Using mathematical modelling to challenge accepted methods and paradigms of tuberculosis control and transmission

Romain Frédéric Corneille Ragonnet

ORCID 0000-0001-8520-2362

Submitted in total fulfilment of the requirements of the degree of

Doctor of Philosophy

October 2018

Faculty of Medicine, Dentistry and Health Sciences

The University of Melbourne
Abstract

Tuberculosis (TB) represents a major public health issue at the global level. Despite the availability of vaccines and treatments, TB still kills around 1.6 million persons each year due to a combination of unresolved challenges. Firstly, around 40% of diseased individuals are never identified and can therefore not be provided with adequate care. A second substantial challenge is the extremely high prevalence of latent tuberculosis infection (LTBI), which serves as a large reservoir of future disease that is difficult to control. Furthermore, the emergence of drug-resistant TB (DR-TB) has hampered the progress made by TB control in the last decades and required novel strategies to be adopted. Optimal approaches to address these challenges are hampered by substantial knowledge gaps. The lack of a comprehensive epidemiological understanding of TB has also resulted in today’s TB control relying heavily on strong assumptions or preconceived opinions, which are not necessarily supported by evidence. In this thesis, I used mathematical modelling to challenge several of these accepted paradigms.

First, this thesis presents a simple model incorporating epidemiological and programmatic characteristics used to quantify the respective contributions of the different pathways leading to DR-TB at re-treatment around the world. This exercise identified failure to detect DR-TB at first presentation as the leading source of DR-TB at re-treatment. This challenges the accepted paradigm that DR-TB results mainly from poor treatment adherence during treatment of drug-susceptible patients. Important geographical heterogeneity was also observed in the results, and so a web-based interface was built to allow the model to be applied immediately to any epidemiological setting.

Next, this thesis presents a novel exploration of the relationship between TB incidence and the effectiveness of preventive treatment (PT). Although it is widely accepted that using PT would be less efficient in high-burden settings, the exploration suggests that PT would yield optimal efficiency where TB incidence is as high as 700 new cases/100,000/year.

To improve TB modelling methods, this thesis next presents an evaluation of the existing approaches used to simulate the transition from LTBI to active disease. This was done by comparing the reactivation dynamics produced by different model structures to those empirically observed in contacts of infectious TB patients. This exercise demonstrated that two latency compartments are needed to replicate the TB reactivation dynamics in a compartmental model. It further highlighted that the usual cut-off of two or five years used to distinguish late from early latency should be revised to a much shorter duration.
Finally, a novel modelling approach combining country-specific social mixing data with time-variant programmatic parameters within a TB agent-based model is presented in this thesis. The newly built tool was used to detail the profile of *Mycobacterium tuberculosis* (*M.tb*) transmission and TB burden in the five highest TB burden countries (India, Indonesia, China, the Philippines and Pakistan). Findings include the unexpectedly high contribution of adolescents and young adults to *M.tb* transmission. This study also provides estimates of the age-specific size of the latent infection pool, along with the age-specific risk that this infection reservoir represents in terms of future disease.
Declaration

This is to certify that:

- the thesis comprises only my original work toward the PhD except where indicated in the Preface;
- due acknowledgement has been made in the text to all other materials used; and
- the thesis is fewer than 100,000 words in length, exclusive of tables, figures, references and appendices.

Romain Ragonnet

Date: 25th October 2018
Preface

I would like to acknowledge the contribution of the following people to the work presented in this thesis. Emma McBryde, James Trauer and Justin Denholm helped to design the model used in Chapters 2 and 3. Ben Marais assisted with identifying the different causal pathways contributing to DR-TB at re-treatment explored in these two Chapters.

In relation to Chapter 4, James Trauer, Emma McBryde, Rein Houben and Tom Sumner helped to define the model structure. Justin Denholm provided epidemiological inputs into the model and Andreas Handel advised on sensitivity analysis methodology.

I would like to thank the nurses and other staff of the Victorian TB Program for collecting the data used in Chapter 5, and particularly Nompilo Moyo and Ee-Laine Tay who compiled the dataset. I also thank Justin Denholm for facilitating access to this data. My thesis supervisors James Trauer, Emma McBryde and Nick Scott helped to design the study and Michael Meehan assisted with the methodological approaches used to fit the different model structures to the data.

Finally, James Trauer, Emma McBryde and Nick Scott provided inputs on all aspects of the model presented in Chapter 6 and Nic Geard provided advice on the demographic component.
Acknowledgements

I want to thank my doctoral supervisors Emma McBryde, James Trauer and Nick Scott who provided continuous moral support and advice during my thesis. I am very grateful to them for giving me the freedom to define my own research while providing immensely beneficial guidance. I believe that I have become a better researcher thanks to them and my hope is that they will continue to be involved in my future research.

I would like to acknowledge the Australian Government for supporting this work through a Research Training Program scholarship. I also want to thank the Centre for Research Excellence in Policy Relevant Infectious diseases Simulation and Mathematical Modelling (PRISM²) for affording many opportunities to network and attend conferences.

I thank Emma McBryde, James Trauer and Tan Doan for giving me the opportunity to be a founding member of the Australian Tuberculosis Modelling Network (AuTuMN) and for letting me be part of the programmatic activities of the team. This involvement has given me some perspective on my thesis work and it has reinforced my motivation to continue research on tuberculosis in the future.

Finally, I want to thank my family for their support during the course of my thesis. I would particularly like to thank my wife Noémie for her constant encouragement and for convincing me that I was making the right decision when embarking on a doctoral journey. I also thank my daughter Andréa who has brought happiness and laughter into my life.
Publications in peer-reviewed journals during the thesis


Trauer JM, Ragonnet R, Doan TN, McBryde ES. Modular programming for tuberculosis control, the "AuTuMN" platform. BMC Infectious Diseases, 2017.


Doan TN, Fox GJ, Meehan MT, Scott N, Ragonnet R, Viney K, Trauer JM, McBryde ES. Cost-effectiveness of three months of weekly rifapentine and isoniazid compared to other standard

Articles submitted for publication


Presentations at international conferences


# Table of contents

Abstract ........................................................................................................................................................ 3  
Declaration ................................................................................................................................................... 5  
Preface .......................................................................................................................................................... 6  
Acknowledgements ...................................................................................................................................... 7  
Publications in peer-reviewed journals during the thesis ............................................................................. 8  
Articles submitted for publication ..............................................................................................................10  
Presentations at international conferences ..............................................................................................11  
Table of contents ........................................................................................................................................ 12  
List of tables ............................................................................................................................................... 16  
List of figures ............................................................................................................................................. 17  
Abbreviations ............................................................................................................................................. 20  
1 Literature review ....................................................................................................................................21  
1.1 Tuberculosis Today ...............................................................................................................................21  
1.2 Drug-resistant tuberculosis and associated challenges .............................................................. 24  
1.3 Latent tuberculosis infection and its control ............................................................................. 27  
1.4 The missing pieces of the tuberculosis epidemic picture .......................................................... 29  
1.5 Mathematical modelling of tuberculosis ...................................................................................31  
2 High rates of multidrug-resistant and rifampicin-resistant tuberculosis among re-treatment cases: where do they come from? .........................................................................................................................35  
2.1 Abstract ..................................................................................................................................... 36  
2.2 Background .................................................................................................................................... 36  
2.3 Methods ........................................................................................................................................ 37  
2.3.1 Study design ..................................................................................................................... 37  
2.3.2 Model principle ................................................................................................................ 38  
2.3.3 Stochastic method for generating parameter values ......................................................... 40  
2.3.4 Observed outputs .............................................................................................................. 41  
2.3.5 Sensitivity analyses .......................................................................................................... 41  
2.4 Results ....................................................................................................................................... 41  
2.5 Discussion .......................................................................................................................................45
2.6 Conclusions ............................................................................................................................... 47
2.7 Supplemental material ............................................................................................................... 48
   2.7.1 Method used for estimating the risk of re-infection .......................................................... 48
   2.7.2 Use of increased uncertainty around the parameter values ............................................ 48
   2.7.3 Results of the sensitivity analyses .................................................................................... 50
   2.7.4 Parameter values and results of analyses by region and by country ................................. 55
3 A user-friendly mathematical modelling web interface to assist local decision making in the fight
   against drug-resistant tuberculosis ............................................................................................. 59
   3.1 Abstract ..................................................................................................................................... 60
   3.2 The threat of drug-resistant TB ............................................................................................... 60
   3.3 The pathways to drug resistance at re-treatment .................................................................. 60
   3.4 The need to make mathematical modelling more applicable and usable ............................... 61
   3.5 The user-friendly modelling interface ..................................................................................... 62
      3.5.1 General description ........................................................................................................ 62
      3.5.2 Personalised inputs ........................................................................................................... 62
      3.5.3 Model outputs ................................................................................................................... 63
      3.5.4 Mapping ........................................................................................................................... 64
      3.5.5 Download personalised reports ....................................................................................... 64
   3.6 Discussion .................................................................................................................................. 64
4 Is IPT more effective in high-burden settings? Modelling the effect of tuberculosis incidence on IPT
   impact ............................................................................................................................................... 67
   4.1 Abstract ..................................................................................................................................... 68
   4.2 Introduction .............................................................................................................................. 68
   4.3 Materials and methods ............................................................................................................. 69
      4.3.1 Model development ........................................................................................................ 69
      4.3.2 Observed model outputs .................................................................................................. 70
      4.3.3 Sensitivity analyses ......................................................................................................... 71
      4.3.4 Model implementation ..................................................................................................... 71
      4.3.5 Ethical approval ............................................................................................................... 71
   4.4 Results ...................................................................................................................................... 71
      4.4.1 Baseline results ................................................................................................................ 71
      4.4.2 Two interacting phenomena ............................................................................................ 73
List of tables

Table 1 Parameter definitions and values associated with the different WHO regions .............................................. 40
Table 2 95% confidence intervals used around the parameter estimates when using increased uncertainty .............................................................................................................................................................................................................. 49
Table 3 Parameter values and results related to the different WHO regions and countries ............................................. 58
Table 4 Main assumptions ......................................................................................................................................................... 70
Table 5 Model parameters ............................................................................................................................................................. 80
Table 6 Parameter estimates ........................................................................................................................................................... 93
Table 7 Classification of the different structures used in past studies to model TB latency ........................................... 101
Table 8 Parameters associated with the different models ........................................................................................................ 102
Table 9 Equations associated with the dynamics of activation for the six different models .......................................... 104
Table 10 Analytical expressions for the proportion of infected individuals progressing to active disease .............................................................................................................................................................................................................. 105
Table 11 Interval widths retained for the Metropolis-Hastings simulations ............................................................................. 109
Table 12 Proposed statistical distributions to fit the posterior distributions obtained from the Metropolis-Hastings simulation .............................................................................................................................................................................................................. 113
Table 13 Parameter estimates obtained from the calibrations of Models 4 and 6 ................................................................. 115
Table 14 Model assumptions regarding the factors affecting the risk of transmission .......................................................... 128
Table 15 Model parameters ............................................................................................................................................................. 138
Table 16 Estimated values of the Siler model parameters ........................................................................................................ 140
Table 17 Estimated parameter values for the dispersion parameters \( \sigma \) associated with workplace contacts .............................................................................................................................................................................................................. 144
Table 18 Five and ten-year survival probability of TB cases reported in Tiemersma et al. ................................................. 146
Table 19 Estimated values for the TB natural history parameters .............................................................................................. 147
Table 20 Crude risk of transmission per contact under scenario SA 1 ...................................................................................... 157
List of figures

Figure 1. Schematic representation of the transmission of M.tb and the possible infection outcomes .....21
Figure 2 Illustration of the treatment effect on disease prevalence: infectious versus non-communicable disease. .................................................................................................................................32
Figure 3 Presentation of the model structure and parameters .............................................................................39
Figure 4 Rates of MDR/RR-TB at re-treatment by WHO region ........................................................................42
Figure 5 Contributions of the different causal pathways leading to MDR/RR-TB at re-treatment in the seven WHO regions ........................................................................................................43
Figure 6 Representation of the leading pathway to MDR/RR-TB at re-treatment around the world ......44
Figure 7 Comparison of the results obtained with and without inclusion of increased uncertainty ..........50
Figure 8 Results of the sensitivity analysis on the parameters $c$, $e$ and $f$ ....................................................51
Figure 9 Results of the sensitivity analysis for the relative mortality in MDR/RR-TB patient on first-line regimen ..........................................................................................................................53
Figure 10 Results of the sensitivity analysis for the relative risk of MDR/RR-TB in re-infection patients ................................................................................................................................................54
Figure 11 Results of the sensitivity analysis on the treatment outcomes experienced by individuals lost to follow-up or not evaluated ........................................................................................................55
Figure 12 General description of the user interface ..........................................................................................62
Figure 13 Partial screen capture of the user interface ......................................................................................63
Figure 14 Model structure ................................................................................................................................70
Figure 15 Baseline results ..................................................................................................................................72
Figure 16 Annual risk of re-infection and the proportion of disease due to recent infection as functions of tuberculosis incidence ........................................................................................................74
Figure 17 Model structure and parameters .....................................................................................................77
Figure 18 One-way sensitivity analyses realized under different assumptions regarding the mechanism of action of IPT ...........................................................................................................................................81
Figure 19 Representation of the multi-dimensional sensitivity analysis .............................................................82
Figure 20 Results associated with a high HIV-endemic setting ......................................................................83
Figure 21 Optimal TB incidence and associated NNT over HIV prevalence ....................................................84
Figure 22 Optimal TB incidence obtained under various scenarios regarding the relative risk of TB among HIV-infected individuals compared to that among HIV-uninfected individuals ..........................................................................................................................85
Figure 23 Representation of the different model structures .............................................................................91
Figure 24 Calibrations obtained with the different models for the percentage of active TB among infected individuals over time since infection ...........................................................................................................92
Figure 25 Simplified model structures adapted to simulate TB latency in young children (<5 years old) 94
Figure 26 Representation of the collinearity observed between the parameters $\kappa$ and $\varepsilon$ for Model 4 .................................................................................................................................95
Figure 27 Distribution of the times spent in the first latency compartment $L_A$ for Model 4 ..........................95
Figure 28 Six model structures seen as a single general model ...................................................................102
Abbreviations

DOTS: Directly Observed Therapy Short course
DR: Drug Resistance
DR-TB: Drug-Resistant Tuberculosis
DST: Drug Susceptibility Testing
DS-TB: Drug-Susceptible Tuberculosis
IPT: Isoniazid Preventive Therapy
LTBI: Latent Tuberculosis Infection

\textit{M\.\textit{tb}: Mycobacterium tuberculosis}

MDR/RR-TB: Multidrug-Resistant or Rifampicin-Resistant Tuberculosis
MDR-TB: Multidrug-Resistant Tuberculosis
NTP: National Tuberculosis Programme
PT: Preventive Therapy
SNAP-TB: Social Network Abstraction to Profile Tuberculosis Burden
TB: Tuberculosis
WHO: World Health Organization
XDR-TB: Extensively Drug-Resistant Tuberculosis
1 Literature review

1.1 Tuberculosis Today
Tuberculosis (TB) has plagued mankind throughout history and its causative agent (*Mycobacterium tuberculosis*, *M. tuberculosis*) was first identified by Robert Koch in 1882 – and yet more than 130 years later, TB is estimated to be the world’s leading infectious cause of death.\(^1\) Each year, more than ten million individuals develop TB and about 1.6 million of them die from the disease.\(^1\) Although the global epidemic is thought to be on the decline, yearly updates of TB incidence that account for new prevalence surveys and improved estimation methods demonstrate that TB burden has been consistently underestimated.\(^1\)\(^-\)\(^3\) It is therefore difficult to determine whether the epidemic is truly under control at the global level, with evidence suggesting extremely high disease burdens in some localities and population subgroups.\(^4\)\(^-\)\(^6\)

*M. tuberculosis* is carried in airborne particles (droplet nuclei) that are generated by persons who have active pulmonary TB disease through coughing, sneezing, shouting or singing.\(^7\)\(^-\)\(^9\) These particles may remain in the air for several hours, such that individuals sharing the same space as the infectious person for an extended period of time (either simultaneously or in the time immediately following) can inhale the pathogen and become infected with *M. tuberculosis*. Latent TB infection (LTBI) occurs when the organism is contained by the immune system and in most cases remains dormant and asymptomatic throughout the individual’s lifetime, although ten to 15 percent of infections will eventually result in active TB disease.\(^10\)\(^-\)\(^11\) Such progression may occur soon after infection (early progression) or many months or years later (late reactivation).\(^12\)

![Figure 1. Schematic representation of the transmission of *M. tuberculosis* and the possible infection outcomes.](image-url)
Conditions that affect the immune system, such as infection with human immunodeficiency virus (HIV), diabetes mellitus and silicosis, lead to an increased risk of disease activation for people with LTBI. Some population subgroups, such as prisoners, homeless people or drug users have also been found to have higher rates of reactivation than the general population, due to poorer general health status. Poverty is also broadly recognised as providing a fertile ground for TB, with poor people more likely to live in overcrowded settings, which provide greater opportunity for transmission due to the high frequency and intensity of inter-personal contacts. Moreover, the specific individual-level risk factors cited above for LTBI reactivation are consistently correlated with poverty, which further enhances the risk of TB in the poorest settings. The absence of high-quality TB care facilities is also common in necessitous communities, which results in a reduced capacity to diagnose and treat patients. Accordingly, longer delays between disease and cure are incurred, perpetuating the spread of TB in the most marginalised populations. TB is therefore often referred to as “disease of the poor”, although the relationship between TB and poverty is not unidirectional as TB can also generate poverty. People with TB are often unable to work for long periods of time which can result in financial hardship for the patient’s family. Patients have to pay for their treatment in some settings and even where TB care is free there are often ancillary costs, such as those associated with travel to clinics. The strong association between TB and poverty highlights the need for the disease to be treated as a social issue as much as it is a health problem. Although the need for universal health coverage has long been acknowledged and advocated for, efforts are still needed to improve access to affordable care for the most vulnerable populations.

The difficulty in accessing TB care results in important detection challenges. Around 40% of all individuals with active TB are currently missed by national TB programmes (NTP) and therefore cannot be provided with adequate TB care by definition. Undetected diseased individuals are at high risk of death since the probability of recovery without treatment is low, with the ten-year case fatality of TB being estimated at 70% and 20% for smear-positive and smear-negative cases, respectively. In addition to increasing disease-related mortality, failure to diagnose infectious individuals promotes new infections as it allows for more \( M.\text{tb} \) transmission to occur. However, barriers to case detection are of multiple types, including economic, sociocultural, geographical and health system related.

The first set of obstacles to case detection concerns access to TB care providers, which are particularly important in low- and middle-income settings. These include difficulties in accessing healthcare centres because of remoteness or lack of awareness of access points, the costs associated with transport and care seeking and the potential for lost income in the absence of...
Other factors contributing to poor case detection include lack of awareness of the dangers of TB, poor health literacy about the treatability of the disease and stigma. Other factors contributing to poor case detection include lack of awareness of the dangers of TB, poor health literacy about the treatability of the disease and stigma.

A second set of barriers to case detection pertains to the technical difficulties associated with TB diagnosis. In resource-limited settings, diagnosis relies mostly on smear microscopy which requires considerable expertise and is not effective for the detection of smear-negative and extrapulmonary patients, who contribute around 50% of the global TB burden. An alternative diagnostic method is culture, which is more sensitive than microscopy and allows for detection of extrapulmonary forms of TB in some situations. However, culture-based techniques are associated with much longer turnaround times and require specimen transportation. Thus, relying on culture alone for the diagnosis of TB would exacerbate detection delays and so allow for greater M.tb transmission. New diagnostic tools such as GeneXpert® have emerged during the last decade and offer greater opportunities for point-of-care rapid testing with lesser technical and material requirements. Although this novel tool has allowed for more innovative and effective TB case-finding activities in specific settings, its impact at the global level has been limited so far, with global case detection rates remaining little changed since GeneXpert® was officially endorsed by the World Health Organization (WHO) in 2010. One explanation for this are the relatively high costs associated with this new tool as compared to standard smear microscopy, precluding GeneXpert® from being used more routinely. Further efforts are therefore urgently needed to overcome the numerous barriers to TB detection, including multifactorial approaches addressing both the technical aspects and the social issues leading to patient delays as these are likely to be the most effective.

The arrival of anti-TB drugs in the middle of the twentieth century revolutionised global TB control. It allowed TB mortality to dramatically diminish from up to 70% in the pre-chemotherapy era to only 3% today among treated individuals. Anti-TB drugs also contribute to limiting M.tb transmission, as the infectiousness of TB patients drops rapidly once effective treatment is initiated. This observation has made the treatment of active disease the cornerstone of TB control programs worldwide during the second half of the last century. However, identifying individuals with TB and initiating therapy only represents the first step towards recovery, as the road towards treatment completion is often long and difficult. Indeed, the standard six-month regimen used to treat TB today remains very similar to that used in the earliest days of the chemotherapy era, and adherence is complicated by the long duration of treatment and associated side effects. In low-income countries, these difficulties in maintaining treatment adherence are exacerbated by poor access to health care and the paucity or absence of social protection policies. Ensuring favourable treatment outcomes for all TB patients has been the cornerstone of global control over the last quarter-century (since the launch of the Directly Observed Therapy Short course (DOTS) strategy in 1995) and has contributed to decreasing disease burden in many
settings. Improving treatment outcomes is also critical to limiting the emergence of drug-resistant TB (DR-TB). However, even after achieving a global treatment success rate nearing 85% in 2016, the current TB burden remains unacceptably high. This suggests that innovative and multifactorial approaches must now be considered to address the disparate challenges still facing TB control.

This thesis focuses on arguably the three most challenging issues in the current context of TB control: drug resistance, the huge global pool of LTBI and insufficient case detection. The following sections will demonstrate how several aspects of current global TB control often rely on preconceived opinions or strong assumptions relating to these issues that have never been formally tested. This thesis work employed mathematical modelling to challenge these paradigms and provide insights into several important epidemiological knowledge gaps by offering novel perspectives. In addition, a review and evaluation of the techniques previously used to model specific aspects of TB natural history is presented. The broad aim of this research is to provide methodological guidance and better TB epidemic understanding in order to contribute to improving control of infection and disease.

1.2 Drug-resistant tuberculosis and associated challenges

Among the many challenges facing TB control today, the emergence of drug resistance (DR) that followed the introduction of anti-TB drugs around 1950 is one of the most difficult to address. Although most patients with DR-TB can theoretically be treated with existing technologies, a number of important obstacles make the path to recovery even more difficult than for patients with drug-susceptible TB (DS-TB).

First, effective diagnosis of DR-TB requires access to specific equipment and a highly skilled health care workforce, which are often unavailable in low-income settings where the burden of TB and DR-TB are greatest. Sputum microscopy, which remains the most widely used diagnostic tool for TB, cannot differentiate DS-TB from DR-TB. Instead, the patient’s drug susceptibility profile is definitively determined by culture of \( M. tb \) isolates in the presence of the various drugs used in constructing the available TB regimens. Although very effective and considered the gold standard for detecting DR-TB, this method is costly and time-consuming and requires access to high-quality laboratories with very high standards of infection control. Alternatively, DR-TB can be detected genotypically by identifying specific mutations within the \( M. tb \) genome. This technique has been automated and is implemented in molecular tests such as the GeneXpert® assay or line probe assays (e.g. MTBDRplus), which offer the advantage of being rapid and not requiring advanced training for laboratory staff. The ability of these tests to detect resistance to rifampicin (one of the two main drugs comprising the first-line regimen) has been shown to be comparable to that of solid culture and to provide better results than liquid culture. However,
such assays only provide partial information concerning the drug susceptibility profile, as they can only detect resistance to rifampicin and isoniazid (the latter in the case of line probe assays only). Moreover, a large-scale roll-out of these tools has been jeopardised by the high costs associated with the initial equipment purchase, as well as the unit cost of testing that is approximately five times that of traditional smear microscopy.\textsuperscript{59-61} A consequence of these issues is that the proportion of individuals with DR-TB that are appropriately detected remains very low today,\textsuperscript{1} critically limiting the opportunity to use appropriately targeted drugs and regimens.

Even when DR-TB patients are appropriately diagnosed and started on an adequate regimen, positive outcomes are still far from guaranteed. WHO estimates that the treatment success rate among rifampicin-resistant TB patients started on second-line regimen is around 54\% at the global level and is much lower in some countries, such as China (41\%) and Peru (34\%).\textsuperscript{1} These poor outcomes are explained by the fact that second-line treatment is often lengthy (typically around 24 months) and has a high level of toxicity, making its completion extremely difficult.\textsuperscript{62,63} This has led to further drug resistance amplification and resulted in the emergence of highly resistant \textit{M.\textit{tb}} strains such as extensively drug-resistant (XDR) or totally drug-resistant (TDR) strains.\textsuperscript{64-67}

Global health policy leaders have long recognised the threat that DR represents for TB control. In 1999, WHO set up the DOTS-Plus strategy that consists of applying the DOTS principles in the context of DR-TB and therefore including the use of second-line regimens.\textsuperscript{68} However, the implementation of DOTS-Plus has been threatened by the cost and poor availability of the high-quality drugs required in the treatment of DR-TB strains.\textsuperscript{69} In 2000, WHO collaborated with the pharmaceutical industry to establish the Green Light Committee and help countries to address issues around availability and affordability of high-quality regimens.\textsuperscript{70,71} The field implementation of programs such as the DOTS-Plus strategy further highlighted the critical need for laboratory facilities adapted to the diagnosis of DR-TB. Subsequently, the Global Laboratory Initiative was created by WHO, the Stop TB Partnership and other development agencies with the aim of providing practical guidance and tools for building and sustaining a high-quality TB diagnostic network.\textsuperscript{72}

The risk represented by DR-TB as well as the emergency of finding adequate solutions to this increasing issue are now well recognised.\textsuperscript{73} Nevertheless, little is still known about the optimal approach that should be taken to fight the issue of antimicrobial resistance in TB. In particular, two fundamentally opposed visions exist regarding what drives the increasing burden of DR-TB, as well as the substantially higher DR-TB rates observed among individuals previously treated for TB than among those presenting for the first time.\textsuperscript{1} The first contention argues that the current burden of DR-TB is primarily driven by resistance acquisition during the treatment of drug-susceptible strains, particularly when there is treatment interruption or default.\textsuperscript{74,75} Although this
mechanism does represent the original pathway leading to the emergence of DR-TB, its current contribution to the burden of resistant TB remains unclear. Opposed to this first view is the alternative perspective that transmission of DR-TB is a greater contributor than DR amplification to the current burden of DR-TB. Although drug-resistant strains of TB may have diminished abilities to survive, reproduce, and be transmitted as compared to drug-susceptible pathogens (a phenomenon known as fitness cost), the potential for transmission of resistant \( M.\text{tb} \) strains was highlighted by a series of outbreaks\(^76\)\(^-\)\(^78\) and further demonstrated by modern molecular diagnostic methods.\(^79\)

Understanding the predominant drivers of DR-TB epidemics is of critical importance for policy makers to design effective control solutions. Specifically, containing the epidemic in a context where DR amplification predominates would require a strong emphasis on DS-TB patient management in order to limit the negative treatment outcomes that fuel the continued emergence of secondary DR-TB. In contrast, addressing primary transmission of DR-TB would involve solutions that target individuals with DR-TB, prioritising drug susceptibility screening and rapid initiation of appropriate treatment. The predominant focus of global TB control over the last three decades on optimising treatment outcomes for DS-TB patients through the DOTS strategy has limited the residual resources available for specifically combatting drug-resistant TB. In particular, use of drug susceptibility testing (DST) remains rare in many settings and treatment success rates are still unacceptably low for DR-TB patients due to the lack of investment in the development of new drugs.\(^1\)

The answer to the question about what drives the drug-resistant epidemic is unlikely to be universal, as the DR-TB epidemic’s characteristics across different regions and settings are likely to vary with the local epidemiological and programmatic background. A simple illustration is the coverage of DST among individuals newly identified with TB, which varies significantly by geography, ranging from 5% in the Eastern Mediterranean region to 50% in the European region.\(^1\) One can anticipate that more DR-TB transmission occurs in settings where resistance is detected poorly than in settings where individuals newly presenting with TB are more systematically tested for DR-TB.

Chapters 2 and 3 of this thesis are dedicated to exploring and quantifying the respective contributions of the different causal pathways leading to DR-TB among individuals treated for recurrent TB. This investigation was applied to all WHO regions and national-level estimates were also computed for the 104 countries reporting a TB incidence greater than 50 new cases/100,000/year in 2015. A web-based user-friendly mathematical modelling interface was also created in the context of this study in order to extend its scope of application and to provide an even more contextualised insight into the drivers of drug resistance.
1.3 Latent tuberculosis infection and its control

Latent infection with *M. tb* is now broadly recognised as a major challenge that needs to be addressed specifically in order to meet the current burden reduction and TB elimination targets set by WHO and the End TB Strategy.\(^80\) The prevalence of LTBI is estimated at around one quarter of the global population\(^81\) and this huge and difficult-to-manage reservoir of infection represents a major source of ongoing incident disease. Furthermore, the faculty of the *M. tb* pathogen to reactivate many years after exposure demonstrates that the current pool of LTBI will play a critical role in driving the future disease burden, including that arising several decades into the future.\(^12\) Predictions based on mathematical modelling suggest that even if all *M. tb* transmission was stopped today, incident disease emanating from the current LTBI reservoir alone would preclude reaching the 2035 and 2050 End TB Strategy targets.\(^81\)

Effectively addressing the LTBI issue involves identifying the individuals at highest risk of developing disease in the future. Major progress has been made in recent years in bringing new insights into the risk of progression from LTBI to active TB disease. The increasing practice of systematic recording of all close contacts of individuals with active pulmonary TB in low-endemic settings has provided great opportunities for meticulous exploration of the dynamics of *M. tb* reactivation. In particular, four studies have recently investigated the age-specific risk of progression over time since *M. tb* infection.\(^10\)\(^11\)\(^82\)\(^83\) Together, they highlight the differences observed in the reactivation dynamics between different age-groups and highlight the extreme vulnerability of young populations, especially children aged under five. In addition, these studies all report a much higher risk of disease occurrence soon after infection than in later times and demonstrate higher frequencies of late reactivation episodes in adults than in children. One study combined the data on close contacts with a censorship imputation method to refine the estimates by explicitly accounting for migration, death, and preventive treatment.\(^11\) Its results suggest that the lifelong risk of TB disease after infection with *M. tb* was previously underestimated, finding the proportion progressing within 4-5 years to be around 15%. This finding underscores the need to address the LTBI issue as a priority and suggests that interventions targeted at the infection reservoir might have more potential than previously thought.

Treatment for LTBI is available and has been used since the earliest days of the anti-TB chemotherapy era. In particular, the finding in 1952 that isoniazid could be used to kill *M. tb* generated the hope in the worldwide medical community that we could easily and effectively prevent TB using this drug as prophylaxis.\(^84\) Accordingly, many experiments and trials arose during the following decades that confirmed the capacity of isoniazid preventive therapy (IPT) to reduce the risk of disease in infected individuals.\(^84\)\(^88\) A review of trials using isoniazid for a six- to 12-month period in people without HIV infection demonstrated that IPT is effective in preventing TB in around 60% of individuals.\(^89\) This review also highlighted that the effectiveness
of IPT is limited by low treatment completion rates, mostly due to the long duration of the IPT course and the potential for side-effects including hepatitis. Recently, new regimens have been designed for the treatment of LTBI, in particular introducing rifampin and rifapentine as alternative or additional chemotherapeutic agents to isoniazid. These new approaches have the potential to shorten the course of preventive treatment (PT), shortening its duration to as little as three months when combination with isoniazid is used. The new regimens are associated with higher treatment completion rates and similar rates of side effects than IPT which constitutes a great hope for future TB control. Nevertheless, the rate of PT completion does not only depend upon the intrinsic characteristics of the drugs that are employed to treat LTBI but also and perhaps more importantly on the socio-economic background of the population that is targeted with the preventive intervention. Indeed, the effect of PT will remain limited in settings where drug-related costs remain the responsibility of the patient or when financial compensation is not available for patients who must stop work due to the side-effects of the treatment.

A consequence of these challenges is that PT may not be a recommended control tool in all settings. In this regard, recognising the importance of expanding the response to LTBI but also acknowledging the limitations of the available tools, WHO published guidelines regarding the applicability of PT and the settings in which it is likely to be used efficiently. These recommendations are primarily targeted at high-income countries with low- to moderate TB incidence rates, which highlights the fact that settings where transmission is currently intense are not thought to be favourable settings for PT use. One explanation for this is the fact that resource-limited settings may not be able to provide patients with the follow-up care that is required to ensure high treatment completion rates. However, another well recognised mechanism that is likely to diminish PT effect in high TB burden settings is the high risk of repeated infections to which these populations are exposed. That is, providing currently infected individuals with prophylaxis treatment may be inefficient if patients become re-infected with M.tb after receiving therapy. The potential for reinfection following completion of PT course was recently highlighted in a mass IPT trial conducted among South African gold miners and resulted in absence of population-level effectiveness. However, this finding was observed under extremely high transmission pressure and contrasts with those from previous trials conducted in various high-burden settings and showing significant effectiveness of PT. The heterogeneity observed in the effectiveness of LTBI treatment across the different trials underlines the complex interdependency that exists between the effect of the control tool and the epidemic and socio-demographic profile of the setting in which it is employed. Understanding which settings are favourable to PT implementation is crucial to designing contextualised and effective control policies. Despite the paradigm that using PT in a high TB burden context is not efficient, there has been no previous attempt to characterise the exact relationship between TB incidence and PT.
effectiveness. This thesis includes an investigation that challenges this paradigm and characterises the profile of the relationship between TB burden and PT effectiveness. Namely, a simple model of TB transmission dynamics was constructed to investigate the population-level effect of PT under various epidemiological settings. The regimen based on isoniazid was considered in this analysis as it is currently the most commonly used.95

1.4 The missing pieces of the tuberculosis epidemic picture

Many questions remain unanswered today about some key features of TB’s natural history and control. For example, the level of protection against reinfection conferred by current infection with M.tb is still a source of controversy.101-103 BCG vaccination which is currently used with a coverage nearing 100% in most TB-endemic countries still raises important concerns due to the heterogeneity of its estimated effectiveness and its poorly-understood immunity wane profile.104-107 Whether treatment (for LTBI or active TB) protects from future M.tb infection or instead augments the risk of reinfection is also a question that still needs clarification.101 108

In addition to these knowledge gaps about the intrinsic characteristics of M.tb infection and the control tools, TB epidemiology also suffers from a limited understanding of the extent of the current TB burden. A clear evidence of such gaps is the fact that yearly WHO updates on estimates of the global TB incidence have repeatedly shown that the past TB burden has been underestimated.1-3 In the absence of prevalence surveys, a number of techniques are used by WHO to estimate country burden of tuberculosis, including expert opinion and extrapolation from notification data.109 When prevalence surveys are performed, the gap between estimates and actual prevalence is apparent. A striking example is the post-survey estimate of TB incidence in the Philippines that reaches 554 new cases per 100,000 population per year, nearly double the previous estimate.1 Such epidemic knowledge gaps can be explained by the fact that many individuals with active TB are undetected and that a proportion of the identified diseased individuals are not notified, especially in the private health sector. Furthermore, it may be unsafe to rely on the characteristics of the observed cases to draw a faithful profile of the actual TB burden. In particular, the age-distribution of notified individuals may not reflect that of the actual TB burden, since case detection and notification rates are not equal across all age-groups. For example, children have long been neglected within TB control as they are less infectious than adults and are therefore often considered as a lesser priority. As a consequence, childhood TB is less likely to be notified than adult TB even when detected.110 111 Case identification in children is further reduced by the complicated diagnosis of TB due to the low sensitivity of sputum smear in this population.112 Another example is the challenges of diagnosing TB in the elderly population due to the fact that the most common symptoms associated with TB such as cough or weight loss are already prevalent in this group.113 114 Insights into the profile of active disease burden will presumably arise from the future improvement in case detection that can be expected
from the deployment of better diagnostic tools combined with the ongoing development of the
countries that are currently the most affected with TB. However in the meantime, innovative
approaches are urgently needed to attempt to fill the gaps present in the knowledge of the current
TB burden.

Arguably even more challenging to capture than the profile of active disease burden is the profile
of \textit{M.\textit{tb}} transmission. The asymptomatic characteristic of LTBI makes timing and location of
transmission events almost impossible to identify. Several tools are available to diagnose LTBI,
all of which are imperfect at diagnosing LTBI. The specificity of the broadly deployed tuberculin
skin test (TST) is jeopardised by the fact that false-positive results are frequent in individuals with
history of BCG. This issue becomes even more problematic in high-incidence settings where
levels of vaccination coverage are often very high. Interferon-gamma release assays (IGRAs)
have improved specificity in this context, but both tests also have suboptimal sensitivity.

Moreover, LTBI testing is almost exclusively performed in the contacts of identified diseased
individuals, such that tested individuals only represent a portion of the actual at-risk population.
And because the detected proportion of active TB is not representative of the entire TB burden,
the infected individuals that are identified through contact tracing are in turn unlikely to be
representative of the entire reservoir of infection. The capacity of the \textit{M.\textit{tb}} pathogen to reactivate
many years after infection further complicates the inference of the transmission profile. Indeed,
the time span between the initial transmission event and disease onset is unknown in most cases,
making source tracing difficult. However, a better understanding of the drivers of transmission
would provide valuable opportunities to prevent infection from arising in the first place; and
knowing who is currently infected with \textit{M.\textit{tb}} could help policy-makers to design better
recommendations for the management of LTBI.

Some age-categories are already specifically targeted by control polices such as TB prevention
by chemoprophylaxis for LTBI. The main factor currently considered to define the “high-risk”
population in this context is the risk of developing TB after infection with \textit{M.\textit{tb}}. Most NTPs
therefore opt for using PT among children and most commonly among those under five years old
as they are known to be the most susceptible to progress to active disease. However, other
important factors could be taken into account when defining which targeted subgroup would yield
the greatest benefit from a preventive intervention in terms of population-level impact. For
example, consideration of who has the highest potential of transmission once they have active TB
is likely to play an important role in designing optimal TB prevention strategies. The fact that the
current recommendations for LTBI management exclude adolescents and adults from the “at-
risk” populations (unless they have specific risk factors for TB, such as HIV) is an indication that
the transmission potential may not currently be accounted for when establishing guidelines.
Nevertheless, accounting for this factor is not possible at the moment as the age-specific contributions are poorly understood.

Chapter 6 of this thesis is dedicated to using mathematical modelling to build novel TB epidemic knowledge. An attempt to reconstruct TB epidemics by explicitly simulating social contacts between individuals is presented. This exercise relied on an agent-based model incorporating population demography, local history of TB control and age-specific characteristics of TB infection. I used this model to understand and describe the current profile of \( M.\text{tb} \) transmission and TB disease burden in the world’s five highest burden countries: India, Indonesia, China, The Philippines and Pakistan. The respective contributions of the different age-groups to the burden of transmission and disease were captured in order to identify potential alternatives for the populations targeted with TB prevention. This therefore challenges the current paradigm that TB prevention should be targeted at the individuals that are at the greatest risk of developing disease without accounting for their potential for onward transmission.

1.5 Mathematical modelling of tuberculosis

A mathematical model can replicate the dynamics associated with a disease transmission system. That is, the fact that the risk of infection of susceptible individuals is directly dependent upon the size of the currently infectious population can be explicitly accounted for and simulated with such models. This is of particular importance when estimating the population-level effect of an intervention used to control an infectious disease. For example, treating a currently infectious patient will impact the epidemic beyond its effect on that specific individual, as the treated individual’s contribution to transmission of the pathogen across the population will be curtailed. Therefore, there is a broader benefit for the entire population for each individual treatment in the context of infectious diseases, and if this non-linear effect is not considered, estimates of the impact of a control intervention on transmission will be biased. Figure 2 illustrates the difference between infectious and non-communicable diseases in relation to the effect of treatment on infection prevalence.
Figure 2  Illustration of the treatment effect on disease prevalence: infectious versus non-communicable disease.

On the left part, the number of incident diseased individuals (purple arrows) is positively associated with the prevalence of disease (illustrating an infectious disease). On the right part, the number of incident diseased individuals is independent of the size of the prevalent disease reservoir (illustrating a non-communicable disease).

The population-level effectiveness of an intervention can sometimes be estimated from field investigations and trials which naturally capture the non-linearity of the policy effect. However, the slow dynamics of M.tb infection make these traditional approaches very difficult to implement, which underscores the increasing popularity of mathematical models in TB epidemiology and control over the last five decades. TB models have been employed for a wide variety of applications, which have included intervention simulation and the exploration of the mechanisms underlying observed epidemiological phenomena.102 120-126 Even a long time before the extensive use of computers to assist solving of mathematical problems, modelling was already used in TB epidemiology to analyse hidden mechanisms of TB transmission and control, such as the indirect effect of BCG vaccination.127 TB models were also used to estimate different indicators of TB burden, such as the famous Styblo’s rule which defines a simple mathematical relationship between TB incidence and annual risk of infection.128 In recent years, the high value of TB modelling has been increasingly recognised by funding agencies as they work to ensure efficient use of resources to ensure translation of funding into epidemiological impact.

Most TB modelling studies employ a compartmental dynamic transmission model governed by ordinary differential equations.129 Under this approach, the simulated population is stratified into
several categories (termed compartments) according to their infection state and often additional characteristics such as age-groups or comorbidities. The dynamics of such models are governed by an associated system of mathematical equations which characterise the transition of the individuals between the different compartments. The construction process of this type of system consists of two main steps: designing a model structure and assigning values to the parameters that characterise the different flows. These two processes are each associated with uncertainty and addressing the structural and parametric uncertainty is a constant challenge for infectious disease modellers. In the context of TB modelling, important sources of uncertainty include a lack of data to inform model quantities and poor understanding of several epidemiological features of TB. To overcome these issues, modellers must make assumptions that are consistent with available data and understanding of epidemiology and pathogenesis of TB.

A particular feature of TB natural history that is associated with considerable uncertainty are the progression rates associated with LTBI. In a recent doctoral thesis on TB modelling, substantial structural heterogeneity was identified in the approach used to simulate latent infection in a review of the TB modelling literature. It highlights that various levels of complexity have been used to model LTBI, ranging from models that do not simulate the latent phase to models using two latency compartments to reflect the higher risk of reactivation observed soon after infection. This substantial heterogeneity reflects the high level of structural uncertainty in simulating LTBI progression, a finding later confirmed by another systematic review of latency structures used in TB models. In addition to the structural uncertainty around LTBI simulation, little is still known about the parameter values that should be implemented under each latency structure. For example, when models include two latency compartments to simulate an early infection phase associated with a high progression rate followed by a late latency associated with a low reactivation rate, the transition between the two compartments is characterised by the average duration that individuals are assumed to spend at “high-risk”. The assumed duration varies substantially between modelling studies and a cut-off of five years appears to be the most commonly employed. When tracing the original rationale for using this duration, I identified that it relies entirely on the historical convention to define primary disease versus endogenous reactivation, but has been perpetuated through the modelling literature since without empiric evidence.

Such clear evidence of important structural and parametric uncertainty regarding LTBI modelling raises concerns about the ability of existing methods to replicate the specific profile of M.tb reactivation. In Chapter 4 of this thesis, I aim to determine which of the previously employed structures replicate the dynamics of progression most accurately. To this end, I used the activation dynamics observed from 1,352 infected contacts diagnosed in Victoria (Australia) and Amsterdam (Netherlands) to fit the different model structures and obtain the associated parameter estimates. In addition to providing guidance about which latency structure should be used, the
investigation presented in Chapter 4 assessed the validity of the historical paradigm used to separate the early from the late latency periods.
2 High rates of multidrug-resistant and rifampicin-resistant tuberculosis among re-treatment cases: where do they come from?

This Chapter presents an exploration of the causes leading to DR-TB at re-treatment. Its entire content is presented in a published article. The analysis focussed on the case of multidrug-resistant or rifampicin-resistant (MDR/RR) TB, as this is the classification that is currently used by WHO to collect data and report estimates on DR-TB.

This Chapter, together with Chapter 3, constitutes the part of my thesis that focuses on the challenges associated with drug resistance. I also contributed to a conceptually closely related review that investigated the risk of global epidemic replacement with DR-TB. This study, published in The International Journal of Infectious Diseases, was led by my primary supervisor Professor Emma McBryde and one of my other supervisors Doctor James Trauer also contributed to the work.
2.1 Abstract

Background: Globally 3.9% of new and 21% of re-treatment tuberculosis (TB) cases are multidrug-resistant or rifampicin-resistant (MDR/RR), which is often interpreted as evidence that drug resistance results mainly from poor treatment adherence. This study aims to assess the respective contributions of the different causal pathways leading to MDR/RR-TB at re-treatment.

Methods: We use a simple mathematical model to simulate progression between the different stages of disease and treatment for patients diagnosed with TB. The model is parameterised using region and country-specific TB disease burden data reported by the World Health Organization (WHO). The contributions of four separate causal pathways to MDR/RR-TB among re-treatment cases are estimated: I) initial drug-susceptible TB with resistance amplification during treatment; II) initial MDR/RR-TB inappropriately treated as drug-susceptible TB; III) MDR/RR-TB relapse despite appropriate treatment; and IV) re-infection with MDR/RR-TB.

Results: At the global level, Pathways I, II, III and IV contribute 38% (28–49, 95% Simulation Interval), 44% (36–52, 95% SI), 6% (5–7, 95% SI) and 12% (7–19, 95% SI) respectively to the burden of MDR/RR-TB among re–treatment cases. Pathway II is dominant in the Western Pacific (74%; 67–80 95% SI), Eastern Mediterranean (68%; 60–74 95% SI) and European (53%; 48–59 95% SI) regions, while Pathway I makes the greatest contribution in the American (53%; 40–66 95% SI), African (43%; 28–61 95% SI) and South-East Asian (50%; 40–59 95% SI) regions.

Conclusions: Globally, failure to diagnose MDR/RR-TB at first presentation is the leading cause of the high proportion of MDR/RR-TB among re-treatment cases. These findings highlight the need for contextualised solutions to limit the impact and spread of MDR/RR-TB.

2.2 Background

Multidrug-resistant tuberculosis (MDR-TB), defined as resistance to at least rifampicin and isoniazid, is a major threat to global tuberculosis (TB) control. The World Health Organization (WHO) estimates that 3.9% of all new TB cases had MDR-TB or rifampicin-resistant TB (RR-TB) in 2015; in comparison to 21% of TB patients with a history of prior treatment. The dramatic gap between these two estimates can be explained by the potential for a TB patient to acquire drug resistance during treatment, particularly if there is treatment interruption or default. However, in addition to acquired (secondary) drug resistance resulting from poor treatment adherence, multiple other factors may contribute to the higher rate of MDR/RR-TB observed among re-treatment cases.

The potential for primary transmission of drug-resistant TB has long been under-recognised. A large MDR-TB outbreak in New York City, and a cluster of extensively drug-resistant (XDR) TB cases in South Africa provided stark evidence that some drug-resistant strains are highly
transmissible. Epidemic spread of MDR-TB has since been confirmed in multiple settings, and molecular methods have demonstrated the importance of re-infection to TB recurrence, especially in endemic areas. Among clinical MDR-TB strains, the fitness cost associated with acquired drug resistance can be overcome by various compensatory mechanisms, and the opportunity for compensatory evolution is enhanced by selective pressure from poorly targeted treatment.

Although the End TB strategy calls for universal access to drug susceptibility testing (DST), new TB cases remain infrequently tested for drug resistance globally. Therefore, newly presenting MDR/RR-TB patients will often receive the same regimen as drug-susceptible TB (DS-TB) cases. However, although some clinical response is possible, cure rates resulting from standard first-line treatment are low even with adequate treatment adherence and these patients mostly re-present as failure or relapse cases. Given the high rate of drug resistance among re-treatment cases, they are usually prioritised for phenotypic DST or genotypic testing with Xpert MTB/RIF®, which introduces a strong case detection bias. Therefore, re-treatment cases with MDR/RR-TB represent a mixed bag, including secondary acquired and primary transmitted MDR/RR-TB. The contribution of these subgroups to the total burden of MDR/RR-TB among re-treatment cases has been poorly quantified and may be highly setting-dependent. A recent modelling study suggested that the emergence of MDR-TB is mostly driven by transmission of such strains, but the contribution of different causal pathways to MDR/RR-TB at re-treatment and a detailed geographic breakdown of their contribution have never been conducted. Better quantification of the contributing pathways (causes) would therefore provide insight into the evolution of the global MDR/RR-TB epidemic and guide region-specific programmatic approaches to its control.

We present a simple probability tree model, using regional disease estimates, to quantify the proportions of MDR/RR-TB at re-treatment attributed to four principle causal pathways: I) initial drug-susceptible TB with resistance amplification during treatment; II) initial MDR/RR-TB inappropriately treated as drug-susceptible TB; III) MDR/RR-TB relapse despite appropriate treatment; and IV) re-infection with MDR/RR-TB.

2.3 Methods
2.3.1 Study design
We developed a model to quantify the contribution of different causal pathways towards the high burden of MDR/RR-TB observed among re-treatment cases in 2015. Patients were not involved in this study as only data from the WHO and from published literature were used. Model parameters include key characteristics of the different WHO regions, TB burden estimates and reported data from National TB control programmes for 2013. All seven WHO regions were considered: Africa (AFR), the Americas (AMR), Europe (EUR), South East Asia (SEAR), the Eastern Mediterranean (EMR) and Western Pacific (WPR) regions, as well as combined Global
estimates (GLOBAL). Since the model is intended for moderate to high burden countries only, where TB transmission remains poorly controlled, a country-specific analysis was performed on the 104 countries with an estimated TB-incidence $\geq 50$ new cases/100,000/year in 2013.

2.3.2 Model principle

A simple probability tree model was used to simulate progression between the different stages of infection, disease and treatment for patients diagnosed with TB (Figure 3). The use of two distinct pathways based on initial susceptibility of primary TB infection allowed consideration of parameters that are specific to DS-TB and MDR/RR-TB. For simplicity, individuals presenting with mono-resistant or poly-resistant TB without rifampicin resistance were considered to be DS-TB, while resistance beyond MDR/RR-TB was considered to be MDR/RR-TB. The model considered that new MDR/RR-TB cases were treated appropriately only if they were diagnosed as MDR/RR-TB cases and started on a second-line regimen. Accordingly, the probability that a new MDR/RR-TB case is treated appropriately is obtained by multiplying the DST coverage ($b$) by the proportion of notified MDR/RR-TB cases that start on second line regimen ($h$). Any treatment regimen could result in cure, failure (unsuccessful treatment) or death. Individuals lost to follow-up are assumed to experience failure in the baseline analysis but alternate scenarios were considered in a sensitivity analysis. Cured individuals are assumed to have cleared infection and could only be affected by a new episode of TB in case of reinfection.

Only DS-TB patients could develop drug resistance amplification to become an MDR/RR-TB case. Since the treatment success rate for new DS-TB cases ($c$) is not reported by the WHO, we used the reported treatment success rate in all new TB cases as an estimate for $c$. This is consistent with the observations that that although undiagnosed MDR/RR-TB cases (which represent a small proportion of the new cases) are less likely to achieve a favourable treatment outcome, this is counterbalanced by the observation that many patients classified as TB treatment success were not bacteriologically confirmed, which may overestimate treatment success.
Parameters correspond to the probability of a patient transitioning to the state at the end of the corresponding arrow if initially in the state at the start of this arrow. The coloured boxes correspond to the outputs that we observe for quantifying the respective contributions of the different pathways to MDR/RR-TB at re-treatment. **‘new TB case’** stands for a patient presenting primary TB disease and who undergoes therapy against TB. Parameter $a$ is the rate of MDR/RR-TB among new TB-cases. Parameter $b$ is the DST coverage in new TB-cases while parameter $h$ stands for the proportion of notified MDR/RR-TB cases that start on second-line regimen. Parameters $c$ and $d$ are the treatment success rates for new DS-TB cases and new MDR/RR-TB cases respectively. Parameter $e$ represents the treatment success rate for MDR/RR-TB treated with first-line regimen. Parameter $f$ is the risk of drug-resistance amplification for a DS-TB patient failing therapy. Parameter $g$ is the proportion of recovered individual who get re-infected with TB. Parameters $m$ and $k$ are the death rate during treatment for DS-TB and MDR/RR-TB patients respectively.

Re-infection was considered possible once patients had completed treatment, with the proportion estimated from the local TB incidence using the regression equation proposed by Wang and colleagues. That is, parameter $g$ presented in Figure 3 was indirectly estimated from the local TB-incidence and the other model parameters (see 2.7.1). We assumed that the proportion of MDR/RR-TB among re-infection cases was the same as that for new TB cases. Most model parameters (TB-incidence, $a$, $b$, $c$, $d$, $h$, $m$ and $k$) were estimated from the Global TB Report 2016 reporting of local-level data and estimates for the year 2015, while the remaining two parameters ($e$ and $f$) were estimated from the literature. Table 1 presents the definitions of the different parameters along with the values used for each of the WHO regions.
Table 1  Parameter definitions and values associated with the different WHO regions

95% Confidence Intervals as reported in the WHO TB report 2016. iiConfidence Intervals not available. iiiEstimated from literature.

2.3.3  Stochastic method for generating parameter values

For the analysis by WHO region, some parameter values were associated with an uncertainty interval (Table 1). In an earlier version of this work, we also estimated uncertainty for the other parameters by using the cohort sizes reported by WHO. However, given that the cohort sizes were extremely large, the associated uncertainty intervals were very narrow, making the analysis with point estimates equivalent to that including uncertainty ranges. Therefore, we used point estimates for these parameters in the main analysis and considered broader uncertainty ranges in a supplementary analysis (see Section 2.7.2).

We used a stochastic Monte-Carlo method to independently generate a large number of parameter sets (1,000,000). For each run and for each parameter associated with an uncertainty interval, values were independently drawn using beta distributions with shape parameters $\alpha = 2$ and $\beta = 2$, scaled and transposed in order to cover the corresponding uncertainty interval. In contrast, country-specific analysis was performed using the point estimates presented in Table 3 (Section 2.7.4).

Similar to the region-specific analysis, parameters (TB-incidence, $a$, $b$, $c$, $d$, $h$ and $m$) were estimated locally in the country-specific analysis and estimates were extracted from the tuberculosis country profiles available from WHO. Where a country-specific estimate was not available and for the risk of death in MDR/RR-TB patients ($k$), we used the value of the WHO region to which the country belongs. If three or more estimates were not accessible for one country or if the country’s incidence rate was <50 per 100,000 per year, the results of the analysis were excluded. This disease burden limitation was applied, since the epidemiology in low burden
settings mostly represents imported disease and not local transmission. Therefore, we do not consider the model to be applicable to such settings.

2.3.4 Observed outputs

For each geographical area, we estimated the contributions of the four different causal pathways to MDR/RR-TB at re-treatment: I) initial drug-susceptible TB with resistance amplification during treatment; II) initial MDR/RR-TB inappropriately treated as drug-susceptible TB; III) MDR/RR-TB relapse despite appropriate treatment and IV) re-infection with MDR/RR-TB. In the context of this study, drug resistance amplification is defined as acquisition of rifampicin resistance during primary treatment. Each of these contributions was calculated by dividing the proportion of TB cases that arrive in each associated category by the total burden of MDR/RR-TB at re-treatment.

For each of the WHO regions, we observed a fifth output to assess the reliability of the model; the absolute proportion of MDR/RR-TB among re-treatment cases. We verified our model outputs against real world WHO report estimates for each of the different regions.

2.3.5 Sensitivity analyses

Our analysis of the results on the seven WHO regions took into account uncertainty in the estimates of the parameters $c$, $e$ and $f$, which were not directly available in the Global TB Report 2016. Thus, we observed how model outputs were impacted when treatment success rates for DS-TB ($c$) varied between 70% and 95%; probability of treatment success for MDR/RR-TB cases treated as DS-TB cases ($e$) varied between 0% and 50%; and risk of drug resistance amplification when failing first-line treatment for DS-TB ($f$) varied between 0% and 26%.

In our baseline analysis, we assumed that all MDR/RR-TB patients have the same risk of death ($k$), regardless the type of therapy received. A sensitivity analysis was performed to test this assumption by considering a modified mortality for MDR/RR-TB patients treated inappropriately. An additional sensitivity analysis was conducted to test the assumption concerning the proportion of MDR/RR-TB among re-infection cases, which was considered to be the same as for new TB cases in the baseline analysis.

Finally, in another sensitivity analysis we considered different scenarios concerning the treatment outcomes for individuals who were lost to follow-up or not evaluated.

2.4 Results

Figure 4 shows the proportions of MDR/RR-TB at re-treatment obtained from the model when applied to the seven WHO regions, compared to corresponding estimates provided by the WHO TB report 2016. We observed closely matching rates of MDR/RR-TB for every region.
Figure 4 Rates of MDR/RR-TB at re-treatment by WHO region
Blue crosses show the estimates presented in the WHO Global Tuberculosis Report 2015 and vertical blue bars represent the associated 95% confidence intervals. Orange dots show the average model outputs while vertical orange bars represent the 95% central ranges obtained from the uncertainty analysis. WHO regions are designated as following: African region (AFR), American region (AMR), Eastern Mediterranean region (EMR), European region (EUR), South East Asian region (SEAR), Western Pacific region (WPR) and Global region (GLOBAL).

Figure 5 quantifies the contributions of the different causal pathways of MDR/RR-TB at re-treatment in each of the seven WHO regions. At the global level, the model suggests that the greatest number of MDR/RR-TB cases identified at re-treatment result from initial MDR/RR-TB that was inappropriately treated as DS-TB (44%, 36–52, 95% simulation interval). This was a leading pathway in every WHO region, with rates ranging from 35% (28-42) in South-East Asia to 74% (67-80) in the Western Pacific region. MDR/RR-TB at re-treatment resulting from drug resistance amplification represented 38% (28-49) of the total burden globally. Drug resistance amplification was estimated to be the leading pathway to MDR/RR-TB at re-treatment in the American, South-East Asian and African regions; accounting for 53% (40-66), 50% (40-59) and 43% (28-61) of the total burden respectively. Elsewhere, the contribution of drug resistance amplification during primary treatment ranged from 17% (11-25) (Western Pacific) to 24% (Eastern Mediterranean).

Model outputs suggested that failure of appropriate second-line regimens against MDR/RR-TB contributes little to the total burden of MDR/RR-TB at re-treatment (6% globally). The highest contribution from this pathway was found in Europe, with 18% (16-20) of the total burden of MDR/RR-TB at re-treatment. The role of re-infection was also low across all WHO regions, with an estimated global contribution of 12% (7-19); regional estimates varied from 3% (2-6) in America to 16% (8-27) in Africa.
Figure 5 Contributions of the different causal pathways leading to MDR/RR-TB at re-treatment in the seven WHO regions

Results are expressed as percentages of the total burden of MDR/RR-TB at re-treatment. For each region, the mean values and the intervals containing 95% of the values obtained from simulation of 1,000,000 sets of parameters are presented by the bars and the lines respectively. WHO regions are designated as following: African region (AFR), American region (AMR), Eastern Mediterranean region (EMR), European region (EUR), South East Asian region (SEAR), Western Pacific region (WPR) and Global region (GLOBAL).

Sensitivity analysis noted no sensitivity to parameter $e$ (treatment success rate in MDR/RR-TB patients treated as DS-TB cases), whereas a lower treatment success rate for DS-TB ($c$) or a higher risk of drug resistance amplification ($f$) led to similar impacts on the results. Specifically, the main contributors to MDR/RR-TB at re-treatment would remain failure to provide appropriate anti-TB treatments and drug resistance amplification during treatment in all settings, although the respective contributions of these two pathways would be modified. The contribution of drug resistance amplification would increase, while the contribution of inappropriate diagnosis and treatment would decrease.

Our analyses including broader uncertainty ranges led to very similar results compared to the baseline analysis (see Section 2.7.2). The additional explorations testing our assumptions regarding both the mortality of MDR/RR-TB cases and the rate of MDR/RR-TB at re-infection demonstrate that our baseline assumptions represented at most a minimal source of bias. Finally, our analysis concerning the treatment outcomes in individuals who were lost to follow-up or not evaluated revealed that the contribution of pathway II (initial MDR/RR-TB inappropriately treated) would become more important in all WHO region if more of the unknown treatment
outcomes were actually success. Detailed results of the different sensitivity analyses are presented in Section 2.7.3.

Figure 6 presents the leading cause of MDR/RR-TB among re-treatment cases in the 105 countries with a TB-incidence ≥50 new cases/100,000/year and sufficient data for analysis. The quantitative results regarding the contribution of each of the different pathways are available in Section 2.7.4. At the country-level, the leading contributor to drug resistance at re-treatment showed marked geographic variation, broadly similar to those observed in the regional analysis, but with interesting local findings. In the African region, while drug resistance amplification during primary treatment was found to be dominant in the northern part of the region, inappropriate treatment of primary MDR/RR-TB was the leading causal pathway to MDR/RR-TB at re-treatment in the countries of the Southern part of Western Africa (from Guinea Bissau to Cameroon). In the rest of the African region, we observed a relatively even division between the two main pathways leading to MDR/RR-TB at re-treatment (inappropriate therapy and drug resistance amplification). Re-infection with an MDR/RR-TB strain was the leading pathway in only one country, Lesotho, contributing 37% of cases. This cause was also common in Swaziland where it accounted for 34% of MDR/RR-TB at re-treatment. Failure of second-line regimens was the leading pathway to MDR/RR-TB at re-treatment in three countries: Lithuania (50%), Georgia (33%) and Peru (31%). In South Africa, 36% of cases were due to drug resistance amplification, while inappropriate treatment of primary MDR/RR-TB and re-infection with MDR/RR-TB contributed 23% and 33% respectively to the total burden of MDR/RR-TB at re-treatment.

**Figure 6** Representation of the leading pathway to MDR/RR-TB at re-treatment around the world

Only countries with TB-incidence ≥50 new cases/100,000/year and for which sufficient data was available (see the methods section for a full description) are represented.
2.5 Discussion

This study is the first to use a probabilistic mathematical model to explore the different causal pathways leading to MDR/RR-TB at re-treatment and to quantify their respective contributions. By using regional and country-specific inputs, the resulting model incorporated local variations in TB control activity and disease burden. Despite these local variations, broad regional trends were observed. Most importantly, and contrary to previous dogma that emphasised the central role of drug resistance acquisition, undetected MDR/RR-TB at initial diagnosis was the most important reason for the high rates of MDR/RR-TB found among re-treatment cases in most regions. Moreover, this finding was obtained under the conservative assumption that all individuals who were lost to follow-up or not evaluated experienced treatment failure, and our sensitivity analysis demonstrates that the contribution of undetected MDR/RR-TB would increase further if some of these unknown outcomes were favourable.

Our findings therefore indicate that drug resistance amplification due to poor first-line treatment adherence is not the predominant pathway to MDR/RR-TB at re-treatment. Instead, the greatest number of MDR/RR-TB cases result from transmission of MDR/RR-TB strains and it is the lack of appropriate MDR/RR-TB identification at initial presentation that underlies the high rates of MDR/RR-TB at re-presentation. These observations emphasize the importance of universal MDR/RR-TB screening followed by rapid initiation of appropriate treatment. They therefore highlight the potential impact that novel rapid diagnostic tests that include rifampicin sensitivity testing such as Xpert MTB/RIF® could have on the MDR-TB epidemic. Our findings concur with the outcomes of recent studies demonstrating that primary transmission contributes more substantially to the MDR/RR-TB burden than drug resistance acquisition or amplification during treatment.150 154 Interestingly, the model also suggests that failure of second-line regimens may make a significant contribution to the burden of MDR/RR-TB at re-treatment, especially in settings such as Eastern Europe where MDR vigilance is high and patients are able to access MDR/RR-TB treatment. Our analysis has crucial implications for TB control as it highlights regional variation regarding the causes of MDR/RR-TB at re-treatment, indicating that targeted programmatic strategies may be more effective than elaborating a single global plan. In all regions and particularly in the Western Pacific and the Eastern Mediterranean, the introduction of universal drug resistance screening of newly diagnosed TB cases seems critical. Universal drug resistance screening would reduce the burden of MDR/RR-TB at re-treatment and limit on-going MDR/RR-TB transmission within the community, as well as directly benefiting patients who would otherwise have been inappropriately managed with first-line treatment during their initial disease episode.

Access to appropriate therapy is crucial as DS-TB cases that are not properly treated may experience drug resistance amplification. In the Americas, South-East Asia and Africa, the
greatest contribution of MDR/RR-TB identified at re-treatment resulted from drug resistance amplification during first-line treatment of DS-TB. Amplification is driven by high treatment failure rates on first-line therapy, which indicates that improved treatment adherence should be a major public health priority in these settings. The DOTS strategy has demonstrated ability to improve treatment outcomes and therefore, meticulous scale-up should reduce the MDR/RR-TB burden in these regions.\textsuperscript{50, 155-157} This requires strong political commitment together with substantial and sustainable financing, especially in low and middle income countries.

Re-infection with MDR/RR-TB was found to play an important role in Lesotho, Swaziland and South Africa, which were the only countries where it contributed more than one third to the total burden of MDR/RR-TB at re-treatment. This may be explained by the exceptional infection pressure that exists in such settings with a TB-incidence ranging between 565-834 cases/100,000 people in 2015.\textsuperscript{2} Accordingly, in settings with very high infection pressure, as occur in particular disease “hot-spots”, a more comprehensive response is required to limit TB transmission and case numbers of both DS-TB and MDR/RR-TB. In these three countries of Southern Africa, such an approach would include better control of the severe HIV epidemic, enhanced active case finding strategies, and creative interventions to reduce TB transmission within communities.\textsuperscript{158} In South Africa, transmission of MDR/RR-TB caused around 64\% of MDR/RR-TB cases diagnosed at re-treatment, which is supported by molecular epidemiology studies indicating substantial clonal spread of multiple MDR-TB strains.\textsuperscript{78} In addition to a strong emphasis on improved treatment adherence, consideration should be given to additional efforts that may reduce TB transmission within disease “hot spots”.\textsuperscript{159, 160}

Despite the relative simplicity of our model, uncertainty analysis demonstrated robust conclusions across plausible parameter ranges. We are also reassured by the comparison between model outputs and independently calculated WHO estimates of the total rate of MDR/RR-TB at re-treatment, which demonstrates very close approximation at both the global and region-specific level. Moreover, the model was most sensitive to variation in parameters for which programmatic (treatment success rate in new DS-TB cases, $c$) or evidence-based (risk of drug resistance amplification during treatment, $f$) data were available and of reasonable quality, whereas it was insensitive to variation in the most uncertain parameter (treatment success rate for MDR/RR -TB treated as DS-TB, $e$). In particular, the sensitivity analyses demonstrated that a lower treatment success rate for DS-TB and a higher risk of drug resistance amplification would both contribute to a higher contribution of drug resistance amplification to the burden of MDR/RR-TB at re-treatment.

Model limitations include the fact that only two phenotypes of TB were considered, DS and MDR/RR-TB. Other profiles such as mono- or poly-resistant, or additional resistance beyond
MDR-TB were reclassified into these two categories, since the available WHO data do not provide additional sub-classification. Further investigations could be conducted in settings where more detailed drug resistance profile data are available. However, our sensitivity analyses indicate that our general conclusions are maintained in settings with high prevalence of mono- or poly-resistant TB. In such settings, treatment success rates for these strains are expected to be lower, while the risk of drug resistance amplification leading to MDR/RR-TB would increase. Our sensitivity analyses indicate that in these settings, the contribution of drug resistance amplification during primary treatment would increase, while the contribution of inappropriate diagnosis and treatment would diminish. Another limitation is linked to the uncertainty around some parameter estimates, in particular those that were not directly available from the WHO. As discussed above, although our results were sensitive to some model parameters, we do not believe this would jeopardise our general findings. Our model does not take into account nosocomial transmission of MDR/RR-TB. While we acknowledge this as a possible cause of MDR/RR-TB presentation at re-treatment, insufficient data were available to inform its isolated contribution at the local level. Nevertheless, we can anticipate that our model may underestimate the contribution of reinfection in settings where nosocomial transmission of MDR/RR-TB is significant. Future works could investigate this issue more specifically and distinguish the contribution of nosocomial transmission from that of general reinfection with MDR/RR-TB strains.

The resolution of our analysis was restricted to the national level and we were unable to consider sub-national heterogeneity. Moreover, our regional-level estimates were based on common analyses of aggregate data due to missing country-level data and as countries were excluded from the analysis if TB incidence was $<50$ cases/100,000/year. This may not lead to the same estimates as aggregating the results of separate analyses of the different countries as the model that we use is non-linear. National TB programmes need to consider particular settings within the country, since transmission dynamics may be altered within “hot-spot” areas, while cultural issues and specific service delivery challenges also require consideration. In future, our model could be adapted to guide local policies, for example through an online tool usable by policy makers who could input parameters from local programmatic data. Such a tool could be modified in real-time as new data become available to improve and update parameter estimates. Indeed, it is important to note that our estimates correspond to the situation in 2015 and that the fractions attributable to each pathway are likely to vary over time.

2.6 Conclusions

Our findings highlight the need for contextualised solutions to limit the impact and spread of MDR/RR-TB. Although more effective MDR/RR-TB treatment is a universal need and certain common factors should be addressed, a better understanding of the local causal pathways could assist better targeted public health responses. Importantly, our findings suggest that simply
“turning off the tap” through improved programmatic management of drug-susceptible TB will be insufficient to contain the spread of drug-resistant TB.

2.7 Supplemental material

2.7.1 Method used for estimating the risk of re-infection

The proportion of recurrent cases that are due to re-infection is calculated from the regression equation proposed in Wang et al.96 taking local incidence as predictive variable:

\[ Rp = -29.7 + 36.8 \times \log(Inc) \]

\( Rp \): Re-infection proportion  \( Inc \): Local TB-incidence

In our model, the proportion \( Rp \) is expressed as:

\[
\left( \frac{[1-a].c+a.(1-b).e+a.b.d]}{[1-a].c+a.(1-b).e+a.b.d]} \right) \times g + \left( 1-a \right) \times (1-c-m) + a.(1-b) \times (1-e-k) + a.b.(1-d-k) 
\]

Then an estimate for the parameter \( g \) is given by:

\[
g = \frac{(1-a).(1-c-m)+a.(1-b).(1-e-k)+a.b.(1-d-k)}{(1-a).c+a.(1-b).e+a.b.d} \times \frac{Rp}{1-Rp}
\]

In the analysis involving the WHO regions, uncertainty is included at two different levels:

- The value of incidence is drawn from a beta distribution \( (\alpha = \beta = 2) \) on the 95% confidence intervals presented in the WHO TB report 2016.2

- The regression multiplier appearing in Wang’s equation is generated by a beta distribution \( (\alpha = \beta = 2) \) on the interval \([29.4, 44.2]\) corresponding to the baseline value 36.8 ±20%.

2.7.2 Use of increased uncertainty around the parameter values

In this analysis, we add uncertainty to the parameters that were only considered as point estimates in the baseline analysis \( (b, c, d, h, m, \text{and } k) \). To this end, the parameter values are generated from beta distributions that are defined as follows.

When \( x \) designates the point estimate for the parameter value and \( N \) an integer, we use the shape parameters \( \alpha = N \times x \) and \( \beta = N \times (1 - x) \). This approach is equivalent to what could be used to estimate the distribution of a success probability where the observed value is \( x \) during an experiment that includes \( N \) repetitions.

Table 2 presents the 95% confidence intervals obtained for the parameter values when using this approach with \( N = 1,000, N = 500 \) and \( N = 200 \). Such values are much lower than the cohort sizes reported by the WHO for the different parameters in the different regions, suggesting that this analysis may overestimate the uncertainty associated with the data.
<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>b (%)</th>
<th>c (%)</th>
<th>d (%)</th>
<th>h (%)</th>
<th>m (%)</th>
<th>k (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFR</td>
<td>1,000</td>
<td>21</td>
<td>81</td>
<td>54</td>
<td>68.64</td>
<td>5.76</td>
<td>20.58</td>
</tr>
<tr>
<td></td>
<td>500</td>
<td>(18.54-23.59)</td>
<td>(78.53-83.36)</td>
<td>(50.9-57.07)</td>
<td>(65.74-71.48)</td>
<td>(4.41-7.28)</td>
<td>(18.15-23.16)</td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>(17.53-24.71)</td>
<td>(77.43-84.3)</td>
<td>(49.62-58.34)</td>
<td>(64.53-72.62)</td>
<td>(3.9-7.97)</td>
<td>(17.14-24.24)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(15.63-26.87)</td>
<td>(75.29-86.11)</td>
<td>(47.04-60.78)</td>
<td>(62.04-74.9)</td>
<td>(2.99-9.39)</td>
<td>(15.27-26.51)</td>
</tr>
<tr>
<td>AMR</td>
<td>1,000</td>
<td>29</td>
<td>76</td>
<td>55</td>
<td>75.16</td>
<td>6.95</td>
<td>8.22</td>
</tr>
<tr>
<td></td>
<td>500</td>
<td>(26.22-31.84)</td>
<td>(73.3-78.59)</td>
<td>(51.94-58.09)</td>
<td>(72.43-77.8)</td>
<td>(5.46-8.59)</td>
<td>(6.61-10)</td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>(25.09-33.07)</td>
<td>(72.15-79.64)</td>
<td>(50.64-59.34)</td>
<td>(71.3-78.66)</td>
<td>(4.9-9.32)</td>
<td>(5.98-10.78)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(22.94-35.5)</td>
<td>(69.84-81.66)</td>
<td>(48.09-61.85)</td>
<td>(68.94-80.85)</td>
<td>(3.86-10.82)</td>
<td>(4.84-12.39)</td>
</tr>
<tr>
<td>EMR</td>
<td>1,000</td>
<td>2</td>
<td>91</td>
<td>68</td>
<td>82.5</td>
<td>1.84</td>
<td>16.03</td>
</tr>
<tr>
<td></td>
<td>500</td>
<td>(1.23-2.96)</td>
<td>(89.14-92.7)</td>
<td>(65.06-70.85)</td>
<td>(80.08-84.8)</td>
<td>(1.1-2.76)</td>
<td>(13.83-18.37)</td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>(0.96-3.39)</td>
<td>(88.38-93.36)</td>
<td>(63.84-72.01)</td>
<td>(79.03-85.71)</td>
<td>(0.85-3.18)</td>
<td>(12.95-19.37)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.55-4.34)</td>
<td>(86.65-94.56)</td>
<td>(61.39-74.26)</td>
<td>(76.97-87.44)</td>
<td>(0.47-4.11)</td>
<td>(11.32-21.42)</td>
</tr>
<tr>
<td>EUR</td>
<td>1,000</td>
<td>44</td>
<td>76</td>
<td>52</td>
<td>100</td>
<td>7.85</td>
<td>15.61</td>
</tr>
<tr>
<td></td>
<td>500</td>
<td>(40.94-47.07)</td>
<td>(73.3-78.6)</td>
<td>(48.91-55.07)</td>
<td>(80.08-84.8)</td>
<td>(1.1-2.76)</td>
<td>(13.83-17.92)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(37.24-50.9)</td>
<td>(69.86-81.62)</td>
<td>(45.08-58.9)</td>
<td>(76.97-87.44)</td>
<td>(0.47-4.11)</td>
<td>(11.32-21.42)</td>
</tr>
<tr>
<td>SEAR</td>
<td>1,000</td>
<td>5.1</td>
<td>79</td>
<td>49</td>
<td>90.81</td>
<td>3.52</td>
<td>20.59</td>
</tr>
<tr>
<td></td>
<td>500</td>
<td>(3.82-6.55)</td>
<td>(76.43-81.46)</td>
<td>(45.9-52.08)</td>
<td>(88.95-92.51)</td>
<td>(2.47-4.74)</td>
<td>(18.14-23.17)</td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>(3.35-7.18)</td>
<td>(75.33-82.45)</td>
<td>(44.64-53.39)</td>
<td>(88.13-93.18)</td>
<td>(2.09-5.29)</td>
<td>(17.16-24.23)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(2.51-8.55)</td>
<td>(73.1-84.38)</td>
<td>(42.11-55.89)</td>
<td>(86.4-94.4)</td>
<td>(1.44-4.64)</td>
<td>(15.3-26.45)</td>
</tr>
<tr>
<td>WPR</td>
<td>1,000</td>
<td>8.8</td>
<td>92</td>
<td>57</td>
<td>76.14</td>
<td>2.05</td>
<td>9.51</td>
</tr>
<tr>
<td></td>
<td>500</td>
<td>(7.13-10.64)</td>
<td>(90.24-93.6)</td>
<td>(53.91-60.06)</td>
<td>(73.45-78.74)</td>
<td>(1.27-3.01)</td>
<td>(7.78-11.39)</td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>(6.47-11.42)</td>
<td>(89.47-94.2)</td>
<td>(52.65-61.3)</td>
<td>(72.31-79.8)</td>
<td>(1.37)</td>
<td>(7.09-12.22)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(5.29-13.1)</td>
<td>(87.86-95.32)</td>
<td>(50.14-63.76)</td>
<td>(70.06-81.78)</td>
<td>(0.57-4.42)</td>
<td>(5.86-13.97)</td>
</tr>
<tr>
<td>GLOB AL</td>
<td>1,000</td>
<td>24</td>
<td>83</td>
<td>52</td>
<td>94.6</td>
<td>3.84</td>
<td>16.84</td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>(20.35-27.84)</td>
<td>(79.58-86.16)</td>
<td>(47.62-56.37)</td>
<td>(92.47-96.41)</td>
<td>(2.33-5.7)</td>
<td>(13.7-20.26)</td>
</tr>
</tbody>
</table>

Table 2: 95% confidence intervals used around the parameter estimates when using increased uncertainty

Figure 7 represents a comparison of the results obtained with and without inclusion of increased uncertainty. The central estimates obtained from the different approaches are the same. The black bars represent the uncertainty obtained in the baseline analysis while the colored bars represent the uncertainty obtained when using the approach described above for different values of N (1000, 500 and 200). We note that the central estimates obtained from the different methods are the same and the amplitude of the uncertainty ranges around the model outputs are not significantly impacted when using increased uncertainty for the model parameters.
Figure 7  Comparison of the results obtained with and without inclusion of increased uncertainty

The bars represent the uncertainty obtained in model outputs when using different approaches to include uncertainty in model parameters.

2.7.3  Results of the sensitivity analyses

Figure 8 presents the results of the sensitivity analysis performed for the parameters $c$, $e$, and $f$. In every region, considering higher treatment success rates for DS-TB ($c$) results in fewer cases of drug resistance amplification (DRA), which is intuitive given that patients only amplify resistance if treatment fails under our model. Consequently, a reduction in DRA is compensated for by an increase in the contributions of the two other causes involving patients that were initially MDR/RR-TB cases and vice versa. In Europe – where DST coverage is high – we observe that this increase is equally distributed between the two categories “initial MDR/RR-TB treated with a failing first line regimen” and “initial MDR/RR-TB treated with a failing second line regimen”. By contrast, in the other regions – where DST coverage is either low or very low – only the contribution of initial MDR/RR-TB cases treated with a failing first line regimen increases, as fewer patients received second line regimen.
As parameter $f$ increases (the risk of DRA among DS-TB patients in whom treatment fails), the contribution of DRA to the burden of MDR/RR-TB at re-treatment unsurprisingly increases in every region. As described for parameter $c$, changes in parameter $f$ lead to compensatory changes in the two other contributing factors. As $f$ increases, there is a combined decrease distributed between the two categories “initial MDR-TB treated with a failing first line regimen” and “initial MDR/RR-TB treated with a failing second line regimen”. This distribution is evenly shared for Europe, while the decrease only affects the contribution of initial MDR/RR-TB cases treated with a failing first line regimen for the other regions, for the same reasons outlined above for parameter $c$.

Figure 8  Results of the sensitivity analysis on the parameters $c$, $e$ and $f$

Variability in the contributions of the different pathways to MDR/RR-TB at re-treatment when considering different values for the treatment success rate against DS-TB ($c$); for the treatment success rate against MDR/RR-TB treated with 1st line regimen ($e$); and for the risk of drug resistance amplification among DS-TB patients in whom treatment failed ($f$). Results are presented as percentages of the total burden of MDR/RR-TB at re-treatment. WHO regions are designated as following: African region (AFR), American region (AMR), Eastern Mediterranean region (EMR), European region (EUR), South East Asian region (SEAR), Western Pacific region (WPR) and Global region (GLOBAL).
Two additional sensitivity analyses described below were performed in order to test alternate assumptions in our model.

First, in the baseline analysis, we assumed that all MDR/RR-TB patients had the same risk of death (parameter $k$), regardless the type of therapy received. However, one may consider that MDR/RR-TB patients receiving first-line regimens are at higher risk of death than appropriately treated patients given that their infection is more likely to persist. On the other hand, patients who are treated with second-line regimens are exposed to a higher level of toxicity induced by the drugs, which may therefore increase their risk of death. The fact that these two phenomena represent compensative effects for the risk of death demonstrates that it was reasonable to assume a same mortality for all MDR/RR-TB patients. Nevertheless, in this sensitivity analysis, we explore the effect of considering alternate assumptions regarding the mortality in MDR/RR-TB patients. Namely, we varied the relative risk of death for MDR/RR-TB patients receiving first-line regimen between 0.5 and 1.5. Figure 9 represents the corresponding variations in the model outputs.
Figure 9  Results of the sensitivity analysis for the relative mortality in MDR/RR-TB patient on first-line regimen

The vertical dashed line represents the baseline scenario with a same risk of death in all MDR/RR-TB patients.

We note that considering alternate scenarios concerning the risk of death in inappropriately treated MDR/RR-TB patients does not lead to substantial changes in the findings and therefore conclude that our initial assumption does not constitute a source of bias for our conclusions.

The second assumption that we tested as a sensitivity analysis concerns the risk of contracting MDR/RR-TB during a re-infection episode. In the initial analysis, we assumed that this risk was equal to the rate of MDR/RR-TB in new cases (parameter $a$) as we are not aware of any reason why this assumption should be invalid. Here we explore alternate scenarios where the relative risk of MDR/RR-TB in re-infection cases compared to the one in new cases varies between 0.5 and 1.5. Figure 10 represents the results of this exploration.
Figure 10  Results of the sensitivity analysis for the relative risk of MDR/RR-TB in re-infection patients

The vertical dashed line represents the baseline scenario where the risk of MDR/RR-TB in new and re-infection cases was the same.

We observe that the contribution of re-infection to the burden of MDR-TB at re-treatment only increases slightly when we consider an augmented risk of MDR-TB for re-infection cases compared to new cases. Indeed, the greatest change induced by the consideration of an alternate assumption would be for the African region but its amplitude would be very limited, even when considering a relative risk of 1.5. In this case, the contribution of re-infection would reach 20% while it was estimated at 16% in the initial analysis. At the Global level, the contribution of re-infection would only increase by 5% compared to the baseline estimate if we assumed a relative risk of MDR-TB at re-infection of 1.5 (18% vs. 12%).

We can conclude that our findings would not be jeopardized by alternate assumptions concerning the risk of MDR-TB at re-infection.

In another sensitivity analysis, we investigated alternate assumptions concerning the treatment outcome of individuals classified as lost to follow-up or not evaluated. While these individuals were assumed to experience treatment failure in our baseline analysis, we now consider different assumptions that allow for treatment success for a proportion of them (up to 50%). Figure 11 represents the results of this analysis.

This analysis highlights the fact that misdiagnosis and inappropriate treatment of primary MDR/RR-TB cases would become even more important contributor to the burden of MDR/RR-TB at re-treatment if we considered positive treatment outcomes for individuals who are lost to
follow-up or not evaluated. In the African region for example, inappropriate treatment of primary MDR/RR-TB would become the leading cause of MDR/RR-TB at re-treatment if more than 10% of unknown treatment outcomes were positive.

Figure 11 Results of the sensitivity analysis on the treatment outcomes experienced by individuals lost to follow-up or not evaluated

2.7.4 Parameter values and results of analyses by region and by country

Table 3 presents the parameter values used in our analyses as well as the results regarding the contributions of the different mechanisms leading to MDR-TB at re-treatment. Local estimates come from the Global TB report 2016 of the WHO. The background colors that are used in the columns of Table 3 correspond to the color code that we use in Figure 5 and Figure 6 for designating the different causes of MDR-TB at re-treatment.
<table>
<thead>
<tr>
<th>Region</th>
<th>Parameters</th>
<th>% of MDR/RR-TB at re-treatment due to</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EUR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEAR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WPR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GLOBAL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Country</th>
<th>Incidence</th>
<th>d (%, CI)</th>
<th>k (%, CI)</th>
<th>&amp; (%, CI)</th>
<th>u (%, CI)</th>
<th>m (%, CI)</th>
<th>k1 (%, CI)</th>
<th>k2 (%, CI)</th>
<th>Complex d (%, CI)</th>
<th>Amplification during treatment</th>
<th>Inappropriate regimen</th>
<th>Inappropriate regimen failing</th>
<th>Resistance with MDR/RR-TB strain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afghanistan</td>
<td>189</td>
<td>3.90</td>
<td>0.00</td>
<td>87.00</td>
<td>63.00</td>
<td>100.00</td>
<td>1.28</td>
<td>-</td>
<td>32</td>
<td>35</td>
<td>0</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Algeria</td>
<td>75</td>
<td>1.40</td>
<td>2.00</td>
<td>88.00</td>
<td>-</td>
<td>100.00</td>
<td>1.70</td>
<td>-</td>
<td>59</td>
<td>37</td>
<td>0</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Angola</td>
<td>370</td>
<td>2.80</td>
<td>-</td>
<td>34.00</td>
<td>74.00</td>
<td>100.00</td>
<td>2.65</td>
<td>-</td>
<td>79</td>
<td>13</td>
<td>0</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Azerbajan</td>
<td>69</td>
<td>13.00</td>
<td>32.00</td>
<td>83.00</td>
<td>59.00</td>
<td>70.62</td>
<td>3.39</td>
<td>-</td>
<td>15</td>
<td>65</td>
<td>0</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Bangladesh</td>
<td>225</td>
<td>1.60</td>
<td>5.00</td>
<td>93.00</td>
<td>75.00</td>
<td>92.24</td>
<td>3.79</td>
<td>-</td>
<td>29</td>
<td>65</td>
<td>0</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Belarus</td>
<td>55</td>
<td>37.00</td>
<td>69.00</td>
<td>88.00</td>
<td>54.00</td>
<td>100.00</td>
<td>5.28</td>
<td>-</td>
<td>3</td>
<td>41</td>
<td>17</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Benin</td>
<td>60</td>
<td>1.20</td>
<td>8.00</td>
<td>89.00</td>
<td>93.00</td>
<td>82.61</td>
<td>5.84</td>
<td>-</td>
<td>44</td>
<td>54</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Bhutan</td>
<td>155</td>
<td>2.60</td>
<td>53.00</td>
<td>90.00</td>
<td>92.00</td>
<td>100.00</td>
<td>4.13</td>
<td>-</td>
<td>42</td>
<td>49</td>
<td>0</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Bolivia</td>
<td>117</td>
<td>3.00</td>
<td>6.00</td>
<td>83.00</td>
<td>61.00</td>
<td>51.90</td>
<td>5.32</td>
<td>-</td>
<td>38</td>
<td>53</td>
<td>3</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Botswana</td>
<td>356</td>
<td>3.60</td>
<td>-1</td>
<td>77.00</td>
<td>71.00</td>
<td>100.00</td>
<td>8.75</td>
<td>-</td>
<td>37</td>
<td>44</td>
<td>0</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Brunei</td>
<td>58</td>
<td>0.00</td>
<td>79.00</td>
<td>65.00</td>
<td>65.00</td>
<td>0.00</td>
<td>-</td>
<td>7.07</td>
<td>-</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Darussalam</td>
<td>55</td>
<td>0.00</td>
<td>90.00</td>
<td>65.00</td>
<td>-</td>
<td>0.00</td>
<td>-</td>
<td>7.07</td>
<td>-</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Burkina Faso</td>
<td>52</td>
<td>2.80</td>
<td>2.00</td>
<td>81.00</td>
<td>62.00</td>
<td>66.67</td>
<td>9.53</td>
<td>-</td>
<td>40</td>
<td>55</td>
<td>0</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Burundi</td>
<td>122</td>
<td>3.20</td>
<td>9.00</td>
<td>91.00</td>
<td>89.00</td>
<td>93.18</td>
<td>5.77</td>
<td>-</td>
<td>16</td>
<td>79</td>
<td>0</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Cambodia</td>
<td>380</td>
<td>1.80</td>
<td>-1</td>
<td>93.00</td>
<td>75.00</td>
<td>97.46</td>
<td>1.87</td>
<td>-</td>
<td>31</td>
<td>66</td>
<td>0</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Cameroon</td>
<td>212</td>
<td>3.20</td>
<td>-1</td>
<td>84.00</td>
<td>92.00</td>
<td>100.00</td>
<td>7.39</td>
<td>-</td>
<td>29</td>
<td>61</td>
<td>0</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Central African Republic</td>
<td>391</td>
<td>0.40</td>
<td>-1</td>
<td>70.00</td>
<td>81.00</td>
<td>61.29</td>
<td>5.90</td>
<td>-</td>
<td>88</td>
<td>7</td>
<td>0</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Chad</td>
<td>152</td>
<td>2.80</td>
<td>1.00</td>
<td>68.00</td>
<td>-</td>
<td>100.00</td>
<td>3.38</td>
<td>-</td>
<td>60</td>
<td>28</td>
<td>0</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>China</td>
<td>67</td>
<td>6.60</td>
<td>8.00</td>
<td>94.00</td>
<td>55.00</td>
<td>58.90</td>
<td>1.01</td>
<td>-</td>
<td>11</td>
<td>81</td>
<td>2</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>China Macao</td>
<td>72</td>
<td>2.50</td>
<td>75.00</td>
<td>86.00</td>
<td>88.00</td>
<td>45.45</td>
<td>6.75</td>
<td>-</td>
<td>42</td>
<td>52</td>
<td>1</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Congo</td>
<td>379</td>
<td>3.20</td>
<td>-</td>
<td>69.00</td>
<td>-</td>
<td>31.71</td>
<td>1.56</td>
<td>-</td>
<td>52</td>
<td>25</td>
<td>1</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Cote d'Ivoire</td>
<td>159</td>
<td>3.10</td>
<td>-</td>
<td>79.00</td>
<td>85.00</td>
<td>84.38</td>
<td>10.41</td>
<td>-</td>
<td>40</td>
<td>50</td>
<td>0</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Democratic People's</td>
<td>561</td>
<td>2.20</td>
<td>0.00</td>
<td>91.00</td>
<td>84.00</td>
<td>59.81</td>
<td>3.11</td>
<td>-</td>
<td>30</td>
<td>56</td>
<td>0</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Country</td>
<td>300</td>
<td>200</td>
<td>100</td>
<td>50</td>
<td>10</td>
<td>5</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congo</td>
<td>324</td>
<td>3.20</td>
<td>2.00</td>
<td>89.00</td>
<td>63.00</td>
<td>82.77</td>
<td>4.16</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Djibouti</td>
<td>378</td>
<td>4.30</td>
<td>5.00</td>
<td>81.00</td>
<td>-</td>
<td>83.53</td>
<td>2.18</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dominican Republic</td>
<td>60</td>
<td>3.00</td>
<td>7.00</td>
<td>83.00</td>
<td>73.00</td>
<td>100.00</td>
<td>4.84</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ecuador</td>
<td>52</td>
<td>7.30</td>
<td>20.00</td>
<td>77.00</td>
<td>49.00</td>
<td>21.26</td>
<td>4.95</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Equatorial Guinea</td>
<td>172</td>
<td>2.80</td>
<td>11.00</td>
<td>58.00</td>
<td>-</td>
<td>66.67</td>
<td>3.27</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eritrea</td>
<td>65</td>
<td>2.80</td>
<td>-</td>
<td>91.00</td>
<td>83.00</td>
<td>100.00</td>
<td>4.65</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethiopia</td>
<td>192</td>
<td>2.70</td>
<td>9.00</td>
<td>89.00</td>
<td>68.00</td>
<td>100.00</td>
<td>3.14</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fiji</td>
<td>51</td>
<td>0.00</td>
<td>6.00</td>
<td>87.00</td>
<td>-</td>
<td>-</td>
<td>8.25</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabon</td>
<td>465</td>
<td>3.20</td>
<td>1.00</td>
<td>58.00</td>
<td>-</td>
<td>26.67</td>
<td>1.49</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gambia</td>
<td>174</td>
<td>2.80</td>
<td>0.00</td>
<td>88.00</td>
<td>-</td>
<td>0.00</td>
<td>6.10</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Georgia</td>
<td>99</td>
<td>12.00</td>
<td>65.00</td>
<td>83.00</td>
<td>63.00</td>
<td>100.00</td>
<td>3.25</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ghana</td>
<td>160</td>
<td>2.80</td>
<td>5.00</td>
<td>85.00</td>
<td>69.00</td>
<td>83.33</td>
<td>10.26</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greenland</td>
<td>164</td>
<td>2.30</td>
<td>0.00</td>
<td>68.00</td>
<td>-</td>
<td>-</td>
<td>3.03</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guam</td>
<td>51</td>
<td>0.00</td>
<td>57.00</td>
<td>89.00</td>
<td>-</td>
<td>50.00</td>
<td>3.57</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guinea</td>
<td>177</td>
<td>2.80</td>
<td>1.00</td>
<td>83.00</td>
<td>58.00</td>
<td>27.64</td>
<td>5.40</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guinea-Bissau</td>
<td>373</td>
<td>2.80</td>
<td>10.00</td>
<td>81.00</td>
<td>40.00</td>
<td>88.24</td>
<td>8.42</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guyana</td>
<td>93</td>
<td>3.00</td>
<td>5.00</td>
<td>69.00</td>
<td>-</td>
<td>100.00</td>
<td>9.72</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haiti</td>
<td>194</td>
<td>3.00</td>
<td>7.00</td>
<td>78.00</td>
<td>83.00</td>
<td>88.24</td>
<td>4.73</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>India</td>
<td>217</td>
<td>2.50</td>
<td>6.00</td>
<td>74.00</td>
<td>46.00</td>
<td>93.39</td>
<td>3.52</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indonesia</td>
<td>393</td>
<td>2.80</td>
<td>0.50</td>
<td>84.00</td>
<td>51.00</td>
<td>71.15</td>
<td>2.29</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kazakhstan</td>
<td>89</td>
<td>25.00</td>
<td>65.00</td>
<td>90.00</td>
<td>72.00</td>
<td>100.00</td>
<td>5.16</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kenya</td>
<td>233</td>
<td>1.30</td>
<td>8.00</td>
<td>87.00</td>
<td>82.00</td>
<td>100.00</td>
<td>6.35</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kiribati</td>
<td>551</td>
<td>5.20</td>
<td>0.00</td>
<td>87.00</td>
<td>-</td>
<td>-</td>
<td>6.99</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Republic of Korea</td>
<td>80</td>
<td>3.70</td>
<td>45.00</td>
<td>81.00</td>
<td>59.00</td>
<td>100.00</td>
<td>8.60</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kyrgyzstan</td>
<td>144</td>
<td>32.00</td>
<td>33.00</td>
<td>84.00</td>
<td>57.00</td>
<td>100.00</td>
<td>4.27</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lao People’s Democratic Republic</td>
<td>182</td>
<td>5.20</td>
<td>36.00</td>
<td>86.00</td>
<td>71.00</td>
<td>100.00</td>
<td>7.36</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesotho</td>
<td>788</td>
<td>4.80</td>
<td>21.00</td>
<td>70.00</td>
<td>63.00</td>
<td>65.36</td>
<td>12.01</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liberia</td>
<td>308</td>
<td>2.80</td>
<td>-</td>
<td>34.00</td>
<td>-</td>
<td>-</td>
<td>4.12</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lithuania</td>
<td>56</td>
<td>12.00</td>
<td>76.00</td>
<td>81.00</td>
<td>40.00</td>
<td>100.00</td>
<td>10.76</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Madagascar</td>
<td>236</td>
<td>0.49</td>
<td>-</td>
<td>83.00</td>
<td>64.00</td>
<td>17.07</td>
<td>3.92</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malawi</td>
<td>193</td>
<td>0.75</td>
<td>&lt;1</td>
<td>85.00</td>
<td>53.00</td>
<td>69.89</td>
<td>8.69</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malaysia</td>
<td>89</td>
<td>1.50</td>
<td>44.00</td>
<td>78.00</td>
<td>62.00</td>
<td>38.12</td>
<td>9.24</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maldives</td>
<td>53</td>
<td>2.60</td>
<td>24.00</td>
<td>37.00</td>
<td>-</td>
<td>0.00</td>
<td>3.97</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mali</td>
<td>57</td>
<td>2.80</td>
<td>2.00</td>
<td>73.00</td>
<td>42.00</td>
<td>100.00</td>
<td>8.09</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marshall Islands</td>
<td>344</td>
<td>0.00</td>
<td>20.00</td>
<td>86.00</td>
<td>100.00</td>
<td>100.00</td>
<td>7.99</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mauritania</td>
<td>107</td>
<td>2.80</td>
<td>12.00</td>
<td>70.00</td>
<td>43.08</td>
<td>54.17</td>
<td>2.89</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Micronesia</td>
<td>124</td>
<td>5.20</td>
<td>&lt;1</td>
<td>94.00</td>
<td>-</td>
<td>100.00</td>
<td>3.61</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moldova</td>
<td>152</td>
<td>32.00</td>
<td>56.00</td>
<td>79.00</td>
<td>57.00</td>
<td>97.89</td>
<td>11.39</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mongolia</td>
<td>428</td>
<td>2.20</td>
<td>23.00</td>
<td>86.00</td>
<td>58.00</td>
<td>100.00</td>
<td>2.16</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morocco</td>
<td>107</td>
<td>1.00</td>
<td>-</td>
<td>86.00</td>
<td>42.00</td>
<td>100.00</td>
<td>2.08</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mozambique</td>
<td>551</td>
<td>3.70</td>
<td>17.00</td>
<td>89.00</td>
<td>52.00</td>
<td>100.00</td>
<td>6.12</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myanmar</td>
<td>365</td>
<td>5.10</td>
<td>7.00</td>
<td>87.00</td>
<td>83.00</td>
<td>79.02</td>
<td>4.71</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

57
| Country                      | Parameter Values and Results | Region                        | Result  
|------------------------------|------------------------------|-------------------------------|--------
| Namibia                      | 489 5.00 9.00 87.00 74.00 94.83 6.33 - 17 | WHO Regions and Countries     | 18     | 18 | 21 |
| Nauru                        | 113 2.30 0.00 100.00 - - 0.00 - | WHO Regions and Countries     | 0      | 98 | 0   | 2   |
| Nepal                        | 156 2.20 12.00 92.00 71.00 84.04 2.68 - | WHO Regions and Countries     | 34     | 59 | 17 |
| Nicaragua                    | 51 0.94 19.00 85.00 78.00 80.56 5.01 - | WHO Regions and Countries     | 67     | 30 | 2   |
| Niger                        | 95 2.80 9.00 79.00 81.00 75.56 6.68 - | WHO Regions and Countries     | 47     | 45 | 0   | 8   |
| Nigeria                      | 322 4.30 40.00 87.00 77.00 52.86 5.44 - | WHO Regions and Countries     | 26     | 57 | 17 |
| Northern Mariana Islands     | 58 5.30 52.00 62.00 - - 15.38 - | WHO Regions and Countries     | 45     | 36 | 10  | 10  |
| Pakistan                     | 270 4.20 1.00 93.00 69.00 83.46 1.44 - | WHO Regions and Countries     | 18     | 70 | 0   | 12  |
| Palau                        | 76 0.00 57.00 57.00 - - 14.29 - | WHO Regions and Countries     | 100    | 0  | 0   | 0   |
| Panama                       | 50 3.00 21.00 79.00 50.00 100.00 8.36 - | WHO Regions and Countries     | 43     | 46 | 0   | 5   |
| Papua New Guinea             | 432 3.40 - 70.00 - 88.58 3.53 - | WHO Regions and Countries     | 46     | 30 | 1   | 23  |
| Peru                         | 119 5.90 70.00 87.00 55.00 100.00 3.54 - | WHO Regions and Countries     | 27     | 29 | 31  | 12  |
| Philippines                  | 322 2.60 1.00 92.00 49.00 100.00 2.23 - | WHO Regions and Countries     | 26     | 64 | 0   | 10  |
| Republic of Korea            | 80 3.70 45.00 81.00 59.00 100.00 8.60 - | WHO Regions and Countries     | 38     | 41 | 15  | 8   |
| Republic of Moldova          | 152 32.00 56.00 79.00 57.00 97.89 11.39 - | WHO Regions and Countries     | 44     | 45 | 20  | 30  |
| Romania                      | 84 3.00 48.00 85.00 41.00 100.00 7.42 - | WHO Regions and Countries     | 36     | 38 | 20  | 6   |
| Russian Federation           | 80 23.00 38.00 69.00 48.00 100.00 9.54 - | WHO Regions and Countries     | 12     | 50 | 15  | 22  |
| Rwanda                       | 56 1.50 26.00 86.00 81.00 98.94 7.80 - | WHO Regions and Countries     | 52     | 45 | 8   | 3   |
| Sao Tome and Principe        | 97 2.80 1.00 74.00 83.00 - - 12.75 - | WHO Regions and Countries     | 45     | 47 | 0   | 7   |
| Senegal                      | 139 0.90 44.00 87.00 - - 4.38 - | WHO Regions and Countries     | 69     | 23 | 8   | 4   |
| Solomon Islands              | 89 5.20 14.00 91.00 - - 100.00 4.64 - | WHO Regions and Countries     | 13     | 76 | 5   | 6   |
| Somalia                      | 274 8.70 0.00 86.00 77.00 98.67 4.32 - | WHO Regions and Countries     | 14     | 66 | 6   | 20  |
| South Africa                 | 834 3.50 65.00 78.00 48.00 63.87 6.71 - | WHO Regions and Countries     | 36     | 23 | 7   | 33  |
| South Sudan                  | 146 3.20 7.00 71.00 - - 0.00 4.36 - | WHO Regions and Countries     | 53     | 35 | 0   | 12  |
| Sri Lanka                    | 65 0.54 13.00 84.00 50.00 86.67 6.82 - | WHO Regions and Countries     | 78     | 19 | 1   | 2   |
| Sudan                        | 88 2.80 1.00 82.00 64.00 50.66 3.19 - | WHO Regions and Countries     | 47     | 45 | 0   | 7   |
| Swaziland                    | 565 8.00 31.00 78.00 60.00 100.00 10.21 - | WHO Regions and Countries     | 18     | 43 | 5   | 34  |
| Tajikistan                   | 87 14.00 50.00 89.00 60.00 94.22 4.68 - | WHO Regions and Countries     | 9      | 60 | 19  | 14  |
| Tanzania                     | 306 1.30 13.00 90.00 68.00 69.10 5.76 - | WHO Regions and Countries     | 40     | 52 | 1   | 7   |
| Thailand                     | 172 2.20 10.00 80.00 - - 100.00 7.37 - | WHO Regions and Countries     | 51     | 38 | 2   | 9   |
| Togo                         | 52 2.80 0.00 88.00 56.00 0.00 6.46 - | WHO Regions and Countries     | 28     | 68 | 0   | 4   |
| Tuvalu                       | 232 5.20 5.00 47.00 - - 33.33 - | WHO Regions and Countries     | 33     | 47 | 1   | 19  |
| Uganda                       | 202 1.60 8.00 75.00 73.00 100.00 7.52 - | WHO Regions and Countries     | 65     | 26 | 0   | 9   |
| Ukraine                      | 91 25.00 62.00 72.00 39.00 100.00 10.42 - | WHO Regions and Countries     | 90     | 33 | 37  | 1   |
| Uzbekistan                   | 79 24.00 28.00 87.00 53.00 100.00 4.60 - | WHO Regions and Countries     | 55     | 66 | 11  | 18  |
| Vanuatu                      | 63 0.00 0.00 87.00 - - 5.13 - | WHO Regions and Countries     | 100    | 0  | 0   | 0   |
| Viet Nam                     | 137 4.10 8.00 91.00 89.00 81.90 2.51 - | WHO Regions and Countries     | 21     | 69 | 11  | 8   |
| Zambia                       | 391 1.10 1.00 85.00 33.00 50.51 5.43 - | WHO Regions and Countries     | 59     | 32 | 0   | 9   |
| Zimbabwe                     | 242 3.20 - 81.00 59.00 92.52 8.99 - | WHO Regions and Countries     | 37     | 46 | 3   | 13  |

*Table 3  Parameter values and results related to the different WHO regions and countries*
3 A user-friendly mathematical modelling web interface to assist local decision making in the fight against drug-resistant tuberculosis

Chapter 2 provided new insights into the pathways leading to the high rates of DR-TB among individuals retreated for TB. It drew several important conclusions at the global, regional and country levels regarding the mechanisms that drive the current DR-TB epidemic. In particular, the significant amount of heterogeneity observed in the contributions of the different causal pathways in different settings highlighted the need for contextualised solutions. This conclusion along with the fact that the estimates presented in Chapter 2 are only relevant to the current context underscore the need for a tool that could be applied to various levels of geographical granularity and that would remain usable over time.

This Chapter describes a user-friendly interface based on the model presented in Chapter 2. This web-based tool is publicly available at the following location:

\texttt{tb-modelling.com/mdr\_tb\_at\_retreatment/}.

The interface allows users to manipulate the existing model and to input their own parameter values, such that outputs could be generated for any specific setting. Furthermore, model estimates could easily be updated in the future as new data become available.

The entire content of this Chapter was presented in a published article.\textsuperscript{165} A web-analytics algorithm was incorporated into the webpage in order to track the visits and to assess the interest generated by the tool. A detailed record of the pageviews since the public release of the interface is presented in the Appendix of this thesis.
3.1 Abstract
Multidrug-resistant and rifampicin-resistant tuberculosis (MDR/RR-TB) represent an important challenge for global tuberculosis (TB) control. The high rates of MDR/RR-TB observed among re-treatment cases can arise from diverse pathways: de novo amplification during initial treatment, inappropriate treatment of undiagnosed MDR/RR-TB, relapse despite appropriate treatment, or reinfection with MDR/RR-TB. Mathematical modelling allows quantification of the contribution made by these pathways in different settings. This information provides valuable insights for TB policy-makers, allowing better contextualised solutions. However, mathematical modelling outputs need to consider local data and be easily accessible to decision makers in order to improve their usefulness. We present a user-friendly web-based modelling interface, which can be used by people without technical knowledge. Users can input their own parameter values and produce estimates for their specific setting. This innovative tool provides easy access to mathematical modelling outputs that are highly relevant to national TB control programs. In future, the same approach could be applied to a variety of modelling applications, enhancing local decision making.

3.2 The threat of drug-resistant TB
Drug-resistant tuberculosis (TB) is a threat to TB control and a barrier to disease elimination. TB treatment is complicated by resistance to rifampicin and/or isoniazid, the two most active first-line TB drugs. At the global level, 3.9% (95% confidence interval [CI]: 2.7-5.1%) of all new TB cases are multidrug-resistant (defined as resistant to at least rifampicin and isoniazid) or rifampicin-resistant (MDR/RR-TB). However, the proportion of MDR/RR-TB globally is even higher among re-treatment cases, reaching 21% (95% CI: 15-28%) according to estimates by the World Health Organization (WHO). Mathematical modelling suggests that MDR-TB strains could become dominant over the drug-susceptible (DS) ones in the coming decades, threatening the success of WHO’s End TB Strategy and targets for TB elimination. A more comprehensive understanding of the different mechanisms leading to MDR/RR-TB at re-treatment is important to provide enhanced insight into the local determinants of drug-resistant TB emergence and to support the development of better contextualised solutions.

3.3 The pathways to drug resistance at re-treatment
The higher proportion of MDR/RR-TB in re-treatment cases compared to new cases has long been attributed to resistance amplification due to poor treatment adherence, focusing the response to emergent drug-resistant TB on better treatment supervision of patients treated with first-line therapy. Among re-treated cases, finding of MDR/RR-TB rarely triggers consideration of pathways that involve primary transmission of drug-resistant strains, i.e. involving infection with an already drug-resistant pathogen. However, three different causal pathways to MDR/RR-TB at
re-treatment can be identified that do not involve resistance amplification and are therefore illustrations of primary transmission. First, the low rate of drug susceptibility testing among new TB cases results in a large proportion of initially drug-resistant cases being treated with inappropriate regimens, leading to treatment failure or disease relapse and re-presentation as a "re-treatment case". In addition, among new cases correctly diagnosed with MDR/RR-TB, treatment outcomes are often unfavourable, making resistant cases more likely to present for re-treatment. Finally, reinfection with a drug-resistant strain may also contribute to the burden of MDR/RR-TB seen at re-treatment, especially in settings where TB transmission is poorly controlled. We developed a modelling approach to quantify the likely proportions of MDR/RR-TB at re-treatment attributed to the different causal pathways specified. Findings highlighted the failure to identify drug resistance at first presentation as a leading source of MDR/RR-TB among re-treatment cases at the global level. However, when applying our model to different regions and countries, we demonstrated substantial variability in the respective contributions of the various sources at the national and local levels. This finding highlights the need for better contextualised solutions that utilise local data to guide local TB control priorities and interventions.

3.4 The need to make mathematical modelling more applicable and usable

While our previous study provided estimates at the national level for more than 100 countries, detailed assessment of the dominant drug resistance pathways in specific settings would assist local control efforts. Strong spatial heterogeneity in the burden of MDR/RR-TB has been identified in several countries, with demonstration that transmission can reach extreme intensities in small localities, emphasising the need for better contextualised solutions. In such settings, refined estimates incorporating local information would be invaluable in producing realistic and actionable model outputs. Estimates reported in our previous study only provided insight relevant to 2015 data, as reported in the 2016 WHO Global Tuberculosis Report. However, this fails to take account of the changing aspects of the TB epidemic and the need for real-time decision making in order to optimize programmatic responses. Allowing real-time assessment of likely MDR/RR-TB pathways will provide updated estimates as routine data are gathered and refreshed over time. In addition, policy makers may wish to test alternate assumptions or to use parameter values that they believe more appropriate. Such continuity and flexibility cannot be provided by occasional external expert support or traditional research project-based approaches, and thus represent a major barrier to the effective use of mathematical modelling for everyday policy guidance.

To overcome this limitation, present in most modelling outputs reported to date, we developed a user-friendly interface for real-time analysis of local data using our recently published model of MDR/RR-TB pathways. In the current paper we introduce a web-based interactive tool to
quantify the likely contribution of different MDR/RR-TB pathways among re-treatment cases, accommodating localised parameterisation via a user-friendly interface.

3.5 The user-friendly modelling interface

3.5.1 General description

The user interface is available online at www.tb-modelling.com/mdr_tb_at_retreatment. Its main objective is to quantify the proportions of MDR/RR-TB at re-treatment attributed to four principle causal pathways: I) initial drug-susceptible TB with resistance amplification during treatment; II) initial MDR/RR-TB inappropriately treated as drug-susceptible TB; III) MDR/RR-TB relapse despite appropriate treatment; and IV) re-infection with MDR/RR-TB. The model employed to estimate these contributions was described in detail in our previous publication.\textsuperscript{140} The online tool allows users to produce estimates by using the model in combination with their own inputs. The associated model outputs are produced in real time and exporting features allow the user to download personalised reports in a PDF format. Figure 12 summarises the general principle and the different functionalities of the platform. Javascript language was used to build the interactive platform as we needed immediate responsiveness to produce model outputs instantaneously when users specify new inputs. Thus, the webpage is only loaded once from the remote server and calculations are then performed on the user’s device in real time when parameter values are changed. We used Chart, jVectorMap and jsPDF libraries to generate the charts, maps and exporting functionalities, respectively.

![Figure 12 General description of the user interface](image)

3.5.2 Personalised inputs

The user must specify the area (WHO region or country) to which the model will apply. This process allows preselected parameter sets to be generated based on local WHO data. While these
default values correspond to the ones that were used in the initial study, they can here be adjusted using a set of slider bars. Parameters are classified into two main categories: ‘area-specific’ and ‘global’, with only parameters of the first category updated when a new area is selected. Compatibility tests on parameter values are run in the background to ensure that the parameterisation remains realistic. For example, if the user selected a treatment success rate for DS-TB of 80%, a ceiling is set for the death proportion during treatment for DS-TB at 20%.

3.5.3 Model outputs

The Model Outputs panel consists of two charts that are automatically updated when any of the parameter values is modified. First, a doughnut chart represents the proportions of MDR/RR-TB at re-treatment attributed to the four principle causal pathways I-IV. Second, a bar chart displays the proportion of MDR/RR-TB among all re-treatment TB cases. A comparison between the model output and the WHO estimate regarding this proportion is also presented on the second chart when relevant data are available from WHO for the selected area. Quantitative estimates are displayed when the user moves the pointer over the different shares of the two charts. Figure 13 presents a screen capture of the interface containing the Inputs and Model Outputs panels for an example model estimation.

Figure 13  Partial screen capture of the user interface
The Inputs panel contains the predefined parameter values associated with Viet Nam. The results displayed in the Model Outputs panel are instantaneously updated when any of the parameters is adjusted through the sliders of the Inputs panel.
3.5.4 Mapping

An interactive world map is incorporated in the user interface to provide a global visualisation of the different country-level estimates. The user can select one of the six model outputs that can be displayed on the choropleth map: individual contribution of Cause I, II, III or IV; leading cause of MDR/RR-TB at re-treatment; and proportion of MDR/RR-TB among all re-treatment TB cases. The results presented on the maps are calculated using the user-defined values for the global parameters and the default values for the area-specific parameters. That is, changes to the area-specific parameter values associated with a selected country will not affect the maps (see Figure 12). When the user clicks on a country, the Inputs panel will be updated and the Model Outputs panel will display estimates related to the selected country.

3.5.5 Download personalised reports

Exporting functionalities are available allowing the users to download PDF documents incorporating the model outputs associated with their own parameterisation. Two different types of report can be produced: one including the charts as displayed in the Model Outputs panel and one containing the selected map. The values of the parameters that are defined by the user also appear in the generated documents.

3.6 Discussion

We introduce a user-friendly online tool capable of quantifying the proportions of MDR/RR-TB at re-treatment attributed to different causal pathways. This interface will help policy-makers to better identify the pathways to drug resistance and to design tailored programs to fight drug-resistant TB. While the higher rates of MDR/RR-TB at re-treatment by comparison to new cases have long been recognised and reported by WHO, the pathways leading to such gaps and their implications for effective local control strategies have remained unexplored for too long. Our findings suggest that primary transmission of drug-resistant strains is the predominant pathway in most settings. This challenges the old dogma that drug resistance amplification as a result of poor quality or adherence to treatment was the main explanation for the high rates of MDR/RR-TB at re-treatment. It highlights the need to refocus TB control interventions towards solutions that are specific to the drivers of MDR/RR-TB in a particular location.

The modelling interface presented in this report will enhance the applicability of this finding and we believe that it provides an important “proof of principle” of how modelling approaches can be adapted to provide a user-friendly interface for assisting local decision making. In this instance it could assist countries to estimate the contribution of different pathways to the generation of drug resistant TB cases, allowing for better targeted and better contextualized interventions to be considered. For example, finding high proportion of MDR/RR-TB at re-treatment arising from pre-existing MDR/RR-TB primary transmission may lead to a response to universally test all new
cases of TB for resistance, whereas a finding of acquired amplification of MDR/RR-TB being the dominant source may lead to examination of the failure/loss to follow-up rates of those with DS-TB. As a “proof of principle” this tool demonstrates how user-friendly interfaces can be developed to allow public health decision makers, at different levels of care, access to modelling data that is relevant to their local setting.

The platform allows our existing model to be used in combination with flexible parameterisation entered by the user. In addition to offering the possibility for alternate parameter sets from those employed in our previous study, this interface also allows estimates to be obtained for a broader range of settings, and in particular at local levels. Most importantly, this tool will allow users with no specific technical knowledge to use a mathematical model and to compute personalised estimates.

We chose not to include uncertainty around parameter values when building this online interface in order to maximise the tool’s simplicity and to make it accessible to the broadest possible audience. Nevertheless, the users will be able to assess the sensitivity of the model estimates to the different parameters by using the different input sliders and produce outputs related to alternate parameter sets. In contrast, our previous study incorporated uncertainty and sensitivity analyses that highlighted the influence of some parameters on the contributions of the respective pathways. In particular, we demonstrated that the contribution of inappropriate diagnosis to the burden of MDR/RR-TB at re-treatment was significantly affected when varying the rate of drug susceptibility testing or the parameters that relate to treatment outcomes (success and death rates). Further, we noted that the contribution of the pathway involving drug resistance amplification increased when reducing the treatment success rate for DS-TB and the individual-level risk of drug resistance amplification in unsuccessfully treated patients. Other conceptual assumptions than those considered in the baseline analysis may also be explored using the sliders. For example, patients who are lost to follow-up are assumed to experience unsuccessful treatment under the default behaviour of our model but alternate scenarios may be considered by increasing the parameter values that define the treatment success rates.

The web-based tool addresses some of the limitations of the original model, especially regarding the level of resolution of the analysis and the uncertainty around parameter values and underlying assumptions. However, some limitations that are linked to the intrinsic structure of the model could not be addressed here. For example, only two phenotypes of TB are considered in the model – DS-TB and MDR/RR-TB – although we know that other resistance profiles exist. This simplification was made in order to make the model broadly applicable and to match with the approach used by WHO to classify drug-resistant TB. Another limitation is that some more specific causal pathways such as nosocomial transmission of MDR/RR-TB are not considered in
the model although there is evidence of their importance in some settings. More specific model structures may be designed to investigate the causes of MDR/RR-TB among re-treatment cases in such contexts. It is also important to note that the estimates provided by our interface are relative contributions of the different pathways expressed as percentage of the total burden of MDR/RR-TB at re-treatment. Therefore, the overall absolute burden of MDR/RR-TB at re-treatment should also be taken into account by users if they wished to estimate the absolute number of cases that are attributed to each of the four causal pathways.

User-friendly tools such as ours can contribute to building confidence in the use of modelling, which is essential to facilitate the bidirectional exchange between modellers and TB control program developers and improve the understanding of the local epidemic. We believe that this user-friendly adaptation presents an important exemplar of how modelling approaches could become more useful to guide everyday decision making processes using local data inputs for optimal contextualisation.
4 Is IPT more effective in high-burden settings? Modelling the effect of tuberculosis incidence on IPT impact

After exploring issues associated with drug resistance in Chapters 2 and 3, this thesis will now focus on another major challenge of TB control that is latent infection with \textit{M.tuberculosis}. This Chapter presents an investigation of the relationship between TB incidence and effectiveness of LTBI treatment using a conceptually simple model. The following text is a reproduction of the article published in the \textit{International Journal of Tuberculosis and Lung Disease}.\textsuperscript{170}

Treatment based on isoniazid is considered in this study as it is currently the most commonly used. Although other drug regimens have recently emerged for the treatment of LTBI as discussed in Section 1.3, it remains unclear which one would be the most efficient for large-scale implementation. After publication of this research project, I also contributed to a cost-effectiveness analysis comparing different LTBI treatment regimens. This project, led by Doctor Tan Doan, was published in the \textit{Journal of Antimicrobial Chemotherapy}.\textsuperscript{171} It suggests that combination of isoniazid with rifapentine would be the most cost-effective approach at the individual level. Nevertheless, the sensitivity analyses presented in Section 4.7.3 of this thesis show that the conclusions of Chapter 4 would remain valid when considering the treatment efficacy of the combined regimen isoniazid/rifapentine. Doctor Doan’s article also demonstrates that preventive treatment with any regimen is cost-saving compared with no treatment, reinforcing the importance of the prophylaxis tool for global TB control.
4.1 Abstract

Setting: Isoniazid preventive therapy (IPT) is effective for preventing active tuberculosis (TB), although its mechanism of action is poorly understood and the optimal disease burden for IPT use has not been defined.

Objective: To describe the relationship between TB incidence and IPT effectiveness.

Methods: We constructed a model of TB transmission dynamics to investigate IPT effectiveness under various epidemiological settings. The model structure was intended to be highly adaptable to uncertainty in both input parameters and the mechanism of action of IPT. To determine the optimal setting for IPT use, we identified the lowest number needed to treat (NNT) with IPT to prevent one case of active TB.

Results: We found that the NNT as a function of TB incidence shows a “U-shape”, whereby IPT impact is greatest at an intermediate incidence and is attenuated in both lower and higher incidence levels. This U-shape was observed over a broad range of parameter values, and the optimal TB incidence was found between 500 and 900 cases/100,000/year.

Conclusions: TB burden is a critical factor to consider when making decisions about IPT community-wide implementation. We demonstrate that total burden of disease should not preclude programmatic application of IPT.

4.2 Introduction

TB is a global health problem with 9.6 million cases and 1.5 million deaths worldwide in 2014. According to an estimate from the World Health Organization (WHO), around one third of the world’s population is latently infected with TB. However, assessment of the future risk posed by this reservoir of potential disease is challenging, due to several issues, including the inability of currently available diagnostic tests to predict whether or not an infected individual will progress to active disease. Therefore, while preventive treatment against latent TB infection (LTBI) may be a vital tool in achieving the WHO and the Stop TB partnership’s ambitious objective of TB elimination by 2050, the optimal setting in which to employ this intervention is uncertain.

Isoniazid preventive therapy (IPT) for LTBI is known to be effective at the individual level in reducing the risk of subsequent disease. However, its impact at the population level remains unclear. Community-wide IPT interventions in Alaska, Greenland and Tunisia have demonstrated the ability of IPT to reduce TB-incidence. The number needed to treat (NNT) to avert one case of active disease was found to range between 35 and several hundred, depending on the baseline risk of TB activation, demonstrating that IPT can be very efficient provided that relevant populations are targeted. However, the results of the recent Thibela trial conducted among South African gold-miners are less clear, with no durable population-level impact demonstrated, despite
a reduction in the risk of TB during therapy. These observations highlight the potential for different population-level impact of IPT interventions by disease burden.

Questions have been raised around the mechanism of action of IPT as it is unclear whether this intervention reduces the risk of later progression to active disease or cures infection. Furthermore, the ability of IPT to protect against subsequent infections has not been demonstrated and re-infection is therefore likely to be a major modifier of IPT effectiveness, with the potential to markedly attenuate the public health effects. As a direct correlation exists between TB-incidence and re-infection rates, one may expect that the success of IPT interventions might be modified by the local TB-incidence.

We constructed a mathematical model that allows for variation in TB burden and incorporated a flexible structure for exploring different assumptions regarding IPT efficacy.

4.3 Materials and methods

4.3.1 Model development

Using ordinary differential equations and the assumption of homogeneous mixing, we build a deterministic model of TB transmission. The simplest feasible structure that can adequately capture both TB transmission dynamics and IPT is employed (Figure 14). Newly born individuals enter via the fully susceptible compartment ($S$). Two distinct compartments ($L_A$ and $L_B$) are used to model LTBI in order to reflect the higher risk of disease progression during the early stages following infection. The modelled intervention is community-wide treatment for LTBI, which consists of treating infected individuals with a 9 month course of IPT after detecting infection from tuberculin skin test (TST) or interferon–gamma release assays (IGRA) (see details in Section 4.7).

Individuals with LTBI treated with IPT transition to two equivalent compartments $P_A$ and $P_B$. In these compartments, we assume a reduced risk of progression to disease compared to that existing prior to IPT commencement. This model structure allows exploration of a wide range of possibilities regarding the effectiveness and mechanism of action of IPT. That is, different levels of reduction in the risk of progression achieved through IPT can be considered, as well as a situation where IPT can completely cure infection. Infected individuals developing active TB progress to the compartment $I$ and eventually transition to the compartment $R$ in case of recovery.

In our model, all individuals with a history of TB infection can be re-infected. Various assumptions concerning the risk of re-infection are considered, some degree of immunity may be conferred by previous infection, although non-biological factors could enhance the risk of re-infection (e.g. such as social mixing patterns).
Figure 14  Model structure
Rectangular boxes represent the different categories in which the population is structured: Susceptible (S), Latently infected untreated \((L_A\) and \(L_B\)), Latently infected treated with isoniazid preventive therapy (IPT) \((P_A\) and \(P_B\)), Infected with active TB \((I)\) and Recovered \((R)\). Arrows represent the transitions permitted between categories. Blue arrows indicate flows related to IPT. Infected individuals treated with IPT transition to corresponding compartments where the rate of disease activation is reduced. Re-infection may occur for both recovered and latently infected individuals. Birth and death flows are not represented on this diagram (See full description in Section 4.7.1).

Table 4 presents the main assumptions made in our model and a detailed description of the model and the associated differential equations are available in Section 4.7.2.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Assumption</th>
<th>Tested in sensitivity analysis?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reinfection while latently infected</td>
<td>Individuals return to the early infection compartment ((L_A)).</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Already infected individuals are assumed to be less susceptible than infection-naïve individuals (50% relative risk)</td>
<td></td>
</tr>
<tr>
<td>Re-infection after receiving treatment (for active or latent infection)</td>
<td>Individuals with history of treatment have the same susceptibility to re-infection as untreated infected individuals.</td>
<td>Yes</td>
</tr>
<tr>
<td>Effect of IPT at the individual level</td>
<td>Four scenarios: reduction in the risk of activation by 25%, 50%, 75% or 100%.</td>
<td>No further</td>
</tr>
<tr>
<td>Impact of HIV co-infection</td>
<td>The rate of progression to active disease is enhanced in both early and late latency compartments</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Table 4  Main assumptions
IPT: isoniazid preventive therapy; HIV: human immunodeficiency virus.

4.3.2  Observed model outputs
Disease burden indicators, including incidence, prevalence and mortality are recorded before the intervention starts and over ten years of IPT implementation. From these measures, three different indicators are calculated and reported: 1) the primary outcome, which is the NNT in order to avert one case of active TB; 2) the proportional reduction in incidence of active TB; and 3) the absolute number of active TB-cases averted in the population through IPT. These three outputs allow us to consider both the absolute and relative impact of treatment, as well as NNT, which is our primary consideration as it describes the population-level effectiveness of the strategy per
treatment provided. NNT is defined as the number of active TB cases averted over ten years of intervention divided by the total number of individuals treated with IPT. The optimal incidence is then obtained by minimizing this indicator.

We also estimate the proportion of disease due to early progression versus late reactivation, as well as the risk of re-infection in the different incidence settings; since these factors are expected to play an important role in the IPT efficiency.

4.3.3 Sensitivity analyses
We perform a sensitivity analysis to observe whether the optimal incidence for implementing IPT is modified by alternative parameter set selections. First, we consider one-dimensional variations in each parameter across the ranges presented in Table 5 (Section 4.7). Next, considering the same numeric ranges, we perform a multi-dimensional sensitivity analysis employing a Latin hypercube method to obtain 1,000 parameters sets. Finally, we consider additional scenarios where the model parameterization was adjusted in order to simulate HIV-endemic settings, considering various levels of HIV prevalence as well as different assumptions regarding the effect that HIV infection has on the risk of TB disease activation.

4.3.4 Model implementation
The model was implemented in R version v3.1.2 and the code to reproduce all the results presented here is supplied in the Web Appendix.178

4.3.5 Ethical approval
Ethical approval was not required for the study as no patients were involved.

4.4 Results
4.4.1 Baseline results
Figure 15 presents the outcome measures for IPT effectiveness as a function of TB-incidence, considering different efficacy levels for IPT. Four examples of countries/region are represented in Figure 15 to illustrate different levels of TB-incidence: Micronesia (MIC), Cambodia (CAM), Kiribati (KIR) and the Gulf Province of Papua New Guinea (PNG-GP) with respective estimated TB-incidences of 195, 390, 497 and 1290 cases/100,000/year.34 As our baseline analysis does not apply to HIV-endemic settings, only settings with low HIV prevalence are presented.
Figure 15 Baseline results
Three indicators of isoniazid preventive therapy (IPT) effectiveness are presented: a: the number needed to treat to avert one case of active tuberculosis; b: the proportional reduction of incidence; and c: the absolute number of cases averted due to IPT. All three indicators are calculated over a period of 10 years of intervention. In each panel, four curves are presented corresponding to different assumptions regarding the IPT efficacy. The vertical dashed lines represent four countries/region that illustrate different levels of TB incidence: Micronesia (MIC), Cambodia (CAM), Kiribati (KIR), and the Gulf Province of Papua New Guinea (PNG-GP).

We observe a U-shaped curve for NNT to avert one case of active TB regardless of efficacy (Figure 15.a). That is, the NNT is lowest at an intermediate incidence (500 – 900 cases/100,000/year), but increases in both lower and higher incidence settings. As would be intuitively expected, NNT values are lower under the most optimistic assumptions (i.e. complete cure or strong protection provided by IPT). However, the optimal TB-incidence for implementing IPT is relatively unaffected by different values for the proportion cured by IPT assumptions and ranges between 717 and 726 cases/100,000/year. Both the U-shaped curve and the location of the optimum are conserved. The corresponding values of optimal NNT range from 94 to 396.

In contrast, the proportional reduction in TB-incidence decreases with background incidence (Figure 15.b). While IPT produces significant reductions in TB-incidence in low to moderate burden settings (5 – 19 % reduction in 10 years for an incidence of 50 cases/100,000/y), its impact in very highly endemic settings is small (1 – 3 % reduction in 10 years for an incidence of 1,500...
cases/100,000/ y), although in high burden settings even a slight reduction in incidence results in a significant absolute number of averted cases.

Finally, the absolute number of averted cases reveals another non-monotonic relationship with TB-incidence, regardless of the assumption made about IPT efficacy (Figure 15.c), with a similar (although inverse) pattern to that seen for NNT. The maximal number of averted cases is obtained when TB-incidence is between 827 and 835 cases/100,000/year. At this incidence and among a total population of 1,000,000, the model predicts that IPT would prevent between 1,006 (when IPT reduces risk of activation by 25%) and 4,199 (when IPT cures LTBI) cumulative active TB-cases over ten years of intervention.

4.4.2 Two interacting phenomena

Figure 16 presents two measures to quantify the contribution of two phenomena that were suspected to explain the dynamics driving the U-shape: 1) the proportion of TB-incidence attributable to recently infected individuals; and 2) the annual risk of re-infection for individuals with latent tuberculosis. At less extreme incidence rates (0-500), the picture is dominated by the rapid increase in the proportion of disease due to recent infection, explaining the decrease in NNT over this range of incidence (see Figure 15.a). In contrast, when incidence reaches very high levels (>1,000), the proportion of disease due to recent infection increases more slowly as it approaches its saturation level of 100%. At the same time, re-infection continues to increase linearly with incidence and dominates the picture over this range. Accordingly, at such high incidence levels, the NNT increases with incidence.
4.4.3 Sensitivity analyses

Figure 18 (Section 4.7.3) presents the results of the sensitivity analysis performed in order to observe the impact of single variations in parameter values on the optimal incidence obtained by minimizing the NNT. The sensitivity analysis highlights that a faster rate of progression from early latency to active disease results in a higher estimate of the optimal incidence.

Another parameter with a marked impact on our conclusions is the risk of re-infection. Specifically, we find that the risk of re-infection after treatment by comparison to the risk during LTBI plays a major role in determining the incidence that correlates with optimal IPT impact. In particular, if we assume that susceptibility to re-infection is enhanced after treatment completion, the nadir of the NNT U-shape occurs at a lower TB-incidence. In contrast, when the risks of re-infection before and after treatment are varied together, we observe minimal impact on the optimal incidence. Single variations in other parameters have no pronounced effect on the optimal incidence.

Figure 19 (Section 4.7.4) presents the results of the multi-dimensional sensitivity analysis using a Latin hypercube method for sampling 1,000 parameters sets. We measured a median optimal incidence of 811 cases/100,000/year (IQR 582-1,066). We noted that 100% of the runs led to a strictly positive value for the optimal incidence and that its lowest value was 154 cases/100,000/year, indicating that the U-shape was conserved over all model runs. This
multivariate sensitivity analysis confirms the results of the previous analysis, showing that only variations in the rate of progression from early latency to active disease and the risk of re-infection after treatment by comparison to the risk during LTBI significantly impact on the results.

Finally, our analysis relating to HIV-endemic settings revealed that the findings concerning the U-shape curve associated with a high level of optimal TB incidence for IPT use were not jeopardised, even when considering a very high HIV prevalence (Section 4.7.5). We found that the optimal TB incidence increases with HIV prevalence and that IPT use becomes more efficient (NNT reduced) in HIV-endemic settings, reaching NNT levels as low as 14 when TB incidence is 3,767 (optimal configuration) and for an HIV prevalence of 26%. These findings remained valid under various scenarios concerning the effect of HIV infection of the risk of TB activation.

4.5 Discussion

We find that the optimal epidemiological settings for the programmatic use of IPT against LTBI occur at surprisingly high levels of TB-incidence. The NNT initially falls as TB-incidence increases and then follows a U-shaped curve, with the maximal impact of IPT found at a TB-incidence of around 720 cases/100,000/year. This finding remained valid regardless of the assumptions made about the IPT efficacy, from assuming a weak reduction (25%) in the risk of disease progression through to allowing complete cure of infection. This consideration of different scenarios is of particular importance given the uncertainty around the individual-level effect of IPT. In a recent modelling study, this concern was approached and it was found that IPT is unlikely to totally cure infection in HIV-positive individuals not on ART. However, no similar investigations have been conducted in the general population. Our different sensitivity analyses provide confidence in the U-shape finding, as the exploration of a wide parameter space did not affect this qualitative result even when considering HIV-endemic settings.

Such optimal levels of incidence might seem very high when considering country-specific estimates, as only South-Africa, Lesotho and Swaziland exceeded annual incidences of 700 new TB-cases per 100,000 in 2014, and HIV is a critical driver of the huge disease burden in these settings. However, a similar TB burden might also occur in more moderate HIV-burden settings, when considering smaller sub-national populations or local communities (e.g. Gulf Province, Papua New Guinea) within countries of much lower national incidence. Our results suggest that it is only when incidence reaches extremely high levels (over 1,400 cases/100,000/year) that the effects of IPT begin to attenuate. In these settings, IPT would result in limited reduction of incidence and few averted cases, leading to unreasonable NNTs.

We propose an explanation for the U-shaped curve by the interaction of two competing phenomena that vary in intensity as incidence increases: the rise in the level of re-infection and the rise in the proportion of disease that is due to recent infection. On the one hand, higher
incidence leads to higher risks of re-infection in both recovered and latently infected individuals. Thus, patients who have been treated for LTBI are more likely to be re-infected and consequently have a high risk of active TB in the early phase of this new infection. Accordingly, the benefit of IPT diminishes with higher incidence. On the other hand, in high incidence settings, the proportion of latent cases recently infected is greater than in lower incidence settings. Thus, the risk represented by the LTBI reservoir is higher given that early infections have the highest risk of progression to active disease, leading to a greater benefit from IPT in higher burden settings. This profile had been demonstrated previously and are confirmed by the findings of our simulations.96 97 179

We further demonstrate that the risk of re-infection plays an important role in the estimation of the optimal incidence, finding that it is crucial to distinguish susceptibility to re-infection for latently infected individuals from that occurring after treatment. Indeed, our results imply that if isoniazid attenuates the immunity conferred by prior infection the corresponding optimal incidence may be much lower, particularly if rates of progression following recent infection are low. Unfortunately, little is known about the true effect that IPT has on acquired immunity and accordingly, our study indicates that further work that would allow distinction between these two risks of re-infection would bring crucial knowledge to better understand the potential impact of IPT.

Our sensitivity analysis emphasizes the importance of detailed knowledge of the dynamics of the TB latency, and especially of its early stages. Fortunately, several studies have now reported the rate of disease progression from recent infection, generating consistent estimates.10 11 102 176 Factors such as HIV infection or young age at infection have been shown to increase the risk of TB disease progression,11 14 102 which – according to our model – may lead to higher optimal incidences. Our additional analysis focusing on HIV-endemic settings confirmed this assumption and also suggested that it becomes more efficient to use IPT when HIV is endemic, due to the higher potential of TB disease represented by the infection reservoir. Future modelling investigations based on this work but incorporating a more specific model structure could be conducted in order to provide stronger evidence regarding HIV endemic settings. Although age structures along with non-homogeneous population mixing could also be incorporated in future works to enhance the realism of the model in local contexts, such features were not considered in this exercise as we aimed to provide broad insights and to minimize the complexity of our model.

A further limitation of our study is that we did not consider multi-drug resistant TB (MDR-TB) settings. If we assume that specific MDR LTBI regimens have similar effectiveness to IPT for drug-susceptible LTBI, as suggested by recent observational studies,180 our results could be extended to high MDR-TB settings. Nevertheless, even though our model is potentially applicable
to high MDR-TB burden settings, the diagnosis of MDR LTBI is much more complicated and often assumed on the basis of contact history, making our model too limited to fully understand these considerations. Finally, potential side effects as well as cost of IPT were not considered in this study as we aimed to observe the impact on the TB epidemic. While further works could help to better understand these aspects, our choice of NNT as the primary outcome allows implicit consideration of the costs and risks involved in this intervention, alongside its benefits.

4.6 Conclusions
While the WHO recommend mostly using IPT in low endemic settings, our study suggests that the optimal TB-incidence for employing IPT is considerably higher than expected, indicating that total burden of disease should not preclude the programmatic application of IPT. In light of the ambitious new End-TB global targets for the post-2015 era, bold new strategies will be required, potentially incorporating preventive therapy. While our results were robust to most model inputs, better understanding of post-treatment immunity is critical to refining our estimates.

4.7 Supplemental material
4.7.1 Description of the mathematical model
Figure 17 presents the model structure along with the parameters.

![Model structure and parameters](image)

Figure 17  Model structure and parameters
Rectangular boxes represent the different categories in which the population is structured. Arrows represent the transitions permitted between categories. Blue arrows indicate flows related to isoniazid preventive therapy (IPT). Infected individuals treated with IPT transition to corresponding compartments where the rate of disease activation is reduced (multipliers $\rho_A$ and $\rho_B$). Re-infection may occur for both recovered and latently infected individuals. Treated individuals have a reduced risk of re-infection (\(\kappa\)) compared to treatment-naive latently infected individuals. Birth and death flows not represented on this diagram (See full description in the main text).
A natural mortality rate ($\mu$) applies to every compartment and an additional TB specific mortality rate ($\mu_I$) is added to the active disease population ($I$). Recruitment is set equal to total mortality to maintain a constant population size. Newly born individuals enter via the fully susceptible compartment ($S$). As described in the main text, two compartments ($L_A$ and $L_B$) are used to model untreated LTBI while two additional compartments ($P_A$ and $P_B$) are used to represent LTBI treated with IPT. In these compartments, we assume a reduced risk of progression to disease compared to that existing prior to IPT commencement by using the multipliers $\rho_A$ and $\rho_B$. In this way, different levels of reduction in the risk of progression achieved through preventive therapy can be considered, as well as a situation where IPT completely cures infection ($\rho_A = \rho_B = 0$). Furthermore, this structure allows for different efficacies of IPT according to whether the infection is acquired recently or remotely (by setting $\rho_A \neq \rho_B$).

In our model, all individuals with a history of TB infection can be re-infected, although we systematically varied the rate at which reinfection occurs. In the base-case, we assumed that prior (or current) TB infection confers 50% immunity against subsequent infection ($\psi = 0.5$), in accordance with previous estimates. Even if prior infection is assumed to provide some protection during an infectious contact, it should be noted that re-infection is not only driven by biological factors but also by social mixing patterns, as previously infected individuals are more likely to live in settings with higher exposure to TB. Accordingly, we choose to consider a wide range of values for the risk of re-infection, even considering situations in which risk is augmented by prior infection ($\psi > 1$), as suggested by Verver et al. The effect of treatment on subsequent risk of TB reinfection is unclear. Treatment may provide some biological protection, reducing the risk of reinfection, or treatment could reduce the degree of immunity conferred by infection, increasing the risk of reinfection. Thus, even though we assumed an equivalent risk of re-infection for any history of infection (treated or not) in the base-case ($\kappa = 1$), we explored alternative configurations in sensitivity analyses ($\kappa$ varied from 0.5 to 1.5). In earlier model iterations, we found that the critical issue in susceptibility to re-infection was the relative susceptibility of treated (either for LTBI or TB) versus untreated individuals. Therefore, we chose to use the multiplier $\kappa$ to represent the relative susceptibility after treatment by comparison to treatment-naïve individuals who are latently infected.

Simulation was realised in two stages. First, we assumed no IPT coverage and ran the model to equilibrium. Next, from this equilibrium state, we ran the model over ten years of IPT implementation. Treatment rates ($\delta_A$, $\delta_B$, and $\delta_S$, which represent annual coverage) remain constant during this second phase and apply to the whole population of the corresponding category ($L_A$, $L_B$, and $S$ respectively), but may differ according to the stage of latency (i.e. $\delta_A \neq \delta_B$). These differences permit consideration of higher IPT coverage among recently infected cases, to reflect a more targeted intervention, such as case finding among TB contacts.
Furthermore, given the difficulties encountered with LTBI diagnosis – and particularly given the poor specificity of the tuberculin skin test (TST) which is predominantly used – we allow for IPT to be given to a proportion of uninfected individuals. Thus, in the sensitivity analysis, we allow for IPT use in the fully susceptible population ($\delta_s > 0$), although treatment of this population is assumed to be ineffective and would therefore have no epidemiological impact. We consider relatively low treatment coverage in the infected population in order to account for the fact that treatment would not be initiated in all infected individuals in the real world, as some of them may not complete testing or even if diagnosed, may not start treatment. We assume a null IPT coverage for individuals who have already successfully completed a treatment course for LTBI (in compartments $P_A$ and $P_B$).

At baseline, we assume a combined rate of efficacy, completion and sensitivity of LTBI detection of 48%. This results from the multiplication of a test sensitivity (for TST or Interferon-Gamma–Release Assays) of around 80%, and a combined rate of compliance and treatment efficacy of 60%. This latter figure was obtained from the Cochrane review of Smieja et al. reporting a risk ratio of 0.40 of developing TB when receiving INH for 6 to 12 months.

The definitions and values of the model parameters are presented in Table 5.

### 4.7.2 Differential equations corresponding to the compartmental model

$$\frac{dS}{dt} = -\beta.S.I + \mu.N + \mu_I.I - \mu.S$$

$$\frac{dL_A}{dt} = (\beta.S + \kappa\psi R + \psi \beta.L_B + \kappa\psi \beta.P_A + \kappa\psi \beta.P_B ).I - (\epsilon + \gamma + \delta_A \theta + \mu).L_A$$

$$\frac{dL_B}{dt} = \epsilon.L_A - \psi \beta.L_B.I - (\nu + \delta_B \theta + \mu).L_B$$

$$\frac{dI}{dt} = \gamma.L_A + \nu.L_B + \rho_A\gamma.P_A + \rho_B\nu.P_B - (\tau + \mu + \mu_I).I$$

$$\frac{dR}{dt} = (\tau - \kappa\psi \beta.R).I - \mu.R$$

$$\frac{dP_A}{dt} = \delta_A \theta.L_A - \kappa\psi \beta.P_A.I - (\epsilon + \rho_A\gamma + \mu).P_A$$

$$\frac{dP_B}{dt} = \epsilon.P_A + \delta_B \theta.L_B - \kappa\psi \beta.P_B.I - (\rho_B\nu + \mu).P_B$$
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Value (sensitivity range)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease dynamic parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\beta$</td>
<td>Transmission rate</td>
<td>Calibrated to incidence</td>
<td>-</td>
</tr>
<tr>
<td>$-$</td>
<td>Incidence</td>
<td>0 – 1500 cases/100,000/year</td>
<td>184</td>
</tr>
<tr>
<td>$1 / \varepsilon$</td>
<td>Duration of recent infection phase</td>
<td>5 years (3 – 7)</td>
<td>10 102</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>Rate of rapid progression to disease</td>
<td>0.09 over 5 years (0.05 – 0.15)</td>
<td>10 102</td>
</tr>
<tr>
<td>$\nu$</td>
<td>Rate of slow progression to disease</td>
<td>0.0005 /year (0.0003 – 0.001)</td>
<td>130 185</td>
</tr>
<tr>
<td>$1 / \tau$</td>
<td>Duration of infectiousness</td>
<td>1 year (0.5 – 1.5)</td>
<td>Assumption*</td>
</tr>
<tr>
<td>$\mu$</td>
<td>Natural death rate</td>
<td>$1 / 70$ years (1/80 – 1/60)</td>
<td>186</td>
</tr>
<tr>
<td>$\mu$</td>
<td>TB-specific mortality</td>
<td>0.03 years$^2$ (0.02 – 0.04)</td>
<td>Assumption</td>
</tr>
<tr>
<td><strong>Partial immunity parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\psi$</td>
<td>Relative susceptibility to re-infection if latently infected and not treated (reference: fully susceptible population)</td>
<td>0.5 (0.25 – 1.5)</td>
<td>89 101</td>
</tr>
<tr>
<td>$\kappa$</td>
<td>Relative susceptibility if history of treatment (reference: latently infected population)</td>
<td>1 (0.5 – 1.5)</td>
<td>89 101</td>
</tr>
<tr>
<td><strong>LTBI treatment parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\rho_A$</td>
<td>Hazard ratio of disease progression in early latency after receiving IPT (ref: early latency not treated)</td>
<td>0 – 0.75</td>
<td>Model exploration</td>
</tr>
<tr>
<td>$\rho_B$</td>
<td>Hazard ratio of disease reactivation in late latency after receiving IPT (ref: late latency not treated)</td>
<td>0 – 0.75</td>
<td>Model exploration</td>
</tr>
<tr>
<td>$\theta$</td>
<td>Combined rate of treatment efficacy, completion and test sensitivity</td>
<td>0.48 (0.3 – 0.7)</td>
<td>89 90 183 187</td>
</tr>
<tr>
<td>$\delta_A$</td>
<td>LTBI treatment rate in early latency</td>
<td>5% annually (1% - 25%)</td>
<td>Implementation-dependent</td>
</tr>
<tr>
<td>$\delta_B$</td>
<td>LTBI treatment rate in late latency</td>
<td>5% annually (1% - 25%)</td>
<td>Implementation-dependent</td>
</tr>
<tr>
<td>$\delta_S$</td>
<td>LTBI treatment rate for susceptible individuals</td>
<td>0% annually (0% - 25%)</td>
<td>Implementation-dependent</td>
</tr>
</tbody>
</table>

**Table 5 Model parameters**  
Presentation of the parameter values. The figures in brackets indicate the ranges used for the sensitivity analysis.* This value leads to a reasonable ratio between incidence and prevalence.
4.7.3 One-way sensitivity analyses under different assumptions regarding the mechanism of action of IPT

Figure 18 represents the results of one-way sensitivity analyses realized under different assumptions regarding the mechanism of action of IPT (i.e. different values of $\rho_A$ and $\rho_B$). The upper left panel corresponds to the analysis presented in the main text.

Figure 18 One-way sensitivity analyses realized under different assumptions regarding the mechanism of action of IPT

The ranges considered for the parameter values are presented in Table 5. Values on the x-axis represent the optimal TB-incidence obtained by minimizing the number needed to treat. The vertical line indicates the result obtained with the baseline parameter set (see Table 5) under the different assumptions regarding the mechanism of action of IPT. Black (resp. white) rectangles correspond to parameter values that are lower (resp. higher) than the corresponding baseline value. The hatched rectangles indicate situations where the variation of the optimal incidence over the parameter range is not monotonic.

4.7.4 Multi-dimensional sensitivity analysis

Figure 19 is a scatter plot representing the results of the fully varied sensitivity analysis. Each of the 14 panels corresponds to the same sampling of 1,000 parameter sets, but the different parameters are represented on the x-axis.
Consideration of HIV-endemic settings

In order to observe how the model predictions would be affected by considering an HIV-endemic setting, we undertook analyses with parameter values to simulate populations with HIV prevalence. Specifically, we assumed that the risk of progression to active TB disease is higher for this population during both the early and late stage of latent infection. In particular, this corresponds to an increase in the values of the parameters $\gamma$ and $\nu$ (see Table 5 for descriptions). These parameters are then recalculated by using the HIV prevalence ($Prev_{HIV}$) and the relative risk of activation among HIV-infected individuals compared to that among HIV-uninfected individuals ($RR$), as follows:

$$\nu_{HIV} = Prev_{HIV} RR \nu + (1 - Prev_{HIV}) \nu,$$

$$\gamma_{HIV} = Prev_{HIV} RR \gamma + (1 - Prev_{HIV}) \gamma,$$

where $\nu_{HIV}$ and $\gamma_{HIV}$ denote the risks of progression to active disease for an HIV-endemic setting.
The relative risk $RR$ is known to be around 26 according to the World Health Organization.\textsuperscript{3}

Figure 20 presents the results of our analysis when we assume a relative risk $RR$ of 26 and for a very high HIV prevalence of 26%, which corresponds to that in the country with the highest HIV prevalence in the world: Swaziland.

![Figure 20 Results associated with a high HIV-endemic setting](image)

We observe the same U-shape phenomena as that reported in absence of HIV infection. However, the model suggests that the TB-incidence corresponding to the optimal use of IPT is much higher when HIV is endemic, reaching 3,767 new cases/100,000/year when considering a high HIV prevalence of 26%. We also note that the associated NNT is much lower than in the absence of HIV infection, suggesting that it becomes more efficient to use IPT when HIV is endemic than in absence of HIV. This result is in agreement with previous findings that demonstrated that the NNT for IPT is lower when the baseline risk of TB is higher.\textsuperscript{89} Next, we considered various levels of HIV prevalence and observed the associated optimal TB incidences for IPT use, as well as the corresponding NNT (Figure 21). This analysis confirms the previous finding that the optimal TB incidence for IPT use increases with HIV prevalence while the associated NNT decreases.
Figure 21  Optimal TB incidence and associated NNT over HIV prevalence

Finally, we wanted to explore alternate scenarios regarding the relative risk of activation among HIV-infected individuals compared to that among HIV-uninfected individuals ($RR$), by considering different relative risks for the early and late latency compartments. While it was shown that HIV infection increases the risk of TB activation after recent infection,\textsuperscript{13, 14} as well as the risk of late reactivation,\textsuperscript{188, 189} it remains unclear whether these two risks are affected in the same way. Accordingly, we performed an additional analysis where different relative risks apply to the early and late latency compartments.

Figure 22 presents the optimal TB incidence obtained when the relative risks in early latency and that in late latency are varied separately (between 1 and 26) and when considering an HIV prevalence of 26%. We observe that the relative risk that applies to the early latency has a much higher impact than that applying to the late latency compartment. This suggests that the impact of HIV infection on the efficiency of IPT is mostly caused by the fact that HIV-infected individuals present a higher risk of TB activation after recent infection.
Figure 22 Optimal TB incidence obtained under various scenarios regarding the relative risk of TB among HIV-infected individuals compared to that among HIV-uninfected individuals. $RR_A$ corresponds to the relative risk that applies to the early latency compartment ($L_A$) while $RR_B$ corresponds to the relative risk that applies to the late latency compartment ($L_B$). The bottom-left corner point ($RR_A = RR_B = 1$) corresponds to our baseline situation in absence of HIV infection. The top-right corner point ($RR_A = RR_B = 26$) corresponds to the situation studied previously, with detailed results reported in Figure 20.
5 Optimally capturing latency dynamics in models of tuberculosis transmission

The sensitivity analyses presented in Chapter 4 underlined the importance of refining the parameter values used to simulate TB natural history, especially those characterising the dynamics of progression from latent infection to active disease. Even more fundamental than employing accurate parameterisation is using appropriate model structures to conceptualise LTBI. The fact that systematic registering of data on close contacts of active pulmonary TB patients has become increasingly common in developed countries provides a great opportunity to update the methodology surrounding LTBI modelling.

In particular, two studies from Amsterdam (the Netherlands) and Victoria (Australia) have recently produced estimates for the risk of active TB in infected individuals over time since infection. Although such analyses have provided important epidemiological insights into the dynamics of progression to active disease, the implications of their findings for TB modelling remain to be appraised. This Chapter presents an exploration and evaluation of the different methodological approaches used to simulate LTBI in previous TB modelling studies. This exercise combined the data published in the Dutch and Australian studies to obtain a comprehensive profile of the dynamics of reactivation in infected individuals. This merged dataset was used to determine whether the dynamics produced by the previously employed model structures correspond to those observed empirically. The content of this Chapter is a reproduction of the manuscript published in the journal *Epidemics*.190
5.1 Abstract
Although different structures are used in modern tuberculosis (TB) models to simulate TB latency, it remains unclear whether they are all capable of reproducing the particular activation dynamics empirically observed. We aimed to determine which of these structures replicate the dynamics of progression accurately. We reviewed 88 TB-modelling articles and classified them according to the latency structure employed. We then fitted these different models to the activation dynamics observed from 1,352 infected contacts diagnosed in Victoria (Australia) and Amsterdam (Netherlands) to obtain parameter estimates. Six different model structures were identified, of which only those incorporating two latency compartments were capable of reproducing the activation dynamics empirically observed. We found important differences in parameter estimates by age. We also observed marked differences between our estimates and the parameter values used in many previous models. In particular, when two successive latency phases are considered, the first period should have a duration that is much shorter than that used in previous studies. In conclusion, structures incorporating two latency compartments and age-stratification should be employed to accurately replicate the dynamics of TB latency. We provide a catalogue of parameter values and an approach to parameter estimation from empiric data for calibration of future TB-models.

5.2 Introduction
TB is a major health issue with 10.4 million active cases and 1.8 million deaths worldwide in 2015. Furthermore, around one quarter of the world’s population is estimated to be infected with TB, representing a huge reservoir of potential disease. Accordingly, fully understanding latent TB infection is crucial for assessing the future epidemic trajectory and designing effective TB control policies. Despite this, much reinfection occurs in high incidence cohorts, hampering accurate estimation of latency dynamics. Therefore, insights into the activation dynamics following a single infection episode of Mycobacterium tuberculosis provided by recent studies in very low transmission settings are particularly valuable. These works provide detailed information on patterns of activation, highlighting that most active cases occur within the first few months of infection.

Mathematical modelling has informed TB control programs by simulating interventions, or by explaining the mechanisms underlying observed epidemiological trends, yet little is known about whether such modelling has been able to capture latency dynamics accurately. In the past, TB models have been constructed to capture the lifelong probability of disease and, although some models allowed for marked differences between the early and late dynamics of infection, estimates for the associated parameters have not been fit closely to longitudinal data. Despite this, it has been shown that when modelling infectious diseases, it is critical to employ appropriate distributions of latent periods. Focusing on emerging infectious diseases,
Wallinga and Lipsitch further demonstrated that capturing the mean of the generation times is not sufficient to characterise transmission accurately, as the shape of the distribution of the generation intervals also plays a critical role in infection dynamics.\textsuperscript{194} Although TB is an ancient disease, its epidemiology is continuously evolving. In particular, changes in TB epidemiology in response to emerging phenomena, such as introduction of drug-resistant forms of TB or stronger control programs, are likely to affect the shape of the generation time distribution. Therefore, the recent detailed characterisation of TB activation dynamics represent a valuable opportunity to review and improve modelling practices for the simulation of TB latency.

Compartmental dynamic transmission models – the most common type of TB mathematical model – simulate TB latency with various levels of complexity. While some modellers employ a single latency compartment that precedes the active disease compartment,\textsuperscript{195,196} others incorporate a second latency compartment in order to capture two different rates of progression from latent infection to active disease.\textsuperscript{197-199} When two latency compartments are incorporated, they can either be positioned in series or in parallel, involving different underlying assumptions regarding the progression pathways to active disease. First, the serial structure implies that newly infected individuals remain at high risk of disease during the initial phase and then, if TB activation has not occurred, they transition to another compartment where their risk of developing active TB is reduced. By contrast, with a parallel compartmental structure, the underlying assumption is that a proportion of infected individuals belong to a high-risk category, while the remainder are at lower risk of TB disease. While TB modelling has been used extensively for over 40 years, it remains unclear which of these structures are best adapted to the natural history of TB.

In this study, we aim to determine the most appropriate model structures to simulate TB latency and provide estimates for the parameters associated with these structures across different age categories. We use the distribution of the estimated times from infection to TB activation in 1,352 infected contacts of individuals with active pulmonary TB from Victoria (Australia) and Amsterdam (Netherlands) to calibrate the latency structures of different candidate models to the dynamics observed in the data.

5.3 Methods

5.3.1 Literature review

Our search was based on the literature review of mathematical and economic TB modelling articles provided by the TB Modelling and Analysis Consortium, available online at http://tb-mac.org/Resources/Resource/4 (see Section 5.7.1 for more details). From this database we identified all 88 publications reporting the use of a deterministic compartmental transmission dynamic model. All selected papers were reviewed independently by two authors (RR, JMT) who classified the manuscripts according to the structure used to model TB latency. These two
independent investigations led to the same classification which is presented in Section 5.7.1 (Table 7).

5.3.2 Analytical solution
For each latency structure found in the literature, we associated a basic dynamic model comprised of the latency structure in combination with compartments representing susceptibility to infection and active disease. We then found analytical solutions for the TB activation dynamics corresponding to each model. Namely, considering that individuals were infected at time $t = 0$, we determined the proportion $I(t)$ of infected individuals that had developed active TB after each time $t$ $(t \geq 0)$. Analytical expressions are also presented for the total proportion of infected individuals progressing to active disease, obtained by calculating the limit of $I(t)$ as $t$ approaches plus infinity. The detailed method used to obtain the analytic solutions is described in Section 5.7.

5.3.3 Data used to calibrate the models
The models described above were calibrated to individual data on close contacts of individuals with active pulmonary TB notified in the Australian state of Victoria from January 2005 to December 2013. These data are derived from a very low endemic setting and were described in detail by Trauer et al. They consist of 613 infected contacts of whom 67 (10.9%) developed active TB during the study period. To enhance our dataset, we also used the published data on close contacts of pulmonary TB patients from Amsterdam (Netherlands) notified between 2002 and 2011, as reported by Sloot et al. These data include 739 infected individuals, of whom 71 (9.6%) developed active TB. The detailed approaches used to determine both dates of infection and activation in individuals in the two studies are presented in the respective manuscripts. The activation times measured in these data were used to calibrate the different models. In order to validate our approach involving merging of two datasets, we present a comparison of the estimates obtained from the separate fittings to the two datasets (Section 5.7.8.2). The approach used to extract data from Sloot and colleagues’ article is described in detail in Section 5.7.8.1, along with a validation analysis of the extraction method while the distribution of the times to activation measured in the two datasets (Victoria and Amsterdam) is presented in Figure 30.

Trauer et al. also proposed an imputation method which takes into account the censorship for migration, death, and preventive treatment. We used this approach, which is associated with higher estimates concerning the risk of TB activation, in a supplementary analysis.

5.3.4 Model fitting
Model fitting to data was made by building the survival likelihood defined as follows. For a given model associated with a given set of parameters, $\theta$, we obtain an analytical survival function $S_\theta(t)$ which represents the probability that activation has not occurred yet at time $t$ given that infection occurred at $t = 0$. This function is associated with a hazard function $\lambda_\theta(t)$ defined by
\[ \lambda_\theta(t) = -S'_\theta(t)/S_\theta(t) \], characterising the chance that progression to active TB occurs at precisely time \( t \), given survival up to that time. Then, for each infected case \( i \) of our dataset, for whom \( t_i \) designates the time of either TB activation or end of follow-up, we define an individual likelihood component by \( L_{\theta,i} = S_\theta(t_i) \) if the case was not known to develop active TB; and \( L_{\theta,i} = \lambda_\theta(t_i) \times S_\theta(t_i) \) if the case effectively activated TB at time \( t_i \). Finally, we aim to maximise the multi-dimensional likelihood obtained by multiplying all the individual likelihood components together: \( L_\theta = \Pi_i L_{\theta,i} \). This problem is equivalent to maximising the following log-likelihood that we define as the fitting score: \( FS_\theta = \Sigma_i \log(L_{\theta,i}) \).

Another fitting method was used for validation and when the data did not allow for the survival likelihood to be utilised. Specifically, a least squares optimisation was performed to minimise the distance between the survival curves generated by the data and by the model. The time-points considered when performing this optimisation were equally spaced by one day and ranged between 0 and the maximal time \( t_i \) measured in the data.

The two methods introduced above are conceptually different. In effect, the survival likelihood approach searches for the set of model parameter values that maximises the probability of observing the data, given a particular model and a particular parameter set. In contrast, the least squares optimisation is based on a measure of a distance between two curves: the activation curve observed from the data and the one produced by a model. Although these two approaches are fundamentally distinct, they are both forms of optimisation applied to the model’s parameter values. This optimisation is based on an iterative method which allows the parameters to vary in a multi-dimensional space, from which we retain only the parameter set that yields the optimal measure, i.e. the greatest likelihood (for the probabilistic approach) or the smallest distance (for the least squares method). This process was obtained using R v.3.3 and its incorporated function “constrOptim”.

Model fitting was performed separately using three age categories (“<5 years old”, “5 to 14 years old” and “≥15 years old”) in addition to a pooled analysis including the whole population. In order to fully explore the parameter spaces and to report all acceptable parameter sets, we used a Metropolis-Hastings algorithm presented in detail in Section 5.7.5.

5.4 Results

5.4.1 Literature review

From our review of 88 publications related to TB modelling, we found that six different compartmental structures had been employed to model TB latency and these form the basis of the following analysis. The six models are represented in Figure 23, along with the labels used for the associated parameters. The level of complexity ranges from a model incorporating no latency
compartment (Model 1) to models based on two latency compartments positioned either in series (Models 4 and 5) or in parallel (Model 6). Some structures incorporate a bypass from the susceptible compartment to the active disease compartment, allowing for consideration of instantaneous activation of TB disease after exposure (Models 1, 3 and 5). Table 7 reports our classification of the 88 reviewed studies according to the latency structure employed.

![Model Diagrams](image)

**Figure 23 Representation of the different model structures**
Solid lines represent progressive transitions between compartments that are parameterised with rates, while dashed lines represent instantaneous transitions between compartments that are associated with proportions. The flows related to natural death are not represented and are associated with the natural mortality $\mu$.

### 5.4.2 Model calibration

Figure 24 presents the dynamics of TB activation obtained from each model when optimally calibrated to our data (see Section 5.3.4 for fitting approach). Only the models incorporating two latency compartments (Models 4, 5 and 6) suitably replicate the dynamics of TB activation. Model 1, which is not shown, does not contain any free parameters and assumes that all infected patients progress to active disease immediately after exposure. This is not compatible with our data nor our knowledge of the lifelong risk of TB disease in infected individuals.$^{10,11}$ Both Models 2 and 3 produce unreasonably poor fits to the data. In Section 5.7.2.3 we show that the equations describing Models 2 and 3 only involve a single exponential function, which is not sufficient to replicate the two distinct patterns observed in the dynamics of activation—a high risk of disease activation over the first few months, followed by a dramatically lower risk in a second phase. In contrast, in Models 4, 5 and 6, which include two latency compartments, the activation dynamics are driven by two exponential components that are associated with two independent growth rates,
leading to accurate replication of the patterns empirically observed for each age category. The fitting scores (see Figure 24) for Models 4, 5 and 6 indicate that none provides a significantly better fit than the others; however, Model 5 presents a higher level of complexity than Models 4 and 6, as it involves estimating one additional parameter. Since the inclusion of this parameter did not improve model fitting, we consider that it is unnecessary to employ this structure. This proposition is strongly supported by a more detailed analysis of Model 5 where different approaches all support that the additional parameter does not improve fitting (see Section 5.7.6). Accordingly, the remainder of our analysis relates only to Models 4 and 6.

**Figure 24  Calibrations obtained with the different models for the percentage of active TB among infected individuals over time since infection**

The black lines and grey shade represent the estimates (central and 95% CI) obtained from the Kaplan-Meier analysis of our data. The blue line represents the percentage of active TB over time obtained from the different models, when optimally calibrated with the survival likelihood method. The x-scales were chosen in order to allow for a decent visualisation of the early stages of infection and do not cover the entire time windows corresponding to the dataset. Fitting was realised by maximising the fitting score (FS).

Table 6 presents the parameter values (with units of days$^{-1}$) obtained from the calibration of Models 4 and 6 to the data. We observe that the rate of re-activation ($\nu$) is much lower in the age
category “<5 years old” than in the other age categories for both Model 4 and Model 6. In contrast, the rate of rapid progression is higher in the “<5 years old” category than in the other age categories when considering Model 4; and when considering Model 6, the proportion of infected individuals experiencing a high risk of TB disease (1 − \(g\)) is higher for children than for the other categories (35% for “<5 y.o.”, 19% for “5 to 14 y.o.”, 5% for “15 y.o. and more”, and 9% for all ages together).

\[
\begin{array}{cccc}
\varepsilon & \kappa & \nu & g \\
\hline
\text{Model 4 All ages} & 1.1e^{-3} & 1.0e^{-2} & 5.5e^{-6} & \\
& (8.4e^{-4} - 1.5e^{-3}) & (8.5e^{-3} - 1.4e^{-2}) & (2.5e^{-6} - 1.1e^{-5}) & \\
& <5 y.o. & 6.6e^{-3} & 1.2e^{-2} & 1.9e^{-11} & \\
& & (4.4e^{-3} - 9.5e^{-3}) & (8.5e^{-3} - 1.8e^{-2}) & (5.0e^{-9} - 1.6e^{-5}) & \\
& 5-14 y.o & 2.7e^{-3} & 1.2e^{-2} & 6.4e^{-6} & \\
& & (1.7e^{-3} - 3.9e^{-3}) & (7.9e^{-3} - 1.6e^{-2}) & (6.7e^{-7} - 1.9e^{-5}) & \\
& \geq 15 y.o & 2.7e^{-4} & 5.4e^{-3} & 3.3e^{-6} & \\
& & (1.6e^{-4} - 5.1e^{-4}) & (3.5e^{-3} - 1.1e^{-2}) & (1.9e^{-6} - 1.0e^{-5}) & \\
\hline
\text{Model 6 All ages} & 1.1e^{-2} & - & 5.5e^{-6} & 0.91 \\
& & (9.2e^{-3} - 1.5e^{-2}) & (3.4e^{-6} - 1.0e^{-5}) & (0.89 - 0.93) & \\
& <5 y.o & 1.9e^{-2} & - & 3.4e^{-11} & \\
& & (1.2e^{-2} - 2.5e^{-2}) & (2.7e^{-9} - 2.0e^{-5}) & (0.55 - 0.73) & \\
& 5-14 y.o & 1.4e^{-2} & - & 6.4e^{-6} & 0.91 \\
& & (9.4e^{-3} - 1.8e^{-2}) & (8.0e^{-7} - 2.2e^{-5}) & (0.75 - 0.86) & \\
& \geq 15 y.o & 5.6e^{-3} & - & 3.3e^{-6} & 0.95 \\
& & (3.8e^{-3} - 9.6e^{-3}) & (7.3e^{-7} - 9.3e^{-6}) & (0.94 - 0.97) & \\
\end{array}
\]

Table 6 Parameter estimates
Calibration issued from the survival likelihood maximisation applied to the merged dataset (Victoria and Amsterdam data). Point estimates correspond to the parameters maximising the likelihood while values into brackets indicate the narrowest interval containing 95% of the accepted values during the Metropolis-Hastings simulation. Rates are presented as daily values.

The lifelong risk of TB activation in infected individuals can be calculated analytically for the different models (see Section 5.7.2.3). The parameter values reported in Table 6 for Models 4 and 6 correspond to total proportions of activation ranging between 10% (“15 y.o. and more”) and 32% (“<5 y.o.”).

Given the very low values observed for the rate of reactivation (\(\nu\)) in the “<5 years old” category, we undertook an additional analysis in order to explore the possibility of the absence of late reactivation in this category. In this analysis, Models 4 and 6 were fitted to the data under the constraint that \(\nu = 0\), with both models found to perform equally well in absence of reactivation.

Figure 25 presents the corresponding simplified models as well as the best fits obtained. A further exploration of the contribution of endogenous reactivation versus primary activation is presented in Section 5.7.3 for Model 4 and for the different age categories. This analysis demonstrates that endogenous reactivation contributes very little to the burden of active TB, especially in young individuals (“<5 years old” and “5 to 14 y.o.”). Although this contribution is more substantial in the “\(\geq 15\) years old” category, we estimate that only 1% of infected individuals of this category
would have progressed to active disease transitioning from compartment $L_B$ after five or less years from infection (using equation 23 in Section 5.7.3).

Figure 25 Simplified model structures adapted to simulate TB latency in young children (<5 years old)  

Here, it is assumed that progression from the previous compartments $L_B$ of Model 4 and Model 6 to active disease $I$ cannot occur. The compartment $L_B$ therefore becomes a protected state which is labelled $R$ in this illustration. Fitting was realised by maximising the fitting score (FS).

Our analysis of the analytical solutions associated with Model 4 and Model 6 demonstrated that the two expressions coincide if the parameter values of the two models satisfy the following relationships:

$$
\varepsilon_6 = \varepsilon_4 + \kappa_4 \\
\nu_6 = \nu_4 \\
g_6 = \frac{\kappa_4}{\kappa_4 + \varepsilon_4 - \nu_4}
$$

where the subscripts indicate to which of Models 4 or 6 the parameters apply. This finding indicates that the dynamics of activation simulated by the two models are identical, differing only in the value of the parameter values that should be applied.

### 5.4.3 Probability distribution of parameters

We used a Bayesian framework to infer the posterior distributions for the parameters in the model. Uniform priors were used and tools of Bayesian inference applied including Markov Chain Monte-Carlo exploration using the Metropolis-Hastings acceptance algorithm. The resulting posterior distributions for the different parameters of Models 4 and 6 are presented (Table 6). Proposed statistical distributions that could be used to generate similar sets of parameters are available in Section 5.7.7, along with the posterior distributions obtained for all parameters. The acceptable ranges of values for the parameter $\nu$ are wide for the category “<5 y.o.”, due to the small number of reactivation cases in our dataset. However, our analysis showed that the rate of
reactivation is limited by an upper bound of around $2.3e^{-5}$ in all categories, which represents a relatively small annual risk of re-activation of 0.8%.

By analysing the distributions of each of the retained parameter sets in pairs, we observed a collinearity between the parameters $\kappa$ and $\varepsilon$ for Model 4. This correlation (represented in Figure 26) suggests that when individuals are assumed to stabilise infection more rapidly ($\kappa$ increases), the rate of rapid progression to TB disease ($\varepsilon$) tends to increase to compensate. This affine relationship between parameters $\kappa$ and $\varepsilon$ is also described through a formal mathematical analysis (Section 5.7.10.1).

**Figure 26  Representation of the collinearity observed between the parameters $\kappa$ and $\varepsilon$ for Model 4**

The red dots represent the 10,000 accepted parameter sets obtained from the Metropolis-Hastings simulation. The black line represents the affine model approximating the data with a least square minimisation.

Another result provided by the Metropolis-Hastings simulation was the distribution of the average duration spent in the first latency compartment for Model 4. This quantity was obtained via the formula $\frac{1}{\kappa + \varepsilon + \mu}$ where $\mu$ represents the natural death rate. Figure 27 presents the distribution of these durations for the different age categories. The average duration spent in the first latency compartment is estimated at 82 days for all age categories combined, this duration being shorter for children (52 days for “<5 y.o.” category) than for older individuals (70 days for “5 to 14 y.o.” and 146 days for “≥15 y.o.”).

**Figure 27  Distribution of the times spent in the first latency compartment $L_A$ for model 4**

Distribution associated with 10,000 accepted parameters sets from the Metropolis-Hastings simulation.
5.4.4 Validation and sensitivity analyses

Our findings were consistent when we employed an alternate fitting method (least squares minimisation), performed separate fits for each dataset (Victoria and Amsterdam) instead of the single merged dataset, or used alternate extraction methods for the data of Sloot et al. When fitting Model 3 using least squares minimisation, we obtained a model calibration that differed from that obtained with the survival likelihood method (Figure 35). However, while this second calibration allowed for a better simulation of the late stages of latency compared to the baseline fitting method (Figure 24), it completely failed to capture the early dynamics of activation. More details about the different sensitivity analyses are available in Section 5.7.

Finally, by using imputed data as described in Trauer et al. accounting for the censorship for migration, death, and preventive treatment and therefore associated with higher estimates for the risk of TB disease\(^1\), our conclusions regarding optimal model selection remained unchanged, while we obtained slightly different optimised parameter values (see Section 5.7.8.4). In particular, in Model 4, imputation led to a slight increase in the rate of rapid progression (\(\varepsilon\)) combined with a slight reduction in the rate of transition towards the late latency compartment (\(\kappa\)). Concerning Model 6, the best calibration to imputed data was obtained with a higher proportion of infected individuals transitioning to the high risk compartment (\(1 - g\)) while the rate of rapid progression (\(\varepsilon\)) was slightly reduced.

5.4.5 Comparison of our results with previous works

We reviewed the parameter values that had been employed in the previous studies incorporating the latency structures of Model 4 and Model 6 and compared these values to our estimates (see Section 5.7.9). Concerning Model 4, we found that the rate of progression from compartment \(L_A\) to compartment \(L_B\) (\(\kappa\)) was considerably lower than our estimate in all previous studies, which typically assume long periods spent in early latency (2 – 5 years). Similarly, the rate of fast progression to active TB (\(\varepsilon\)) used in the existing literature was much lower than our estimate. For Model 6, the proportion of slow progressors (\(g\)) found in previous works was close to our estimate, whereas the rate of fast progression (\(e\)) had been markedly underestimated. Finally, while the rate of slow progression to active TB (\(v\)) was generally underestimated in studies incorporating either structure (Models 4 or 6), two studies used point estimates that fall inside of the 95% CI we report, and nine other studies used parameter ranges overlapping our 95% CI.

5.4.6 Rapid estimation of the parameters for future works

A theoretical analysis of the equations governing the dynamic models allowed us to develop a method to estimate rapidly the different parameters of Models 4 and 6 from any dataset. This approach involves simple graphical measurements performed on the curve representing the proportion of active cases among infected individuals over time from infection (denoted \(\Gamma\)), such
as the curves represented in Figure 24. The detailed description and demonstration of the method is available in Section 5.7.10 and the main results are presented here. The profile of \( \Gamma \) can be decomposed into two phases (see Figure 24). The method consists of first measuring the initial slope of \( \Gamma \) (denoted \( s_0 \)) as well as the characteristics of a tangent to \( \Gamma \) on a point situated at the beginning of the second rise phase (slope denoted \( s \), and y-intercept denoted \( y_0 \)). Then, estimates for the different parameters (\( \hat{\epsilon}, \hat{k}, \hat{v} \) and \( \hat{g} \)) can be obtained by using the three measures \( (s_0, s \) and \( y_0) \) as follows:

For Model 4:  
\[
\hat{\epsilon} = s_0 \quad \hat{k} = \frac{s}{y_0} - \hat{\epsilon} - \mu \quad \hat{v} = \frac{s(\hat{k}+\hat{\epsilon}+\mu)}{\hat{k}}
\]

For Model 6:  
\[
\hat{\epsilon} = \frac{s_0}{y_0} - \mu \quad \hat{\nu} = \frac{s_0 s}{s_0 - y_0(s_0 + \mu)} \quad \hat{g} = \frac{\hat{\epsilon} - s_0}{\hat{\nu} - \hat{\nu}}
\]

where \( \mu \) designates the natural mortality rate.

5.5 Discussion

5.5.1 Main contributions of the study

In this study, we determine the most appropriate model structures for accurately simulating TB latency. We demonstrate that of the structures employed in the past, only those that incorporate two compartments for latent infection are able to reproduce the specific dynamics of TB activation. Such approaches therefore involve two different levels for the rate of activation, allowing for more TB cases to occur after recent infection than through late reactivation. This work also provides a detailed and flexible catalogue of parameter values associated with the retained model structures, that was validated by the use of two independent fitting methods leading to similar estimates and that highlighted marked gaps with parameter values employed in previous works. This study may become a reference for calibration of future TB models and our approach involving estimations with and without age stratification will allow our findings to be directly applied whether models are age-structured or not.

5.5.2 Serial versus parallel structure

We demonstrate that the two compartments required to model TB latency could be placed either in series or in parallel, and would lead to identical activation dynamics. The difficulty in making this distinction between the two models is unfortunate because they reflect two alternate biological mechanisms that could explain the higher burden of disease observed after recent infection, each leading to different recommendations for TB prevention strategies. First, the serial structure models a decreasing risk of activation over time in every individual, indicating that preventive care should be targeted at the most recent infections as a priority through interventions such as contact tracing. On the other hand, the parallel structure suggests that individual predispositions may make some infected individuals more or less likely to develop disease,
regardless of the time from infection. If this second scenario was verified with epidemiological data, these results would suggest that identifying and finding priority populations could dramatically enhance efficiency of interventions. Some factors such as HIV-infection, diabetes or smoking are already known to enhance the risk of TB activation, although our parameter estimates under the parallel structure scenario suggest that around 9% of infected individuals would belong to a high-risk group in which the risk of TB activation would be as high as 2,000-fold that of the low-risk group. Alternatively, for the series structure of the latency compartments, rapid identification and early treatment of infected people would be the priority.

5.5.3 Age dependency
Our estimations highlight important discrepancies between age categories, with parameter estimates for young children (<5 years old) differing markedly from the other age categories. In particular, our study suggests that for young children, the rate of disease activation in the high-risk population (early latency for serial structure or high-risk group for parallel structure) is much greater than for 15+ year olds. In contrast, among the lower risk population (late latency for serial structure or low risk group for parallel structure), young children seem to be at lower risk of activation than the other individuals. These findings indicate that the youngest infected population presents a much higher risk of TB activation early after infection, while their risk of activation reduces dramatically in the later stages of infection. Previous works have already identified age as an important factor influencing the natural history of TB, and our analysis brings additional insight that reinforces the importance of providing young children with early preventive treatment for infection as late treatments would be useless. By revealing such age-specific characteristics, our study also implies that future TB modelling works should incorporate age-stratified structures in order to replicate TB activation dynamics accurately. Our analysis also demonstrates that simplified model structures incorporating no reactivation are adapted to simulate TB latency in the “<5 years old” category, suggesting that a significant proportion of infected children will never reactivate. Depending on the model structure employed, these young individuals could either become immune after some duration of infection (serial structure) or be protected immediately after infection (parallel structure).

5.5.4 Comparison with previous works
When two latency compartments are positioned in series, the rate of transition from early latency to late latency reflects the period for which individuals remain at high risk of disease. We estimate that the average early latency period is 52, 70 days and 146 days, for child (<5), adolescents (5-14) and adults, respectively. Most previous works employing the serial structure have used 5 years to define early latency, based on a previous convention to define primary disease versus endogenous disease, and therefore may have greatly overestimated the actual duration of high risk. Our review of articles showed that the models with these long durations at high risk
were also associated with lower rates of fast progression to active disease than the rates estimated from our study which compensates for the long early latency and leads to similar overall risks of activation over a lifetime. However, we have shown that our approach, which has dramatically shorter durations for the time spent in early latency and at high risk, is required in order to reproduce the profile of activation dynamics accurately.

Our estimate for the rate of late reactivation corresponds to a risk of 0.20 cases per 100 person-years for all ages, but is much lower among the ‘<5 years old’ category. However, although our analysis clearly highlights different patterns of reactivation by age, accurate estimation of the reactivation parameter for the ‘<5 years old’ category was limited by the small number of reactivation cases observed in this sub-group, which explains the wide variation in the associated confidence intervals. While previous works reported somewhat lower estimates for the late reactivation rate for all ages, ranging from 0.04 to 0.16 cases per 100 person-years, our findings suggest that these results can only be interpreted in the context of age mix in the studies, and we can speculate that some of this variability may be accounted for by different proportions of “<5 year olds” in the study populations. Detailed data by age are not available from previous works so formal analysis by age has not been possible. Another possible explanation for the difference between our estimate and previous values for the reactivation rate is that the definition of infection in our datasets may be more specific than what was used in previous studies. In particular, looser definitions for infection may include false positives which would tend to increase the number of persons “at risk” and therefore reduce the inferred reactivation rate.

While our study shows that previous TB models have not always incorporated the optimal structure or parameterisation to account for the specific patterns observed in TB activation dynamics, the potential consequences of using suboptimal approaches remains undetermined. However, an analysis by Dowdy and colleagues of the most influential parameters to TB dynamics demonstrated that the parameters describing early latency are among those with the greatest impact on model predictions of steady-state TB incidence. This suggests that it is critical to reproduce early dynamics of TB infection closely in order to provide accurate insight into the epidemics trajectory. Therefore, future works investigating the consequences of employing inappropriate model structures or parameterisation are needed.

5.5.5 Potential for other future works

Our analysis was based on data from very low TB endemic settings where re-infection is expected not to play an important role. This allowed our estimation to focus on the potential progression to active disease following a single infection event and to avoid the confusion that would emerge from repeated infections when estimating the time from infection to activation. In the event that similar datasets became available in higher endemic settings, a follow-up study could be
conducted by integrating our “re-infection free” parameterisation into a model that would include an additional pathway for re-infection during latency. By fitting such a model to the new data, the re-infection parameter could then be estimated, thus providing valuable insights into the relative contribution of re-infection compared to the risk of first infection.

It is important to remember that the calibrations presented in this study are associated with the specific models that we selected. Accordingly, such estimates could not directly be used in models that incorporate a different structure or that do not belong to the category of deterministic compartmental transmission dynamic models. However, provided that both the structure and the nature of the model correspond to those used in this study, our work could also be used to re-estimate parameters associated with many different settings. To this end, we provide a step-by-step method which allows for rapid estimation of the different model parameters by performing simple measures on the reactivation failure curve. Consequently, our study could also be used to inform models in settings that present different characteristics, such as high HIV-endemic settings where the activation dynamics are known to be different.14,185

One natural limitation of this work is that it is linked to the epidemiological challenges of timing infection and reactivation accurately. However, the estimated durations that we use in this study are derived from two recently published works that employed rigorous definitions for both dates of infection and activation.10,11

5.6 Conclusions

Only models employing two latency compartments are able to reproduce TB latency dynamics accurately. We provide parameter values to optimally simulate epidemiological observations in such models along with an approach to obtaining such values from future epidemiological studies. Our analysis also reinforces the importance of age-stratification for capturing the dramatic differences between age groups in patterns of reactivation, which imply fundamental biological differences between age groups. However, we also demonstrate that data of the type this analysis is based upon cannot be used to determine the ideal configuration for the two latency compartments.

5.7 Supplemental material

5.7.1 Review of TB modelling studies

We used the database published by the TB Modelling and Analysis Consortium (TB-MAC) publicly available at http://tb-mac.org/Resources/Resource/4 as a basis for our review. This database consists of a review of all “existing academic papers that describe mathematical and economic modelling of TB”. The methods for the search are available at the website above, and
consist of a database search in conjunction with a review of the personal libraries of five leading international TB modellers.

An analysis of this database is presented in detail in James Trauer’s thesis entitled “Mathematical Modelling for Programmatic Responses to Tuberculosis in the Asia-Pacific”, publicly available at: https://minerva-access.unimelb.edu.au. In this thesis, a more general summary that also includes models that are not based on ordinary differential equations is presented.

Among the publications listed in this library, we identified 88 publications that report the use of a deterministic compartmental transmission dynamic model governed by ordinary differential equations. All the selected papers were then reviewed independently by two of the authors (RR and JMT) who classified the manuscripts according to the structure used to model TB latency. The results of this classification are presented in Table 7. A representation of the corresponding model structures is available in Figure 23.

<table>
<thead>
<tr>
<th>Model</th>
<th>Articles</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Naresh 2009,201 Naresh 2005,201</td>
</tr>
<tr>
<td>5</td>
<td>Wu 2010,266</td>
</tr>
</tbody>
</table>

**Table 7** Classification of the different structures used in past studies to model TB latency
5.7.2 Analytical analysis

5.7.2.1 Generalization of the problem

The six latency structures found in the literature review can be obtained by using the same general model as follows:

Accordingly, we will solve the differential equations corresponding to the general model to obtain analytical solutions for all the above models.

Table 8 lists the different parameters associated with the model structures presented in Figure 28.

<table>
<thead>
<tr>
<th>Notation</th>
<th>Definition</th>
<th>Interval</th>
<th>Associated model(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$f$</td>
<td>Proportion of infected individuals activating TB immediately after infection.</td>
<td>$[0, 1]$</td>
<td>Models 3 and 5</td>
</tr>
<tr>
<td>$g$</td>
<td>Proportion of infected individuals transitioning to a low-risk compartment ($L_B$) immediately after infection.</td>
<td>$[0, 1]$</td>
<td>Model 6</td>
</tr>
<tr>
<td>$\epsilon$</td>
<td>Rate of progression to active TB from the high-risk compartment ($L_A$).</td>
<td>$[0, +\infty)$</td>
<td>Models 2, 3, 4, 5 and 6</td>
</tr>
<tr>
<td>$\kappa$</td>
<td>Rate of transition from the high-risk compartment ($L_A$) to the low-risk compartment ($L_B$).</td>
<td>$[0, +\infty)$</td>
<td>Models 4 and 5</td>
</tr>
<tr>
<td>$\nu$</td>
<td>Rate of progression to active TB from the low-risk compartment ($L_B$).</td>
<td>$[0, +\infty)$</td>
<td>Models 4, 5 and 6</td>
</tr>
</tbody>
</table>

Table 8 Parameters associated with the different models
5.7.2.2 System of equations

We consider that at time $t = 0$, a population of $N_L$ individuals becomes infected with TB. Accordingly, these individuals instantaneously progress to one of the three compartments $L_A, L_B$ or $I$ at time $t = 0$.

The differential equations associated with the three compartments corresponding to the infected statuses in the general model are as follows:

$$\begin{align*}
L_A'(t) &= -(\kappa + \epsilon + \mu)L_A(t), \quad (1) \\
L_B'(t) &= \kappa L_A(t) - (\nu + \mu)L_B(t), \quad (2) \\
I'(t) &= \nu L_B(t) + \epsilon L_A(t) \quad (3)
\end{align*}$$

where $'$ denotes differentiation with respect to time and $\mu$ represents the natural death rate. We do not apply this rate to the active disease compartment as we intend to record the cumulative number of cases newly arriving in $I$.

This system of equations is associated with the following initial conditions:

$$\begin{align*}
L_A(0) &= (1 - f - g)N_L, \quad (4) \\
L_B(0) &= gN_L, \quad (5) \\
I(0) &= fN_L. \quad (6)
\end{align*}$$

5.7.2.3 Analytical solution

The solution to equation (1) is obtained by direct integration:

$$L_A(t) = (1 - f - g)N_L e^{-(\kappa + \epsilon + \mu)t}. \quad (7)$$

The solution to the homogeneous equation associated with equation (2) is:

$$\tilde{L}_B(t) = Q e^{-\nu t}, \quad Q \in \mathbb{R}. \quad (8)$$

Then, using the variation of constants method, we obtain the following solution to equation (2):

$$\tilde{L}_B(t) = \frac{\kappa(1 - f - g)N_L}{\nu - \kappa - \epsilon} e^{-(\kappa + \epsilon + \mu)t}. \quad (9)$$

Note that $(\nu - \kappa - \epsilon)$ is non-zero as long as $\epsilon > \nu$, which is the case in our model as the rate of rapid progression from compartment $L_A$ is higher than the rate of re-activation from compartment $L_B$.

By combining equations (8) and (9) and by using the initial condition (5), we obtain:
An expression for $I'(t)$ comes directly by substituting equations (7) and (10) into equation (3):

$$I'(t) = (1 - f - g)N_L \left( e + \frac{\kappa \mu}{\nu - \kappa - \epsilon} \right) e^{-(\kappa + \epsilon + \mu)t} + \nu \left( gN_L - \frac{\kappa (1 - f - g) N_L}{\nu - \kappa - \epsilon} \right) e^{-(\nu + \mu)t}. \quad (11)$$

Finally, by integrating equation (11) and using the initial condition (6), we obtain an analytical expression for $I(t)$:

$$I(t) = N_L \left\{ (1 - f - g) \left( \frac{e}{\kappa + \epsilon + \mu} + \frac{\kappa \mu}{(\nu - \kappa - \epsilon)(\kappa + \epsilon + \mu)} \right) (1 - e^{-(\kappa + \epsilon + \mu)t}) + \frac{\nu}{\nu + \mu} \left( g - \frac{1 - f - g}{\nu - \kappa - \epsilon} \right) \left( 1 - e^{-(\nu + \mu)t} \right) + f \right\}. \quad (12)$$

Table 9 presents the equations governing the dynamics of activation for the six different models. For each model, the total proportion of infected individuals who progress to active disease is obtained by calculating the limit of $I(t)$ as $t$ approaches plus infinity. The analytical expressions describing this proportion are presented in Table 10.

<table>
<thead>
<tr>
<th>Model</th>
<th>Expression of $I(t)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$N_L$</td>
</tr>
<tr>
<td>2</td>
<td>$N_L \left( \frac{e}{\kappa + \epsilon + \mu} \right) (1 - e^{-(\kappa + \epsilon + \mu)t}) \right) + f$</td>
</tr>
<tr>
<td>3</td>
<td>$N_L \left{ (1 - f) \left( \frac{e}{\kappa + \epsilon + \mu} \right) (1 - e^{-(\kappa + \epsilon + \mu)t}) + \frac{\mu}{\nu + \mu} \left( \frac{1}{(\nu + \mu)(\kappa + \epsilon + \mu)} \right) - e^{-(\nu + \mu)t} \right}$</td>
</tr>
<tr>
<td>4</td>
<td>$N_L \left{ \left( \frac{e}{\kappa + \epsilon + \mu} + \frac{\mu}{(\nu - \kappa - \epsilon)(\kappa + \epsilon + \mu)} \right) \left( 1 - e^{-(\kappa + \epsilon + \mu)t} \right) + \frac{\mu}{\nu + \mu} \left( 1 - e^{-(\nu + \mu)t} \right) \right}</td>
</tr>
<tr>
<td>5</td>
<td>$N_L \left{ (1 - f) \left( \frac{e}{\kappa + \epsilon + \mu} + \frac{\mu}{(\nu - \kappa - \epsilon)(\kappa + \epsilon + \mu)} \right) (1 - e^{-(\kappa + \epsilon + \mu)t}) + \frac{\mu}{(\nu + \mu)(\kappa + \epsilon + \mu)} (1 - e^{-(\nu + \mu)t}) \right}$</td>
</tr>
<tr>
<td>6</td>
<td>$N_L \left{ (1 - f) \left( \frac{e}{\kappa + \epsilon + \mu} + \frac{\mu}{(\nu - \kappa - \epsilon)(\kappa + \epsilon + \mu)} \right) (1 - e^{-(\kappa + \epsilon + \mu)t}) + \frac{\mu}{(\nu + \mu)(\kappa + \epsilon + \mu)} (1 - e^{-(\nu + \mu)t}) \right}$</td>
</tr>
</tbody>
</table>

Table 9 Equations associated with the dynamics of activation for the six different models
Table 10 Analytical expressions for the proportion of infected individuals progressing to active disease

### 5.7.2.4 Equivalence between Model 4 and Model 6

In this section, we demonstrate that the dynamics of TB activation obtained from Model 4 and Model 6 are identical. Namely, we determine the relations that should be satisfied between the parameters of the two models in order to obtain the same expression for $I(t)$, i.e.

\[
N_L \left\{ \left( \frac{\epsilon_4}{\kappa_4 + \epsilon_4 + \mu} + \frac{\kappa_4 \nu_4}{(\nu_4 - \kappa_4 - \epsilon_4)(\kappa_4 + \epsilon_4 + \mu)} \right) \left( 1 - e^{-(\kappa_4 + \epsilon_4 + \mu)t} \right) + \frac{\nu_4 \kappa_4}{(\nu_4 + \mu)(\kappa_4 + \epsilon_4 - \nu_4)} \left( 1 - e^{-(\kappa_4 + \epsilon_4 - \nu_4)t} \right) \right\} 
= N_L \left( \frac{1 - g_6 \epsilon_6}{\epsilon_6 + \mu} \left( 1 - e^{-(\kappa_4 + \epsilon_4)t} \right) + \frac{\nu_6 g_6}{\nu_6 + \mu} \left( 1 - e^{-(\kappa_4 + \epsilon_4 + \mu)t} \right) \right),
\]

where the subscripts indicate to which of Models 4 or 6 the parameters apply.

Given that the natural death rate ($\mu$) must be the same for the two models, we directly obtain two relationships by comparing the exponential components of the two members of equation (13):

\[
\epsilon_6 = \kappa_4 + \epsilon_4, \tag{14}
\]

\[
\nu_6 = \nu_4. \tag{15}
\]

Then, by comparing the quantities that multiply the second exponential component in each member of equation (13), we obtain:

\[
\frac{\nu_6 g_6}{\nu_6 + \mu} = \frac{\nu_4 \kappa_4}{(\nu_4 + \mu)(\kappa_4 + \epsilon_4 - \nu_4)} \tag{16},
\]

which becomes

\[
g_6 = \frac{\kappa_4}{\kappa_4 + \epsilon_4 - \nu_4}, \tag{17}
\]

when using equation (15).

Finally, we can verify that the quantities multiplying the first exponential components in the two members of equation (13) are identical by using equations (14) and (17):
The parameter estimates presented in Table 6 (Section 5.4.2) for Model 4 and Model 6 were obtained by independent fitting, without using the equivalence equations presented in (14), (15) and (17). However, these equations have been used in a second phase to verify the consistency of the results between the two models.

### 5.7.3 Contribution of primary activation versus endogenous re-activation

When we employ the serial structure (Model 4) to simulate *M.tb* infection, we assume that TB latency is decomposed into two successive phases: a high-risk period represented by the compartment $L_A$ and a low-risk phase represented by the compartment $L_B$. While both phases represent pathways that can potentially lead to TB disease, their respective contribution to the burden of active TB may differ.

Employing a similar analysis to that presented in section 2, we determine analytical expressions for the cumulative number of active TB cases that are due to primary activation and endogenous reactivation respectively. For example, in order to calculate the cumulative number of individuals progressing from compartment $L_A$ to $I$ (primary activation) over time, we need to solve the system made of equations (1), (2) and

\[
I'(t) = \epsilon L_A(t).
\]

We obtain the following expressions for the separate contributions of primary activation ($I_{primary}$) and endogenous reactivation ($I_{endogenous}$) to the burden of active TB in Model 4:

\[
I_{primary}(t) = N_L \left\{ \frac{\epsilon}{\kappa + \epsilon + \mu} \left( 1 - e^{-\left(\kappa + \epsilon + \mu\right)t} \right) \right\},
\]

\[
I_{endogenous}(t) = N_L \left\{ \frac{\kappa \nu \mu}{\left(\nu - \kappa - \epsilon\right)\left(\kappa + \epsilon + \mu\right)} \left( 1 - e^{-\left(\kappa + \epsilon + \mu\right)t} \right) + \frac{\nu \kappa}{\left(\nu + \mu\right)\left(\kappa + \epsilon - \nu\right)} \left( 1 - e^{-\left(\nu + \mu\right)t} \right) \right\}
\]

Figure 29 represents these respective contributions for the different age categories.
5.7.4 Distribution of the time to activation: data versus model prediction

The distribution of the time to TB activation is presented in Figure 30. The histogram represents the results extracted from the dataset gathering patients from Victoria (Australia) and Amsterdam (Netherlands). The solid line shows the corresponding model prediction based on the best fit obtained with Model 4, 5, or 6.
5.7.5 Details about the Metropolis-Hastings algorithm

5.7.5.1 General approach
When fitting models to the data, we used a Metropolis-Hastings algorithm based on the likelihood $L_{\theta}$ defined in Section 5.3.4 in order to fully explore the parameter spaces and to report all acceptable parameter sets. At each iteration, a new candidate parameter set $\theta_j$ is randomly generated by using a multivariate normal distribution centered at the latest accepted parameter set $\theta_r$. Then, the new parameter set $\theta_r$ is accepted with the probability $\min(1, \frac{L_{\theta_j}}{L_{\theta_r}})$. The algorithm stops once 10,000 parameter sets have been accepted.

5.7.5.2 Technical details
At each iteration, we use a multivariate Gaussian distribution to generate a new candidate parameter set. This distribution is centred at the parameter set obtained from the previous iteration. The standard deviations associated with each parameter are calculated such that 95% of the generated values fall in a range of “reasonable width”. This approach is adopted because too large a range would lead to very low acceptance rates while too narrow a range would not allow for complete exploration of the parameter space. Then, the widths of the parameter ranges are determined according to the order of magnitude of each parameter value that was obtained during the optimization exercise. Early runs of the algorithms allowed manual adjustment of widths, by visualizing the parameter moves during the simulations. We used the same algorithm tuning for all age categories.

The widths retained for the simulations are reported in Table 11.

Figure 30 Distribution of the time to activation: data versus model prediction
Parameter | \( f \) | \( g \) | \( \kappa \) | \( \epsilon \) | \( \nu \)  
--- | --- | --- | --- | --- | ---  
Width of the interval containing 95% of the drawn values | 0.3 | 0.3 | 0.1 | 0.02 | 0.00005  

*Table 11 Interval widths retained for the Metropolis-Hastings simulations*

**Burn-in period**

For each simulation, the first 1,000 iterations were discarded in order to avoid parameter sets of low density. Apart from that, all accepted parameter sets were retained to produce the posterior distributions.

**5.7.6 Exploration of Model 5**

In Section 5.4.2, we noted that Model 5 did not lead to better fits than Models 4 or 6 despite a higher level of complexity. In this section, we demonstrate that the best calibration of Model 5 is obtained when \( f \) is equal to or very close to 0, which makes this model equivalent to Model 4.

This observation is attributable to the fact that no immediate activation was observed in the data while \( f \) designates the proportion of infected individuals that activate TB immediately after infection. Section 5.7.6.3 will further consider the possibility of immediate activation and explore the impact on the value of \( f \).

**5.7.6.1 Variation of the optimal fitting score over \( f \)**

Here we explore how considering various values for \( f \) in Model 5 impacts on the corresponding optimal fitting score obtained. Figure 31 (panel a.) presents the variation of the optimal score over \( f \) for both fitting methods (survival likelihood and Least squares optimization) applied to Model 5. For both methods, a score of 0 would correspond to a perfect fit.

We observe that optimal fitting scores are obtained when \( f \) is null for both fitting approaches. Indeed, the sum of squares to be minimised increases over \( f \) for the least squares method, and the likelihood to be maximised for the survival likelihood method decreases over \( f \). These observations are valid for all categories of age.
5.7.6.2 Metropolis-Hastings algorithm applied to Model 5

We used the Metropolis-Hastings algorithm to investigate the same issue using a stochastic approach. The simulation was run until 1,000 parameter sets had been accepted. Figure 31 (panel b.) presents the distributions obtained for the parameter $f$ for each age category.

Once again, our analysis demonstrates that the accepted values for the parameter $f$ are all very close to 0, which reinforces the conclusion that it is not beneficial to choose Model 5 over Models 4 and 6.

5.7.6.3 Uncertainty around the cases of immediate activation

A possible explanation for why $f$ is very close to 0 is that our datasets do not include cases that activated TB disease on the day of infection (time $t = 0$). However, given that it is challenging to estimate the exact dates of infection and activation for TB, it may be possible that immediate activations occurred but were not identified as such. To investigate this issue, we performed a sensitivity analysis in which all cases associated with an estimated time to activation of less than 15 days are assumed to experience immediate activation. We then fitted the parameters of Model 5 by using this edited dataset.

We found that under this scenario allowing for immediate activations, the estimates of $f$ were once again very close to 0 (“All ages”: $2.5e^{-9}$; “< 5 y.o.”: $2.3e^{-8}$; “5 to 14 y.o.”: $1.8e^{-9}$; “≥ 15 y.o.”: $2.1e^{-9}$).
3.2e⁻⁹), reaffirming that Model 5 does not provide substantial additional value to the modelling of TB latency, compared with Model 4.

5.7.7 Posterior distributions obtained for the parameters

5.7.7.1 Selection of a statistical model

For each sample of parameter values, we systematically applied the same method to select an appropriate statistical distribution:

- When the parameter represents a proportion (f or g), we used a Beta distribution and determined the parameters by maximum likelihood estimation.
- When the parameter represents a rate, then its value could theoretically be any number greater than 0 and we selected the most appropriate distribution among Gamma, Log-normal and Beta distributions. Maximum likelihood estimation was performed for each type of distribution and the model was selected using the Akaike Information Criterion.

5.7.7.2 Posterior distributions obtained for Models 4 and 6

We present the posterior distributions obtained from the Metropolis-Hastings simulations applied to Models 4 and 6 (Figure 32). The blue lines represent the density functions of the statistical distributions retained to fit the data as reported in the main text. The characteristics of the different statistical distributions are presented in Table 12.

Concerning the parameter $\nu$, we note that the posterior distributions are less smooth than for the other parameters concerning the age categories “<5 y.o.” and “5 to 14 y.o.”. This is due to the fact that very few cases activated TB at advanced stages of infection in these categories of age. It is therefore more difficult to identify a definite pattern for these distributions, which explains why the statistical models fit less well to the data. Nevertheless, for each age category, the value of $\nu$ has an upper bound which is well marked, and which varies between 1.6e⁻⁵ and 2.3e⁻⁵ depending on the model and on the age-category.

These observations clearly indicate that the rate of reactivation must remain very low in order to replicate accurately the data empirically observed. Indeed, its greatest acceptable value of 2.3e⁻⁵ corresponds to an annual risk of reactivation of about 0.8%.
Figure 32  Distributions of the parameter values obtained from the Metropolis-Hastings simulation (Models 4 and 6)
Table 12  Proposed statistical distributions to fit the posterior distributions obtained from the Metropolis-Hastings simulation.

*LogN*: Log-normal distribution.

### 5.7.8 Validation analyses

#### 5.7.8.1 Presentation and validation of the approach used to extract the data from Sloot et al.’s article

While the dates of activation for TB cases and the dates of censorship for individuals not known to have activated TB were fully available from the Victorian dataset, such detailed data were not available for Sloot et al.’s article.10 Nevertheless, detailed tables and graphs were presented to report survival analyses based on the same age classification as the one we use in this study. From the tables, we were able to calculate the exact numbers of active cases and censored individuals associated with each time window (0-0.5 y; 0.5-1y; 1-2 y; ...; 10-11 y). Next, we determined the dates of both activations and censorships as follows: we used graph digitizer software (Plot Digitizer v2.6.8) to measure the times of TB activations when a graphical measure was possible and the remaining dates were randomly generated using uniform distributions on the corresponding time windows. Sensitivity analyses were performed by considering two extreme alternate scenarios regarding the generation of the data that were not readable graphically. In the first scenario, we assumed that all unknown dates were equal to the lower limit of the associated time window whereas in the second scenario, these dates were assumed to be equal to the upper limit of the intervals.

Figure 33 presents the results of the validation analysis described above.
**Figure 33  Parameter best estimates and 95% CIs under different scenario of data extraction**
Baseline: Random generation of activation and censorship times across the time windows reported in Sloot et al.’s. Scenario A: Activation and censorship times set equal to the lower bounds of the time windows. Scenario B: Activation and censorship times set equal to the upper bounds of the time windows. A linear scale is used for the x-axis.

**5.7.8.2 Validation of the merging of the two datasets**
Figure 34 presents a comparison of the two calibrations obtained by fitting Models 4 and 6 to the two separate datasets (from Victoria and Amsterdam). The posterior distributions of the parameter values obtained for the two datasets matched perfectly for the age categories “< 5 y.o.” and “5 to 14 y.o.”. Victorian data for the “≥ 15 y.o.” category were insufficient (only 11 active cases) to allow for adequate estimation from this dataset alone.

We observed that although age-specific estimates obtained from the two separate settings were very similar, the separate fittings based on the pooled “All ages” populations led to different results. This result is due to the fact that the age distributions are appreciably different between the two datasets. Specifically, the proportion of “≥ 15 y.o.” patients is perceptibly higher in the Amsterdam dataset than in the Victorian dataset (84% versus 65%).
5.7.8.3 Results obtained with the Least Squares Optimization calibration

The dataset used in this analysis is the same as in the baseline analysis. However, we now use the Least Squares Optimization approach to fit the models to the data. Figure 35 represents the best fits obtained with this method. The blue lines represent the model outputs.

The parameter estimates for Models 4 and 6 when calibrated with the Least Squares Optimization method are available in Table 13. The results were found to be consistent with the baseline method (survival likelihood).

<table>
<thead>
<tr>
<th>Dataset</th>
<th>Model 4</th>
<th>Model 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages &lt; 5 y.o.</td>
<td>1.0e-3 9.2e-3 3.0e-6</td>
<td>1.5e-3 1.0e-2 8.4e-6</td>
</tr>
<tr>
<td>5 to 14 y.o.</td>
<td>6.6e-3 1.2e-2 1.5e-14</td>
<td>8.5e-3 6.7e-3 1.5e-13</td>
</tr>
<tr>
<td>≥ 15 y.o.</td>
<td>2.4e-3 9.9e-3 3.1e-6</td>
<td>3.1e-3 8.1e-3 2.1e-6</td>
</tr>
<tr>
<td>All ages</td>
<td>2.7e-4 5.2e-3 2.7e-5</td>
<td>7.3e-5 1.5e-3 1.9e-6</td>
</tr>
<tr>
<td>&lt; 5 y.o.</td>
<td>1.0e-2</td>
<td>1.2e-2</td>
</tr>
<tr>
<td>5 to 14 y.o.</td>
<td>1.9e-2 1.7e-14 0.65</td>
<td></td>
</tr>
<tr>
<td>≥ 15 y.o.</td>
<td>1.2e-2 3.1e-6 0.81</td>
<td></td>
</tr>
<tr>
<td>All ages</td>
<td>1.55e-3 2.7e-6 0.95</td>
<td>1.6e-3 2.0e-6 0.96</td>
</tr>
<tr>
<td>Dataset</td>
<td>Model 4</td>
<td>Model 6</td>
</tr>
<tr>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Imputed Dataset - Least Squares[b,\dagger]</td>
<td>Imputed Dataset - Least Squares[b,\dagger]</td>
<td></td>
</tr>
<tr>
<td>All ages</td>
<td>1.5e-3 1.0e-2 8.4e-6</td>
<td>1.2e-2 8.4e-6 0.87</td>
</tr>
<tr>
<td>&lt; 5 y.o.</td>
<td>6.7e-3</td>
<td>1.5e-13</td>
</tr>
<tr>
<td>5 to 14 y.o.</td>
<td>3.1e-3 8.1e-3 2.1e-6</td>
<td></td>
</tr>
<tr>
<td>≥ 15 y.o.</td>
<td>7.3e-5 1.5e-3 1.9e-6</td>
<td></td>
</tr>
<tr>
<td>All ages</td>
<td>1.2e-2 1.5e-2 3.1e-13</td>
<td>1.6e-3 2.0e-6 0.96</td>
</tr>
</tbody>
</table>

Table 13 Parameter estimates obtained from the calibrations of Models 4 and 6

*Dataset obtained from merging the data from the Victorian TB Program and the data extracted from Sloot et al.\[10\]

\[\dagger\]Imputed dataset based on Victorian data, using the method presented by Trauer et al.\[11\]

\[\dagger\]Fitting method performed by least squares minimization.
Figure 35  Proportion of active TB among infected cases over time: data versus model predictions (Least Squares Optimization)

5.7.8.4  Calibration of the models using imputed data
We used a dataset obtained from the imputation method presented by Trauer et al. in order to take into account the censorship for migration, death, and preventive treatment. Figure 36 presents the model calibrations obtained for the different models when using the imputed dataset. The quantitative estimates for the corresponding parameters are presented in Table 13.

5.7.9  Comparison of our results with previous works
We compare the estimates obtained from our model calibrations with parameter values that have been used in previous works. Figure 37 and Figure 38 provide comparison of parameter estimates for Model 4 and Model 6, respectively.
Figure 36  Proportion of active TB among infected cases over time: data versus model predictions (Least Squares Optimization applied to imputed data)
In Figure 39, we present a comparison between our estimates and previous works concerning two explicit quantities that are associated with Model 4: the average time spent in early latency compartment and the proportion of recent infections that progress to active disease.
5.7.10 Rapid estimation of the parameters

In this section, we present approximate analytical formulae to rapidly estimate the parameters of Models 4 and 6. This allows modellers to obtain reasonable calibrations for any dataset without implementing fitting methods such as least squares optimization or survival likelihood maximization. While using a rigorous theoretical approach, a part of these methods involves approximations that are based on observations made from the data.

In the following demonstrations, we consider that the natural mortality rate $\mu$ is known and can be obtained by calculating the inverse of the life expectancy.

5.7.10.1 Rapid calibration of Model 4

Estimation of $\epsilon$

In Model 4, the compartment $L_B$ is initially empty. Accordingly, by using equation (3) for $t = 0$, we obtain

$$I'(0) = \epsilon L_A(0) = \epsilon N_L.$$  \hspace{1cm} (24)

Consequently, we find that parameter $\epsilon$ is equal to the initial slope of the normalized activation curve $i(t) = \frac{I(t)}{N_L}$ depicted in Figure 24.

Estimation of $\kappa$ and $\nu$

From our analyses, we observe that $\nu \ll \epsilon$, which reflects the fact that progression to active disease is much more rapid from $L_A$ than from $L_B$. Consequently, compartment $L_A$ empties much
more rapidly than the compartment $L_B$ and this is why we observe two distinct phases in the curves that fit the data:

- An initial phase with a pronounced increase in the proportion of active TB, corresponding to the period when rapid progression is predominant
- A secondary phase with a less marked increase in the proportion of active TB, corresponding to the period when re-activation is predominant as the compartment $L_A$ has emptied.

Figure 40 (panel a.) presents a description of these phases.

![Figure 40 Two phases observed in the variation of the proportion of active TB over time since infection (a.) and illustration of the rapid estimation method applied to Model 4 (b.)](image)

Following this observation, let us consider a time $\tau$ at which compartment $L_A$ becomes approximately empty, i.e. at the beginning of the second phase described previously. We can write the Taylor expansion of $I$ at the time $\tau + \Delta t$ for a small $\Delta t$ as

$$I(\tau + \Delta t) \simeq I(\tau) + \Delta t I'(\tau). \tag{25}$$

From the analysis presented in Section 5.4.2, we observe that $\nu \ll \epsilon$. Then, while compartment $L_A$ is not empty, we can reasonably neglect the flow between $L_B$ and $I$. Accordingly, $I(\tau)$ can be approximated by the proportion of $L_A$ that flowed directly to $I$:

$$I(\tau) \simeq N_L \frac{\epsilon}{\epsilon + \kappa + \mu}, \tag{26}$$

and $L_B(\tau)$ can be approximated by the proportion of $L_A$ that flowed to $L_B$:

$$L_B(\tau) \simeq N_L \frac{\kappa}{\epsilon + \kappa + \mu}. \tag{27}$$
Besides, at \( t = \tau \), \( L_A' \approx 0 \) which implies from equation (3) that

\[
I'(\tau) \approx \nu L_B(\tau).
\] (28)

Finally, by combining equations (25), (26), (28) and (27), and by normalizing \( I(t) \), we obtain:

\[
i(\tau + \Delta t) \approx \frac{\varepsilon}{\epsilon + \kappa + \mu} + \Delta t \frac{\nu K}{\epsilon + \kappa + \mu}.
\] (29)

Then, the slope of the tangent to the curve of \( i(t) \) at \( t = \tau \) is equal to \( \frac{\nu K}{\epsilon + \kappa + \mu} \) and its y-intercept is equal to \( \frac{\varepsilon - \nu K \tau}{\epsilon + \kappa + \mu} \), which can be approximated by \( \frac{\varepsilon}{\epsilon + \kappa + \mu} \) given that \( \nu \ll \epsilon \).

In conclusion, the estimates of the three parameters of Model 4 are obtained as follows:

1. \( \epsilon \) is the initial slope of the curve representing \( i(t) \)

2. \( \kappa \) is estimated by using the y-intercept of the tangent to the curve of \( i(t) \) at the beginning of the second phase. If we name this y-intercept \( y_0 \), \( \kappa \) is obtained by: \( \kappa \approx \frac{\varepsilon}{y_0} - \epsilon - \mu \). We note that this affine relationship between \( \kappa \) and \( \epsilon \) was also observed empirically (see Section 5.4.3).

3. \( \nu \) is obtained by using the slope \( s \) of this same tangent. The formula leading to its estimate is:

\( \nu \approx \frac{s(\kappa + \epsilon + \mu)}{\kappa} \).

Figure 40 (panel b.) illustrates the method described above.

5.7.10.2 Rapid calibration of Model 6

To obtain approximate estimates for the parameters of Model 6, we use the approximations obtained in the previous section for Model 4, and the relationships that we demonstrated between the two models (Section 5.7.2.4).

The approximations associated with Model 6 after simplification are:

\[
\epsilon = \frac{s_0}{y_0} - \mu,
\] (30)

\[
\nu = \frac{s_0 s}{s_0 - y_0(s_0 + \mu)},
\] (31)

\[
g = \frac{\varepsilon - s_0}{\varepsilon - \nu}.
\] (32)

Where \( s_0 \), \( s \) and \( y_0 \) designate the same quantities as in the previous section.
6 Profiling *Mycobacterium tuberculosis* transmission and the resulting disease burden in the five highest tuberculosis burden countries: a modelling study

This final thesis project builds new TB epidemiological knowledge that is currently not attainable either due to imperfect case detection or because of intrinsic epidemiological characteristics of TB that make *M. tb* transmission challenging to track. This Chapter introduces a novel modelling approach using agent-based simulation to model the most fundamental component of any infectious disease transmission: the social contacts between individuals.

The TB reactivation dynamics characterised in Chapter 5 were directly used to parameterise individuals’ progression from LTBI to active disease. That is, the findings of the preceding Chapter around the age-specific and time-variant risk of activation have informed this new model, which is used to infer the age-profile of TB transmission and burden. This Chapter presents an application of the model to the five highest TB burden countries according to WHO: India, Indonesia, China, the Philippines and Pakistan. Section 6.7 provides a detailed description of the methodological approach used to design and build the modelling tool. The general strategy employed to conceive the model was to make the tool as flexible as possible, such that it could be used in the future to consider the effect of different interventions. The general finding of Chapter 4 that IPT may be efficient in high-burden settings can now be tested by carefully replicating specific contexts using this model. In particular, targeting specific groups and contact-tracing-based implementation of preventive treatment could be explicitly simulated using the modelling platform introduced in this Chapter. This will be the subject of future work that will aim to identify the optimal approach for PT use in various settings. Such exploration is critically needed in the current context as world political leaders have just declared their commitment to provide 30 million people with PT by 2022. This announcement was made during the United Nations High-Level Meeting held in September 2018.

The following text is a reproduction of a manuscript that was submitted for publication on the 25th of September 2018.
6.1 Abstract

**Background** Tuberculosis (TB) control efforts are hampered by an imperfect understanding of TB epidemiology. In particular, the true age-distribution of TB disease is unknown as a large proportion of individuals with active TB remain undetected. Understanding of transmission is hampered by the asymptomatic nature of latent infection and the capacity for late reactivation of the pathogen. A better understanding of TB epidemiology is critically needed to ensure effective use of existing and future control tools.

**Methods** We use an agent-based model to simulate TB epidemiology in the five highest TB burden countries—India, Indonesia, China, the Philippines and Pakistan—providing unique insights into patterns of transmission and disease. Our model replicates demographically realistic populations, explicitly capturing social contacts between individuals based on local estimates of age-specific contact in household, school and workplace settings. Time-varying programmatic parameters are incorporated to account for the local history of TB control. The model is calibrated using national TB prevalence aggregated for all ages.

**Findings** We estimate that the 15-19 year-old age-group is responsible for more than 20% of transmission events in India, the Philippines and Pakistan, despite representing only 5% of the local TB incidence. According to our model, childhood TB represents around one-quarter of the incident TB cases in these three countries. In China, nearly three-quarters of incident TB occurs in the ≥45 year-old population as a consequence of recent improvements in control programs. The calibrated per-contact transmission risk was found to be similar in each of the five countries despite their very different TB burdens.

**Interpretation** Adolescents and young adults are a major driver of TB in high-incidence settings. Relying only on the observed distribution of disease to understand the age-profile of *Mycobacterium tuberculosis* transmission is potentially misleading.

**Funding** Australian Government Research Training Program Scholarship.

6.2 Research in context

**Evidence before this study**

National TB prevalence surveys have been conducted in Indonesia in 2014 and in the Philippines in 2016, providing age-specific estimates of disease burden for the ≥15 year-old population. No data were collected on childhood TB during these surveys and no national prevalence surveys have been implemented in India, China or Pakistan in the last eight years. Some important age-dependent features of TB epidemiology were previously documented, including the evolution in the rates of progression from latent infection to active disease with age, the wane of BCG vaccination immunity over time, and the age-specific infectiousness of individuals with active
TB. However, the effect of these individual-level patterns combined with the age-specific characteristics of social mixing on the profile of transmission and disease burden remains to be explored. We did a literature review in Medline using the following combination of MeSH terms and keywords: (tuberc* OR ‘tb’) AND (computer simulation OR ‘model*’) AND (‘social mixing’ OR ‘contact*’). We identified no previous studies which had simulated TB transmission dynamics at the country-level by using age-specific and location-specific estimates of social contact rates. We also reviewed all TB-related studies listed in a recently published literature review on individual-based modelling for infectious diseases and reached the same conclusion.

**Added value of this study**

To our knowledge, this study is the first to provide age-specific estimates for the current burden of active disease and the current pool of latent infection by explicitly simulating social interactions between individuals and the past dynamics of transmission and disease control. We also report estimates of the age-specific risk of future TB disease represented by the current infection reservoir. This approach highlights the substantial contribution of the social contacts involving 15-19 year-old individuals to the TB burden, especially to that observed in the older age-groups. Our model also suggests that the per-contact risk of transmission is very similar in the five countries considered in this analysis despite their very different TB burdens.

**Implications of all the available evidence**

Although young children are at the greatest risk of disease activation once infected with *Mycobacterium tuberculosis*, targeting adolescents and young adults with preventive tools may result in greater reductions in disease incidence due to their high potential of transmission. Our findings highlight the importance of accounting for the specific patterns of social mixing in addition to individual-level epidemiological characteristics to understand the drivers of transmission in the context of TB.

**6.3 Introduction**

Tuberculosis (TB) is now the leading cause of death worldwide from a single infectious agent. While effective prevention and treatment tools have been available for many decades, their impact on the global epidemic has been limited by challenges that TB control programs still face today. Among them, the difficulties in identifying diseased individuals and providing them with adequate care may be the most critical, as only 61% of cases receive effective treatment. These issues are even more alarming among the youngest populations, with estimates suggesting that the global case detection rate could be as low as 35% in children. As well as ensuring that control policies are as effective as possible, comprehensive knowledge of the epidemic age-profile is essential for estimating burden of disease and predicting the course of the epidemic.
TB epidemiology is also clouded by the propensity of *Mycobacterium tuberculosis* (*M.*t*b*) to enter a latent infection state within its host (latent TB infection, LTBI), in which it may persist for many years before reactivating.\(^{12}\) Source tracing is therefore difficult due to the unknown time-lag between infection and activation, making transmission events even more challenging to infer than disease burden. However, better understanding pathogen transmission in the population and the resulting infection burden would provide a valuable opportunity to better target high-risk groups.

The slow dynamics of TB also limit the feasibility of field investigations that could build additional epidemic knowledge and mean that historical trends for many decades into the past may have significance for the modern epidemic. For these reasons, mathematical modelling provides a valuable tool to investigate hidden features of the disease.\(^{120}\) In particular, agent-based simulation can replicates real-world environments and offers the possibility to incorporate a high level of heterogeneity regarding individual characteristics and social interactions while avoiding excessive complexity. Meanwhile, the recent availability of contact survey data has dramatically improved our understanding of social mixing.\(^{277-279}\) In particular, estimates of age-specific contact frequency and intensity in different contexts/locations are now publicly available and provide empiric evidence of preferential mixing patterns, such as age-assortativity.

In this study, we combine data on social mixing and population demography with data on historical indicators of TB control to parametrise an agent-based model. We use the model to build a rich picture of the current profile of *M.*t*b* transmission and disease burden in the world’s five highest burden countries in 2016 according to the World Health Organization (WHO): India, Indonesia, China, the Philippines and Pakistan.\(^{275}\)

### 6.4 Methods

We developed the SNAP-TB platform (Social Network Abstraction to Profile TB Burden) to simulate *M.*t*b* transmission and the resulting burden of infection and disease. SNAP-TB is a stochastic agent-based model developed in Python (v.2.7.11) that uses a household, school and workplace framework to generate realistic demographic patterns and social mixing. The population model is overlaid with a TB model that simulates infection, transmission and several control interventions (Figure 41). The main model principles are described in the following sections and detailed in the supplemental material (Section 6.7).
Figure 41  Schematic illustration of the agent-based model

The upper panel represents the structure of the simulated population and the diverse types of contacts simulated (household, school, workplace, other location). The lower panel illustrates individuals’ progression through the various stages of life and infection/disease using diamonds to represent events and boxes for extended phases. Solid arrows indicate deterministic progressions that occur in all surviving individuals, while dashed arrows represent possible but not universal progressions. *Only a fraction of the individuals enters the organised workforce.

Model initial conditions – replicating the demographic and epidemic configuration of year 2018 – were reached by running a burn-in phase to allow demographic processes, age-distributions and TB distribution to emerge naturally. This burn-in lasts 200 years, with TB only introduced after the first 100 years of this simulation. The system was then run for an additional duration of five years to produce the outputs presented below.

Population model
All individuals are assigned a household at birth. Life events such as forming a couple, moving home and having babies are simulated such that realistic household compositions emerge naturally from the model. A Siler model is used to derive age-specific natural mortality rates, and back-calculated birth rates are used during the burn-in phase in order to reproduce the desired country age-distribution at the time of analysis.
All children are assumed to attend school over an age range that varies by individual (commencing school from 3-5 years old and completing by 15-21 years old), before optionally entering the workforce outside of the household, with individuals explicitly assigned to specific schools and workplaces.

**Social mixing**

Individuals interact with each other through social contacts that occur in four different contexts: households, schools, workplaces and other locations. A social contact is considered conceptually as either a physical contact or a two-way conversation involving three or more words (the definition that was used to report the social mixing data inputs to our model). All individuals of the same household are assumed to contact each other every day—an assumption that is supported in the context of epidemic modelling by two recent studies. In contrast, social contacts occurring within congregate settings (schools and workplaces) and in other locations are generated stochastically at each time step. Their frequency and age-assortativity pattern are derived for each country from estimates of the location and age-specific contact matrices.

**TB model**

Figure 1 illustrates the infection stages simulated. Age-specific parameters derived from empiric data are used to determine whether and when infected individuals progress to active disease. Active cases may be smear-positive, smear-negative or extrapulmonary TB and will either spontaneously cure or die from their disease in the absence of treatment. The type of natural history outcome and the time at which it occurs are randomly generated based on the TB natural history characteristics observed during the pre-chemotherapy era.

*M.tuberculosis* transmission may occur when a person with active TB contacts a susceptible individual. The baseline probability that a social contact leads to transmission is automatically calibrated to reproduce observed national TB prevalence aggregated for all ages (Section 6.7.3.2). Empirical estimates of the age-specific TB prevalence (only available for Indonesia and the Philippines) were compared to the model outputs for independent validation but were not used for calibration. We assume that school contacts are less likely to lead to transmission than household contacts (RR=0.89), as are work contacts (RR=0.82) or other contacts (RR=0.75). These relative risks are based on the reported proportions of high-intensity contacts by location, and the assumption that low-intensity contacts are half as likely to lead to transmission as high-intensity contacts. Section 6.7.3.2 describes this approach to relative risk calculation in detail, with sensitivity analyses used to explore alternative assumptions. The transmission probability also depends on the characteristics of the two individuals making contact, as described in Table 14.
<table>
<thead>
<tr>
<th>Modification in risk of transmission</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Affecting index infectiousness</strong></td>
<td></td>
</tr>
<tr>
<td>Extrapulmonary TB</td>
<td>Not infectious.</td>
</tr>
<tr>
<td>Smear-negative TB</td>
<td>One quarter as infectious as smear-positive cases.</td>
</tr>
<tr>
<td>Age</td>
<td>Infectiousness increases with age (see Section 6.7.3.2).*</td>
</tr>
<tr>
<td>Detection</td>
<td>The transmission probability is halved once the index case has been detected.</td>
</tr>
<tr>
<td><strong>Affecting contact susceptibility</strong></td>
<td></td>
</tr>
<tr>
<td>BCG vaccination</td>
<td>Reduces the risk of the vaccinee becoming infected. Vaccine immunity wanes over time (see Section 6.7.3.2).</td>
</tr>
<tr>
<td>Current <em>M.tb</em> infection</td>
<td>Reduces the risk of novel infection (RR=0·21).</td>
</tr>
</tbody>
</table>

*Assumption explored in sensitivity analysis.

The time to detection of active TB is assumed to be exponentially distributed and the associated rate is calculated based on the country’s estimated case detection rate (Section 6.7.3.3). Although a detection time is generated for all TB cases, detection only actually occurs if this time precedes the pre-determined time of the natural history outcome.

In our model, all detected cases are commenced on treatment from seven days following detection. Successfully treated individuals (i.e. cured or completing treatment) are assumed to clear *M.tb* infection and become susceptible again. If unsuccessfully treated, patients remain active and the TB episode outcome (cure or death) and time of the outcome remain as defined by the TB natural history that was originally generated. Time-variant parameters are used to specify BCG vaccine coverage as well as rates of case detection and treatment success. The associated scale-up functions for BCG vaccine coverage and rates of case detection and treatment success are based on WHO data and are presented in Figure 54 (Section 6.7.3.4). In order to understand the role played by the past programmatic conditions in shaping the current epidemic picture, we run an additional analysis where all programmatic parameter values are assumed constant and equal to their most recent estimates.

### 6.5 Results

**Model calibration and validation against age-specific TB prevalence**

We replicate the current TB burden (based on national TB prevalence, aggregated for all ages) in the five countries by using the following calibrated values for the crude probability of transmission per contact: 0·0021 (India, China and Pakistan), 0·0023 (Indonesia), and 0·0025 (the Philippines). Our resulting age-specific prevalence estimates and those obtained from the prevalence surveys conducted in the Philippines in 2016 and in Indonesia in 2014 closely match
Figure 42. Age-specific estimates of prevalence are also presented for India, China and Pakistan in Figure 50 (Section 6.7.4.1) although comparison to data was not possible in absence of recent prevalence survey.

Figure 42  Validation of model outputs against prevalence survey estimates for the age-specific TB prevalence in the Philippines and Indonesia

No data were available for the less than 15 years old individuals from these surveys. Error bars represent the 95% confidence intervals of the survey estimates (in purple) and the 95% simulation intervals (in green).

Profile of M. tb transmission

During simulation, we record the contact characteristics by tracking their location (school, work, home, other) and the age of the individuals involved. The same information is recorded for each transmission event, along with whether the associated infection eventually results in active TB. Figure 43 shows the respective contributions of the four different location types to the burden of contact and transmission. Contacts occurring in locations other than home, school or workplace are a major driver of M. tb transmission in each of the five countries, with contributions ranging from 30% (27-34, 95% simulation interval) of the total number of transmission events in Pakistan to 48% (43-53) in China. Household contacts are the predominant driver of M. tb transmission in
Pakistan (43%, 40-45). The proportion of active TB burden attributable to household contacts varies between 18% (7-30) in China and 49% (42-55) in Pakistan.

Figure 43 Contributions of the various locations to the burden of contact and transmission
Error bars represent the 95% simulation intervals.

A significant share of the TB burden is attributable to work contacts, with estimated contributions ranging from 19% (13-25) in Pakistan to 31% (16-45) in China. Although around 10% of social contacts occur within schools, their role with regards to the burden of transmission and disease remains very limited, with their greatest contribution to active TB being 4% (2-6%) in Indonesia.

Figure 44 presents the age-specific contact and transmission patterns obtained from simulation. Contact patterns disaggregated by location are presented in Figure 50 (Section 6.7.2.3). We note that our approach of allowing for household compositions to emerge naturally during simulation leads to realistic age-specific contact patterns that are similar to those described in several social mixing studies.277-279 The high-intensity contact zones naturally translate into high densities of \( M.tb \) transmission, except where index individuals are less than 15 years old (due to lack of infectiousness) and where contact recipients are young and therefore likely to retain partial immunity from BCG vaccination. In contrast, the effect of immunity from infection is no longer observed when considering only contacts that lead to active disease. This finding is due to the fact that young individuals are at higher risk of progression to active disease than adults.10 11 Our results highlight that the 15-19 years age-category represents a critical driver of transmission in all countries except China. In India, the Philippines and Pakistan, we estimate that more than 20% of transmission events involve this age-category as either index or recipient.
Figure 44  Age-specific pattern of social mixing and transmission
Age-distribution and risk associated with the current latency reservoir

We estimate the country-level prevalence of LTBI at 11%, 27%, 9%, 34% and 12% in India, Indonesia, China, the Philippines and Pakistan, respectively. Figure 45 presents the age-specific size of the LTBI reservoir as estimated for 2018 (green spheres), as well as the risk that it represents in terms of future TB disease (purple spheres). We observe that the relative LTBI prevalence steadily increases with age in all countries, whereas the absolute LTBI burden decreases at advanced ages due to population mortality. Note that LTBI prevalence is predicted to reach extremely high levels among the oldest age-category, which is explained by the high historical intensity of transmission in these countries and by the fact that we do not incorporate the possibility for LTBI clearance.

![Figure 45: Age-distribution of latent tuberculosis infection](image)

Coloured discs should be interpreted as spheres (to increase the relative size of the smaller spheres), with the volume of the spheres being proportional to the following quantities: 2018 total population (grey), size of the LTBI pool in 2018 (green), and number of individuals currently infected in 2018 who will ever develop active TB (purple).

The age-category that represents the highest risk in terms of future disease emanating from current infections is the “30-39 year-old” in India (28% of future burden), the Philippines (25%) and Pakistan (30%); while the “40-49 year-old” age-category was most prominent in Indonesia (27%) and China (34%). The youngest age-category “0-9 year-old” includes very few infected
individuals in all countries, although the per-infection risk of disease is much higher in this age-category than in older populations.

**Age-profile of active TB**

Figure 46 shows the age-distribution of TB cases in the five countries. In China, we estimate that TB affects the $\geq 45$ year-old category much more severely than the younger age-categories, accounting for 72% of the national TB burden. In particular, the age-category 45-49 is the most represented, alone contributing 12% (11-14) to the Chinese TB burden.

![Age-distribution of TB cases](image)

*Figure 46 Age-distribution of TB cases*

The population age-distribution (green) was captured at the starting time of analysis (year 2018). Age of TB cases at activation (red) were recorded over a period of five years starting from 2018. Error bars represent the 95% simulation intervals obtained for the TB age-distribution.

In India and Indonesia, similar TB age-profiles are obtained and feature a burden peaking in the 35-39 year age-category and remaining high across the adjacent categories. Young individuals (particularly those aged less than five or between ten and 14) are also severely affected in these two countries.

Although the Philippines and Pakistan present similar population-pyramids, their TB age-distributions differ noticeably. We find a prominent peak for the 45-49 year age-category in Pakistan (contributing 11% of the TB burden), which is not observed in the Philippines (6% for the same age-category). In contrast, young adults (aged 20-29 years) constitute a considerably greater proportion of the burden in the Philippines (16%) than in Pakistan (11%). Finally, the
youngest age-category (0-4 year-old) is a major contributor to the TB epidemic in both the Philippines and Pakistan, with estimated contributions reaching 12% (11-12) and 11% (10-12), respectively. The proportion of paediatric TB (<15 years old) among all TB cases is estimated to be 20%, 17%, 4%, 25% and 26% in India, Indonesia, China, the Philippines and Pakistan, respectively.

Figure 61 (Section 6.7.4.3) presents the TB age-distribution obtained for the Philippines when assuming constant historical programmatic conditions (that is, removing time-variant programmatic parameters). We note that a substantial share of the estimated TB burden is shifted towards the youngest age-categories under this scenario, making the TB age-profile more similar to the population age-distribution which is highly inconsistent with the results of the 2016 prevalence survey.

6.6 Discussion

We present a detailed representation of \textit{M.tuberculosis} transmission and the resulting burden of infection and TB disease in the five highest TB burden countries. Using an agent-based model that combines household structure, social mixing matrices, age-specific infectiousness and reactivation rates, and the history of national TB control, we provide insights into major TB epidemic characteristics that would be otherwise unattainable. These include the age-profile of \textit{M.tuberculosis} transmission, the age-specific LTBI prevalence and associated risk of future disease, the age-distribution of incident TB cases, and the contributions of different contact types to the burden of transmission and disease. Furthermore, we demonstrate that the demographic and programmatic model inputs alone are sufficient to explain the considerable heterogeneity in burden observed between countries, with calibrated per contact transmission rates being very similar.

We show that the 15-19 year-old age-category is a major driver of \textit{M.tuberculosis} transmission in all countries except China. This observation, which is due to the high frequency of contacts among this age group combined with the waning of immunity conferred by BCG at this age, contrasts with the relatively low estimated burden of active disease observed in this age-group. This finding highlights the marked difference between the age-profile of \textit{M.tuberculosis} transmission and that of TB burden and implies that relying only on the observed burden of active disease to understand the age-profile of a TB epidemic would provide an incomplete and misleading picture. The relatively low TB burden estimated in the 15-19 year old age group may explain why adolescents and young adults constitute a neglected group in global TB control, and are rarely considered as a target population for preventive measures. However, our model suggests that preventing infection and reactivation within this group could potentially yield significant burden
reductions in the older age-categories. Further work will follow to quantify the impact of implementing control interventions targeted at adolescents.

Another age-specific transmission peak was identified between parents and their children in all settings, which is especially concerning for children under five years old, as they are more likely to progress to active disease once infected. This observation underscores the critical importance of implementing rapid screening and control measures for the youngest contacts of identified adult pulmonary TB cases. We estimate that childhood TB (<15 years old) contributes to around one quarter of the total TB incidence in India, the Philippines and Pakistan. Such high proportions are in line with previous estimates obtained in other high-incidence settings and are a consequence of the countries’ young populations and their high contact intensities. Incorporating age-specific epidemiological characteristics such as infectiousness, risk of activation and waning BCG immunity allowed us to further refine the distribution of TB cases among <15 year-olds using five year age-brackets. This insight is particularly valuable because it is difficult to directly assess in real-world settings due to the challenges encountered with the diagnosis and surveillance of paediatric TB.

The TB age-profile in China is dramatically different to that reported for the other four countries modelled in this study. China experiences TB principally in the oldest part of the population, with nearly three quarters of the TB burden attributed to the ≥45 year-old category, although population ageing is not the only explanation for this phenomenon. The dramatic improvement in case detection since 2000 combined with high treatment success rates (over 90%) maintained over the last three decades has resulted in a dramatic fall in \( M. tb \) transmission over recent years, such that younger cohorts have now been much less exposed to the pathogen than preceding generations. This suggests that the current burden of active TB in China results primarily from reactivation of old infections that were acquired when transmission was still intense, consistent with previous work. The importance of the programmatic history in shaping the current age-profile of TB was further highlighted by the discrepancies observed in our sensitivity analysis performed without time-variant parameters and ignoring past TB control.

We provide estimates of the age-specific size of the LTBI reservoir, along with the risk that it represents in terms of future disease. Knowing who is latently infected provides valuable knowledge for policy-makers when designing contextualised preventive strategies. Our country-specific predictions could be used to estimate the yield of mass LTBI screening/treatment programs targeted at specific age-categories, both in terms of the number of current infections treated and future disease episodes prevented. Although broad recommendations for the management of LTBI have been adopted, little is known about how best to adapt these to local programmatic and epidemiological contexts.
Social interactions occurring outside of homes, schools and workplaces were identified as the main driver of transmission in India, Indonesia, China and the Philippines. This finding implies that control measures focusing on close and easy-to-identify contacts of diagnosed TB cases may have a limited impact at the population level in these settings. This is consistent with other modelling works which suggest a limited role of household transmission due to contact saturation, a phenomenon that only agent-based models can capture. In contrast, simulated *M. tuberculosis* transmission in Pakistan occurs primarily in homes due to Pakistan’s large average household size (6.8 persons). Therefore, interventions such as providing household contacts with screening and prophylaxis treatment are likely to be more efficient in Pakistan. We found that the contribution to the TB burden from household contacts and those occurring in “other locations” was sensitive to our assumptions about the relative risk of transmission through low-intensity contacts as compared to high-intensity contacts. However, it is important to note that the two scenarios considered in our sensitivity analyses are extreme and likely unrealistic, as they represented either a null risk of transmission for low-intensity contacts or a risk that is equal to that of high-intensity contacts.

The fact that the calibrated transmission probability is found to be very similar in the five countries despite their very different TB burdens provides confidence in the robustness of the model. Moreover, it indicates that the socio-demographic characteristics included, along with the simulated time-variant programmatic background, are able to account for the bulk of the heterogeneity in TB burden. This finding also suggests that the per-contact risk of transmission could be similar in all settings after adjustment for age and other factors relevant to infectiousness and susceptibility. The validity of our model was further reinforced by the closely matching estimates obtained when comparing our simulated age-specific prevalence to the equivalent estimates from the prevalence surveys conducted in the Philippines and Indonesia.

A limitation of this study is that the social mixing matrices that we input into the model were not directly obtained from contact surveys. Instead, we used country-specific estimates generated by combining survey data from other countries with an extrapolation model. Our estimates could therefore be refined further if local mixing data such as those provided by the POLYMOD study became available for a greater range of contexts. Another potential limitation of the study is that we opted for some parsimonious features in the model, omitting factors including gender, comorbidities and sub-national geography. This could be incorporated in future model developments.

In conclusion, we show that it is possible to create new and valuable insights into the profile of local TB epidemics by combining agent-based simulation with social mixing data and TB control history. We demonstrate that social contacts involving 15-19 year-old individuals are a critical
driver of TB and we identify substantial gaps between the age-profile of M.tb transmission and the age-distribution of TB cases. Our model also highlights the high burden of childhood TB in high-incidence settings and underlines the critical role played by parents-to-children transmission.

6.7 Supplemental material

6.7.1 General description of the agent-based model

This document describes our approach to developing an agent-based model that simulates a dynamic population of individuals who each have their own characteristics in terms of demographics and disease status. These individuals interact with one another and social contacts between them are explicitly simulated, allowing for transmission of Mycobacterium tuberculosis (M. tb) to occur and to be fully traced. Individuals are assigned to households and may attend schools or workplaces, which allows for implementation of various types and frequencies of contacts between them. This framework also makes possible the simulation of TB-specific control interventions. For example, contact tracing following diagnosis of an active tuberculosis (TB) case or blanket preventive treatment within a school or a workplace could easily be explored.

We simulate a population of 50,000 individuals whose actions and interactions are computed through an iterative process, in which a time-step represents a given duration (seven days in this study). The population size was determined so that the number of individuals simulated is sufficiently high to be considered as a representative “sample” of a country population, while retaining reasonable computation times. At each iteration, the demographic and TB-specific characteristics of the individuals are updated through processes that pertain to natural transitions (ageing, death, birth and starting/finishing school or work) and disease-related events (transmission, activation, detection, treatment and TB-related death). Most of these processes are stochastic, such that running multiple simulations with an identical parameter set will result in different outcomes. For each scenario, a number of independent simulations (typically 100) are run and the mean and central 95% credible interval are reported for each model output.

Before running the simulations presented in the main text, we obtained model initial conditions by performing a burn-in to allow demographic processes, age distributions and TB distribution to emerge naturally. This burn-in phase runs for 200 years in total, with TB only introduced after the first 100 years of simulation. The model is run for a further period of five years during which model outputs are recorded. One full simulation (simulating 205 years) is completed in about three hours using an Intel Xeon E3-12xx v2 processor (3.1 GHz, 8MB Cache).

Table 15 lists the parameters used in the model. A more detailed description of model assumptions and parameterisation is provided in the remainder of this document.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>India</th>
<th>Indonesia</th>
<th>China</th>
<th>Philippines</th>
<th>Pakistan</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simulated population size</td>
<td>50,000</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>Average household size</td>
<td>4.8</td>
<td>3.9</td>
<td>3</td>
<td>4.7</td>
<td>6.8</td>
<td></td>
</tr>
<tr>
<td>Number of schools (/100,000 population)</td>
<td>115</td>
<td>96</td>
<td>37</td>
<td>57</td>
<td>157</td>
<td></td>
</tr>
<tr>
<td>Average number of potential contacts at work outside of</td>
<td>53.8</td>
<td>66.3</td>
<td>68.9</td>
<td>62.3</td>
<td>54.4</td>
<td>Assumption</td>
</tr>
<tr>
<td>the household (%)</td>
<td>10</td>
<td>46 / 30 / 20 / 10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of the adult population engaged in regular</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>work outside of the household (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Assumption</td>
</tr>
<tr>
<td>Proportion contacts which are of high intensity by</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>location, with locations listed as households / schools</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>/ workplaces / other locations (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion active TB cases sm+ / sm- / extra-p (%)</td>
<td>50 / 25 / 25</td>
<td>62 / 19 / 19</td>
<td>52 / 24 / 24</td>
<td>60 / 20 / 20</td>
<td>44 / 28 / 28</td>
<td></td>
</tr>
<tr>
<td>Probability of spontaneous clearance (sm+ / closed TB)</td>
<td>0.27 / 0.52</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>Rate parameter of the exponential distribution used to</td>
<td>0.336 / 0.058</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>generate the time to natural outcome (sm+ / closed TB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>years'1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probability of TB transmission during a household</td>
<td>0.0021</td>
<td>0.0023</td>
<td>0.0021</td>
<td>0.0025</td>
<td>0.0021</td>
<td></td>
</tr>
<tr>
<td>contact</td>
<td>0.5</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>Relative probability of transmission per contact if low</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>intensity contact</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative infectiousness of smear-negative cases4</td>
<td>0.25</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>Relative infectiousness after detection1</td>
<td>0.5</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>Relative susceptibility if currently infected with M. tb</td>
<td>0.21</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>Natural history of TB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion active TB cases sm+ / sm- / extra-p (%)</td>
<td>50 / 25 / 25</td>
<td>62 / 19 / 19</td>
<td>52 / 24 / 24</td>
<td>60 / 20 / 20</td>
<td>44 / 28 / 28</td>
<td></td>
</tr>
<tr>
<td>Probability of spontaneous clearance (sm+ / closed TB)</td>
<td>0.27 / 0.52</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>Rate parameter of the exponential distribution used to</td>
<td>0.336 / 0.058</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>generate the time to natural outcome (sm+ / closed TB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>years'1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probability of TB transmission during a household</td>
<td>0.0021</td>
<td>0.0023</td>
<td>0.0021</td>
<td>0.0025</td>
<td>0.0021</td>
<td></td>
</tr>
<tr>
<td>contact</td>
<td>0.5</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>Relative probability of transmission per contact if low</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>intensity contact</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative infectiousness of smear-negative cases4</td>
<td>0.25</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>Relative infectiousness after detection1</td>
<td>0.5</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>Relative susceptibility if currently infected with M. tb</td>
<td>0.21</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>Programmatic parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCG vaccine coverage (average 2002-2016, %)</td>
<td>Time-variant 8</td>
<td>Time-variant</td>
<td>Time-variant</td>
<td>Time-variant</td>
<td>Time-variant</td>
<td>157</td>
</tr>
<tr>
<td>Relative susceptibility if BCG-vaccinated and BCG still</td>
<td>0.50</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>effective6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of BCG efficacy (years)</td>
<td>15</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>Case detection rate (%)</td>
<td>Time-variant 7</td>
<td>Time-variant</td>
<td>Time-variant</td>
<td>Time-variant</td>
<td>Time-variant</td>
<td>296</td>
</tr>
<tr>
<td>Time from detection to treatment (days)</td>
<td>Time-variant 7</td>
<td>Time-variant</td>
<td>Time-variant</td>
<td>Time-variant</td>
<td>Time-variant</td>
<td>296-302</td>
</tr>
<tr>
<td>Treatment success rate (%)</td>
<td>Time-variant 7</td>
<td>Time-variant</td>
<td>Time-variant</td>
<td>Time-variant</td>
<td>Time-variant</td>
<td>112</td>
</tr>
<tr>
<td>TB prevalence (/100,000 population)</td>
<td>320 (280-380)</td>
<td>647 (513-797)</td>
<td>89 (78-102)</td>
<td>1,159 (1,016-1,301)</td>
<td>341 (283-402)</td>
<td>12</td>
</tr>
</tbody>
</table>

Table 15 Model parameters

4 smear-positive TB; 5 smear-negative TB; 6 extrapulmonary TB; 7 either smear-negative or extrapulmonary TB; 8 reference: smear-positive TB; 9 reference: undetected TB; 10 reference: non-vaccinated.
6.7.2 Demographic structure and contacts between individuals

6.7.2.1 Household structure, birth and death processes

A number of households (obtained by dividing the total population by the average household size) is created to host the individuals. Household creations or removals may also occur as the total population size varies during simulation in order to maintain the country average household size. At birth, individuals are allocated to households which they may or may not leave as they enter adulthood. Individuals ‘enter adulthood’ and become eligible to leave their original home at an age which is generated at random from a uniform distribution between 18 and 30 years old (could be adjusted for other model applications). If an empty household is available at the time that an individual enters adulthood, they move to the available household and form a couple with an individual who also entered adulthood within the last 12 months. This household then becomes eligible to receive newborn individuals for a period of ten years. If an individual is not selected to enter an empty household within one year of entering adulthood (the number of places available in empty households being fewer than the number of new adults), they remain in their original household for the remainder of their life. However, they may still procreate in their original household (and without living with a partner), which similarly becomes eligible to receive newborns for ten years. Households are not permitted to receive two successive newborns within the same twelvemonth period, in order to maintain realistic age differences between siblings.

The age at which individuals die is randomly generated from a Siler model. This model is defined by an age-dependent hazard function that defines the force of mortality:

\[
h(x) = e^{\alpha_1 - \beta_1 x} + e^{\alpha_2 + \beta_2 x} + e^{\alpha_3}
\]

where \(x\) represents the individual’s age. \(\alpha_1, \alpha_2\) and \(\alpha_3\) are scale parameters which reflect the level of mortality at younger ages, older ages, and overall respectively. \(\beta_1\) and \(\beta_2\) are age-trend parameters describing the slope of the hazard trajectory at younger ages and older ages.

We fit the associated survival function (obtained after calculation)

\[
S(x) = \exp \left[ - \int_0^x h(a) \, da \right] = \exp \left[ \frac{e^{\alpha_1}}{\beta_1} (e^{-\beta_1 x} - 1) - \frac{e^{\alpha_2}}{\beta_2} (e^{\beta_2 x} - 1) - e^{\alpha_3 x} \right]
\]

to real-world survival data obtained from the country-level life tables published by WHO\(^{303}\) (Figure 47). Fitting is achieved by sum of squares minimisation. Table 16 presents the values of the Siler model parameters obtained for the five different countries.

The life duration density function corresponding to the Siler model is obtained by multiplying \(S(x)\) by \(h(x)\). Finally, the resulting density function is used in the model to sample ages at death using rejection sampling.
Three different fertility scenarios are implemented and used sequentially during each phase of simulation. First, fertility replacement is assumed during the first (100 year) phase of burn-in, introducing a newborn into the population every time that an individual dies. Next, a variable birth rate is used during the second (100 year) burn-in phase, in order to reach a targeted age-distribution (country age-pyramid) at the commencement of the analysis phase, as follows. Let \( \tau \) denote the time remaining before burn-in completion (\( 0 \leq \tau \leq 100 \) years). The number of births occurring at time \( t = 200 - \tau \) is calculated by dividing the desired number of individuals of age \( \tau \) that should be alive at the end of the burn-in phase by the probability of survival after \( \tau \) years obtained from the Siler mortality model. Finally, once burn-in is completed, a constant rate equal to the inverse of the mean life expectancy is used to generate births during the analysis phase (of five years).
For each birth simulated, a newborn is allocated to an eligible household (see description of eligible households in the first paragraph of this section). The household receiving a newborn is selected using a probabilistic approach that favours smaller households. Let $s_i$ denote the size of the eligible household $i$. The newborn’s household is chosen using a multinomial distribution where the eligible household $i$ is selected with probability $\frac{\gamma}{s_i}$, where $\gamma$ is a normalising constant (i.e. $\gamma = \frac{1}{\sum 1/s_i}$).

Figure 48 shows the household size distributions from ten simulations of 50,000 individuals for the five different countries analysed. These outcomes emerge naturally according to the input average household size and from the process described in the above paragraph.

6.7.2.2 Schools and workplaces

The population model described is overlayed with a framework of schools and workplaces. We assume that each household is associated with a single school, such that children who live in the same household necessarily attend the same school. Schools are randomly assigned to each household during model initialisation. Every “school-aged” individual is considered to attend school. A school-age range is drawn for each individual using uniform distributions for the starting age (3-5 years old) and the leaving age (15-21 years old). When individuals complete
school, they may become active workforce participants (and are then randomly assigned to a workplace), and otherwise will never engage in employment outside of the household.

In the context of this study, a workplace is intended to capture a group of individuals who are working at the same location and between whom the intensity of contact in their professional context is sufficient to allow for TB transmission. That is, the term “workplace” may actually refer to a subsection (department) of a company or a subgroup of individuals who are working together on a regular basis rather than a whole corporation. This entity is characterised by its average size, which is assumed to be the same in each country (Table 15) in the absence of country-specific data to inform this quantity. The number of workplaces is calculated by dividing the number of working individuals in the population by the average workplace size. When individuals enter active employment, they are randomly assigned to a workplace in which they remain until retirement. Each individual’s retirement age is randomly drawn from a uniform distribution in the 55-70 age range.

Schools and workplaces may be created or removed during simulation as the number of households varies with variation in the total population size.

### 6.7.2.3 Social contacts

**Definition of a social contact and general approach to contact generation**

We define a social contact between two individuals as either a physical contact or a two-way conversation involving three or more words, because this definition was used in the studies from which the contact matrices were extracted. Social contacts are recorded on a daily basis, such that for each index individual, we record a list of contacted individuals along with the number of times (days) that interactions occurred. Social contacts are classified into four categories according to the context in which they occur: household, school, workplace and other locations. Note that social contact generation is only performed for individuals who are infectious (unless specifically requested for the purpose of illustration, e.g. to generate Figure 50).

**Household contacts**

In our model, all individuals of the same household contact one another every day. While contact patterns between household members are likely to be more complex in the real world, two recent studies support the use of within-household homogenous mixing assumptions for epidemic modelling.

**School and workplace contacts**

We use a similar approach for both schools and workplaces to the generation of social contacts between individuals. Each day, a contact is generated between individuals $a$ and $b$ with probability $P_c(a, b) = p \cdot f_\sigma(a, b)$ where $f_\sigma$ is an age-preference multiplier function which
depends on the age difference between individuals $a$ and $b$ and $p$ represents the probability that two individuals within the same structure and of the same age contact one another during a typical day. Our approach to determining $f_\sigma$ and $p$ is described in the following section.

The age-preference function for contact between individuals is simulated using a Gaussian function $f_\sigma(x) = e^{-\frac{x^2}{2\sigma^2}}$, where $x$ is the age difference between two individuals and $\sigma$ is a dispersion parameter. $f_\sigma$ represents the relative likelihood that two individuals contact each other given their age-difference as compared to two individuals of same age. Due to lack of available data, we could not estimate country-specific values for the parameter $\sigma$ associated with schools. Specifically, five-year age categories were used to report the contact matrices that inform our model, which is too broad to allow for any preference profile to be extracted within school ages alone. We therefore assume a constant value $\sigma = 2$ years for all countries, which is equivalent to saying that 68% of within-school contacts involve individuals with an age gap <2 years. This intended to reflect significant cohorting by single year of age due to school classes being largely comprised of children born in the same twelve month period, while also allowing for significant mixing outside of the classroom. In contrast, the parameter value associated with workplaces is estimated from the workplace-specific contact matrices reported by Prem et al. $\sigma$ is obtained by minimising the following distance:

$$d_\sigma = \sum_i \sum_j \left( \frac{A_{i,j}}{A_{i,i}} - \frac{P_j}{P_i} f_\sigma(5 |j - i|) \right)^2,$$

where we only sum over the indices $i$ and $j$ that are associated with working age-groups and where $A_{i,i}, P_i \neq 0$ (always verified in practice). The term $\frac{A_{i,j}}{A_{i,i}}$ corresponds to the relative contact rate between an individual from group $i$ and an individual from group $j$, as compared to the contact rate between two individuals form group $i$. The distance $d_\sigma$ compares these quantities to their associated measure under our model assumption, which is the Gaussian function $f_\sigma$ evaluated for $x = 5 |j - i|$, the average age-difference between group $i$ and group $j$. Note that this quantity is adjusted by multiplying with the age-distribution ratio $\frac{P_j}{P_i}$ where $P_i$ represents the proportion of the population belonging to age-category $i$. This approach allows us to isolate the behavioural age-preference component of age-assortativity from the effect of the background age-distribution which affects the absolute reported age-specific contact rate values.
Figure 49 presents the age-preference profiles obtained for the five different countries considered in our analysis and Table 17 reports the estimated values of $\sigma$ corresponding to workplace contacts.

![Figure 49](image_url)

**Figure 49  Age-preference functions used to calculate the probabilities of contact within workplaces and schools**

<table>
<thead>
<tr>
<th></th>
<th>India</th>
<th>Indonesia</th>
<th>China</th>
<th>Philippines</th>
<th>Pakistan</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\sigma$</td>
<td>21.1</td>
<td>21.7</td>
<td>25.2</td>
<td>19.3</td>
<td>16.8</td>
</tr>
</tbody>
</table>

*Table 17  Estimated parameter values for the dispersion parameters $\sigma$ associated with workplace contacts*

To estimate $p$ (the probability of contact with an age-matched person in the individual’s school or workplace) for each index individual, we extract the total number of contacts $N$ expected to occur during one day within the school or workplace from the contact rate matrices. This number should be equal to the sum of all the individual probabilities of contact with the other members of the school or workplace, because it is Poisson binomial distributed. That is, $N = \sum_b P_C(a, b) = \sum_b f_\sigma(x_{a,b})$ where $a$ designates the index individual and $b$ the other members of the congregate setting. Given that $f_\sigma$ has been previously estimated (see preceding paragraph), we obtain $p$ using the following equation: $p = N/\sum_b f_\sigma(x_{a,b})$.

**Contacts in other locations**
Prem and colleagues also provided age-specific contact rates for social interactions occurring outside of households, schools and workplaces. We use these estimates to generate such social contacts in the model. For a given index individual belonging to age category $i$, we generate the numbers of contacts for all the different age categories $j$ using Poisson distributed variables. The mean of each of these Poisson variables is the age-specific contact rate $A_{i,j}$. The contacted individuals are then selected at random from the population.

**Simulated overall contact patterns**

Figure 50 presents the age-related contact patterns obtained for each contact locations, along with the aggregated contact patterns.

![Simulated age-specific contact patterns by country and location](image)

**Figure 50** Simulated age-specific contact patterns by country and location
6.7.3 Model of tuberculosis

6.7.3.1 Natural history

Once infected with *M. tuberculosis*, individuals may or may not progress to active disease. The estimates obtained from our previous study are used to determine whether and when activation occurs. On development of active TB, an organ-status (smear-positive, smear-negative or extrapulmonary) is randomly assigned to the diseased individual using a multinomial distribution (Table 15). The natural history of disease for active TB cases is characterised by two variables. First, we randomly generate the type of natural outcome resulting (death or spontaneous cure) using a Bernoulli distribution, with parameter \( \Lambda \) representing the probability of spontaneous cure (i.e. the complement of the case fatality ratio). In parallel, the time from TB activation to the natural outcome occurrence is generated from an exponential distribution with rate parameter \( \lambda_N \).

Thus, the overall survival function resulting from our natural history model can be written as follows:

\[ S(t) = A + (1 - A)e^{-\lambda_N t}, \]

where \( t \) is the time from TB activation. To estimate parameters \( A \) and \( \lambda_N \), we use the survival probability reported by Tiemersma and colleagues after five years and ten years, in smear-positive and closed TB (smear-negative or extrapulmonary) cases. These data are summarised in Table 18.

<table>
<thead>
<tr>
<th></th>
<th>Five-year survival probability</th>
<th>Ten-year survival probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smear-positive TB</td>
<td>0.41</td>
<td>0.30</td>
</tr>
<tr>
<td>Closed TB (smear-negative or extrapolmonary)*</td>
<td>0.88</td>
<td>0.79</td>
</tr>
</tbody>
</table>

*Survival probabilities were not reported directly in the paper for closed TB patients. Calculation is based here on the weighted average of the studies that reported both five-year and ten-year survival.

Using these data, we obtain two survival equations for each category of disease:

\[ S_5: = S(5) = A + (1 - A)e^{-5\lambda_N} \]
\[ S_{10}: = S(10) = A + (1 - A)e^{-10\lambda_N} \]

Noting that \( e^{-10\lambda_N} = (e^{-5\lambda_N})^2 \), we can solve the system above by rearranging the equations as follows:

\[ e^{-10\lambda_N} = \frac{S_{10} - A}{1 - A} = (e^{-5\lambda_N})^2 = \left( \frac{S_5 - A}{1 - A} \right)^2 \]

Solving this equation for \( A \) and \( \lambda_N \),

\[ A = \frac{s_{10} - S_5}{1 + s_{10} - 2s_5} \quad \text{and} \quad \lambda_N = -\frac{\ln(\frac{S_5 - A}{1 - A})}{5}. \]
Figure 51 represents the survival functions for smear-positive TB cases and closed TB cases.

Figure 51  Survival probability of untreated active TB cases as simulated in our model

The parameter values obtained for the different disease categories are:

<table>
<thead>
<tr>
<th>Disease Category</th>
<th>( A )</th>
<th>( \lambda_N )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smear-positive TB</td>
<td>0.27</td>
<td>0.336</td>
</tr>
<tr>
<td>Closed TB (smear-negative or extrapulmonary)</td>
<td>0.52</td>
<td>0.058</td>
</tr>
</tbody>
</table>

Table 19  Estimated values for the TB natural history parameters

6.7.3.2  TB transmission

TB transmission may occur when an active TB case contacts a susceptible individual (see Section 6.7.2.3 for social contact description). A parameter is used to define the crude probability that a social contact results in effective contact and therefore leads to transmission (Table 15). This parameter is automatically calibrated to reproduce observed national TB prevalence aggregated for all ages. We use a two-sample Kolmogorov-Smirnov test to assess goodness of fit. We retain the parameter value that minimises the test statistic (empirical distribution distance) when comparing the distribution of prevalence values obtained from 20 isoparametric runs with a normal distribution fitted by maximum-likelihood-estimation to the prevalence estimated empirically.

The crude transmission probability is then adjusted by contact location (household, school, …) to account for various levels of contact intensities. We first derive the proportions of high-intensity contacts by location using data from a contact survey in Viet Nam and follow the authors’
suggestion that the proportions of physical contact reported for each location can be used as a proxy for the proportions of social contacts that are of high-intensity with regard to contact duration and frequency. We then assume that low-intensity contacts are half as likely to lead to transmission as high-intensity contacts (Table 15) in the base case. However, two alternate assumptions are also explored in sensitivity analyses regarding this aspect:

- **SA 1:** Only high-intensity contacts result in transmission.
- **SA 2:** Low-intensity contacts are assigned the same transmission probability as high-intensity contacts.

The probabilities of transmission per contact may then be adjusted depending on the characteristics of the two individuals involved in the contact. First, active TB cases who are extrapulmonary TB are assumed to be non-infectious (probability of transmission = 0) while a sigmoidal function ($\frac{1}{1+e^{-(age-15)}}$) is used to model a progressive infectiousness increase between ten and 20 years old (Figure 52). Next, smear-negative TB cases are assumed to be less infectious than smear-positive cases and the associated transmission probability is therefore multiplied by the parameter defining the relative infectiousness of smear-negative cases as compared to smear-positive cases (Table 15). In addition, the transmission probability is assumed to be reduced if the index TB case has been detected (Table 15), reflecting simple preventive measures implemented following TB diagnosis.

![Figure 52 Assumed infectiousness profile with age](image)

The reference used to define relative infectiousness is the infectiousness of adult individuals.

The level of susceptibility of the contacted individual may be further reduced if the individual is currently infected with *M. tb* (Table 15) or has been vaccinated at birth with Bacillus Calmette-Guérin (BCG). We use the profile described in Figure 53 to simulate the wane of BCG efficacy over time from vaccination, based on estimates provided by a retrospective population-based cohort study in Norway, and a controlled clinical trial conducted in England in 1950.
Although the latter trial reports on vaccination provided to adolescents, there is evidence to suggest that age at vaccination is not an important predictor of BCG efficacy.\textsuperscript{106} Also, note that although Nguipdop-Djomo and colleagues suggest that BCG could possibly be effective for extended periods of time, their estimates of vaccine efficacy were not significant 20-30 years and 30-40 years after vaccination.\textsuperscript{104} We therefore make the assumption that BCG is no longer effective 30 years after vaccination.

\textbf{Figure 53  Assumed wane profile of BCG efficacy}

Green and grey lines represent estimates obtained from literature (MRC 1972\textsuperscript{107} and Nguipdop-Djomo 2016\textsuperscript{104}) while the red line shows the simulated vaccine effect. Dashed lines show literature estimates associated with non-significant efficacy.

\textbf{6.7.3.3 Detection and treatment of active TB}

In addition to TB natural history events (described in Section 6.7.3.1), events related to TB detection and treatment are simulated for each diseased individual. A detection time is generated for each TB case, although detection only actually occurs if this time precedes the pre-determined time of spontaneous clearance or death. The time from TB disease onset to detection is generated from an exponential distribution. Its parameterisation relies on the value of the programmatic case detection rate, as well as the parameters defining TB natural history. The following sections describe the calculation of this exponential distribution.)

\textbf{Case detection rate (proportion)}

Let $\lambda_N$ denote the rate of the exponential distribution generating the time to the natural outcome of TB (spontaneous clearance or TB death). Let $\lambda_D$ denote the rate of the exponentially distributed variable $t_D$ representing the time to TB detection. A TB case will ever become detected if and only if $t_D \leq t_N$. Thus, the case detection rate $CDR$ can be obtained from:

$$CDR = P(t_D \leq t_N)$$
$$= P(\exists t \geq 0; \{ t_D = t \} \cap \{ t \leq t_N \})$$
\[\int_0^{+\infty} f_D(t) \cdot (1 - F_N(t)) \cdot dt = \int_0^{+\infty} \lambda_D e^{-\lambda_D t} \cdot e^{-\lambda_N t} \cdot dt\]

\[= \frac{\lambda_D}{\lambda_D + \lambda_N}\]

**Calculation of the rate of the exponential process associated with the time to detection**

As the case detection rate (proportion) is more commonly available than the average time to detection, the input parameter used in the model is the \(C_{DR}\). That is, the rate of the exponential distribution used to generate the time to detection is obtained by rearranging the latest equation to obtain:

\[\lambda_D = \frac{C_{DR}}{1 - C_{DR}} \lambda_N.\]

Note that the detection parameter \(\lambda_D\) differs according to the type of disease, as TB natural history (characterised by \(\lambda_N\)) is different for smear-positive cases compared to smear-negative or extrapulmonary cases. Specifically, assuming the same \(C_{DR}\) for all forms of TB leads to a greater average time to detection of smear-negative and extrapulmonary cases.

**Treatment of active TB**

Detected cases of TB are assumed to be started on treatment seven days after detection. In case of successful completion of treatment, infection is assumed to be cleared as a consequence of treatment, such that the individual returns to a susceptible state. If treatment fails, the patient’s TB will remain active and the individual’s outcome will be defined by his/her associated TB natural history as initially generated (Section 6.7.3.1).

**6.7.3.4 Time-variant programmatic parameters**

In order to account for the changing characteristics of TB control in the different countries, we allow parameter values to vary over time for three important programmatic indicators: BCG vaccination coverage, case detection rate and treatment success rate. Data extracted from the WHO (case detection and treatment success rates) and UNICEF (vaccination) databases are used to fit the associated scale-up curves (Figure 54). These time-variant parameters are used during the TB burn-in phase, simulating the period 1918-2018.
Figure 54  Fitting of time-variant programmatic parameters to data

Red dots: data. Black line: scale-up function
6.7.4 Additional results

6.7.4.1 Estimated age-specific active TB prevalence for India, China and Pakistan

Figure 55 Age-specific active TB prevalence for India, China and Pakistan
Error bars represent the 95% simulation intervals
6.7.4.2 Considering an alternative age-specific infectiousness profile

This section presents the results of our analysis performed considering a different age-specific profile of infectiousness as presented on Figure 56.

![Alternative age-specific infectiousness profile for sensitivity analysis](image)

**Figure 56 Alternative age-specific infectiousness profile for sensitivity analysis**

This profile is based on a linear infectiousness increase between the ages of 10 and 15 years old. The age-category 10-15 years old is now assumed to be more infectious compared to the baseline assumption presented in Figure 52.

Figure 57 to Figure 60 present the results associated with this sensitivity analysis for the five countries.

This sensitivity analysis shows similar findings to those obtained at baseline. However, we note a higher TB burden in the 10-15 year-old population under this scenario, which highlights the sensitivity of our estimates regarding the young populations to the assumed infectiousness profile. The other model outputs pertaining to transmission and LTBI age-distribution were unaffected by the change in infectiousness profile.
Figure 57 Contributions of the various locations to the burden of contact and transmission (alternative infectiousness profile)
Error bars represent the 95% confidence intervals obtained from simulation.
Figure 58  Age-specific profile of social mixing and transmission (alternative infectiousness profile)
Figure 59  **Age-distribution of latent tuberculosis infection (alternative infectiousness profile)**
The volume of the spheres is proportional to the following quantities: 2018 population (grey), latent tuberculosis infection (LTBI) prevalence in 2018 (green), and number of individuals currently infected in 2018 who will ever develop active TB (purple).

Figure 60  **Age-distribution of TB cases (alternative infectiousness profile)**
Age of TB cases at activation (red) were recorded over a period of five years starting from 2018. Error bars represent the 95% confidence intervals obtained from simulation for the TB age-distribution.
6.7.4.3 *Ignoring the past programmatic background*

The results presented in this section relate to our analysis performed without time-variant parameters such that the programmatic background is supposed to have remained unchanged over time and equal to the most recent one. This analysis was applied to the Philippines.

![Figure 61  Results for the Philippines when no time-variant parameters are included.](image)

6.7.4.4 *Alternative scenarios for the risk of transmission through low- versus high-intensity contacts*

This section presents the results of the two sensitivity analyses that consider alternative relative risks of transmission through low-intensity contacts as compared to high-intensity contacts:

- **SA 1**: Only high-intensity contacts result in transmission.
- **SA 2**: Low-intensity contacts are assigned the same transmission probability as high-intensity contacts.

Note that new calibrations of the per contact crude risk of transmission were required under these scenarios. Table 20 presents the parameter values obtained for the five countries:

<table>
<thead>
<tr>
<th></th>
<th>India</th>
<th>Indonesia</th>
<th>China</th>
<th>Philippines</th>
<th>Pakistan</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(RR=0.5)</td>
<td>0.0021</td>
<td>0.0023</td>
<td>0.0021</td>
<td>0.0025</td>
<td>0.0021</td>
</tr>
<tr>
<td><strong>SA 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(RR=0)</td>
<td>1</td>
<td>0.0039</td>
<td>0.0043</td>
<td>0.0038</td>
<td>0.0050</td>
</tr>
<tr>
<td><strong>SA 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(RR=1)</td>
<td>2</td>
<td>0.0014</td>
<td>0.0017</td>
<td>0.0014</td>
<td>0.0021</td>
</tr>
</tbody>
</table>

*Table 20  Crude risk of transmission per contact under scenario SA 1*

RR: Relative risk of transmission for a low-intensity contact as compared to a high-intensity contact.

**Only high-intensity contacts can result in transmission (SA 1)**

In this sensitivity analysis, we assume that low-intensity contacts cannot lead to *M. tb* transmission.
Figure 62 Contributions of the various locations to the burden of contact and transmission (scenario SA 1)
Error bars represent the 95% confidence intervals obtained from simulation.
Figure 63  Age-specific profile of social mixing and transmission (scenario SA 1)
Figure 64  Age-distribution of latent tuberculosis infection (scenario SA 1)
The volume of the spheres is proportional to the following quantities: 2018 population (grey), latent tuberculosis infection (LTBI) prevalence in 2018 (green), and number of individuals currently infected in 2018 who will ever develop active TB (purple).

Figure 65  Age-distribution of TB cases (scenario SA 1)
Age of TB cases at activation (red) were recorded over a period of five years starting from 2018. Error bars represent the 95% confidence intervals obtained from simulation for the TB age-distribution.
Equal risk of transmission for low- and high-intensity contacts (SA 2)

In this sensitivity analysis, we assume that the risk of transmission for low-intensity contacts is equal to that of high-intensity contacts.

Figure 66 Contributions of the various locations to the burden of contact and transmission (scenario SA 2)

Error bars represent the 95% confidence intervals obtained from simulation.
Figure 67  Age-specific profile of social mixing and transmission (scenario SA 2)
Figure 68  Age-distribution of latent tuberculosis infection (scenario SA 2)
The volume of the spheres is proportional to the following quantities: 2018 population (grey), latent tuberculosis infection (LTBI) prevalence in 2018 (green), and number of individuals currently infected in 2018 who will ever develop active TB (purple).

Figure 69  Age-distribution of TB cases (scenario SA 2)
Age of TB cases at activation (red) were recorded over a period of five years starting from 2018. Error bars represent the 95% confidence intervals obtained from simulation for the TB age-distribution.

Findings from sensitivity analyses SA 1 and SA 2
When assuming that only high-intensity contacts can result in transmission, household contacts become the predominant driver of *M.tb* transmission in all countries except China. We also observe an increased TB burden affecting the 0-5 year-old category as a result of the enhanced contribution of household transmission. In contrast, assuming that the risk of transmission is independent of contact intensity results in a greater contribution of “other locations” to the TB burden as compared to the baseline scenario. As a consequence, the relative TB burden in those aged 40 years and above is diminished due to the lower frequency of contacts in “other locations” for this age-group.
7 Discussion

This Chapter presents an integrated discussion of the overall findings of the individual thesis chapters and their implications. More specific discussions are contained in each chapter.

7.1 Lessons learned

With this thesis, I aim to challenge existing paradigms of TB transmission and control using mathematical modelling. Some findings emerging from this work refute very important dogmas on which past and current TB control have consistently relied. Firstly, Chapters 2 and 3 provide substantial evidence at the global level against the current paradigm that drug resistance results mainly from poor treatment adherence and resistance acquisition. Secondly, the assumption that preventive therapy is not efficient in high-burden settings is refuted in Chapter 4. Finally, Chapter 5 highlights that the usual cut-offs of two or five years used to distinguish late latency from early latency are not appropriate to characterise the dynamics of progression from LTBI to active TB.

This thesis also clearly shows that one dogma should not necessarily be replaced by another, as results were influenced substantially by context. First, drug resistance acquisition was still found to be the primary driver of DR-TB at re-treatment in some settings, such as the American and South-East Asian regions. Second, although this thesis suggests that IPT would be most efficient in settings with a high TB incidence of 500-900 new cases per 100,000 per year, it also showed that effectiveness would be hampered under extremely high transmission pressure. Finally, characterising the TB epidemic profiles in different countries underlined the substantial heterogeneity in both the drivers of transmission and the resulting burden of disease. Such observations reveal the risk associated with rigidly adhering to broad statements and universal paradigms and highlight the need for contextualised understanding.

Perhaps more important than assessing the validity of TB-related dogmas, this thesis highlights unexpected or under-recognised mechanisms that deserve attention when designing control policies. Firstly, the exploration of the relationship between TB incidence and IPT effect has redefined the role played by repeated infections in the effectiveness of preventive therapy. Specifically, the high risk of reinfection present in high-burden settings does not only counter the effect of IPT, but also implies that latently infected individuals in these settings are at higher risk of developing disease since they are more likely to have been infected recently. Second, Chapter 5 demonstrates that the usual conceptualisation of LTBI as a phase associated with a decreasing risk of activation over time in every individual is not the only possible explanation for the profiles of reactivation empirically observed. Instead, the model fitting analysis found that individual predispositions that make some infected individuals more or less likely to progress to disease can explain these dynamics equally well. Moreover, other latency patterns than those explored in
Chapter 5 and incorporating additional transition phases and/or risk categories could possibly explain the activation dynamics observed empirically. A limitation of the model structures considered in Chapter 5 is that they systematically imply that LTBI and active TB are distinct compartmentalised states. That is, the simulated dynamics associated with these models may not be able to represent the important amount of heterogeneity observed in latent TB, and the fact that it may be difficult to distinguish subclinical active disease from quiescent infection. Alternative conceptualisations allowing for more continuous progression profiles have been suggested in previous works, offering alternatives to the classic paradigms based on a binary distinction of LTBI from active TB. Finally, Chapter 6 shows another example of an underappreciated factor in TB control, that overall epidemiology is impacted much more by preventing adult disease (which has high transmission potential) than preventing childhood disease which does not. While this has been a strong consideration in active disease treatment, it has not been considered in latent TB treatment. In the current policy context, in which individual risk of progression to active disease appears to be the main consideration in formulating guidelines on LTBI management, I believe that it is important that a larger set of factors are considered for decision making, such as the infectiousness level or the intensity of social contact. These more nuanced perspectives need to be considered to improve future decision making in global TB control.

Preventive therapy is currently deployed as a programmatic intervention predominantly through linkage to contact tracing and provided to some of the identified close contacts of active pulmonary TB patients. However, Chapter 6 of this thesis demonstrates the limited contribution of easily identifiable contacts to the burden of transmission in many settings, providing evidence that larger-scale interventions may be required to achieve significant reductions in disease burden. The findings of Chapter 4 also highlight that mass preventive programs may be efficient in high-burden settings. Moreover, the recent availability of shorter and safer regimens for LTBI treatment may overcome the obstacles that previously limited the use of preventive treatment as a population-wide intervention, such as the issues around treatment completion. Further findings from Chapter 6 highlight the unexpectedly large contribution of the adolescents and young adults to transmission and the resulting burden of active TB in high incidence settings. Consideration of these findings may result in a shift in the paradigm that young children are the main priority group for the provision of preventive therapy.

The modelling exercises presented in this thesis have also helped to uncover several important data gaps in relation to TB epidemiology and control. For example, Chapter 6 demonstrates the importance of better characterising the waning profile of the immunity conferred by BCG in order to identify the age-groups that are the most vulnerable to \( M.\text{tb} \) infection. Another example is the risk of subsequent infection in individuals previously treated for TB that is currently poorly
characterised and was shown to have a substantial impact on the estimates of IPT effectiveness in Chapter 4.

A possible criticism of some investigations conducted in this thesis is that they were based on conceptual models and that the associated conclusions may not be directly actionable in the field as they may remain too theoretical or too general. However, in anticipation of this issue, the findings have been reported flexibly in order to make them adaptable and applicable to a broad range of settings. One example is the step-by-step methodology provided in Section 5.4.6, which will allow other modellers to parameterise their TB latency structure using alternate data on the risk of progression from LTBI to active TB over time. As systematic registering of close contacts of active pulmonary TB patients is increasingly common in many settings, more insights into TB reactivation dynamics are likely to emerge over the coming years. Providing such flexibility is crucial to ensure that the methodology used for TB epidemiology and modelling remains in synchrony with the progress made in collating empirical evidence. The current format of medical research drives us to undertake single studies that are published as single journal articles, but the benefit from continued integration with policy and programs is often lost. Another example is the user-friendly web-based interface that I constructed for the project that explored the pathways leading to DR-TB at re-treatment (Chapter 3). In addition to providing the opportunity to apply the study to any setting by varying all model inputs, this tool offers a hands-on experience for policy-makers wanting to use models incorporating assumptions that reflect their understanding of local epidemiology. A necessary condition for mathematical modelling to be useful is that the persons making the decisions fully understand and trust the technical tool upon which recommendations rely. I believe that this web-based interface contributes to building such comprehension and therefore increases the potential impact of the research findings. 276 webpage visits were recorded between the public release of the interface in May 2017 and the 20th of September 2018. 60% of these pageviews originated from overseas and the average time spent using the tool was over three minutes. This suggests that this type of initiative generates considerable interest in many parts of the world (Appendix).

### 7.2 Future research and application

Future studies emerging from this work include extensions of the investigations presented here as well as further applications of the tools that were built during the research undertaken in this thesis. The investigation presented in Chapter 2 allowed identification of the important pathways generating DR-TB and highlighted local programmatic weaknesses responsible for the high rates of DR-TB among individuals previously treated for TB. These insights could directly translate into recommendations for which control interventions should be prioritised to achieve the greatest impact on the DR-TB epidemic. For example, in settings where misdiagnosis of DR-TB at initial presentation was identified as the most important cause of DR-TB among previously treated
individuals, it seems clear that increasing the coverage of drug susceptibility screening among treatment-naïve individuals with active TB should be a high priority. Nevertheless, it would be more difficult to provide detailed recommendations on the exact programmatic policies that should be adopted without quantifying their potential impact of such interventions on the DR-TB epidemic. Such insights could be provided by using a TB transmission dynamic model accounting for past and current epidemiological and programmatic backgrounds and simulating specific control interventions.

Chapter 5 demonstrates that a large majority of TB modelling studies were unable to account for the specific dynamics of progression to active TB, either because they used suboptimal model structures, or because they employed inaccurate parameter values. Although these findings raise important concerns about the previous methods employed to model LTBI, what remains unknown is the impact of using such inaccurate approaches when predicting epidemic trajectories or intervention impact. Notably, it is critical to know which specific model applications would require reactivation dynamics to be accurately captured and to assess the bias that would result from the use of suboptimal techniques in those contexts. The conclusions presented in Chapter 5 also revealed that two different model structures could be used to simulate the dynamics of reactivation identically. That is, the two compartments needed to model LTBI could be placed either in series or in parallel. Although this thesis analytically demonstrated that the dynamics associated with these two approaches are equivalent in absence of interventions, they may lead to different recommendations when simulating TB control strategies as suggested in Section 5.5.2. Therefore, an exploration of these potential differences on the programmatic impact of preventive treatment could be conducted, as the predicted effect of this intervention is likely to be sensitive to the structure used to model LTBI.

A future application of the SNAP-TB platform presented in Chapter 6 will be an investigation of the effectiveness of various approaches to LTBI treatment in specific high-incidence settings. This thesis has already highlighted the potential for efficient use of IPT in high-burden settings using a simple compartmental model and considering mass interventions (Chapter 4). SNAP-TB provides a framework to simulate additional implementation strategies such as contact-tracing-based and targeted preventive treatment and will be employed to extend the original investigation. Additionally, as most of the model features of SNAP-TB are agnostic to the actual disease being simulated, the core component of the platform could easily be used to model other infectious diseases. These core components include simulation of a household, school and workplace structure, demographic processes and social mixing. Similar insights to those provided in Chapter 6 could therefore emerge for infectious pathogens other than TB using a refitted version of the existing model.
From a broader perspective, it is hoped that the newly acquired epidemiological knowledge as well as the methodological guidance arising from this thesis will be used in the future to improve not only TB modelling techniques but also to consider new perspectives when making decisions related to disease control. During this thesis I had the chance to be directly involved in programmatic applications of TB modelling to assist country-level decision making in collaboration with the Global Fund to Fight AIDS, TB and Malaria. This experience gave me the opportunity to incorporate some freshly generated findings of this thesis – in particular those related to LTBI modelling – into the modelling methods employed. I also realised how important it is from the perspective of the funders and NTPs to have evidence of the validity and robustness of the tools that are used. This observation emphasises the vital importance of the interaction between research and programmatic application. I have chosen to continue to be involved in these two components after my thesis. This will undoubtedly give me further opportunities to apply some of the conceptual findings highlighted during this thesis to additional real-world settings and specific questions.

The availability of new TB control tools generates great hope for a rapid attenuation of this global epidemic as we look towards disease elimination in the coming decades. Even so, we should also remember that the end of TB was thought to be imminent after the discovery of anti-TB drugs almost 70 years ago and that despite this, TB still killed 1.6 million people in 2017. Experience therefore teaches us that technical progress alone will not achieve elimination and that improving epidemic understanding is critical to ensure effective use of the existing control tools. This thesis provides a demonstration that mathematical modelling can help to accomplish this task.
References

35. Lawn SD, Nicol MP. Xpert(R) MTB/RIF assay: development, evaluation and implementation of a new rapid molecular diagnostic for tuberculosis and rifampicin resistance. Future Microbiol 2011;6(9):1067-82.


52. TB prevalence down 30% in China after DOTS. Bull World Health Organ 2004;82(9):716.


69. Olle-Goig JE. Control of multidrug resistant tuberculosis. DOTS-plus strategy will be hard to implement. BMJ 1999;318(7185):736.


166. Frieden TR, Driver CR. Tuberculosis control: past 10 years and future progress. Tuberculosis (Edinb) 2003;83(1-3):82-5.


Appendix

Statistics of the web-based interface

<table>
<thead>
<tr>
<th>Page</th>
<th>Country</th>
<th>Pageviews</th>
<th>Unique Pageviews</th>
<th>Avg Time on Page</th>
<th>Entrance</th>
<th>Bounce Rate</th>
<th>% Exit</th>
<th>% Fail</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>/index.html</td>
<td>776</td>
<td>802</td>
<td>00:00:30</td>
<td>37</td>
<td>75.91%</td>
<td>59.78%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(3.4%)</td>
<td>(3.0%)</td>
<td>(3.1%)</td>
<td>(27.6%)</td>
<td>(32.3%)</td>
<td>(35.6%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>/index.html</td>
<td>33</td>
<td>33</td>
<td>00:01:11</td>
<td>24</td>
<td>70.83%</td>
<td>56.67%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1.1%)</td>
<td>(1.1%)</td>
<td>(1.1%)</td>
<td>(1.8%)</td>
<td>(2.1%)</td>
<td>(2.6%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>/index.html</td>
<td>25</td>
<td>24</td>
<td>00:02:11</td>
<td>22</td>
<td>85.40%</td>
<td>50.00%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.9%)</td>
<td>(0.8%)</td>
<td>(0.8%)</td>
<td>(1.9%)</td>
<td>(3.0%)</td>
<td>(6.7%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>/index.html</td>
<td>20</td>
<td>24</td>
<td>00:02:11</td>
<td>22</td>
<td>85.40%</td>
<td>50.00%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1.2%)</td>
<td>(1.2%)</td>
<td>(1.2%)</td>
<td>(1.9%)</td>
<td>(3.0%)</td>
<td>(6.7%)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>/index.html</td>
<td>17</td>
<td>12</td>
<td>00:02:11</td>
<td>12</td>
<td>83.33%</td>
<td>75.67%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.9%)</td>
<td>(0.6%)</td>
<td>(0.6%)</td>
<td>(0.7%)</td>
<td>(1.4%)</td>
<td>(3.5%)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>/index.html</td>
<td>13</td>
<td>12</td>
<td>00:02:11</td>
<td>12</td>
<td>83.33%</td>
<td>75.67%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.5%)</td>
<td>(0.6%)</td>
<td>(0.6%)</td>
<td>(0.7%)</td>
<td>(1.4%)</td>
<td>(3.5%)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>/index.html</td>
<td>6</td>
<td>6</td>
<td>00:01:15</td>
<td>3</td>
<td>100.00%</td>
<td>56.67%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1.9%)</td>
<td>(2.5%)</td>
<td>(2.5%)</td>
<td>(2.1%)</td>
<td>(4.4%)</td>
<td>(10.2%)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>/index.html</td>
<td>5</td>
<td>5</td>
<td>00:02:50</td>
<td>4</td>
<td>100.00%</td>
<td>83.33%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(2.1%)</td>
<td>(2.6%)</td>
<td>(2.6%)</td>
<td>(2.1%)</td>
<td>(4.4%)</td>
<td>(10.2%)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>/index.html</td>
<td>3</td>
<td>3</td>
<td>00:01:15</td>
<td>3</td>
<td>100.00%</td>
<td>40.00%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1.0%)</td>
<td>(1.0%)</td>
<td>(1.0%)</td>
<td>(1.0%)</td>
<td>(2.0%)</td>
<td>(5.1%)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>/index.html</td>
<td>4</td>
<td>4</td>
<td>00:01:15</td>
<td>1</td>
<td>100.00%</td>
<td>40.00%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1.6%)</td>
<td>(1.6%)</td>
<td>(1.6%)</td>
<td>(1.6%)</td>
<td>(3.2%)</td>
<td>(8.0%)</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>/index.html</td>
<td>3</td>
<td>3</td>
<td>00:02:50</td>
<td>2</td>
<td>100.00%</td>
<td>100.00%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1.1%)</td>
<td>(1.1%)</td>
<td>(1.1%)</td>
<td>(1.1%)</td>
<td>(2.2%)</td>
<td>(5.5%)</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>/index.html</td>
<td>3</td>
<td>3</td>
<td>00:00:00</td>
<td>3</td>
<td>100.00%</td>
<td>100.00%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1.1%)</td>
<td>(1.1%)</td>
<td>(1.1%)</td>
<td>(1.1%)</td>
<td>(2.2%)</td>
<td>(5.5%)</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>/index.html</td>
<td>2</td>
<td>2</td>
<td>00:00:00</td>
<td>2</td>
<td>100.00%</td>
<td>100.00%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.8%)</td>
<td>(0.8%)</td>
<td>(0.8%)</td>
<td>(0.8%)</td>
<td>(1.6%)</td>
<td>(4.0%)</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>/index.html</td>
<td>2</td>
<td>2</td>
<td>00:00:00</td>
<td>2</td>
<td>100.00%</td>
<td>100.00%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.8%)</td>
<td>(0.8%)</td>
<td>(0.8%)</td>
<td>(0.8%)</td>
<td>(1.6%)</td>
<td>(4.0%)</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>/index.html</td>
<td>2</td>
<td>2</td>
<td>00:00:00</td>
<td>2</td>
<td>100.00%</td>
<td>100.00%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.8%)</td>
<td>(0.8%)</td>
<td>(0.8%)</td>
<td>(0.8%)</td>
<td>(1.6%)</td>
<td>(4.0%)</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>/index.html</td>
<td>2</td>
<td>2</td>
<td>00:00:00</td>
<td>2</td>
<td>100.00%</td>
<td>100.00%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.8%)</td>
<td>(0.8%)</td>
<td>(0.8%)</td>
<td>(0.8%)</td>
<td>(1.6%)</td>
<td>(4.0%)</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>/index.html</td>
<td>2</td>
<td>2</td>
<td>00:00:00</td>
<td>2</td>
<td>100.00%</td>
<td>100.00%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.8%)</td>
<td>(0.8%)</td>
<td>(0.8%)</td>
<td>(0.8%)</td>
<td>(1.6%)</td>
<td>(4.0%)</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>/index.html</td>
<td>2</td>
<td>2</td>
<td>00:00:00</td>
<td>2</td>
<td>100.00%</td>
<td>100.00%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.8%)</td>
<td>(0.8%)</td>
<td>(0.8%)</td>
<td>(0.8%)</td>
<td>(1.6%)</td>
<td>(4.0%)</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>/index.html</td>
<td>2</td>
<td>2</td>
<td>00:00:00</td>
<td>2</td>
<td>100.00%</td>
<td>100.00%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.8%)</td>
<td>(0.8%)</td>
<td>(0.8%)</td>
<td>(0.8%)</td>
<td>(1.6%)</td>
<td>(4.0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Study ID</td>
<td>Country</td>
<td>Treatment</td>
<td>N</td>
<td>Death</td>
<td>Death Code</td>
<td>Date of death</td>
<td>Code of death</td>
</tr>
<tr>
<td>---</td>
<td>----------</td>
<td>-------------</td>
<td>-----------</td>
<td>----</td>
<td>-------</td>
<td>------------</td>
<td>----------------</td>
<td>---------------</td>
</tr>
<tr>
<td>20</td>
<td>185.01</td>
<td>Belgium</td>
<td>1</td>
<td>(0.0%)</td>
<td>(0.0%)</td>
<td>00.00.00</td>
<td>09.22.11</td>
<td>00.00.00</td>
</tr>
<tr>
<td>21</td>
<td>185.01</td>
<td>Canada</td>
<td>1</td>
<td>(0.0%)</td>
<td>(0.0%)</td>
<td>00.00.00</td>
<td>09.02.44</td>
<td>00.00.00</td>
</tr>
<tr>
<td>22</td>
<td>185.01</td>
<td>Egypt</td>
<td>1</td>
<td>(0.0%)</td>
<td>(0.0%)</td>
<td>00.00.00</td>
<td>09.00.00</td>
<td>00.00.00</td>
</tr>
<tr>
<td>23</td>
<td>185.01</td>
<td>Ethiopia</td>
<td>1</td>
<td>(0.0%)</td>
<td>(0.0%)</td>
<td>00.00.00</td>
<td>09.00.00</td>
<td>00.00.00</td>
</tr>
<tr>
<td>24</td>
<td>185.01</td>
<td>Honduras</td>
<td>1</td>
<td>(0.0%)</td>
<td>(0.0%)</td>
<td>00.00.00</td>
<td>09.00.00</td>
<td>00.00.00</td>
</tr>
<tr>
<td>25</td>
<td>185.01</td>
<td>India</td>
<td>1</td>
<td>(0.0%)</td>
<td>(0.0%)</td>
<td>00.00.00</td>
<td>09.00.00</td>
<td>00.00.00</td>
</tr>
<tr>
<td>26</td>
<td>185.01</td>
<td>Italy</td>
<td>1</td>
<td>(0.0%)</td>
<td>(0.0%)</td>
<td>00.00.00</td>
<td>09.00.00</td>
<td>00.00.00</td>
</tr>
<tr>
<td>27</td>
<td>185.01</td>
<td>Kenya</td>
<td>1</td>
<td>(0.0%)</td>
<td>(0.0%)</td>
<td>00.00.00</td>
<td>09.00.00</td>
<td>00.00.00</td>
</tr>
<tr>
<td>28</td>
<td>185.01</td>
<td>Morocco</td>
<td>1</td>
<td>(0.0%)</td>
<td>(0.0%)</td>
<td>00.00.00</td>
<td>09.00.00</td>
<td>00.00.00</td>
</tr>
<tr>
<td>29</td>
<td>185.01</td>
<td>Nigeria</td>
<td>1</td>
<td>(0.0%)</td>
<td>(0.0%)</td>
<td>00.00.00</td>
<td>09.00.00</td>
<td>00.00.00</td>
</tr>
<tr>
<td>30</td>
<td>185.01</td>
<td>Serbia</td>
<td>1</td>
<td>(0.0%)</td>
<td>(0.0%)</td>
<td>00.00.00</td>
<td>09.00.00</td>
<td>00.00.00</td>
</tr>
<tr>
<td>31</td>
<td>185.01</td>
<td>Sweden</td>
<td>1</td>
<td>(0.0%)</td>
<td>(0.0%)</td>
<td>00.00.00</td>
<td>09.00.00</td>
<td>00.00.00</td>
</tr>
<tr>
<td>32</td>
<td>185.01</td>
<td>Uganda</td>
<td>1</td>
<td>(0.0%)</td>
<td>(0.0%)</td>
<td>00.00.00</td>
<td>09.00.00</td>
<td>00.00.00</td>
</tr>
</tbody>
</table>