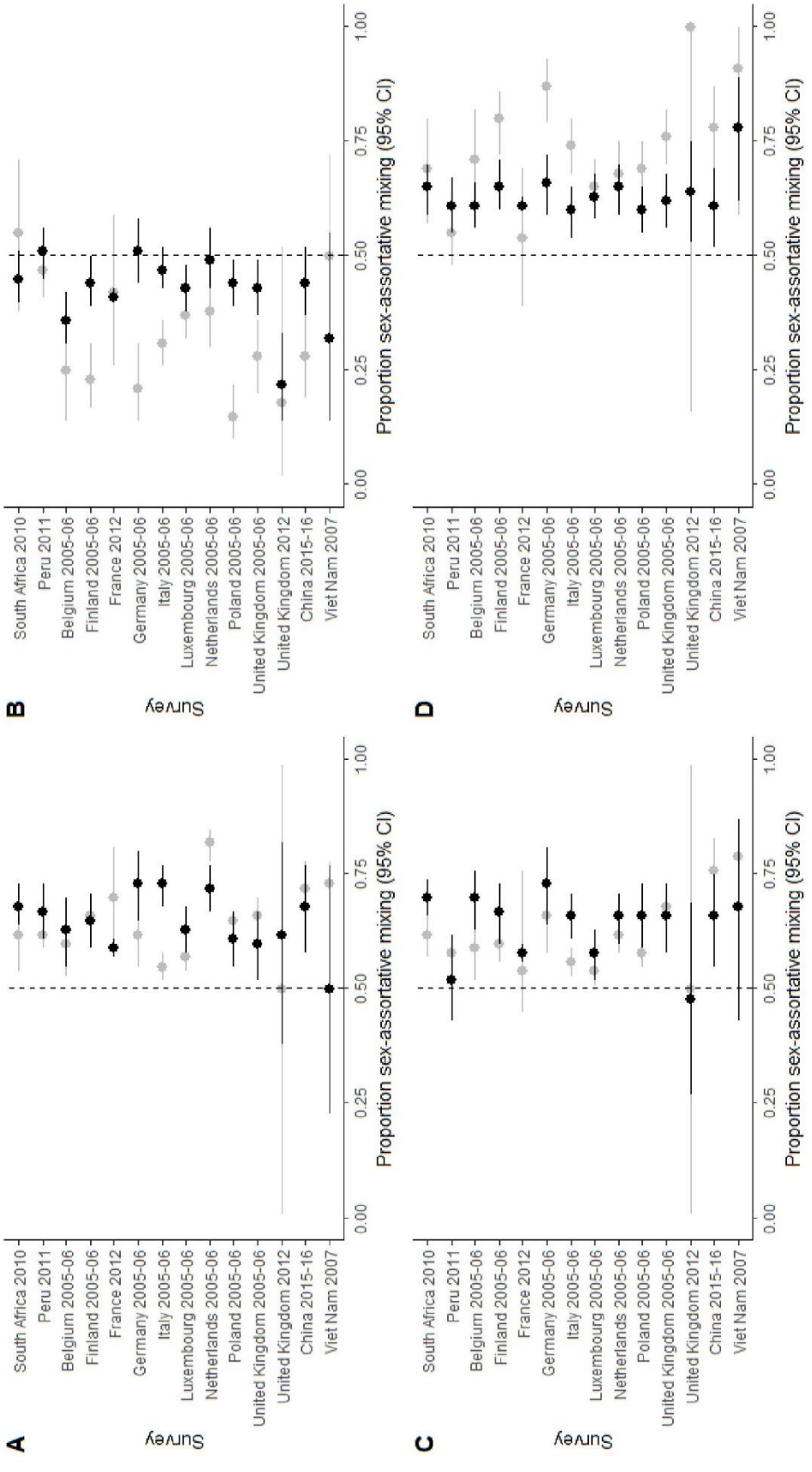
Region	Survey	Partici-pants	At School										Elsewhere Outside the Home									
			Children				Adults				Total		Children				Adults				Total	
			Boys		Girls		Men		Women				Boys		Girls		Men		Women			
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
WPR	Viet Nam 2007	Boys	3.3	60	1.2	22	0.2	4	0.2	4	4.9	89	0.1	2	0.1	2	0.1	2	0.3	5	0.6	11
		Girls	0.9	16	3.4	62	0.0	0	0.2	4	4.5	82	0.1	2	0.2	4	0.2	4	0.5	9	1.0	18

Appendix 1 Table 10: Sex-Assortative Mixing Reported by Boys and Girls in Contacts with Children and Adults at School and Elsewhere Outside the Home

Region	Survey	Partici-pants	At School				Elsewhere Outside the Home			
			Children		Adults		Children		Adults	
			%	95% CI	%	95% CI	%	95% CI	%	95% CI
AFR	South Africa 2010	Boys	62	(54-69)	55	(38-71)	68	(64-73)	45	(40-51)
		Girls	62	(57-67)	69	(57-80)	70	(66-74)	65	(59-70)
AMR	Peru 2011	Boys	62	(59-66)	47	(41-53)	67	(61-73)	51	(45-56)
		Girls	58	(54-62)	55	(48-62)	52	(43-62)	61	(55-67)
EUR	Belgium 2005-06	Boys	60	(53-67)	25	(14-38)	63	(55-70)	36	(31-42)
		Girls	59	(52-66)	71	(57-82)	70	(63-76)	61	(56-66)
	Finland 2005-06	Boys	66	(62-70)	23	(17-31)	65	(59-71)	44	(39-50)
		Girls	60	(56-65)	80	(72-86)	67	(60-73)	65	(60-71)
	France 2012	Boys	70	(57-81)	42	(26-59)	59	(57-61)	41	(40-43)
		Girls	65	(56-74)	54	(39-69)	58	(56-60)	61	(60-63)
	Germany 2005-06	Boys	62	(55-69)	21	(14-31)	73	(65-80)	51	(44-58)
		Girls	66	(58-73)	87	(79-93)	73	(64-81)	66	(59-72)
	Italy 2005-06	Boys	55	(52-58)	31	(26-36)	73	(68-77)	47	(43-52)
		Girls	56	(53-59)	76	(68-80)	66	(61-71)	60	(54-65)
	Luxembourg 2005-06	Boys	57	(54-61)	37	(32-43)	63	(58-68)	43	(38-48)
		Girls	54	(51-57)	65	(59-71)	58	(52-63)	63	(58-68)
	Netherlands 2005-06	Boys	82	(78-85)	38	(30-47)	72	(67-77)	49	(43-46)
		Girls	62	(58-66)	68	(60-75)	66	(60-71)	65	(59-70)
	Poland 2005-06	Boys	62	(59-65)	15	(10-22)	61	(55-67)	44	(39-49)
		Girls	58	(55-62)	69	(62-75)	66	(59-73)	60	(55-65)
	United Kingdom 2005-06	Boys	66	(62-70)	28	(20-36)	60	(52-67)	43	(37-49)
		Girls	68	(64-71)	76	(70-82)	66	(58-73)	62	(56-68)
	United Kingdom 2012	Boys	50	(1-99)	18	(2-52)	62	(38-82)	22	(14-33)
		Girls	50	(1-99)	100	(16-100)	48	(27-69)	64	(53-75)
WPR	China 2015-16	Boys	72	(65-78)	28	(19-40)	68	(58-77)	44	(37-52)
		Girls	76	(67-83)	78	(67-87)	66	(55-75)	61	(52-69)
	Viet Nam 2007	Boys	73	(67-78)	50	(28-72)	50	(23-77)	32	(14-55)
		Girls	79	(73-84)	91	(59-100)	68	(43-87)	78	(62-89)

Appendix 1 Figure 1: Forest Plots of Sex-Assortative Mixing in Contacts Reported by Boys (A, B) and Girls (C, D) With Children (A, C) and With Adults (B, D) at School (Black) and Elsewhere Outside the Home (Grey)

Plots show the proportion of contacts (with 95% confidence intervals) with the same sex, disaggregated by location, as reported for (A) boys with boys, (B) boys with men, (C) girls with girls, and (D) girls with women.



Appendix 1 Table 11: Contacts Reported by Men and Women with Boys, Girls, Men, and Women

Region	Survey	Partici-pants	Contacts												
			Children						Adults						Total
			Boys		Girls		Total		Men		Women		Total		
			n	%	n	%	n	%	n	%	n	%	n	%	n
AFR	South Africa 2010	Men	0.8	6	0.7	5	1.5	10	7.9	52	5.7	38	13.6	90	15.1
		Women	1.2	7	1.6	9	2.7	16	5.5	33	8.4	51	13.9	84	16.7
	South Africa 2011	Men	0.4	7	0.3	7	0.7	14	2.5	50	1.8	36	4.3	86	5.0
		Women	0.6	10	0.7	13	1.3	23	1.6	28	2.7	49	4.3	77	5.5
	Zambia 2011	Men	0.2	5	0.3	5	0.5	10	2.9	59	1.5	31	4.4	90	4.9
		Women	0.4	8	0.4	8	0.7	16	1.3	27	2.7	57	4.0	84	4.7
	Zimbabwe 2013	Men	1.0	9	1.2	11	2.2	21	3.3	31	5.1	48	8.4	79	10.6
		Women	1.0	11	0.8	8	1.8	19	4.2	44	3.5	37	7.7	81	9.5
AMR	Peru 2011	Men	2.0	12	1.8	11	3.8	24	7.2	45	5.1	32	12.3	76	16.1
		Women	1.8	13	1.9	14	3.7	27	4.6	33	5.5	40	10.1	73	13.8
EUR	Belgium 2005-06	Men	0.3	3	0.3	3	0.6	6	6.2	53	5.0	42	11.2	95	11.8
		Women	0.6	5	0.7	6	1.3	11	4.7	39	6.1	51	10.8	89	12.0
	Belgium 2010-11	Men	0.4	3	0.4	3	0.9	7	6.6	51	5.5	42	12.1	93	13.0
		Women	0.6	5	0.6	5	1.2	10	4.8	38	6.6	52	11.4	90	12.6
	Finland 2005-06	Men	0.5	5	0.5	5	1.0	10	4.7	49	3.9	41	8.6	90	9.6
		Women	0.7	6	0.7	6	1.4	12	3.5	31	6.4	57	9.9	88	11.3
	France 2012	Men	0.3	3	0.2	2	0.5	5	5.3	51	4.6	44	9.9	95	10.4
		Women	0.4	4	0.4	4	0.8	8	4.3	41	5.4	51	9.7	92	10.5
	Germany 2005-06	Men	0.2	3	0.2	3	0.5	6	4.3	53	3.3	41	7.6	94	8.1
		Women	0.3	4	0.3	5	0.6	9	2.8	39	3.7	52	6.5	91	7.1
	Italy 2005-06	Men	0.9	4	0.5	2	1.3	7	10.3	53	7.9	40	18.2	93	19.5
		Women	1.3	7	1.3	7	2.5	14	6.8	37	9.0	49	15.8	86	18.3
	Luxembourg 2005-06	Men	0.6	4	0.4	3	1.0	6	9.5	55	6.7	39	16.2	94	17.2
		Women	1.3	8	1.3	8	2.6	15	6.5	38	8.1	47	14.6	85	17.1
	Netherlands 2005-06	Men	0.6	5	0.5	4	1.1	10	5.9	51	4.6	40	10.5	91	11.6
		Women	0.7	6	0.8	7	1.5	12	4.4	35	6.6	53	11.0	88	12.5

Continued on following page

Region	Survey	Partici-pants	Contacts													
			Children						Adults						Total	
			Boys		Girls		Total		Men		Women		Total			
			n	%	n	%	n	%	n	%	n	%	n	%	n	
EUR	Poland 2005-06	Men	0.5	3	0.4	3	0.9	6	8.9	55	6.5	40	15.4	94	16.3	
		Women	0.5	3	0.7	5	1.2	8	5.9	37	8.7	55	14.6	92	15.8	
	United Kingdom 2005-06	Men	0.7	7	0.5	5	1.2	12	5.1	48	4.2	40	9.3	88	10.5	
		Women	0.9	8	1.1	9	2.0	17	4.0	34	5.7	49	9.7	83	11.6	
WPR	Australia 2008	Men	2.4	11	2.2	10	4.6	21	8.9	40	8.8	40	17.8	79	22.4	
		Women	3.5	14	2.1	9	5.5	23	6.8	28	12.0	49	18.8	77	24.3	
	Australia 2013	Men	0.3	5	0.2	4	0.5	9	2.3	43	2.6	48	4.9	91	5.4	
		Women	0.3	6	0.4	7	0.7	12	2.1	36	3.0	52	5.1	88	5.8	
	China 2010	Men	0.4	3	0.4	4	0.8	7	6.5	54	4.7	39	11.2	93	12.0	
		Women	0.6	5	0.6	5	1.2	10	4.5	38	6.0	52	10.5	90	11.7	
	China 2015-16	Men	0.3	4	0.2	3	0.4	7	2.7	45	2.9	48	5.6	93	6.0	
		Women	0.3	5	0.3	5	0.6	10	2.2	33	3.8	57	6.0	91	6.6	
	Viet Nam 2007	Men	0.7	9	0.6	8	1.3	17	3.6	45	3.1	38	6.7	83	8.1	
		Women	0.7	9	0.7	9	1.5	18	2.4	30	4.2	52	6.6	82	8.1	

Appendix 1 Table 12: Sex-Assortative Mixing Reported by Men and Women in Contacts with Children and Adults

Region	Survey	Partici-pants	Contacts			
			Children		Adults	
			%	95% CI	%	95% CI
AFR	South Africa 2010	Men	54	(48-60)	58	(56-60)
		Women	58	(53-62)	61	(59-62)
	South Africa 2011	Men	52	(47-56)	58	(56-60)
		Women	55	(51-58)	63	(61-65)
	Zambia 2011	Men	47	(43-51)	66	(64-67)
		Women	52	(49-55)	67	(65-68)
	Zimbabwe 2013	Men	45	(43-48)	39	(38-41)
		Women	47	(43-50)	45	(44-47)
AMR	Peru 2011	Men	53	(49-58)	59	(56-61)
		Women	51	(47-55)	54	(52-57)
EUR	Belgium 2005-06	Men	48	(40-56)	56	(54-58)
		Women	54	(49-60)	56	(55-58)
	Belgium 2010-11	Men	51	(47-55)	55	(54-56)
		Women	49	(46-53)	58	(57-59)
	Finland 2005-06	Men	53	(47-58)	55	(53-56)
		Women	50	(45-54)	64	(63-66)
	France 2012	Men	53	(48-58)	53	(52-54)
		Women	51	(48-54)	55	(55-56)
	Germany 2005-06	Men	51	(44-58)	57	(55-58)
		Women	53	(47-58)	57	(55-58)
	Italy 2005-06	Men	65	(60-70)	57	(55-58)
		Women	50	(46-53)	57	(56-58)
	Luxembourg 2005-06	Men	59	(53-64)	59	(57-60)
		Women	50	(47-53)	56	(54-57)
	Netherlands 2005-06	Men	57	(50-63)	56	(54-58)
		Women	54	(49-59)	60	(58-62)
	Poland 2005-06	Men	56	(50-61)	58	(56-59)
		Women	57	(52-61)	59	(58-61)
	United Kingdom 2005-06	Men	58	(53-63)	55	(53-57)
		Women	54	(51-58)	59	(57-60)
WPR	Australia 2008	Men	52	(44-60)	50	(46-54)
		Women	37	(34-41)	64	(62-66)
	Australia 2013	Men	54	(48-61)	47	(45-49)
		Women	52	(48-56)	58	(57-60)
	China 2010	Men	49	(45-53)	58	(57-59)
		Women	49	(45-52)	57	(56-58)
	China 2015-16	Men	59	(52-65)	48	(46-50)
		Women	48	(42-53)	64	(62-66)
	Viet Nam 2007	Men	53	(47-58)	54	(52-56)
		Women	50	(46-55)	64	(62-66)

Appendix 1 Table 13: Contacts Reported by Men and Women with Boys, Girls, Men, and Women at Home and Outside the Home

Region	Survey	Partici-pants	At Home										Outside the Home									
			Children				Adults				Total		Children				Adults				Total	
			Boys		Girls		Men		Women				Boys		Girls		Men		Women			
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
AFR	South Africa 2010	Men	0.4	3	0.3	2	1.3	9	1.5	10	3.5	23	0.5	3	0.4	3	6.5	43	4.2	28	11.6	77
		Women	0.6	4	0.8	5	1.6	10	2.1	13	5.1	31	0.6	4	0.7	4	3.9	23	6.4	38	11.6	69
	South Africa 2011	Men	0.3	6	0.3	6	1.2	25	1.5	31	3.3	69	0.0	0	0.0	0	1.2	25	0.3	6	1.5	31
		Women	0.6	11	0.7	13	1.3	24	1.7	31	4.3	78	0.0	0	0.0	0	0.3	5	0.9	16	1.2	22
	Zambia 2011	Men	0.2	4	0.2	4	0.8	17	0.9	20	2.1	46	0.0	0	0.0	0	2.0	43	0.5	11	2.5	54
		Women	0.3	6	0.3	6	0.9	19	1.1	23	2.6	55	0.0	0	0.1	2	0.4	9	1.6	34	2.1	45
AMR	Peru 2011	Men	1.4	9	1.4	9	2.0	13	2.5	16	7.3	46	0.6	4	0.4	3	5.1	32	2.6	16	8.7	54
		Women	1.5	11	1.6	12	2.4	17	2.3	17	7.8	57	0.3	2	0.3	2	2.2	16	3.2	23	6.0	43
EUR	Belgium 2005-06	Men	0.2	2	0.3	3	1.0	8	1.6	13	3.1	26	0.1	1	0.1	1	5.2	44	3.4	29	8.8	74
		Women	0.3	2	0.4	3	1.5	12	1.1	9	3.3	27	0.3	2	0.3	2	3.2	26	5.0	41	8.8	73
	Finland 2005-06	Men	0.3	3	0.3	3	0.5	5	1.1	12	2.2	23	0.2	2	0.1	1	4.2	44	2.8	29	7.3	77
		Women	0.4	4	0.3	3	1.2	11	0.6	5	2.5	22	0.3	3	0.3	3	2.4	21	5.8	51	8.8	78
	France 2012	Men	0.1	1	0.0	0	1.3	12	0.7	7	2.1	20	0.2	2	0.2	2	4.0	38	4.0	38	8.4	80
		Women	0.1	1	0.1	1	0.7	7	0.7	7	1.6	15	0.3	3	0.4	4	3.7	35	4.7	44	9.1	85
	Germany 2005-06	Men	0.1	1	0.1	1	0.8	10	1.3	16	2.3	29	0.1	1	0.1	1	3.5	44	2.0	25	5.7	71
		Women	0.2	3	0.2	3	1.2	16	1.1	15	2.7	37	0.2	3	0.1	1	1.6	22	2.7	37	4.6	63
	Italy 2005-06	Men	0.3	2	0.2	1	0.9	5	1.7	9	3.1	16	0.5	3	0.3	2	9.3	48	6.2	32	16.3	84
		Women	0.4	2	0.4	2	1.6	9	1.5	8	3.9	21	0.9	5	0.9	5	5.2	28	7.6	41	14.6	79
	Luxembourg 2005-06	Men	0.3	2	0.2	1	1.1	6	1.7	10	3.3	19	0.3	2	0.2	1	8.3	49	5.0	29	13.8	81
		Women	0.4	2	0.3	2	1.7	10	1.3	8	3.7	21	0.9	5	1.0	6	4.8	28	6.9	40	13.6	79
	Netherlands 2005-06	Men	0.4	3	0.3	3	0.8	7	1.4	12	2.9	25	0.3	3	0.2	2	5.1	44	3.2	27	8.8	75
		Women	0.3	2	0.4	3	1.5	12	1.1	9	3.3	26	0.4	3	0.4	3	2.9	23	5.5	44	9.2	74
	Poland 2005-06	Men	0.3	2	0.3	2	1.4	9	2.1	13	4.1	25	0.2	1	0.1	1	7.4	46	4.4	27	12.1	75
		Women	0.3	2	0.4	3	1.8	11	1.9	12	4.4	28	0.3	2	0.3	2	4.1	26	6.8	43	11.5	72
	United Kingdom 2005-06	Men	0.4	4	0.4	4	0.9	8	1.5	14	3.2	30	0.3	3	0.1	1	4.3	41	2.7	25	7.4	70
		Women	0.5	4	0.5	4	1.6	14	1.3	11	3.9	34	0.4	3	0.5	4	2.4	21	4.3	37	7.6	66

Continued on following page

Region	Survey	Partici-pants	At Home										Outside the Home									
			Children				Adults				Total		Children				Adults				Total	
			Boys		Girls		Men		Women				Boys		Girls		Men		Women			
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
WPR	China 2015-16	Men	0.2	3	0.1	2	0.5	8	1.1	18	1.9	31	0.1	2	0.1	2	2.2	36	1.8	30	4.2	69
		Women	0.2	3	0.2	3	0.8	12	0.8	12	2.0	30	0.2	3	0.1	1	1.4	21	3.0	45	4.7	70
	Viet Nam 2007	Men	0.6	8	0.5	6	1.9	24	2.3	29	5.3	67	0.1	1	0.1	1	1.7	22	0.7	9	2.6	33
		Women	0.6	7	0.6	7	1.8	22	2.4	29	5.4	66	0.2	2	0.2	2	0.6	7	1.8	22	2.8	34

Appendix 1 Table 14: Sex-Assortative Mixing Reported by Men and Women in Contacts with Children and Adults at Home and Outside the Home

Region	Survey	Partici-pants	At Home				Outside the Home			
			Children		Adults		Children		Adults	
			%	95% CI	%	95% CI	%	95% CI	%	95% CI
AFR	South Africa 2010	Men	54	(45-63)	47	(43-51)	62	(60-64)	61	(59-63)
		Women	59	(53-65)	57	(53-61)	56	(50-63)	62	(60-64)
	South Africa 2011	Men	52	(47-56)	45	(43-48)	75	(72-78)	80	(77-82)
		Women	54	(51-58)	58	(55-60)	74	(52-90)	75	(72-78)
	Zambia 2011	Men	45	(40-49)	47	(45-49)	79	(77-80)	79	(77-80)
		Women	51	(47-55)	55	(53-57)	55	(46-64)	79	(77-80)
AMR	Peru 2011	Men	51	(46-56)	45	(41-49)	59	(56-63)	67	(64-70)
		Women	52	(47-56)	49	(45-53)	49	(39-60)	59	(56-63)
EUR	Belgium 2005-06	Men	43	(34-53)	40	(36-44)	61	(59-63)	61	(58-63)
		Women	55	(48-62)	42	(39-46)	54	(46-61)	61	(59-63)
	Finland 2005-06	Men	50	(43-57)	32	(28-36)	71	(69-72)	60	(58-62)
		Women	49	(42-55)	36	(32-39)	51	(44-58)	71	(69-72)
	France 2012	Men	63	(52-74)	65	(63-67)	56	(55-57)	50	(49-52)
		Women	49	(42-55)	52	(49-54)	52	(48-55)	56	(55-57)
	Germany 2005-06	Men	45	(35-54)	39	(36-42)	62	(60-64)	63	(61-65)
		Women	57	(50-64)	46	(44-49)	48	(40-56)	62	(60-64)
	Italy 2005-06	Men	61	(52-69)	36	(32-40)	59	(58-61)	60	(58-61)
		Women	49	(43-55)	48	(45-51)	50	(46-54)	59	(58-61)
	Luxembourg 2005-06	Men	57	(50-65)	40	(37-43)	59	(58-60)	63	(61-64)
		Women	46	(40-52)	42	(40-45)	52	(48-55)	59	(58-60)
	Netherlands 2005-06	Men	54	(46-62)	36	(32-40)	66	(64-68)	62	(60-64)
		Women	56	(49-63)	41	(37-45)	52	(46-59)	66	(64-68)
	Poland 2005-06	Men	53	(46-60)	41	(38-44)	62	(61-64)	63	(61-64)
		Women	57	(51-64)	51	(48-53)	56	(49-63)	62	(61-64)
	United Kingdom 2005-06	Men	54	(48-60)	36	(33-40)	64	(62-66)	61	(59-63)
		Women	52	(47-57)	46	(43-49)	57	(51-62)	64	(62-66)
WPR	China 2015-16	Men	53	(44-62)	30	(27-34)	69	(66-71)	55	(53-58)
		Women	52	(44-60)	51	(47-54)	43	(35-51)	69	(66-71)
	Viet Nam 2007	Men	53	(47-58)	45	(42-48)	74	(70-76)	69	(66-73)
		Women	49	(44-54)	58	(55-61)	54	(44-63)	74	(70-76)

Appendix 1 Table 15: Contacts Reported by Men and Women with Boys, Girls, Men, and Women at Work and Elsewhere Outside the Home

Region	Survey	Partici-pants	At Work										Elsewhere Outside the Home									
			Children				Adults				Total		Children				Adults				Total	
			Boys		Girls		Men		Women				Boys		Girls		Men		Women			
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
AFR	South Africa 2010	Men	0.0	0	0.1	1	1.4	12	0.9	7	2.4	20	0.5	4	0.3	2	5.4	45	3.5	29	9.7	80
		Women	0.1	1	0.1	1	0.5	4	0.7	6	1.4	11	0.5	4	0.7	6	3.6	30	6.0	49	10.8	89
	South Africa 2011	Men	0.0	0	0.0	0	0.5	22	0.1	4	0.6	26	0.0	0	0.0	0	1.3	57	0.4	17	1.7	74
		Women	0.0	0	0.0	0	0.1	5	0.4	19	0.5	24	0.0	0	0.0	0	0.4	19	1.2	57	1.6	76
	Zambia 2011	Men	0.0	0	0.0	0	0.4	12	0.1	3	0.5	15	0.0	0	0.0	0	2.2	67	0.6	18	2.8	85
		Women	0.0	0	0.0	0	0.1	3	0.9	23	1.0	25	0.1	3	0.1	3	0.6	15	2.2	55	3.0	75
AMR	Peru 2011	Men	0.0	0	0.0	0	0.9	9	0.3	3	1.2	12	0.7	7	0.5	5	5.2	50	2.8	27	9.2	88
		Women	0.0	0	0.0	0	0.1	1	0.2	3	0.3	4	0.4	5	0.4	5	2.7	35	3.9	51	7.4	96
EUR	Belgium 2005-06	Men	0.0	0	0.0	0	2.0	21	1.0	10	3.0	31	0.1	1	0.1	1	3.7	39	2.7	28	6.6	69
		Women	0.0	0	0.0	0	1.1	12	1.4	15	2.5	26	0.3	3	0.3	3	2.4	25	4.0	42	7.0	74
	Finland 2005-06	Men	0.0	0	0.0	0	2.0	24	1.0	12	3.0	37	0.2	2	0.1	1	2.7	33	2.2	27	5.2	63
		Women	0.1	1	0.1	1	0.9	9	2.4	25	3.5	36	0.3	3	0.3	3	1.7	18	3.9	40	6.2	64
	France 2012	Men	0.0	0	0.0	0	1.1	14	1.3	16	2.4	30	0.2	3	0.2	3	2.9	37	2.2	28	5.5	70
		Women	0.0	0	0.0	0	0.9	10	1.5	17	2.4	28	0.0	0	0.3	3	2.8	32	3.2	37	6.3	72
	Germany 2005-06	Men	0.0	0	0.0	0	1.8	27	0.8	12	2.6	39	0.1	1	0.1	1	2.3	34	1.6	24	4.1	61
		Women	0.0	0	0.0	0	0.6	11	1.1	20	1.7	31	0.2	4	0.1	2	1.3	24	2.1	39	3.7	69
	Italy 2005-06	Men	0.1	1	0.1	1	3.7	22	2.0	12	5.9	35	0.4	2	0.2	1	5.9	35	4.4	26	10.9	65
		Women	0.3	2	0.3	2	1.6	10	2.1	14	4.3	28	0.6	4	0.6	4	3.9	25	5.9	39	11.0	72
	Luxembourg 2005-06	Men	0.1	1	0.0	0	4.0	27	1.8	12	5.9	40	0.3	2	0.2	1	5.0	34	3.5	23	9.0	60
		Women	0.4	3	0.4	3	2.0	13	2.2	15	5.0	34	0.6	4	0.7	5	3.3	22	5.3	36	9.9	66
	Netherlands 2005-06	Men	0.0	0	0.0	0	2.5	26	1.0	10	3.5	36	0.3	3	0.2	2	3.2	33	2.6	27	6.3	64
		Women	0.1	1	0.1	1	1.0	10	1.8	18	3.0	29	0.4	4	0.3	3	2.2	22	4.3	42	7.2	71
	Poland 2005-06	Men	0.0	0	0.0	0	3.5	27	1.5	12	5.0	39	0.2	2	0.1	1	4.4	34	3.2	25	7.9	61
		Women	0.1	1	0.1	1	2.1	17	3.1	24	5.4	43	0.2	2	0.2	2	2.5	20	4.4	35	7.3	57
	United Kingdom 2005-06	Men	0.0	0	0.0	0	1.7	21	0.9	11	2.6	32	0.3	4	0.2	2	3.0	37	2.1	26	5.6	68
		Women	0.2	2	0.2	2	0.9	10	1.7	20	3.0	34	0.3	3	0.4	5	1.8	21	3.2	37	5.7	66

Continued on following page

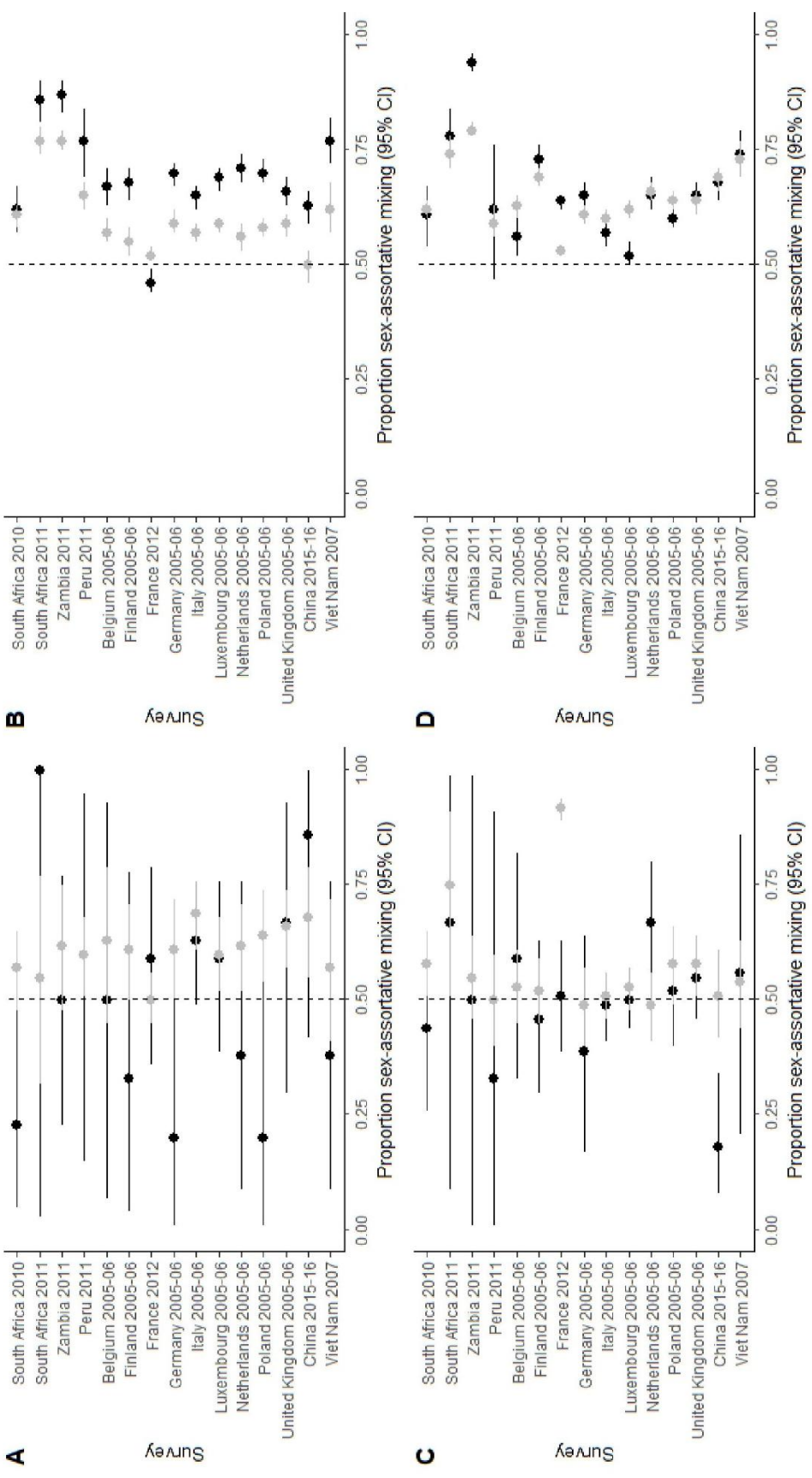
Region	Survey	Partici-pants	At Work										Elsewhere Outside the Home									
			Children				Adults				Total		Children				Adults				Total	
			Boys		Girls		Men		Women				Boys		Girls		Men		Women			
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
WPR	China 2015-16	Men	0.0	0	0.0	0	1.4	26	0.8	15	2.2	41	0.1	2	0.1	2	1.5	28	1.5	28	3.2	59
		Women	0.1	2	0.0	0	0.6	10	1.4	23	2.1	34	0.2	3	0.2	3	1.1	18	2.5	41	4.0	66
	Viet Nam 2007	Men	0.0	0	0.0	0	1.6	34	0.5	11	2.1	45	0.2	4	0.1	2	1.4	30	0.9	19	2.6	55
		Women	0.0	0	0.0	0	0.4	8	1.2	25	1.6	33	0.3	6	0.3	6	0.7	15	1.9	40	3.2	67

Appendix 1 Table 16: Sex-Assortative Mixing Reported by Men and Women in Contacts with Children and Adults at Work and Elsewhere Outside the Home

Region	Survey	Partici-pants	At Work				Elsewhere Outside the Home			
			Children		Adults		Children		Adults	
			%	95% CI	%	95% CI	%	95% CI	%	95% CI
AFR	South Africa 2010	Men	57	(48-65)	62	(57-67)	57	(48-65)	61	(58-63)
		Women	44	(26-62)	61	(54-67)	58	(51-65)	62	(60-64)
	South Africa 2011	Men	55	(32-77)	86	(81-90)	55	(62-77)	77	(74-80)
		Women	67	(9-99)	78	(71-84)	75	(51-91)	74	(71-78)
	Zambia 2011	Men	62	(48-75)	87	(83-90)	62	(48-75)	77	(75-79)
		Women	50	(1-99)	94	(92-96)	55	(46-64)	79	(78-81)
AMR	Peru 2011	Men	60	(51-68)	77	(69-84)	60	(51-68)	65	(62-68)
		Women	33	(1-91)	62	(47-76)	50	(40-60)	59	(56-63)
EUR	Belgium 2005-06	Men	63	(45-79)	67	(63-71)	63	(45-79)	57	(55-60)
		Women	59	(33-82)	56	(52-60)	53	(45-61)	63	(60-65)
	Finland 2005-06	Men	61	(50-71)	68	(64-71)	61	(50-71)	55	(52-58)
		Women	46	(30-63)	73	(71-76)	52	(45-59)	69	(67-71)
	France 2012	Men	50	(45-56)	46	(44-49)	50	(45-56)	52	(51-54)
		Women	51	(39-63)	64	(62-65)	92	(89-94)	53	(52-54)
	Germany 2005-06	Men	61	(50-72)	70	(67-72)	61	(50-72)	59	(57-62)
		Women	39	(17-64)	65	(61-68)	49	(40-57)	61	(59-63)
	Italy 2005-06	Men	69	(61-76)	65	(62-67)	69	(61-76)	57	(55-59)
		Women	49	(41-56)	57	(54-60)	51	(46-56)	60	(59-62)
	Luxembourg 2005-06	Men	60	(52-68)	69	(66-71)	60	(52-68)	59	(57-60)
		Women	50	(44-56)	52	(50-55)	53	(48-57)	62	(60-64)
	Netherlands 2005-06	Men	62	(52-71)	71	(68-74)	62	(52-71)	56	(53-59)
		Women	67	(51-80)	65	(62-69)	49	(41-56)	66	(64-68)
	Poland 2005-06	Men	64	(54-74)	70	(68-73)	64	(54-74)	58	(56-60)
		Women	52	(40-64)	60	(58-62)	58	(49-66)	64	(62-66)
	United Kingdom 2005-06	Men	66	(57-74)	66	(63-69)	66	(57-74)	59	(56-61)
		Women	55	(46-64)	65	(62-68)	58	(51-64)	64	(61-66)
WPR	China 2015-16	Men	68	(55-79)	63	(59-66)	68	(55-79)	50	(46-53)
		Women	18	(8-34)	68	(64-71)	51	(42-61)	69	(66-71)
	Viet Nam 2007	Men	57	(41-72)	77	(72-82)	57	(41-72)	62	(57-68)
		Women	56	(21-86)	74	(69-79)	54	(44-63)	73	(69-77)

Appendix 1 Figure 2: Forest Plots of Sex-Assortative Mixing in Contacts Reported by Men (A, B) and Women (C, D) With Children (A, C) and With Adults (B, D) at Work (Black) and Elsewhere Outside the Home (Grey)

Plots show the proportion of contacts (with 95% confidence intervals) with the same sex, disaggregated by location, as reported for (A) men with boys, (B) men with men, (C) women with girls, and (D) women with women.



Appendix 1 Table 17: Survey Characteristics Measured by the AXIS Tool

Region	Survey	Intro.	Methods										Results				Discussion		Oth.
		Were the aims/objectives of the study clear?	Was the study design appropriate for the stated aim(s) and aligned with understanding population-level social contact patterns?	Was the sample size justified?	Was the target/reference population clearly defined and is that population the general population?	Was the sample frame taken from an appropriate population base so that it closely represented the target/reference population under investigation?	Was the selection process likely to select subjects/participants that were representative of the target/reference population under investigation?	Were measures undertaken to address and categorise non-responders?	Were the risk factor and outcome variables measured appropriate to the aims of the study?	Were the risk factor and outcome variables measured correctly using instruments that had been trialled, piloted or published previously?	Is it clear what was used to determined statistical significance and/or precision estimates?	Were the methods (including statistical methods) sufficiently described to enable them to be repeated?	Were the basic data adequately described?	Does the response rate raise concerns about non-response bias?	If appropriate, was information about non-responders described?	Were the results internally consistent?	Were the results for the analyses described in the methods, presented?	Were the authors' discussions and conclusions justified by the results?	Were the limitations of the study discussed?	Were there any funding sources or conflicts of interest that may affect the authors' interpretation of the results?	Was ethical approval or consent of participants attained?
AFR	South Africa 2010	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes
	South Africa 2011	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes
	Zambia 2011	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes
	Zimbabwe 2013	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Unk	No	Yes	Yes	Yes	No	Yes
AMR	Peru 2011	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Unk	No	Yes	Yes	Yes	No	Yes
EUR	Belgium 2005-06	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Unk	No	Yes	Yes	Yes	No	Yes

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Region	Survey	Intro.	Methods										Results				Discussion		Oth.
		Were the aims/objectives of the study clear?	Was the study design appropriate for the stated aim(s) and aligned with understanding population-level social contact patterns?	Was the sample size justified?	Was the target/reference population clearly defined and is that population the general population?	Was the sample frame taken from an appropriate population base so that it closely represented the target/reference population under investigation?	Was the selection process likely to select subjects/participants that were representative of the target/reference population under investigation?	Were measures undertaken to address and categorise non-responders?	Were the risk factor and outcome variables measured appropriate to the aims of the study?	Were the risk factor and outcome variables measured correctly using instruments that had been trialled, piloted or published previously?	Is it clear what was used to determined statistical significance and/or precision estimates?	Were the methods (including statistical methods) sufficiently described to enable them to be repeated?	Were the basic data adequately described?	Does the response rate raise concerns about non-response bias?	If appropriate, was information about non-responders described?	Were the results internally consistent?	Were the results for the analyses described in the methods, presented?	Were the authors' discussions and conclusions justified by the results?	Were the limitations of the study discussed?	Were there any funding sources or conflicts of interest that may affect the authors' interpretation of the results?	Was ethical approval or consent of participants attained?
EUR	Belgium 2010-11	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Unk	No	Yes	Yes	Yes	No	Yes
	Finland 2005-06	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Unk	No	Yes	Yes	Yes	No	Yes
	France 2012	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes
	Germany 2005-06	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Unk	No	Yes	Yes	Yes	No	Yes
	Italy 2005-06	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Unk	No	Yes	Yes	Yes	No	Yes
	Luxembourg 2005-06	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Unk	No	Yes	Yes	Yes	No	Yes

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Region	Survey	Intro.	Methods										Results					Discussion		Oth.
		Were the aims/objectives of the study clear?	Was the study design appropriate for the stated aim(s) and aligned with understanding population-level social contact patterns?	Was the sample size justified?	Was the target/reference population clearly defined and is that population the general population?	Was the sample frame taken from an appropriate population base so that it closely represented the target/reference population under investigation?	Was the selection process likely to select subjects/participants that were representative of the target/reference population under investigation?	Were measures undertaken to address and categorise non-responders?	Were the risk factor and outcome variables measured appropriate to the aims of the study?	Were the risk factor and outcome variables measured correctly using instruments that had been trialled, piloted or published previously?	Is it clear what was used to determined statistical significance and/or precision estimates?	Were the methods (including statistical methods) sufficiently described to enable them to be repeated?	Were the basic data adequately described?	Does the response rate raise concerns about non-response bias?	If appropriate, was information about non-responders described?	Were the results internally consistent?	Were the results for the analyses described in the methods, presented?	Were the authors' discussions and conclusions justified by the results?	Were the limitations of the study discussed?	Were there any funding sources or conflicts of interest that may affect the authors' interpretation of the results?	Was ethical approval or consent of participants attained?
EUR	Netherlands 2005-06	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Unk	No	Yes	Yes	Yes	No	Yes
	Poland 2005-06	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Unk	No	Yes	Yes	Yes	No	Yes
	United Kingdom 2005-06	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Unk	No	Yes	Yes	Yes	No	Yes
	United Kingdom 2012	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
WPR	Australia 2008	Yes	No	No	No	No	Unk	No	Yes	Yes	Yes	Yes	Yes	Unk	No	Yes	Yes	Yes	No	Yes
	Australia 2013	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes

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Region	Survey			
		China 2010	China 2015-16	Viet Nam 2007
Intro.	Were the aims/objectives of the study clear?	Yes	Yes	Yes
Methods	Was the study design appropriate for the stated aim(s) and aligned with understanding population-level social contact patterns?	Yes	Yes	Yes
	Was the sample size justified?	Yes	No	No
	Was the target/reference population clearly defined and is that population the general population?	Yes	Yes	Yes
	Was the sample frame taken from an appropriate population base so that it closely represented the target/reference population under investigation?	Yes	Yes	Yes
	Was the selection process likely to select subjects/participants that were representative of the target/reference population under investigation?	Yes	Yes	Yes
	Were measures undertaken to address and categorise non-responders?	No	No	No
	Were the risk factor and outcome variables measured appropriate to the aims of the study?	Yes	Yes	Yes
	Were the risk factor and outcome variables measured correctly using instruments that had been trialled, piloted or published previously?	Yes	Yes	Yes
	Is it clear what was used to determined statistical significance and/or precision estimates?	Yes	Yes	Yes
	Were the methods (including statistical methods) sufficiently described to enable them to be repeated?	Yes	Yes	Yes
	Were the basic data adequately described?	Yes	Yes	Yes
Results	Does the response rate raise concerns about non-response bias?	No	Unk	Unk
	If appropriate, was information about non-responders described?	No	No	No
	Were the results internally consistent?	Yes	Yes	Yes
	Were the results for the analyses described in the methods, presented?	Yes	Yes	Yes
	Were the authors' discussions and conclusions justified by the results?	Yes	Yes	Yes
Discussion	Were the limitations of the study discussed?	Yes	Yes	Yes
	Were there any funding sources or conflicts of interest that may affect the authors' interpretation of the results?	No	No	No
Oth.	Was ethical approval or consent of participants attained?	Yes	Yes	Yes

Appendix 1 Table 18: Subgroup Analyses

Sub-group	Proportion of adult contacts with men (random effects summary estimates)													
	Children							Adults						
	n	Boys			Girls			n	Men			Women		
		%	95% CI	I^2	%	95% CI	I^2		%	95% CI	I^2	%	95% CI	I^2
Region														
African Region	2	39	(35-44)	78.9	38	(34-43)	79.0	4	55	(42-68)	99.6	41	(32-51)	99.2
Region of the Americas	1	46	(44-49)	-	43	(40-46)	-	1	59	(56-61)	-	46	(43-48)	-
European Region	11	42	(40-43)	47.5	38	(37-40)	26.4	10	56	(55-57)	84.1	42	(40-43)	92.6
Western Pacific Region	3	42	(38-47)	74.3	37	(35-40)	0.0	5	51	(46-57)	97.2	39	(36-42)	94.8
Setting														
National	10	42	(40-43)	51.1	39	(38-40)	24.0	9	56	(55-57)	84.9	42	(40-44)	93.4
Sub-national	7	42	(39-45)	85.5	38	(36-40)	64.2	11	54	(49-59)	98.9	40	(37-44)	98.0
Tuberculosis burden														
High	5	41	(38-44)	81.7	38	(36-40)	50.8	7	54	(47-62)	99.3	40	(35-45)	98.7
Low	12	42	(41-44)	62.1	39	(38-40)	46.5	13	55	92		42	(40-43)	93.2
Sampling														
Random	1	47	(42-52)	-	39	(35-44)	-	2	50	(43-58)	95.5	39	(34-44)	94.2
Stratified	4	41	(38-44)	82.7	38	(36-40)	61.8	6	56	(48-63)	99.4	41	(36-47)	98.7
Quota	11	41	(40-43)	53.1	39	(37-40)	27.4	10	55	(54-57)	91.7	41	(39-43)	94.4
Convenience	1	46	(44-49)	-	43	(40-46)	-	1	59	(56-61)	-	46	(43-48)	-
Unknown	0	-	(---)	-	-	(---)	-	1	50	(46-54)	-	36	(34-38)	-
Reporting duration														
24 hours	15	42	(41-44)	62.0	38	(37-40)	46.0	17	56	(54-58)	95.6	40	(39-42)	94.6
48 hours	2	40	(35-44)	93.6	39	(37-41)	59.3	2	46	(33-60)	99.6	50	(40-60)	99.1
72 hours	0	-	(---)	-	-	(---)	-	1	50	(46-54)	-	36	(34-38)	-

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Sub-group	Proportion of adult contacts with men (random effects summary estimates)														
	Children							Adults							
	n	Boys			n	Girls			n	Men			Women		
		%	95% CI	I^2		%	95% CI	I^2		%	95% CI	I^2	%	95% CI	I^2
Age of adult participants															
18+	0	-	(---)	-	0	-	(---)	-	3	57	(46-67)	99.1	37	(32-43)	96.8
16+	1	47	(42-52)	-	1	39	(35-44)	-	1	54	(52-56)	-	36	(34-38)	-
15+	14	42	(41-43)	56.7	15	38	(37-40)	48.0	15	56	(54-57)	90.6	41	(40-43)	93.7
13+	1	37	(36-39)	-	1	40	(38-42)	-	1	39	(38-41)	-	55	(53-56)	-
n/a	1	37	(32-43)	-	1	40	(34-47)	-	0	-	(---)	-	-	(---)	-
Age of adult contacts															
16+	1	47	(42-52)	-	1	39	(35-44)	-	1	54	(52-56)	-	36	(34-38)	-
15+	15	42	(41-43)	57.6	15	38	(37-40)	44.7	16	55	(53-57)	93.4	41	(40-43)	93.3
13+	1	37	(36-39)	-	1	40	(38-42)	-	3	54	(37-70)	99.7	42	(29-55)	99.5
Participation															
Equitable	15	42	(40-43)	76.6	15	39	(38-40)	47.0	11	57	(54-59)	95.8	40	(37-42)	95.0
Excess males	2	42	(40-44)	0.1	2	38	(36-40)	0.0	1	39	(38-41)	-	55	(53-56)	-
Excess females	0	-	(---)	-	0	-	(---)	-	8	54	(52-56)	94.1	41	(40-43)	94.2

Appendix 2: Dataset

The dataset used for study analyses is available at https://wwwnc.cdc.gov/eid/article/26/5/19-0574-techapp2.xlsx.

Appendix D Supplemental materials for Chapter 5 manuscript "The epidemiological impact of sex disparities in timely access to TB diagnosis and treatment in Viet Nam: a modelling study"

1 Model structure

1.1 Tuberculosis model

We developed a sex-stratified dynamic compartmental model of *Mtb* transmission and TB disease based on a model previously published by Houben et al. [1]. The core TB model has four states related to *Mtb* infection and TB disease: susceptible, latent infection, smear-positive TB disease, and smear-negative TB disease, as shown in Figure 1. (There is no compartment for post-preventive therapy, unlike the model by Houben et al.)

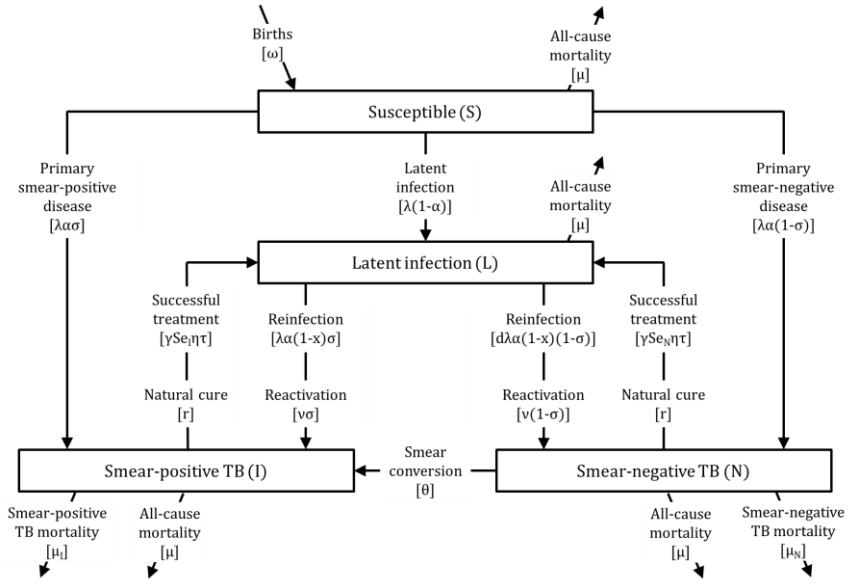

Figure 1: TB model structure

Individuals enter the susceptible compartment (S) at birth and are at risk of all-cause mortality throughout the model.

Susceptible individuals (S) are at annual risk of infection λ. Proportion α of infected individuals progress to disease, with proportion σ developing smear-positive TB (I) and proportion (1-σ) develop smear-negative (N) disease. The remaining proportion *(1-α)* are latently infected (L). Individuals with latent infection are at risk of progressing to disease through reinfection, at rate $\lambda*\alpha*(1-x)$, where x is the proportion of protection provided by previous infection against progression to disease following reinfection, with proportion σ developing smear-positive disease and proportion *(1-σ)* developing smear-negative disease. Latently infected individuals also progress to disease through reactivation at rate ν, with proportion σ developing smear-positive disease and proportion *(1-σ)* developing smear-negative disease.

Individuals with smear-negative disease convert to smear-positive disease at rate θ. Individuals with smear-positive or smear-negative disease experience TB-associated mortality at rates μ_I and μ_N, respectively.

Individuals who recover from TB disease return to the latent infection compartment where they are at risk of reactivation or reinfection as described above. Individuals recover through natural cure at rate r or through successful treatment following access to TB care, diagnosis, and linkage to care. Individuals are screened for disease at rate γ, the inverse of time to presentation, with individuals with smear-negative disease screened at a lower rate $d^*\gamma$ and individuals with neither smear-positive nor smear-negative disease screened at lower rate $h^*\gamma$. Screened individuals are diagnosed based on the net sensitivity *Se* and specificity *Sp* of the diagnostic algorithm, the proportion ψ who receive drug-susceptibility testing (DST), and the sensitivity and specificity of DST. Proportion η of those diagnosed with TB are linked to treatment, and proportion τ successfully complete treatment.

Infection and disease compartments (L, I, and N) are stratified based on treatment history (treatment naïve, indicated by subscript *X*, and previously treated, subscript *P*) and drug resistance status (drug-susceptible, subscript *S*, and multidrug-resistant, MDR, subscript *R*).

Individuals move from the treatment naïve stratum to the previously treated stratum after completing treatment or after initiating unsuccessful treatment, as shown in Figure 2 and detailed elsewhere [1]. Those who complete treatment move from I_X and N_X to L_P, while those who initiate unsuccessful treatment move from I_X to I_P and N_X to N_P.

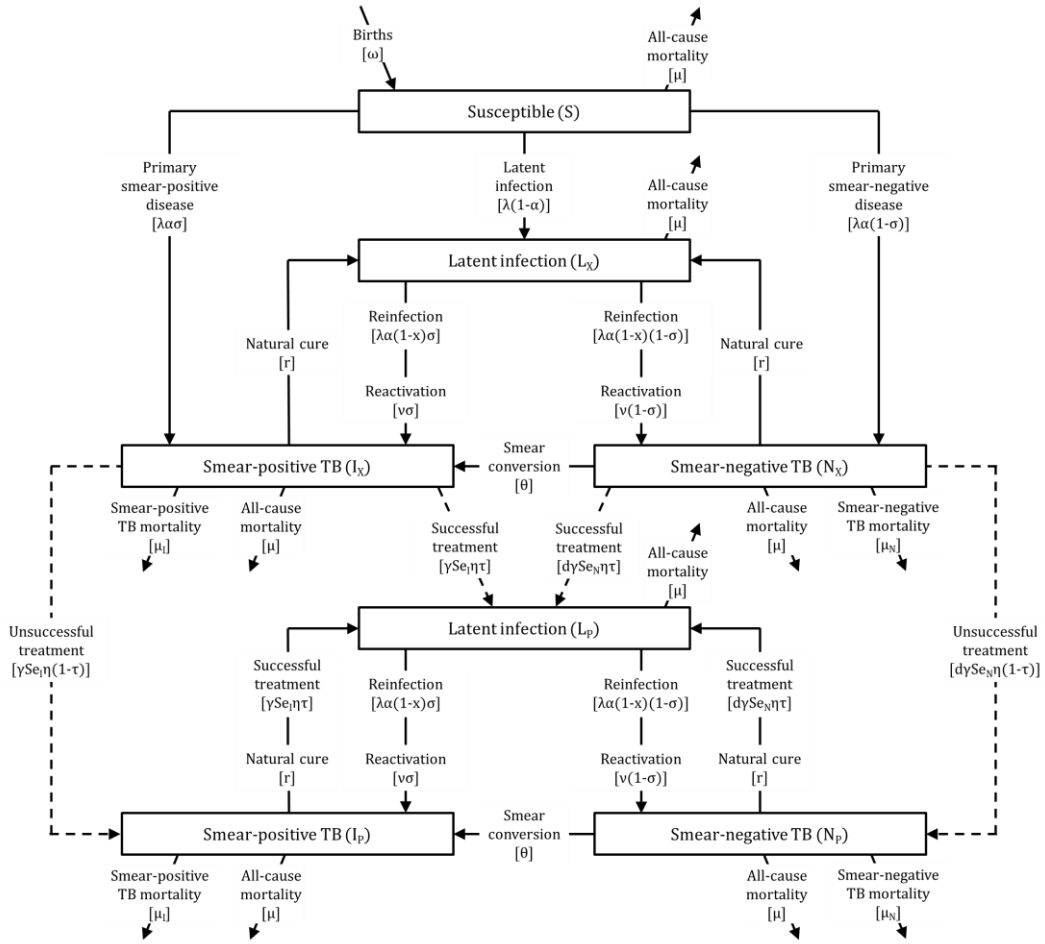

Figure 2: Model structure with treatment history strata. Top of the figure shows treatment naïve stratum (subscript X); bottom shows previously treated stratum (subscript P). Transitions between treatment naïve and previously treated strata are indicated by dashed lines.

MDR is acquired either by transmission of an MDR strain or development during treatment, as shown in Figure 3 and detailed elsewhere [1]. MDR transmission is specified by a separate annual risk of infection λ_R adjusted by φ to indicate the relative fitness of MDR strains. Mixed infections are not explicitly modelled. Superinfections that rapidly progress to disease move to the disease compartment matching the drug resistance profile of the superinfecting strain (I_S, N_S, I_R, or N_R), regardless of the resistance profile of the previous infection. The movement of individuals with latent superinfection is determined by parameter $\iota = \frac{\varphi}{1+\varphi}$ such that among individuals with latent drug sensitive infection who are reinfected with an MDR strain, proportion ι move from L_S to L_R and proportion $(1-\iota)$ remain in L_S, and among individuals with latent MDR infection who are reinfected with a drug resistant strain, proportion $(1-\iota)$ move from L_R to L_S and proportion ι remain in L_R. Individuals with drug susceptible TB who are diagnosed and initiate treatment develop MDR at rate ξ.

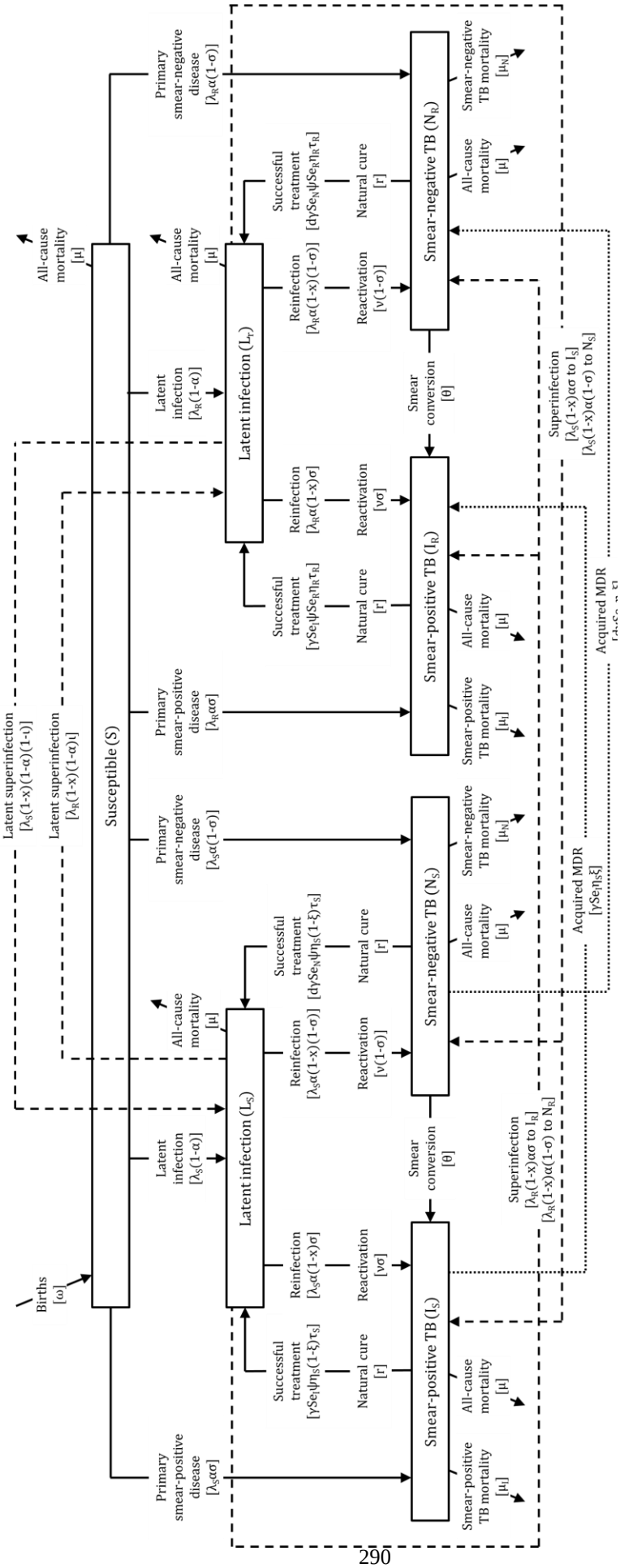

Figure 3: Model diagram illustrating drug susceptible and MDR strata. Left side of the diagram shows drug susceptible stratum (subscript S); right side shows MDR stratum (subscript R). Dashed lines indicate superinfections. Dotted lines indicated acquired resistance.

The full model is stratified by sex (male and female), age (five-year age groups, i.e., 0-4, 5-9, ...75-79, ≥80), and HIV status (positive and negative), with HIV-positive individuals further stratified by CD4 count (<50, 50-99, 100-199, 200-249, 250-349, 350-499, and ≥500 cells/μL) and duration of anti-retroviral treatment (ART) (none, 0-6, 7-12, >12 months).

Model equations are provided in Section 0, and model parameters are provided in Section 0.

1.2 Demographic model

The demographic model is designed to reflect the demographic projection model (DemProj) of the Spectrum software suite [2]. The demographic model accounts for births, migration, and all-cause mortality and divides the population across two sex strata (male and female) and 17 age strata (five year age groups, i.e., 0-4, 5-9, ..., 75-79, ≥80). Sex is assumed constant through an individual's lifetime.

Births are modelled using the crude birth rate based on United Nations (UN) Population Division estimates [3], acknowledging the sex distribution of new births according to UN World Population Prospects estimates (Figure 4) [4]. New births are added to the susceptible compartment of the TB model. Aging is modelled such that one-fifth of the population of each five-year age group moves to the subsequent age group each year.

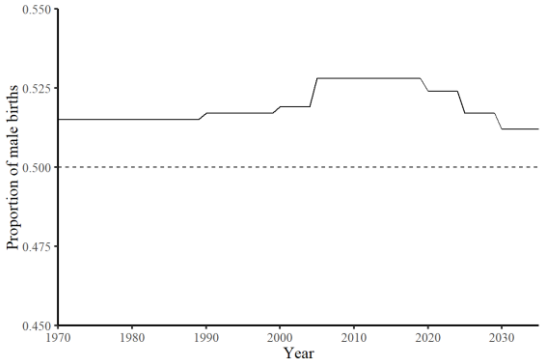

Figure 4: Proportion of male births (Dashed line at 0.5 for reference)

Migration is calculated by age and sex for each year according to DemProj estimates. Migration is considered independent of TB or HIV disease status, and migrants are distributed across disease states based on the relative size of each compartment.

All-cause mortality is modelled using rates derived from UN Population Division life tables [3]. Because TB and HIV deaths are included in background mortality rates, duplicate TB- and HIV-associated deaths are removed at each time point.

1.3 HIV model

The HIV model is designed to reflect the AIDS Impact Model (AIM) of the Spectrum software suite [2]. Individuals who are HIV-positive are categorized into seven stages based on CD4 count (<50, 50-99, 100-199, 200-249, 250-349, 350-499, and >500 cells/μL) and into four stages based on ART duration (none, 0-6, 7-12, >12 months). HIV incidence and progression (the latter indicated by CD4 count), ART initiation and duration, and HIV-associated mortality are modelled as described elsewhere [1].

HIV incidence is based on age- and sex-specific incidence estimates from AIM [2]. HIV incidence is considered independent of TB status. New infections are assigned to CD4 categories according to age-specific distributions from AIM (Table 1).

Table 1: Proportional distribution of new HIV infections by age group and CD4 category

CD4 count	Age group (years)				
	0-14	15-24	25-34	35-44	45+
>500	64.3	64.3	60.7	58.5	55.2
350-500	35.7	35.7	39.3	41.5	44.8
250-349	0	0	0	0	0
200-249	0	0	0	0	0
100-199	0	0	0	0	0
50-99	0	0	0	0	0
<50	0	0	0	0	0

Individuals progress through CD4 categories at age- and CD4-specific rates, which are derived from risks used in AIM (Table 2) [2].

Table 2: Rates of progression through CD4 count categories by age group and CD4 category

CD4 count	Age group (years)				
	0-14	15-24	25-34	35-44	45+
>500	0.298	0.117	0.147	0.183	0.213
350-500	0.239	0.223	0.240	0.355	0.535
250-349	0.183	0.294	0.452	0.581	0.855
200-249	0.183	0.508	1.087	1.250	1.818
100-199	0.130	0.214	0.637	0.676	0.952
50-99	0.130	0.348	1.449	1.449	2.000

HIV-associated mortality rates in the absence of ART are based on age- and CD4-specific rates from AIM (Table 3) [2]. Mortality rates in ages 0-4 years are assumed eight times those in ages 5-14 years [1]. Duplicate TB- and HIV-associated deaths are removed at each time point.

Table 3: HIV mortality rates (in the absence of ART) by age group and CD4 category

CD4 count	Age group (years)					
	0-4	5-14	15-24	25-34	45-44	45-54
>500	0.312	0.039	0.005	0.004	0.005	0.005
350-500	0.382	0.048	0.011	0.01	0.013	0.013
250-349	0.466	0.058	0.026	0.026	0.036	0.032
200-249	0.466	0.058	0.061	0.069	0.096	0.08
100-199	0.569	0.071	0.139	0.185	0.258	0.203
50-99	0.569	0.071	0.321	0.499	0.691	0.513
<50	0.569	0.071	0.737	1.342	1.851	1.295

The number of individuals who should be on ART is calculated from age- and sex-specific estimates of the number of individuals on ART and the number of individuals in need of ART from AIM [2], based on the CD4 threshold for ART initiation (Table 4). ART coverage does not take into account risk of HIV infection during TB disease nor diagnosis of TB disease as an indicator of ART eligibility.

Table 4: CD4 threshold for ART initiation by year

Year	CD4 threshold (cells/μL)
1970-2009	200
2010-2050	350

The number of individuals who start ART within a given time step is calculated as the difference between the number of individuals who should be on ART and the number who are currently on ART, plus the number who will die on ART during that time step. The distribution of individuals starting ART across CD4 categories is based on the proportion of individuals eligible for ART in each CD4 category and the proportion of deaths among individuals eligible for ART (but not currently on ART) in each CD4 category.

HIV-associated mortality rates for individuals on ART, by age, sex, CD4 count at ART initiation, and duration of ART, are taken from AIM [2].

2 Model equations

Transitions between compartments are defined as follows. Uppercase subscripts indicate states of and parameters specific to infection and disease strata based on treatment history (treatment-naïve, indicated by subscript *X*, and previously treated, subscript *P*) and drug resistance status (drug-susceptible, subscript *S*, and multidrug-resistant, MDR, subscript *R*). Lowercase subscripts denote states of and parameters specific to strata by sex (subscript *g*), age (subscript *a*), HIV status (subscript *h*), and duration of ART (subscript *k*), and time-step (subscript *t*).

$$\frac{\mathrm{d}S_{g,a,h,k,t}}{\mathrm{dt}} = -\left(\lambda_{\mathrm{S_{g,a,t}}} + \lambda_{\mathrm{R_{g,a,t}}}\right) * S_{g,a,h,k,t}$$

$$\begin{aligned}\frac{\mathrm{dL_{SX}}_{g,a,h,k,t}}{\mathrm{dt}} = &\left(\lambda_{\mathrm{S_{g,a,t}}}(1-\alpha_{g,a,h,k,t})\right) * S_{g,a,h,k,t}\\ &-\left(\lambda_{\mathrm{S_{g,a,t}}}(1-\mathrm{x}_{a,h,k})\alpha_{g,a,h,k,t} + \lambda_{\mathrm{R_{g,a,t}}}(1-\mathrm{x}_{a,h,k})\alpha_{g,a,h,k,t} + \lambda_{\mathrm{R_{g,a,t}}}(1-\mathrm{x}_{a,h,k})(1-\right.\\ &\left.\alpha_{g,a,h,k,t})\iota + \nu_{g,a,h,k,t}\right) * \mathrm{L}_{SX_{g,a,h,k,t}}\\ &+(\mathrm{r}_h) * \mathrm{I_{SX}}_{g,a,h,k,t}\\ &+(\mathrm{r}_h) * \mathrm{N_{SX}}_{g,a,h,k,t}\\ &+\left(\lambda_{\mathrm{S_{g,a,t}}}(1-\mathrm{x}_{a,h,k})(1-\alpha_{g,a,h,k,t})(1-\iota)\right) * \mathrm{L_{RX}}_{g,a,h,k,t}\end{aligned}$$

$$\begin{aligned}\frac{\mathrm{dI_{SX}}_{g,a,h,k,t}}{\mathrm{dt}} = &\left(\lambda_{\mathrm{S_{g,a,t}}}\alpha_{g,a,h,k,t}\sigma_{a,h}\right) * S_{g,a,h,k,t}\\ &+\left(\lambda_{\mathrm{S_{g,a,t}}}(1-\mathrm{x}_{a,h,k})\alpha_{g,a,h,k,t}\sigma_{a,h} + \nu_{g,a,h,k,t}\sigma_{a,h}\right) * \mathrm{L_{SX}}_{g,a,h,k,t}\\ &-\left(\mathrm{r}_h + \gamma_{g,a,t}\mathrm{Se}_{\mathrm{I}_{h,t}}\psi_{\mathrm{X}_t}\mathrm{Sp}_{\mathrm{R}_t}\eta_{\mathrm{S}_t} + \gamma_{g,a,t}\mathrm{Se}_{\mathrm{I}_{h,t}}(1-\psi_{\mathrm{X}_t})\eta_{\mathrm{S}_t} + \gamma_{g,a,t}\mathrm{Se}_{\mathrm{I}_{h,t}}\psi_{\mathrm{X}_t}(1-\mathrm{Sp}_{\mathrm{R}_t})\eta_{\mathrm{R}_t}\right) *\\ &\mathrm{I_{SX}}_{g,a,h,k,t}\\ &+(\theta_h) * \mathrm{N_{SX}}_{g,a,h,k,t}\\ &+\left(\lambda_{\mathrm{S_{g,a,t}}}(1-\mathrm{x}_{a,h,k})\alpha_{g,a,h,k,t}\sigma_{a,h}\right) * \mathrm{L_{RX}}_{g,a,h,k,t}\end{aligned}$$

States S: susceptible; L: latent infection; I: smear-positive TB; N: smear-negative TB.
Parameters λ: force of infection; x: proportion protection due to previous infection against progression to active disease following reinfection; α: proportion of new infections developing primary disease; ν: reactivation rate; σ: proportion of cases developing smear-positive disease; θ: rate of conversion from smear-negative to smear-positive disease; r: rate of TB self-cure; d: relative detection of smear-negative TB; γ: rate of access to TB care; Se: net sensitivity of diagnostic algorithm; Sp: net specificity of diagnostic algorithm; ψ: DST coverage; η: proportion of diagnosed individuals who are linked to treatment; τ: proportion of individuals linked to care who successfully complete treatment; ξ: rate of acquisition of resistance during treatment; ι: proportion of non-progressing superinfections.
Subscripts X: treatment-naïve; P: previously treated; S: drug-susceptible; R: MDR; g: sex; a: age; h: HIV status; k: ART duration; t: time-step.

$$\frac{\mathrm{dN_{SX}}_{g,a,h,k,t}}{\mathrm{dt}} = \left(\lambda_{\mathrm{S_{g,a,t}}}\alpha_{g,a,h,k,t}(1-\sigma_{a,h})\right) * \mathrm{S}_{g,a,h,k,t}$$
$$+\left(\lambda_{\mathrm{S_{g,a,t}}}(1-\mathrm{x}_{a,h,k})\alpha_{g,a,h,k,t}(1-\sigma_{a,h}) + \nu_{g,a,h,k,t}(1-\sigma_{a,h})\right) * \mathrm{L_{SX}}_{g,a,h,k,t}$$
$$-(\mathrm{r}_h + \mathrm{d}_N\gamma_{g,a,t}\mathrm{Se}_{\mathrm{N}_{h,t}}\psi_{\mathrm{X}_t}\mathrm{Sp}_{\mathrm{R}_t}\eta_{\mathrm{S}_t} + \mathrm{d}_N\gamma_{g,a,t}\mathrm{Se}_{\mathrm{N}_{h,t}}(1-\psi_{\mathrm{X}_t})\eta_{\mathrm{S}_t} + \mathrm{d}_N\gamma_{g,a,t}\mathrm{Se}_{\mathrm{N}_{h,t}}\psi_{\mathrm{X}_t}(1-\mathrm{Sp}_{\mathrm{R}_t})\eta_{R_t} + \theta_h) * \mathrm{N_{SX}}_{g,a,h,k,t}$$
$$+\left(\lambda_{\mathrm{S_{g,a,t}}}(1-\mathrm{x}_{a,h,k})\alpha_{g,a,h,k,t}(1-\sigma_{a,h})\right) * \mathrm{L_{RX}}_{g,a,h,k,t}$$

$$\frac{\mathrm{dL_{SP}}_{g,a,h,k,t}}{\mathrm{dt}} = (\gamma_{g,a,t}\mathrm{Se}_{\mathrm{I}_{h,t}}\psi_{\mathrm{X}_t}\mathrm{Sp}_{\mathrm{R}_t}\eta_{S_t}(1-\xi_h)\tau_{\mathrm{S}_{h,k,t}} + \gamma_{g,a,t}\mathrm{Se}_{\mathrm{I}_{h,t}}(1-\psi_{\mathrm{X}_{h,t}})\eta_{\mathrm{S}_t}(1-\xi_h)\tau_{\mathrm{S}_{h,k,t}} + \gamma_{g,a,t}\mathrm{Se}_{\mathrm{I}_{h,t}}\psi_{\mathrm{X}_t}(1-\mathrm{Sp}_{\mathrm{R}_t})\eta_{\mathrm{R}_t}\tau_{\mathrm{R}_{h,k,t}}) * \mathrm{I_{SX}}_{g,a,h,k,t}$$
$$+(\mathrm{d}_N\gamma_{g,a,t}\mathrm{Se}_{\mathrm{N}_{h,t}}\psi_{\mathrm{X}_t}\mathrm{Sp}_{\mathrm{R}_t}\eta_{\mathrm{S}_t}(1-\xi_h)\tau_{\mathrm{S}_{h,k,t}} + \mathrm{d}_N\gamma_{g,a,t}\mathrm{Se}_{\mathrm{N}_{h,t}}(1-\psi_{\mathrm{X}_t})\eta_{\mathrm{S}_t}(1-\xi_h)\tau_{\mathrm{S}_{h,k,t}} + \mathrm{d}_N\gamma_{g,a,t}\mathrm{Se}_{\mathrm{N}_{h,t}}\psi_{\mathrm{X}_t}(1-\mathrm{Sp}_{\mathrm{R}_t})\eta_{\mathrm{R}_t}\tau_{\mathrm{R}_{h,k,t}}) * \mathrm{N_{SX}}_{g,a,h,k,t}$$
$$-\left(\lambda_{\mathrm{S_{g,a,t}}}(1-\mathrm{x}_{a,h,k})\alpha_{g,a,h,k,t} + \lambda_{\mathrm{R_{g,a,t}}}(1-\mathrm{x}_{a,h,k})\alpha_{g,a,h,k,t} + \lambda_{\mathrm{R_{g,a,t}}}(1-\mathrm{x}_{a,h,k})(1-\alpha_{g,a,h,k,t})\iota + \nu_{g,a,h,k,t}\right) * \mathrm{L_{SP}}_{g,a,h,k,t}$$
$$+(\mathrm{r}_h + \gamma_{g,a,t}\mathrm{Se}_{\mathrm{I}_{h,t}}\psi_{\mathrm{P}_t}\mathrm{Sp}_{\mathrm{R}_t}\eta_{\mathrm{S}_t}(1-\xi_h)\tau_{\mathrm{S}_{h,k,t}} + \gamma_{g,a,t}\mathrm{Se}_{\mathrm{I}_{h,t}}(1-\psi_{\mathrm{P}_t})\eta_{\mathrm{S}_t}(1-\xi_h)\tau_{\mathrm{S}_{h,k,t}} + \gamma_{g,a,t}\mathrm{Se}_{\mathrm{I}_{h,t}}\psi_{\mathrm{P}_t}(1-\mathrm{Sp}_{\mathrm{R}_t})\eta_{\mathrm{R}_t}\tau_{\mathrm{R}_{h,k,t}}) * \mathrm{I_{SP}}_{g,a,h,k,t}$$
$$+(\mathrm{r}_h + \mathrm{d}_N\gamma_{g,a,t}\mathrm{Se}_{\mathrm{N}_{h,t}}\psi_{\mathrm{P}_t}\mathrm{Sp}_{\mathrm{R}_t}\eta_{\mathrm{S}_t}(1-\xi_h)\tau_{\mathrm{S}_{h,k,t}} + \mathrm{d}_N\gamma_{g,a,t}\mathrm{Se}_{\mathrm{N}_{h,t}}(1-\psi_{\mathrm{P}_t})\eta_{\mathrm{S}_t}(1-\xi_h)\tau_{\mathrm{S}_{h,k,t}} + \mathrm{d}_N\gamma_{g,a,t}\mathrm{Se}_{\mathrm{N}_{h,t}}\psi_{\mathrm{P}_t}(1-\mathrm{Sp}_{\mathrm{R}_t})\eta_{\mathrm{R}_t}\tau_{\mathrm{R}_{h,k,t}}) * \mathrm{N_{SP}}_{g,a,h,k,t}$$
$$+\left(\lambda_{\mathrm{s_{g,a,t}}}(1-\iota)(1-\mathrm{x}_{a,h,k})(1-\alpha_{g,a,h,k,t})\right) * \mathrm{L_{RX}}_{g,a,h,k,t}$$

States S: susceptible; L: latent infection; I: smear-positive TB; N: smear-negative TB.
Parameters λ: force of infection; x: proportion protection due to previous infection against progression to active disease following reinfection; α: proportion of new infections developing primary disease; ν: reactivation rate; σ: proportion of ca2ses developing smear-positive disease; θ: rate of conversion from smear-negative to smear-positive disease; r: rate of TB self-cure; d: relative detection of smear-negative TB; γ: rate of access to TB care; Se: net sensitivity of diagnostic algorithm; Sp: net specificity of diagnostic algorithm; ψ: DST coverage; η: proportion of diagnosed individuals who are linked to treatment; τ: proportion of individuals linked to care who successfully complete treatment; ξ: rate of acquisition of resistance during treatment; ι: proportion of non-progressing superinfections.
Subscripts X: treatment-naïve; P: previously treated; S: drug-susceptible; R: MDR; g: sex; a: age; h: HIV status; k: ART duration; t: time-step.

$$\frac{\mathrm{dI_{SP}}_{g,a,h,k,t}}{\mathrm{dt}} = \Big(\gamma_{g,a,t}\mathrm{Se}_{\mathrm{I}_{h,t}}\psi_{\mathrm{X}_t}\mathrm{Sp}_{\mathrm{R}_t}\eta_{\mathrm{S}_t}(1-\xi_h)\big(1-\tau_{\mathrm{S}_{h,k,t}}\big) + \gamma_{g,a,t}\mathrm{Se}_{\mathrm{I}_{h,t}}\big(1-\psi_{\mathrm{X}_t}\big)\eta_{\mathrm{S}_t}(1-\xi_h)(1-\tau_{\mathrm{S}_{h,k,t}}) + \gamma_{g,a,t}\mathrm{Se}_{\mathrm{I}_{h,t}}\psi_{\mathrm{X}_t}\big(1-\mathrm{Sp}_{\mathrm{R}_t}\big)\eta_{\mathrm{R}_t}\big(1-\tau_{\mathrm{R}_{h,k,t}}\big)\Big) * \mathrm{I_{SX}}_{g,a,h,k,t}$$
$$+\Big(\lambda_{\mathrm{S_{g,a,t}}}\big(1-\mathrm{x}_{a,h,k}\big)\alpha_{g,a,h,k,t}\sigma_{a,h} + \nu_{g,a,h,k,t}\sigma_{a,h}\Big) * \mathrm{L_{SP}}_{g,a,h,k,t}$$
$$-\big(\mathrm{r}_h + \gamma_{g,a,t}\mathrm{Se}_{\mathrm{I}_{h,t}}\psi_{\mathrm{P}_t}\mathrm{Sp}_{\mathrm{R}_t}\eta_{\mathrm{S}_t}(1-\xi_h)\tau_{\mathrm{S}_{h,k,t}} + \gamma_{g,a,t}\mathrm{Se}_{\mathrm{I}_{h,t}}\big(1-\psi_{\mathrm{P}_t}\big)\eta_{\mathrm{S}_t}(1-\xi_h)\tau_{\mathrm{S}_{h,k,t}} + \gamma_{g,a,t}\mathrm{Se}_{\mathrm{I}_{h,t}}\psi_{\mathrm{P}_t}\big(1-\mathrm{Sp}_{\mathrm{R}_t}\big)\eta_{\mathrm{R}_t}\tau_{\mathrm{R}_{h,k,t}} + \gamma_{g,a,t}\mathrm{Se}_{\mathrm{I}_{h,t}}\psi_{\mathrm{P}_t}\mathrm{Sp}_{\mathrm{R}_t}\eta_{\mathrm{S}}\xi_h + \gamma_{g,a,t}\mathrm{Se}_{\mathrm{I}_{h,t}}\big(1-\psi_{\mathrm{P}_t}\big)\eta_{\mathrm{S}_t}\xi_h\big) * \mathrm{I_{SP}}_{g,a,h,k,t}$$
$$+(\theta_h) * \mathrm{N_{SP}}_{g,a,h,k,t}$$
$$+\Big(\lambda_{\mathrm{S_{g,a,t}}}\big(1-\mathrm{x}_{a,h,k}\big)\alpha_{g,a,h,k,t}\sigma_{a,h}\Big) * \mathrm{L_{RP}}_{g,a,h,k,t}$$

$$\frac{\mathrm{dN_{SP}}_{g,a,h,k,t}}{\mathrm{dt}} = \Big(\mathrm{d}_N\gamma_{g,a,t}\mathrm{Se}_{\mathrm{N}_{h,t}}\psi_{\mathrm{X}_t}\mathrm{Sp}_{\mathrm{R}_t}\eta_{\mathrm{S}_t}(1-\xi_h)\big(1-\tau_{\mathrm{S}_{h,k,t}}\big) + \mathrm{d}_N\gamma_{g,a,t}\mathrm{Se}_{\mathrm{N}_{h,t}}\big(1-\psi_{\mathrm{X}_t}\big)\eta_{\mathrm{S}_t}(1-\xi_h)\big(1-\tau_{\mathrm{S}_{h,k,t}}\big) + \mathrm{d}_N\gamma_{g,a,t}\mathrm{Se}_{\mathrm{N}_{h,t}}\psi_{\mathrm{X}_t}\big(1-\mathrm{Sp}_{\mathrm{R}_t}\big)\eta_{\mathrm{R}_t}\big(1-\tau_{\mathrm{R}_{h,k,t}}\big)\Big) * \mathrm{N_{SX}}_{g,a,h,k,t}$$
$$+\Big(\lambda_{\mathrm{S_{g,a,t}}}\big(1-\mathrm{x}_{a,h,k}\big)\alpha_{g,a,h,k,t}\big(1-\sigma_{a,h}\big) + \nu_{g,a,h,k,t}\big(1-\sigma_{a,h}\big)\Big) * \mathrm{L_{SP}}_{g,a,h,k,t}$$
$$-\big(\mathrm{r}_h + \mathrm{d}_N\gamma_{g,a,t}\mathrm{Se}_{\mathrm{N}_{h,t}}\psi_{\mathrm{P}_t}\mathrm{Sp}_{\mathrm{R}_t}\eta_{\mathrm{S}_t}(1-\xi_h)\tau_{\mathrm{S}_{h,k,t}} + \mathrm{d}_N\gamma_{g,a,t}\mathrm{Se}_{\mathrm{N}_{h,t}}\big(1-\psi_{\mathrm{P}_t}\big)\eta_{\mathrm{S}_t}(1-\xi_h)\tau_{\mathrm{S}_{h,k,t}} + \mathrm{d}_N\gamma_{g,a,t}\mathrm{Se}_{\mathrm{N}_{h,t}}\psi_{\mathrm{P}_t}\big(1-\mathrm{Sp}_{\mathrm{R}_t}\big)\eta_{\mathrm{R}_t}\tau_{\mathrm{R}_{h,k,t}} + \mathrm{d}_N\gamma_{g,a,t}\mathrm{Se}_{\mathrm{N}_{h,t}}\psi_{\mathrm{P}_t}\mathrm{Sp}_{\mathrm{R}_t}\eta_{\mathrm{S}_t}\xi_h + \mathrm{d}_N\gamma_{g,a,t}\mathrm{Se}_{\mathrm{N}_{h,t}}\big(1-\psi_{\mathrm{P}_t}\big)\eta_{\mathrm{S}_t}\xi_h + \theta_h\big) * \mathrm{N_{SP}}_{g,a,h,k,t}$$
$$+\Big(\lambda_{\mathrm{S_{g,a,t}}}\big(1-\mathrm{x}_{a,h,k}\big)\alpha_{g,a,h,k,t}\big(1-\sigma_{a,h}\big)\Big) * \mathrm{L_{RP}}_{g,a,h,k,t}$$

$$\frac{\mathrm{dL_{RX}}_{g,a,h,k,t}}{\mathrm{dt}} = \Big(\lambda_{\mathrm{R_{g,a,t}}}\big(1-\alpha_{g,a,h,k,t}\big)\Big) * \mathrm{S}_{g,a,h,k,t}$$
$$+\Big(\lambda_{\mathrm{R_{g,a,t}}}\big(1-\mathrm{x}_{a,h,k}\big)\big(1-\alpha_{g,a,h,k,t}\big)\iota\Big) * \mathrm{L_{SX}}_{g,a,h,k,t}$$
$$-\Big(\lambda_{\mathrm{S_{g,a,t}}}\big(1-\mathrm{x}_{a,h,k}\big)\alpha_{g,a,h,k,t} + \lambda_{\mathrm{S_{g,a,t}}}\big(1-\mathrm{x}_{a,h,k}\big)\big(1-\alpha_{g,a,h,k,t}\big)(1-\iota) + \lambda_{\mathrm{R_{g,a,t}}}\big(1-\mathrm{x}_{a,h,k}\big)\alpha_{g,a,h,k,t} + \nu\Big) * \mathrm{L_{RX}}_{g,a,h,k,t}$$
$$+(\mathrm{r}_h) * \mathrm{I_{RX}}_{g,a,h,k,t}$$
$$+(\mathrm{r}_h) * \mathrm{N_{RX}}_{g,a,h,k,t}$$

States S: susceptible; L: latent infection; I: smear-positive TB; N: smear-negative TB.
Parameters λ: force of infection; x: proportion protection due to previous infection against progression to active disease following reinfection; α: proportion of new infections developing primary disease; ν: reactivation rate; σ: proportion of cases developing smear-positive disease; θ: rate of conversion from smear-negative to smear-positive disease; r: rate of TB self-cure; d: relative detection of smear-negative TB; γ: rate of access to TB care; Se: net sensitivity of diagnostic algorithm; Sp: net specificity of diagnostic algorithm; ψ: DST coverage; η: proportion of diagnosed individuals who are linked to treatment; τ: proportion of individuals linked to care who successfully complete treatment; ξ: rate of acquisition of resistance during treatment; ι: proportion of non-progressing superinfections.
Subscripts X: treatment-naïve; P: previously treated; S: drug-susceptible; R: MDR; g: sex; a: age; h: HIV status; k: ART duration; t: time-step.

$$\frac{\mathrm{dI_{RX}}_{g,a,h,k,t}}{\mathrm{dt}} = \left(\lambda_{\mathrm{R_{g,a,t}}}\alpha_{g,a,h,k,t}\sigma_{a,h}\right) * \mathrm{S}_{g,a,h,k,t}$$
$$+\left(\lambda_{\mathrm{R_{g,a,t}}}(1-\mathrm{x}_{a,h,k})\alpha_{g,a,h,k,t}\sigma_{a,h}\right) * \mathrm{L_{SX}}_{g,a,h,k,t}$$
$$+\left(\lambda_{\mathrm{R_{g,a,t}}}(1-\mathrm{x}_{a,h,k})\alpha_{g,a,h,k,t}\sigma + \nu_{g,a,h,k,t}\sigma_{a,h}\right) * \mathrm{L_{RX}}_{g,a,h,k,t}$$
$$-\left(\mathrm{r}_h + \gamma_{g,a,t}\mathrm{Se_{I}}_{h,t}\psi_{\mathrm{X}_t}\mathrm{Se_{R}}_t\eta_{\mathrm{R}_t} + \gamma_{g,a,t}\mathrm{Se_{I}}_{h,t}(1-\psi_{\mathrm{X}_t})\eta_{\mathrm{S}_t} + \gamma_{g,a,t}\mathrm{Se_{I}}_{h,t}\psi_{\mathrm{X}_t}(1-\mathrm{Se_{R}}_t)\eta_{\mathrm{S}_t}\right) * \mathrm{I_{RX}}_{g,a,h,k,t}$$
$$+(\theta_h) * \mathrm{N_{RX}}_{g,a,h,k,t}$$

$$\frac{\mathrm{dN_{RX}}_{g,a,h,k,t}}{\mathrm{dt}} = \left(\lambda_{\mathrm{R_{g,a,t}}}\alpha_{g,a,h,k,t}(1-\sigma_{a,h})\right) * \mathrm{S}_{g,a,h,k,t}$$
$$+\left(\lambda_{\mathrm{R_{g,a,t}}}(1-\mathrm{x}_{a,h,k})\alpha_{g,a,h,k,t}(1-\sigma_{a,h})\right) * \mathrm{L_{SX}}_{g,a,h,k,t}$$
$$+\left(\lambda_{\mathrm{R_{g,a,t}}}(1-\mathrm{x}_{a,h,k})\alpha_{g,a,h,k,t}(1-\sigma_{a,h}) + \nu_{g,a,h,k,t}(1-\sigma_{a,h})\right) * \mathrm{L_{RX}}_{g,a,h,k,t}$$
$$-\left(\mathrm{r}_h + \mathrm{d}_N\gamma_{g,a,t}\mathrm{Se_{N}}_{h,t}\psi_{\mathrm{X}_t}\mathrm{Se_{R}}_t\eta_{\mathrm{R}_t} + \mathrm{d}_N\gamma_{g,a,t}\mathrm{Se_{N}}_{h,t}(1-\psi_{\mathrm{X}_t})\eta_{\mathrm{S}_t} + \mathrm{d}_N\gamma_{g,a,t}\mathrm{Se_{N}}_{h,t}\psi_{\mathrm{X}_t}(1-\mathrm{Se_{R}}_t)\eta_{\mathrm{S}_t} + \theta_h\right) * \mathrm{N_{RX}}_{g,a,h,k,t}$$

$$\frac{\mathrm{dL_{RP}}_{g,a,h,k,t}}{\mathrm{dt}} = \left(\lambda_{\mathrm{R_{g,a,t}}}(1-\mathrm{x}_{a,h,k})(1-\alpha_{g,a,h,k,t})\iota\right) * \mathrm{L_{SP}}_{g,a,h,k,t}$$
$$+\left(\gamma_{g,a,t}\mathrm{Se_{I}}_{h,t}\psi_{\mathrm{X}_t}\mathrm{Se_{R}}_t\eta_{\mathrm{R}_t}\tau_{\mathrm{R}_{h,k,t}} + \gamma_{g,a,t}\mathrm{Se_{I}}_{h,t}(1-\psi_{\mathrm{X}_t})\eta_{\mathrm{S}_t}\tau_{\mathrm{S}_{h,k,t}}\mathrm{RR_X} + \gamma_{g,a,t}\mathrm{Se_{I}}_{h,t}\psi_{\mathrm{X}_t}(1-\mathrm{Se_{R}}_t)\eta_{\mathrm{S}_t}\tau_{\mathrm{S}_{h,k,t}}\mathrm{RR_X}\right) * \mathrm{I_{RX}}_{g,a,h,k,t}$$
$$+\left(\mathrm{d}_N\gamma_{g,a,t}\mathrm{Se_{N}}_{h,t}\psi_{\mathrm{X}_t}\mathrm{Se_{R}}_t\eta_{\mathrm{R}_t}\tau_{\mathrm{R}_{h,k,t}} + \mathrm{d}_N\gamma_{g,a,t}\mathrm{Se_{N}}_{h,t}(1-\psi_{\mathrm{X}_t})\eta_{\mathrm{S}_t}\tau_{\mathrm{S}_{h,k,t}}\mathrm{RR_X} + \mathrm{d}_N\gamma_{g,a,t}\mathrm{Se_{N}}_{h,t}\psi_{\mathrm{X}_t}(1-\mathrm{Se_{R}}_t)\eta_{\mathrm{S}_t}\tau_{\mathrm{S}_{h,k,t}}\mathrm{RR_X}\right) * \mathrm{N_{RX}}_{g,a,h,k,t}$$
$$-\left(\lambda_{\mathrm{S_{g,a,t}}}(1-\mathrm{x}_{a,h,k})\alpha_{g,a,h,k,t} + \lambda_{\mathrm{S_{g,a,t}}}(1-\mathrm{x}_{a,h,k})(1-\alpha_{g,a,h,k,t})(1-\iota) + \lambda_{\mathrm{R_{g,a,t}}}(1-\mathrm{x}_{a,h,k})\alpha_{g,a,h,k,t} + \nu_{g,a,h,k,t}\right) * \mathrm{L_{RP}}_{g,a,h,k,t}$$
$$+\left(\mathrm{r}_h + \gamma_{g,a,t}\mathrm{Se_{I}}_{h,t}\psi_{\mathrm{P}_t}\mathrm{Se_{R}}_t\eta_{\mathrm{R}_t}\tau_{\mathrm{R}_{h,k,t}} + \gamma_{g,a,t}\mathrm{Se_{I}}_{h,t}(1-\psi_{\mathrm{P}_t})\eta_{\mathrm{S}_t}\tau_{\mathrm{S}_{h,k,t}}\mathrm{RR_P} + \gamma_{g,a,t}\mathrm{Se_{I}}_{h,t}\psi_{\mathrm{P}_t}(1-\mathrm{Se_{R}}_t)\eta_{\mathrm{S}_t}\tau_{\mathrm{S}_{h,k,t}}\mathrm{RR_P}\right) * \mathrm{I_{RP}}_{g,a,h,k,t}$$
$$+\left(\mathrm{r}_h + \mathrm{d}_N\gamma_{g,a,t}\mathrm{Se_{N}}_{h,t}\psi_{\mathrm{P}_t}\mathrm{Se_{R}}_t\eta_{\mathrm{R}_t}\tau_{\mathrm{R}_{h,k,t}} + \mathrm{d}_N\gamma_{g,a,t}\mathrm{Se_{N}}_{h,t}(1-\psi_{\mathrm{P}_t})\eta_{\mathrm{S}_t}\tau_{\mathrm{S}_{h,k,t}}\mathrm{RR_P} + \mathrm{d}_N\gamma_{g,a,t}\mathrm{Se_{N}}_{h,t}\psi_{\mathrm{P}_t}(1-\mathrm{Se_{R}}_t)\eta_{\mathrm{S}_t}\tau_{\mathrm{S}_{h,k,t}}\mathrm{RR_P}\right) * \mathrm{N_{RP}}_{g,a,h,k,t}$$

States S: susceptible; L: latent infection; I: smear-positive TB; N: smear-negative TB.
Parameters λ: force of infection; x: proportion protection due to previous infection against progression to active disease following reinfection; α: proportion of new infections developing primary disease; ν: reactivation rate; σ: proportion of cases developing smear-positive disease; θ: rate of conversion from smear-negative to smear-positive disease; r: rate of TB self-cure; d: relative detection of smear-negative TB; γ: rate of access to TB care; Se: net sensitivity of diagnostic algorithm; Sp: net specificity of diagnostic algorithm; ψ: DST coverage; η: proportion of diagnosed individuals who are linked to treatment; τ: proportion of individuals linked to care who successfully complete treatment; ξ: rate of acquisition of resistance during treatment; ι: proportion of non-progressing superinfections.
Subscripts X: treatment-naïve; P: previously treated; S: drug-susceptible; R: MDR; g: sex; a: age; h: HIV status; k: ART duration; t: time-step.

$$\frac{\mathrm{dI}_{RP_{g,a,h,k,t}}}{\mathrm{dt}} = \left(\gamma_{g,a,t}\mathrm{Se}_{\mathrm{I}_{h,t}}\psi_{\mathrm{X}_t}\mathrm{Sp}_{\mathrm{R}_t}\eta_{\mathrm{S}_t}\xi_h + \gamma_{g,a,t}\mathrm{Se}_{\mathrm{I}_{h,t}}(1-\psi_{\mathrm{X}_t})\eta_{\mathrm{S}_t}\xi_h\right) * \mathrm{I}_{\mathrm{SX}_{g,a,h,k,t}}$$
$$+\left(\lambda_{\mathrm{R_{g,a,t}}}(1-\mathrm{x}_{a,h,k})\alpha_{g,a,h,k,t}\sigma_{a,h}\right) * \mathrm{L}_{\mathrm{SP}_{g,a,h,k,t}}$$
$$+\left(\gamma_{g,a,t}\mathrm{Se}_{\mathrm{I}_{h,t}}\psi_{\mathrm{P}_t}\mathrm{Sp}_{\mathrm{R}_t}\eta_{\mathrm{S}_t}\xi_h + \gamma_{g,a,t}\mathrm{Se}_{\mathrm{I}_{h,t}}(1-\psi_{\mathrm{P}_t})\eta_{\mathrm{S}_t}\xi_h\right) * \mathrm{I}_{\mathrm{SP}_{g,a,h,k,t}}$$
$$+\Big(\gamma_{g,a,t}\mathrm{Se}_{\mathrm{I}_{h,t}}\psi_{\mathrm{X}_t}\mathrm{Se}_{\mathrm{R}_t}\eta_{\mathrm{R}_t}(1-\tau_{\mathrm{R}_{h,k,t}}) + \gamma_{g,a,t}\mathrm{Se}_{\mathrm{I}_{h,t}}(1-\psi_{\mathrm{X}_t})\eta_{\mathrm{S}_t}(1-\tau_{\mathrm{S}_{h,k,t}}\mathrm{RR}_{\mathrm{X}}) +$$
$$\gamma_{g,a,t}\mathrm{Se}_{\mathrm{I}_{h,t}}\psi_{\mathrm{X}_t}(1-\mathrm{Se}_{\mathrm{R}_t})\eta_{\mathrm{S}_t}(1-\tau_{\mathrm{S}_{h,k,t}}\mathrm{RR}_{\mathrm{X}})\Big) * \mathrm{I}_{\mathrm{RX}_{g,a,h,k,t}}$$
$$+\left(\lambda_{\mathrm{R_{g,a,t}}}(1-\mathrm{x}_{a,h,k})\alpha_{g,a,h,k,t}\sigma_{a,h} + \nu_{g,a,h,k,t}\sigma_{a,h}\right) * \mathrm{L}_{\mathrm{RP}_{g,a,h,k,t}}$$
$$-\big(\mathrm{r}_h + \gamma_{g,a,t}\mathrm{Se}_{\mathrm{I}_{h,t}}\psi_{\mathrm{P}_t}\mathrm{Se}_{\mathrm{R}_t}\eta_{\mathrm{R}_t}\tau_{\mathrm{R}_{h,k,t}} + \gamma_{g,a,t}\mathrm{Se}_{\mathrm{I}_{h,t}}(1-\psi_{\mathrm{P}_t})\eta_{\mathrm{S}_t}\tau_{\mathrm{S}_{h,k,t}}\mathrm{RR}_{\mathrm{P}} +$$
$$\gamma_{g,a,t}\mathrm{Se}_{\mathrm{I}_{h,t}}\psi_{\mathrm{P}_t}(1-\mathrm{Se}_{\mathrm{R}_t})\eta_{\mathrm{S}_t}\tau_{\mathrm{S}_{h,k,t}}\mathrm{RR}_{\mathrm{P}}\big) * \mathrm{I}_{\mathrm{RP}_{g,a,h,k,t}}$$
$$+(\theta_h) * \mathrm{N}_{\mathrm{RP}_{g,a,h,k,t}}$$

$$\frac{\mathrm{dN}_{\mathrm{RP}_{g,a,h,k,t}}}{\mathrm{dt}} = \left(\mathrm{d}_N\gamma_{g,a,t}\mathrm{Se}_{\mathrm{N}_{h,t}}\psi_{\mathrm{X}_t}\mathrm{Sp}_{\mathrm{R}_t}\eta_{\mathrm{S}_t}\xi_h + \mathrm{d}_N\gamma_{g,a,t}\mathrm{Se}_{\mathrm{N}_{h,t}}(1-\psi_{\mathrm{X}_t})\eta_{\mathrm{S}_t}\xi_h\right) * \mathrm{N}_{\mathrm{SX}_{g,a,h,k,t}}$$
$$+\left(\lambda_{\mathrm{R_{g,a,t}}}(1-\mathrm{x}_{a,h,k})\alpha_{g,a,h,k,t}(1-\sigma_{a,h})\right) * \mathrm{L}_{\mathrm{SP}_{g,a,h,k,t}}$$
$$+\left(\mathrm{d}_N\gamma_{g,a,t}\mathrm{Se}_{\mathrm{N}_{h,t}}\psi_{\mathrm{P}_t}\mathrm{Sp}_{\mathrm{R}_t}\eta_{\mathrm{S}_t}\xi_h + \mathrm{d}_N\gamma_{g,a,t}\mathrm{Se}_{\mathrm{N}_{h,t}}(1-\psi_{\mathrm{P}_t})\eta_{\mathrm{S}_t}\xi_h\right) * \mathrm{N}_{\mathrm{SP}_{g,a,h,k,t}}$$
$$+\Big(\mathrm{d}_N\gamma_{g,a,t}\mathrm{Se}_{\mathrm{N}_{h,t}}\psi_{\mathrm{X}_t}\mathrm{Se}_{\mathrm{R}_t}\eta_{\mathrm{R}_t}(1-\tau_{\mathrm{R}_{h,k,t}}) + \mathrm{d}_N\gamma_{g,a,t}\mathrm{Se}_{\mathrm{N}_{h,t}}(1-\psi_{\mathrm{X}_t})\eta_{\mathrm{S}_t}(1-\tau_{\mathrm{S}_{h,k,t}}\mathrm{RR}_{\mathrm{X}}) +$$
$$\mathrm{d}_N\gamma_{g,a,t}\mathrm{Se}_{\mathrm{N}_{h,t}}\psi_{\mathrm{X}_t}(1-\mathrm{Se}_{\mathrm{R}_t})\eta_{\mathrm{S}_t}(1-\tau_{\mathrm{S}_{h,k,t}}\mathrm{RR}_{\mathrm{X}})\Big) * \mathrm{N}_{\mathrm{RX}_{g,a,h,k,t}}$$
$$+\left(\lambda_{\mathrm{R_{g,a,t}}}(1-\mathrm{x}_{a,h,k})\alpha_{g,a,h,k,t}(1-\sigma_{a,h}) + \nu_{g,a,h,k,t}(1-\sigma_{a,h})\right) * \mathrm{L}_{\mathrm{RP}_{g,a,h,k,t}}$$
$$-\big(\mathrm{r}_h + \mathrm{d}_N\gamma_{g,a,t}\mathrm{Se}_{\mathrm{N}_{h,t}}\psi_{\mathrm{X}_t}\mathrm{Se}_{\mathrm{R}_t}\eta_{\mathrm{R}_t}\tau_{\mathrm{R}_{h,k,t}} + \mathrm{d}_N\gamma_{g,a,t}\mathrm{Se}_{\mathrm{N}_{h,t}}(1-\psi_{\mathrm{P}_t})\eta_{\mathrm{S}_t}\tau_{\mathrm{S}_{h,k,t}}\mathrm{RR}_{\mathrm{P}} +$$
$$\mathrm{d}_N\gamma_{g,a,t}\mathrm{Se}_{\mathrm{N}_{h,t}}\psi_{\mathrm{P}_t}(1-\mathrm{Se}_{\mathrm{R}_t})\eta_{\mathrm{S}_t}\tau_{\mathrm{S}_{h,k,t}}\mathrm{RR}_{\mathrm{P}} + \theta_h\big) * \mathrm{N}_{\mathrm{RP}_{g,a,h,k,t}}$$

States S: susceptible; L: latent infection; I: smear-positive TB; N: smear-negative TB.
Parameters λ: force of infection; x: proportion protection due to previous infection against progression to active disease following reinfection; α: proportion of new infections developing primary disease; ν: reactivation rate; σ: proportion of cases developing smear-positive disease; θ: rate of conversion from smear-negative to smear-positive disease; r: rate of TB self-cure; d: relative detection of smear-negative TB; γ: rate of access to TB care; Se: net sensitivity of diagnostic algorithm; Sp: net specificity of diagnostic algorithm; ψ: DST coverage; η: proportion of diagnosed individuals who are linked to treatment; τ: proportion of individuals linked to care who successfully complete treatment; ξ: rate of acquisition of resistance during treatment; ι: proportion of non-progressing superinfections.
Subscripts X: treatment-naïve; P: previously treated; S: drug-susceptible; R: MDR; g: sex; a: age; h: HIV status; k: ART duration; t: time-step.

3 Model parameters

Parameter structures and adjustments across model strata, as well as prior ranges and data sources used for model calibration, are discussed below. Prior ranges for all parameters are summarised (and compared with posterior medians and ranges) in Section 6.1.

3.1 Force of infection

The force of infection for drug susceptible TB ($\lambda_{S_{g,a,h,t}}$) and for MDR TB ($\lambda_{R_{g,a,h,t}}$) are time-dependent parameters specific to sex, age, and HIV status. Terms for annual risk of infection for both drug susceptible TB and MDR TB acknowledge heterogeneous patterns of social contacts between men, women, and children and preferential mixing among HIV-positive individuals, as well as time-dependent sex-specific relative risks of infection attributable to tobacco smoking and constant sex-specific relative risk of infection attributable to biological or other factors.

The force of infection for drug susceptible TB (indicated by subscript *s*) is as follows:

$$\lambda_{S_{g,a,h,t}} = \left(\mathrm{c\_M}_{g,a} \frac{\mathrm{I}_{\mathrm{S_{M},}t} + c\mathrm{N}_{\mathrm{S_{M},}t}}{\mathrm{T}_t} + \mathrm{c\_F}_{g,a} \frac{\mathrm{I}_{\mathrm{S_{F},}t} + c\mathrm{N}_{\mathrm{S_{F},}t}}{\mathrm{T}_t} + \mathrm{c\_C}_{g,a} \frac{\mathrm{I}_{\mathrm{S_{C},}t} + c\mathrm{N}_{\mathrm{S_{C},}t}}{\mathrm{T}_t} \right) \times$$

$$(\mathrm{z})(\mathrm{cscal})(amp_h) \left(\mathrm{RR}_{\mathrm{sm\_inf}_{g,a,t}} \mathrm{RR}_{\mathrm{sex}_{g,a}} \right)$$

for sex *g*, age *a*, HIV status *h*, and time-step *t*, where c_M$_{g,a}$ is the average number of contacts with men, $\mathrm{I}_{\mathrm{S_{M},}t}$ is the number of men with drug susceptible smear-positive TB, *c* is the relative infectiousness of smear-negative TB compared to smear-positive TB, $\mathrm{N}_{\mathrm{S_{M},}t}$ is the number of men with drug susceptible smear-negative TB, T is the total population, c_F$_{g,a}$ is the average number of contacts with women, $\mathrm{I}_{\mathrm{S_{F},}t}$ is the number of women with drug susceptible smear-positive TB, $\mathrm{N}_{\mathrm{S_{F},}t}$ is the number of women with drug susceptible smear-negative TB, c_C$_{g,a}$ is the average number of contacts with children, $\mathrm{I}_{\mathrm{S_{C},}t}$ is the number of children with drug susceptible smear-positive TB, $\mathrm{N}_{\mathrm{S_{C},}t}$ is the number of children with drug susceptible smear-negative TB, *z* is the probability of *Mtb* transmission per respiratory contact between an infectious and an uninfected individual, *cscal* is a scaling factor to adjust the total number of contacts, amp_h is a scaling factor to acknowledge more frequent preferential mixing among HIV-positive individuals, $RR_{sm\_inf_{g,a,t}}$ is the relative risk of infection attributable to tobacco smoking, and $RR_{sex_{g,a}}$ is the relative risk of infection attributable to additional sex- or gender-based risks. Prior ranges and data sources for parameters are described in Table 35 and described below.

The annual risk of infection for MDR TB (indicated by subscript *r*) is as follows:

$$\lambda_{R_{g,a,h,t}} = \left(c_{M_{g,a}} \frac{I_{R_{M,t}} + cN_{R_{M,t}}}{T_t} + c_{F_{g,a}} \frac{I_{R_{F,t}} + cN_{R_{F,t}}}{T_t} + c_{C_{g,a}} \frac{I_{R_{C,t}} + cN_{R_{C,t}}}{T_t} \right) \times$$

$$(z)(\varphi)(cscal)(amp_h)(RR_{sm\_inf_{g,a,t}} RR_{sex_{g,a}})$$

for sex *g*, age *a*, HIV status *h*, and time-step *t*, where $I_{R_{M,t}}$ is the number of men with drug susceptible smear-positive TB, $N_{R_{M,t}}$ is the number of men with drug susceptible smear-negative TB, $I_{R_{F,t}}$ is the number of women with drug susceptible smear-positive TB, $N_{R_{F,t}}$ is the number of women with drug susceptible smear-negative TB, $I_{R_{C,t}}$ is the number of children with drug susceptible smear-positive TB, $N_{R_{C,t}}$ is the number of children with drug susceptible smear-negative TB, φ is the relative fitness of MDR strains, and remaining terms are defined as above. Prior ranges and data sources for parameters are described in Table 5.

Table 5: Prior ranges and data sources for parameters related to annual risk of infection

Parameter	Description	Prior range or set value	Reference
c	Relative infectiousness of smear-negative TB compared to smear-positive TB	0.10-0.37	[1, 5-7]
z	Probability of transmission per respiratory contact between infectious and uninfected individuals	0.1	[8-10]
cscal	Scaling factor to adjust the total number of contacts	10-25	Assumption
φ	Relative fitness of MDR strains compared to drug-susceptible strains	0.58-0.85	[1, 7, 11]

Adjustments for heterogeneous mixing

The force of infection acknowledges heterogeneous mixing by sex and age by incorporating the average number of contacts between men (male, age ≥ 15 years), women (female, age ≥ 15 years), and children (both sexes, age < 15 years). Estimates for average number of contacts are based on a 2007 social contact survey in northern Viet Nam [12]. The contact matrix (Table 6) reports the average number of close contacts within a 24-hour period between each participant group and each contact group, with smoothing per Baguelin et al. to ensure symmetry [13].

Table 6: Contact matrix

Participants	Average number of close contacts		
	Men	Women	Children
Men	3.64	3.12	1.36
Women	2.38	4.21	1.42
Children	1.44	1.97	3.46

Adjustments for tobacco smoking

The relative risk of *Mtb* infection attributable to tobacco smoking ($RR_{sm_{g,a,t}}$) is defined as follows:

$$\mathrm{RR}_{\mathrm{sm\_inf}_{g,a,t}} = p_{sm_{g,a,t}} * RR_{sm\_inf} + \left(1 - p_{sm_{g,a,t}}\right)$$

for sex g, age a, and time-step t, where $p_{sm_{g,a,t}}$ is the proportion of current smokers and RR_{sm_inf} refers to the relative risk of *Mtb* infection attributable to tobacco smoking.

The sex-specific proportion of current smokers ($p_{sm_{g,a,t}}$) is based on IHME estimates for the number of daily smokers (Figure 5) [14] divided by UN World Population Prospects population estimates [15]. Estimates are specific to the population age 15 years and older; the proportion of current smokers in ages 0-14 years is assumed 0. Trends in the proportion of current smokers over the period 1980 through 1984 were extended to generate estimates for 1970 through 1979. The proportions of male and female smokers were assumed constant from 2015 through 2035. IHME estimates were used because estimates are available annually from 1980 through 2015 to allow more accurate estimates of historical trends, compared to WHO estimates and projections, which were only available at five-year intervals from 2000 through 2025 [16].

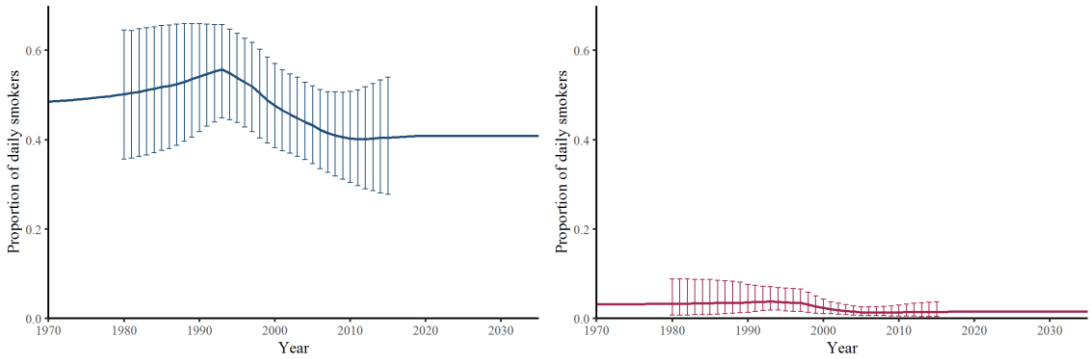

Figure 5: Model priors (line) and IHME estimates (error bars) for proportion of current tobacco smokers for men (on left in blue) and women (on right in red)

The relative risk of *Mtb* infection among current tobacco smokers (RR_{sm_inf}) is based on estimates from systematic reviews and meta-analyses (Table 7).

Table 7: Prior range for relative risk of *Mtb* infection among current tobacco smokers relative to non-smokers

Parameter	Description	Prior range or set value	Reference
RR_{sm_inf}	Relative risk of *Mtb* infection among current smokers	1.46-2.30	[17-19]

Adjustments for additional sex- or gender-based risks

Relative risk of infection attributable to additional sex- or gender-based risks ($\mathrm{RR}_{\mathrm{sex}_{g,a}}$) reflects further unspecified risks that may contribute to men's increased risk of *Mtb* infection relative to women and children (Table 8). Such factors could include anatomical and immunological

factors [20, 21], and their relative risks are considered constant over time. The relative risk of infection attributable to additional sex- or gender-based risks is assumed 1 for women (females, age ≥15 years) and children (both sexes, age 0-14 years).

Table 8: Prior ranges and data sources for relative risks of *Mtb* infection attributable to additional sex- or gender-based risks

Parameter	Description	Prior range or set value	Reference
$\mathrm{RR}_{\mathrm{sex}_{g=M,a\geq 15}}$	Relative risk of infection attributable to additional sex- or gender-based risks in men	1-2	Assumption
$\mathrm{RR}_{\mathrm{sex}_{g=F,a\geq 15}}$	Relative risk of infection attributable to additional sex- or gender-based risks in women	1	Assumption
$\mathrm{RR}_{\mathrm{sex}_{g,a=0-14}}$	Relative risk of infection attributable to additional sex- or gender-based risks in children	1	Assumption

Amplified mixing among HIV-positive individuals

Contacts between HIV-positive individuals, regardless of TB, CD4, or ART category, are amplified by a scaling factor ($amp_{h=HIV+}$) to acknowledge more frequent preferential mixing among HIV-positive individuals within the context of a concentrated HIV epidemic (Table 9). We do not assume any further amplification of mixing among HIV-negative individuals.

Table 9: Prior range for scaling factor to acknowledge more frequent preferential mixing among HIV-positive individuals

Parameter	Description	Prior range or set value	Reference
$\mathrm{amp}_{h=HIV+}$	Scaling factor to amplify contacts between HIV-positive individuals	1-5	Assumption
$\mathrm{amp}_{h=HIV-}$	Scaling factor to amplify contacts between HIV-negative individuals	1	Assumption

3.2 Progression to active disease

3.2.1 Proportion protection due to previous infection against progression to active disease following reinfection

The proportion protection due to previous infection against progression to active disease following reinfection ($\mathrm{x}_{a,h,k}$) is a constant parameter specific to age, HIV status, and ART duration.

Prior ranges and data sources for proportion protection against progression to active disease following reinfection due to previous infection in HIV-negative individuals are shown in Table 10.

Table 10: Prior ranges and data sources for proportion protection due to previous infection against progression to active disease following reinfection in HIV-negative individuals

Parameter	Description	Prior range or set value	Reference
$x_{a\geq 15}$	Proportion protection due to previous infection against progression to active disease following reinfection for age ≥ 15 years	0.37-0.90	[1, 6, 7, 22, 23]
$x_{a=0-14}$	Proportion protection due to previous infection against progression to active disease following reinfection for ages 0-14 years	0.37-0.90	[1, 6, 7, 22, 23]

HIV-positive strata

Following the structure used by Houben et al. [1], proportion protection due to previous infection against progression to active disease following reinfection is adjusted for HIV status based on CD4 count using two relative risks: RR1 as the initial change in risk due to HIV infection, and RR2 as the change in risk attributable to each 100 cell/μL change in CD4 count (Table 11). The CD4-dependent value for the proportion protection due to previous infection against progression to active disease following reinfection is defined as follows:

$$x_i = x * RR_1 * RR_2^{\frac{(500-mid_i)}{100}}$$

where *i* indicates the CD4 category, RR_1 and RR_2 are parameter dependent relative risks, and mid_i is the midpoint of CD4 category *i*. The midpoint of the CD4 category for counts greater than 500 cells/μL is defined as 500 such that $x_{>500} = x * RR_1$.

Table 11: Prior ranges and data sources for risk ratios for protection due to previous infection against progression to active disease following reinfection in HIV-positive individuals

Parameter	Description	Prior range or set value	Reference
$RR1_x$	Risk ratio for protection due to previous infection against progression to active disease following reinfection in HIV-positive individuals with CD4 > 500 cells/μL	0.60-1.00	[1, 6, 7, 23]
$RR2_x$	Risk ratio for protection due to previous infection against progression to active disease following reinfection in HIV-positive individuals for each 100 cell/μL change in CD4	0.50-1.00	[1, 6, 7, 23]

ART strata

ART reduces the difference between the CD4-dependent value and the value for an HIV-negative individual, with increasing effect for increasing duration of ART. ART increases the proportion protection due to previous infection against progression to active disease following reinfection as follows:

$$x_{j,l}^A = \min\left(1 - 1 - \left(x_j^H\right) * (1 - ART_l), x\right)$$

where *A* refers to HIV-positive individuals on ART, *H* refers to HIV-positive individuals not on ART, *j* refers to CD4 category, and *l* refers to ART duration such that ART_l is the protective effect of ART by ART duration (Table 12). The *min* function ensures that ART does not raise protection above that experienced by HIV-negative individuals.

Table 12: Prior ranges and data sources for protective effect of ART on TB disease progression by ART duration

Parameter	Description	Prior range or set value	Reference
$ART_{TB_{l<6}}$	Protective effect of ART on TB disease progression for duration < 6 months	0.16-0.27	[1, 24]
$ART_{TB_{l=6-12}}$	Protective effect of ART on TB disease progression for duration 6-12 months	0.43-0.73	[1, 24]
$ART_{TB_{l\geq 12}}$	Protective effect of ART on TB disease progression for duration ≥ 12 months	0.54-0.92*	[1, 24]

*$ART_{l\geq 12}$ must be greater than $ART_{l=6-12}$

3.2.2 Proportion of new infections developing primary disease

The proportion of new infections developing primary disease ($\alpha_{g,a,h,k,t}$) is a time-dependent parameter specific to sex, age, HIV status, and ART duration.

The proportion of new infections developing primary disease in HIV-negative individuals is defined as follows:

$$\alpha_{g,a} = \alpha_a \mathrm{RR}_{\mathrm{sm\_prog}_{g,a,t}} \mathrm{RR}_{\mathrm{alc}_{g,a,t}} RR_{BCG}$$

for sex *g*, age *a*, and time-step *t*, where α_a is the base proportion of new infections developing primary disease (Table 13), $RR_{sm\_prog_{g,a,t}}$ is the relative risk of progression from *Mtb* infection to disease attributable to tobacco smoking, $RR_{alc_{g,a,t}}$ is the relative risk of progression from *Mtb* infection to disease attributable to alcohol consumption, and RR_{BCG} is the relative risk of progression from *Mtb* infection to disease attributable to BCG vaccination.

Table 13: Prior ranges and data sources for base proportion of new infections developing primary disease in HIV-negative individuals

Parameter	Description	Prior range or set value	Reference
$\alpha_{a\geq 15}$	Base proportion of new infections developing primary disease in ages ≥ 15 years	0.08-0.15*	[1, 6, 7, 25]
$\alpha_{a=10-14}$	Base proportion of new infections developing primary disease in ages 10-14 years	0.032-0.104†	[1, 7, 25, 26]
$\alpha_{a=5-9}$	Base proportion of new infections developing primary disease in ages 5-9 years	0.080-0.260‡	[1, 7, 25, 26]
$\alpha_{a=0-4}$	Base proportion of new infections developing primary disease in ages 0-4 years	0.151-0.495	[1, 7, 25, 26]

* $\alpha_{a\geq 15}$ must be greater than $\alpha_{a=10-14}$
† $\alpha_{a=10-14}$ must be greater than $\alpha_{a=5-9}$
‡ $\alpha_{a=5-9}$ must be greater than $\alpha_{a=0-4}$

Adjustments for tobacco smoking

The relative risk of progression from *Mtb* infection to disease attributable to tobacco smoking ($RR_{sm\_prog_{g,a,t}}$) is defined as follows:

$$\mathrm{RR}_{\mathrm{sm\_prog}_{g,a,t}} = p_{sm_{g,a,t}} * RR_{sm\_prog} + \left(1 - p_{sm_{g,a,t}}\right)$$

for sex *g*, age *a*, and time-step *t*, where $p_{sm_{g,a,t}}$ is the proportion of current smokers (see Section 3.1.1) and RR_{sm_prog} refers to the relative risk of progression from *Mtb* infection to disease attributable to tobacco smoking (Table 14).

Table 14: Prior ranges and data sources for relative risks of progression from *Mtb* infection to disease among current tobacco smokers relative to non-smokers

Parameter	Description	Prior range or set value	Reference
RR_{sm_prog}	Relative risk of progression from *Mtb* infection to disease among current smokers	1.46-2.30	[17-19]

Adjustments for alcohol consumption

The relative risk of progression from *Mtb* infection to disease attributable to alcohol consumption ($RR_{alc_{\mathrm{g,a,t}}}$) is defined as follows:

$$\mathrm{RR}_{alc_{g,a,t}} = p_{alc_{g,a,t}} * cons_{alc_{g,a,t}} RR_{alc} + \left(1 - p_{alc_{g,a,t}}\right)$$

for sex *g*, age *a*, and time-step *t*, where $p_{alc_{g,a,t}}$ is the proportion of current alcohol drinkers, $cons_{alc_{g,a,t}}$ is the standard drinks (in grams) consumed daily by current alcohol drinkers, and RR_{alc} refers to the relative risk of progression from *Mtb* infection to disease attributable to alcohol consumption.

The sex-specific proportion of current alcohol drinkers ($p_{alc_{g,a,t}}$) is based on IHME estimates (Figure 6) [27]. Although the model is designed to use alcohol consumption estimates for ages 15 years and older, only age-standardised prevalence estimates were available; the proportion of current alcohol drinkers in ages 0-14 years is assumed 0. Estimates are available for five-year intervals from 1990 through 2016; estimates for intermediate time points assume linear trends within each five-year interval. Trends in the proportion of current alcohol drinkers over the period 1980 through 1984 were extended to generate estimates for 1970 through 1979. Proportions of male and female drinkers were assumed constant from 2015 through 2035.

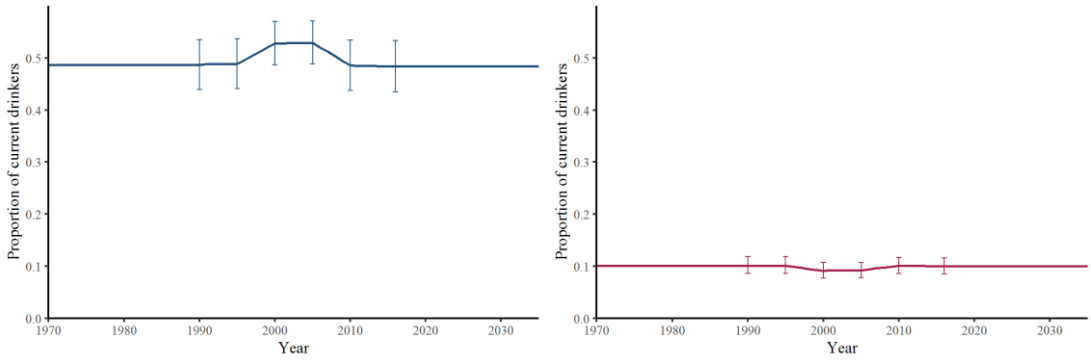

Figure 6: Model priors (line) and IHME estimates (error bars) for proportion of current alcohol drinkers for men (on left in blue) and women (on right in red)

Estimates for standard drinks (in grams) consumed daily by current alcohol drinkers ($cons_{alc_{g,a,t}}$) are based on IHME estimates (Figure 7) [27]. Although the model is designed to use alcohol consumption estimates for ages 15 years and older, only age-standardised prevalence estimates were available; the proportion of current alcohol drinkers in ages 0-14 years is assumed 0. Estimates are available for five-year intervals from 1990 through 2016. We assume linear trends between five-year estimates during this time period. We assume continued increase in alcohol consumption over the period 2016-2020 proportional to the declining rate of increase observed between 2005-2010 and 2010-2015. Alcohol consumption is assumed constant from 2020 through 2035. IHME estimates were used because estimates are available at five-year intervals from 1990 through 2016 to allow more accurate estimates of historical trends, compared to World Bank estimates and projections, which were only available for 2010 and 2016 [28, 29].

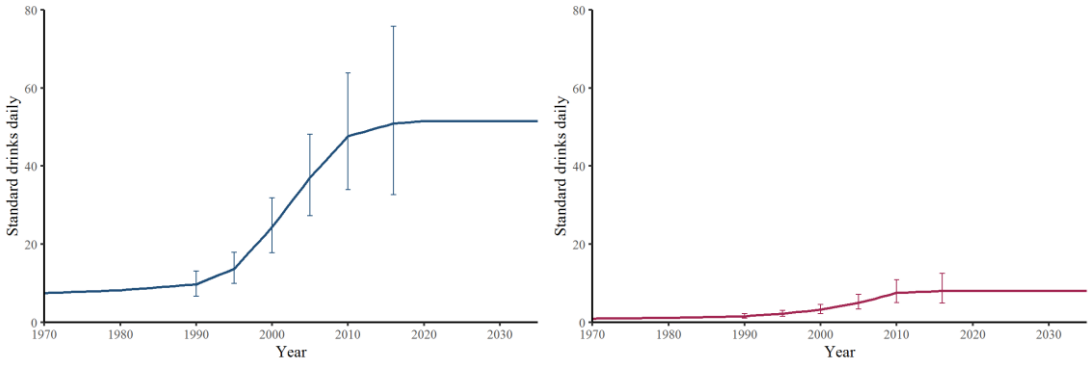

Figure 7: Model priors (line) and IHME estimates (error bars) for alcohol consumption (grams per day) for men (on left in blue) and women (on right in red)

The relative risk of TB disease associated with alcohol consumption is based on a systematic review and meta-analysis (Table 15). The review examined associations between alcohol consumption and TB disease and was not able to differentiate an association with *Mtb* infection from an association with progression from *Mtb* infection to disease. We assume increased risk of progression from *Mtb* infection to disease based on another study that controlled for infection status suggests such a causal pathway [30].

Table 15: Prior ranges and data sources for relative risks of progression from *Mtb* infection to disease among current alcohol drinkers

Parameter	Description	Prior range or set value	Reference
RR_{alc}	Relative risk of progression from *Mtb* infection to disease among current alcohol drinkers	0.004-0.032	[REF]

Overlap between the proportion of the population classified as tobacco smokers and those classified as alcohol drinkers is not directly acknowledged in the model.

Adjustments for BCG vaccination

The relative risk of progression from Mtb infection to disease attributable to BCG vaccination is defined as follows:

$$\mathrm{RR}_{BCG_a} = BCG_{cov} * \left(1 - BCG_{eff_a}\right) + (1 - BCG_{cov})$$

for age a, where BCG_{cov} is the coverage of BCG vaccination in infants and BCG_{eff_a} is the efficacy of BCG vaccination.

The coverage of BCG vaccination in infants is shown in Figure 8. Vaccine coverage is 0 prior to introduction in 1984 [31] and is then scaled up from 48% in 1984 to 95% in 2018 according to WHO estimates [32]. We assume the average coverage from 2014 through 2018 is maintained through 2035. A 2009 WHO Expanded Programme on Immunizations survey found similar coverage for boys and girls [33]; therefore BCG coverage is assumed equal by sex.

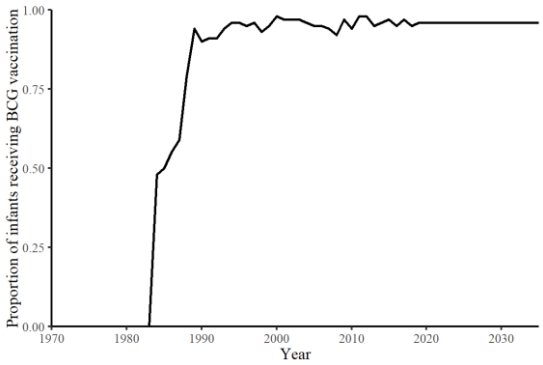

Figure 8: Proportion of infants receiving BCG vaccination

The efficacy of BCG vaccination is shown in Table 16.

Table 16: Prior ranges and data sources for efficacy of BCG vaccination

Parameter	Description	Prior range or set value	Reference
$BCG_{eff_{a=0-14}}$	Efficacy of BCG vaccination in ages 0-14 years	0.39-0.72	[1, 34]
$BCG_{eff_{a\geq 15}}$	Efficacy of BCG vaccination in ages ≥ 15 years	0	Assumption

HIV-positive strata

The proportion of new infections developing primary disease is adjusted for HIV status following the structure described in Section 3.2.1 using relative risks shown in Table 17.

Table 17: Prior ranges and data sources for risk ratios for proportion of new infections developing primary disease in HIV-positive individuals

Parameter	Description	Prior range or set value	Reference
$RR1_\alpha$	Risk ratio for new infections developing primary disease in HIV-positive individuals with CD4 > 500 cells/μL	2.11-3.20	[1, 25, 35]
$RR2_\alpha$	Risk ratio for new infections developing primary disease in HIV-positive individuals for each 100 cell/μL change in CD4	1.30-1.42	[1]

ART strata

ART reduces the difference between the CD4-dependent value and the value for an HIV-negative individual, with increasing effect for increasing duration of ART. The proportion of new infections developing primary disease as follows:

$$x_{i,j,l}^{A} = \max\left(\left(x_{i,j}^{H}\right) * (1 - ART_l), x_i\right)$$

where *A* refers to HIV-positive individuals on ART, *H* refers to HIV-positive individuals not on ART, *i* refers to age, *j* refers to CD4 category, and *l* refers to ART duration such that ART_l is the protective effect of ART by ART duration (Table). The *max* function ensures that ART does not reduce risks below those experienced by HIV-negative individuals of age *i*.

3.2.3 Reactivation rate

The reactivation rate ($\upsilon_{g,a,h,k,t}$) is a time-dependent parameter specific to sex, age, HIV status, and ART duration.

The reactivation rate in HIV-negative individuals is defined as follows:

$$\upsilon_{g,a} = \upsilon_a \mathrm{RR}_{\mathrm{sm\_prog}_{g,a,t}} \mathrm{RR}_{\mathrm{alc}_{g,a,t}}$$

for sex *g*, age *a*, and time-step *t*, where υ_a is the base proportion of new infections developing primary disease (Table 18), $RR_{sm\_prog_{g,a,t}}$ is the relative risk of progression from *Mtb* infection to disease attributable to tobacco smoking (see Section 3.2.2), and $RR_{alc_{g,a,t}}$ is the relative risk of progression from *Mtb* infection to disease attributable to alcohol consumption (see Section 3.2.2).

Table 18: Prior ranges and data sources for base reactivation rate in HIV-negative individuals

Parameter	Description	Prior range or set value	Reference
$\upsilon_{a\geq 15}$	Base reactivation rate in ages ≥ 15 years	0.0001-0.0025	[1, 6, 7, 25, 36]
$\upsilon_{a=0-14}$	Base reactivation rate in ages 0-14 years	0.0001-0.0025	[1, 6, 7, 25, 36]

HIV-positive strata

The reactivation rate is adjusted for HIV status following the structure described in Section 3.2.1 using two relative risks shown in Table 19.

Table 19: Prior ranges and data sources for protective effect of ART on reactivation rate by ART duration

Parameter	Description	Prior range or set value	Reference
$RR1_v$	Risk ratio for reactivation rate in HIV-positive individuals with CD4 > 500 cells/μL	2.11-3.20	[1, 6, 25, 35, 37]
$RR2_v$	Risk ratio for reactivation rate in HIV-positive individuals for each 100 cell/μL change in CD4	1.30-1.42	[1, 6, 25, 35, 37]

Adjustments for ART strata

The reactivation rate is adjusted for ART duration following the structure and protective effects described in Section 3.2.1.

3.3 Infectious disease

3.3.1 Proportion of cases developing smear-positive disease

The proportion of cases developing smear-positive disease ($\sigma_{a,h,k}$) is a constant parameter specific to age, HIV status, and ART duration. Prior ranges and data sources for proportion of cases developing smear-positive disease in HIV-negative individuals are shown in Table 20.

Table 20: Prior ranges and data sources for proportion of cases developing smear-positive disease in HIV-negative individuals

Parameter	Description	Prior range or set value	Reference
$\sigma_{a\geq 15}$	Proportion of cases developing smear-positive disease in ages ≥ 15 years	0.40-0.80*	[1, 6, 7, 25, 38]
$\sigma_{a=0-14}$	Proportion of cases developing smear-positive disease in ages 10-14 years	0.228-0.792	[1, 7, 25, 39]
$\sigma_{a=5-9}$	Proportion of cases developing smear-positive disease in ages 5-9 years	0.116-0.400	[1, 7, 25, 39]
$\sigma_{a=0-4}$	Proportion of cases developing smear-positive disease in ages 0-4 years	0.008-0.024	[1, 7, 25, 39]

* $\sigma_{a\geq 15}$ must be greater than $\sigma_{a=10-14}$

HIV-positive strata

The proportion of cases developing smear-positive disease in HIV-positive individuals is defined as:

$$\sigma_{a,h=HIV+} = \sigma_{a,h=HIV-}\ RR\sigma_{HIV}$$

for age *a* and HIV status h, where $\sigma_{a,h=HIV-}$is proportion of cases developing smear-positive disease in HIV-negative individuals and $RR\sigma_{HIV}$ is the relative risk for proportion of cases developing smear-positive disease in HIV-positive individuals (Table 21).

Table 21: Prior ranges and data sources for proportion of cases developing smear-positive disease in HIV-negative individuals

Parameter	Description	Prior range or set value	Reference
$RR\sigma_{HIV}$	Relative risk for proportion of cases developing smear-positive disease in HIV-positive individuals	0.548-0.850	[1, 7]

3.3.2 Rate of conversion from smear-negative to smear-positive disease

The rate of conversion from smear-negative to smear-positive disease (θ_h) is a constant parameter specific to HIV status. Prior ranges and data sources for the rate of conversion from smear-negative to smear-positive disease are shown in Table 22.

Table 22: Prior ranges and data sources for rate of conversion from smear-negative to smear-positive disease

Parameter	Description	Prior range or set value	Reference
$\theta_{h=HIV-}$	Rate of conversion from smear-negative to smear-positive disease in HIV-negative individuals	0.007-0.030	[1, 6, 7, 25]
$\theta_{h=HIV+}$	Rate of conversion from smear negative to smear positive in HIV-positive individuals	0.015-0.030	[1]

3.4 Self-cure

The rate of self-cure (r_h) is a constant parameter specific to HIV status. Prior ranges and data sources for the rate of self-cure are shown in Table 23.

Table 23: Prior ranges and data sources for rate of self-cure

Parameter	Description	Prior range or set value	Reference
$r_{h=HIV-}$	Rate of TB self-cure in HIV-negative individuals	0.10-0.25*	[1, 7, 11, 25, 40]
$r_{h=HIV+}$	Rate of TB self-cure in HIV-positive individuals	0.06-0.16	[1, 7, 23]

* $r_{h=HIV-}$ must be greater than $r_{h=HIV+}$

3.5 Care cascade

3.5.1 Rate of access to TB care

The rate of access to TB care ($\gamma_{g,a,t}$) is a time-dependent parameter specific to sex and age. Rates of access to TB care are defined by generalised logistic functions as follows:

$$\gamma_{g,a,t} = \gamma\text{min} \frac{\gamma\text{max}_{g,a} - \gamma\text{min}}{\left(1 + e^{-\gamma\text{growth}_{g,a}(t-\gamma\text{midyear}_{g,a})}\right)^{\frac{1}{\gamma\text{shape}}}}$$

for sex *g*, age *a*, and time-step *t*, where γmin is the lower asymptote, $\gamma\text{max}_{g,a}$ is the upper asymptote, and $\gamma\text{growth}_{g,a}$, $\gamma\text{year}_{g,a}$, and γshape are parameters controlling the shape of the function. Rates of access to TB care are assumed the same for HIV-negative and HIV-positive individuals, regardless, among the latter, of ART duration.

Upper asymptote values were determined following the methodology used in Horton et al. [40] to approximate untreated disease duration. We estimate upper and lower limits for 2017 untreated disease duration by sex using results from the second national prevalence survey [41] and relate untreated disease duration to rate of access to TB care as follows:

$$\gamma \approx \frac{1}{untreated\ disease\ duration * Se * \eta}$$

where γ is the rate of access to TB care , Se is the net sensitivity of the diagnostic algorithm, and η is the proportion of diagnosed individuals linked to care.

Prior ranges and values and data sources for parameters related to the rate of access to TB care are shown in Table 24, and prior curves for rates of access to TB care in men and women are shown in Figure 9.

Table 24: Prior ranges and data sources for parameters related to rate of access to TB care in adults

Parameter	Description	Prior range or set value	Reference
$\gamma shape$	Shape parameter	5	Assumption
$\gamma growth_{g=M,a\geq 15}$	Growth parameter in men (male, age ≥ 15 years)	0.5	Assumption
$\gamma growth_{g=F,a\geq 15}$	Growth parameter in women (female, age ≥ 15 years)	0.3	Assumption
$\gamma growth_{g,a=0-14}$	Growth parameter in children (both sexes, age 0-14 years)	0.5	Assumption
$\gamma year_{g=M,a\geq 15}$	Midyear parameter in men (male, age ≥ 15 years)	1990-2015	Assumption
$\gamma year_{g=F,a\geq 15}$	Midyear parameter in women (female, age ≥ 15 years)	1990-2015	Assumption
$\gamma year_{a=0-14}$	Midyear parameter in children (both sexes, age 0-14 years)	2012	Assumption
γmin	Lower asymptote	0	Assumption
$\gamma max_{g=M,a\geq 15}$	Upper asymptote in men (male, age ≥ 15 years)	1.12-2.53	[40]
$\gamma max_{g=F,a\geq 15}$	Upper asymptote in women (female, age ≥ 15 years)	0.91-2.82	[40]
$\gamma max_{a=0-14}$	Upper asymptote in children (both sexes, age 0-14 years)	0.05-0.20	Assumption

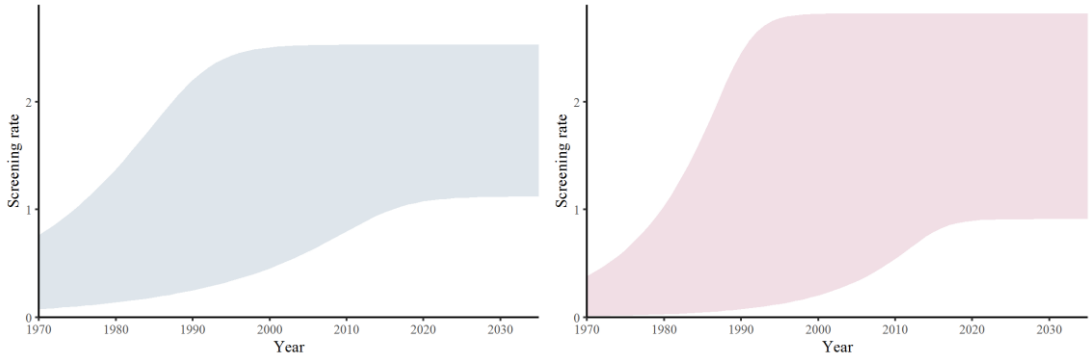

Figure 9: Prior rates of access to TB care ranges for men (on left in blue) and women (on right in red)

Relative rates of access to TB care for individuals with smear-negative TB and for healthy individuals (with neither smear-positive nor smear-negative TB), both relative to individuals with smear-positive TB, are shown in Table 25.

Table 25: Prior ranges and data sources for relative rates of access to TB care in individuals with smear-negative TB and in healthy individuals

Parameter	Description	Prior range or set value	Reference
d_N	Relative rate of access to TB care for smear-negative TB compared to smear-positive TB	0.5	[42]
d_{health}	Relative rate of access to TB care for healthy individuals (with neither smear-positive nor smear-negative TB) relative to smear-positive TB	0.0058	[42]

3.5.2 Diagnostic algorithm

The diagnostic algorithm encompasses the net sensitivity and specificity of diagnostic algorithms for drug susceptible and MDR TB, as well as the coverage of DST. All parameters are time-dependent; the net sensitivity and specificity for drug susceptible TB ($Se_{I_{h,t}}, Se_{N_{h,t}}, Sp_{h,t}$) are also specific to HIV status. Net sensitivities and specificities are a weighted average based on the coverage of different diagnostic algorithms in a given year under the national guidelines for TB diagnosis in Viet Nam. Values for the net sensitivity, specificity, and DST coverage are shown in Table 26.

Table 26: Values for sensitivity, specificity, and DST coverage in HIV-negative individuals

Parameter	Description	Years	Prior range or set value	Reference
$Se_{I_{h=HIV-,t}}$	Net sensitivity of diagnostic algorithm for drug susceptible, smear-positive TB in HIV-negative individuals	1970-2035	0.5780	[42]
$Se_{I_{h=HIV+,t}}$	Net sensitivity of TB diagnostic algorithm for drug susceptible, smear-positive TB in HIV-positive individuals	1970-2035	0.5780	[42]
$Se_{N_{h=HIV-,t}}$	Net sensitivity of diagnostic algorithm for drug susceptible, smear-negative TB in HIV-negative individuals	1970-2011	0.2400	[42]
		2012-2035	0.2457	
$Se_{N_{h=HIV+,t}}$	Net sensitivity of TB diagnostic algorithm for drug susceptible, smear-negative TB in HIV-positive individuals	1970-2011	0.2400	[42]
		2012-2035	0.2531	
$Sp_{h=HIV-,t}$	Net specificity of diagnostic algorithm for drug susceptible TB in HIV-negative individuals	1970-2011	0.9300	[42]
		2012-2035	0.9330	
$Sp_{h=HIV+,t}$	Net specificity of diagnostic algorithm for drug susceptible TB in HIV-positive individuals	1970-2011	0.9300	[42]
		2012-2035	0.9400	
ψ_{X_t}	Proportion DST coverage in treatment-naïve individuals	1970-1999	0	[42]
		2000-2035	0.0570	
ψ_{P_t}	Proportion DST coverage in previously-treated individuals	1970-1999	0	[42]
		2000-2035	0.0480	
Se_{R_t}	Net sensitivity of diagnostic algorithm for MDR TB	1970-2035	1	[42]
Sp_{R_t}	Net specificity of diagnostic algorithm for MDR TB	1970-2035	1	[42]

3.5.3 Linkage to care

The proportion of diagnosed individuals who are linked to treatment for drug-susceptible TB (η_{S_t}) and MDR TB (η_{R_t}) are time-dependent parameters, as shown in Figure 10 [42].

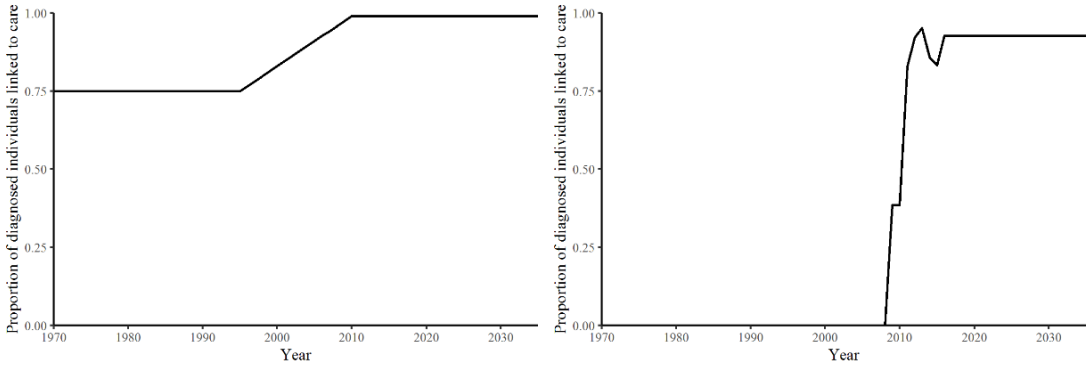

Figure 10: Proportion of diagnosed individuals linked to care for drug-susceptible TB (on left) and MDR TB (on right)

3.5.4 Treatment success

The proportion of individuals linked to care who successfully complete treatment for drug-susceptible TB ($\tau_{S_{h,k,t}}$) and MDR TB ($\tau_{R_{h,k,t}}$) are time-dependent parameters specific to HIV status and ART duration, as shown in Figure 11, Figure 12, and Figure 13 [42].

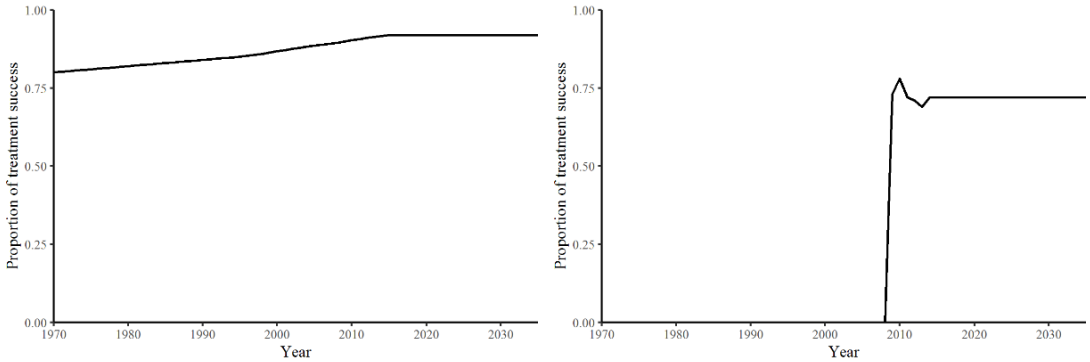

Figure 11: Proportion treatment success in HIV-negative individuals for drug-susceptible TB (on left) and MDR TB (on right)

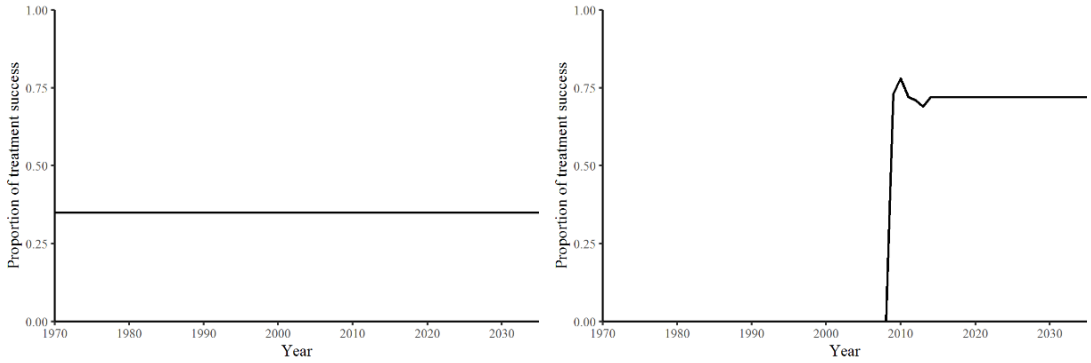

Figure 12: Proportion treatment success in HIV-positive individuals for drug-susceptible TB (on left) and MDR TB (on right)

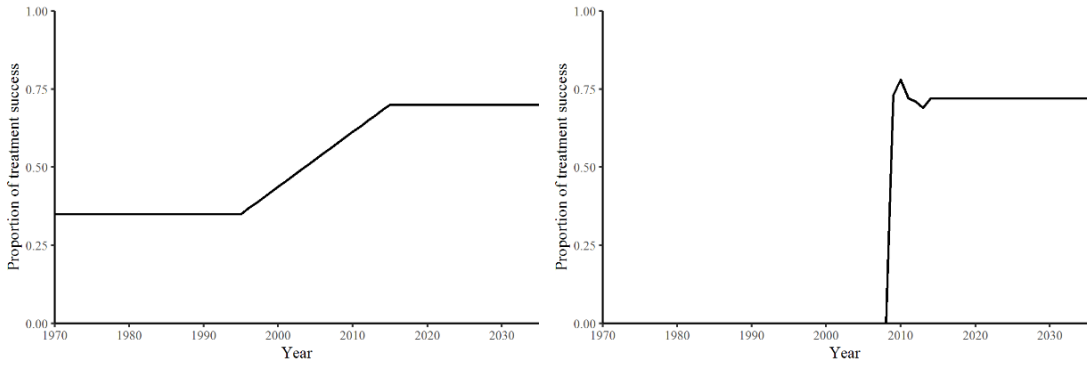

Figure 13: Proportion treatment success in HIV-positive individuals on ART for drug-susceptible TB (on left) and MDR TB (on right)

Prior ranges and data sources for the relative efficacy of first-line treatment for MDR TB in treatment naïve and previously treated individuals are shown in Table 27.

Table 27: Prior ranges and data sources for TB mortality in HIV-negative individuals

Parameter	Description	Prior range or set value	Reference
RR_X	Relative success of using first-line treatment for MDR in treatment naïve individuals	0.53-0.70	[1, 43]
RR_P	Relative success of using first-line treatment for MDR in previously treated individuals	0.35-0.58	[1, 43]

3.6 Mortality

Mortality rates for smear-positive TB ($\mu_{I_{a,h,k}}$) and smear-negative TB ($\mu_{I_{a,h,k}}$) are constant parameters specific to age, HIV status, and ART duration. Prior ranges and data sources for TB mortality rates in HIV-negative individuals are shown in Table 28.

Table 28: Prior ranges and data sources for TB mortality in HIV-negative individuals

Parameter	Description	Prior range or set value	Reference
μ_I	Smear-positive TB mortality rate	0.10-0.41	[1, 7, 23, 25, 40]
μ_N	Smear-negative TB mortality rate	0.09-0.25*	[1, 7, 23, 25, 40]

* μ_I must be greater than μ_N

The mortality rate in individuals ages 0-4 years is defined as:

$$\mu_{I_{a=0-4}} = \mu_I RR\mu_{I_0} \quad \text{and} \quad \mu_{N_{a=0-4}} = \mu_N RR\mu_{N_0}$$

for age *a* and HIV status h, where μ_I and μ_N are mortality rates for smear-positive TB and smear-negative TB, respectively, in HIV-negative individuals and $RR\mu_{I_0}$ and $RR\mu_{N_0}$ are the relative risks for mortality in individuals ages 0-4 years for smear-positive TB and smear-negative TB, respectively (Table 29).

Table 29: Prior ranges and data sources for TB mortality in HIV-negative individuals

Parameter	Description	Prior range or set value	Reference
$RR\mu_{I_0}$	Relative risk of smear-positive TB mortality in ages 0-4 years	1.70-2.98	[1]
$RR\mu_{N_0}$	Relative risk of smear-negative TB mortality in ages 0-4 years	1.70-2.98	[1]

HIV-positive strata

The mortality rate in HIV-positive individuals is defined as:

$$\mu_{a,h=HIV+} = \mu_{a,h=HIV-}\, RR\mu_{HIV}$$

for age *a* and HIV status h, where $\mu_{a,h=HIV-}$is mortality rate in HIV-negative individuals and $RR\mu_{HIV}$ is the relative risk for mortality in HIV-positive individuals (Table 30).

Table 30: Prior ranges and data sources for TB mortality in HIV-negative individuals

Parameter	Description	Prior range or set value	Reference
$RR\mu_{HIV}$	Relative risk of smear-positive or smear-negative TB mortality in HIV-positive individuals	2	[1]

ART strata

The reactivation rate is adjusted for ART duration following the structure described in Section 3.2.1 and protective effects in Table 31.

Table 31: Protective effect of ART by ART duration

Parameter	Description	Prior range or set value	Reference
$ART_{\mu_{l<6}}$	Protective effect of ART for duration < 6 months	0.11-0.28	[1, 24]
$ART_{\mu_{l=6-12}}$	Protective effect of ART for duration 6-12 months	0.51-0.75	[1, 24]
$ART_{\mu_{l\geq 12}}$	Protective effect of ART for duration ≥ 12 months	0.64-0.95*	[1, 24]

* $ART_{l\geq 12}$ must be greater than $ART_{l=6-12}$

3.7 MDR

The movement of individuals with latent superinfection is determined by parameter $\iota = \frac{\varphi}{1+\varphi}$ with φ as defined in Section 3.1.

The rate of acquisition of MDR during treatment (ξ_h) is specific to HIV status. Prior ranges and data sources for the rate of acquisition of MDR during treatment are shown in Table 32.

Table 32: Rate of acquisition of MDR during treatment in HIV-negative individuals by HIV status

Parameter	Description	Prior range or set value	Reference
ξ	Rate of acquisition of MDR during treatment in HIV-negative individuals	0.010-0.017	[1, 44]
ξ_{HIV}	Rate of acquisition of MDR during treatment in HIV-positive individuals	0.010-0.017	[1, 44]

4 Model implementation

The model is initialised with the 1970 population with sex and age structure and 50 smear-positive, drug-susceptible, treatment-naïve TB cases in the age group 20-24 years. The model is run for 200 years with all parameters set at 1970 values and no HIV.

The resulting population is then scaled to the 1970 population, and the model is run through 2035 with time-dependent parameter values and HIV and ART.

The model is implemented in R [45]. Model equations are implemented as ordinary differential equations with a time step of 0.5 years and are solved using the fourth order Runge-Kutta integration method [46].

5 Calibration

The model was calibrated to demographic and epidemiologic targets in a two phase approach.

5.1 Population calibration

The model was first manually calibrated to demographic data on population size estimates from UN World Population Prospects [15]. Calibration targets included estimates for total population, men, women, and children for 2000, 2005, 2010, and 2015, as well as projections for 2035 (Table 33). Model estimates fell within 10% of each point estimate for population size.

Table 33: Demographic calibration targets

Demographic	Population size (in thousands)				
	2000	2005	2010	2015	2035
Total	79 910	83 833	87 968	92 677	106 296
Men	26 635	29 856	32 951	35 013	42 217
Women	28 045	31 256	34 232	36 321	43 495
Children	25 231	22 720	20 784	21 343	20 584

5.2 Epidemiological calibration

The model was calibrated to a set of epidemiological targets to reflect the magnitude and time trends of the TB epidemic (Table 34) using an adaptive approximate Bayesian computation (ABC) Markov chain Monte Carlo (MCMC) method [47] with a modified version of the easyABC package that accepts seed parameter values [48] in R [45]. MCMC was initially seeded with the 14 best-fitting parameter sets from 2 million random parameter sets. Acceptance criterion were increased iteratively from 30 to 37 calibration targets, with the best fits from each iteration used to seed chains in subsequent iterations. Epidemiological calibration was reached when we sampled from a posterior distribution consistent with all 37 epidemiological targets .

Table 34: Epidemiological calibration targets

Category	Calibration target	Year	Range	Reference
Incidence	Incidence per 100,000	2000	157-479	[49]
		2010	143-342	
		2018	116-263	
	HIV-positive incidence per 100,000	2018	4-9	[49]
	Proportion of incidence in children *	2018	0.04-0.06	[49]
Mortality	Mortality per 100,000 †	2000	25-59	[49]
		2010	18-40	
		2018	9-25	
	Mortality per 100,000 in HIV-positive individuals	2018	1.5-3.4	[49]
	Total case notification rate per 100,000 ‡	2000	112-176	[50, 51]
		2010	111-173	

Case notification rate		2018	104-163	
	New smear-positive case notification rate per 100,000 in men §	2000	136-175	[50, 51]
		2010	117-151	
	New and relapse case notification rate per 100,000 in men §	2018	197-253	[50, 51]
	New smear-positive case notification rate per 100,000 in women §	2000	60-93	[50, 51]
		2010	39-62	
	New and relapse case notification rate per 100,000 in women §	2018	72-112	[50, 51]
	Proportion of case notifications in children < 15 years of age	2015	0.01-0.02	[50]
	Proportion of case notifications in HIV-positive individuals ‖	2015	0.015-0.060	[42]
Prevalence	Bacteriologically positive prevalence per 100,000 adults	2007	415-507	[52]
		2017	260-399	[41]
	Bacteriologically positive prevalence per 100,000 men ¶	2007	697-818	[52]
		2017	420-648	[41]
	Bacteriologically positive prevalence per 100,000 women ¶	2007	168-266	[52]
		2017	89-198	[41]
	Smear-positive prevalence per 100,000 adults	2017	55-115	[41]
	Smear-positive prevalence per 100,000 men	2017	78-180	[41]
	Smear-positive prevalence per 100,000 women	2017	23-79	[41]
M:F ratios	M:F ratio in total prevalence	2007	2.6-4.9	[52]
		2017	2.8-5.8	[41]
	M:F ratio smear-positive prevalence	2017	1.4-5.6	[41]
	M:F ratio in *Mtb* infection prevalence	2015	1.4-2.2	[53]
MDR	Proportion MDR in new cases	2005	0.020-0.037	[42]
		2011	0.025-0.054	
	Proportion MDR in retreatment cases	2005	0.140-0.250	
		2011	0.167-0.299	

* Calculated as incidence in ages 0-14 years divided by total incidence with range ± 20%
† Upper limit for 2018 extended to match linear trend from previous (2000 and 2010) estimates
‡ Calculated as total new and relapse cases and cases with unknown previous TB treatment history, divided by population estimate, with ranges assuming 70-95% of cases reported to NTP
§ Ranges assuming 70-95% of cases reported to NTP
‖ Range ± 50%
¶ Estimates for 2007 calculated by applying upper and lower limit of M:F ratio to upper and lower limit of revised estimate for overall prevalence

6 Calibrated model

6.1 Posterior parameters

Median values and ranges for posterior parameter estimates are summarised, with prior ranges for comparison, in Table 35.

Table 35: Summary of prior and posterior parameter values

Parameter	Parameter definition	Prior range	Posterior median and range
c	Relative infectiousness of smear-negative TB compared to smear-positive TB	0.10-0.37	0.25 (0.10-0.36)
cscal	Scaling factor to adjust the total number of contacts	6-12	10.67 (8.54-11.99)
φ	Relative fitness of MDR strains compared to drug-susceptible strains	0.58-0.85	0.75 (0.65-0.85)
RR_{sm_inf}	Relative risk of *Mtb* infection among current smokers	1.46-2.30	2.19 (1.69-2.30)
$\mathrm{RR}_{\mathrm{sex}_{g=M,a\geq 15}}$	Relative risk of infection attributable to additional sex- or gender-based risks in men	1-2	1.57 (1.35-1.94)
amp_{HIV}	Scaling factor to amplify contacts between HIV-positive individuals	1-5	4.47 (3.46-4.99)
$\mathrm{x}_{a\geq 15}$	Proportion protection due to previous infection against progression to active disease following reinfection for age ≥ 15 years	0.37-0.90	0.50 (0.37-0.64)
$\mathrm{x}_{a=0-14}$	Proportion protection due to previous infection against progression to active disease following reinfection for ages 0-14 years	0.37-0.90	0.54 (0.37-0.78)
$RR1_x$	Risk ratio for protection due to previous infection against progression to active disease following reinfection in HIV-positive individuals with CD4 > 500 cells/μL	0.60-1.00	0.82 (0.60-0.99)
$RR2_x$	Risk ratio for protection due to previous infection against progression to active disease following reinfection in HIV-positive individuals for each 100 cell/μL change in CD4	0.50-1.00	0.58 (0.50-0.72)
$ART_{TB_{l<6}}$	Protective effect of ART for duration < 6 months	0.16-0.27	0.21 (0.16-0.27)
$ART_{TB_{l=6-12}}$	Protective effect of ART for duration 6-12 months	0.43-0.73	0.46 (0.43-0.59)
$ART_{TB_{l\geq 12}}$	Protective effect of ART for duration ≥ 12 months	0.54-0.92	0.66 (0.54-0.87)
$\alpha_{a\geq 15}$	Base proportion of new infections developing primary disease in ages ≥ 15 years	0.08-0.15	0.11 (0.08-0.14)
$\alpha_{a=10-14}$	Base proportion of new infections developing primary disease in ages 10-14 years	0.032-0.104	0.059 (0.032-0.098)

Parameter	Parameter definition	Prior range	Posterior median and range
$\alpha_{a=5-9}$	Base proportion of new infections developing primary disease in ages 5-9 years	0.080-0.260	0.182 (0.081-0.240)
$\alpha_{a=0-4}$	Base proportion of new infections developing primary disease in ages 0-4 years	0.151-0.495	0.248 (0.159-0.365)
RR_{sm_prog}	Relative risk of progression from *Mtb* infection to disease among current smokers	1.46-2.30	1.21 (1.14-1.58)
RR_{alc}	Relative risk of progression from *Mtb* infection to disease among current alcohol drinkers	0.004-0.032	0.014 (0.007-0.020)
BCG_{eff}	Efficacy of BCG vaccination	0.39-0.72	0.42 (0.39-0.52)
$RR1_{\alpha}$	Risk ratio for new infections developing primary disease in HIV-positive individuals with CD4 > 500 cells/μL	2.11-3.20	2.78 (2.18-3.19)
$RR2_{\alpha}$	Risk ratio for new infections developing primary disease in HIV-positive individuals for each 100 cell/μL change in CD4	1.30-1.42	1.38 (1.33-1.42)
$\upsilon_{a\geq15}$	Base reactivation rate in ages ≥ 15 years	0.0001-0.0025	0.0013 (0.0008-0.0019)
$\upsilon_{a=0-14}$	Base reactivation rate in ages 0-14 years	0.0001-0.0025	0.0010 (0.0001-0.0025)
$RR1_{\upsilon}$	Risk ratio for reactivation rate in HIV-positive individuals with CD4 > 500 cells/μL	2.11-3.20	2.61 (2.11-3.19)
$RR2_{\upsilon}$	Risk ratio for reactivation rate in HIV-positive individuals for each 100 cell/μL change in CD4	1.30-1.42	1.32 (1.30-1.38)
$\sigma_{a\geq15}$	Proportion of cases developing smear-positive disease in ages ≥ 15 years	0.40-0.80	0.58 (0.49-0.64)
$\sigma_{a=10-14}$	Proportion of cases developing smear-positive disease in ages 10-14 years	0.228-0.792	0.425 (0.229-0.595)
$\sigma_{a=5-9}$	Proportion of cases developing smear-positive disease in ages 5-9 years	0.116-0.400	0.140 (0.116-0.221)
$\sigma_{a=0-4}$	Proportion of cases developing smear-positive disease in ages 0-4 years	0.008-0.024	0.010 (0.008-0.019)
$RR\sigma_{HIV}$	Relative risk for proportion of cases developing smear-positive disease in HIV-positive individuals	0.548-0.850	0.76 (0.55-0.85)
$\theta_{h=HIV-}$	Rate of conversion from smear-negative to smear-positive disease in ages ≥ 15 years	0.007-0.030	0.019 (0.010-0.030)
$\theta_{h=HIV+}$	Rate of conversion from smear negative to smear positive in HIV-positive individuals	0.015-0.030	0.023 (0.015-0.029)
$r_{h=HIV-}$	Rate of TB self-cure in HIV-negative individuals	0.10-0.25	0.13 (0.10-0.17)
$r_{h=HIV+}$	Rate of TB self-cure in HIV-positive individuals	0.06-0.16	0.07 (0.06-0.11)
$\gamma max_{g=M,a\geq15}$	Upper asymptote in men (male, age ≥ 15 years)	1.12-2.53	1.45 (1.18-1.78)
$\gamma max_{g=F,a\geq15}$	Upper asymptote in women (female, age ≥ 15 years)	0.91-2.82	1.37 (1.01-1.63)
$\gamma max_{a=0-14}$	Upper asymptote in ages 0-14 years	0.05-0.20	0.13 (0.10-0.20)
$\gamma year_{g=M,a\geq15}$	Midyear parameter in men (male, age ≥ 15 years)	1990-2015	2010 (2005-2015)

Parameter	Parameter definition	Prior range	Posterior median and range
$\gamma year_{g=F,a\geq 15}$	Midyear parameter in women (female, age ≥ 15 years)	1990-2015	2000 (1990-2007)
μ_I	Smear-positive TB mortality rate	0.10-0.41	0.11 (0.10-0.13)
μ_N	Smear-negative TB mortality rate	0.09-0.25	0.09 (0.09-0.10)
$RR\mu_{I0}$	Relative risk of smear-positive TB mortality in ages 0-4 years	1.70-2.98	2.34 (1.92-2.78)
$RR\mu_{N0}$	Relative risk of smear-negative TB mortality in ages 0-4 years	1.70-2.98	2.10 (1.70-2.73)
$ART_{\mu_{l<6}}$	Protective effect of ART for duration < 6 months	0.11-0.28	0.26 (0.18-0.28)
$ART_{\mu_{l=6-12}}$	Protective effect of ART for duration 6-12 months	0.51-0.75	0.67 (0.51-0.75)
$ART_{\mu_{l\geq 12}}$	Protective effect of ART for duration ≥ 12 months	0.64-0.95	0.82 (0.69-0.95)
ξ	Rate of acquisition of MDR during treatment in HIV-negative individuals	0.010-0.017	0.014 (0.011-0.017)
ξ_{HIV}	Rate of acquisition of MDR during treatment in HIV-positive individuals	0.010-0.017	0.012 (0.010-0.017)
RR_X	Relative success of using first-line treatment for MDR in treatment naïve individuals	0.53-0.70	0.66 (0.56-0.70)
RR_P	Relative success of using first-line treatment for MDR in previously treated individuals	0.35-0.58	0.46 (0.35-0.56)

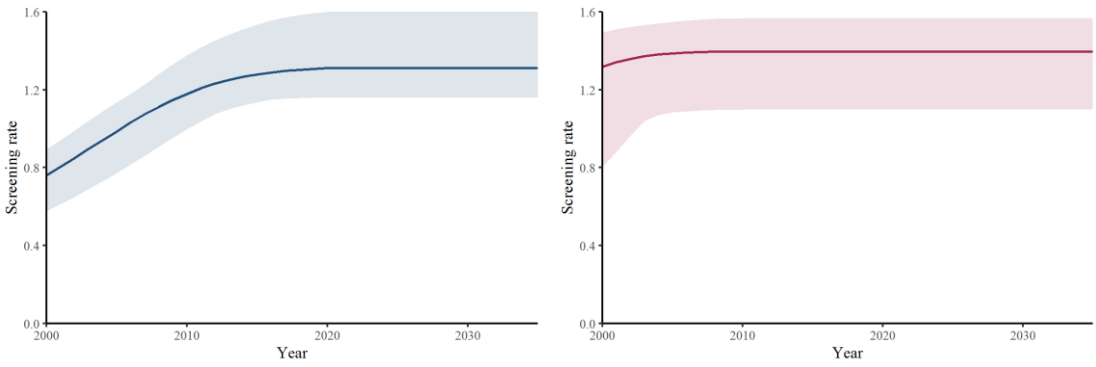

Figure 14: Rate of access to TB care for men (blue on left) and women (red on right) for the calibrated model. Figure shows median values (line) and range (shaded area).

6.2 Population calibration

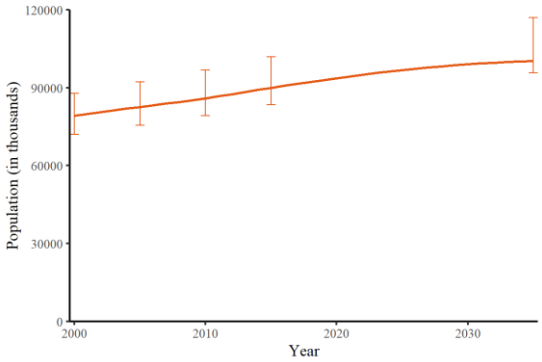

Figure 15: Population for total population for the calibrated model. Figure shows median model estimates (line) and calibration targets (error bars).

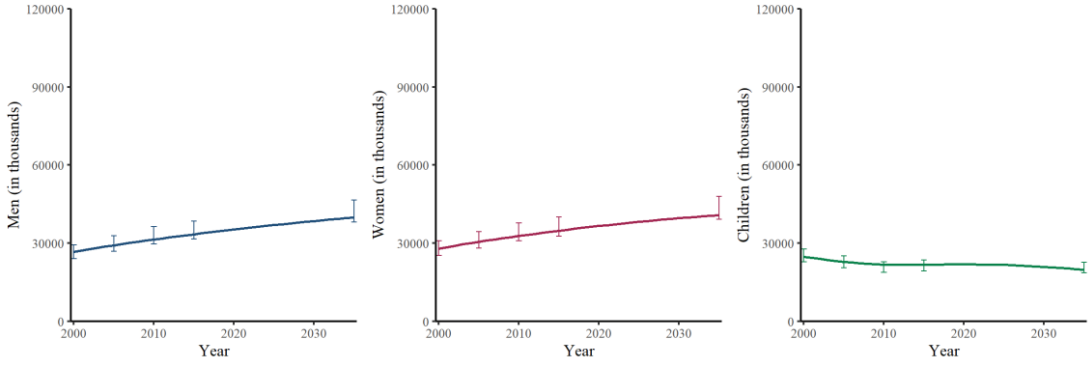

Figure 16: Population for men (left in blue), women (centre in red), and children (right in green) for the calibrated model. Figure shows median model estimates (line) and calibration targets (error bars).

6.3 Epidemiological calibration

6.3.1 Incidence

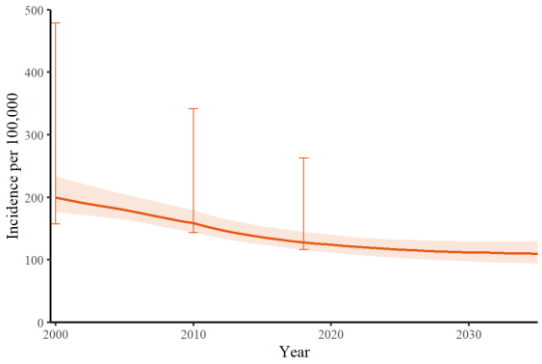

Figure 17: Incidence for total population for the calibrated model. Figure shows median model estimates (line), model uncertainty (shaded area), and calibration targets (error bars).

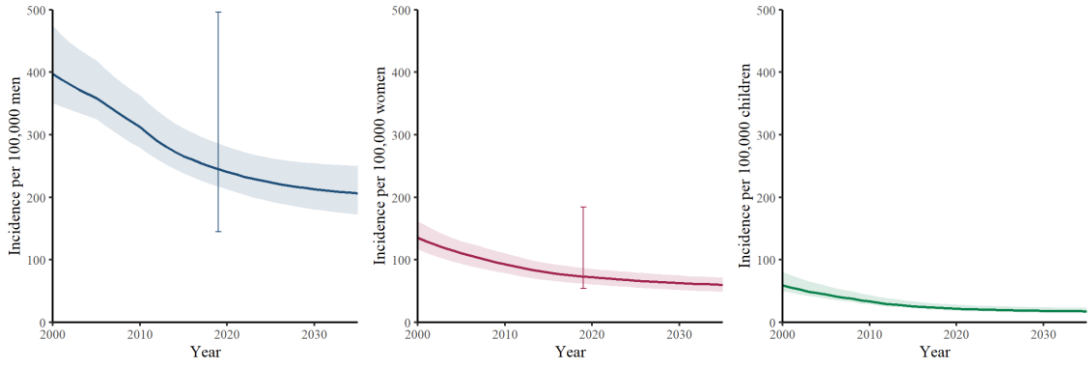

Figure 18: Incidence for men (left in blue), women (centre in red), and children (right in green) for the calibrated model. Figures show median model estimates (line) and model uncertainty (shaded area).

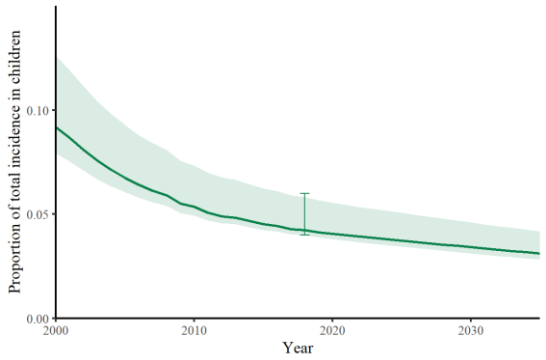

Figure 19: Proportion of total incidence in children for the calibrated model. Figure shows median model estimates (line), model uncertainty (shaded area), and calibration targets (error bars).

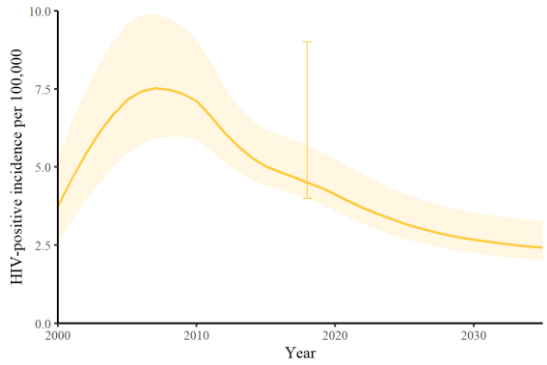

Figure 20: HIV-positive TB incidence for the calibrated model. Figure shows median model estimates (line), model uncertainty (shaded area), and calibration targets (error bars).

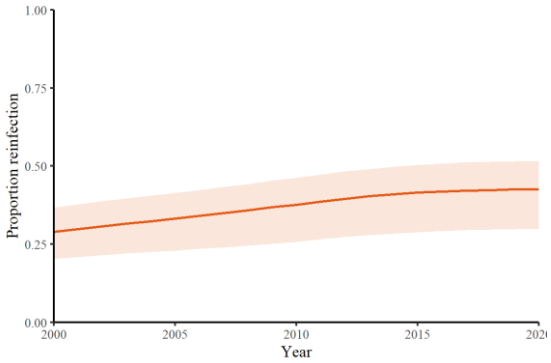

Figure 21: Proportion of incident cases attributable to reactivation for total population for the calibrated model. Figures show median model estimates (lines) and model uncertainty (shaded area).

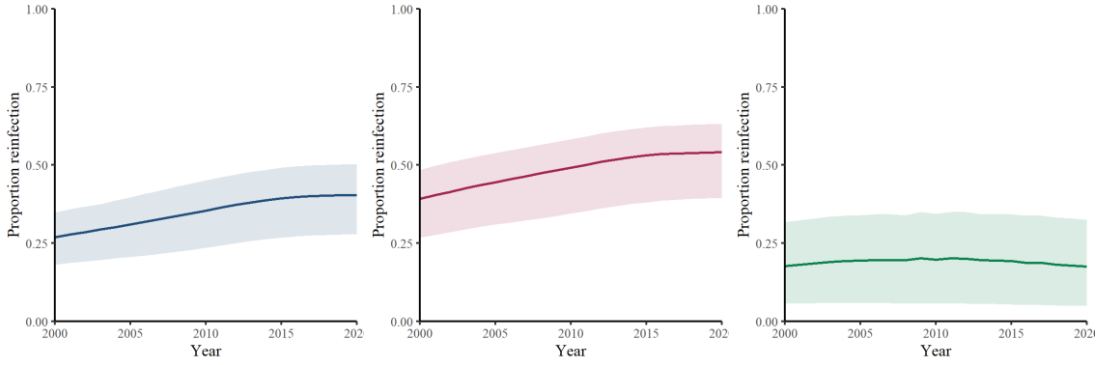

Figure 22: Proportion of incident cases attributable to reactivation for men (left in blue), women (centre in red), and children (right in green) for the calibrated model. Figures show median model estimates (lines) and model uncertainty (shaded area).

6.3.2 Mortality

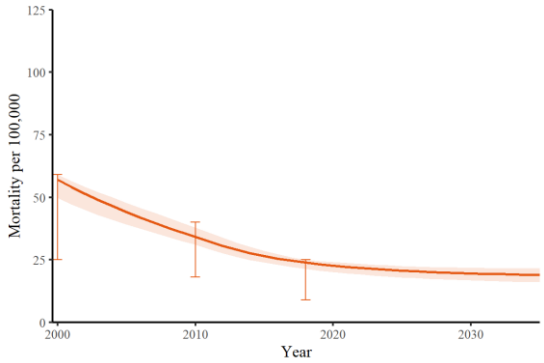

Figure 23: Mortality for total population for the calibrated model. Figure shows median model estimates (line), model uncertainty (shaded area), and calibration targets (error bars).

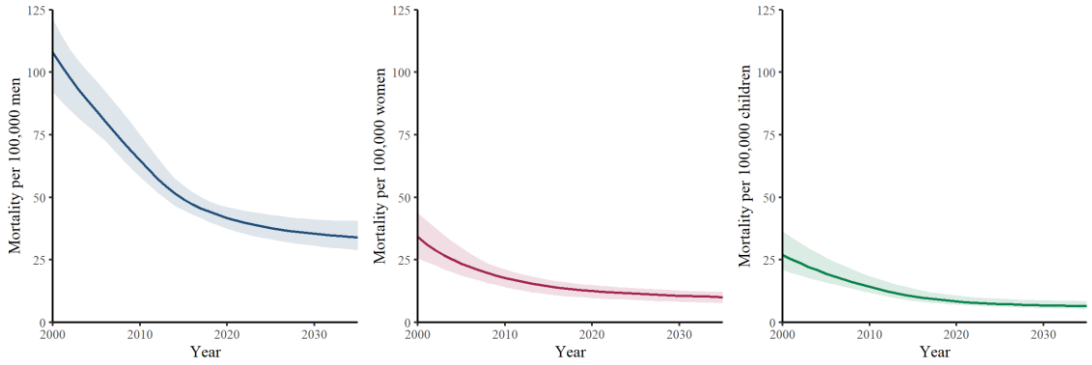

Figure 24: Mortality for men (left in blue), women (centre in red), and children (right in green) for the calibrated model. Figures show median model estimates (line) and model uncertainty (shaded area).

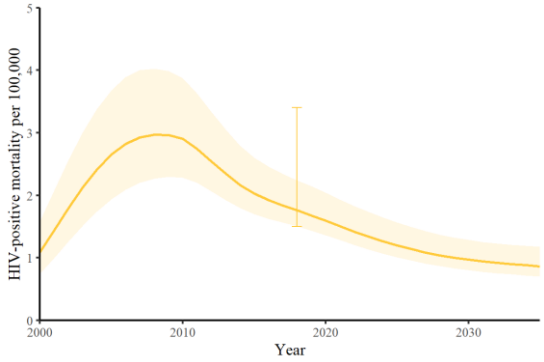

Figure 25: HIV-positive TB mortality for the calibrated model. Figure shows median model estimates (line), model uncertainty (shaded area), and calibration targets (error bars).

6.3.3 Case notification rates

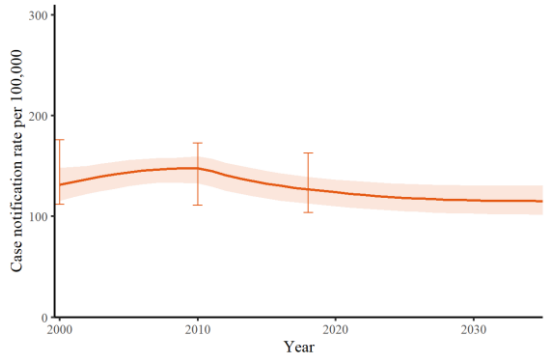

Figure 26: Case notification rate for total population for the calibrated model. Figure shows median model estimates (line), model uncertainty (shaded area), and calibration targets (error bars).

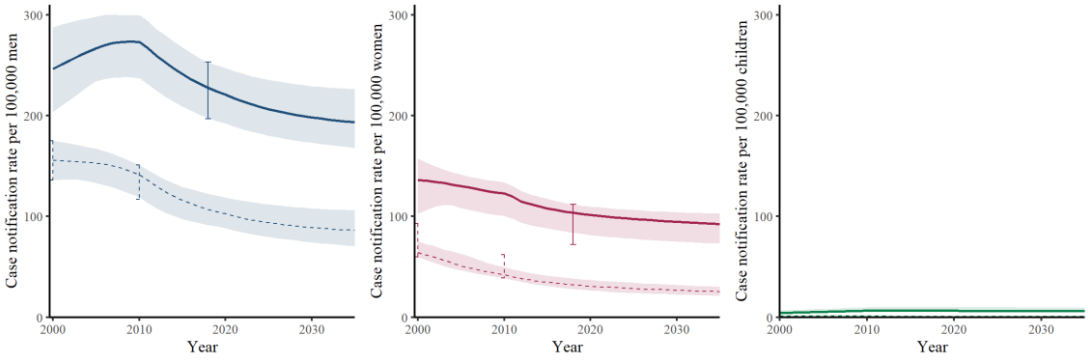

Figure 27: Case notification rate (smear-positive in dashed line, total in solid line) for men (left in blue), women (centre in red), and children (right in green) for the calibrated model. Figures show median model estimates (line), model uncertainty (shaded area), and calibration targets (error bars).

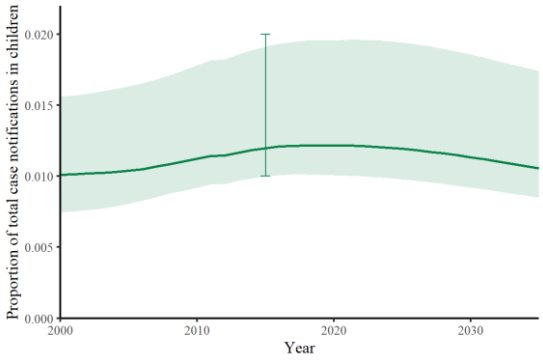

Figure 28: Proportion of total case notifications in children for the calibrated model. Figure shows median model estimates (line), model uncertainty (shaded area), and calibration targets (error bars).

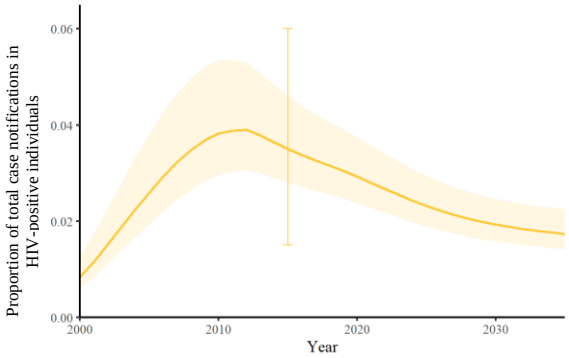

Figure 29: Proportion of total case notifications in HIV-positive individuals. Median model estimate (line), model uncertainty (shaded area) and calibration targets (error bars).

6.3.4 Prevalence

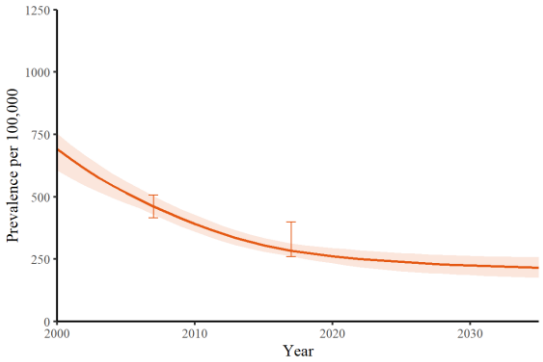

Figure 30: Prevalence for total population for the calibrated model. Figure shows median model estimates (line), model uncertainty (shaded area), and calibration targets (error bars).

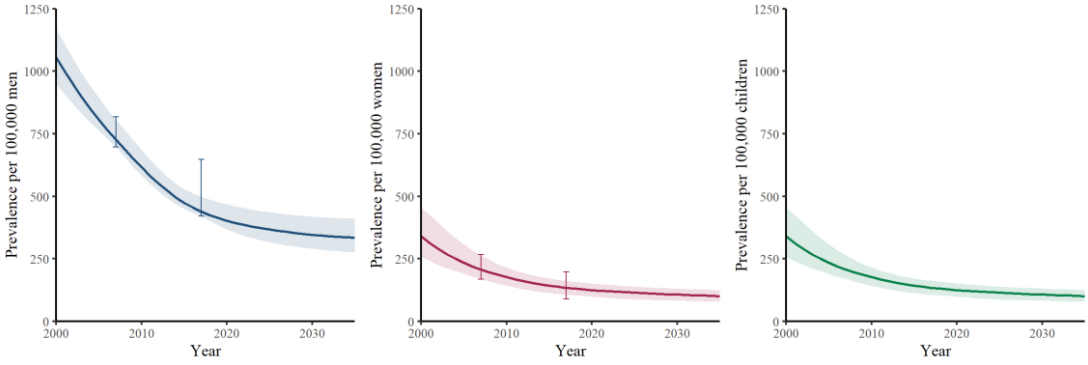

Figure 31: Prevalence for men (left in blue), women (centre in red), and children (right in green) for the calibrated model. Figures show median model estimates (line), model uncertainty (shaded area), and calibration targets (error bars).

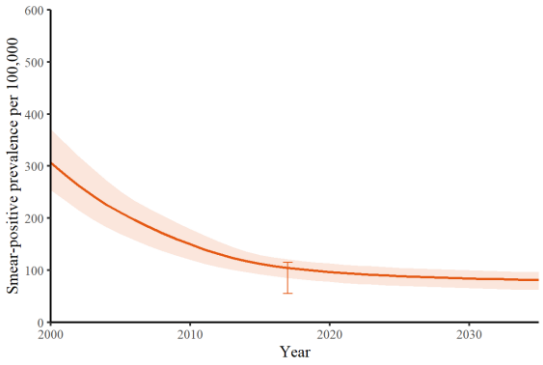

Figure 32: Smear-positive prevalence for total population for the calibrated model. Figure shows median model estimates (line), model uncertainty (shaded area), and calibration targets (error bars).

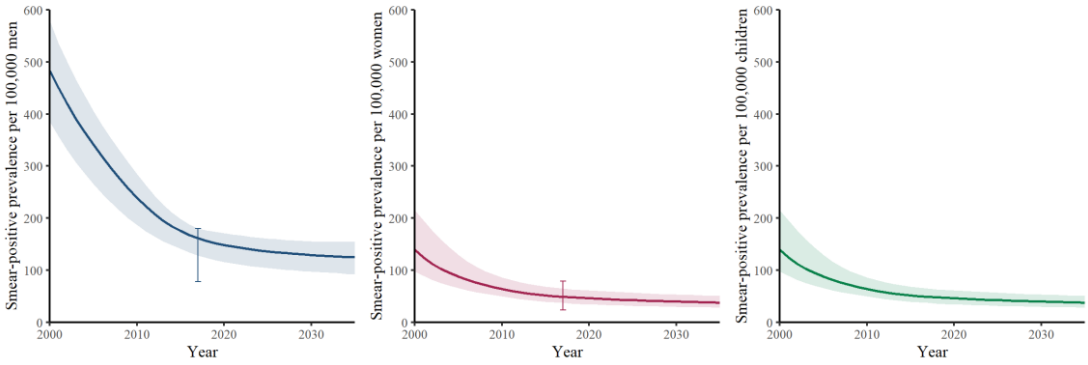

Figure 33: Smear-positive prevalence for men (left in blue), women (centre in red), and children (right in green) for the calibrated model. Figures show median model estimates (line), model uncertainty (shaded area), and calibration targets (error bars).

6.3.5 Male-to-female ratios

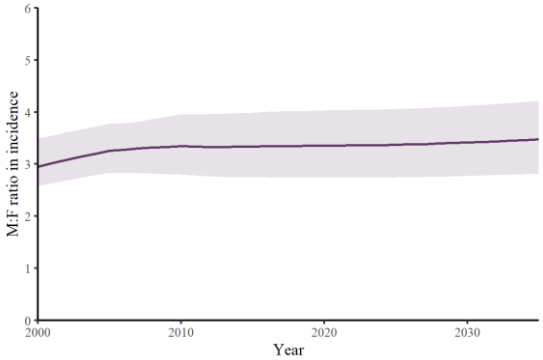

Figure 34: Male-to-female ratio in adult incidence for the calibrated model. Figure shows median model estimates (line) and model uncertainty (shaded area).

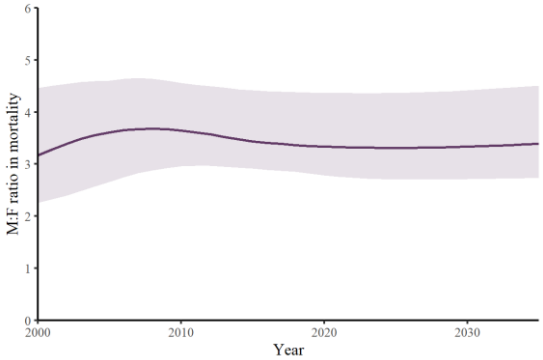

Figure 35: Male-to-female ratio in adult mortality for the calibrated model. Figure shows median model estimates (line) and model uncertainty (shaded area).

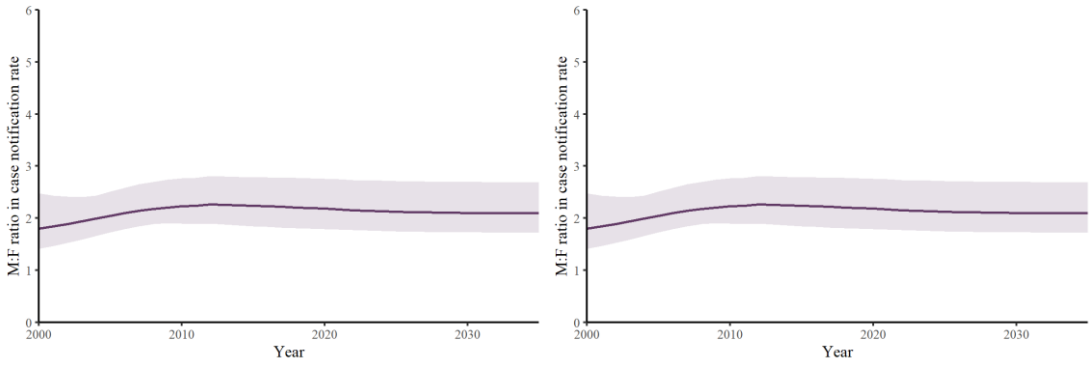

Figure 36: Male-to-female ratio in adult case notification rate (total on left, smear-positive on right) for the calibrated model. Figure shows median model estimates (line) and model uncertainty (shaded area).

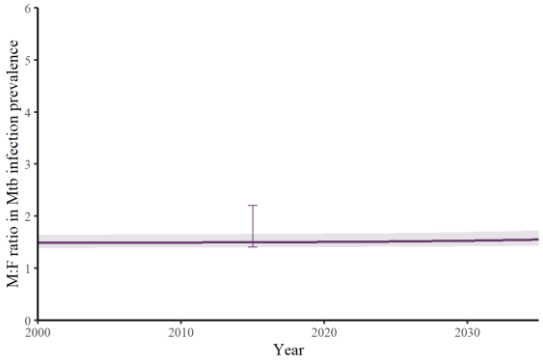

Figure 37: Male-to-female ratio in adult *Mtb* infection prevalence for the calibrated model. Figure shows median model estimates (line), model uncertainty (shaded area), and calibration targets (error bars).

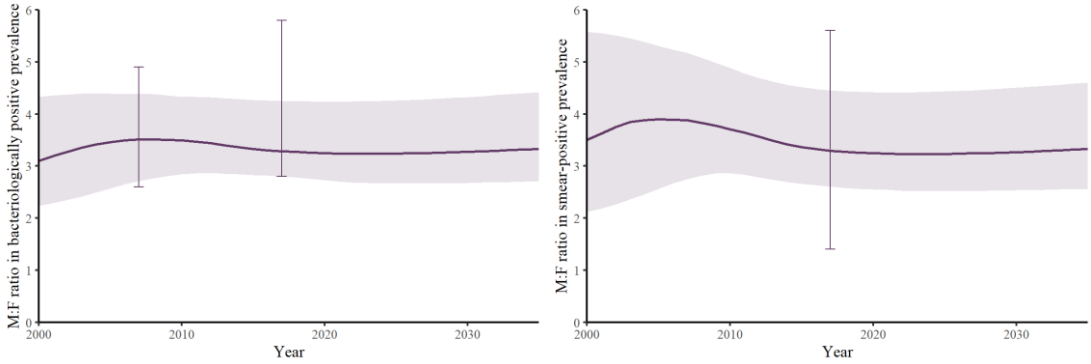

Figure 38: Male-to-female ratio in adult *Mtb* infection prevalence (bacteriologically positive on left, smear-positive on right) for the calibrated model. Figure shows median model estimates (line), model uncertainty (shaded area), and calibration targets (error bars).

6.3.6 MDR TB

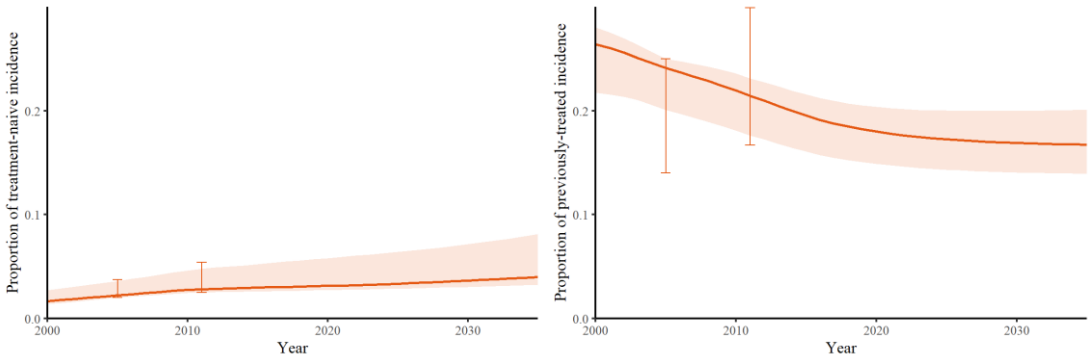

Figure 39: Proportion of MDR TB in incident TB (treatment naïve on left, previously-treated on right) for the calibrated model. Figure shows median model estimates (line), model uncertainty (shaded area), and calibration targets (error bars).

7 Analyses

7.1 Examining the historical impact of sex differences in access to timely diagnosis and treatment

We examined the contribution of improvements in men's access to timely diagnosis and treatment between 2000 and 2020 to declines in TB burden during this period. To do so, we fixed the male-to-female ratio in rates of access to TB care from 2000 onwards to values from 2000. Rates of access to TB care are shown in Figure 40.

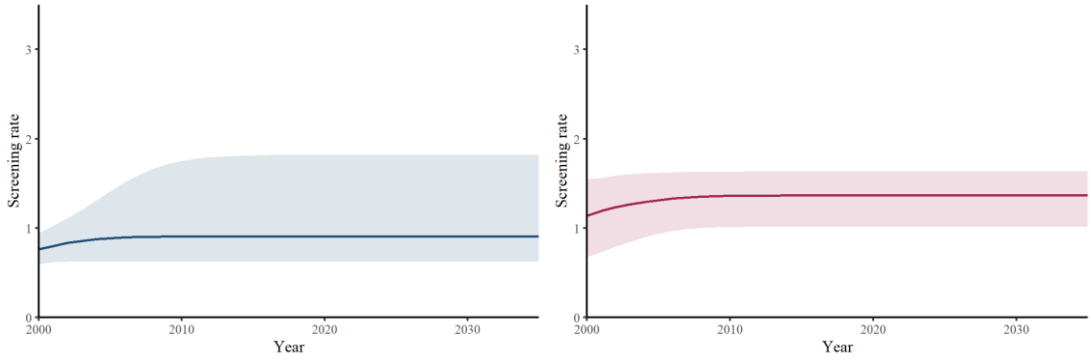

Figure 40: Rates of access to TB care for men (left in blue) and women (right in red) for the historical impact model. Figure shows median values (line) and range (shaded area).

Table 36: 2020 incidence, mortality, and prevalence for the calibrated model and the historical impact model, and percent decline in the calibrated model relative to the historical impact model, for the total population, men, women, and children.

Estimate and demographic		Calibrated model		Historical impact model		Percent decline	
		median	UI	median	UI	median	UI
Incidence	Total	124	(112-140)	171	(104-232)	27	(-27-49)
	Men	241	(213-281)	335	(201-468)	28	(-29-50)
	Women	72	(61-86)	93	(60-122)	22	(-21-43)
	Children	22	(19-28)	33	(17-53)	35	(-40-58)
Mortality	Total	23	(20-24)	35	(17-49)	36	(-41-57)
	Men	42	(37-46)	69	(31-101)	40	(-49-61)
	Women	13	(10-15)	16	(9-21)	20	(-20-40)
	Children	8	(7-11)	12	(6-19)	31	(-38-52)
Prevalence	Total	200	(179-226)	314	(153-426)	36	(-41-57)
	Men	403	(367-467)	669	(307-941)	39	(-48-61)
	Women	125	(98-151)	157	(94-203)	20	(-20-39)
	Children	67	(57-91)	96	(50-146)	30	(-37-51)

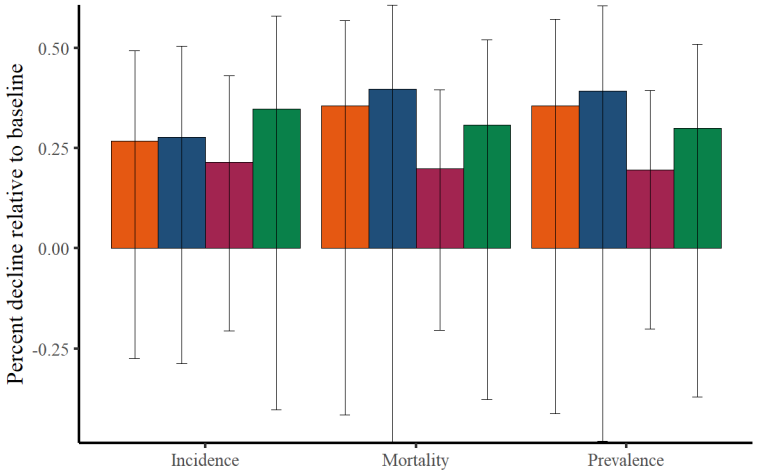

Figure 41: Percent decline in 2020 incidence, mortality, and prevalence for the calibrated model relative to the historical impact model for (from left to right) the total population (orange), men (blue), women (red), and children (green). Figure shows median model estimates (bar) and model uncertainty (error bars).

Table 38: Percent decline in incidence, mortality, and prevalence from 2000 to 2020 attributable to improvements in men's access to timely diagnosis and treatment in the total population, men, women, and children.

Estimate and demographic		Percent decline attributable to improvements in men's access to timely diagnosis and treatment	
		median	UI
Incidence	Total	61	(-35-145)
	Men	59	(-37-149)
	Women	32	(-17-75)
	Children	31	(-16-73)
Mortality	Total	37	(-20-82)
	Men	42	(-26-91)
	Women	15	(-6-39)
	Children	20	(-12-47)
Prevalence	Total	41	(-22-92)
	Men	41	(-25-88)
	Women	15	(-6-38)
	Children	19	(-12-44)

Table 38: Cumulative incident cases and deaths (2000-2020) for the calibrated model and the historical impact model, and percent decline in the calibrated model relative to the historical impact model, for the total population, men, women, and children.

Estimate and demographic		Calibrated model		Historical impact model		Percent decline	
		median	UI	median	UI	median	UI
Incident cases	Total	2,852,000	(2,633,000-3,214,000)	3,218,000	(2,539,000-3,822,000)	12	(-13-23)
	Men	2,025,000	(1,837,000-2,335,000)	2,308,000	(1,776,000-2,801,000)	13	(-15-25)
	Women	650,000	(551,000-762,000)	716,000	(574,000-881,000)	9	(-10-19)
	Children	171,000	(149,000-224,000)	193,000	(147,000-271,000)	12	(-14-24)
Deaths	Total	643,000	(579,000-688,000)	743,000	(563,000-884,000)	14	(-16-25)
	Men	436,000	(399,000-486,000)	521,000	(364,000-646,000)	17	(-20-29)
	Women	131,000	(106,000-159,000)	140,000	(110,000-165,000)	7	(-7-14)
	Children	73,000	(61,000-97,000)	79,000	(62,000-109,000)	8	(-9-17)

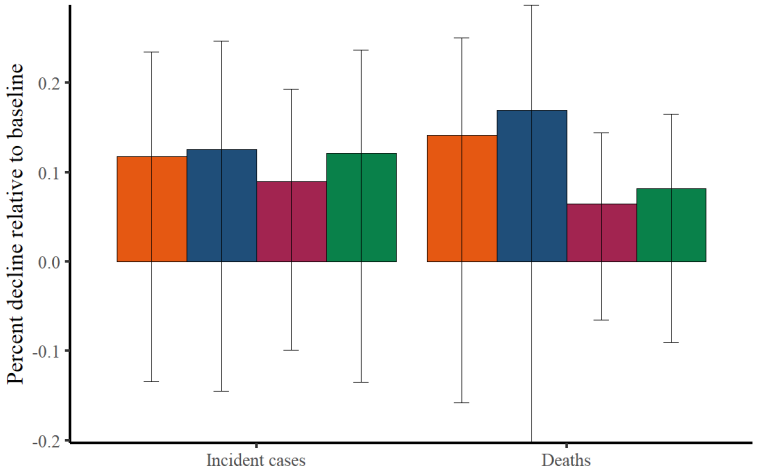

Figure 42: Percent decline in cumulative incident cases and deaths (2000-2020) for the calibrated model relative to the historical impact model in (from left to right) the total population (orange), men (blue), women (red), and children (green). Figure shows median model estimates (bar) and model uncertainty (error bars).

7.2 Estimating the impact of future interventions to further improve access to timely diagnosis and treatment

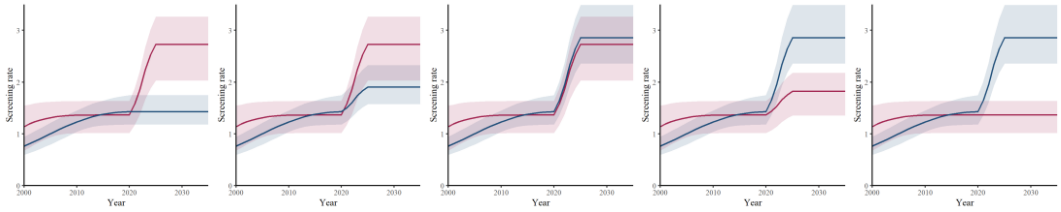

Figure 43: Rate of access to TB care for future intervention scenario models for men (blue) and women (red) for Scenarios 1-5 (from left to right). Figures show median model estimates (line) and range (shaded area).

Table 39: 2035 incidence, mortality, and prevalence for the calibrated model and each intervention scenario model for the total population, men, women, and children.

Estimate and demographic		Calibrated model		Scenario 1		Scenario 2		Scenario 3		Scenario 4		Scenario 5	
		median	UI	median	UI	median	UI	median	UI	median	UI	median	UI
Incidence	Total	110	(94-129)	96	(81-113)	80	(66-94)	66	(50-80)	74	(54-84)	74	(58-89)
	Men	206	(172-250)	181	(152-221)	149	(125-179)	121	(93-146)	129	(101-155)	136	(108-163)
	Women	60	(49-72)	52	(42-63)	46	(35-58)	40	(28-52)	43	(31-55)	45	(33-58)
	Children	18	(14-23)	14	(11-18)	10	(8-14)	7	(6-10)	9	(7-11)	10	(7-13)
Mortality	Total	19	(16-22)	15	(13-18)	11	(9-13)	8	(6-9)	9	(7-11)	10	(8-12)
	Men	34	(29-41)	30	(25-36)	21	(18-25)	14	(11-16)	14	(12-17)	15	(12-18)
	Women	10	(8-12)	6	(5-7)	5	(4-7)	5	(3-6)	6	(4-8)	8	(5-10)
	Children	6	(5-8)	5	(4-7)	4	(3-5)	3	(2-4)	3	(3-4)	4	(3-5)
Prevalence	Total	173	(141-206)	141	(114-171)	105	(82-127)	72	(52-90)	82	(60-103)	91	(67-113)
	Men	334	(276-411)	295	(240-367)	211	(167-259)	134	(101-168)	143	(109-178)	151	(116-186)
	Women	101	(78-124)	60	(44-75)	53	(36-68)	46	(29-62)	63	(41-83)	77	(52-101)
	Children	52	(40-71)	43	(33-58)	33	(26-45)	24	(19-33)	27	(22-38)	30	(24-42)

Table 40: Percent decline in 2035 incidence, mortality, and prevalence for each intervention scenario model relative to the calibrated model for the total population, men, women, and children.

Estimate and demographic		Scenario 1		Scenario 2		Scenario 3		Scenario 4		Scenario 5	
		median	UI	median	UI	median	UI	median	UI	median	UI
Incidence	Total	13	(10-17)	27	(22-37)	40	(32-53)	36	(28-49)	33	(25-46)
	Men	12	(10-17)	28	(22-38)	42	(33-55)	38	(30-51)	34	(26-47)
	Women	13	(10-17)	24	(18-34)	33	(26-47)	29	(22-42)	25	(18-38)
	Children	21	(18-24)	40	(36-47)	58	(52-67)	51	(44-61)	45	(38-56)
Mortality	Total	19	(16-22)	40	(35-47)	59	(53-68)	53	(47-63)	48	(41-58)
	Men	12	(9-16)	37	(32-46)	60	(55-69)	58	(52-67)	55	(50-64)
	Women	41	(39-45)	48	(44-56)	55	(50-64)	38	(32-50)	24	(17-37)
	Children	19	(16-23)	38	(33-44)	55	(49-63)	48	(41-58)	42	(35-52)
Prevalence	Total	19	(16-22)	39	(35-47)	58	(53-68)	53	(47-62)	48	(41-58)
	Men	12	(9-16)	37	(32-45)	60	(54-69)	57	(52-66)	55	(49-63)
	Women	41	(38-44)	48	(44-55)	54	(49-64)	38	(32-49)	24	(17-36)
	Children	19	(16-22)	37	(32-43)	54	(47-62)	47	(40-57)	42	(34-52)

Table 41: Cumulative incident cases and deaths (2021-2035) for the calibrated model and each impact scenario model for the total population, men, women, and children.

Estimate and demographic		Calibrated model		Scenario 1		Scenario 2		Scenario 3		Scenario 4		Scenario 5	
		median	UI	median	UI	median	UI	median	UI	median	UI	median	UI
Incident cases	Total	1,678,000	(1,474,000-1,927,000)	1,546,000	(1,354,000-1,782,000)	1,395,000	(1,197,000-1,609,000)	1,237,000	(1,017,000-1,438,000)	1,330,000	(1,065,000-1,494,000)	1,330,000	(1,105,000-1,539,000)
	Men	1,239,000	(1,060,000-1,467,000)	1,145,000	(986,000-1,361,000)	1,027,000	(894,000-1,203,000)	902,000	(757,000-1,047,000)	938,000	(791,000-1,085,000)	967,000	(820,000-1,117,000)
	Women	377,000	(313,000-450,000)	348,000	(286,000-420,000)	324,000	(256,000-397,000)	299,000	(227,000-373,000)	311,000	(238,000-386,000)	321,000	(247,000-397,000)
	Children	60,000	(50,000-78,000)	53,000	(44,000-69,000)	46,000	(38,000-60,000)	38,000	(31,000-50,000)	41,000	(34,000-54,000)	44,000	(36,000-57,000)
Deaths	Total	295,000	(255,000-326,000)	262,000	(230,000-292,000)	223,000	(195,000-250,000)	182,000	(156,000-206,000)	195,000	(167,000-220,000)	206,000	(176,000-232,000)
	Men	207,000	(181,000-239,000)	195,000	(170,000-224,000)	161,000	(141,000-185,000)	124,000	(108,000-143,000)	128,000	(111,000-147,000)	131,000	(114,000-151,000)
	Women	64,000	(50,000-77,000)	46,000	(35,000-56,000)	44,000	(33,000-54,000)	41,000	(30,000-51,000)	49,000	(36,000-62,000)	56,000	(42,000-70,000)
	Children	22,000	(19,000-29,000)	20,000	(17,000-26,000)	18,000	(16,000-24,000)	16,000	(14,000-21,000)	17,000	(15,000-22,000)	18,000	(15,000-23,000)

Table 42: Percent decline in cumulative incident cases and deaths (2021-2035) for each impact scenario model relative to the calibrated model for the total population, men, women, and children.

Estimate and demographic		Scenario 1		Scenario 2		Scenario 3		Scenario 4		Scenario 5	
		median	UI	median	UI	median	UI	median	UI	median	UI
Incident cases	Total	8	(6-10)	17	(13-23)	26	(21-35)	23	(18-32)	21	(16-29)
	Men	8	(6-10)	17	(14-23)	27	(22-36)	24	(19-33)	22	(17-30)
	Women	8	(6-10)	14	(11-20)	21	(16-30)	18	(13-26)	15	(11-23)
	Children	12	(10-15)	24	(21-29)	37	(32-44)	32	(27-39)	28	(23-35)
Deaths	Total	11	(10-13)	24	(22-28)	38	(35-44)	34	(30-40)	30	(26-36)
	Men	6	(5-8)	22	(20-27)	40	(36-46)	38	(35-44)	37	(33-42)
	Women	29	(26-31)	32	(30-37)	36	(33-42)	23	(20-30)	12	(9-19)
	Children	9	(8-11)	18	(15-21)	27	(23-33)	24	(20-29)	21	(17-26)

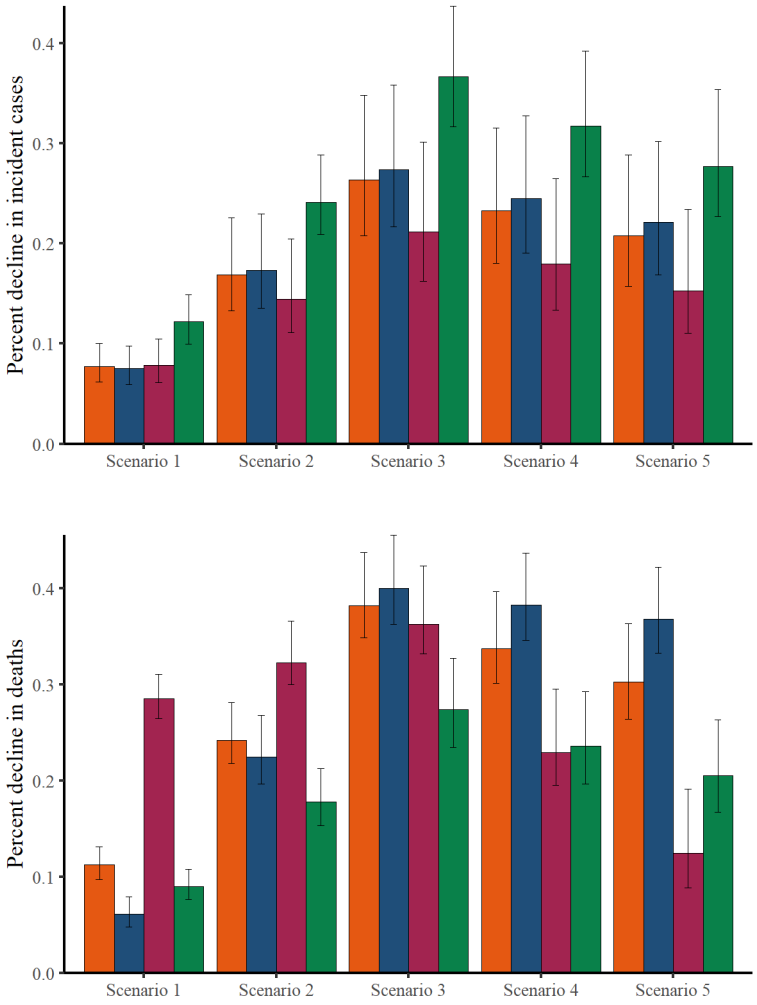

Figure 44: Percent decline in cumulative incident cases (upper) and deaths (lower) (2021-2035) for each impact scenario model relative to the calibrated model for (from left to right) the total population (orange), men (blue), women (red), and children (green).

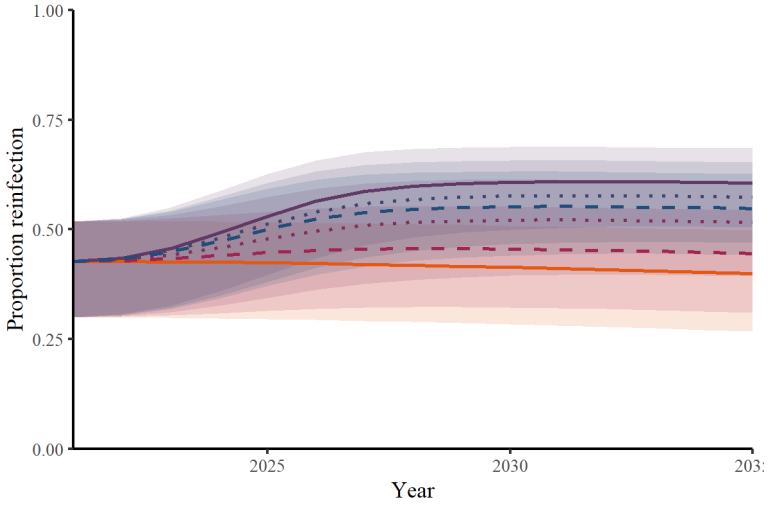

Figure 45: Proportion of incident cases attributable to reactivation for total population for the calibrated model (solid orange line) and each intervention scenario: 1 (dashed red line), 2 (dotted red line), 3 (solid purple line), 4 (dotted blue line), 5 (dashed blue line). Figures show median model estimates (lines) and model uncertainty (shaded area).

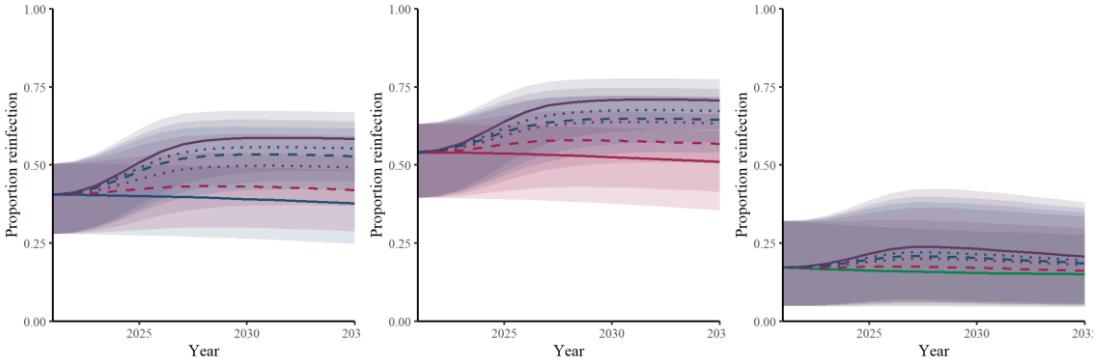

Figure 46: Proportion of incident cases attributable to reactivation for men (left), women (centre), and children (right) for the calibrated model (blue for men, red for women, green for children) and each intervention scenario: 1 (dashed red line), 2 (dotted red line), 3 (solid purple line), 4 (dotted blue line), 5 (dashed blue line). Figures show median model estimates (lines) and model uncertainty (shaded area).

Table 43: Annual case notifications (2021-2035) for the calibrated model and each intervention scenario model.

Year	Calibrated model		Scenario 1		Scenario 2		Scenario 3		Scenario 4		Scenario 5	
	median	UI	median	UI	median	UI	median	UI	median	UI	median	UI
2021	116,000	(103,000-128,000)	121,000	(108,000-134,000)	125,000	(111,000-138,000)	133,000	(118,000-147,000)	129,000	(115,000-143,000)	127,000	(113,000-141,000)
2022	115,000	(102,000-128,000)	128,000	(114,000-141,000)	136,000	(121,000-151,000)	152,000	(135,000-168,000)	144,000	(128,000-160,000)	140,000	(124,000-155,000)
2023	115,000	(102,000-128,000)	135,000	(120,000-150,000)	148,000	(132,000-164,000)	172,000	(153,000-190,000)	159,000	(141,000-176,000)	152,000	(135,000-168,000)
2024	115,000	(102,000-128,000)	139,000	(123,000-154,000)	153,000	(136,000-169,000)	176,000	(157,000-194,000)	161,000	(144,000-178,000)	153,000	(137,000-170,000)
2025	115,000	(102,000-128,000)	140,000	(124,000-155,000)	153,000	(136,000-169,000)	173,000	(154,000-191,000)	158,000	(141,000-174,000)	149,000	(133,000-166,000)
2026	115,000	(102,000-128,000)	137,000	(121,000-152,000)	146,000	(129,000-161,000)	160,000	(142,000-177,000)	147,000	(130,000-163,000)	139,000	(124,000-155,000)
2027	115,000	(102,000-129,000)	135,000	(119,000-150,000)	141,000	(125,000-156,000)	152,000	(134,000-169,000)	140,000	(124,000-156,000)	133,000	(118,000-149,000)
2028	115,000	(102,000-129,000)	134,000	(118,000-149,000)	138,000	(122,000-153,000)	149,000	(130,000-165,000)	136,000	(120,000-152,000)	130,000	(115,000-146,000)
2029	115,000	(102,000-129,000)	133,000	(117,000-149,000)	137,000	(120,000-152,000)	146,000	(127,000-163,000)	134,000	(118,000-150,000)	128,000	(113,000-144,000)
2030	115,000	(102,000-130,000)	133,000	(116,000-149,000)	136,000	(118,000-150,000)	145,000	(125,000-162,000)	133,000	(116,000-149,000)	127,000	(112,000-143,000)
2031	115,000	(102,000-130,000)	132,000	(116,000-148,000)	135,000	(117,000-150,000)	144,000	(124,000-161,000)	132,000	(115,000-148,000)	126,000	(111,000-142,000)
2032	115,000	(102,000-130,000)	132,000	(116,000-149,000)	134,000	(116,000-149,000)	143,000	(123,000-160,000)	131,000	(114,000-147,000)	125,000	(110,000-141,000)
2033	115,000	(102,000-131,000)	132,000	(115,000-149,000)	134,000	(116,000-149,000)	143,000	(122,000-159,000)	130,000	(113,000-147,000)	125,000	(109,000-141,000)
2034	116,000	(102,000-131,000)	132,000	(115,000-149,000)	134,000	(115,000-148,000)	142,000	(122,000-159,000)	130,000	(113,000-146,000)	124,000	(109,000-141,000)
2035	116,000	(102,000-131,000)	132,000	(115,000-149,000)	133,000	(115,000-148,000)	142,000	(121,000-158,000)	129,000	(112,000-146,000)	124,000	(108,000-140,000)

Table 44: Excess annual case notifications (2021-2035) for each intervention scenario model relative to the calibrated model.

Year	Scenario 1		Scenario 2		Scenario 3		Scenario 4		Scenario 5	
	median	UI	median	UI	median	UI	median	UI	median	UI
2021	6,000	(4,000-6,000)	9,000	(8,000-10,000)	17,000	(15,000-19,000)	13,000	(12,000-15,000)	11,000	(10,000-13,000)
2022	12,000	(10,000-14,000)	21,000	(18,000-23,000)	37,000	(33,000-41,000)	29,000	(26,000-32,000)	25,000	(22,000-27,000)
2023	20,000	(16,000-22,000)	33,000	(29,000-36,000)	57,000	(51,000-62,000)	44,000	(39,000-48,000)	37,000	(33,000-41,000)
2024	24,000	(19,000-26,000)	38,000	(33,000-41,000)	61,000	(55,000-67,000)	46,000	(42,000-51,000)	38,000	(34,000-43,000)
2025	25,000	(20,000-28,000)	38,000	(32,000-42,000)	58,000	(52,000-64,000)	43,000	(38,000-48,000)	34,000	(30,000-39,000)
2026	22,000	(17,000-26,000)	31,000	(26,000-35,000)	45,000	(39,000-51,000)	32,000	(26,000-37,000)	24,000	(19,000-29,000)
2027	20,000	(14,000-24,000)	26,000	(21,000-30,000)	37,000	(30,000-44,000)	25,000	(18,000-30,000)	18,000	(12,000-24,000)
2028	19,000	(13,000-23,000)	23,000	(18,000-28,000)	33,000	(26,000-41,000)	21,000	(13,000-27,000)	15,000	(8,000-21,000)
2029	18,000	(12,000-23,000)	22,000	(16,000-26,000)	31,000	(23,000-39,000)	19,000	(11,000-26,000)	13,000	(5,000-19,000)
2030	18,000	(11,000-22,000)	20,000	(14,000-25,000)	30,000	(21,000-37,000)	17,000	(9,000-24,000)	12,000	(3,000-18,000)
2031	17,000	(11,000-22,000)	19,000	(13,000-25,000)	28,000	(19,000-37,000)	16,000	(7,000-24,000)	11,000	(1,000-18,000)
2032	17,000	(10,000-22,000)	19,000	(12,000-24,000)	28,000	(18,000-36,000)	15,000	(6,000-23,000)	10,000	(0-17,000)
2033	17,000	(10,000-22,000)	18,000	(11,000-24,000)	27,000	(17,000-35,000)	15,000	(5,000-22,000)	9,000	(-1,000-17,000)
2034	16,000	(10,000-22,000)	18,000	(10,000-23,000)	26,000	(17,000-35,000)	14,000	(4,000-22,000)	9,000	(-2,000-16,000)
2035	16,000	(9,000-21,000)	17,000	(10,000-23,000)	26,000	(16,000-35,000)	14,000	(3,000-22,000)	8,000	(-3,000-16,000)

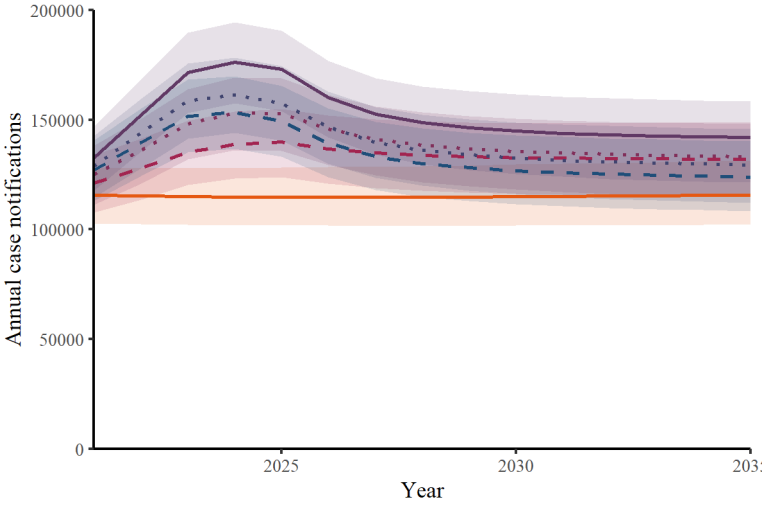

Figure 47: Annual case notifications (2021-2035) for the calibrated model (solid orange line) and each intervention scenario model: 1 (dashed red line), 2 (dotted red line), 3 (solid purple line), 4 (dotted blue line), 5 (dashed blue line). Figure shows median model estimates (lines) and model uncertainty (shaded area).

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