EPIDEMIOLOGIC IMPACT OF TREATMENT INTERVENTIONS FOR TUBERCULOSIS CONTROL

by
Mariam Olivia Fofana

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ABSTRACT

Background

Once thought to be on its way to elimination, tuberculosis (TB) has resurged in recent decades and is now the leading cause of death among infectious diseases globally. Effective TB control will require optimal implementation of treatment interventions in order to maximize the potential benefits not only for individual patients but also at the population level.

Methods

We conducted three studies using dynamic compartmental models of TB transmission to project the potential impact of shortened duration of first-line TB therapy on TB incidence and mortality (Chapter II), the effect of re-using pyrazinamide in both first- and second-line treatment on the emergence of extensive drug resistance (Chapter III), and the value of treatment scale-up and programmatic improvements in the control of multidrug-resistant (MDR) TB (Chapter IV).

Results

Contrary to previous studies, we find that shortening the duration of first-line TB therapy is unlikely to yield major reductions in incidence over a time span of 15 years (projected reduction 1.9% with 4-month vs. 6-month treatment). We then demonstrate how the routine use of pyrazinamide in both first- and second-line TB treatment may promote the emergence of extensively drug-resistant TB. In the last study, we find that although

scaling up treatment of MDR TB may substantially reduce future prevalence (median reduction in MDR TB prevalence 28.1% over 20 years), combining scale-up with programmatic interventions that improve linkage to care and treatment completion maximizes impact (median reduction 74.5%).

Conclusions

This work provides valuable guidance in optimizing treatment interventions to achieve population-level impact in global TB control.

DISSERTATION READERS AND FINAL ORAL EXAMINATION COMMITTEE

Richard Chaisson, MD

Committee Chair

Professor, Department of Medicine

David Dowdy, MD, PhD

Dissertation Advisor

Associate Professor, Department of Epidemiology

Justin Lessler, PhD

Associate Professor, Department of Epidemiology

Lawrence Moulton, PhD

Professor, Department of International Health

ALTERNATE READERS

Colleen Hanrahan, PhD

Assistant Scientist, Department of Epidemiology

Ying Zhang, MD

Professor, Department of Molecular Microbiology and Immunology

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"Le chemin de la connaissance est toujours à sens unique."

~Claire France

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~Alain Ayache, Lettres à Prunelle

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"A journey is best measured in friends rather than miles."

~Tim Cahill

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~Ahmadou Kourouma, En attendant le vote des bêtes sauvages

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CHAPTER I

"No pestilence had ever been so fatal, or so hideous. Blood was its avatar and its seal."

~ Edgar Allan Poe, "The Masque of the Red Death"

"La phtisie sociale s'appelle misère."

~Victor Hugo, Les Misérables

INTRODUCTION

Clinical and epidemiological significance of tuberculosis

Once thought to have been conquered, tuberculosis (TB) has resurged as a public health threat in recent decades. It is now the leading cause of death among infectious diseases, with an estimated 9.6 million new cases annually resulting in 1.5 million deaths [1]. Individuals become infected when they inhale airborne droplet nuclei containing bacilli of *Mycobacterium tuberculosis* (*M. tb*) into the alveoli of the lungs [2]. Most persons with an intact immune system clear these bacilli or enter a state of so-called latent infection, in which they remain asymptomatic [3]. Although TB can infect and cause disease in nearly every human organ and tissue (e.g., brain, bone) pulmonary TB accounts for the vast majority of cases and deaths [1, 4]. It also accounts for the majority of transmission, as sick individuals expel *M. tb*-containing droplets when they cough or speak. These droplets can then remain suspended in the air for hours to days, to be inhaled by susceptible individuals [2].

It has been estimated that nearly one-third of the world population harbors latent TB infection, which can be diagnosed by immune sensitization using tuberculin skin testing or interferon-gamma release assays [3, 5]. However, the majority of such infections never

cause disease: only ~5% of immunocompetent persons will progress to active disease—characterized by cough, fever, weight loss, and cavitary lung lesions—within weeks to months. An additional ~5% will experience reactivation over the course of their lifetime and become symptomatic and infectious [3, 6]. The risk of developing active disease is much greater among immunocompromised individuals: HIV-infected persons experience an estimated 5-10% risk of progression to disease annually (as opposed to 5-10% lifetime risk for immunocompetent persons), making TB one of the leading causes of morbidity and mortality among HIV patients [1, 7].

Treatment and epidemiological control of TB

TB control in the 20th and 21st centuries has relied heavily on treatment of active disease. The first drug active against TB, streptomycin, became available in the 1940s. The subsequent development of additional drugs and clinical trials of various drug combinations and treatment durations led to the adoption of the standard six-month, four-drug regimen still in use today [8]. For patients with no previous history of tuberculosis and no known drug resistance, this first-line treatment consists of a two-month intensive phase with a combination of isoniazid (INH), rifampin (RIF), ethambutol (EMB) and pyrazinamide (PZA), followed by an additional four months of INH and RIF [9].

With the advent of an effective treatment regimen came the hope that TB would soon be eliminated. By shortening the course of disease—and thus the duration of infectiousness—successful treatment had the potential to interrupt the chain of transmission and stem TB rates. In the 1990s, the World Health Organization (WHO)

developed the directly observed treatment-short course (DOTS) strategy, aiming to control the global TB epidemic by detecting at least 70% of cases and successfully treating at least 85% of detected cases, ensuring adherence via direct observation of treatment by healthcare providers [10, 11]. Despite initial success in decreasing the incidence and prevalence of TB, the DOTS strategy was soon faced with major challenges, including poor treatment outcomes, resistance to available drugs, and the spread of HIV, leading to the resurgence of this age-old disease as a major global health threat [1, 12]. The WHO "Stop TB Strategy", established in 2006 in accord with the Millennium Development Goals and the Stop TB Partnership, has set targets of reducing both TB incidence and TB mortality by 90% between 2015 and 2035, with the ultimate goal of elimination (incidence of active disease below 1 case per million) by 2050 [13, 14]. These targets were carried forth in the new "End TB Strategy", established in 2014 in alignment with the Sustainable Development Goals [15, 16]. Currently, global TB incidence is declining at less than 2% per year but this decline falls far short of the estimated 20% annual decline that would be needed to achieve these targets for TB control [1, 17].

TB treatment challenges: treatment duration and drug resistance

Unlike most respiratory infections (e.g., community-acquired pneumonia), which can be treated with a few days or weeks of antibiotics, TB treatment currently requires at least 6 months [9, 18], and approximately 8% of patients who initiate first-line TB treatment do not complete the full course. Although this figure may seem relatively low, it is important

to note that it varies widely across countries and/or TB control programs, with some settings reporting as many as 50% of patients discontinuing treatment [1].

The success of the DOTS strategy has also be greatly hampered by the rise of resistance to available drugs. Resistance to streptomycin, which was initially used as monotherapy, arose quickly in the early days of TB pharmacotherapy. Selection of drug-resistant mutants occurs via a variety of mechanisms at the pathogen level [19]. With regard to the infected host, drug-resistant TB occurs either during inadequate treatment, or by primary transmission. Inadequate treatment due to administration of ineffective drugs, poor adherence, or other factors (e.g., variations in host pharmacokinetics, differential drug penetration in specific tissues or lesions, drug-drug interactions—especially in the context of HIV treatment) can exert selective pressure leading to preferential survival and growth of bacilli that are resistant to one or more drugs in the treatment regimen [19-22]. Such resistance is likely acquired early in the course of treatment, when bacterial populations are sufficiently large and there is enough replication for spontaneous resistance-conferring mutations to arise. Resistance to any one (or more) drug(s) in a treatment regimen decreases the number of effective drugs and thus lowers the barrier to selection of additional resistance. Individuals with resistance acquired in this manner may then transmit their drug-resistant bacilli to susceptible individuals; such events constitute primary transmission of drug resistance [23]. Although drug resistance initially emerges via inadequate treatment in a fully susceptible population (as was the case for streptomycin in the early treatment era), as more and more individuals harbor and transmit drug-resistant disease, primary transmission accounts for an increasing

proportion of drug resistance [24, 25]. Even as the overall incidence of TB has declined, there has been an increase in multidrug-resistant (MDR) TB, defined as TB that is resistant to both INH and RIF—the two primary drugs in first-line treatment.

Globally, approximately 4% of new TB cases and 20% of previously treated cases are due to MDR strains but the epidemiology of MDR TB varies widely by country and region. Some of the highest levels of MDR TB are reported in Eastern Europe: in Belarus, as many as 34% of new TB cases and 69% of previously treated cases are resistant to at least RIF and INH [1]. Currently, available treatment regimens for MDR TB rely on drugs that are less efficacious against *M. tb* than RIF and INH, and much less tolerable. Typical combination regimens include a fluoroquinolone and an injectable aminoglycoside, supplemented with pyrazinamide, bacteriostatic antimycobacterials (e.g., para-aminosalicylic acid), and antibiotics with uncertain efficacy and/or safety in TB treatment (e.g., linezolid) [9, 26]. Treatment typically requires 18-24 months, of which 6 months require daily injections of an aminoglycoside, at great discomfort to patients and high cost to both patients and health systems [9]. Moreover, several of the drugs used to treat MDR TB can cause severe toxic effects (e.g., irreversible hearing loss, cardiac irregularities) [26]. Not surprisingly given the prolonged duration and poor tolerability, many patients are unable to complete a full course of treatment: upwards of 20% of patients with MDR TB discontinue treatment. Even among those who do complete a full course of treatment, the probability of cure is approximately 50% globally [1, 27, 28].

Future prospects for TB treatment and control

The challenges of treatment discontinuation and drug resistance have led to renewed efforts to develop novel drugs and regimens for the treatment of both drug-susceptible and drug-resistant TB [29-31]. In contrast with HIV treatment, which has been continually improved by the development of new, often more effective and less toxic drugs, treatment of TB remains stuck in the 20th century [32]. No new anti-TB drugs were developed for decades since rifampin became available in the 1960s. Indeed, bedaquiline made worldwide headlines in 2012 as the first new TB drug to be approved in 50 years [33]. With several new TB drugs in the development pipeline now, a number of trials have been planned and/or undertaken to evaluate potential new treatment regimens. Among these trials, several have evaluated the possibility of shortening first-line treatment from the current 6 months to 4 months using fluoroquinolone-based regimens. Unfortunately all of the 4-month regimens that have been evaluated in Phase III trials thus far have not met non-inferiority criteria compared to the current 6-month regimen [34-36]. Trials are still ongoing for a 4-month regimen combining a novel drug, pretomanid (formerly known as Pa-824), with moxifloxacin and PZA [37].

Given the limited number and efficacy of drugs for MDR TB, several drugs (including new, repurposed, and existing antimicrobials) have been investigated as potential additions to the current arsenal, with the aims of improving regimen efficacy, shortening treatment duration, and/or reducing toxicity [26, 38-41]. Because current MDR TB treatment is orders of magnitude more costly (and logistically more challenging) to administer than first-line treatment, access remains largely limited to high-resource

countries. One obstacle to treating patients with MDR TB is the poor availability of drug susceptibility diagnostics to identify such patients, and the delay to diagnosis associated with traditional, culture-based methods [1]. The development and deployment of rapid molecular diagnostics for RIF resistance such as GeneXpert could help expand the availability of drug susceptibility testing and MDR TB treatment, but access remains limited, especially in low-resource settings [1, 42]. The End TB Strategy calls for universal access to treatment, as well as the necessary drug susceptibility diagnostics to identify MDR TB patients, but progress remains slow [15, 16]. In 2011, across 30 countries with significant MDR TB burden, an estimated 18% of MDR TB patients received second-line treatment, and a median 53% (interquartile range 41-71%) of those who initiated treatment completed it [43].

Limitations of clinical trials and utility of mathematical models

As new drugs and regimens are developed, evaluated, and made available, policy-makers face the decision of how best to implement them to not only benefit individual patients, but also contribute to TB control efforts at the population level. Without proper guidance, policies may fail to implement interventions that would accelerate the decline of TB or, conversely, adopt harmful and/or wasteful interventions. It is therefore essential that these decisions be informed as best as possible by estimates of their potential impact on long-term epidemiologic trends, and with adequate consideration of sources of uncertainty. Clinical trials provide indispensable information on the effectiveness and tolerability of treatments, but they measure effectiveness only at the level of individual patients, and under optimal conditions. Moreover, infectious diseases are inherently

dynamic and have feedback effects: levels of transmission are dependent on the number of infectious individuals in a population, and the levels of transmission in turn determine the rate of change of the infectious pool over time. Consequently, individual-level effects cannot predict long-term population-level outcomes [44]. Although cluster-randomized studies could estimate population-level effects, the resources and long-term follow-up required makes them unfeasible for a wide range of interventions. This is particularly limiting as policy-makers typically need to make decisions in the present based on the expected future outcomes [45].

Dynamic mathematical models that simulate key mechanistic aspects of the natural history and transmission of infectious agents have increasingly been used to fill these gaps, as ideal tools for the study of so-called "dependent happenings" [46]. A widely applied approach for dynamic modeling of infectious diseases, widely referred to as the Susceptible-Exposed-Infectious-Recovered (SEIR) framework, developed by Kermack and McKendrick and popularized by Anderson and May, uses differential equations to project changes in a population divided into compartments or classes based on disease and infectiousness status [47, 48]. Additional complexity with regard to the number of classes and the rates of transition between them can be incorporated, balancing the detail necessary to capture the relevant aspects of disease and transmission, availability of data to inform model parameters, and interpretability of model behavior and results. Model structure can also reflect various subtypes or strains of the pathogen, pathways of care-seeking, treatment algorithms, etc… [49, 50] Compartmental models can also incorporate stochastic dynamics [51]. As such, dynamic models have become important components

of the policy-making toolbox, providing long-term projections of population-level impact and cost-effectiveness of interventions [52]. Because these models represent mechanistic aspects of disease and transmission, they are also useful in investigating the intrinsic dynamics of disease transmission and the impact of uncertainty in the data that inform the model. These models can be used to project impact in a variety of epidemiologic and resource settings, under alternative implementation scenarios. They are therefore particularly valuable in informing decisions when empirical data are scarce or cannot feasibly be obtained, as they can identify key drivers of outcomes and areas of uncertainty, and thus guide and prioritize the collection of empirical data [45, 53, 54].

Study objectives

Despite the challenges faced by the DOTS strategy, treatment remains a key component of the TB control armamentarium. This work aims to use dynamic mechanistic ("mathematical") models to project the potential population-level impact of treatment interventions on TB epidemiologic trends. Specifically, we examine the potential impact of shortened treatment duration, choice of drugs in sequential regimens, and scale-up of treatment access and programmatic improvements. Chapter II re-examines previous model projections [55] of the impact of shortened first-line treatment on future TB incidence; we refine these previous models by incorporating data on the outcomes of incomplete courses of treatment, demonstrating that previous modeling analyses overestimated the projected epidemiologic impact. In Chapter III, we examine the effect of re-using PZA in sequential treatment regimens on the emergence of extensive drug resistance. Chapter IV projects the potential impact of treatment scale-up for MDR TB in

Southeast Asia, in combination with improvements in linkage to care and treatment completion, to identify intervention combinations that maximize epidemiologic impact. Finally, Chapter IV summarizes the study findings in the context of ongoing research, the limitations and strengths of the work, and public health implications.

Put together, these studies aim to inform forthcoming decisions by providing insight into the value of treatment approaches and interventions as a means of curbing the global TB epidemic.

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CHAPTER II

"Health care is vital to all of us some of the time but public health is vital to all of us all of the time."

~C. Everett Koop

POPULATION-LEVEL IMPACT OF SHORTER-COURSE REGIMENS FOR TUBERCULOSIS

Mariam O. Fofana[1,2], Gwenan M. Knight[3], Gabriela B. Gomez[4,5], Richard G. White[3], David W. Dowdy[1,6]

1. Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA
2. Medical Scientist Training Program, Johns Hopkins School of Medicine, Baltimore, MD, USA
3. TB Modelling Group, TB Centre and Centre for the Mathematical Modelling of Infectious Diseases, London School of Hygiene and Tropical Medicine, London, UK
4. Department of Global Health, University of Amsterdam, Amsterdam, Netherlands
5. Amsterdam Institute for Global Health and Development, Amsterdam, Netherlands
6. Center for Tuberculosis Research, Johns Hopkins University School of Medicine, Baltimore, MD, USA

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ABSTRACT

Despite current control efforts, global tuberculosis (TB) incidence is decreasing slowly. New regimens that can shorten treatment hold promise for improving treatment completion and success, but their impact on population-level transmission remains unclear. Earlier models projected that a four-month regimen could reduce TB incidence by 10% but assumed that an entire course of therapy must be completed to derive any benefit.

We constructed a dynamic transmission model of TB disease calibrated to global estimates of incidence, prevalence, mortality, and treatment success. To account for the efficacy of partial treatment, we used data from clinical trials of early short-course regimens to estimate relapse rates among TB patients who completed one-third, one-half, two-thirds, and all of their first-line treatment regimens. We projected population-level incidence and mortality over 10 years, comparing standard six-month therapy to hypothetical shorter-course regimens with equivalent treatment success but fewer defaults.

The impact of hypothetical four-month regimens on TB incidence after 10 years was smaller than estimated in previous modeling analyses (1.9% [95% uncertainty range 0.6-3.1%] vs. 10%). Impact on TB mortality was larger (3.5% at 10 years) but still modest. Transmission impact was most sensitive to the proportion of patients completing therapy: four-month therapy led to greater incidence reductions in settings where 25% of patients leave care ("default") over six months. Our findings remained robust under one-way

variation of model parameters. These findings suggest that novel regimens that shorten treatment duration may have only a modest effect on TB transmission except in settings of very low treatment completion.

INTRODUCTION

Tuberculosis (TB) is the second leading cause of death from a single infectious agent: it is estimated that one-third of the world population is infected with TB, with 8.7 million developing active disease and 1.4 million dying each year [1]. In the last 25 years, over 20 new drugs to treat human immunodeficiency virus (HIV) infection have been developed; in contrast, the primary first-line treatment for TB—requiring six months of therapy with moderately toxic agents—has remained unchanged [2-5]. Globally, approximately 7% of TB patients who receive first-line therapy do not complete this six-month course [1], but in some settings this percentage is as high as 30-50% [6]. Incomplete treatment results in higher risk of relapse, continued disease transmission, and emergence of drug resistance [6]. If the goal of global elimination of TB by 2050 is to be attained, it is widely recognized that new drugs capable of curing TB more rapidly will be necessary [1, 7].

For the first time in decades, novel treatment regimens hold the realistic promise of shortening the standard six-month first-line TB treatment course [8-10]. If their efficacy is confirmed in ongoing trials, these novel regimens could reduce healthcare costs [11] and improve both patient satisfaction and treatment outcomes [12, 13]. However, a key consideration for public health programs is the potential of novel TB regimens to impact population-level epidemiological outcomes, specifically future incidence and mortality. The expectation that shorter treatment will help control transmission has been a key driver of ongoing efforts by global organizations to develop new drugs and regimens for TB [14, 15].

Mathematical (transmission) models are important tools for estimating the potential impact of new technologies and informing policy [16]. Prior models have projected long-term TB incidence reductions of 10-40% from the introduction of shorter-course TB regimens [17, 18]. However, these models have generally assumed that TB therapy is ineffective unless a full course is completed. In reality, patients who receive no treatment can experience spontaneous resolution [19], and follow-up from early randomized trials demonstrates that partial courses of treatment (two to four months) can achieve durable cure in a considerable proportion of patients [20-22]. Using data from these trials, we constructed a mathematical model of TB treatment (Figure 2.1) to more realistically assess the impact of novel, shorter-course first-line treatment regimens (four months, two months, and two weeks) on population-level transmission and compare our results to previous estimates.

METHODS

Model Structure

We used ordinary differential equations to construct a deterministic compartmental model of TB transmission (Figure 2.1). This model resembles previous TB models [23, 24] in its basic design but adds additional structure to reflect the process of TB treatment.

Specifically, we model TB treatment as consisting of four sequential phases: weeks 1-2, weeks 3-8, months 3-4, and months 5-6. Individuals with active TB must be successfully diagnosed before they can initiate the first phase of treatment. Upon starting treatment,

the bacillary burden decreases rapidly, and individuals on treatment are assumed to be non-infectious after the first two weeks [25, 26]. In each treatment phase, individuals may either die, leave care ("default"), or progress to the next phase (Table 2.1). Patients who default either return to the active (infectious) state or advance to the "cured/recovered" state; the probability of cure increases with increasing duration of therapy, as informed by data from clinical trials of two-month and four-month treatment regimens [20-22]. We took the conservative stance that all individuals who relapse within the longest follow-up period from any available trial (60 months) receive no benefit from treatment and thus return immediately to the active TB compartment; all other individuals are assumed to be cured. Thus, for example, the proportion cured among individuals taking more than four, but less than six, months of standard therapy was set equal to the proportion of individuals who completed a four-month regimen of streptomycin, isoniazid, rifampin, and pyrazinamide and had no long-term relapse. These individuals—like all others who are latently infected or cured (therapeutically or spontaneously) —remain susceptible to reinfection.

Treatment scenarios

Our primary outcomes were TB incidence and mortality at 10 years, comparing continued use of the current six-month regimen to the introduction of novel, shorter regimens (four months, two months and two weeks), assuming that these shorter regimens will have the same efficacy as the current regimen. We defined treatment efficacy as the proportion of people completing the full course of TB therapy who are cured without long-term relapse. Since efficacy is assumed to be similar for all regimens,

shorter regimens are modeled as superior to standard therapy in three ways. First, the proportion of treatment completion is higher; for example, any individual who defaults during months 5-6 of a six-month regimen would have completed therapy on a four-month regimen. Second, completion of any treatment phase represents completion of a greater proportion of total treatment in shorter-course regimens, and we model the probability of cure as a function of the proportion of total treatment course completed (beyond the first two weeks). Thus, for example, taking two months of treatment equates to 33% completion of the six-month regimen but 50% completion of a four-month regimen. Probabilities of cure at each phase of treatment are shown in Figure 2.2. Third, in addition to improving cure rates among those completing therapy, we assume that shorter regimens avert TB-related mortality that otherwise occurs during stages of treatment after the shorter regimen is completed, although this effect may not be large enough to result in statistically superior outcomes in a clinical trial.

Model assumptions, calibration and data inputs

The model was designed to be simple and transparent, in order to increase the interpretability of results and comparability with previous models of shortened treatment duration. We modeled a hypothetical, non-age-structured population with a life expectancy of 70 years, assuming no net migration or population growth. We excluded non-pulmonary TB, as such cases are unlikely to be infectious and constitute only 14% of notified cases worldwide [1]. Although poor treatment adherence may lead to primary drug resistance, our focus was on first-line regimens, so we did not separately model the transmission of drug-resistant TB. There is no evidence that novel treatment regimens

would have differential indications or impact according to HIV status; we therefore modeled our population to reflect the weighted average of WHO-reported outcomes (including both HIV-associated and non-HIV-associated TB). As our focus was on treatment rather than diagnosis, we assumed the "active TB" compartment to be a weighted average of smear-positive and smear-negative pulmonary TB, thus avoiding the requirement to explicitly parameterize smear status. These simplifying procedures allowed us to generate a model with a minimum of parameters and assumptions, ensuring that model behavior was driven by the parameters of greatest interest and limiting the potential for results to be driven by extraneous factors.

We first set the rate at which individuals with active TB are diagnosed and initiate treatment ("TB treatment rate") such that the duration of active TB matched the WHO-estimated duration of disease (prevalence/incidence), using the most recent data available at the time of the analysis (2012); at steady-state, this rate corresponded to 67% of active TB cases initiating treatment before death or spontaneous resolution, similar to WHO global estimates [1]. Using a modified downhill simplex approach, we then estimated a transmission parameter (number of secondary infections per infectious person-year) that resulted in the 2012 WHO-estimated global TB incidence at steady-state to within ±0.1. We used the steady-state model as our initial population, both for mathematical rigor and to improve the ability for others to replicate and generalize our results.

Other model parameters were taken as fixed, based on best available literature; parameters relating to TB mortality and treatment failure, default and success were based

on WHO data (Table 2.2) [1]. Additional details on input derivation are provided in Appendix Table A.2. Primary model outcomes are obtained using the reference values in Tables 2.1 and 2.2 as inputs

Sensitivity and uncertainty analyses

We performed wide sensitivity analyses on model data parameters to assess the robustness of our findings and their generalizability to alternative epidemiological settings. We selected upper and lower bounds for each parameter based on literature estimates (Tables 2.1, 2.2). For parameters that strongly influenced TB incidence (transmission rate, proportion of infections resulting in "primary progressive" TB, protection from reinfection in the latent TB state), we evaluated scenarios corresponding to 50-200% change from the baseline incidence. We therefore evaluated settings of "moderate" (62 per 100,000/year), "global reference" (125 per 100,000/year), "very high" (250 per 100,000/year), and "extreme" (1,000 per 100,000/year) incidence [1], by varying the transmission rate, primary progression, and latent protection parameters individually. The modeled impact of shorter regimens on incidence remained similar regardless of which of these three parameters was varied. For simplicity, therefore, we present only results from varying the proportion of primary progression. Similarly, we evaluated the proportion of treatment default, which varies widely across settings, by constructing alternative scenarios of "low" (3%), "global reference" (7%), "high" (12.5%), and "very high" (25%) default. We assessed all possible combinations of incidence/default scenarios in a two-way sensitivity analysis.

In order to further assess the range of results that might be expected across a wide range of epidemic settings (in which parameter values would be expected to vary simultaneously), we performed a probabilistic uncertainty analysis using Latin Hypercube Sampling to generate at least 1,000 probabilistic combinations of values for all model parameters simultaneously [27]. Values for each parameter were sampled from beta distributions with the baseline value as the mode, upper and lower bounds of ±50% baseline, and shape parameter (alpha) of 4. We excluded simulations resulting in unrealistic scenarios for a globally representative epidemic (i.e., greater than ±50% variation in baseline incidence [62 – 188 per 100,000]) and verified that this did not result in a biased selection of individual parameters (Appendix Figure A.3). Uncertainty ranges for model outcomes were calculated using the 2.5^{th} and 97.5^{th} percentiles of 1,000 simulations after restricting results in this fashion.

We also assessed the ability of our model to replicate the results of previous models of shorter TB treatment that did not consider the efficacy of partial treatment. We modified our model's transition parameters such that default always resulted in treatment failure (and return to the infectious active TB state), and we set the probability of treatment success upon completion of shorter regimens using data inputs from one such model (six-month regimen: 84%; four-month regimen: 89%; two-month regimen: 96%) [17]. Finally, we assessed the effect of changes in structural assumptions (details in Appendix A). All simulations were performed using R, version 3.0.1 (R Foundation for Statistical Computing).

RESULTS

Epidemiologic impact of shorter treatment regimens

Primary model outcomes are shown in Figure 2.3. Starting from a steady-state "global reference" rate of 125 new cases per 100,000 population, introducing a four-month treatment regimen reduced incidence by only 1.9% [95% uncertainty range 0.6-3.1%] over 10 years; the shorter two-month and two-week regimens reduced incidence by 4.3% [1.8-7.0%] and 6.7% [3.0-10.2%], respectively. For all treatment durations, the rate of incidence reduction peaked in years 2-3, suggesting that the greatest impact of shorter TB regimens on transmission would occur within the first few years of implementation. The impact on TB mortality was greater but still modest. The four-month, two-month, and two-week regimens reduced mortality by 3.5%, 7.5%, and 13.1% at 10 years, respectively (Figure 2.3).

Scenario analyses

We assessed the robustness of our findings to a variety of epidemic settings, reflecting the wide variations in disease transmission and treatment infrastructure across countries. Shortening the average duration of infectiousness before diagnosis from 16 to 2 months while maintaining the baseline incidence attenuated the impact of the four-month regimen (1.0% incidence reduction at 10 years). The impact of novel regimens on TB incidence was greater (2.4% 10-year reduction) in a very high-incidence scenario (250 per 100,000/year, similar to Ethiopia [1]) and attenuated (1.0% 10-year reduction) in a moderate-incidence scenario (62 per 100,000/year, similar to China [1]), reflecting the relative proportion of incident TB due to recent transmission in such settings. Effects on

TB mortality were similar in both scenarios (3.2% [moderate incidence] – 3.7% [very high incidence] 10-year reduction). Finally, in the setting of low treatment default (3%), the four-month regimen decreased incidence by only 0.7% at 10 years, whereas in settings of high (12.5%) and very high (25%) default, incidence fell by 3.4% and 7.1%, respectively. To compare our findings with those of previous models, we constructed a scenario in which partial treatment was assumed to have no efficacy, with additional parameter changes as described in the Methods. This resulted in incidence reductions of 10.3% at 10 years and 10.5% at 35 years with a four-month regimen.

Sensitivity analyses

In one-way sensitivity analyses, no scenario resulted in an incidence decrease of more than 2.7% at 10 years with four-month therapy (Figure 2.4, panel A). Other than the protection afforded by latent infection, the two most influential parameters were the baseline TB incidence and the treatment default proportion. We therefore conducted a two-way sensitivity analysis on these parameters; the most extreme combination (incidence 1,000 per 100,000; 25% default) led to 8.3% incidence reduction at 10 years with four-month therapy (Figure 2.4, panel B). In a moderate-incidence setting (100 per 100,000/year) with a well-functioning TB control program (3% default at six months), the four-month regimen was projected to reduce incidence by 0.6% [95% uncertainty range 0.1-1.1%] at 10 years, whereas in a very high-incidence scenario (300 per 100,000/year) with poor follow-up (20% default) incidence decreased by 7.2% [3.0-11.6%]. Even in the high-burden scenario, the uncertainty analysis yielded incidence reductions of ≥10% in only 8.5% of simulations.

DISCUSSION

This mathematical model of TB treatment and transmission suggests that novel treatment regimens are unlikely to have the dramatic impact on global TB incidence projected by earlier models; specifically, we found that immediate implementation of a four-month treatment regimen could reduce TB incidence by 1.9% and mortality by 3.5% over 10 years compared to a six-month regimen of equal efficacy, suggesting that previous analyses significantly overestimated the impact of shortened treatment duration. The impact of novel shorter-course TB regimens is likely to be greater in high-incidence, high-default settings, but in most settings these regimens should be recommended on the basis of their clinical effectiveness and potential cost-effectiveness rather than a large projected impact on population-level incidence and transmission.

As with all modeling analyses, we made assumptions about structure (e.g., uninfected, latent, active TB compartments), parameter values, and transmission dynamics (e.g., homogeneous mixing). However, we selected a model that would minimize extraneous assumptions, in order to clearly demonstrate relationships between input parameters and outputs. We also varied data parameters and structural assumptions to explore a wide range of natural history, treatment, and epidemiological scenarios, with no significant change in our findings. Our results suggest more modest benefits compared to prior analyses that modeled the impact of shorter regimens by increasing the total proportion of patients completing treatment while implicitly assuming no effectiveness of partial treatment (even up to 5.9 months of a six-month treatment course completed). When we likewise assumed that partial treatment had zero efficacy, we were able to replicate the

findings of an earlier model [17] with our simpler, more transparent framework (10.5% [current model] vs. 10% [prior model] incidence reduction at 35 years with a four-month regimen). This suggests that the difference in projected epidemiological impact between previous analyses and the present model is attributable not to differences in the structure or parameter values of the two models, but rather to our incorporation of partial treatment efficacy [17].

In our model, even a two-week regimen resulted in an incidence reduction of only 6.7% at 10 years. However, if TB treatment could be made so short and non-toxic (similar to many typical antibiotic regimens) that clinicians were willing to prescribe it empirically, without waiting for diagnostic confirmation, such regimens might reduce transmission by removing delays and barriers to treatment after diagnosis; these ancillary benefits of shorter-course therapy are not incorporated in our model and may lead to underestimation of the true impact of new regimens. This underestimation is likely to be greater for ultra-short-course regimens (e.g., two weeks) than for regimens (e.g., four months) that may not be perceived as qualitatively shorter than current treatment. Because our estimates of partial treatment efficacy relied on clinical trials of regimens that are similar to the currently recommended first-line regimen, they may not reflect the efficacy of future regimens that will likely include new classes of drugs. Still, our findings remained robust to wide variations around the partial efficacy parameters in sensitivity analyses. It is important to note that novel treatment regimens are expected to provide benefits in terms of patient satisfaction, cost-effectiveness, and increased barrier to drug resistance, and should thus remain a high research priority. However, the primary justification for

deploying these regimens should be that they are beneficial to patients and health systems, not the expectation of significant impact on transmission.

Limitations of this analysis include the simplicity of the model; the model was based on global TB epidemic data and therefore may not generalize to unique epidemiological settings (e.g., prisons and other areas of high drug resistance) or settings of lower TB incidence. We intentionally chose a simple approach in order to generate a transparent modeling framework that could demonstrate the transmission impact of novel regimens in a population that is generalizable, through sensitivity analysis, to a number of potential epidemiologic settings. Nevertheless, our results are not precisely calibrated to any single population, and our sensitivity analyses suggest that the effect of shorter treatment duration on population-level incidence may vary considerably depending on the epidemic setting, with the most important drivers of impact being TB incidence and treatment default proportion. Although our results remained robust in a wide range of sensitivity analyses, our estimation of global average reductions in incidence may not reflect the likely greater impact of shorter regimens in settings of very high incidence and very high treatment default, nor do they take into account co-dynamics with HIV. It will therefore be important to conduct further analyses with models that are closely calibrated to unique epidemic and health system resource settings, particularly those (e.g., Southern Africa) with the highest rates of both TB incidence and HIV/TB co-infection.

In summary, we have used a simple, generalizable modeling framework, populated by data from randomized trials, to demonstrate that novel shorter-course TB treatment

regimens are unlikely to reduce incidence by more than 3% (upper bound of uncertainty range for a four-month regimen) to 7% (two-month regimen) over 10 years in most epidemiological settings. The projection of greater impact by previous models appears to reflect the assumption that TB therapy confers no benefit until the entire course is complete. Future studies should assess the benefits of novel regimens in specific settings with high TB incidence, treatment default, and TB-HIV co-infection, as these settings are where novel first-line regimens may have the most impact. While awaiting the results of such studies, novel TB regimens should be prioritized based on their ability to improve individual clinical outcomes and provide potential benefits to an overburdened healthcare system, not the expectation that they will dramatically reduce TB incidence and mortality at the population level.

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Table 2.1: Model inputs for TB treatment outcomes, by treatment phase

Outcome	Treatment phase					Reference(s)
	Week 0-2	***Week 3-8***	***Month 3-4***	***Month 5-6***	***Total***	
Duration	2 weeks	6 weeks	2 months	2 months	2 weeks-6 months	
Percentage defaulting (sensitivity analysis range)	0.2% (0-1.0%)	1.9% (0-4.1%)	2.7% (0-5.7%)	2.2% (0-4.8%)	7.0% (2-15%)	[1, 6]
Percentage dying (sensitivity analysis range)	1.1% (0.5-2.1%)	1.3% (0.6-2.5%)	0.8% (0.4-1.7%)	0.8% (0.4-1.7%)	4.0%	[1, 28-30]
Percentage completing treatment period	98.7%	96.8%	96.5%	96.9%	-	
Cumulative percentage remaining in therapy	98.7%	95.0%	92.1%	89.0%	89.0%	

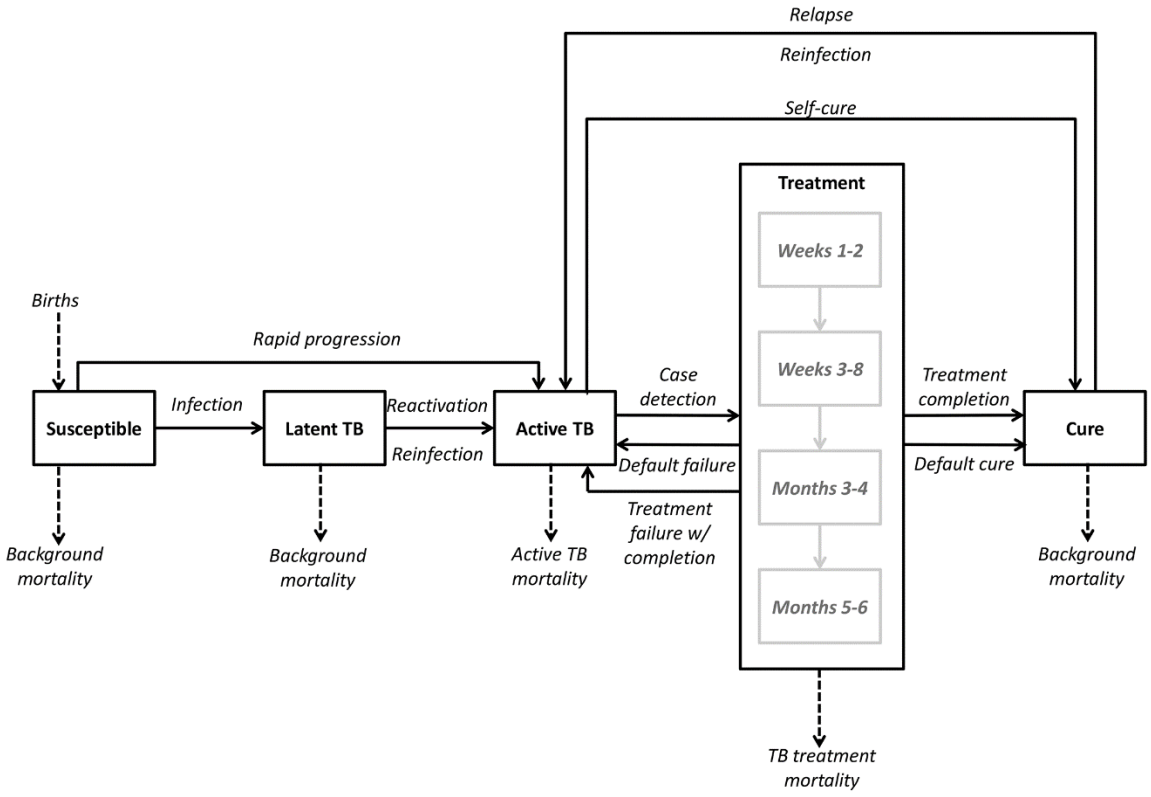
Table 2.2: Selected key input parameters for estimating transmission impact of shorter TB regimens*

Parameter	Reference value	Sensitivity analysis range	Reference(s)
Baseline annual incidence (per 100,000 population)	125	62-250	[1]
Transmissions per person-year†	8.5	6.8-20	[31]
% infections progressing immediately to active TB†	15%	5.0-21.0%	[23]
Protection from reinfection w/ prior infection	60%	30-100%	[32-34]
Relative infectiousness during treatment phase 1 (first 2 weeks) compared to active TB	50%	0-100%	Assumed
Annual risk of reactivation from latent to active TB	0.05%	0.03-0.10%	[35, 36]
Annual risk of relapse after completed treatment	0.10%	0.05-0.20%	[37]
Probability of failure among those who complete treatment	2%	1-4%	[1]
Life expectancy, years	70	40-100	[38]
Active TB mortality, per year	20%	10-40%	[19]
Self-cure without treatment, per year	20%	10-40%	[19]
Case detection ratio	67%	62-70%	[1]

* Additional model parameters are listed in Table 2.1.

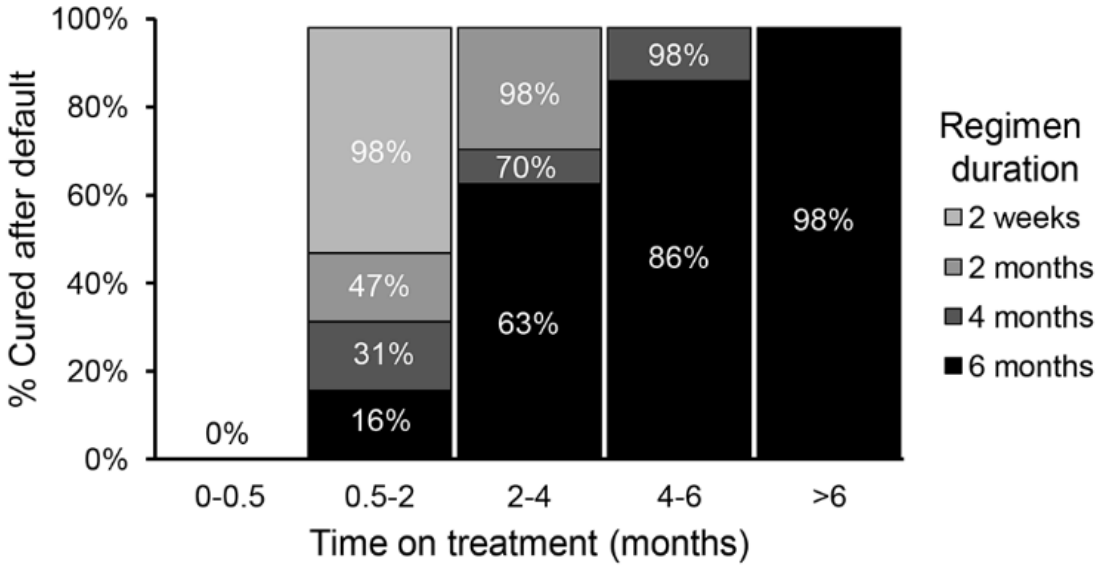
† The transmission rate was initially calibrated to TB incidence. In sensitivity analyses, incidence was varied by varying one of these two parameters (both gave similar results); the two parameters were then also varied over the ranges listed, with the other parameter varied to maintain constant incidence.

Figure 2.1: Model compartments and transition rates



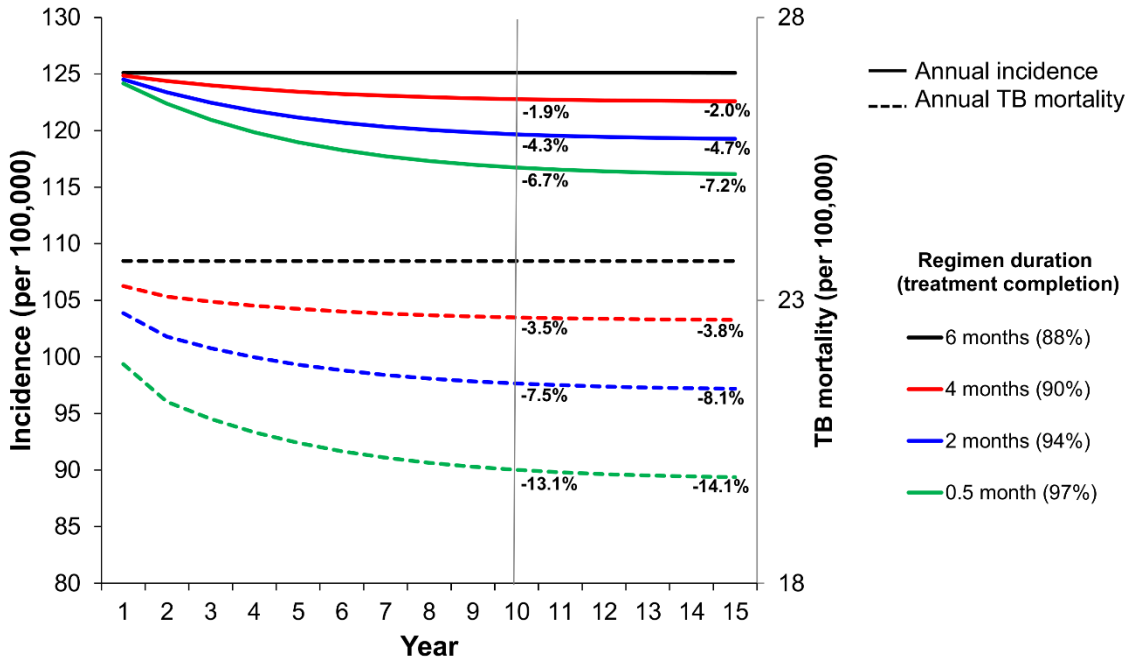
Boxes represent the proportions of the modeled population that are susceptible to infection, latently infected with *M. tuberculosis*, in active TB disease, under treatment, or cured. Arrows represent the transitions between various states, including up to four sequential phases of treatment. Rates of transition are described in the Methods section and Appendix A.

Figure 2.2: Proportion cured after default, by treatment phase and regimen duration



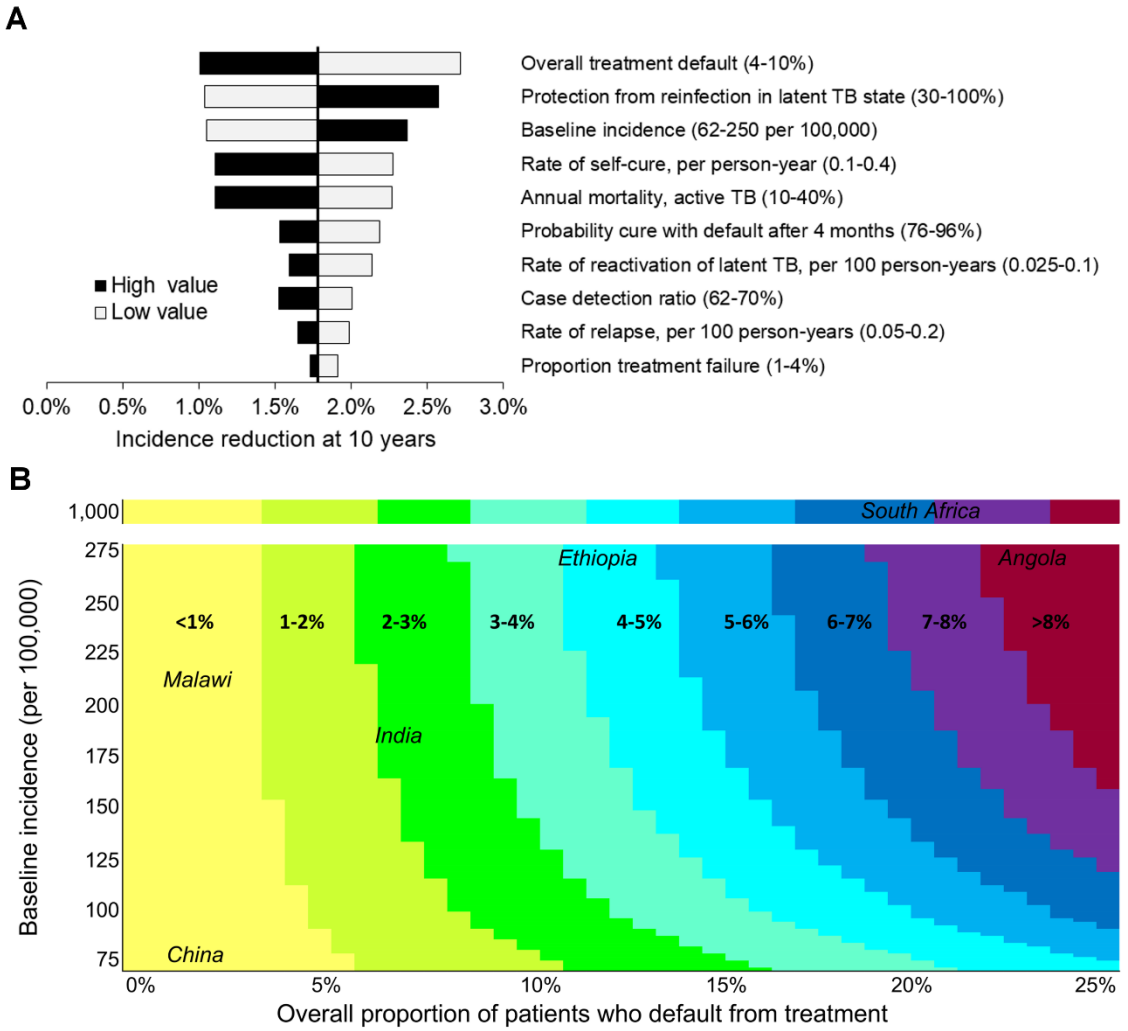
The proportion cured after default in a six-month treatment regimen was based on outcomes of early TB treatment clinical trials. For each hypothetical shortened treatment regimen, the proportion cured after default is increased according to the proportion of the total treatment duration completed. Detailed examples of calculations are provided in Appendix A.

Figure 2.3: Reduction in TB incidence and mortality achievable from shorter-course regimens over time



Assuming TB incidence of 125 per 100,000/year, and 7% overall treatment default, the implementation of a four-month regimen vs. a six-month regimen results in a 1.9% reduction in incidence at 10 years (vertical line marks year 10 after introduction of a new regimen). Hypothetical two-month and two-week regimens decrease incidence by 4.3% and 6.7% respectively.

Figure 2.4: Sensitivity analyses



One-way and two-way sensitivity analyses of the difference in incidence at year 10 after introduction of a four-month regimen versus continuation of a six-month regimen of equal efficacy. (A) One-way sensitivity analyses. Input parameters were varied one at a time within ranges consistent with estimates in the literature (Table 2.2). In this figure, we varied incidence by varying the transmission rate, but no major differences were observed when we instead varied the proportion of rapid progression to active disease. The parameters that most significantly influenced the impact of a four-month vs. six-month treatment regimen were the degree of protection afforded by latent infection,

incidence of TB disease, and the proportion of treated patients who default at baseline. (B) Two-way sensitivity analysis. The two most influential parameters likely to vary widely across epidemiological settings (TB disease incidence and proportion of treated patients defaulting at baseline) were varied simultaneously in a stepwise manner, within a range consistent with estimates in the literature and various epidemiologic settings (Table 2.2). Colors correspond to the range of projected incidence reduction for each combination of baseline incidence and treatment default and selected countries with representative estimates are shown. The highest estimates for both treatment default (25%) and baseline incidence (1,000 per 100,000/year) resulted in no more than 8.3% incidence reduction with a four-month vs. six-month regimen at 10 years.

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CHAPTER III

"Most of us aren't going to win any big victories, but we can win little ones every day, and they mount up."

~George Comstock

ROLE OF PYRAZINAMIDE IN THE EMERGENCE OF EXTENSIVELY DRUG-RESISTANT TUBERCULOSIS: A MULTI-STRAIN MATHEMATICAL MODEL

Mariam O. Fofana[1,2], Sourya Shrestha[1], Gwenan M. Knight[3], Ted Cohen[4], Richard G. White[3], Frank Cobelens[5,6], David W. Dowdy[1,7]

1. Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA
2. Medical Scientist Training Program, Johns Hopkins School of Medicine, Baltimore, MD, USA
3. TB Modelling Group, TB Centre, Centre for the Mathematical Modelling of Infectious Diseases, London School of Hygiene and Tropical Medicine, London, UK
4. Department of Epidemiology of Microbial Diseases, School of Public Health, Yale University, New Haven, CT, USA
5. Amsterdam Institute for Global Health and Development, Amsterdam, Netherlands
6. KNCV Tuberculosis Foundation, The Hague, Netherlands
7. Center for Tuberculosis Research, Johns Hopkins University School of Medicine, Baltimore, MD, USA

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ABSTRACT

Several infectious diseases of global importance—e.g., HIV, tuberculosis (TB)—require prolonged treatment with combination antimicrobial regimens, typically involving high-potency "core" agents coupled with additional "companion" drugs that protect against *de novo* emergence of mutations conferring resistance to the core agents. Often, the most effective (or least toxic) companion agents are re-used in sequential (first-line, second-line, etc…) regimens.

We used a multi-strain model of *M. tuberculosis* transmission in Southeast Asia to investigate how this practice might facilitate the emergence of extensive drug resistance, i.e., resistance to multiple core agents. We calibrated this model to regional TB and drug resistance data using an Approximate Bayesian Computational approach. We reported the proportion of data-consistent simulations in which the prevalence of pre-extensively drug resistant (pre-XDR) TB—defined as resistance to both first-line and second-line core agents (rifampin and fluoroquinolones)—exceeded pre-defined acceptability thresholds (1-2 cases per 100,000 population by 2035).

Using pyrazinamide (the most effective companion agent) in both first-line and second-line regimens increased the proportion of simulations exceeding the pre-XDR acceptability threshold seven-fold, compared to a scenario in which patients with pyrazinamide-resistant TB received an alternative drug. Model parameters related to emergence and transmission of pyrazinamide-resistant TB and resistance amplification were among those most strongly correlated with projected pre-XDR prevalence,

indicating that pyrazinamide resistance acquired during first-line treatment subsequently promotes amplification to pre-XDR TB under pyrazinamide-containing second-line treatment. These findings suggest that appropriate use of companion drugs may be critical to preventing the emergence of strains resistant to multiple core agents.

INTRODUCTION

Antimicrobial resistance has recently been labeled "a problem so serious that it threatens the achievements of modern medicine"[1]. Concerns regarding the emergence of drug resistance in the early antimicrobial era, along with the prospect of improving clinical outcomes, led to a shift from monotherapy to combination treatment for many pathogens of global importance, including HIV, tuberculosis (TB), and malaria, but the success of combination antimicrobial therapy is increasingly threatened by the rise of multidrug resistance [2-5]. Combination regimens often rely on the use of highly effective "core" drugs that have low toxicity, high microbicidal activity, and/or a high barrier to resistance, supplemented by companion drugs that are typically less active on their own but act to enhance the overall effectiveness of the regimen while also potentially preventing the emergence of resistance to core drugs. For example, in HIV combination therapy, nucleoside inhibitors often serve as companion agents to prevent resistance to the core drug classes of protease inhibitors, non-nucleoside reverse transcriptase inhibitors, and integrase inhibitors [6]. These companion drugs are frequently re-used in sequential treatment regimens when alternative companion agents are less effective or more toxic. For instance, due in part to its unique sterilizing activity against *M. tuberculosis (M. tb)* bacilli, pyrazinamide (PZA) is used to augment the effectiveness of several core agents, including rifampin (RIF) in standard first-line TB treatment, and fluoroquinolones (FQs) in most second-line regimens [7].

In evaluating the emergence of extensive drug resistance, research and surveillance efforts have historically focused on the role of core agents. However, the "recycling" of

companion drugs in sequential treatment regimens may play a critical and under-recognized role in the emergence of resistance to the core agents. This is the case for PZA, which is a recommended agent in standardized first- and second-line TB treatment regimens [8]. If concomitant use of PZA prevents the emergence of resistance to RIF and FQs (an unproven hypothesis, but one that is consistent with principles of combination drug therapy), PZA resistance may therefore be an important facilitator of the emergence of strains that are resistant to both RIF and FQs—which we define conventionally as pre-extensively drug resistant (pre-XDR) TB. To illustrate this concept, we constructed a dynamic model of *M. tuberculosis* transmission that incorporates resistance to RIF, PZA, and FQs (Figure 3.1). We use this model to generate a large set of simulations consistent with available epidemiological data up to 2013 (Figure 3.2). We then evaluate projected levels of pre-XDR TB in 2035 assuming that concomitant use of PZA protects against *de novo* resistance to both RIF and FQs. We compare a baseline scenario in which PZA is "recycled" in first- and second-line regimens to a counterfactual scenario in which PZA is replaced by a hypothetical alternative drug of equal efficacy, to demonstrate how repeated use of companion drugs can facilitate the emergence of extensively resistant strains.

METHODS

Approach

Our aim was to understand the population-level dynamics of the emergence of multiple antimicrobial resistance in an infectious pathogen treated with combination therapy but for which empirical data on the effects of different resistance patterns are sparse. To achieve this aim, we used mechanistic simulation of TB transmission and drug resistance

to project a range of plausible epidemiologic trajectories, randomly sampling parameter values to reflect inherent uncertainty in key variables related to TB drug resistance (Figure 3.1). First, we identified an outcome that could serve as a useful metric for decision-making; in our primary analysis, we use the proportion of data-consistent trajectories in which the prevalence of pre-XDR TB exceeds an acceptability threshold of 1 case per 100,000 population at 20 years. We then selected epidemiological data to which we could calibrate the model. These calibration targets, shown in Appendix Table B.4, included the prevalence and incidence of TB disease from 1990 to 2013 in Southeast Asia [9, 10]—selected as a target setting because of its high rates of TB and highly drug-resistant TB—as well as the prevalence of resistance against specific drugs for which empirical data were available. Further details of model initialization and calibration are provided in Appendix B [11-15]. For each epidemiologic calibration target, we set a tolerance range based on the degree of uncertainty around available data estimates (Appendix Table B.4). We then constructed a representative set of scenarios that might be consistent with existing data by randomly sampling parameter sets using an approximate Bayesian process, retaining those sets that resulted in simulated outcomes within our tolerance ranges. We used these data-consistent parameter sets to project epidemiologic trajectories over the ensuing 20 years. These selected parameter sets are therefore not meant to represent the entirety of all possible scenarios, nor to indicate which scenarios are more likely than others; rather, they are meant as a representative sample that can be useful to inform decision-making. This approach is illustrated step by step in Figure 3.2.

Mechanistic model structure

The core structure of our model is similar to previous compartmental models of adult pulmonary tuberculosis, assuming static population size, random mixing, and sequential progression through the stages of TB infection [16-18]. As shown in Figure 3.1, people are born in the uninfected state and can progress to latent TB infection (an asymptomatic, non-infectious state) and active pulmonary TB disease (symptomatic and infectious). Each compartment of TB infection or disease is sub-divided to explicitly track eight (i.e., 2^3) possible combinations of resistance to the three drugs considered. For any individual being treated for active TB, we assume that the treatment course will be "effective", "insufficient", or "ineffective" (defined below), with the probability of each outcome being conditional on both the pathogen's resistance profile and the drug regimen being used (Table 3.2).

We assume that "effective" treatment is curative treatment that rapidly renders individuals non-infectious, reflecting the steep decrease in bacillary burden upon treatment initiation [19, 20]. We include the possibility that some incomplete treatment courses may nonetheless be "effective," reflecting the range of possible interactions between antimicrobial agents and host immune responses. Those patients who do not complete a full course of treatment and are not cured (i.e., "insufficient" treatment) are assumed to remain ill and infectious. Treatment that results in early relapse is also represented in the model as insufficient.

In contrast to "insufficient" treatment (representing a treatment course that has curative potential but is simply not taken for a sufficient duration of time), "ineffective" treatment in this model represents a regimen that does not provide additional curative potential beyond the host's natural immune response. People on ineffective regimens remain infectious in this model, albeit at a reduced level, reflecting treatment that reduces bacillary burden sufficiently to result in negative sputum smears but does not achieve sterilization and cure. Explicitly modeling ineffective treatment allows us to account for failing treatment regimens, which we assume to last for six months on average, reflecting a time point at which treatment effectiveness is commonly assessed [8]. Individuals on ineffective regimens are assumed to remain symptomatic and/or test positive on follow-up evaluation (e.g., TB smear or culture), triggering the initiation of a repeat course of treatment. Repeat treatment may in turn be effective (leading to immediate transition to the latent compartment), insufficient (transition to the active TB compartment) or ineffective (maintenance in the ineffective treatment state), depending on the regimen chosen and the resistance profile of the pathogen.

The model distinguishes patients undergoing their first course of TB treatment from those who have previously been treated, incorporating the greater prevalence of drug resistance among treatment-experienced patients. In the baseline scenario, we assume that 5% and 26% of treatment-naïve and treatment-experienced patients with RIF-resistant TB have access to a standardized second-line treatment regimen, reflecting a combination of access to drug susceptibility diagnostics and presumptive treatment as estimated in this region [9].

Incorporation of data

Selected model inputs are shown in Tables 3.1 and 3.2 (see Appendix Table B.3 for more details). Parameters relating to diagnosis and treatment outcomes are based on WHO data and published literature. These data were incorporated in the model using logical assumptions; for instance, with the same regimen, the probability of cure for a patient with TB resistant to two drugs in the regimen cannot be greater than the probability of cure for a patient with TB resistant to just one drug [9, 21-25]. We incorporate uncertainty around these baseline outcome probabilities by varying the probability of treatment failure from zero to twice the baseline value, for each of the eight strains.

Some key parameters that lack reliable empirical estimates include: (1) the reduction in transmissibility (transmission fitness) associated with each pattern of drug resistance, (2) the probability of acquiring new antimicrobial resistance during treatment, and (3) the effect of each resistance pattern on treatment outcomes, for each combination of pre-existing drug resistance profile and treatment regimen. For these parameters, we selected values for each simulation from broad and uniform prior distributions, reflecting the inherent uncertainty in the value of these parameters and allowing sufficient coverage of extreme values. Distributions for the probability of acquiring resistance on each regimen were informed by a published meta-analysis [26], allowing for the acquisition of resistance to more than one drug under the assumption of sequential acquisition, with pre-existing drug resistance favoring the emergence of further resistance by reducing the number of active drugs.

Baseline and comparison scenarios

Using these distributions, we randomly sampled 100,000 distinct parameter sets to project trajectories and calibrate the mechanistic model as described above. We initiated simulations from a steady-state condition in the pre-chemotherapy era, sequentially introducing resistance to RIF, PZA, and FQ. All parameters were varied as described above in the baseline scenario. We also attempted to calibrate the model under the assumption that PZA confers no protection against *de novo* resistance to RIF or FQs—and thus that PZA resistance imposes no additional risk of such mutations—by setting the probability of acquiring resistance to RIF or FQs among individuals with PZA-resistant TB equal to that of patients with PZA-susceptible TB. We conducted all subsequent analyses assuming a protective effect of PZA, and compared the baseline scenario to an alternative scenario in which all patients with PZA-resistant TB receive a hypothetical drug of equal efficacy (with regard to its impact on the probability of cure and relapse).

Sensitivity and uncertainty analyses

For each parameter set considered to be consistent with current epidemiologic data, we compared the proportion of trajectories with levels of pre-XDR TB that exceeded the 20-year prevalence acceptability threshold between the baseline scenario and the alternative scenario, in which PZA is replaced by another drug. We then used multivariable logistic regression of standardized input parameter values on the expected probability of exceeding the threshold in order to identify parameters ("drivers") that are most strongly correlated with this outcome, varying the acceptability threshold and also considering partial rank correlation between inputs and pre-XDR prevalence in sensitivity analyses.

We conducted additional analyses in which we blocked specific pathways of resistance amplification by setting the corresponding probabilities to zero, reflecting a hypothetical situation in which RIF and/or FQs are replaced by another drug of equal efficacy for patients with PZA-resistant TB. For all scenarios, we express uncertainty by providing the proportion of data-consistent simulations that reached certain acceptability thresholds (rather than point estimates of pre-XDR TB resistance prevalence), and also the median and interquartile ranges of key intermediate outputs (e.g., the proportion of pre-XDR strains with concomitant PZA resistance) across all data-consistent simulations.

In order to assess the potential impact of stochastic events in the emergence (and potential die-out) of drug resistance, we constructed a stochastic adaptation of the model using the Gillespie stochastic simulation algorithm adaptive tau method [27] and replicated the analysis using this stochastic framework.

Software

The simulation model and all analyses were implemented using the software R [28]. All the code necessary to replicate the analyses, tables and figures presented here is available in an online repository: https://github.com/m-fofana/TB-PZA-model.git.

RESULTS

We first attempted to calibrate the model under our baseline assumption that PZA provides protection against *de novo* resistance to concomitantly administered RIF and FQs, as well as under the alternative assumption that PZA offers no such protection. Attempts to calibrate the model without a protective effect yielded 20-fold fewer

simulations consistent with existing epidemiologic data (47 vs. 1,015 out of 100,000 sampled parameter sets), suggesting that this assumption is probably less consistent with the available data than the assumption that PZA protects against resistance to co-administered drugs. We therefore conducted all subsequent analyses assuming that PZA protects against resistance amplification.

Across the 1,015 simulations consistent with epidemiological data (assuming a protective effect of PZA on acquired resistance), the median projected prevalence of pre-XDR TB in 2015 was 0.64 per 100,000 (interquartile range [IQR] 0.51-0.79). The proportion of RIF-resistant strains in 2035 that harbored additional resistance to PZA was greater in the baseline scenario (median 51.7% [IQR 43.7-59.5%]) compared to the alternative scenario in which PZA was replaced (median 44.7%, IQR 36.4-51.3%), although overall TB incidence was similar in both scenarios (median 205.0 per 100,000 [IQR 188.6-222.5] baseline vs. 203.7 [IQR 187.6-221.1] PZA replacement). There was an even more pronounced difference in the proportion of pre-XDR strains with additional PZA resistance (80.2% [IQR 72.9-85.6%] vs. 65.8% [IQR 57.9-72.2%]) (Figure 3.3, panels A and B). Overall, the proportion of simulations in which pre-XDR prevalence exceeded pre-defined acceptability thresholds of 1, 1.5, and 2 per 100,000 population in 2035 was 64.7%, 29.7% and 13.9% respectively in the baseline scenario, versus 23.1%, 8.1%, and 4.5% in the PZA replacement scenario. This corresponds to relative reductions of 64-73% in the proportion of simulations in which the prevalence of pre-XDR TB exceeded each acceptability threshold. Similar results are obtained using a stochastic modeling framework: the proportion of simulations in which pre-XDR prevalence exceeds the

acceptability thresholds by 2035 decreases from 52.1%, 35.7% and 24.9% in the baseline scenario, to 25.1%, 13.7% and 8.2% in the PZA replacement scenario (Appendix Figure B.8).

We used multivariable sensitivity analysis to investigate those parameters that were most closely associated with the emergence of pre-XDR TB to a prevalence of 1 case per 100,000 population by 2035 (Figure 3.4). Five of the ten most influential parameters involved PZA; these included the probability of cure for RIF/PZA-resistant TB, the transmission fitness of strains resistant to at least both RIF and PZA, and the probabilities of acquiring PZA resistance and subsequently developing additional resistance (Figure 3.4). Under the PZA replacement scenario, the odds ratios associated with the probabilities of acquiring PZA resistance and subsequent resistance amplification were most attenuated towards a null effect (i.e., OR=1). Sensitivity analyses varying the threshold to 1.5 and 2 pre-XDR cases per 100,000 population yielded similar findings, as did alternative analyses using partial rank correlation coefficients (Appendix Figure B.9).

Finally, we evaluated model scenarios in which specific steps in the progression to pre-XDR TB were inhibited, reflecting the potential effect of tailored therapy for patients diagnosed with PZA-resistant TB (Figure 3.5). In these analyses, we found that the acquisition of FQ resistance among strains already dually resistant to RIF and PZA was a key step in the development of pre-XDR TB. Blocking this single step in resistance amplification (i.e., allowing pre-XDR TB to emerge only from strains other than RIF/PZA-resistant strains) reduced the proportion of simulations exceeding each pre-

XDR acceptability threshold by four- to seven-fold, suggesting that dual RIF/PZA resistance is an important precursor of pre-XDR TB at the population level. In contrast, blocking the emergence of pre-XDR TB from RIF-monoresistant or FQ-monoresistant strains—or from FQ/PZA resistant strains—had a minimal effect on the projected pre-XDR prevalence in 2035.

DISCUSSION

This novel population-level modeling framework incorporating resistance to three distinct antimicrobial drugs suggests that, when companion drugs select against *de novo* resistance mutations in combination regimens, re-using these drugs in both first- and second-line treatment may critically facilitate the emergence of strains that are resistant to multiple core agents. Specifically, projecting the hypothetical effect of perfect susceptibility testing for PZA and replacement of PZA with another drug for patients with PZA-resistant TB dramatically reduced the proportion of data-consistent model simulations in which the projected prevalence of pre-XDR TB exceeded pre-defined acceptability thresholds within 20 years. Simulations in which we assumed that PZA does not apply selection pressure against concomitantly administered core agents were far less likely to match available epidemiologic data. These findings highlight the urgent importance of understanding the potential mechanisms by which PZA (and other companion drugs) enhances combination antimicrobial regimens, and of expanding drug susceptibility testing and surveillance for resistance to these agents, rather than focusing such efforts on core drugs alone.

Available evidence from both laboratory and clinical studies supports the sequential acquisition of resistance in TB [29, 30]. Our results suggest a similar pattern at the population level, and that re-using companion drugs could promote sequential progression to pre-XDR TB during first- and second-line treatment. Specifically, we found that the prevalence of PZA resistance was greatly increased among RIF-resistant strains, and even more so among pre-XDR strains, when PZA was re-used in both first- and second-line TB treatment. Moreover, strains resistant to both RIF and PZA featured as major precursors of pre-XDR TB. These results suggest that initial acquisition of RIF or PZA resistance may allow for the emergence of resistance to the other agent during first-line treatment, resulting in a large number of RIF/PZA-resistant strains. These strains are then more likely to develop FQ resistance during second-line therapy that includes both PZA and FQs.

These results are highly relevant to the deployment of standardized treatment regimens for MDR TB prescribed without prior diagnostic testing for resistance to drugs other than RIF—a practice that may become increasingly common with the scale-up of rapid molecular testing for RIF resistance alone [31-33]. In settings where resistance to PZA is common, indiscriminately starting patients on FQ- and PZA-containing standardized second-line regimens [8]—at the very time when mycobacterial burden, and thus incidence of spontaneous resistance-conferring mutations, is highest—may result in the selection of bacilli resistant to other drugs in the regimen, including FQs, before the results of complete drug susceptibility testing (e.g., from TB culture) are available. If PZA does indeed protect against the development of resistance to FQs during second-line

therapy, consistent with our model calibration and previous empirical studies, routine rapid testing for PZA resistance among patients with demonstrated RIF resistance would be an important means of preventing the emergence of pre-XDR TB [34, 35]. This finding takes on even greater significance in the current drug development climate, as FQs and PZA are considered key agents in the development of many novel regimens for first-line treatment of TB [36, 37].

Overall, our findings highlight the importance of considering not only the interplay between individual antimicrobial drugs, but also how these drugs are incorporated into sequential treatment regimens, in order to better control the spread of extensive drug resistance in the long term. Although our model is specific to TB, our insights regarding the importance of "recycled" companion drugs in facilitating the emergence of multi-resistant pathogens may be relevant to other infectious diseases in which resistance to the current arsenal of drugs represents a major public health threat. For example, HIV is a pathogen of major global health significance in which sequential resistance to antiretroviral drugs occurs over the course of treatment [38, 39]. As in our study, a previous model of HIV that explicitly modeled combinations of resistance to three drug classes provided important insights into drug class-specific effects on resistance trajectories [40]. Furthermore, by combining a population-level transmission model with policy-relevant outcome thresholds, our study provides useful guidance to decision-makers in the setting of sparse empirical data on key parameters related to drug resistance. This approach, which leverages available epidemiologic data and mechanistic

understanding of disease to shed light on future trajectories of drug resistance, can be adapted to other pathogens to inform risk prediction and disease control policies.

This model has several limitations. In seeking to optimize the balance of detail and parsimony, we made several simplifying assumptions, including restricting the model to adult pulmonary TB in an equilibrium population. As our focus was on exploring long-term epidemiologic trajectories rather than clinical outcomes, we chose to exclude forms of TB (i.e., childhood and strictly extrapulmonary disease) that, despite a significant disease burden, do not contribute significantly to transmission. Similarly, we chose the Southeast Asia region, where HIV is not a major driver of the TB epidemic [9], because Southeast Asia currently has higher levels of TB drug resistance. Future adaptations of this model could evaluate different epidemiologic settings, including those in which TB is driven by HIV and those (e.g., the former Soviet Union) with a long history of drug-resistant TB that may reflect high transmission of drug-resistant TB in congregate living settings (e.g., prisons).

We limited our model to three key drugs for simplicity, as the addition of additional drugs creates exponentially increasing complexity. As we used a simple acceptance/rejection algorithm to select plausible parameter sets, our results should not be interpreted as probabilistic projections of future TB epidemiology. Rather, our approach allowed us to explore a representative range of data-consistent scenarios—akin to an epidemiological study selecting a representative sample of the population—and benchmark those scenarios against potentially meaningful decision thresholds. This

approach enables us to quantify both the key considerations and the level of uncertainty in such decisions, providing a risk management tool that can inform TB control policies without the need to project the precise future of drug-resistant TB. Our conclusions were unchanged when using a stochastic modeling framework that better takes into account rare events in the emergence of drug resistance. Finally, in order to simplify our inferences on the acquisition, transmission fitness and treatment outcomes of drug-resistant strains, we kept most other model parameters at fixed values, and did not explicitly model changes in transmission fitness over time nor potential epistatic effects; our projections may therefore underestimate the true level of uncertainty in future epidemiologic trajectories.

In summary, using a novel, multi-strain modeling approach, we evaluated the impact of a companion drug on future trajectories of TB strains resistant to multiple core agents. This approach suggests that, if the companion agent (such as PZA) is used to augment the role of core drugs in both first-line and second-line regimens, the emergence of strains resistant to multiple core drugs may be dramatically hastened. As such, better data to understand how and to what degree companion drugs enhance the effectiveness of combination regimens (e.g., increased probability of cure, protection against acquired resistance)—and particularly how PZA impacts TB treatment—should be a key research priority. In the absence of such data, our results support the need for drug susceptibility testing for PZA prior to initiating second-line regimens that include PZA without a sufficient number of additional companion agents. These findings may generalize to other microbial pathogens treated with sequential combination regimens, and they highlight an

analytic approach that may become increasingly valuable for decision-making in the setting of sparse data on resistance to multiple antimicrobial regimens.

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Table 3.1: Selected input parameters (additional details in Appendix Table B.3)

Variable description	Baseline Value	References
Protection from reinfection in latent infection state	0.5	[41, 42]
Proportion progressing rapidly to active TB	0.15	[43]
Baseline life expectancy, years	70	[44]
TB-specific mortality rate, per year	0.17	[45]
Probability of endogenous reactivation, lifetime	5%	[46]
Rate of diagnosis/treatment initiation, per year	0.69	[9]
Relative infectiousness of patients on ineffective treatment	0.2	[47]
Rate of spontaneous recovery from active TB, per year	0.17	[45]
Proportion discontinuing treatment prior to completion, first-line treatment	6%	[9]
Proportion discontinuing treatment prior to completion, second-line treatment	23%	[23]
Proportion experiencing early relapse, drug-sensitive TB	4%	[48, 49]
Proportion experiencing early relapse, RIF-resistant TB	16%	[50]
Proportion experiencing early relapse, FQ-resistant TB	12%	[50]
Proportion experiencing early relapse, PZA-resistant TB	8%	[34]

RIF: rifampin; FQ: fluoroquinolone; PZA: pyrazinamide.

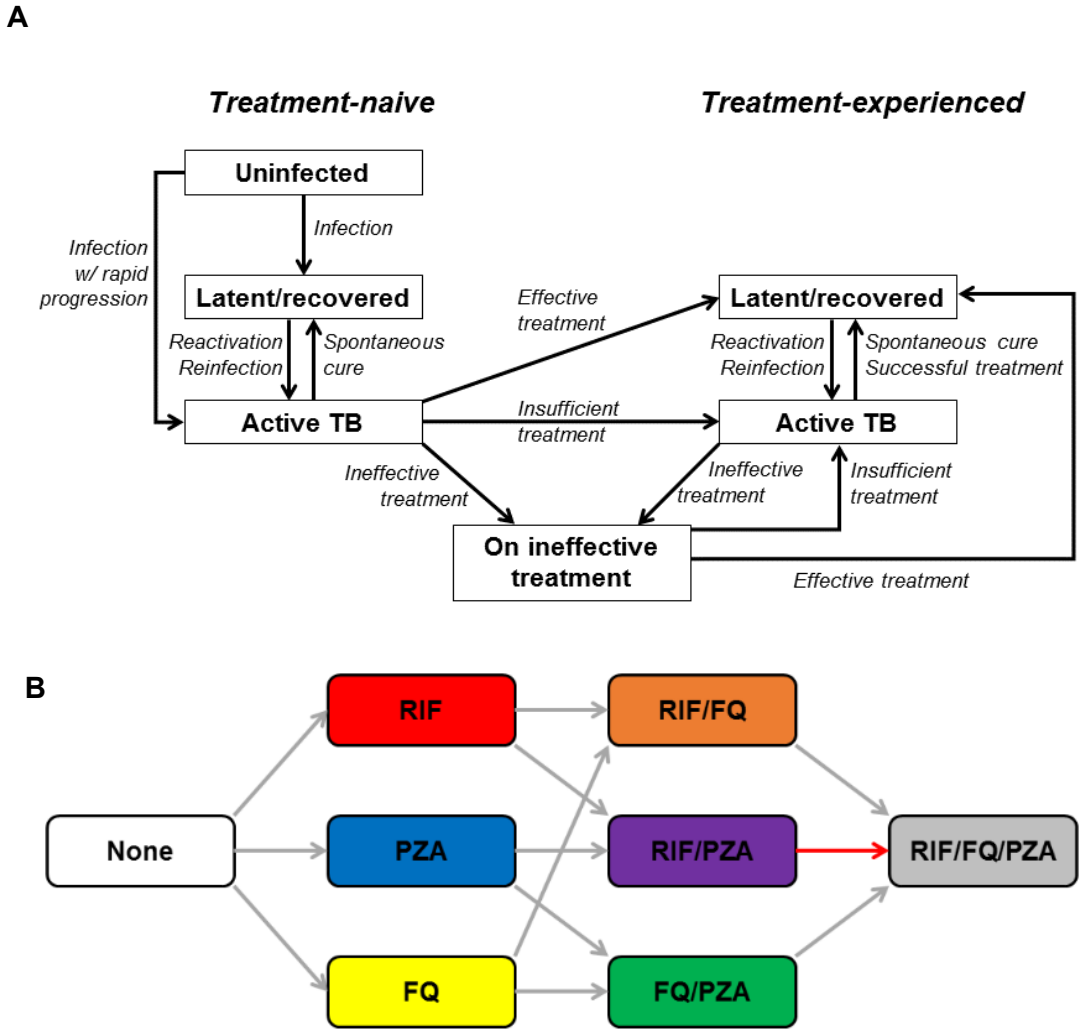
Table 3.2: Outcomes upon treatment completion, by resistance profile and treatment regimen (additional details in Appendix Table B.1)

Final drug resistance profile	Probability of cure		Probability of early relapse after cure	
	1st-line	*2nd-line*	*1st-line*	*2nd-line*
Drug-susceptible	89-99%	--	4%	--
RIFr	40-64%	89-94%	16%	4%
FQr	89-99%	--	4%	--
PZAr	83-90%	--	8%	--
RIF/FQr	40-64%	57-74%	16%	12%
RIF/PZAr	32-59%	76-86%	16%	8%
FQ/PZAr	83-90%	--	8%	--
RIF/FQ/PZAr	32-59%	47-68%	16%	12%

--: not applicable as second-line regimen is assumed to be given only to patients with resistance to at least rifampin (RIF).

PZA: pyrazinamide; FQ: fluoroquinolone.

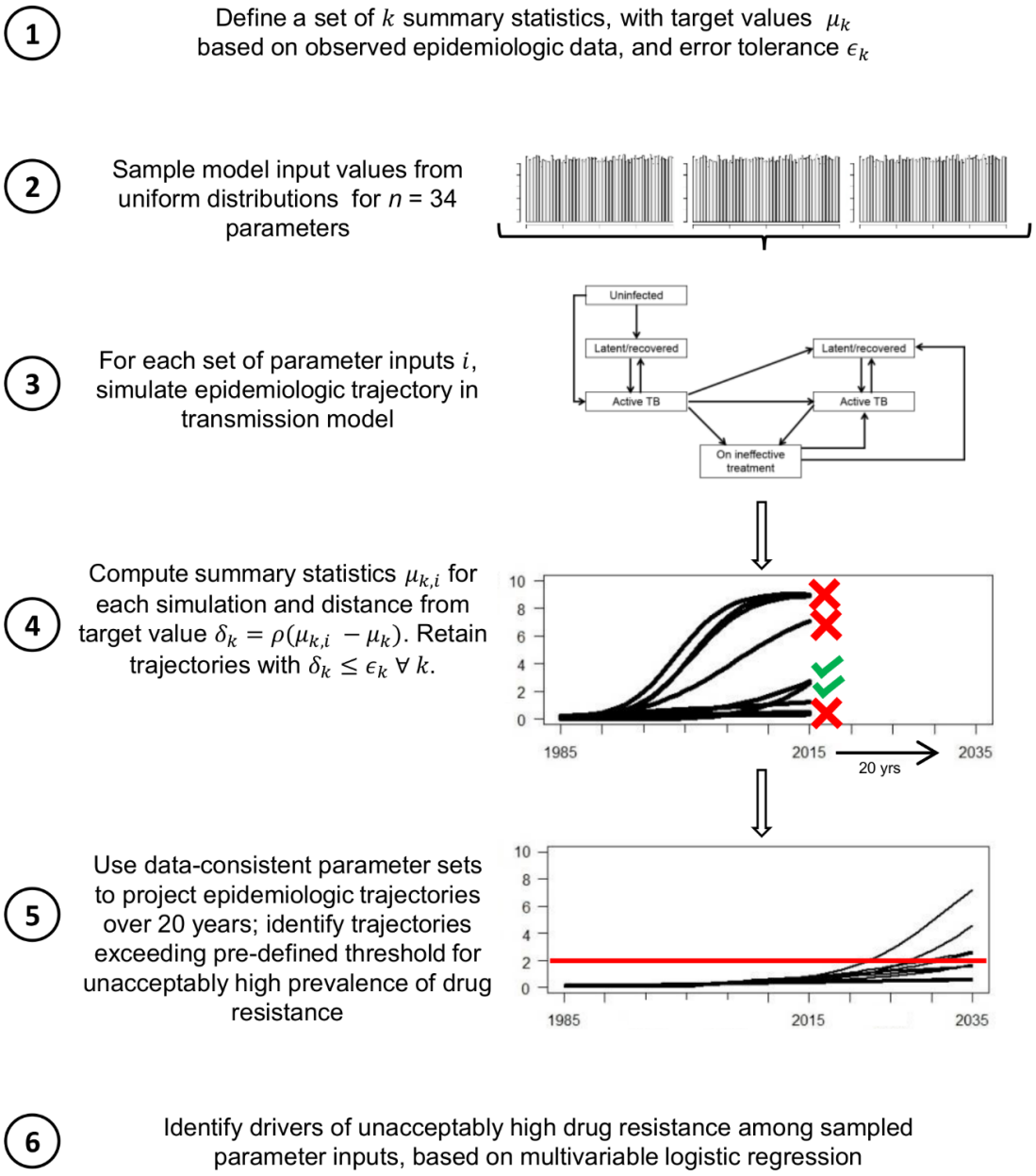
Figure 3.1: Model structure diagram



(A) The model features separate compartments for individuals who are uninfected, latently infected with TB, or experiencing active disease. Individuals with TB are further distinguished based on prior treatment experience. A separate compartment exists for patients who are receiving ineffective treatment; these individuals remain ill with TB and are then initiated on a repeat course of treatment. All five TB compartments (with the exception of "Uninfected") are replicated for each of eight drug resistance states, for a total of 41 unique compartments. Births and deaths are not shown here for simplicity.

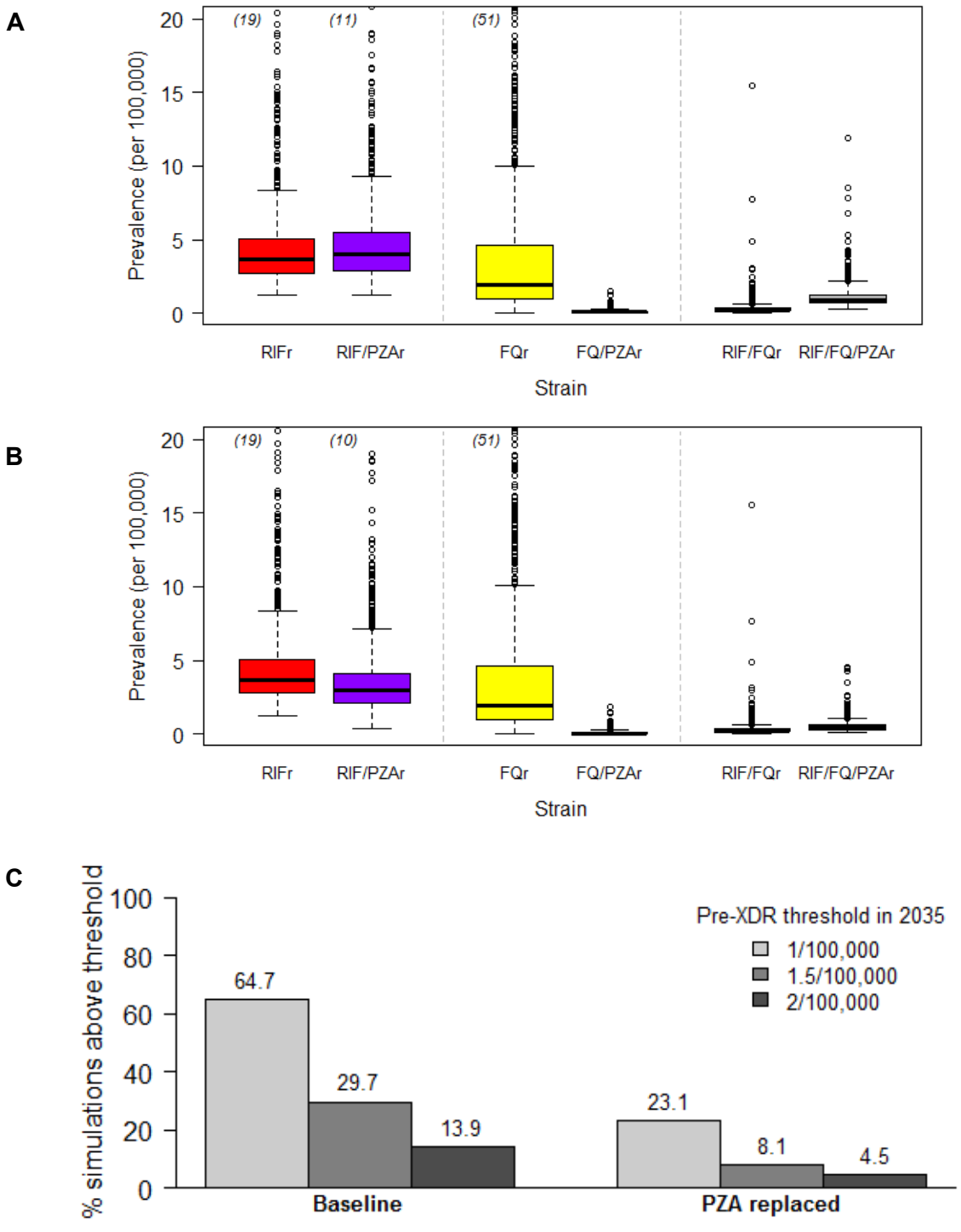
(B) Progression between drug resistance states is assumed to result only in increasing resistance. In addition to the transitions shown here, resistance to multiple drugs can be acquired within a single course of treatment. The primary mode of acquiring pre-XDR TB (defined as concomitant resistance to at least rifampin [RIF] and fluoroquinolones [FQ]), is highlighted in red and includes acquisition of resistance to pyrazinamide (PZA), a companion drug that is routinely used in both first- and second-line treatment.

Figure 3.2: Experimental approach



Shown here is the step-by-step approach of selecting simulations that are consistent with existing epidemiological data and projecting outcomes under those simulations, for purposes of elucidating dynamics between strains with different patterns of resistance to multiple antimicrobial agents.

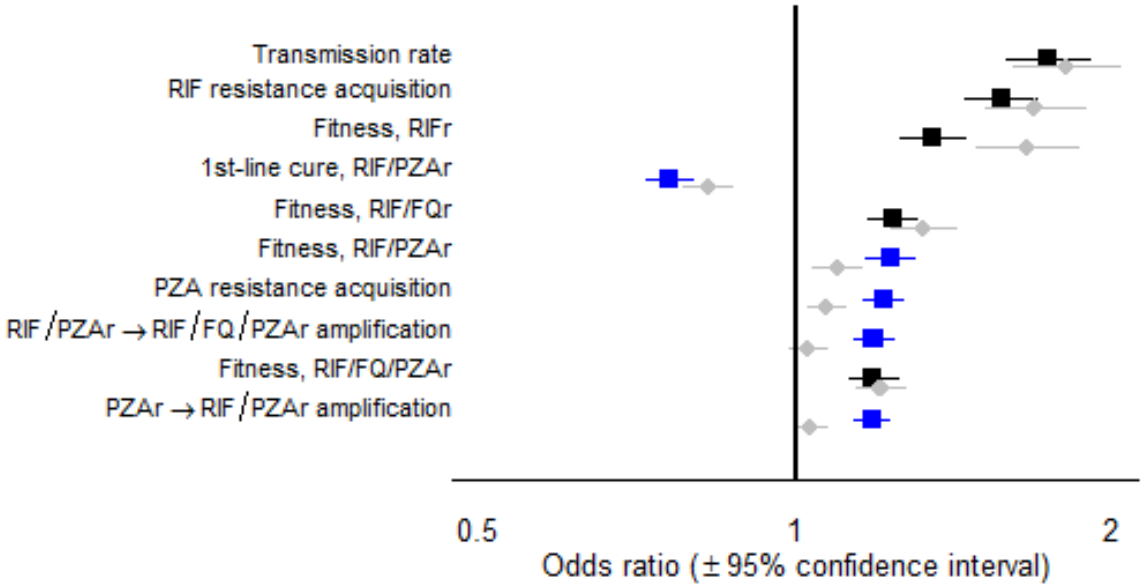
Figure 3.3: Re-use of PZA increases the projected prevalence of pre-XDR TB



Projected prevalence of RIF-resistant (RIFr), FQ-resistant (FQr), and pre-XDR (RIF/FQr or RIF/FQ/PZAr) TB, with and without additional resistance to PZA, in 2035 under the

baseline (A) and PZA replacement (B) scenarios. Boxplots show the median, 25th, and 75th percentile values across all data-consistent simulations. Outlier simulations with a projected pre-XDR TB prevalence greater than 20 per 100,000 are not shown; the number of such outliers, if applicable, is indicated in parentheses at the top of each boxplot. (C) Proportion of data-consistent simulations in which projected pre-XDR TB prevalence in 2035 exceeds three pre-defined acceptability thresholds. Replacing PZA with an alternative drug of equal efficacy among patients with PZA-resistant TB greatly reduces the proportion of trajectories exceeding the pre-XDR TB acceptability threshold in 2035. *RIF: rifampin; FQ: fluoroquinolone; PZA: pyrazinamide*

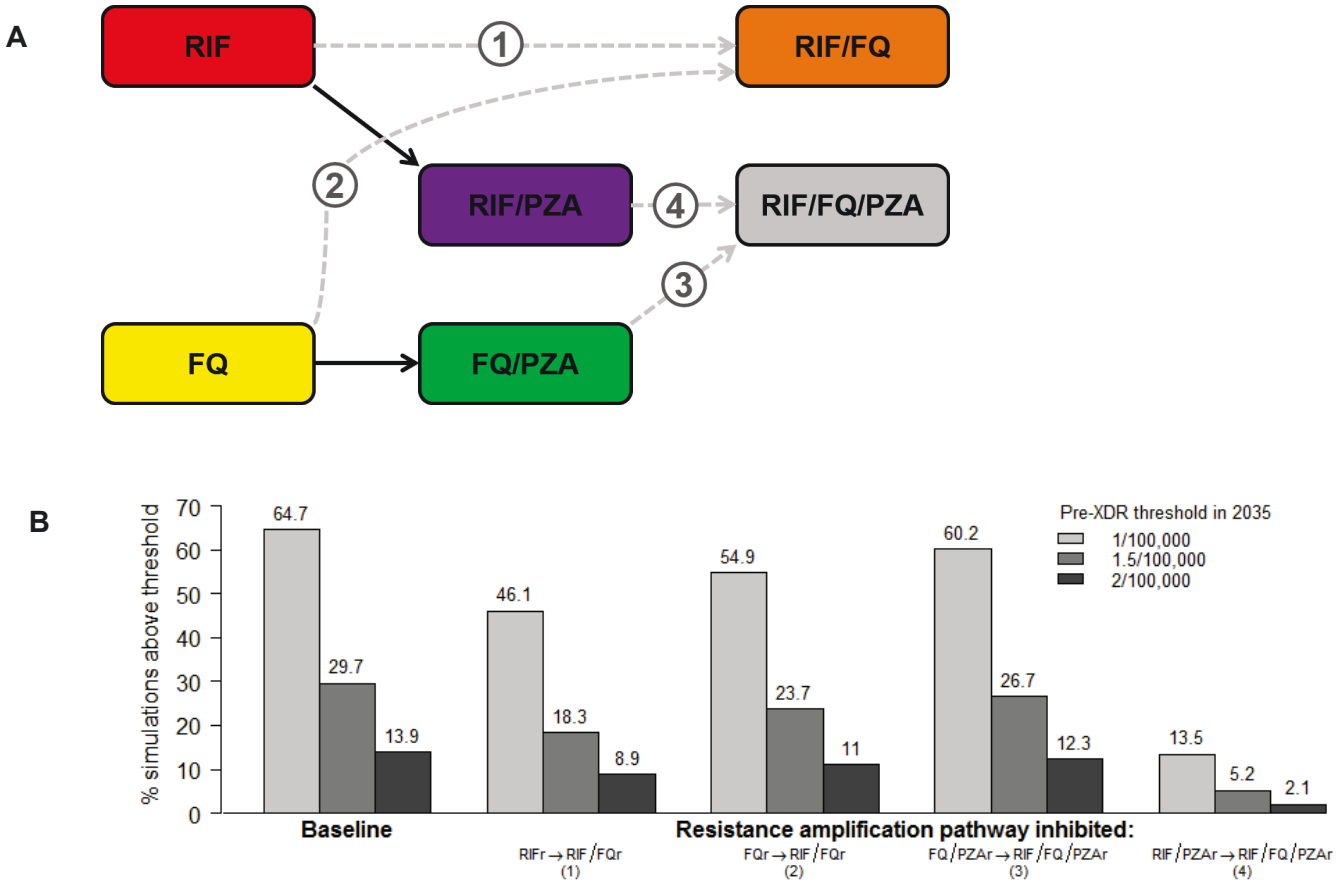
Figure 3.4: Parameters associated with high future prevalence of pre-XDR TB



Leading drivers of future pre-XDR TB prevalence as assessed by logistic regression on the odds of the primary outcome, namely exceeding a pre-defined acceptability threshold of 1 case per 100,000 population in 2035, comparing baseline conditions (blue and black squares) to the alternative scenario in which PZA is replaced (gray diamonds). Odds ratios reflect the change in the primary outcome associated with an increase of one-tenth of a standard deviation in the independent variable. Parameters related to strains resistant to PZA only (PZAr) or resistant to both RIF and PZA (RIF/PZAr) are highlighted in blue. As an example of scale, one-tenth of a standard deviation corresponds to absolute changes of 0.5% in the probability of acquiring RIF resistance in a single course of treatment, 6% in the transmission fitness of RIF/PZAr strains, or 5% in the probability of cure for RIF/PZAr strains on the first-line regimen.

RIF: rifampin; FQ: fluoroquinolone; PZA: pyrazinamide

Figure 3.5: Sequential acquisition of resistance and emergence of pre-XDR TB



(A) Pathways from RIF and FQ resistance, with and without additional PZA resistance. We demonstrate that, when PZA prevents the development of resistance to RIF and FQs, the primary pathway to developing pre-XDR TB goes through an intermediate step that includes resistance to both RIF and PZA (RIF/PZAr, arrow 4), rather than directly from RIF or FQ resistance (arrows 1 and 2).

(B) Proportion of data-consistent simulations in which projected pre-XDR TB prevalence in 2035 exceeds various acceptability thresholds, after blocking specific pathways of resistance acquisition. Blocking the progression from combined RIF/PZA resistance to RIF/FQ/PZA resistance (corresponding to arrow 4 in panel A) greatly reduces the proportion of trajectories exceeding the acceptability threshold in 2035, as shown in the rightmost bars. In contrast, blocking resistance amplification directly from strains that are RIF- or FQ-monoresistant results in minimal change from the baseline scenario.

RIF: rifampin; FQ: fluoroquinolone; PZA: pyrazinamide

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CHAPTER IV

"The future belongs to Science. More and more she will control the destinies of the nations. Already she has them in her crucible and on her balances."

~Sir William Osler

OPTIMAL IMPLEMENTATION OF SCALE-UP FOR THE TREATMENT OF MULTIDRUG-RESISTANT TUBERCULOSIS IN SOUTHEAST ASIA

Mariam O. Fofana[1,2], David W. Dowdy[1,3]

1. Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA
2. Medical Scientist Training Program, Johns Hopkins School of Medicine, Baltimore, MD, USA
3. Center for Tuberculosis Research, Johns Hopkins University School of Medicine, Baltimore, MD, USA

ABSTRACT

Drug resistance is a major obstacle to global control of tuberculosis (TB). Multidrug-resistant (MDR) TB accounts for 5% of total TB cases but a disproportionate burden of morbidity, mortality, and healthcare costs. Achieving control of MDR TB will require not only expansion of access to diagnosis and treatment, but also improvements to programmatic TB care.

We used a stochastic transmission model of TB calibrated to epidemiologic values from Southeast Asia to project the potential impact of a combination of (1) scale-up of MDR TB diagnosis and treatment to previously treated patients or all patients, (2) immediate linkage to MDR TB diagnosis and treatment for patients who remain culture-positive at the end of first-line therapy, and (3) improvements in the proportion of patients who complete the full course of treatment for MDR TB. We assume linear scale-up of MDR treatment from levels reported in 2015 to 100% by 2020, consistent with established targets.

Scaling up treatment to 100% of previously treated patients or to all patients reduced the projected prevalence of MDR TB at 20 years by a median 28.1% (interquartile range [IQR] 19.8-36.4%) and 32.9% (IQR 23.7-41.3%) respectively. Improvements in linkage to care and treatment completion decreased the projected MDR TB prevalence by 26.7% (IQR 18.2-34.3%) and 15.5% (IQR 8.2-23.9%). Combining treatment scale-up with these programmatic improvements maximized the projected impact, reducing the projected prevalence of MDR TB by 74.5% (IQR 61.5-83.9%) at 20 years.

These findings suggest that a combination of treatment scale-up and programmatic interventions (e.g., patient support) is necessary to optimally control MDR TB in high-burden settings.

INTRODUCTION

Drug resistance is widely recognized as a major obstacle to the global control of tuberculosis (TB). While the overall prevalence of TB has been declining over the past decade, there has been an increase in multidrug-resistant (MDR) TB, defined as TB that is resistant to both isoniazid and rifampin (RIF), two key drugs in the current standard first-line treatment regimen [1]. Multidrug-resistant (MDR) TB occurs in about 5% of TB cases worldwide but accounts for a disproportionate burden of morbidity, mortality, and costs [1, 2]. Although there are prospects for shorter treatment durations, treatment for MDR TB currently requires 18-24 months (vs. 6 months for first-line treatment) and relies on drugs that are more toxic yet less effective than those used in first-line therapy [3, 4]. Many patients are unable to complete the required course of treatment and, even among those who do, the proportion who are durably cured remains suboptimal (~50% global average) [1, 5].

In Southeast Asia, a region of high TB burden, an estimated 2% of treatment-naïve and 16% of previously treated TB patients have MDR TB, with only a minority of these patients (~5% treatment-naïve and 26% previously treated) getting appropriately diagnosed and treated [1]. With the development of rapid testing for MDR TB and potentially shorter, more effective regimens, widespread access to treatment for patients with MDR TB is becoming increasingly achievable even in high-burden, low-resource settings [6-8]. For example, India, the country with the largest MDR TB burden, has been scaling up diagnosis and treatment rapidly, with a target of providing universal access by 2019 [9]. As TB control programs face the challenge of curbing MDR TB and achieving the Sustainable Development Goals' target of 80% reduction in incidence by 2030, it is

crucial that available resources be expended in a way that maximizes impact at the population level as well as for individual patients.

Achieving this goal requires considering a wide range of potential interventions and improvements to TB control programs. Previous studies have projected the impact of alternate scale-up strategies (e.g., private vs. public sector, rapid molecular diagnostics) on the epidemiology of MDR TB [8, 10]. Here, we sought to provide further insight into optimal strategies for MDR TB control in Southeast Asia by evaluating the potential impact of various combinations of increased access to diagnosis and treatment, improved treatment completion, and enhanced linkage to care.

METHODS

Model structure and calibration

We modified the deterministic transmission model of TB previously described in Chapter III to incorporate both stochasticity and the combination of multiple interventions for MDR TB control. Briefly, the model structure features three main states of TB infection and disease (susceptible, latent infection, active disease), and differentiates treatment-naïve patients from those who have previously received treatment for active TB (Figure 1). Each compartment is further subdivided into eight categories of drug resistance, allowing for every possible combination of resistance to rifampin (RIF), fluoroquinolones (FQ), and pyrazinamide (PZA). Further details of the base model structure are provided in Chapter III and Appendix B. We adapted the previously described deterministic system of differential equations to a stochastic system using the Gillespie stochastic simulation algorithm adaptive tau method, implemented using the R

package “adaptivetau”. We further incorporated scale-up of MDR TB treatment, improvements in case detection, and decline in TB incidence reflective of trends in Southeast Asia in 1995-2013, as shown in Table 4.1 [1, 11]. We assume that there is no availability of second-line treatment in 2010, and that treatment access increases linearly from 2011 to reported 2015 levels. Similarly, we assume that the delay to treatment initiation decreases linearly between 2000 and 2013. We apply a 2% annual decrease in the force of infection to reflect regional trends in TB incidence [1].

We calibrate the model by first generating 200,000 simulations, each based on randomly sampled values for key model inputs (transmission fitness, probability of resistance amplification during treatment, treatment outcomes conditional on drug resistance profile and choice of treatment regimen), and a population size of 10 million individuals. We initiate each simulation in 1954, prior to the widespread use of the current first-line curative treatment, using parameters that would achieve a steady state in a deterministic model framework. We then carry out each simulation from 1954 until 2013, retaining parameter sets that meet calibration targets based on available epidemiologic data from Southeast Asia (Table 4.2). Using this procedure, we obtained 1,751 data-consistent (posterior) simulations from the original 200,000 randomly sampled (prior) parameter sets. These posterior simulations thus provide a broadly representative sample of possible epidemiologic trajectories that are consistent with available data.

Experimental overview

We use the posterior simulations described above to compare the impact of expansion of treatment for MDR TB on future epidemiologic outcomes (prevalence of drug-resistant TB, TB-related mortality) under various programmatic conditions in order to assess the relative impact of (1) the magnitude of treatment scale-up, (2) the quality of linkage to MDR TB treatment, and (3) improved treatment completion.

Treatment scale-up

The baseline scenario, reflecting no change from current conditions, assumes that 5% of treatment-naïve and 26% of treatment-experienced patients with MDR TB are properly diagnosed and initiated on MDR-specific treatment in 2015; this reflects a combination of drug susceptibility testing and presumptive diagnosis based on patient risk factors (e.g., shared household with a person with MDR TB), consistent with routine clinical practice in Southeast Asia [1, 12, 13]. We consider both a "modest" scale-up scenario in which MDR treatment is made available to patients at high risk of MDR TB (i.e., those with previous treatment history), and an "expanded" scenario in which MDR TB treatment is available to all patients. We assume linear scale-up from 2015 coverage levels to 100% by 2020, consistent with targets set by TB control programs such as in India [9], with drug susceptibility testing available for RIF only. Sensitivity (98%) and specificity (98%) for the detection of RIF resistance are set to reflect the use of currently available molecular diagnostics (e.g., GeneXpert) [14]. Patients diagnosed with RIF-resistant TB are assumed to receive a standardized treatment regimen regardless of individual resistance patterns. Patients whose RIF resistance is not appropriately diagnosed are

prescribed the standard first-line regimen, with poorer treatment outcomes and increased probability of resistance amplification during treatment [5, 15-17].

Linkage to MDR TB treatment

Under the baseline scenario, patients with MDR TB who fail an initial course of treatment for drug-susceptible TB (either because initial resistance was not detected, or because resistance emerged during treatment) are assumed to experience a delay before MDR TB is diagnosed and treated. For example, symptoms for these patients may improve on first-line therapy, leading to an initial assessment of treatment completion, but these patients then relapse with MDR TB soon after completing treatment, and their rifampin resistance is only detected when they present as being previously treated. We approximate the duration of this delay using the ratio of prevalence to incidence, thus assuming (in the absence of data to the contrary) that this delay is similar to the initial delay to care experienced by new patients [1]. We then consider an improved linkage-to-care system in which all patients are tested for culture conversion at the end of treatment. In this scenario, patients who do not achieve culture conversion at the end of first-line therapy are tested for rifampin resistance and, when appropriate, they initiate treatment for MDR TB immediately after completing their initial course of first-line therapy. In this scenario, patients who discontinue treatment or experience reinfection after cure continue to experience the same delay to re-entry into care; only those with MDR TB who successfully complete their initial course of therapy are rapidly linked to treatment.

Improved treatment completion

Based on literature estimates, we assume that 77% of patients who initiate MDR TB treatment successfully complete therapy [1, 18]. From this baseline, we simulate improvements in treatment completion, such as might be achieved by enhanced patient support or shortened treatment, by setting the proportion of patients who complete the full course of MDR treatment equal to that for first-line treatment (94%).

Outcomes and sensitivity analyses

We compare the baseline scenario (no change from current conditions) to combinations of the three interventions described above, over a time horizon of 20 years, and report the change in projected prevalence of MDR TB at 20 years. Results are reported as the median and interquartile range (IQR) of 1,751 data-consistent simulations, which incorporate variation due to both parameter uncertainty and event stochasticity. We also report the cumulative number of patients treated for MDR TB, cumulative MDR TB mortality, as well as the change in projected prevalence of MDR TB cases with additional resistance to fluoroquinolones ("pre-extensively drug-resistant" [XDR] TB).

We additionally assess the sensitivity of our results to model parameters that were taken as fixed values in the main analyses, by individually varying the pace of scale-up of MDR treatment (3 years vs. 5 years), and the sensitivity (93% vs. 98%) and specificity (93% vs. 98%) of RIF resistance detection. Because undetected resistance to fluoroquinolones (FQ) can result in further amplification of resistance, with much poorer treatment outcomes compared to MDR TB with no additional resistance,

we also assess the influence of fluoroquinolone resistance on the potential benefit of scaling up MDR TB treatment. We do this by comparing baseline estimates against a scenario in which an equally efficacious but FQ-free regimen for MDR TB could be developed and scaled-up. For this hypothetical regimen, we assume that treatment outcomes for MDR and pre-XDR TB are equivalent.

Software

All analyses were conducted using the software R, version 3.2.2 [19].

RESULTS

Projected impact of treatment scale-up

Projected trajectories of the prevalence of MDR TB under the modest and expanded scale-up scenarios (compared to baseline) are shown in Figure 4.2. Scaling up the diagnosis and treatment of MDR TB to 100% of previously treated patients is projected to reduce the prevalence of MDR TB by a median 28.1% (IQR 19.8-36.4%) after 20 years, compared to baseline conditions (median prevalence [IQR] at 20 years: 2.2 [1.8-2.8] per 100,000 vs. 3.0 [2.4-4.0] per 100,000). Expansion of MDR TB treatment to all patients (rather than previously treated patients only) has a modest additional impact, reducing MDR TB prevalence at 20 years by 32.9% (IQR 23.7-41.3%). The scale-up of MDR TB treatment has less impact on 20-year pre-XDR TB prevalence, and in some simulations it even results in increased prevalence of pre-XDR TB. The 25th and 75th percentile values for the change in the prevalence of pre-XDR TB at 20 years range from a 41.2% reduction to a 13.2% increase (median 18.8% reduction) under the modest scale-

up scenario, and from a 36.3% reduction to a 31.3% increase (median 9.1% reduction) under the expanded scale-up scenario.

Projected impact of programmatic improvements

Improving linkage to care such that patients who have failed a course of treatment are immediately initiated on a repeat course of treatment reduces the projected prevalence of MDR TB by 26.7% (IQR 18.2-34.3%), to a median 2.3 cases (IQR 1.8-2.8) per 100,000 at 20 years. Improving treatment completion to levels similar to those of first-line treatment has somewhat less impact, reducing the projected prevalence by 15.5% (IQR 8.2-23.9%) to 2.6 cases (IQR 2.0-3.3) per 100,000 at 20 years. When combined, these programmatic interventions—in the absence of any increase in scale-up of MDR TB diagnosis and treatment in the broader population—reduce the projected MDR TB prevalence at 20 years by 38.8% (IQR 31.1-47.0%) to 1.9 cases (IQR 1.5-2.3) per 100,000. The distribution of projected MDR and pre-XDR TB prevalence is shown in Figure 4.3, panels A and B.

Combined interventions

Combining treatment scale-up with programmatic improvements provides substantial additional impact on MDR TB prevalence. When MDR TB treatment is scaled-up to all TB cases, combination with improved treatment completion reduces projected MDR TB prevalence by 60.6% (IQR 54.4-67.3%), to a median 1.2 per 100,000 (IQR 1.0-1.5) at 20 years. Combining expanded scale-up of MDR TB treatment with better treatment linkage after failure reduces projected prevalence of MDR TB by 42.7% (IQR 34.7-51.0%), to a

median 1.8 (IQR 1.4-2.2) cases per 100,000 at 20 years. Projected impact on pre-XDR prevalence is greater when treatment scale-up is combined with improved completion than when it is combined with enhanced linkage to repeat treatment (Figure 4.3, panel B). Combining all interventions together maximizes the projected impact: the projected prevalence of MDR TB decreases by 67.1% (IQR 60.8-73.1%), to a median 1.0 (IQR 0.8-1.3) case per 100,000, and the projected prevalence of pre-XDR TB decreases by 74.5% (IQR 61.5-83.9%), to 0.1 (IQR 0.0-0.1) case per 100,000. When both linkage and treatment completion are improved, expanding MDR TB treatment to all patients rather than only those who have been previously treated actually reduces the total number of patients treated for MDR TB over 20 years (Figure 4.3, panel C). Maximizing scale-up along with programmatic improvements nearly halves the cumulative number of deaths among MDR TB patients (Figure 4.3, panel D).

Sensitivity analyses

Assuming a hypothetical fluoroquinolone-free regimen for MDR TB has little effect on the projected reduction in MDR TB prevalence under scale-up of MDR TB treatment (Figure 4.4, panel A). In contrast, there is a significant reduction in projected levels of pre-XDR TB (Figure 4.4, panel B): scaling up treatment access to all MDR TB cases reduces projected prevalence of pre-XDR TB at 20 years by 75.0% (IQR 60.8-85.7%) compared to baseline (vs. median reduction of 18.8% [IQR 13.2-41.2%] under existing treatment access). Additional sensitivity analyses, in which we varied model parameters on the sensitivity and specificity of RIF resistance diagnostics and the rate of treatment scale-up, had little impact on the primary outcomes (Figure 4.4, panel C).

DISCUSSION

Significant efforts and resources are being expended to scale up the availability of diagnosis and treatment for MDR TB in Southeast Asia, in accordance with the region's TB control targets [9, 20]. Considering only the impact of scaling up diagnosis and treatment, however, ignores the fact that other programmatic elements—including patient support and better regimens to improve treatment outcomes and linkage to MDR TB treatment after failing first-line therapy—are also critical for the control of MDR TB. This stochastic transmission model of TB illustrates that, while any intervention in isolation can likely have only limited impact on MDR TB prevalence over a 20-year time span, combining scale-up of diagnosis and treatment with better linkage to care and improved treatment success has the potential to dramatically reduce the prevalence of MDR TB during that same timeframe.

Resource constraints are a major reason why treatment for MDR TB has not achieved sufficient levels of population scale-up to date [1, 20]. Our results show that impact on MDR TB is not simply a function of the quantity of resources allocated to MDR TB control, but also how those resources are used. For example, expanding MDR TB treatment—even for previously treated cases only—leads to a substantial increase in the number of people treated for MDR TB (Figure 3D), but without improvements in linkage or treatment success, it has only modest impact on MDR TB prevalence and mortality. In contrast, when both treatment linkage and completion are improved, treating all MDR TB patients regardless of treatment history may actually result in fewer courses of treatment needed over 20 years (relative to treating only previously treated cases). Although this model does not explicitly estimate the cost of each intervention, these projections of the

cumulative number of MDR TB patients treated suggest that a combination package of scaled-up diagnosis and treatment with improved linkage and treatment success is likely to represent a better use of resources than any one intervention in isolation.

Support interventions to help patients complete their full course of treatment and ensure that those who are not successfully cured are rapidly linked to repeat treatment are likely to be crucial in achieving MDR TB control. Shorter treatment regimens for MDR TB, such as the 9-month regimen currently undergoing clinical trials, could significantly increase the proportion of patients who complete treatment [21]. The incorporation of drugs with fewer and less severe side effects would also help to bring the level of treatment completion for MDR TB closer to levels observed in first-line treatment. It is important to note that, even with shorter and more tolerable regimens, optimal treatment completion will require adequate follow-up and adherence support, as treatment completion even for first-line treatment is low in many settings [1].

Regarding more extensively resistant TB strains, our model projections suggest that, under certain circumstances, expanded scale-up of MDR TB treatment could result in a higher prevalence of pre-XDR TB. Broader exposure to fluoroquinolones without concomitant drug susceptibility testing (and adapted treatment regimens) in a population with considerable levels of pre-existing fluoroquinolone-resistant TB (~ 24% of treatment-experienced TB cases in India) could undermine efforts to control drug resistance [22, 23]. Expanding capacity for additional drug susceptibility testing and developing a more diverse set of effective second-line regimens should therefore be an important research priority.

As our model focuses on the transmission of drug-resistant TB, we simplified other aspects of the model, assuming uniform mixing of the population and limiting our model to adult pulmonary TB. Similarly, we do not consider heterogeneities in patient susceptibility and/or contact and spatial variations in incidence that may enhance the transmission of TB, as our analyses focus on the comparative impact of selected interventions. Although our model does not explicitly account for sub-regional variations in TB epidemiology and control, we simulate a broad range of epidemiologic trajectories and assess outcomes over a distribution of simulations, which partially accounts for parameter variation across smaller regional scales [1].

Overall, our results emphasize that improving programmatic conditions is key to reaping the benefits of scaling up diagnosis and treatment for MDR TB. Under current programmatic conditions, scale-up to all MDR TB cases yields minimal benefits compared to a limited expansion of access to previously treated patients only, suggesting that, when MDR TB treatment is available to all previously treated patients, additional resources might be better invested in improving linkage to care and treatment completion before they are expended on full MDR TB treatment coverage. However, once strong programmatic conditions are in place, scaling up MDR TB treatment access to all patients can have major population-level benefits. Thus, the optimal path to improving MDR TB treatment programs may be to first combine limited expansion of diagnosis and treatment with programmatic interventions optimizing linkage to care and treatment success. Once these improvements are in place, to have optimal impact, diagnosis and treatment must eventually be expanded to all patients with MDR TB. These findings

provide important guidance for the scale-up of MDR TB treatment in high-burden settings.

Table 4.1: Selected model inputs (additional details in Tables 3.1 and B.3)

Parameter	Baseline value	Sensitivity range	Reference(s)
MDR TB treatment coverage for new cases*		--	[1]
2010 and prior	0		
2015	5.4%		
MDR TB treatment coverage for previously treated cases*		--	[1]
2010 and prior	0		
2015	26.1%		
Rate of scale-up to full MDR TB treatment coverage	5 years	3-10 years	[9]
Time to treatment initiation (months)*			[1]
2000 and prior	25.2		
2013 and onward	17.4		
TB incidence decline, 2005 onwards	2% per year		[1]
Rifampin resistance detection sensitivity	98%	93-98%	[14]
Rifampin resistance detection specificity	98%	93-98%	[14]

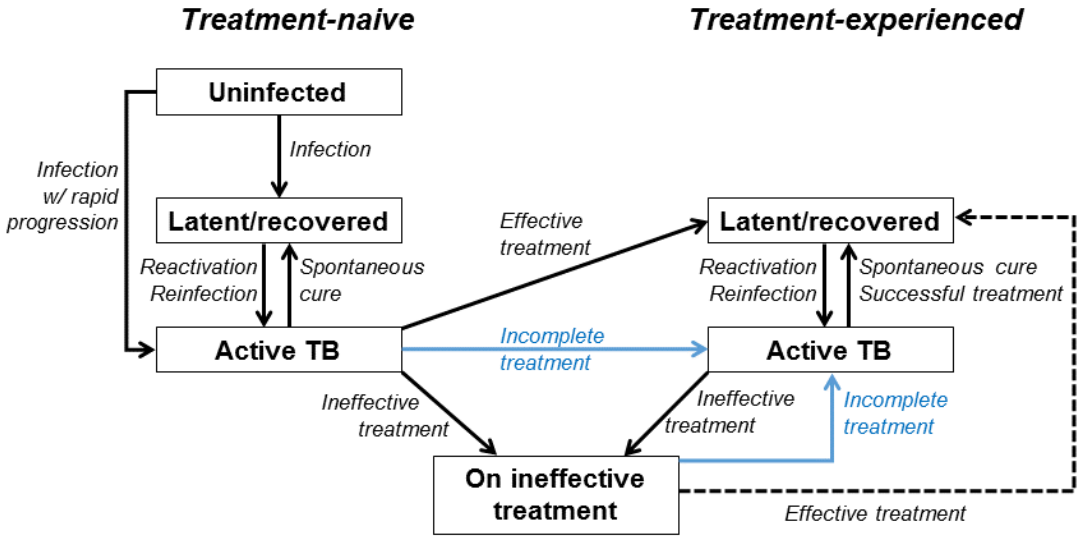
* *We assume linear scale-up of MDR TB treatment coverage from 2010 to 2015, and linear reduction in the time to treatment initiation from 2000 to 2013.*

Table 4.2: Model calibration to epidemiologic data

Epidemiologic criteria	Target value		References	Calibration range	Trajectories within range (%)
	Year	*Value*			
Annual TB incidence, per 100,000	2013	183	[1]	137-229	38%
	2010	194		145-242	
	2005	213		160-266	
	2000	220		165-275	
	1995	218		163-272	
	1990	218		163-272	
RIF-resistant among new cases (%)	2013	2.2%	[1]	1.1-3.3%	24%
RIF-resistant among retreatment cases (%)	2013	16%	[1]	8-24%	35%
RIF-resistant among retreatment cases with FQ resistance (%)	2013	25%	[22]	10-40%	10%
RIF-resistant among retreatment cases with PZA resistance (%)	2013	55%	[24]	40-70%	42%
PZA-monoresistant among new cases (%)	2013	< % RIF resistance	[25, 26]	--	71%
FQ-monoresistant among new cases (%)	2013	< % RIF resistance	[27, 28]	--	98%

RIF: rifampin; FQ: fluoroquinolone; PZA: pyrazinamide.

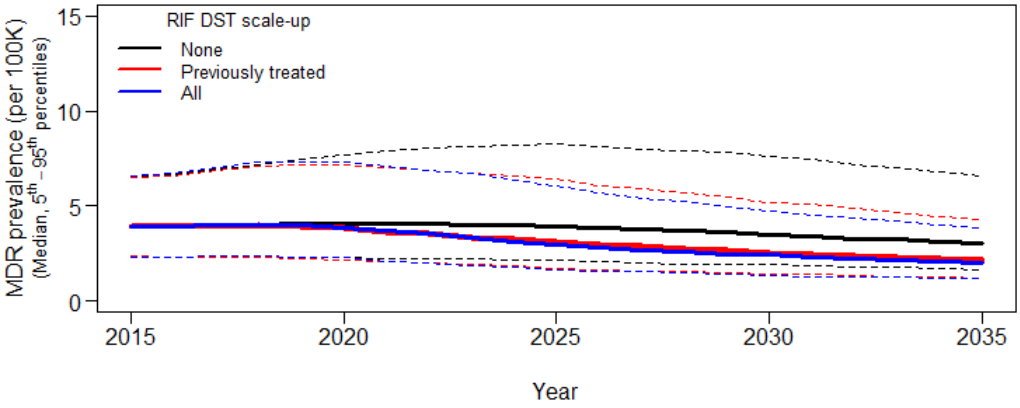
Figure 4.1: Model states



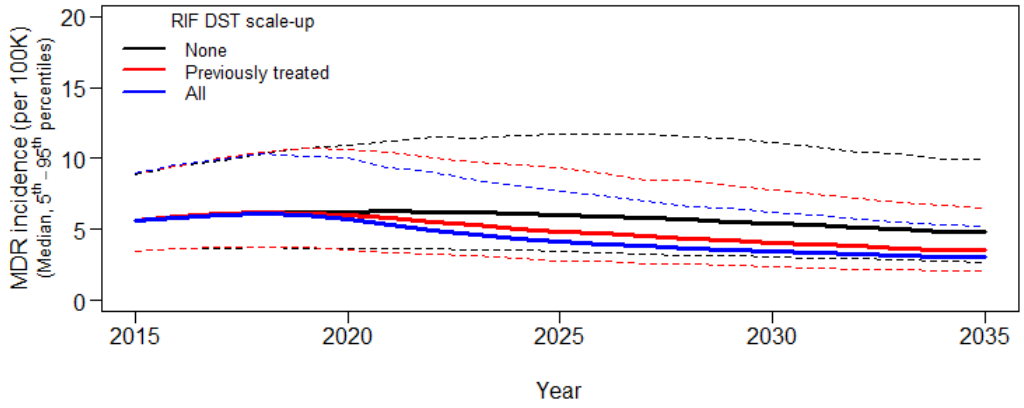
The model is a stochastic realization of the compartmental structure described in detail in Chapter III. In addition to scale-up of MDR TB treatment, the model evaluates improvements in treatment completion (as highlighted by the blue arrows). Patients who are diagnosed as having failed a course of treatment may also be linked to a repeat course of treatment immediately, shortening their delay to care (dashed arrow). Each model state shown here (other than TB-uninfected) is further subdivided in the model to represent a total of eight drug resistance profiles, representing all possible combinations of resistance to rifampin, fluoroquinolones, and pyrazinamide.

Figure 4.2: Projected trajectories of MDR and pre-XDR TB under scale-up of MDR TB treatment

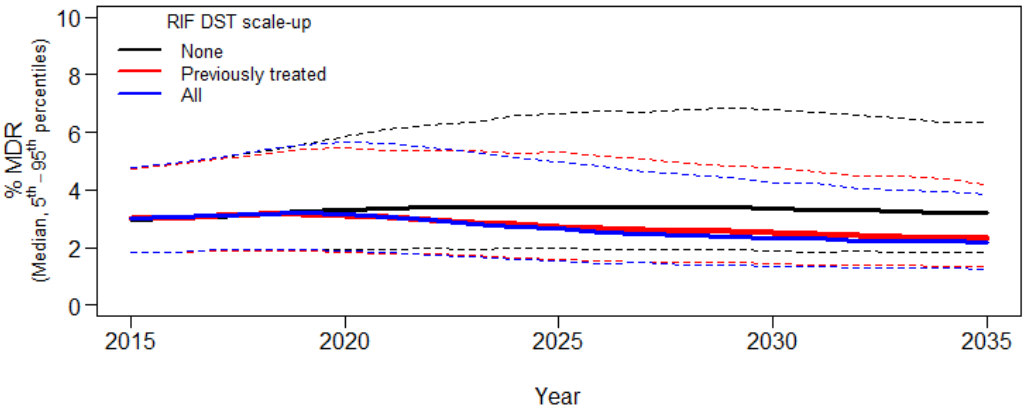
A



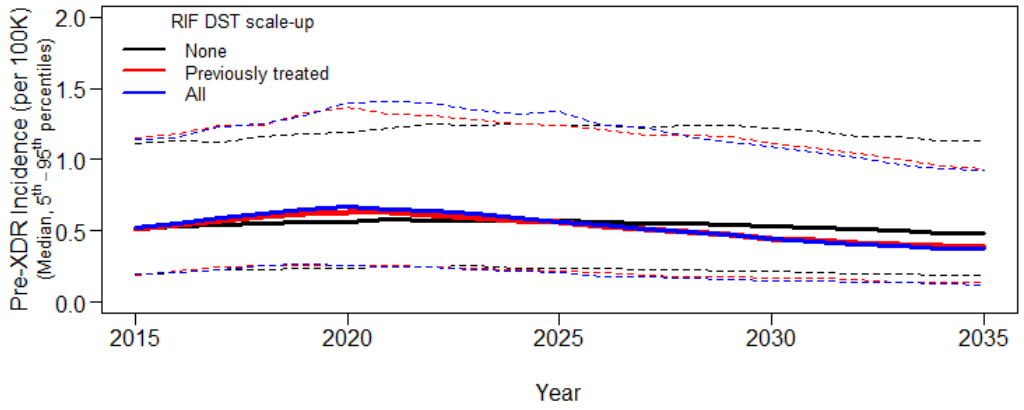
B



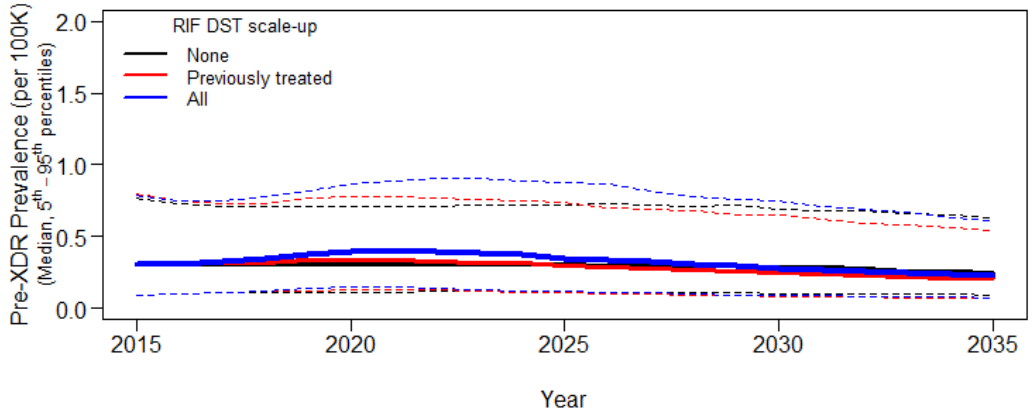
C



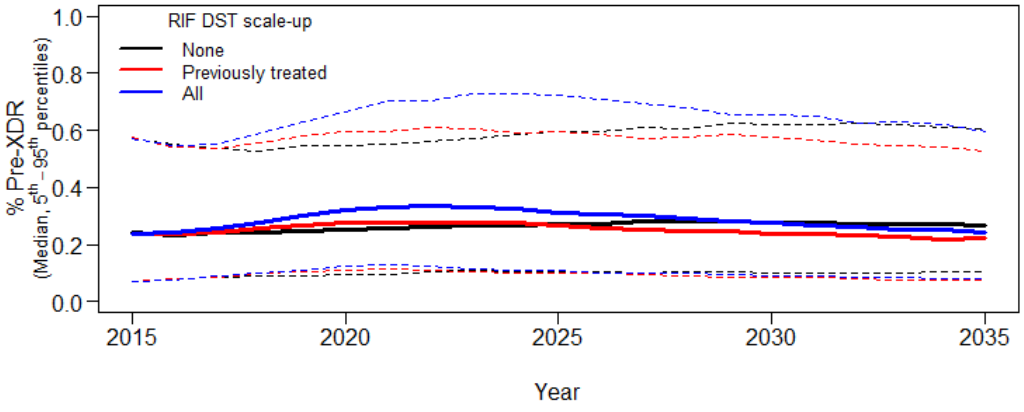
D



E



F

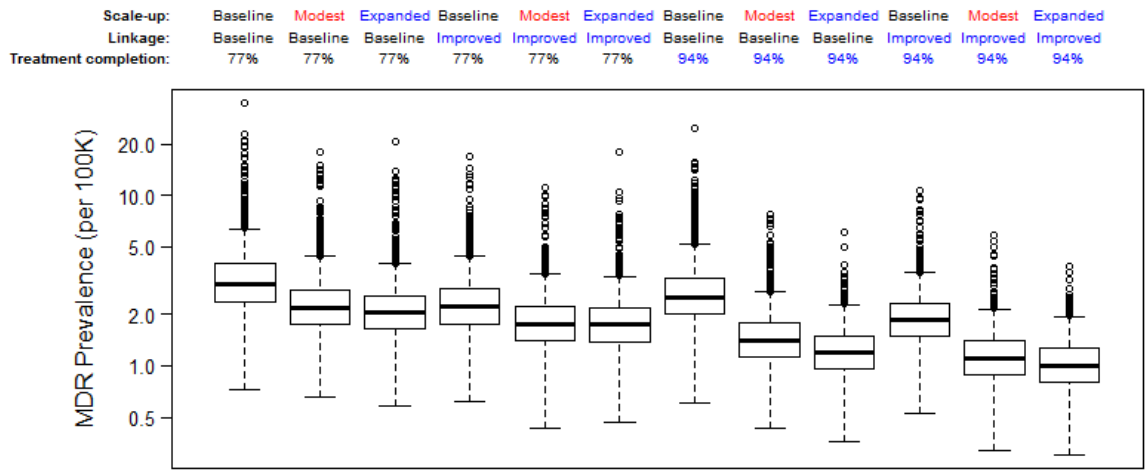


The first three panels (A, B, C) show projected trajectories of prevalence, incidence, and proportion of MDR TB, respectively, under expansion of treatment to previously treated patients (red) or all patients (blue), compared to the baseline condition (black), with no

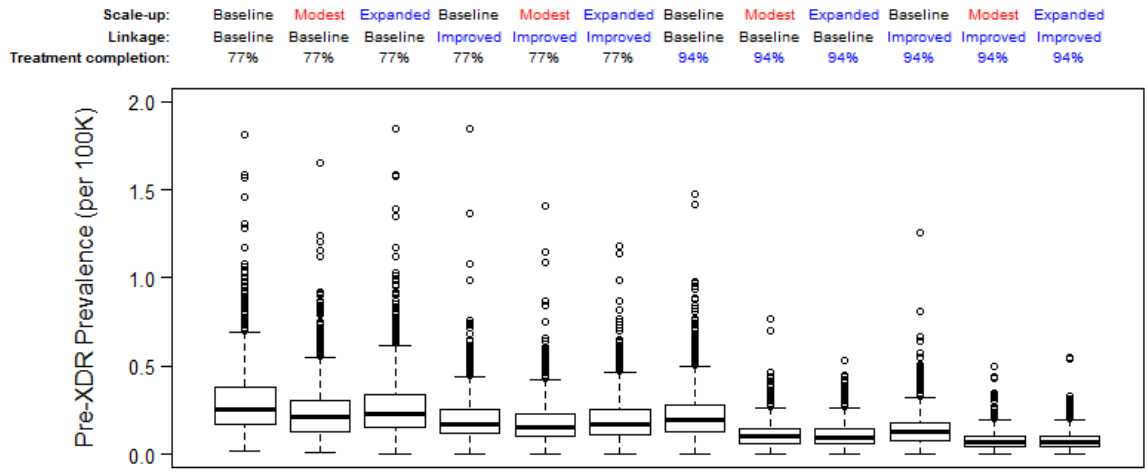
additional programmatic interventions. The following panels (D, E, F) show corresponding projected trajectories of prevalence, incidence, and proportion of pre-XDR TB. In all panels, thick solid lines show the median trajectories and thin dotted lines indicate the boundaries of the 95% credible intervals.

Figure 4.3: Projected prevalence of MDR and pre-XDR TB at 20 years under various combinations of interventions

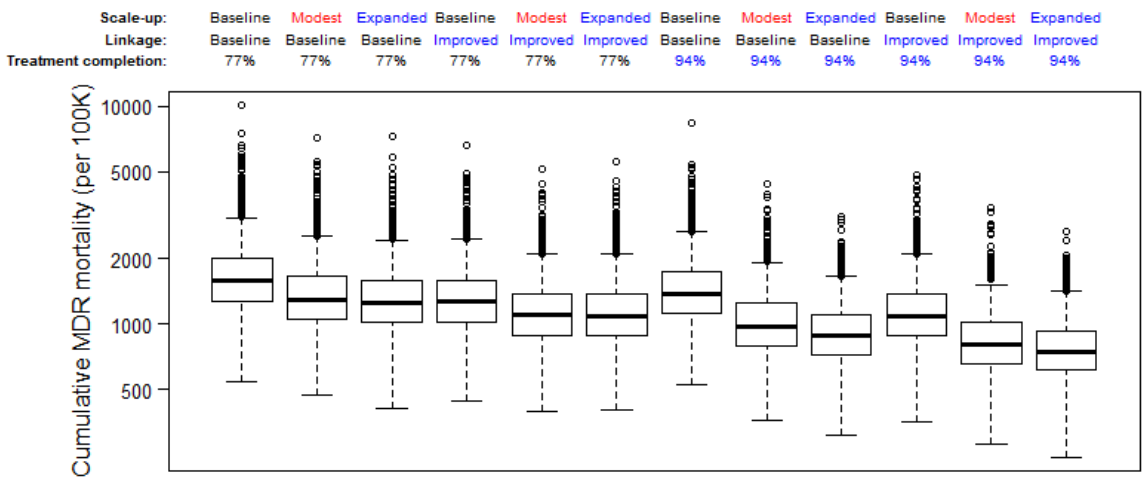
A



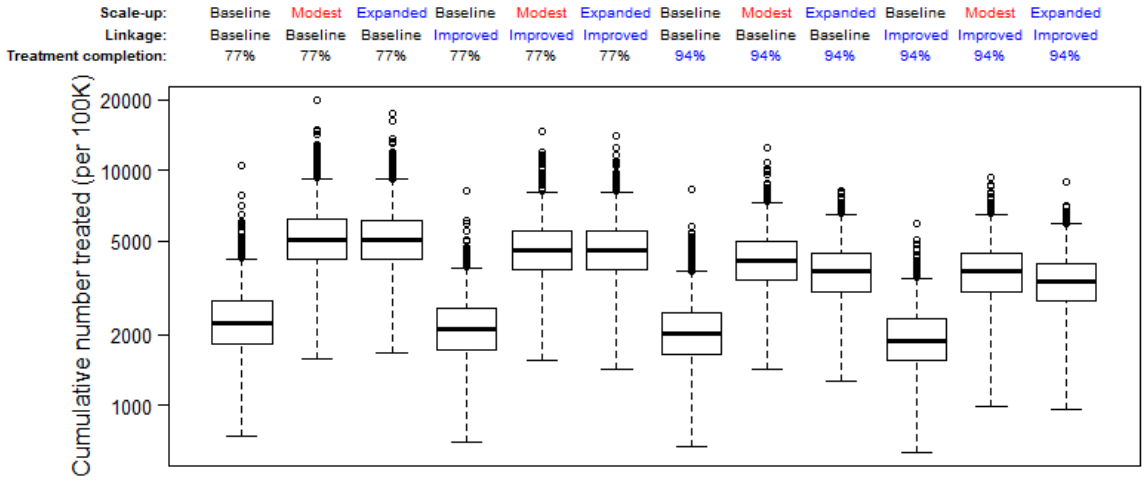
B



C



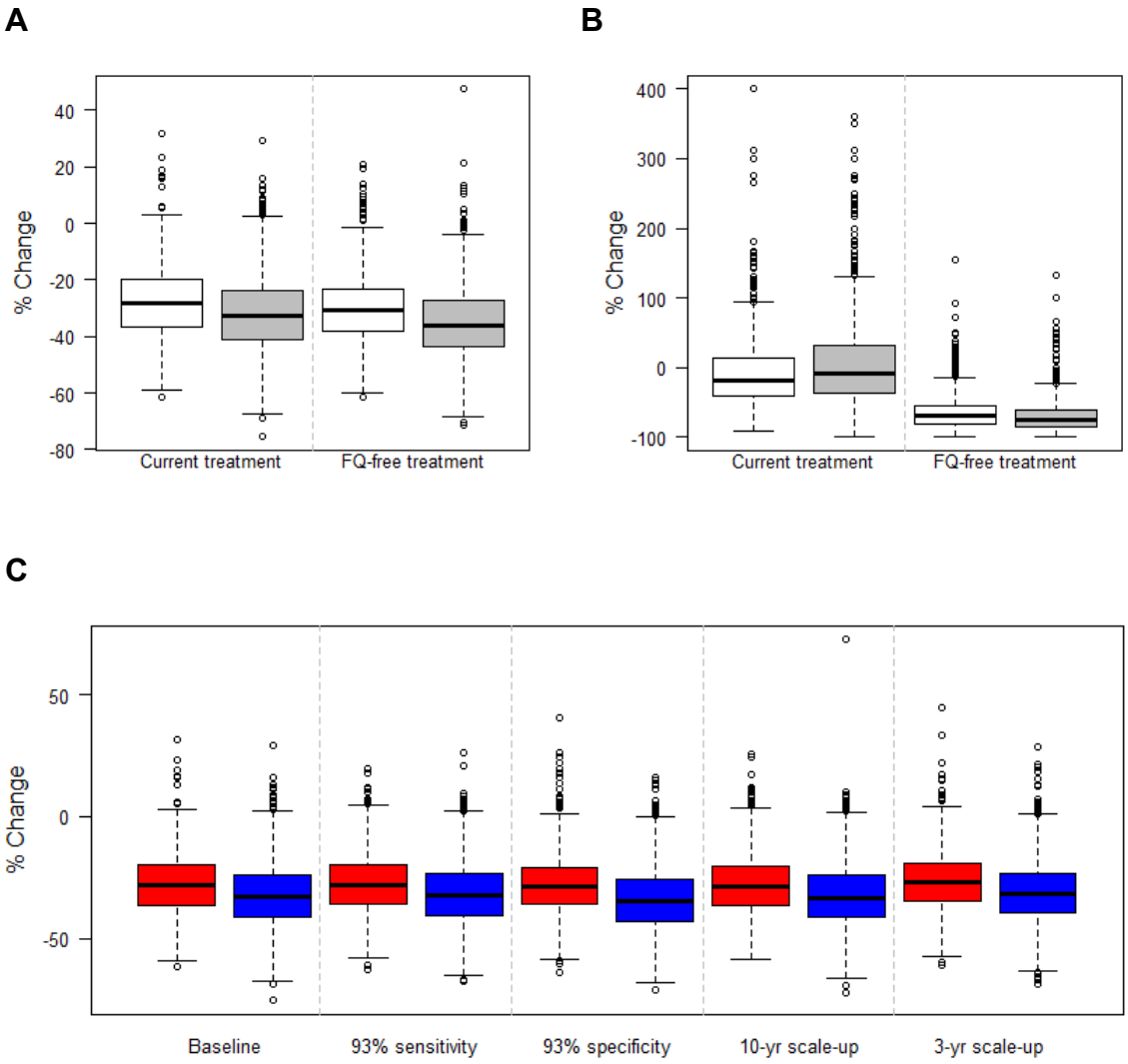
D



Panels A and B show the projected prevalence of MDR and pre-XDR TB at 20 years under alternative combinations of interventions. Panels C and D show the cumulative number of patients treated for MDR TB and the cumulative mortality among MDR TB patients over 20 years. “Modest” scale-up refers to drug susceptibility testing and treatment for previously treated cases, whereas “expanded” scale-up refers to these interventions for all TB cases. “Improved” linkage refers to culture for all individuals at

five months of treatment, with placement of those found to have MDR TB onto second-line therapy by the end of the initial treatment course.

Figure 4.4: Sensitivity analyses



Panels A and B show the projected reduction in prevalence of MDR (A) and pre-XDR TB (B) with treatment scale-up to previously treated (white) and all (gray) TB cases, assuming a hypothetical fluoroquinolone-free regimen for MDR TB of equal efficacy to current treatment. Panel C shows the projected impact of treatment scale-up to previously treated (red) or all (blue) MDR TB cases under variations in the sensitivity and specificity of rifampin resistance detection, as well as variations in the rate of treatment scale-up.

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CHAPTER V

"All scientific work is incomplete—whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time."

~Sir Austin Bradford Hill

DISCUSSION

This work describes projections of the potential population-level impact of tuberculosis (TB) treatment, focusing on shortened duration of first-line treatment (Chapter II), the re-use of ancillary drugs in the treatment of multidrug-resistant (MDR) TB (Chapter III), and scale-up of MDR TB treatment (Chapter IV). The results of these studies provide important insights into the implementation of treatment interventions to maximize population-level impact and help achieve TB control targets. In addition to epidemiologic projections, the models featured in these studies contribute to our understanding of TB dynamics, and identify key areas of uncertainty to be explored in collaborative efforts between mathematical modeling experts and field researchers.

Summary of findings

In Chapter II, we find that previous modeling studies that projected a substantial impact of shortened treatment duration on future TB incidence (10% incidence reduction with a 4-month regimen) were biased as they did not account for the fact that many patients become cured even without completing a full course of treatment [1]. In our analysis, we find that shortening first-line treatment to 4 months would reduce TB incidence by only 2% over 15 years. Keeping all other things equal, substantial epidemiologic impact would

require shortening TB treatment to a few weeks, similar to other respiratory infections [2]. In Chapter III, we find that the re-use of pyrazinamide (PZA) in both first-line and second-line TB treatment may augment the emergence of pre-extensively drug-resistant (pre-XDR) TB, which is resistant to INH, RIF, and fluoroquinolones; furthermore, we identify TB strains resistant to both rifampin and PZA as a key intermediate step in the progression to XDR TB. Finally, in Chapter IV, we find that scale-up of treatment for MDR TB in Southeast Asia could reduce incidence by nearly 30% by 2035, with even greater impact when combined with programmatic interventions that improve treatment linkage and completion.

Study strengths and limitations

These studies share limitations common to all models, and it is important to consider these limitations in interpreting the results and their implications. All models necessarily simplify the phenomena that they represent; ideally models should be only as complex as they need to be to capture the relevant aspects of the modeled system (within the constraints of available knowledge and data), and simple enough to keep model results interpretable and transparent [3]. Here, we tailored our models to the specific questions being addressed in order to achieve this balance of complexity and simplicity. It is important to note that our results should not be interpreted as predictions of future TB trends, nor as absolute estimates of impact. Rather, our findings provide important comparisons of the relative impact of a set of interventions, and the qualitative findings are robust. Models cannot predict chance events (e.g., disruption to health systems as was caused by the recent Ebola outbreak in West Africa) or major shifts in technology,

programs, or policy that can significantly impact disease trends [4-6]. Nevertheless, the overall conclusions regarding the relative impact of the evaluated interventions should remain valid and robust, barring any such major shifts to TB dynamics within the next 20 years.

Some of our findings may not be generalizable to epidemiologic and programmatic settings beyond those considered in the study. We did not consider the effect of HIV in our models, which may limit the applicability of our findings to settings where HIV is a major driver of the TB epidemic. In particular, the results in Chapters III and IV may not be generalizable to settings beyond Southeast Asia, given widespread variability in the prevalence of resistance to TB drugs and TB treatment policies across countries. However, given that Southeast Asia is one of the regions with the greatest burden of MDR TB, interventions targeted at this region will go a long way towards curbing global levels.

Perhaps the most significant limitation of this work is that it primarily addresses the epidemiologic impact of treatment, and does not include other key components of the global strategy for TB control, such as case-finding and prevention [7]. Indeed, non-therapeutic interventions may have comparable or greater impact on TB epidemiology, but this was not the focus of this work [8]. It is likely that combined approaches will be necessary, especially in settings with high HIV prevalence [9-11]. Nevertheless, treatment remains an important tool in the TB control strategy, and it will be important to implement it optimally to maximize its impact at the population level.

Last, but not least, it is important to remember that the most important purpose of TB treatment is to cure patients suffering from a debilitating and stigmatizing disease. The direct benefits to patients, as assessed by the outcomes of clinical studies, remain the most important factor in the development of a treatment regimen. However, clinical effect alone does not determine treatment policies, and it is important to provide policy-makers with guidance on the epidemiologic (as well as economic) impact of treatment policies under consideration. As such, studies that demonstrate epidemiologic impact can serve as an advocacy tool for expanding access to safe, effective and impactful treatment.

Future research

Future studies should address some of the remaining gaps and limitations in the present work, in addition to evaluating the potential impact and optimal implementation of new technologies as they become available. Incorporating modeling results into policy remains a challenge, and studies that project impact for the specific epidemiologic and programmatic settings where interventions are being considered may be needed [3]. It will also be important to tie epidemiologic models to economic considerations, something that remains particularly rare in TB research [12]. The present work focuses on treatment, but TB control will require a broad set of interventions that may act synergistically—models incorporating socio-behavioral factors and evaluating combinations of interventions will provide much-needed insights for future policy decisions [13, 14].

Our studies identified important data gaps and sources of uncertainty. In particular, uncertainty regarding the underlying prevalence of resistance to drugs beyond rifampin

and isoniazid, as well as the probability of acquiring resistance to these drugs, were identified as key data limitations in Chapter III. Recently completed drug resistance surveys of first- and second-line TB drugs have helped to fill this gap and provide a more complete understanding of cross-resistance between various drugs [15, 16]. The high prevalence of resistance to PZA and fluoroquinolones reported in these surveys (e.g., as high as 42% PZA resistance in Belarus) highlight the urgency of studies and interventions to prevent the further spread of drug resistance and protect the utility of available antimycobacterial drugs [16]. These data may also help to reduce uncertainty in model projections in addition to providing important epidemiological indicators of current prevalence of drug resistance in a variety of settings. Clinical research investigating the effect of specific combinations of resistance on treatment outcomes would also be highly valuable. Laboratory and epidemiologic approaches to estimating the relative transmissibility of drug-resistant TB strains are being developed and will continue to enhance our understanding of the implications of drug resistance for transmission [17, 18].

Finally, our findings indicate that improvements to current TB diagnostics and treatment could have significant epidemiologic impact (in addition to direct benefits to patients) if they can improve treatment completion and help ensure universal access to treatment. This is consistent with the existing agenda to develop shorter treatment regimens, especially for MDR TB [19]. It will also be important to develop not only technologies but also logistical interventions to ensure rapid diagnosis of TB and drug resistance and prompt initiation of treatment thereafter. Improvements to diagnostics for resistance to

PZA and second-line drugs in particular could significantly bolster efforts to provide universal access to effective treatment for MDR TB. Given the importance of treatment completion, research into patient support and other socio-behavioral interventions to promote adherence throughout the course of treatment will contribute greatly to ensuring optimal patient-level outcomes and population-level impact of TB treatment [20].

Public health implications

Existing evidence suggests that much of TB transmission occurs prior to the initiation of treatment—in part due to prolonged delays to presentation to care, diagnosis, and treatment initiation—thus limiting the potential of treatment to interrupt the chain of transmission [21, 22]. This is not to undermine the importance of treatment—indeed it will remain important to maintain high treatment completion and success in order to achieve TB control. With regard to drug-susceptible TB, treatment shortening can have many benefits for individual patients as well as for health systems, but moderate reductions in treatment duration are unlikely to substantially change population-level outcomes [23-25]. Major reductions in treatment duration are unlikely to happen with drugs that are currently available or in late phases of clinical development—indeed the failure of several trials of four-month regimens indicates that treatment shortening without relapse may require entirely new drugs unlikely to be available before the End TB Strategy's interim target timepoint of 2035 [7, 26]. There is still hope for a four-month, pretomanid-based treatment regimen to be available in the coming years, but such a regimen will likely be more expensive than the current six-month regimen, and thus may not be available in settings of high TB transmission and high treatment

discontinuation where shorter treatment would have the most epidemiologic impact [27]. Improvements to first-line TB treatment given the current set of technological and programmatic tools should focus on identifying as many TB patients as possible, initiating them on treatment early, and developing appropriate program and patient support interventions to ensure high treatment success.

The potential impact of treatment improvements is considerably greater for MDR TB. Indeed, given current poor treatment access and outcomes, the duration of MDR TB infectiousness after presentation to care is longer than in drug-susceptible TB, and a greater proportion of total transmission can be averted with more effective treatment compared to current conditions. Curbing MDR TB may have little impact on overall levels of TB, as most TB cases are drug-susceptible, but it remains an important goal that will require continued advocacy for scale-up of treatment and the necessary ancillary interventions to optimize its benefits for both patients and populations [28]. Whereas major reductions in treatment duration may be far off for first-line regimens, there is very tangible room for improvement on several aspects (duration, efficacy, tolerability) of MDR TB treatment, which could overcome current programmatic challenges [29]. Several observational studies have demonstrated the effectiveness of 12- and 9-month regimens in low-resource settings in Asia and Africa, and the STREAM clinical trial is underway to confirm these findings [30-33]. If approved and implemented, these shorter MDR TB treatment regimens will also require solid programmatic support to maintain optimal outcomes and prevent the emergence of additional resistance [34]. The utility of such regimens may be limited to select settings with low levels of resistance to second-

line drugs: studies in Europe and Latin America found that only approximately 4% of MDR TB patients would be eligible for the 9-month standardized "Bangladesh regimen" due to resistance to one or more drugs in the regimen [35, 36].

Our finding that PZA "recycling" promotes the emergence of XDR TB poses a quandary for TB policy-makers. Ongoing surveys indicate that there are already alarmingly high rates of PZA resistance in some settings, especially among MDR TB patients. A recent systematic review and meta-analysis found a pooled estimate of 16.2% [95% confidence interval 11.2-21.2%] prevalence of PZA resistance among all incident TB cases, and 60.5% [52.3-68.6%] among MDR TB cases; moreover, the studies included in the meta-analysis reported PZA resistance in all WHO regions [16, 37]. There is currently no drug available that could replace PZA and have the same unique effect on eradicating persister bacilli. Without such a drug, it is likely that PZA will continue to be re-used, especially given laboratory data suggesting that it has synergistic activity with pretomanid and bedaquiline [38-40]. Limiting PZA's effect on the spread of XDR TB would thus require expansion of access to resistance diagnostics for second-line drugs, especially in settings where MDR TB treatment is being scaled up, and where there is already a high prevalence of resistance to PZA and/or fluoroquinolones (e.g., Southeast Asia). Although these diagnostics remain poorly sensitive and specific, there is evidence that they improve treatment outcomes [41]; they could also help to curb XDR TB by guiding clinician decisions on whether or not to include PZA in the treatment regimens of MDR TB patients.

As we seek ways to accelerate progress towards our targets, treatment remains a key component of the TB control toolset. Nevertheless, we must make full use of available interventions—and generate the political will and resources to implement them as effectively as possible—if we are to achieve TB control. Success may seem far off, but what seems impossible today may not be so tomorrow; the past century has been one of unprecedented success against infectious diseases old and new, and it is high time to extend these successes to TB [42-44]. Hopefully, the work described here provides valuable insights into ways to maximize the potential impact of TB treatment as a tool for epidemiological control, and make TB a disease of the past once and for all.

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APPENDIX A

"When you can measure what you are speaking about, and express it in numbers, you know something about it. But when you cannot, your knowledge is of a meager and unsatisfactory kind."

~Lord Kelvin

SUPPLEMENTARY MATERIAL TO CHAPTER II

MODEL INPUTS

We derive our model inputs from published data on the natural history and treatment outcomes of TB. In order to account for the four phases of treatment of varying duration in our model, we convert proportions to time-dependent rates by dividing proportion values by the duration (in years) of each treatment phase. Take, for example, treatment phase 1, which lasts two weeks (t_1 = 1/24 of a year). Thus, the sum of all exit rates from this phase (failure, tf_1, phase completion, tc_1, mortality, μ_1, and default, δ_1) should equal 24/year. We next calculate the proportion of individuals entering phase 1 who exit by each of these four routes; for example, the proportion of individuals who die is calculated as the overall proportion of individuals who die (m = 0.04), multiplied by the proportion of those deaths that occur in phase 1 (m_1 = 0.27). The proportion of individuals who default is calculated in similar fashion. The proportion of individuals who fail is assumed to be zero unless the regimen ends at the end of the phase (i.e., in phase 1, the failure proportion is zero for two-month, four-month, and six-month regimens), in which case the failure proportion is assumed to be a value that is the same for all regimens (f = 0.02 at baseline). Thus, f represents the probability of failure, conditional on completing therapy.

Table A.1: Initial state conditions

State	Description	Number of individuals, per 100,000
$S(0)$	# in Susceptible compartment	62,280
$L(0)$	# in Latent TB compartment	31,197
$A(0)$	# in Active TB compartment	104
$T_1(0)$	# in Treatment phase 1 compartment	4
$T_2(0)$	# in Treatment phase 2 compartment	11
$T_3(0)$	# in Treatment phase 3 compartment	14
$T_4(0)$	# in Treatment phase 4 compartment	13
$C(0)$	# in Cured compartment	6,377
N	Total population	100,000

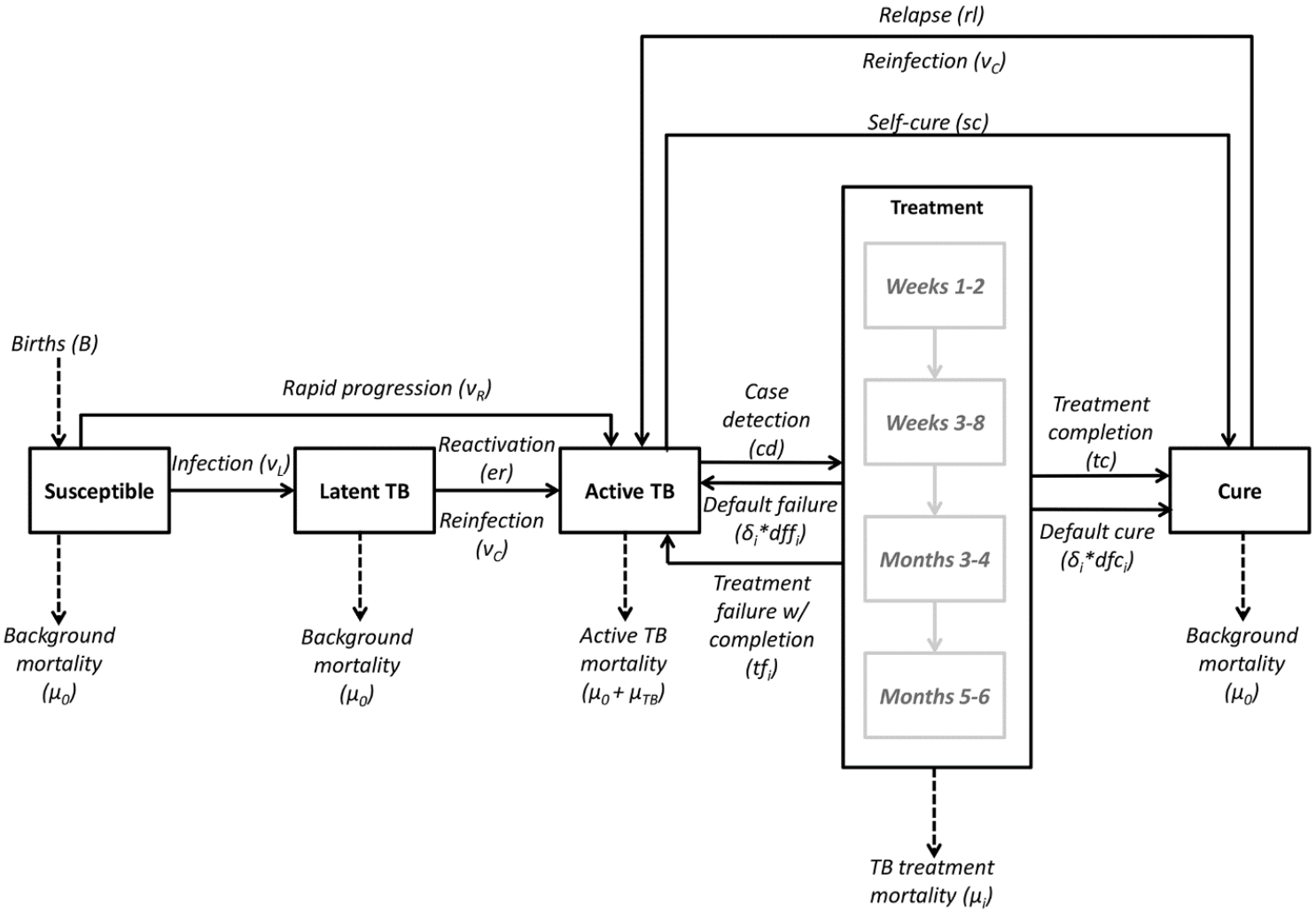
Table A.2: Model parameters

Parameter	Description	Reference/baseline value [95% uncertainty range]	Ref(s)
β	Transmission rate per person-year	8.5 [4.25-12.75]	[1]
p	Relative susceptibility to infection after prior exposure to TB	0.4 [0.20-0.60]	[2, 3]
ri	Relative infectiousness in treatment phase 1 compared to active TB	0.5 [0.25-0.75]	
r	Proportion of infections progressing immediately to active TB	0.15 [0.09-0.26]	[4]
er	Rate of endogenous reactivation from latent to active TB, per year	0.0005 [0.0003-0.0008]	[5, 6]
sc	Self-cure rate, per year	0.2 [0.10-0.30]	[7]
μ_0	Background mortality rate, per year	0.014 [0.01-0.03]	[8]
μ_{TB}	Mortality rate in active TB state, per year	0.2 [0.10-0.30]	[7]
rl	Rate of relapse after treatment, per year	0.001 [0.0005-0.0015]	[9]
cd	TB treatment rate, per year	0.84 [0.42-1.26]	[10]
d	Overall proportion of treatment default	0.07	[10]
m	Overall proportion of deaths on treatment	0.04	[10]
f	Overall proportion of treatment failure	0.02	[10]

Table A.2 (cont.)

Parameter	Description	Reference/baseline value [95% uncertainty range]				Ref (s)
		i= 1	***i= 2***	***i= 3***	***i=4***	
t_i	Duration of treatment phase *i*, in years	1/24	1/8	1/6	1/6	
d_i	Proportion of all defaults from a 6-month regimen that occur in phase *i*	0.03	0.27	0.38	0.32	[11]
δ_i	Treatment default rate in phase *i*, per year: $d*d_i/t_i$	0.05 [0.03-0.08]	0.15 [0.08-0.23]	0.16 [0.08-0.24]	0.13 [0.07-0.20]	[10]
m_i	Proportion of all deaths on a 6-month treatment regimen that occur in phase *i*	0.27	0.32	0.205	0.205	[12-14]
μ_i	Total (background + TB-specific) mortality rate in phase *i*, per year: $m*m_i/t_i$	0.26 [0.13-0.39]	0.10 [0.05-0.15]	0.05 [0.02-0.07]	0.05 [0.02-0.07]	[7]
tf_i	Treatment failure rate in phase *i* for regimen with *n* treatment phases, per year (for $i=n$): f/t_i	0.48 [0.24-0.72]	0.16 [0.08-0.24]	0.12 [0.06-0.18]	0.12 [0.06-0.18]	[10]
	(for $i<n$)	0	0	0	0	
tc_i	Rate of continuation from phase *i* to phase *i+1* (or to cure if $i=n$), per year: $1/t_i - (tf_i+\delta_i+\mu_i)$	23.69	7.75	5.79	5.70	
dfc_i	Proportion in a 6-month regimen who are cured after default in phase *i*	0	0.16 [0.08-0.23]	0.63 [0.31-0.94]	0.86 [0.43-1]	[10]
dff_i	Proportion in a 6-month regimen who return to active TB after default in phase *i*	1	0.84 [0.77-0.92]	0.38 [0.06-0.69]	0.14 [0-0.57]	[15, 16]

Figure A.1: Model structure, including parameter definitions



MODEL EQUATIONS

Figure A.1 shows a schematic representation of the model with relevant equations and rate constants for transitions between compartments. Initial state conditions for each compartment are listed in Table A.1. Model parameters, reference values, and the range of values used in the probabilistic uncertainty analysis are listed in Table A.2.

Force of infection

$$F(t)=\frac{\beta+(ri\cdot T_1(t))}{N}$$

The rate at which individuals in each compartment become infected with TB depends upon the force of infection (probability of an uninfected individual becoming infected per unit time), which varies with time according to the number of infectious (i.e., in active TB or treatment phase 1) individuals in the population. Thus, the force of infection $F(t)$ is the product of the number of transmissions per unit time β, the number of individuals with active TB $A(t)$, the number of individuals in the first treatment phase $T_1(t)$ multiplied by the relative infectiousness of that compartment ri, divided by the total number of individuals in the population N (held constant at 100,000 in this model). We assume homogenous mixing of the population, such that each susceptible individual has an equal chance of coming into contact with an infectious individual.

Infection with rapid progression to active TB

$$\nu_R(t)=F(t)\cdot r$$

Infection with latent TB

$$\nu_L(t)=F(t)\cdot(1-r)$$

A proportion (*r*) of individuals who become infected with TB progress immediately to active disease, such that the rate of progression from the susceptible state to active disease $v_R(t)$ is equal to the force of infection $F(t)$ multiplied by the proportion of rapidly progressing infections *r*.

The remainder (*1-r*) of newly infected individuals progress at a rate $v_L(t)$ to a state of latent disease, in which they are not infectious.

Reinfection from latent or cured state, with rapid progression to active TB

$$\nu_C(t)=F(t)\cdot r\cdot p$$

Individuals in the latent and cured states can become reinfected with TB at a rate determined by the force of infection $F(t)$ and the proportion (*r*) progressing immediately to active disease. Prior exposure to TB confers relative protection against reinfection, such that only a proportion *p* of individuals in the latent or cured states are susceptible to infection. We vary this "latent protection" parameter widely in sensitivity and uncertainty analyses.

Births

$$B(t)=\mu_0(S(t)+L(t)+C(t))+(\mu_0+\mu_{TB})A(t)+\sum_{i=1}^{4}\mu_i\cdot T_i(t)$$

We model a closed population, with the number of births $B(t)$ equivalent to the number of deaths at any time. The mortality rate constants for each compartment are listed in Table

A.2. Individuals in the susceptible, latent and cured states [*S(t)*, *L(t)*, and *C(t)*, respectively] progress to death according to a background mortality rate μ_0 based on a life expectancy at birth of 70 years [8]. Individuals in the active TB state *A(t)* have an additional, TB-related mortality risk μ_{TB}. Individuals in the treatment compartments are subject to a mortality rate μ_i that varies with each treatment phase T_i, with $1 \leq i \leq 4$.

Relapse, reactivation, treatment initiation, self-cure

We assume constant rates of relapse after treatment and reactivation of latent TB to active disease (see Table A.2). Individuals in active disease are detected and diagnosed at a constant rate to progress to the first phase of treatment. They may also experience self-cure and progress to the cured state without going through treatment.

Treatment

We model varying durations of treatment by determining the number of treatment phases (*n*) required for a full treatment course in each simulation, such that the six-month regimen requires completion of $n = 4$ phases and the four-month regimen requires completion of $n = 3$ phases, etc... Entry into the "Cure" compartment requires either completion of treatment phase *n* or cure after default from any treatment phase 1 through *n*. Individuals may complete each phase of treatment, die or default. A proportion of defaulters (*dfc*) will have undergone sufficient treatment to progress to cure, while the remainder (*dff*) returns to the active TB state.

The differential equations describing rates of transition between model compartments are as follows:

- ***Susceptible, S***: $\frac{dS}{dt} = B(t) - S(t)\cdot(\nu_R(t) + \nu_L(t) + \mu_0)$

  At any time, entry into the susceptible state is determined by the number of births *B(t)*. The rate of exit is determined by the sum of the rates of progression to active disease, latent disease, and mortality ($v_R(t)$, $v_L(t)$, and μ_0, respectively).

- ***Latent, L***: $\frac{dL}{dt} = (S(t)\cdot\nu_L(t)) - L(t)\cdot(er + \nu_C(t) + \mu_0)$

  At any time, the number of new latent infections is determined by the number of susceptible individuals *S(t)* multiplied by the rate of progression to latent disease $v_L(t)$. The rate of exit is determined by the number of individuals in the latent TB compartment *L(t)* multiplied by the sum of the rates of endogenous reactivation to active disease *er*, reinfection with rapid progression to active disease $v_C(t)$, and mortality μ_0.

- ***Active TB, A***: $\frac{dA}{dt} = (S(t)\cdot\nu_R(t)) + L(t)\cdot(er + \nu_C(t)) + C(t)\cdot(rl + \nu_C(t)) + \sum_{i=1}^{n}[T_i(t)\cdot[(\delta_i\cdot dff_i) + tf_i]] - A(t)\cdot(\mu_0 + \mu_{TB} + cd + sc)$

  At any time, the number of new cases of active disease includes cases resulting from rapid progression after initial infection at rate $v_R(t)$for individuals in the susceptible state *S(t)*, endogenous reactivation at rate *er* and reinfection at rate $v_C(t)$ for individuals in the latent state *L(t)*, and relapse at rate *rl* and reinfection at rate $v_C(t)$ for individuals in the cured state, in addition to failure after treatment completion at rate tf_i and the proportion dff_i of individuals in each treatment phase $T_i(t)$ who default at

rate δ_i and subsequently return to the active disease state. The rate of exit is determined by the sum of the rates of background mortality μ_0, TB-specific mortality μ_{TB}, TB treatment rate *cd*, and self-cure without treatment *sc*.

- ***Treatment phase 1, T_1***: $\frac{dT_1}{dt} = (A(t) \cdot cd) - T_1(t) \cdot (tc_1 + \delta_1 + tf_1 + \mu_1)$
- ***Treatment phase 2, T_2***: $\frac{dT_2}{dt} = (T_1(t) \cdot tc_1) - T_2(t) \cdot (tc_2 + \delta_2 + tf_2 + \mu_2)$
- ***Treatment phase 3, T_3***: $\frac{dT_3}{dt} = (T_2(t) \cdot tc_2) - T_3(t) \cdot (tc_3 + \delta_3 + tf_3 + \mu_3)$
- ***Treatment phase 4, T_4***: $\frac{dT_4}{dt} = (T_3(t) \cdot tc_3) - T_4(t) \cdot (tc_4 + \delta_4 + tf_4 + \mu_4)$

At any time, entry into the first phase of treatment is determined by the rate of detection *cd* for individuals in the active disease state *A(t).* The number of individuals from each phase of treatment *i* who enter the subsequent phase of treatment *i+1* (or the cured state if phase *i* is the last phase of treatment) is equal to the rate of treatment continuation tc_i multiplied by the number of individuals in each treatment phase $T_i(t)$. Individuals may exit each treatment phase by death at rate μ_i, default at rate δ_i, continuation to the next phase at rate tc_i, and failure of treatment at rate *tfi* if they are in the final phase.

- ***Cure, C***: $\frac{dC}{dt} = (A(t) \cdot sc) + (T_n(t) \cdot tc_n) + \sum_{i=1}^{n} (T_i(t) \cdot \delta_i \cdot dfc_i) - C(t) \cdot (rl + \nu_C(t) + \mu_0)$,

where *n* = index for last phase of treatment in regimen (e.g., *n* = 4 for six-month regimen, *n* = 2 for two-month regimen).

At any time, the number of new cured cases includes self-cure at rate *sc* for *A(t)* individuals in the active disease state, treatment success at rate tc_n for $T_n(t)$ individuals in the last treatment phase, in addition to the proportion dfc_i of the $T_i(t)$ individuals in each treatment phase who experience default at rate δ_i and subsequently

progress to the cured state. Exit from the cured state is determined by the rates of relapse *rl*, reinfection $v_C(t)$, and mortality μ_0.

PARTIAL TREATMENT EFFICACY DATA INPUTS

We estimated the proportion of relapse among those completing one-third, one-half or the entirety of the treatment regimen based on relapse outcomes in early clinical trials of short-course TB regimens [15, 17]. These trials report 24% and 14% relapse after 60 months of follow-up for two-month and four-month treatment regimens consisting of streptomycin, isoniazid, rifampin, and pyrazinamide. Similar outcomes were achieved with a four-month regimen in a trial conducted in East Africa [18]. We estimate the probability of stable cure for patients who default after two months or four months of treatment based on the proportion of patients who did not experience relapse over long-term follow-up in these trials. As a conservative approach, we assume a "stepwise" distribution of the probability of cure after default in each phase of treatment; for example, the probability of cure with default at any point between four and six months is estimated as the probability of cure with completion of four months of treatment.

The best estimate that we found for the probability of cure after two months of treatment was from a clinical trial of a two-month regimen in patients with smear-negative, culture-positive pulmonary tuberculosis [15]. We used data from a review of early clinical trials of first-line TB regimens of two to six months to estimate a correction factor based on the assumption of relatively faster progression to cure among smear-negatives, who are thought to have a lower bacillary burden, compared to smear-positive TB patients [16, 19]. Because these trials were conducted in the 1970s, we presume that HIV was not a

significant factor in the outcomes of smear-positive vs. smear-negative TB. We estimated that the probability of relapse after two months of treatment is twice as high among smear-positive than smear-negative cases; in sensitivity analyses, we vary this correction factor from 1 to 3 and further vary the probability of cure with 2 months of treatment by ±50% to account for the uncertainty in the values of these parameters. We then compute a weighted probability of cure using the relative prevalence of smear-negatives and smear-positives among new TB cases [10].

We used interpolation to derive estimates for the probability of cure after two weeks of treatment, assuming a linear increase between initiation of treatment and the completion of two months. This results in an estimated probability of cure of 15.6% among individuals who complete two to eight weeks of treatment. To account for the scarcity of data for these estimates and the inherent uncertainty related to our assumptions, we used a wide range of estimates in sensitivity analyses around these parameters. We assumed that there is no chance of cure with default during the first two weeks of treatment.

For the shortened treatment regimens, we adjusted these estimates of probability of cure after default as follows: for each 1/3 incremental reduction in total treatment duration from the six-month regimen (to four months and two months), the probability of cure at phase n increases by 1/3 of the difference in probability of cure between phases i and i+1 in the six-month regimen. For example, given probabilities of cure of 16%, 63%, and 86% at two weeks, two months and four months in the six-month regimen, the probability of cure at two months in the four-month regimen is computed as 63% + 1/3 * (86% -

63%) = 70%. In sensitivity analyses, we vary this correction factor for the probability of cure (*cpcf*) from 1/6 to 1/2.

We also assess the impact of using linear interpolation of the clinical trial data to set the probability of cure with default. This represents a less conservative approach, with higher probabilities of cure compared to using the stepwise distribution described above. For instance, the probability of cure for those who default between months 2 and 4 is computed as the mean of the proportions cured with two-month and four-month courses of treatment in the trials, rather than as the proportion cured with the two-month treatment course. This results in probabilities of cure of 31%, 74%, and 92% with default in treatment phases 2, 3, and 4 of standard six-month therapy (vs. 16%, 63%, and 86% with stepwise distribution) but does not significantly alter results on the transmission impact of novel regimens (1.3% incidence reduction at 10 years with four-month vs. six-month regimen compared to 1.9% with stepwise distribution).

STRUCTURAL SENSITIVITY ANALYSES

As a sensitivity analysis, we repeated the main analysis in a setting of declining incidence rather than a steady state. We first initialized the model at a steady state reflective of the TB epidemic a decade ago, then reduced the transmission rate and simulated the course of the epidemic to obtain a decline reflective of current global TB incidence estimates. We then simulated the continuation of the six-month regimen or the introduction of shorter regimens.

We also assessed the robustness of our findings to increased detail in model structure, by repeating the analysis with two alternate models. In Model 2, we replaced the single "Latent TB" compartment with three sequential compartments reflecting "Immediate" (year 1), "Recent" (years 2-5), and "Remote" (years 6 and beyond) latent infection, resulting in a total of 10 compartments (Figure A.2, panel A). In this model, reinfection can occur in the "Recent" and "Remote" latent infection compartments in addition to the "Cured" compartment, and results in return to the "Latent Immediate" compartment. Rapid progression can occur from either "Immediate" or "Recent" latent infection, resulting in transition to the "active TB" compartment. As in the primary model, we set the total proportion of latent infection of cases progressing rapidly to active TB at 15%, with 63% occurring in the first year and 37% occurring in the subsequent four years [3].

In Model 3, we replicated the structure of the original model four times to create four age subdivisions (0-14, 15-29, 30-44, and ≥45 years old), resulting in a total of 32 compartments (Figure A.2, panel B). Rates of background mortality for each age group are derived from global life tables estimates [8]. As in the original model, we maintained the total population constant by setting the number of births in each timestep equal to the total number of deaths, with all individuals being born in the susceptible state in the 0-14 age subdivision. In addition to progressing through the TB states, individuals in the first three age subdivisions progress to the next age subdivision at a rate of 1/15 yr^{-1}. We used this model to replicate the analysis under varying assumptions of (1) equal rates of infection and reactivation across all age subdivisions, (2) rates of infection set to 50% of

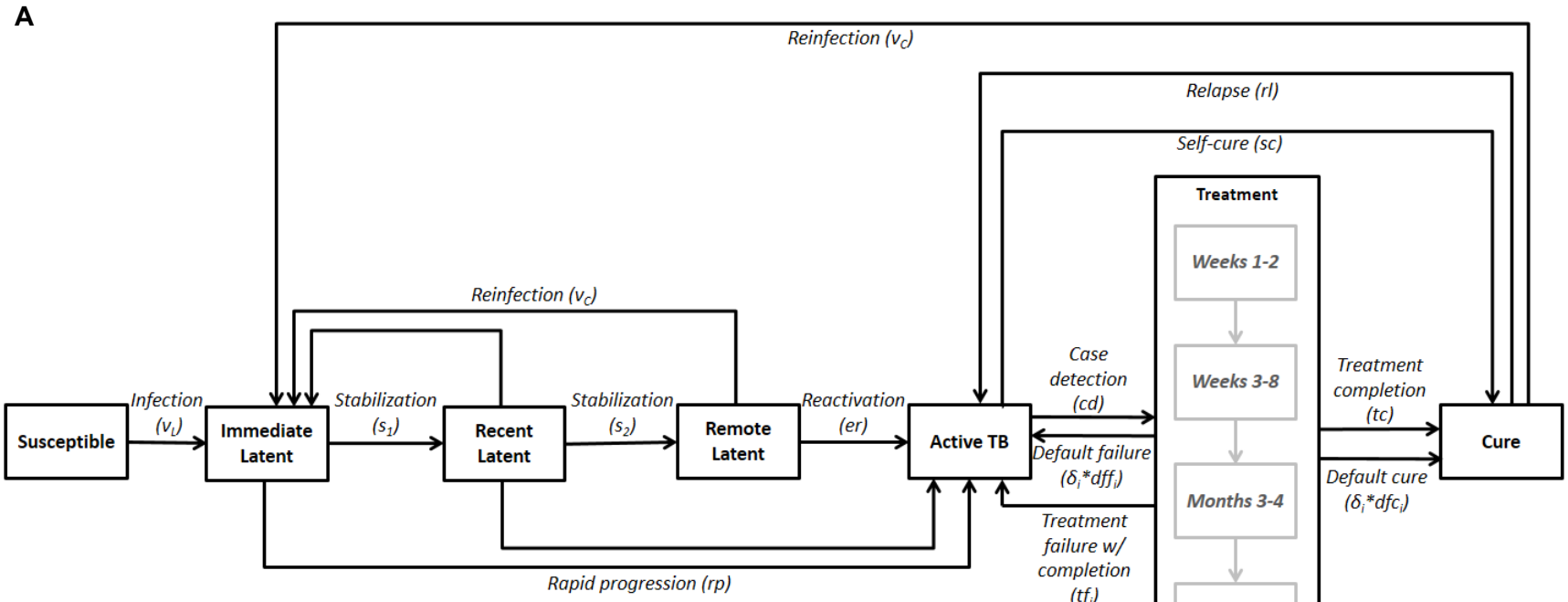
the baseline value among children (ages 0-14), and (3) rates of reactivation set to 50% of the baseline value among children to assess the impact of differential disease progression by age.

For both Model 2 and Model 3, we initialized the model at steady-state and projected incidence using the same procedures as in the primary analysis. The conclusions remained largely unchanged in all of these sensitivity analyses, with the reduction in incidence at 10 years with a four-month vs. six-month regimen ranging from 0.9% to 2.5% when taking into account the efficacy of partial treatment; as in the primary analysis, incidence reduction was overestimated when we did not account for this partial efficacy (5.1% to 13.5%; 5.3 to 5.7-fold). Detailed results are presented in Table A.3.

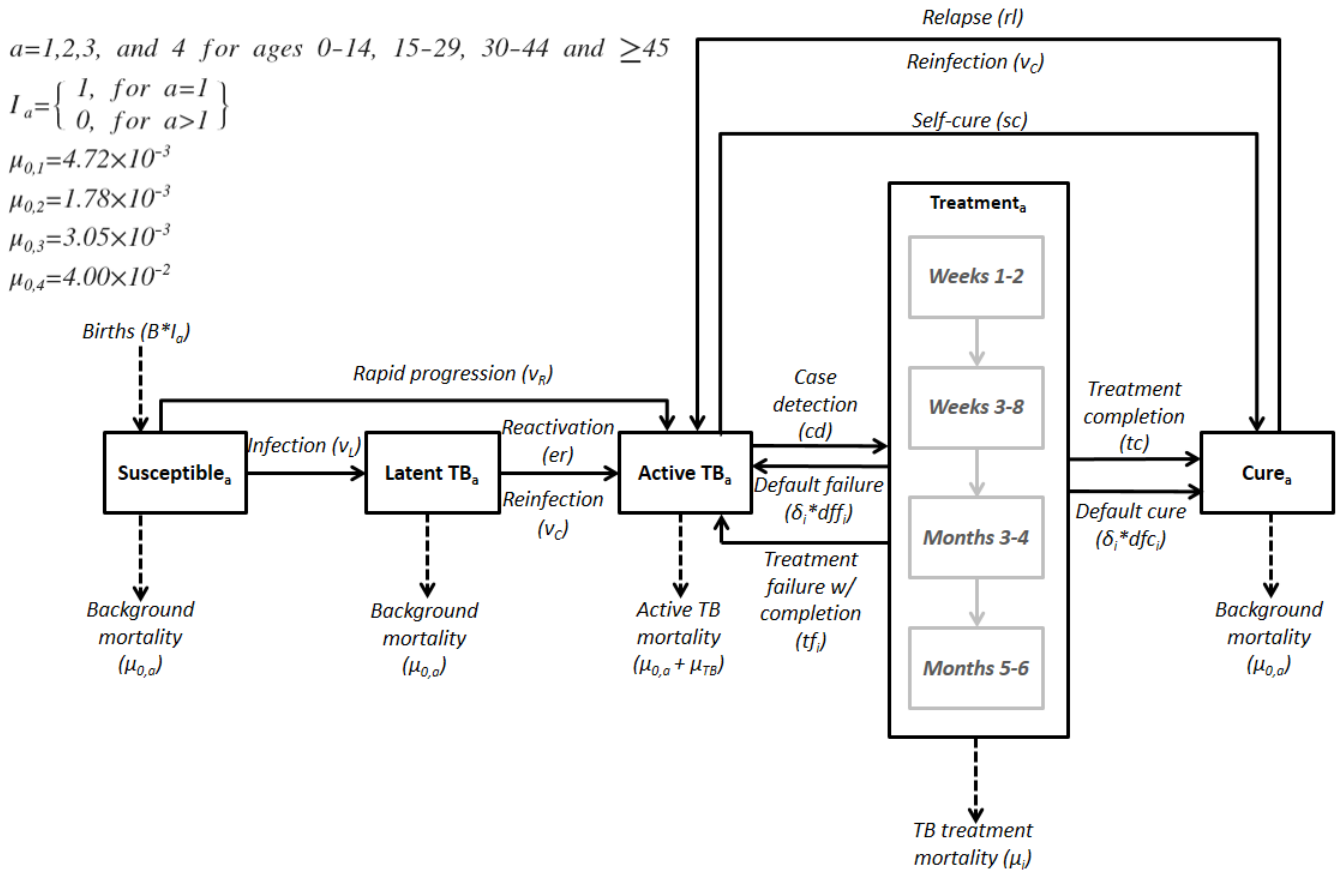
Table A.3: Additional sensitivity analysis results

	Incidence reduction at 10 years	
	With partial efficacy	***No partial efficacy***
Primary analysis	1.9%	10.3%
Declining incidence	1.7%	9.3%
Model 2 (latent infection)	0.9%	5.1%
Model 3 (age structure)	2.4%	12.8%
Model 3, differential infection rates	2.4%	13.0%
Model 3, differential reactivation rates	2.5%	13.5%

Figure A.2: Structural sensitivity analyses



B

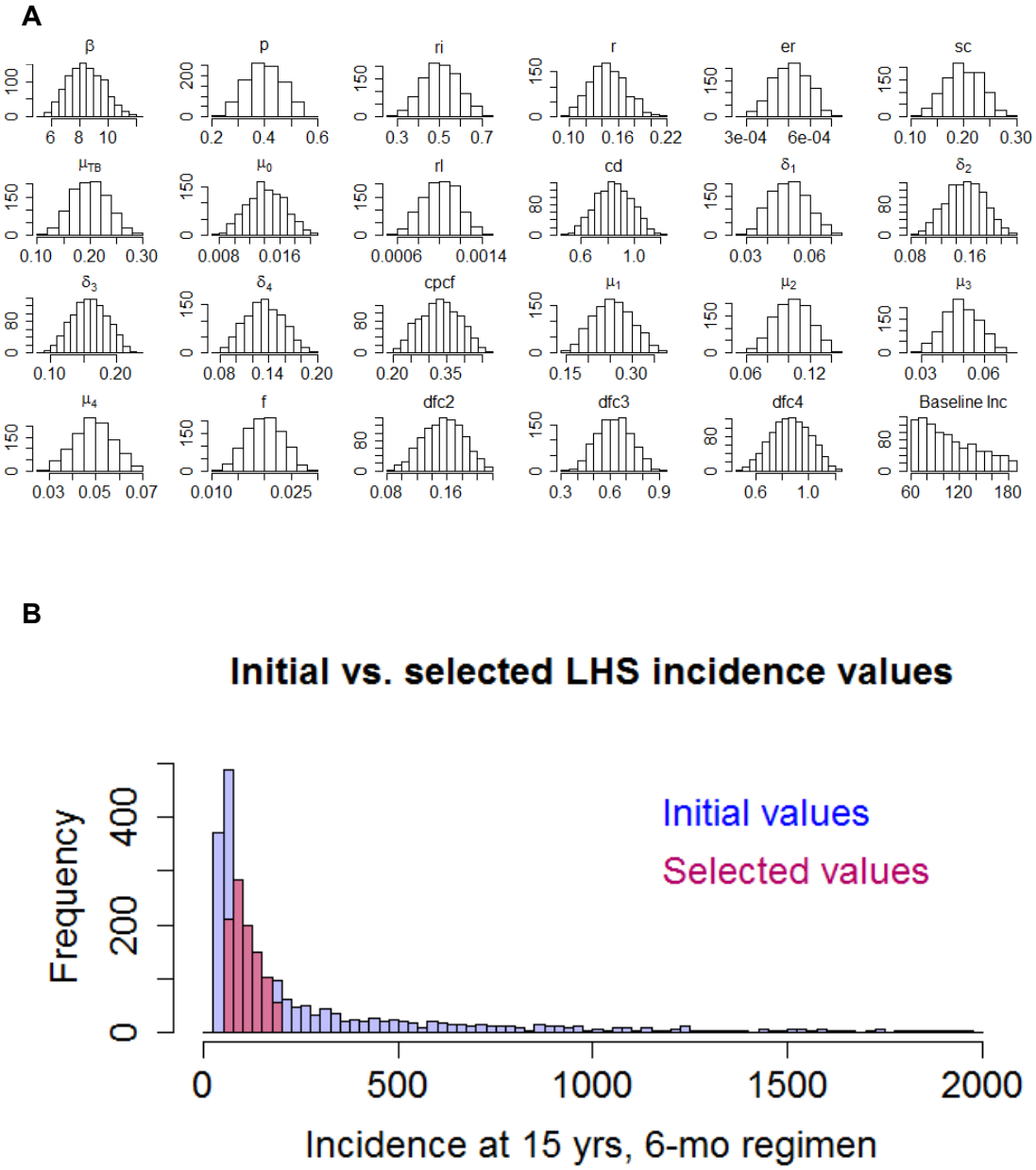


Structural sensitivity analyses on (A) latent infection and (B) age structure. Model parameters are the same as in the primary model except where indicated otherwise in the legend. Illustration of births and deaths in panel A and age progression in panel B are omitted for clarity

UNCERTAINTY ANALYSIS

A total of 2,449 combinations of input values were generated using Latin Hypercube Sampling [20], of which 1,449 were excluded because they resulted in baseline incidence below or above the specified range (62-188 per 100,000). Incidence values from the remaining 1,000 combinations of inputs were used to generate 95% uncertainty ranges. This selection procedure did not induce appreciable bias in the range of selected values for any of the model parameters (Figure A.3). We conducted a similar uncertainty range analysis for a moderate-burden setting (incidence 100 per 100,000 ±50% and 3% default proportion) and a high-burden setting (incidence 300 per 100,000 ±50% and 20% default proportion). A total of 2,086 and 4,009 combinations of input values were generated for the moderate-burden and high-burden settings respectively, of which 1,000 resulted in incidence values within the specified ranges and were used to generate the 95% uncertainty ranges.

Figure A.3: Uncertainty analysis



(A) Distribution of input values for each parameter used in uncertainty analysis and baseline incidence for each combination of input parameters. (B) Distribution of incidence at 15 years with 6-month regimen with full set of initial input values generated by Latin Hypercube sampling (LHS) vs. restricted set (incidence 62-188 per 100,000)

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APPENDIX B

"It is in the admission of ignorance and the admission of uncertainty that there is a hope for the continuous motion of human beings in some direction that doesn't get confined."

~Richard Feynman

SUPPLEMENTARY MATERIAL TO CHAPTER III

METHODOLOGIC DETAILS

Overview

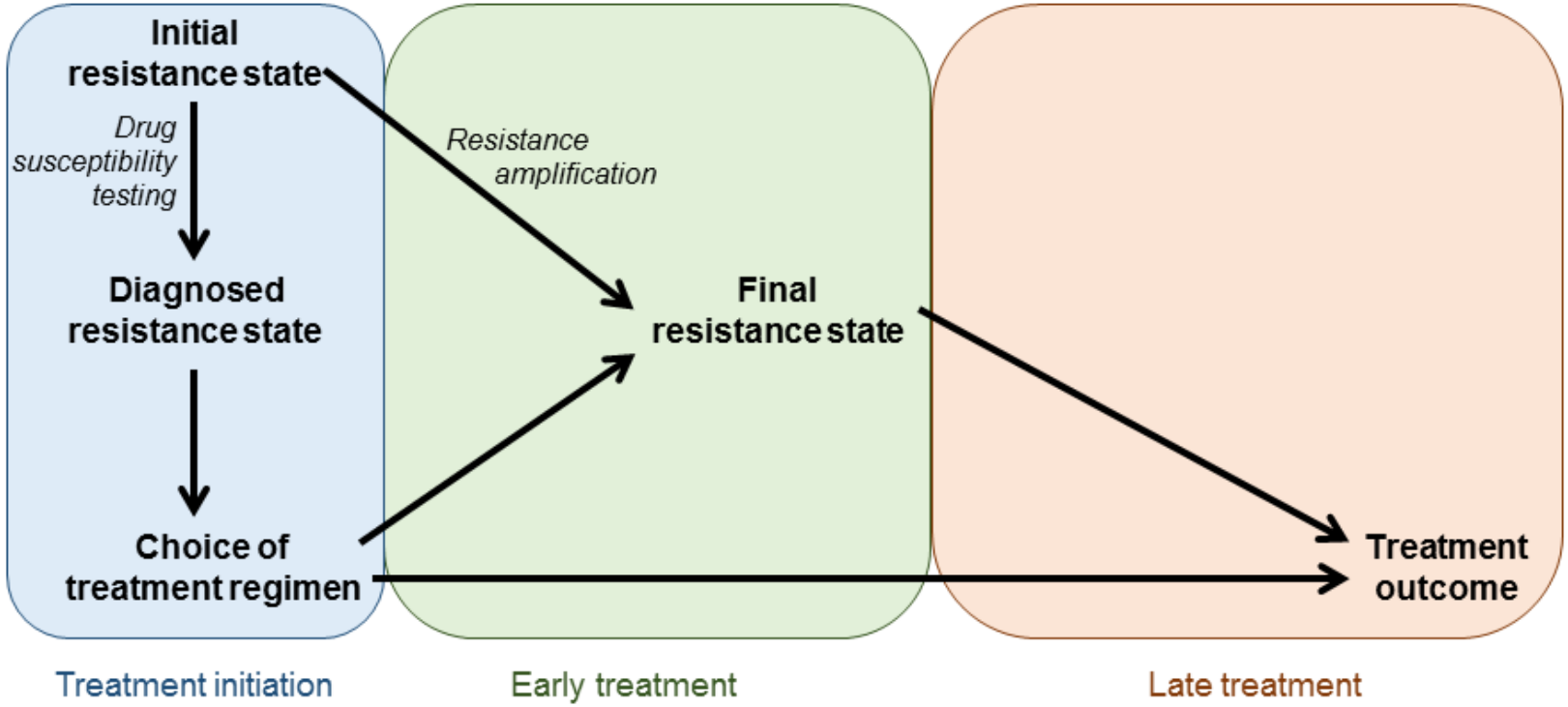
This analysis projects trajectories of drug-resistant TB using a deterministic, dynamic transmission model of TB. Because several key parameters essential to modeling TB drug resistance are poorly supported with empirical data, we sample input values for these parameters. This requires us to define sampling bounds for parameters relating to the probability of acquiring resistance, the relative transmission fitness, and the probabilities of treatment outcomes for every combination of resistance to three distinct drugs, and every treatment regimen modeled in the analysis.

Effects of drug resistance

Acquired resistance to TB drugs arises due to inadequate treatment that exerts selective pressure on populations of bacilli bearing resistance-conferring mutations. In contrast, primary resistance occurs when a previously uninfected person is infected by an individual with drug-resistant TB and thus develops drug-resistant TB without any prior exposure to treatment [1].

Moreover, individuals who initiate TB treatment with pre-existing resistance are even more susceptible to developing additional resistance-conferring mutations (resistance amplification) compared to those with drug-susceptible disease [1]. We assume that genetic mutations conferring drug resistance arise randomly in a bacterial population that is sufficiently large, that is, before treatment or very early in the course of treatment. Once such mutations occur, selection pressure exerted by inadequate treatment allows the mutant bacilli to multiply, resulting in clinical resistance to one or more drugs. With fewer fully effective drugs in their regimen, patients with drug-resistant TB are less likely to be cured at the end of their treatment; they also have fewer active drugs to provide a barrier against the development of further resistance during treatment [2, 3]. The final outcome of treatment is conditional on both (1) the chosen treatment regimen and (2) the final resistance state (Figure B.1).

Figure B.1: Effect of drug resistance and regimen choice on treatment outcomes



Regimen choice

In this analysis patients can receive any of three treatment regimens, depending on previous treatment history and available drug resistance diagnostics. The first is the standard first-line regimen consisting of isoniazid (INH), rifampin (RIF), pyrazinamide (PZA) and ethambutol (EMB) for six months, abbreviated as HRZE. Patients with previous TB treatment history may be prescribed a "Category II" regimen that includes the same drugs as the first-line regimen, with one additional drug, and is given for eight months; we assume that this regimen is no more efficacious than the first-line regimen but has lower probability of completion (83% vs. 94%) [4]. Patients who are identified as having RIF-resistant TB are offered a standardized second-line regimen, abbreviated as STR, consisting of a fluoroquinolone (FQ), PZA, EMB, an injectable aminoglycoside, and ethionamide, as is common practice in Southeast Asia and other settings [5-7]. This regimen is given for 18-24 months, with even poorer treatment completion (77%) [8].

Regimen choice depends on the drug susceptibility diagnostic and treatment algorithm. Our model inputs for the probability of access to second-line treatment reflect not only availability of drug susceptibility testing (DST) in Southeast Asia but also other avenues to treatment. For instance, many patients are prescribed second-line treatment on the basis of clinical suspicion (e.g, failure of previous TB treatment, known contact with MDR TB case) [4]. At baseline, 5% of treatment-naïve patients and 26% of treatment-experienced patients have access to the standardized second-line regimen. The model allows for DST for RIF, FQ and PZA, with differing levels of access for treatment-naïve patients, patients who have previously failed TB treatment, and other patients with

recurrent TB. The sensitivity values for resistance to each drug (RIF: 98%; FQ: 93%; PZA: 80%) reflect the state of current molecular diagnostics and can be altered to investigate hypothetical new testing technologies with improved characteristics [9-13]. We assume that only detection of RIF sensitivity is available, consistent with current availability of DST in Southeast Asia [14]. We assume 100% specificity for simplicity. Thus, all patients without RIF resistance (drug-susceptible or resistant to PZA and/or FQ) receive the first-line or Category II regimen, depending on previous treatment experience. For patients with any RIF resistance, the proportion receiving the standardized second-line regimen is computed as the product of the probability of access to DST and the sensitivity of RIF resistance detection.

Treatment outcomes

Although we do not explicitly model resistance to INH, empirical data indicate that most TB strains resistant to RIF are also resistant to INH [15]. We therefore assume that RIF resistance in the model includes underlying resistance to INH and reflect this assumption in our treatment outcome probabilities. Table B.1 lists the data sources related to the probability of cure vs. failure based on drug resistance and choice of treatment regimen. These data are sufficient to define a baseline probability of cure for every combination of resistance and treatment regimen considered in the model (Table 3.2). We allow for uncertainty around these outcome probabilities by randomly varying the probability of treatment failure in each simulation by a multiplicative factor of 0.75-1.25 for drug-resistant strains, or 0.5-5 for drug-susceptible TB. We apply additional constraints in the sampling procedure to ensure that resistance to any given drug in a regimen results in

poorer treatment outcomes compared to strains that do not harbor resistance to that drug. For example, TB resistant to both RIF and PZA will have poorer treatment outcomes than both RIF-resistant/PZA-susceptible and PZA-resistant/RIF-susceptible TB.

A small proportion of patients who are seemingly cured of TB at the completion of their treatment course will nevertheless experience recurrence soon thereafter (relapse). Based on published data from Southeast Asia, we set the probability of relapse for patients with drug-susceptible TB at 4%, with the remainder of patients experiencing stable cure. We apply a relative risk of 4, 3, and 2 respectively, for patients with resistance to RIF, FQ or PZA, compared to those with drug-susceptible TB, for the first-line treatment regimen [16, 17]. For strains with resistance to multiple drugs, we apply the highest applicable relative risk (e.g., for a strain resistant to both RIF and PZA, we apply a relative risk of 4, for a final relapse probability of 16%). For patients receiving a second-line regimen (which does not contain RIF), we use the same principles but assume that RIF resistance has no effect on the probability of relapse; thus, we define the probabilities of relapse based only on resistance to FQ and PZA (e.g., for a strain resistant to both RIF and PZA, we apply the PZA relative risk of 2, for a final relapse probability of 8%).

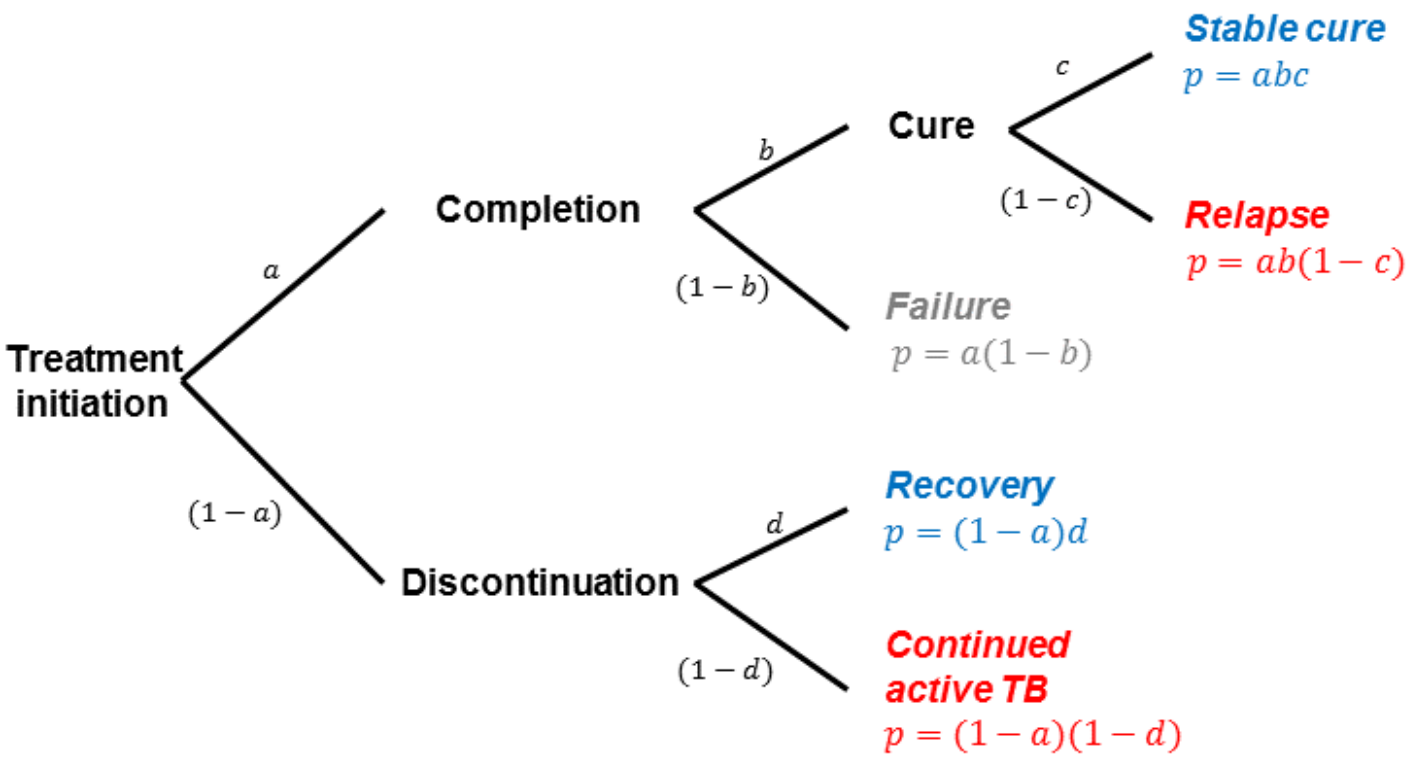
Some patients recover from active TB even without completing a full course of treatment. Thus, as illustrated in Figure B.2, the overall probability of recovering from active TB reflects patients who achieve a stable cure after completing treatment, as well as patients who recover despite discontinuing treatment (shown in blue). The overall probability of receiving an ineffective treatment regimen reflects patients who complete their treatment but remain infectious/symptomatic upon completion, thus prompting an immediate repeat

course of treatment (shown in gray). The overall probability of remaining infectious with active TB reflects patients who are initially thought to be cured upon treatment completion but subsequently experience relapse, as well as patients who remain infectious due to incomplete treatment (shown in red). Each of these outcomes is conditional on the final drug resistance profile j and the choice of treatment regimen k, with $c_{j|k}$, $\phi_{j|k}$, and $\sigma_{j|k}$ denoting the conditional probabilities of cure/recovery, ineffective treatment, and continued active TB, respectively, such that $c_{j|k} + \phi_{j|k} + \sigma_{j|k} = 1$.

Table B.1: Data sources for outcomes upon treatment completion

Outcome	Drug resistance	Value	References
First-line treatment			
Cure	Drug-susceptible	98%	[18]
Failure		2%	
Relative risk of cure vs. drug-susceptible TB	RIF	0.53	[18]
	PZA	0.86	[19]
Individualized second-line treatment			
Cure	RIF	91%	[20]
Failure		9%	
Absolute reduction in probability of cure vs. RIF resistance	RIF/FQ	16%	[21]
	RIF/PZA	0	Assumed
Standardized second-line treatment			
Absolute reduction in probability of cure vs. individualized regimen	RIF	0	Assumed
	RIF/FQ	10%	[20]

Figure B.2: Treatment outcome probabilities



Resistance acquisition

Sampling bounds for the probability of acquiring resistance during a single course of treatment are based on a published meta-analysis [22]. This study reported probabilities of resistance amplification of 0.008 [95% confidence interval 0.005-0.01] and 0.14 [0.09-0.2] among patients whose TB was drug-susceptible and drug-resistant at baseline, respectively. We therefore set the bounds for the probability of resistance amplification to 0-2% for patients with no pre-existing resistance to any drug in their treatment regimen, and 0-25% for patient with pre-existing resistance to one or more drugs in their treatment regimen. Resistance can only be acquired to a drug that is included in a patient's treatment regimen. However, because TB is frequently misdiagnosed as bacterial pneumonia, which is commonly treated with fluoroquinolones, we allow for some probability (0-1%) of acquiring resistance to FQ for treatment-naïve patients on the HRZE regimen. We vary this probability by 1- to 5-fold for previously treated patients, who are more likely to have been exposed to fluoroquinolones.

We assume that increasing levels of pre-existing resistance can only increase the probability of resistance amplification during treatment. For example, the probability of resistance amplification for a TB strain with pre-existing resistance to RIF and PZA must be equal to or greater than the probability for a TB strain with pre-existing resistance to RIF alone or PZA alone. Pre-existing resistance to a drug that is not included in the treatment regimen has no effect. For example, the probability of resistance amplification under treatment with the standardized second-line regimen is the same for fully drug-susceptible strains and RIF-resistant strains, as RIF is not included in this regimen. Using

the above principles and assumptions, we derive sampling bounds for each possible change in resistance profile and each treatment regimen, as shown in Table B.2.

We also allow for the acquisition of resistance to more than one drug in a single course of treatment. If TB bacilli acquire resistance to one drug, they then have an increased probability of acquiring resistance to a second drug within the same treatment course. We therefore assume sequential acquisition of resistance. For example, resistance can arise to drug A first, followed by drug B, or it could arise to drug B first, followed by drug A. If α_A and α_B represent the probabilities of acquiring resistance to drug A and drug B respectively in a drug-susceptible state on a given treatment regimen, and $\alpha_{A|B}$ and $\alpha_{B|A}$ represent the probabilities of acquiring resistance to drugs A and B given pre-existing resistance to drugs B and A, respectively, then the probability of acquiring resistance to both drugs in a single treatment course is computed as: $\alpha_{AB} = \alpha_A\alpha_{B|A} + \alpha_B\alpha_{A|B}$. We can thus define the complete set of probabilities $\eta_{i,j|k}$ and $\eta^R_{i,j|k}$ for transitions from resistance state i to resistance state j, conditional on treatment regimen k, for treatment-naïve and treatment-experienced patients respectively.

Table B.2: Upper sampling bounds, probability of resistance acquisition during treatment

Initial resistance	Acquired resistance	HRZE/ Category II	Standardized 2nd-line	Additional sampling constraints
None	RIF	2%	0	
None	FQ	1%	N/A	
None	PZA	2%	N/A	
RIF	RIF/FQ	1%	2%	*Must be equal to or greater than probability of DS→FQ*
RIF	RIF/PZA	25%	2%	*Must be equal to or greater than probability of DS→PZA*
FQ	RIF/FQ	2% *	0	*Must be equal to or greater than probability of DS→RIF*
FQ	FQ/PZA	2% *	N/A	*Must be equal to or greater than probability of DS→PZA*
PZA	RIF/PZA	25%	0	*Must be equal to or greater than probability of DS→RIF*
PZA	FQ/PZA	1%	N/A	*Must be equal to or greater than probability of DS→FQ*
RIF/FQ	RIF/FQ/PZA	25% **	25%	*Must be equal to or greater than probability of RIF→RIF/PZA and FQ→FQ/PZA*
RIF/PZA	RIF/FQ/PZA	1%	25%	*Must be equal to or greater than probability of RIF→RIF/FQ and PZA→FQ/PZA*
FQ/PZA	RIF/FQ/PZA	25% †	0	*Must be equal to or greater than probability of FQ→RIF/FQ and PZA→RIF/PZA*

DS: drug-susceptible

N/A: not applicable as 2nd-line treatment only available for RIF-resistant TB

** Set equal to probability of amplification from drug-susceptible state*

*** Set equal to probability of RIF→RIF/PZA*

† Set equal to probability of PZA→RIF/PZA

Transmission fitness

We assume that even TB strains with resistance to multiple drugs are at least 50% as transmissible as drug-susceptible TB. This lower bound is supported by laboratory data estimating the fitness cost of specific drug resistance-conferring mutations in competitive growth assays [23]. Although these laboratory assays are not necessarily indicative of the relative transmissibility of these TB strains at the population level, which is more difficult to assess, they do provide a reasonable bound for possible values. Laboratory data also suggest that many resistant strains are nearly as fit as drug-susceptible TB, although resistance to RIF is associated with greater costs, and MDR TB strains are known to be less transmissible [24, 25]. We therefore set the bounds for the relative transmission fitness of TB strains resistant to PZA alone or FQ alone to 0.75-1, and the relative fitness of RIF-resistant strains to 0.5-1. For strains harboring resistance to multiple drugs, we set the lower bound of transmission fitness at 0.5; we further assume that their relative transmission fitness can be no greater than that of strains with less resistance. Thus, if f_A and f_B represent the relative transmission fitness of strains resistant to drug A and drug B respectively, a strain resistant to both drugs has fitness $f_{AB} \leq \min(f_A, f_B)$.

Our model allows for individuals in the latent (i.e., asymptomatic, uninfectious) TB state to become super-infected with a different strain of TB and to subsequently develop active (infectious) disease with one of the two strains [26]. We assign the probability of active disease developing with one strain vs. the other based on each strains' transmission fitness values. Thus, in an individual latently infected with a strain i (fitness f_i) who becomes exposed to strain $j \neq i$ (fitness f_j), the superinfecting strain j will become

dominant with probability $\zeta_{i,j} = f_j/(f_i + f_j)$. For individuals who are reinfected with the same strain (i.e., $i = j$), $\zeta_{i,i} = 1$.

Emergence of resistance and transmission

We randomly sample the time of emergence of resistance to RIF and PZA (t_1; 10 to 40 years in the past), and FQ (t_2; 10 to 30 years in the past, but after the emergence of RIF/PZA resistance). These sampling bounds reflect the timing of availability of the HRZE regimen and fluoroquinolones. The variation in the time of emergence of drug resistance partly accounts for strains that have only begun to circulate in more recent years and have variable transmission fitness due to compensatory mutations that have accumulated over time. Once the time of resistance emergence is reached in a given simulation, the probabilities of resistance acquisition are scaled up linearly over 5 years, reflecting gradual scale-up of the regimen. After setting the sampling bounds for all of the parameters described above, we use the midpoint of each sampling range as a baseline value to calibrate the sampling range of the transmission parameter (β_0) to achieve the desired incidence and prevalence values in 2013. Based on this procedure, we set the sampling bounds for the transmission parameter at 12 ±4.

Table B.3: Model input parameters

Parameter	Description	Value/ sampling range	Reference(s)
β_0	Baseline transmission rate per person-year	8-16	Calibrated
p	Proportion progressing rapidly to active TB	0.15	[27]
ψ	Rate of endogenous reactivation from latent to active TB, per year	0.007	[28]
ω_A	Baseline rate of diagnosis and treatment initiation, per year	0.69	[4]
ω_F	Rate of repeat treatment initiation for patients on ineffective treatment per year	2	[29]
ϵ	Relative susceptibility to reinfection among individuals with previous TB exposure	0.5	[30, 31]
r	Relative infectiousness of patients on ineffective treatment	0.2	[32]
h	Rate of spontaneous recovery from active TB, per year	0.17	[33]
μ_0	Baseline mortality rate, per year	1/70	[34]
μ_{TB}	TB-specific mortality rate, per year	0.17	[33]

Table B.3 (cont.)

Parameter	Description	Value/ sampling range	Reference(s)
Transmission fitness and resistance acquisition			
f_i	Relative transmission fitness, strain i	See details in "Transmission fitness" section	[23-26]
$\eta_{i,j\|k}$ $\eta^R_{i,j\|k}$	Probability of acquiring resistance per treatment course, from strain i to strain j, conditional on treatment regimen k, treatment-naïve or treatment-experienced	See details in "Resistance acquisition" section	[22]
m^R	Relative risk of FQ resistance acquisition on HRZE, treatment-experienced vs. treatment-naïve	1-5	Assumed
Treatment outcomes			
$x_{i,k}$ $x^R_{i,k}$	Proportion receiving regimen k among those with TB strain i, treatment-naïve and treatment-experienced	See details in "Regimen choice" section	[4, 11, 12, 14]
$c_{i\|k}$	Probability of cure/recovery with strain i and treatment regimen k	See details in "Treatment outcomes" section	[18-21]
$\sigma_{i\|k}$	Probability of remaining in active TB state with strain i and treatment regimen k		
$\phi_{i\|k}$	Probability of ineffective treatment with strain i and treatment regimen k		

STATE TRANSITIONS AND MODEL EQUATIONS

Model state compartments

The six major compartments in the model reflect the natural history and treatment of tuberculosis, as shown in Figure 1, with the "R" subscript denoting patients with previous treatment experience:

- U: Uninfected
- L & L^R: Latent infection/recovered from active TB
- A & A^R: Active TB disease
- F: On ineffective (failing) treatment

All compartments (with the exception of the Uninfected compartment) are further subdivided into eight possible resistance profiles according the infecting TB strain, as denoted by the subscript i, where $1 \leq i \leq 8$. Thus,

- $L = \sum_{i=1}^{8} L_i$; $L^R = \sum_{i=1}^{8} L_i^R$
- $A = \sum_{i=1}^{8} A_i$; $A^R = \sum_{i=1}^{8} A_i^R$
- $F = \sum_{i=1}^{8} F_i$

The total population is thus computed as $N = U + \sum_{i=1}^{8}(L_i + L_i^R + A_i + A_i^R + F_i)$.

Force of infection

We define λ_i as the strain-specific force of infection, which depends on the prevalence of each strain in the population as well as the relative transmission fitness. Thus, for any strain i, with transmission fitness f_i:

$\lambda_i = \beta_0 f_i I_i / N$

$I_i = A_i + A_i^R + rF_i$, reflecting the total number of individuals with active TB caused by strain i, and accounting for the reduced transmission among individuals on ineffective treatment (compartments F_i).

Initial infection

A proportion p of individuals who initially become infected with strain i progress immediately to active TB, with the remainder advancing to latent TB. Thus, the *per capita* rates of progression upon initial infection are:

- $U \rightarrow L_i: (1-p)\lambda_i$
- $U \rightarrow A_i: p\lambda_i$

Spontaneous recovery

Spontaneous recovery among both treatment-naïve and treatment experienced individuals occurs at the same rate:

- $A_i \rightarrow L_i: h$
- $A_i^R \rightarrow L_i^R: h$

Reactivation

Progression from latent infection to active disease among both treatment-naïve and treatment-experienced individuals occurs at the same rate:

- $L_i \rightarrow A_i : \psi$
- $L_i^R \rightarrow A_i^R : \psi$

Reinfection

Individuals latently infected with strain i can become reinfected with any other strain j, but have reduced susceptibility to infection. As in initial infection, a proportion p progress immediately to active disease. The probability $\zeta_{i,j}$ that the super-infecting strain j will become dominant is determined by the relative transmission fitness of the two strains, as described earlier.

- $L_i \rightarrow L_j : (1-p)\lambda_j \epsilon \zeta_{i,j}, i \neq j$
- $L_i^R \rightarrow L_j^R : (1-p)\lambda_j \epsilon \zeta_{i,j}, i \neq j$
- $L_i \rightarrow A_j : p\lambda_j \epsilon \zeta_{i,j}, i \neq j$
- $L_i^R \rightarrow A_j^R : p\lambda_j \epsilon \zeta_{i,j}, i \neq j$

Successful treatment

Individuals exit the active TB compartments according to the baseline rate of diagnosis and treatment initiation. The probability of recovery depends on whether additional resistance is acquired during treatment, and on the probability of cure/recovery based on the final resistance state j given treatment regimen k.

- $A_i \rightarrow L_j^R: \omega_A \sum_k (x_{i,k} \eta_{i,j|k} c_{j|k}), i \leq j$
- $A_i^R \rightarrow L_j^R: \omega_A \sum_k (x_{i,k}^R \eta_{i,j|k}^R c_{j|k}), i \leq j$

Patients on ineffective treatment immediately begin a new course of treatment after an average of six months.

- $F_i \rightarrow L_j^R: \omega_F \sum_k (x_{i,k}^R \eta_{i,j|k}^R c_{j|k}), i \leq j$

Ineffective and insufficient treatment

The rates of transition associated with ineffective and insufficient treatment are computed similarly, based on the probabilities for each treatment outcome.

- $A_i \rightarrow F_j: \omega_A \sum_k (x_{i,k} \eta_{i,j|k} \phi_{j|k}), i \leq j$
- $A_i^R \rightarrow F_j: \omega_A \sum_k (x_{i,k}^R \eta_{i,j|k}^R \phi_{j|k}), i \leq j$
- $F_i \rightarrow F_j: \omega_F \sum_k (x_{i,k}^R \eta_{i,j|k}^R \phi_{j|k}), i < j$

- $A_i \rightarrow A_j^R: \omega_A \sum_k (x_{i,k} \eta_{i,j|k} \sigma_{j|k}), i \leq j$
- $A_i^R \rightarrow A_j^R: \omega_A \sum_k (x_{i,k}^R \eta_{i,j|k}^R \sigma_{j|k}), i \leq j$
- $F_i \rightarrow A_j^R: \omega_F \sum_k (x_{i,k}^R \eta_{i,j|k}^R \sigma_{j|k}), i \leq j$

Births and deaths

The baseline mortality rate is applied to the U and L compartments, and an increased mortality rate is applied to patients with active TB. The population is kept constant such that the number of births equals the total number of deaths, with all births occurring in the uninfected compartment:

$$\mu_0 \sum_{i=1}^{8}(L_i + L_i^R) + \mu_{TB} \sum_{i=1}^{8}(A_i + A_i^R + F_i)$$

Full system of equations

The full system of ordinary differential equations in the model can thus be summarized as follows, where subscripts $i, j \in \{1, \ldots, 8\}$ denote each TB strain, and subscript $k \in \{1,2,3\}$ denotes the treatment regimen:

(1) $\frac{dU}{dt} = \mu_0 \sum_i (L_i + L_i^R) + \mu_{TB} \sum_i (A_i + A_i^R + F_i) - U \sum_i \lambda_i$

(2) $\frac{dL_i}{dt} = (1-p)\lambda_i U + h\, A_i + (1-p)\epsilon \sum_{j \neq i} (\lambda_i \zeta_{j,i} L_j) - \left[\epsilon \sum_{j \neq i} (\lambda_j \zeta_{i,j}) + \psi + \mu_0\right] L_i$

(3) $\frac{dA_i}{dt} = p\, \lambda_i U + \psi L_i + p\, \epsilon \sum_{j \neq i} (\lambda_i \zeta_{j,i} L_j)$

$- \left[\omega_A \sum_{j \geq i,k} \left(x_{i,k} \eta_{i,j|k} (c_{j|k} + \phi_{j|k} + \sigma_{j|k})\right) + h + \mu_{TB}\right] A_i$

(4) $\frac{dF_i}{dt} = \omega_A \left[\sum_{j \leq 2,k} (x_{j,k} \eta_{j,i|k} \phi_{i|k} A_j + x_{j,k}^R \eta_{j,i|k}^R \phi_{i|k} A_j^R)\right] + \omega_F \sum_{j<i,k} (x_{j,k}^R \eta_{j,i|k}^R \phi_{i|k} F_j)$

$- \left[\omega_F \sum_{j \geq i,k} (x_{i,k}^R \eta_{i,j|k}^R (c_{j|k} + \sigma_{j|k})) + \omega_F \sum_{j>i,k} (x_{i,k}^R \eta_{i,j|k}^R \phi_{j|k}) + \mu_{TB}\right] F_i$

(5) $\frac{dL_i^R}{dt} = h\, A_i^R + \omega_A \sum_{j \leq i,k} (x_{j,k} \eta_{j,i|k} c_{i|k} A_j) + \omega_A \sum_{j \leq i,k} (x_{j,k}^R \eta_{j,i|k}^R c_{i|k} A_j^R)$

$+ \sum_{j \leq i,k} (x_{j,k}^R \eta_{j,i|k}^R c_{i|k} F_j) + (1-p)\epsilon \sum_{j \neq 2} (\lambda_i \zeta_{j,i} L_j) - \left[\psi + \epsilon \sum_{j \neq i} (\lambda_j \zeta_{i,j}) + \mu_0\right] L_i^R$

(6) $\frac{dA_i^R}{dt} = \psi L_i^R + p\, \epsilon \sum_{j \neq i} (\lambda_i \zeta_{j,i} L_j^R) + \omega_A \sum_{j \leq i,k} (x_{j,k} \eta_{j,i|k} \sigma_{i|k} A_j)$

$+ \omega_F \sum_{j \leq i,k} (x_{j,k}^R \eta_{j,i|k}^R \sigma_{i|k} F_j) + \omega_A \sum_{j \leq i,k} (x_{j,k}^R \eta_{j,i|k}^R \sigma_{i|k} A_j^R)$

$- \left[h + \omega_A \sum_{j \geq i,k} (x_{i,k}^R \eta_{i,j|k}^R (c_{j|k} + \phi_{j|k})) + \omega_A \sum_{j>i,k} (x_{i,k}^R \eta_{i,j|k}^R \phi_{j|k}) + \mu_{TB}\right] A_i^R$

MODEL CALIBRATION AND ADDITIONAL ANALYSES

Simulation selection

After generating 100,000 simulations using inputs sampled from uniform distributions with bounds as described above, we retain trajectories that are consistent with current epidemiologic data, using a procedure analogous to an approximate Bayesian computation rejection algorithm, as illustrated in Figure 3.2 [35]. The choice of uniform prior distributions reflects inherent uncertainty about the values of these parameters. Compared to peaked distributions, uniform distributions also increase sampling from the bounds of the sampling range, thus ensuring that our sampled parameters sets include scenarios that, although unlikely, are important in evaluating the plausibility of extreme epidemiologic scenarios.

We generate simulations under two alternative assumptions: (1) that PZA provides protection against the development de novo mutations conferring resistance to RIF or FQ during treatment and (2) that PZA provides no such protection. In the baseline scenario, we sample all parameters inputs as described above. In the alternative ("no-protection") scenario, we modify the probabilities of resistance acquisition such that PZA resistance has no effect on further resistance amplification. For example, we set the resistance acquisition probabilities for PZAr → RIF/PZAr amplification equal to the sampled values for DS → RIFr amplification. Thus, the "no-protection" scenario features lower probabilities of resistance amplification among all strains with PZA resistance, compared to the baseline scenario.

Overall, 1.1% of simulations under the baseline scenario projected epidemiologic trajectories consistent with available epidemiologic data for Southeast Asia (Figures B.3). The proportion of trajectories meeting each of the calibration criteria is shown in Table B.4. To assess the effect of this procedure, we examine the posterior distributions of our input parameters among the selected trajectories and compare them to the uniform prior distributions using the Kolmogorov-Smirnoff statistic (Table B.5). Attempts to calibrate the model to Southeast Asia data under the "no-protection" scenario had a much lower yield, with only 47 of 100,000 simulations (0.05%) meeting the calibration criteria, primarily due to an inability to match the reported prevalence of RIF resistance among FQ-resistant retreatment cases (Table B.4, Figure B.4). Although it is also possible that our model was unable to match available data under the no-protection scenario because it cannot not fully capture the dynamics of such a system, we interpreted this incongruence of model output and epidemiologic data as indicating that the no-protection scenario is less plausibly reflective of the true effect of PZA. This interpretation is consistent with the ten-fold difference in yield of data-consistent simulations between the two scenarios, and previous empirical studies that support a protective role of PZA [17, 36]. We therefore retain the data-consistent parameters generated under the baseline scenario for all subsequent analyses, and run all simulations assuming a protective effect of PZA against resistance to RIF and FQs.

Regression and correlation analyses

To identify the primary drivers of drug resistance trajectories, we first categorize each selected trajectory based on whether it results in a prevalence of drug resistance

exceeding a set threshold within 20 years. We scale all of the sampled parameters to z-scores based on the empirical distribution of values among the selected trajectories. We then estimate a multivariate logistic regression model, using the z-scores as explanatory variables and report regression coefficients and odds ratios associated with a change of 0.1 standard deviation. We exclude explanatory variables found to have excessive collinearity based on a variance inflation factor >10 in a stepwise procedure, until no such parameters remain in the model [37]. Once the final model is defined, we select variables with a statistically significant regression coefficient ($p<0.05$) and rank them based on the absolute value of the coefficient. We conduct a similar analysis using partial rank correlation coefficients (PRCCs) on the original (i.e., not scaled) values for the prevalence of drug resistance.

Alternate epidemiologic settings

In order to assess the applicability of our results to settings with the highest TB burden, we selected the 100 simulations that were most representative of TB epidemiology in these countries, as well as in the Southeast Asia region, in terms of overall TB incidence and prevalence of MDR TB. For each country (India, Pakistan, Indonesia), we compared WHO data to our simulations assuming a joint Poisson likelihood function with the WHO-reported estimate as the mean. Although the absolute estimates of the proportion of trajectories resulting in a prevalence of pre-XDR TB exceeding the predefined thresholds changes, the overall findings are robust: replacing PZA with an alternative drug of similar efficacy greatly reduces the projected prevalence of pre-XDR TB (Figure B.7).

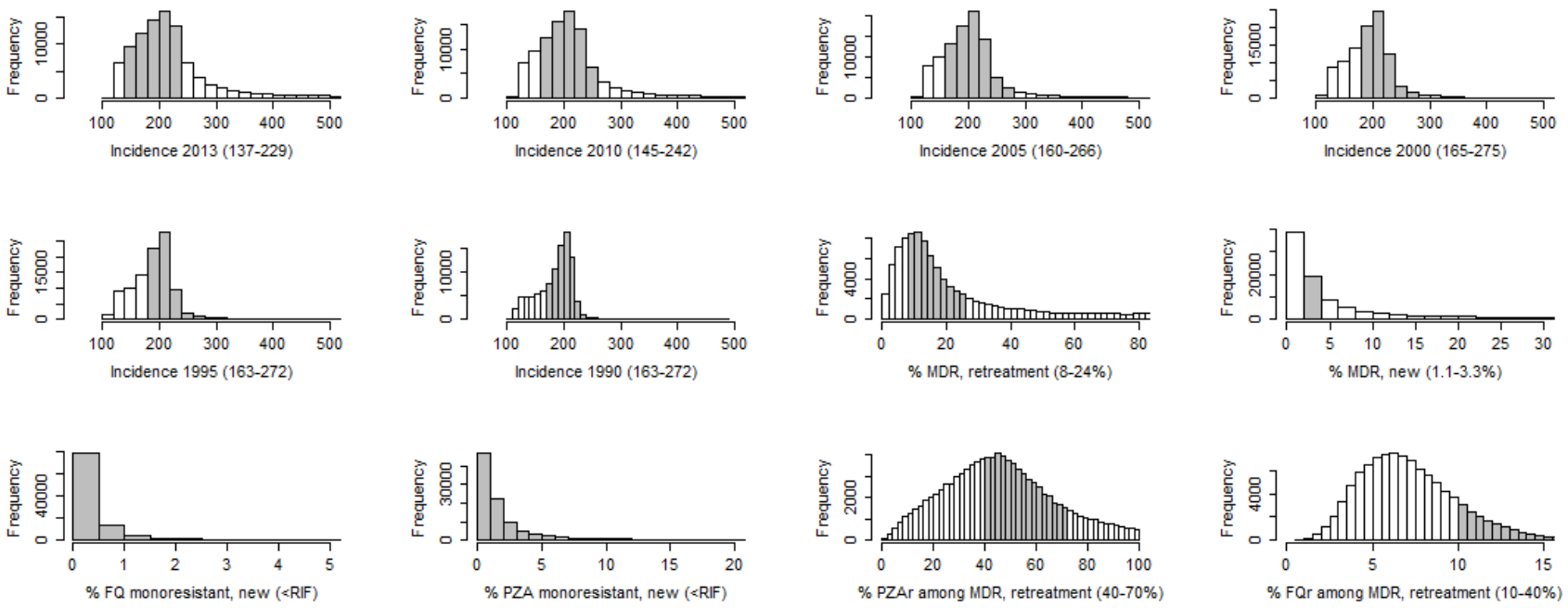
Stochastic model adaptation

We adapted the system of differential equations shown above to a stochastic model using the Gillespie stochastic simulation adaptive tau method, as implemented in the R package "adaptivetau" [38]. We further modified the model by incorporating scale-up of MDR treatment, improvements in case detection, and decline in TB incidence reflective of trends in Southeast Asia in 1995-2013, and applied a 2% annual decrease in incidence to better reflect regional trends [39]. We generated 200,000 randomly sampled values for key model inputs, as described above, and projected 1 stochastic trajectory for each parameter set, using a population size of 10 million individuals. We retained 1,751 trajectories that met our pre-defined calibration targets based on available epidemiologic data from Southeast Asia (Table B.4). We used these simulations to replicate all subsequent analyses and compare our findings to those obtained using the deterministic version of the model.

Table B.4: Calibration criteria

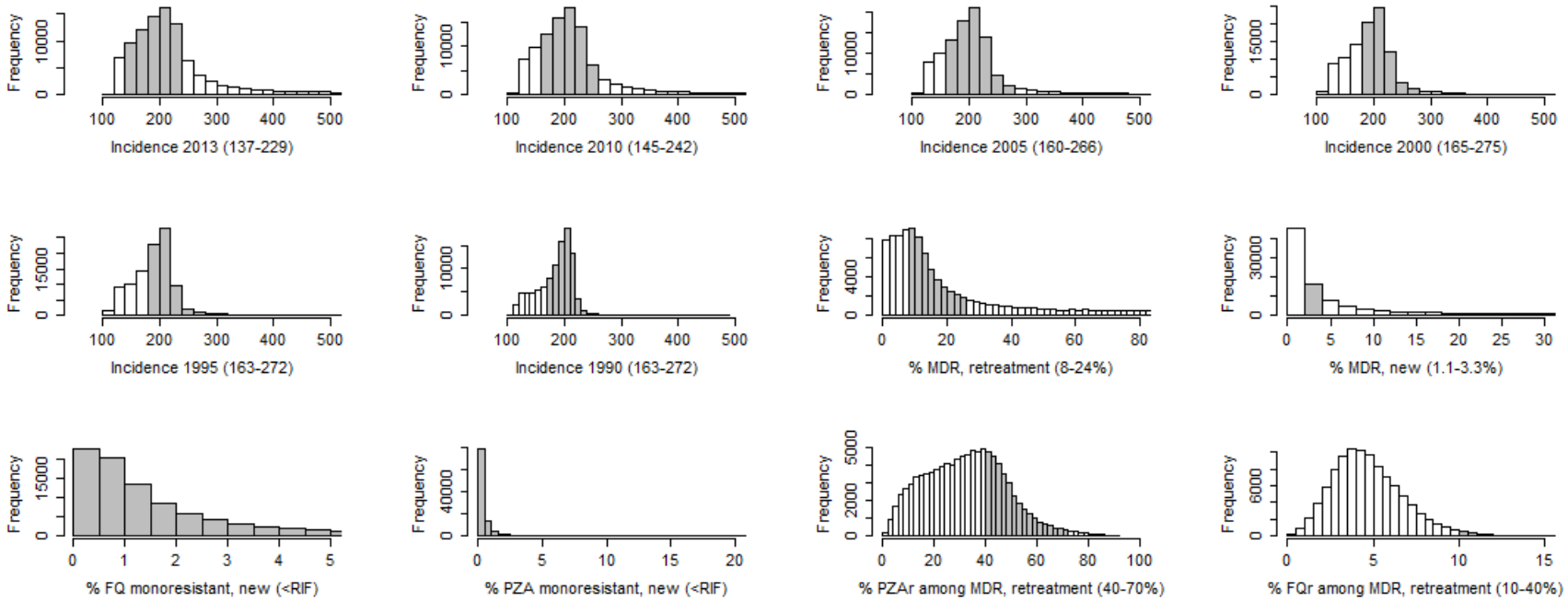
Epidemiologic criteria	Target value		References	Calibration range	Trajectories within range (%)	
	Year	*Value*			*Baseline*	*No protection*
Annual TB incidence, per 100,000	2013	183	[4]	137-229	42%	42%
	2010	194		145-242		
	2005	213		160-266		
	2000	220		165-275		
	1995	218		163-272		
	1990	218		163-272		
RIF-resistant among new cases (%)	2013	2.2%	[4]	1.1-3.3%	32%	29%
RIF-resistant among retreatment cases (%)	2013	16%	[4]	8-24%	46%	40%
RIF-resistant among retreatment cases with FQ resistance (%)	2013	25%	[40]	10-40%	16%	1.8%
RIF-resistant among retreatment cases with PZA resistance (%)	2013	55%	[41]	40-70%	45%	30%
PZA-monoresistant among new cases (%)	2013	< % RIF resistance	[42, 43]	--	86%	84%
FQ-monoresistant among new cases (%)	2013	< % RIF resistance	[44, 45]	--	99%	99%

Figure B.3: Distribution of calibration criteria, baseline scenario



Distribution of simulation outcomes used for model calibration, assuming a protective effect of PZA against the development of mutations conferring resistance to RIF and FQ. Values meeting the calibration criteria (shown in parentheses) are colored in gray.

Figure B.4: Distribution of calibration criteria without protection effect



Distribution of simulation outcomes used for model calibration, assuming that PZA confers no protective effect against the development of mutations conferring resistance to RIF and FQ. Values meeting the calibration criteria (shown in parentheses) are colored in gray. This assumption resulted in 20 times fewer simulations matching epidemiologic calibration criteria compared to the baseline scenario (Figure B.3).

Table B.5: Distribution of sampled input parameters before and after selection of simulations consistent with current epidemiology (baseline scenario)

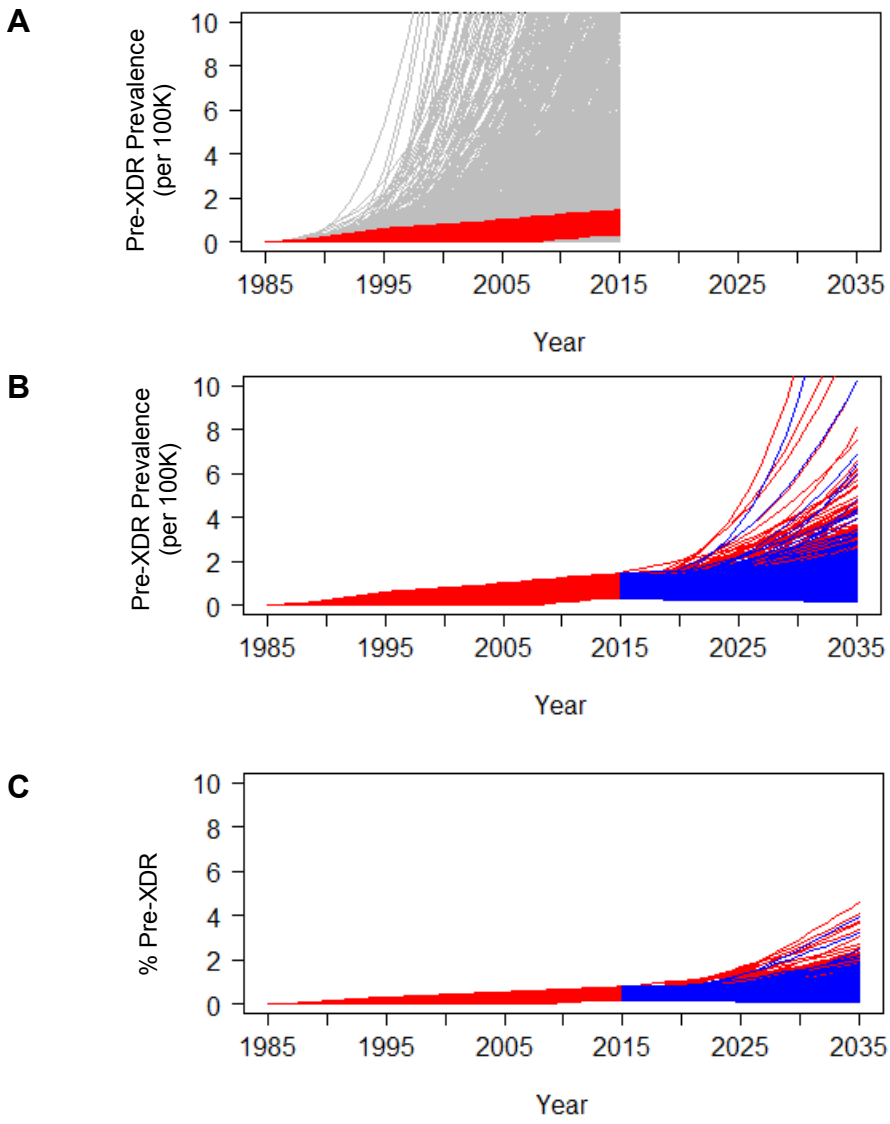
	Sampled values			Data-consistent values			D statistic	p-value
	Median	25th %ile	75th %ile	Median	25th %ile	75th %ile		
Time of emergence of resistance								
RIF, PZA	34.864	27.459	42.444	32.681	26.615	39.278	0.120	0.000
FQ	44.652	39.445	47.997	41.610	36.813	45.512	0.210	0.000
Probability of resistance acquisition, HRZE regimen								
DS→RIFr	0.010	0.005	0.015	0.011	0.008	0.015	0.147	0.000
DS→FQr	0.005	0.002	0.008	0.006	0.004	0.008	0.174	0.000
DS→PZAr	0.010	0.005	0.015	0.010	0.005	0.015	0.019	0.849
RIFr→RIF/FQr	0.008	0.006	0.009	0.009	0.008	0.010	0.201	0.000
RIFr→RIF/PZAr	0.130	0.070	0.190	0.188	0.145	0.220	0.328	0.000
PZAr→RIF/PZAr	0.130	0.070	0.190	0.155	0.098	0.206	0.124	0.000
PZAr→FQ/PZAr	0.008	0.006	0.009	0.009	0.007	0.010	0.119	0.000
RIF/PZAr→RIF/FQ/PZAr	0.010	0.009	0.010	0.010	0.009	0.010	0.136	0.000
Probability of resistance acquisition, standardized 2nd-line regimen								
RIFr→RIF/FQr	0.010	0.005	0.015	0.011	0.006	0.016	0.080	0.000
RIFr→RIF/PZAr	0.010	0.005	0.015	0.011	0.006	0.016	0.054	0.006
RIF/FQr→RIF/FQ/PZAr	0.131	0.070	0.191	0.130	0.067	0.188	0.021	0.760
RIF/PZAr→RIF/FQ/PZAr	0.131	0.070	0.190	0.192	0.139	0.223	0.306	0.000

Table B.5 (cont.)

Transmission fitness								
RIFr	0.750	0.625	0.875	0.634	0.578	0.698	0.388	0.000
FQr	0.875	0.812	0.937	0.869	0.813	0.929	0.046	0.031
PZAr	0.875	0.813	0.938	0.818	0.782	0.866	0.291	0.000
RIF/FQr	0.589	0.532	0.678	0.561	0.524	0.620	0.163	0.000
RIF/PZAr	0.589	0.533	0.677	0.551	0.521	0.597	0.248	0.000
FQ/PZAr	0.661	0.580	0.742	0.651	0.579	0.726	0.062	0.001
RIF/FQ/PZAr	0.515	0.504	0.540	0.512	0.504	0.531	0.074	0.000
Probability of cure, HRZE regimen								
DS, FQr	0.940	0.915	0.965	0.942	0.915	0.965	0.027	0.441
RIFr, RIF/FQr	0.520	0.460	0.580	0.490	0.439	0.560	0.136	0.000
PZAr, FQ/PZAr	0.865	0.847	0.882	0.866	0.846	0.882	0.016	0.956
RIF/PZAr, RIF/FQ/PZAr	0.406	0.363	0.463	0.372	0.344	0.407	0.248	0.000
Probability of cure, standardized 2nd-line regimen								
RIFr	0.915	0.903	0.928	0.914	0.902	0.927	0.028	0.426
RIF/FQr	0.661	0.621	0.701	0.658	0.616	0.697	0.044	0.038
RIF/PZAr	0.810	0.785	0.835	0.808	0.785	0.833	0.038	0.104
RIF/FQ/PZAr	0.583	0.531	0.631	0.574	0.521	0.624	0.061	0.001
Relative risk of FQ resistance acquisition retreatment vs. new cases								
	2.998	2.009	4.001	3.933	3.090	4.539	0.280	0.000
Transmission parameter								
	12.005	10.013	13.999	11.886	10.810	13.149	0.209	0.000

SUPPLEMENTAL RESULTS

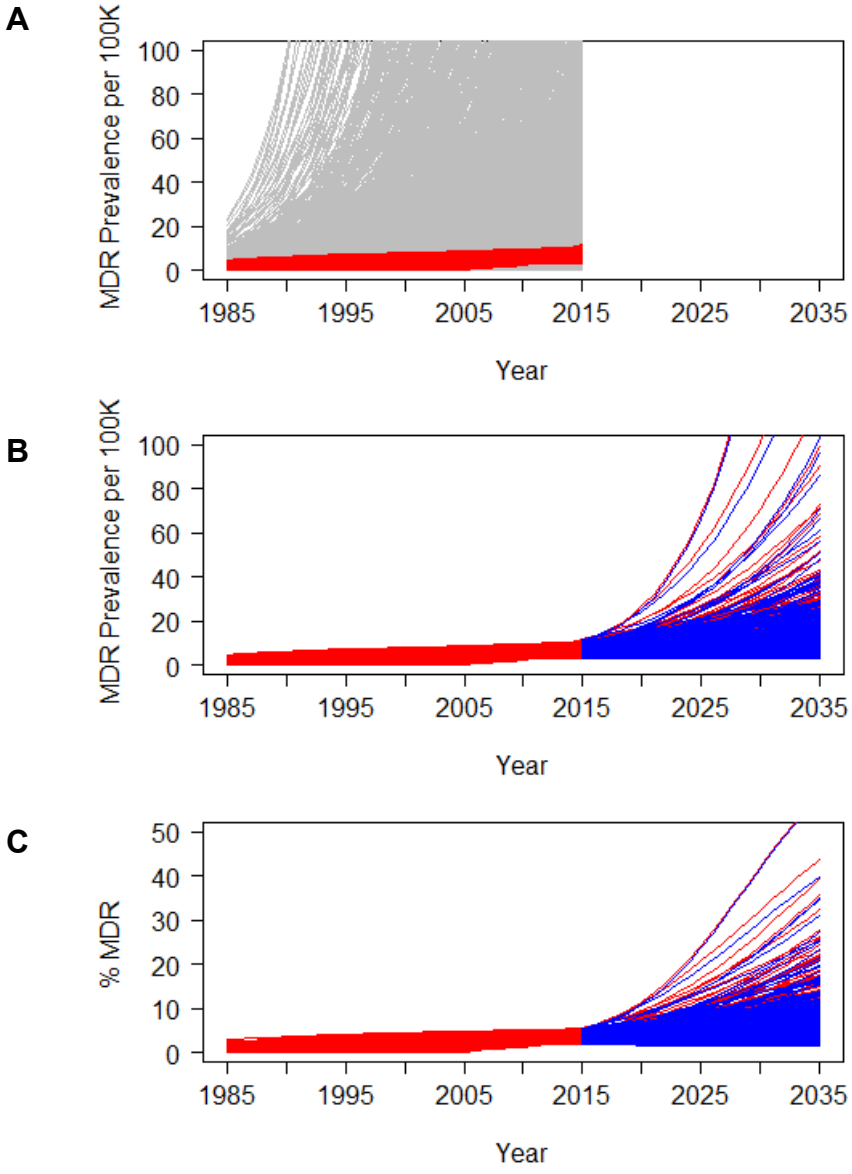
Figure B.5: Projected trajectories of pre-XDR TB



(A) Random subsample of generated trajectories up to 2015, shown in gray.

(B, C) Even after selecting for trajectories consistent with current TB epidemiology, shown in red, the range of drug resistance prevalence (B) and the proportion of drug-resistant TB cases (C) in 2035 vary widely. Replacing PZA with an equally effective drug in the treatment regimens of patients with PZA-resistant TB greatly reduced projected levels of pre-XDR TB, as shown by the overlaid blue curves.

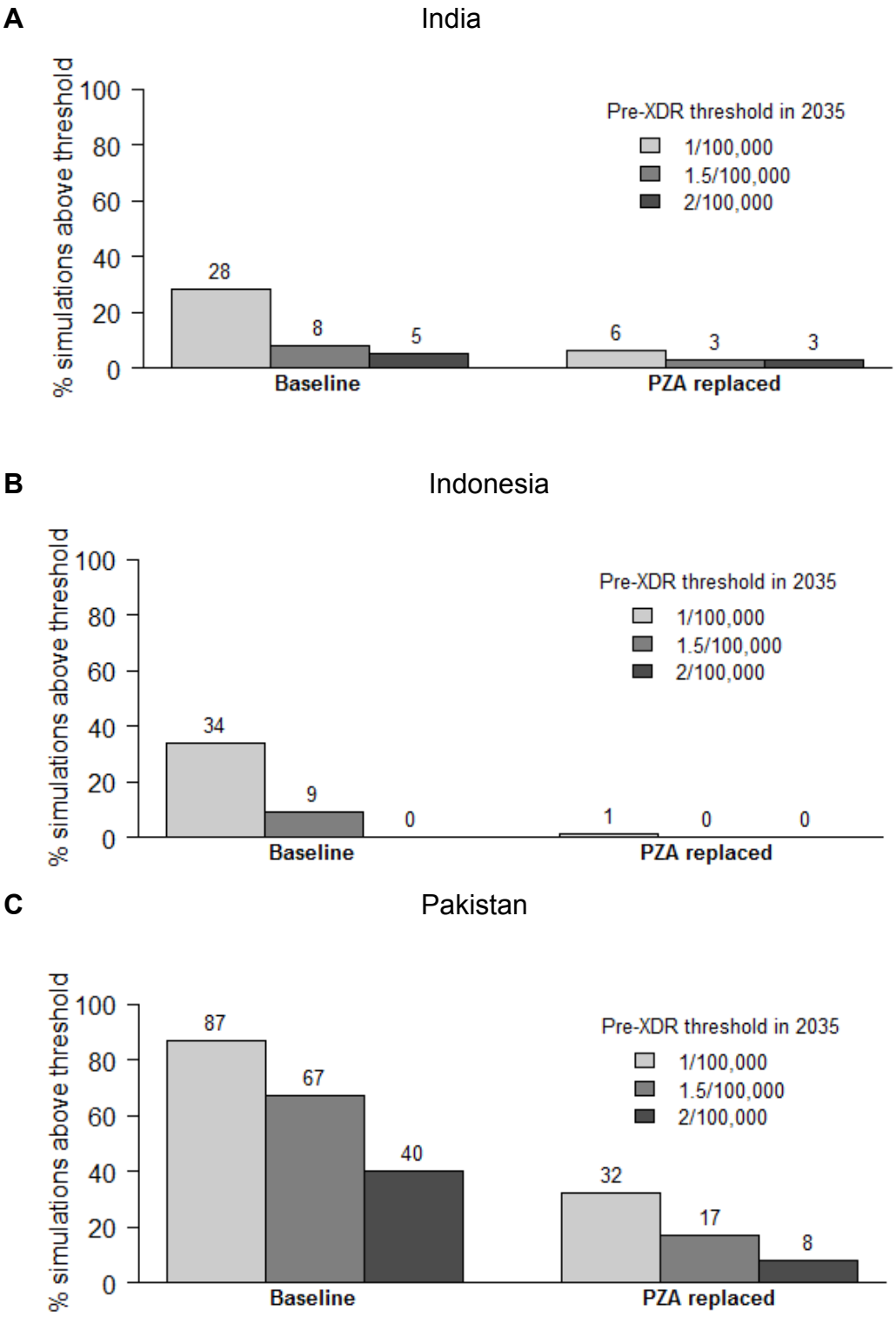
Figure B.6: Projected trajectories of RIF-resistant TB

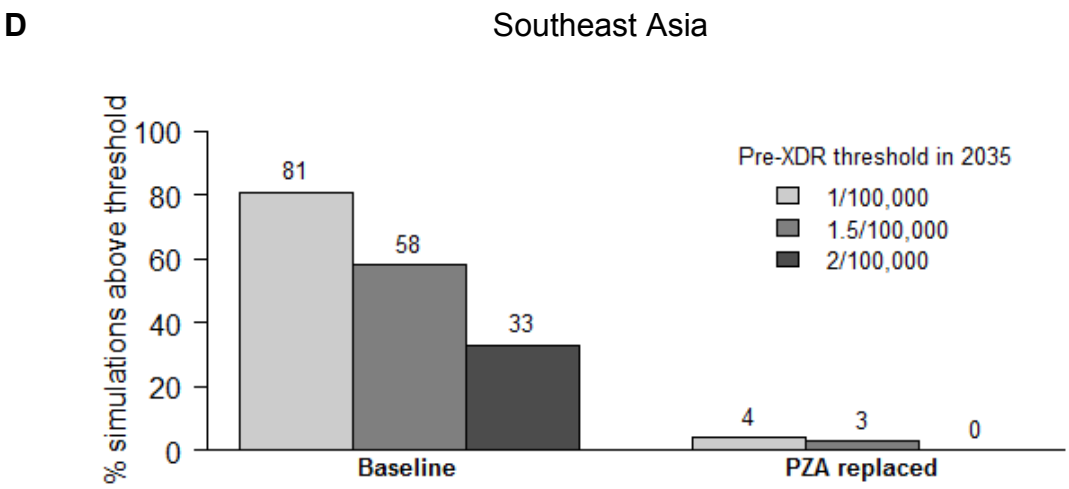


(A) Random subsample of generated trajectories up to 2015, shown in gray.

(B, C) Data-consistent trajectories of prevalence (B) and proportion (C) of pre-XDR TB projected to 2035, shown in red. Replacing PZA with an equally effective drug in the treatment regimens of patients with PZA-resistant TB (blue) had little impact on projected trajectories.

Figure B.7: Impact of PZA replacement on projected prevalence of pre-XDR TB across high TB burden settings

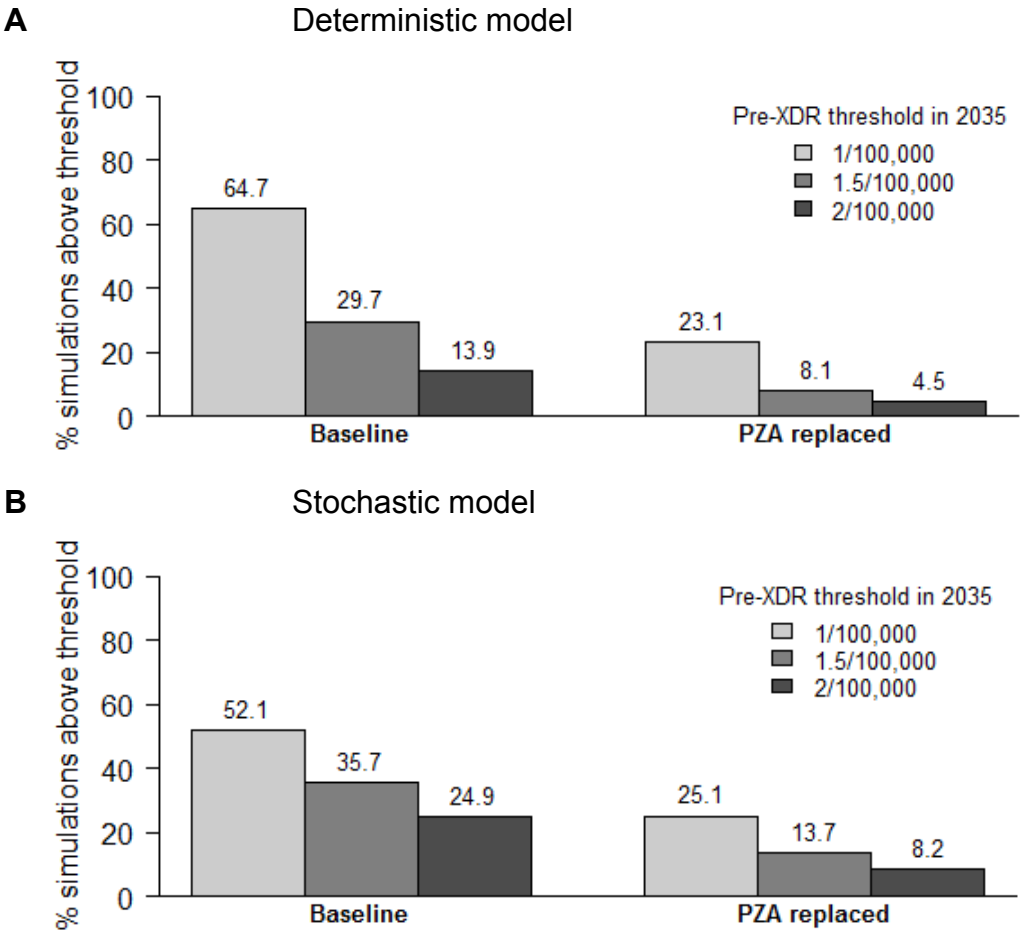




Proportion of data-consistent simulations in which projected pre-XDR TB prevalence in 2035 exceeds three pre-defined acceptability thresholds. We selected the 100 simulations most representative of TB epidemiology in India (A), Indonesia (B), Pakistan (C) and the Southeast Asia region (D). In all cases, replacing PZA with an alternative drug of equal efficacy among patients with PZA-resistant TB greatly reduces the proportion of trajectories exceeding the pre-XDR TB acceptability threshold in 2035.

PZA: pyrazinamide

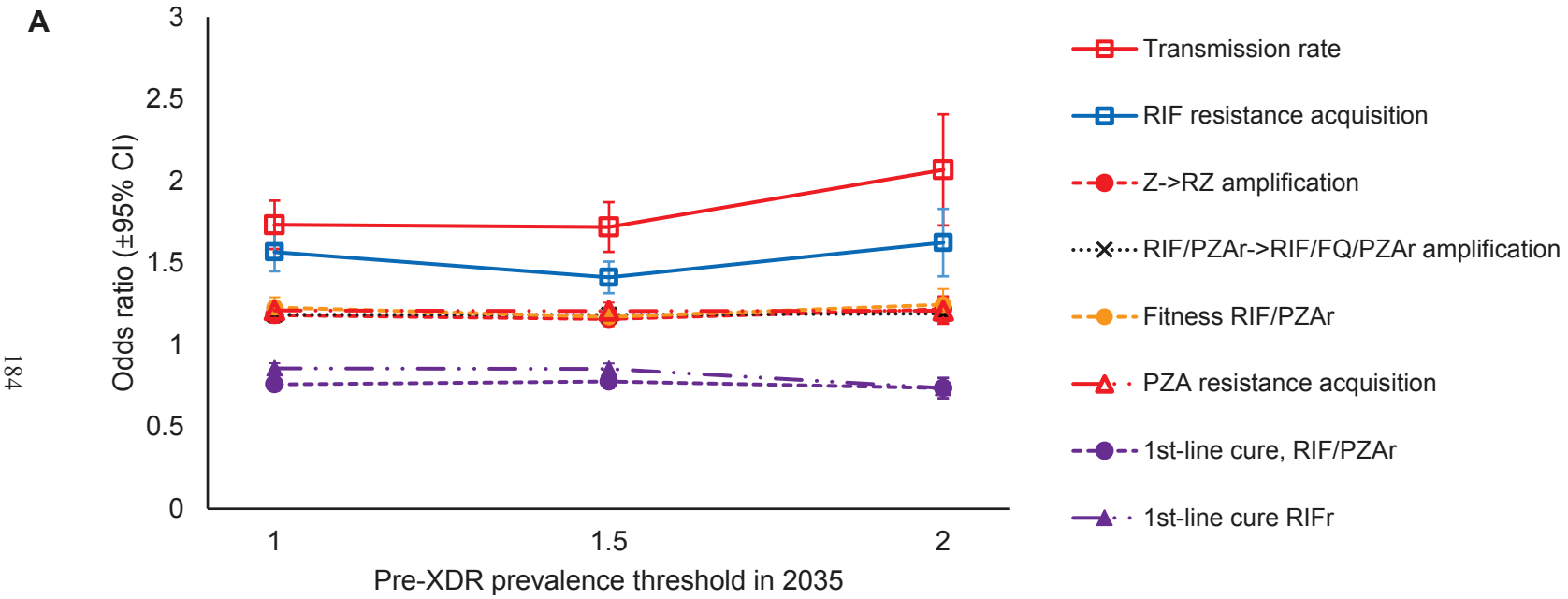
Figure B.8: Impact of PZA replacement on projected prevalence of pre-XDR TB, in deterministic vs. stochastic model

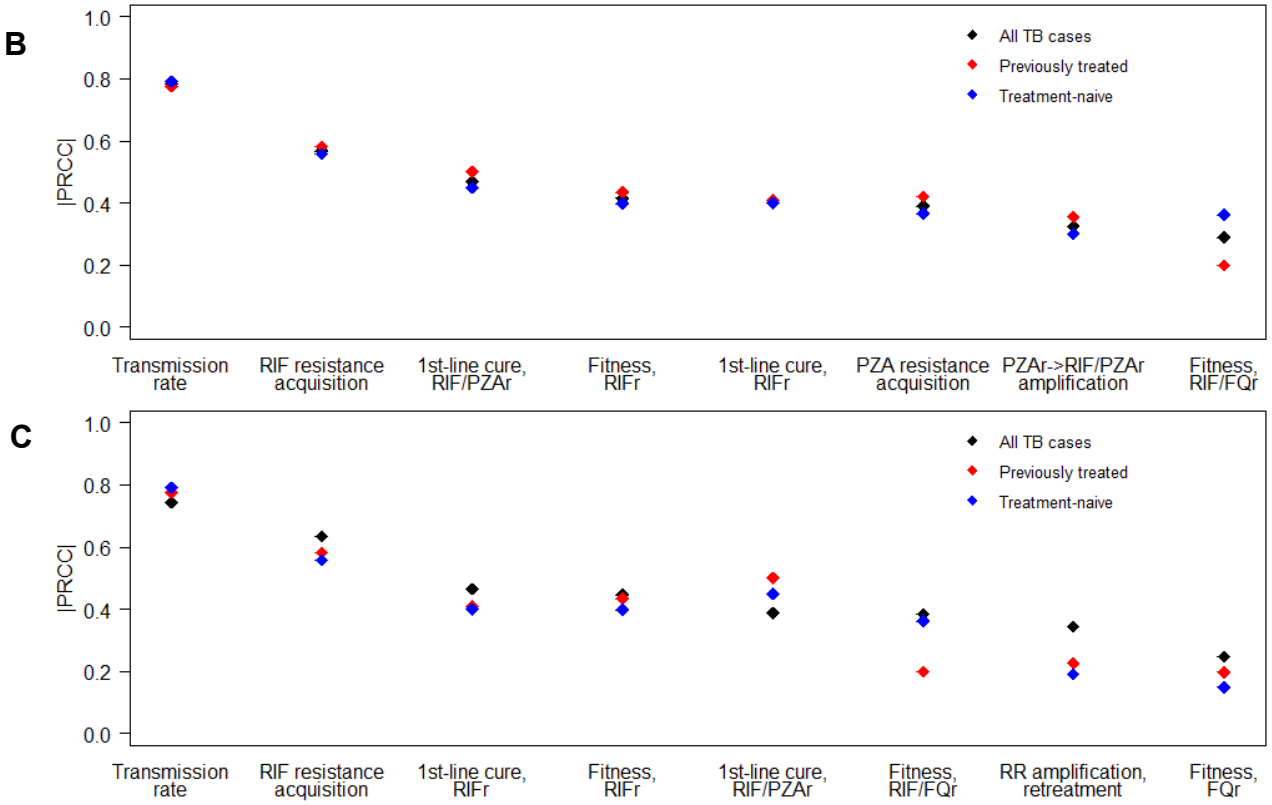


Proportion of data-consistent simulations in which projected pre-XDR TB prevalence in 2035 exceeds three pre-defined acceptability thresholds. In both the deterministic and the stochastic frameworks, replacing PZA with an alternative drug of equal efficacy among patients with PZA-resistant TB greatly reduces the proportion of trajectories exceeding the pre-XDR TB acceptability threshold in 2035.

PZA: pyrazinamide

Figure B.9: Factors associated with high projected pre-XDR TB prevalence





(A) Odds ratios (with 95% confidence intervals) for parameters most strongly correlated with prevalence of pre-XDR TB exceeding 1, 1.5, or 2 cases per 100,000 population in 2035, baseline scenario. Similar results for the baseline scenario are obtained with alternative analyses using partial rank correlation coefficients (B). In contrast, PZA-related parameters became less predictive of pre-XDR prevalence if PZA was replaced with an equivalent alternative drug for patients with PZA-resistant TB (C).

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CURRICULUM VITAE

"We are here to add what we can to, not to get what we can from, Life."

~Sir William Osler

"Dans la vie, rien n'est à craindre. Tout est à comprendre."

~Marie Curie

Mariam O. Fofana

1830 E. Monument St, Ste 2-300
Baltimore, MD 21205
mariam@jhmi.edu
410-989-1985

EDUCATION

2009- **Johns Hopkins School of Medicine, Baltimore MD**
MD, expected May 2017

2012- **Johns Hopkins Bloomberg School of Public Health, Baltimore MD**
PhD, Infectious Disease Epidemiology, expected May 2017
Advisor: David Dowdy, MD, PhD, MSc
Dissertation title: *Epidemiologic impact of treatment interventions for global tuberculosis control*

2002-2006 **Harvard College, Cambridge, MA**
AB *cum laude*, Biology
Citation in Spanish language

RESEARCH EXPERIENCE

2012-2016 **Johns Hopkins Bloomberg School of Public Health, Baltimore MD**
PhD student
Designed mathematical models of TB transmission at global and regional scales to project potential impact of alternative treatment regimens for drug-sensitive and drug-resistant TB.

2010-2011 **Johns Hopkins School of Medicine, Baltimore MD**
Scholarly Concentration in Bioethics
Designed and conducted independent summer project investigating ethical concerns in pediatric HIV testing research in Côte d'Ivoire.

2010 **Johns Hopkins School of Medicine, Baltimore MD**
Summer research assistant (PI: Kelly Dooley)
Worked with Tangiers Pasteur Institute and local NGOs to launch molecular epidemiology study of TB in Northern Morocco's migrant populations.

2008-2009 **Programme PAC-CI, Abidjan, Côte d'Ivoire**
Research intern (PI: Xavier Anglaret)
Assisted data management team on a clinical trial of early antiretroviral treatment and TB prophylaxis; helped train postdoctoral fellow in cost-effectiveness modeling.

2006-2009 **Massachusetts General Hospital, Boston MA**
Research assistant (PI: Kenneth Freedberg)
Conducted simulation-based analyses of clinical outcomes and cost-effectiveness of HIV testing and antiretroviral treatment in South Africa.

HONORS & AWARDS

2016 **Visiting Student Scholarship, Yale University School of Medicine**
$1500 award to support participation in a visiting clinical clerkship in emergency medicine.

2015 **Field Research Award, Johns Hopkins Center for Global Health**
$3500 grant awarded to 6 graduate students annually to support research projects; award supported analysis of HIV treatment data in Côte d'Ivoire.

2015 **SISMID Scholarship, University of Washington**
Tuition and housing support to attend the 2015 Summer Institute in Statistics and Modeling in Infectious Disease.

2013 **Paul and Daisy Soros Fellowship for New Americans**
$90,000 graduate school tuition and stipend support over 2 years, awarded annually to 30 "New Americans" selected from over 1,000 applicants.

2013 **First place, AMA Conley Ethics Essay Contest**
Annual ethics essay contest for students and trainees sponsored by the American Medical Association's *Journal of Ethics* (formerly *Virtual Mentor*).

2012 **Fellowships at Auschwitz for the Study of Professional Ethics (FASPE)**
Fully-funded, intensive course in medical and inter-professional ethics with travel to Germany and Poland, awarded to 15 medical students annually.

2012 **AMSA "Leave No Trace" Global Health Ethics Grant**
Awarded one of four grants from the American Medical Student Association to support a student-led global health ethics pre-departure training program.

2011 **Best Student Abstract, Consortium of Universities for Global Health**
Award to 10 best trainee presentations at the 2011 Global Health Conference.

2011 **Daniels Scholar, Johns Hopkins University**
Selected to participate in longitudinal inter-professional education program with medical and nursing students, focusing on patient-centered care.

2009 **AMSA Global Health Scholar**
Selected to participate in year-long global health seminar course sponsored by the American Medical Student Association.

SERVICE & LEADERSHIP

2014-2017 **Global Health Leadership Program, Johns Hopkins School of Medicine**
Served on committee of students, residents and faculty overseeing global health education activities; led student survey of training needs, and contributed to pre-departure handbook.

2012-2017 **Harvard Alumni Association**
College admissions interviewer
Conducted admissions interviews of Baltimore-area high school students applying to Harvard College.

2009-2017 **Global Health Interest Group**
Co-founder, administrative chair
Created student interest group, secured faculty support and funding to design global health courses; efforts led to establishment of a formal Global Health Leadership Committee.

2013-2015 **Consortium of Universities for Global Health**
Trainee Advisory Committee
Served on national committee of students and trainees advising CUGH on educational materials and programs.

2015 **Medical Student Research Day, Johns Hopkins School of Medicine**
Session moderator
Moderated oral abstract sessions at annual showcase of student research.

2012-2013 **Admissions Committee, Johns Hopkins School of Medicine**
Student interviewer
Elected by peers to serve as non-voting member of admissions committee; conducted interviews of medical school applicants weekly, composed interview reports, and contributed to monthly ranking and decision meetings.

2009-2013 **Incentive Mentoring Program, Johns Hopkins University**
Volunteer
Mentored two high school students as part of a university-wide organization targeting Baltimore students at high risk of dropping out.

2011 **Medical Student Research Day, Johns Hopkins School of Medicine**
Abstract Screening Committee
Reviewed and rated abstracts submitted for annual student research showcase.

TEACHING EXPERIENCE

Johns Hopkins Bloomberg School of Public Health

2013-2016 ***Graduate teaching assistant***

• Developed course materials and graded assignments for online masters-level survey course (Seminars in Public Health).

• Led twice-weekly practical sessions, organized review sessions, graded exams, and held office hours for masters- and doctoral-level epidemiologic methods courses (Epidemiologic Inference in Public Health I, Epidemiologic Methods II, Epidemiologic Methods III).

Johns Hopkins School of Medicine

2015-2017 ***Clinical skills preceptor***

Precepted second-year medical students on "Transitions to the Wards" course. Responsibilities included overseeing students as they performed history and physical exam, and reviewing and providing feedback on written H&P.

2012 ***Small group facilitator***

Assisted faculty in facilitating small group discussion sessions for first-year medical students' "Healthcare Disparities Intersession" course.

2010 ***Instructor***

Created and led four-session Global Health Selective course for first-year "Foundations of Public Health" curriculum.

EDITORIAL ACTIVITIES

2014- **Peer reviewer**

Medicine (Baltimore), *Journal of Acquired Immunodeficiency Syndromes (JAIDS)*, *Journal of Immigrant and Minority Health*, *Medical Humanities*, *PLoS One*, *Lancet Infectious Diseases*. Verified peer review record available at: `https://publons.com/author/766323/mariam-o-fofana#profile`.

2014- **Conference abstract reviewer**

Society for Epidemiologic Research, American Public Health Association.

2008- **Freelance editor**, American Journal Experts, Cary NC

Provide translation and editing services for academic manuscripts.

2014 **Theme Issue Editor**, *Virtual Mentor* (now *AMA Journal of Ethics*)

Selected as one of 12 medical trainees to guest-edit a theme issue focusing on race and ethnicity in medicine; responsibilities included selecting topics, recruiting authors, and providing editorial guidance on manuscripts.

2010-2014 **Student editorial assistant**, *Medicine (Baltimore)*

Worked closely with editors of general internal medicine journal to conduct initial screening of submissions and advise on editorial decisions; reviewed over 40 manuscripts.

INVITED WORKSHOPS & ADVISORY GROUPS

Towards zero new TB infections: research needs for halting TB transmission. Sponsored by: National Institute of Allergy and Infectious Diseases. Mar 15-16 2016, Rockville, MD.

Establishment of technical advisory group for the development of target regimen profiles for TB treatment. Sponsored by: World Health Organization. Feb 18-19 2016, Geneva, Switzerland.

Rapid drug susceptibility testing workshop. Sponsored by: Critical Path to TB Drug Regimens. Sep 22-23 2014, Washington, DC.

Global targets meeting. Sponsored by: Bill and Melinda Gates Foundation TB Modelling and Analysis Consortium. June 2-4 2014, Seattle, WA.

PROFESSIONAL MEMBERSHIPS

2014- International Union Against Tuberculosis and Lung Disease
2014- Society for Epidemiologic Research
2014- American Public Health Association
2012- American Medical Association
2009- American Medical Student Association

CERTIFICATIONS

2017 Basic Life Support
2017 Advanced Cardiac Life Support
2016 Clinician Cultural and Linguistic Assessment: Spanish

INTERESTS & SKILLS

Research: HIV, TB, mathematical modeling, global health, bioethics
Computing: Stata, R, ArcGIS, MS Access, LaTeX
Languages: French (native), Spanish (excellent), Portuguese (proficient)
Hobbies: Travel, crosswords, Capoeira, culinary exploration, storytelling

PUBLICATIONS

PEER-REVIEWED ARTICLES

Fofana MO, Shrestha S, Knight GM, Cohen T, White RG, Cobelens F, Dowdy DW (2017). A multistrain mathematical model to investigate the role of pyrazinamide in the emergence of extensively drug-resistant tuberculosis. *Antimicrob Agents Chemother*, 61(3):e00498–16. doi: 10.1128/AAC.00498-16.

Kendall EA, **Fofana MO**, Dowdy DW (2015). Burden of transmitted multidrug resistance in epidemics of tuberculosis: a transmission modelling analysis. *Lancet Respir Med*, 3(12):963–972. doi: 10.1016/s2213-2600(15)00458-0.

Knight GM, Colijn C, Shrestha S, **Fofana M**, Cobelens F, White RG, Dowdy DW, Cohen T (2015). The distribution of fitness costs of resistance-conferring mutations is a key determinant for the future burden of drug-resistant tuberculosis: a model-based analysis. *Clin Infect Dis*, 61(Suppl 3):S147–154. doi: 10.1093/cid/civ579.

Moran D, Edwardson J, Cuneo CN, Tackett S, Aluri J, Kironji A, Cox J, Carroll B, Lie E, **Fofana M**, Bollinger RC, Ziegelstein RC, Chen CC (2015). Development of global health education at Johns Hopkins University School of Medicine: a student-driven initiative. *Med Educ Online*, 20:28632. doi: 10.3402/meo.v20.28632.

Shrestha S, Knight GM, **Fofana M**, Cohen T, White RG, Cobelens F, Dowdy DW (2014). Drivers and trajectories of resistance to new first-line drug regimens for tuberculosis. *Open Forum Infect Dis*, 1(2):ofu073. doi: 10.1093/ofid/ofu073.

Fofana MO, Knight GM, Gomez GB, White RG, Dowdy DW (2014). Population-level impact of shorter-course regimens for tuberculosis: a model-based analysis. *PLoS One*, 9(5):e96389. doi: 10.1371/journal.pone.0096389.

Fofana MO (2013). The spectre of race in American medicine. *Med Humanit*, 39(2):137–141. doi: 10.1136/medhum-2013-010374.

Owens JP, **Fofana MO**, Dowdy DW (2013). Cost-effectiveness of novel first-line therapeutic regimens for tuberculosis. *Int J Tuberc Lung Dis*, 17(5):590–596. doi: 10.5588/ijtld.12.0776.

Walensky RP, Wood R, **Fofana MO**, Martinson NA, Losina E, April MD, Bassett IV, Morris BL, Freedberg KA, Paltiel AD (2011). The clinical impact and cost-effectiveness of routine, voluntary HIV screening in South Africa. *J Acq Imm Def*, 56(1):26–35. doi: 10.1097/QAI.0b013e3181fb8f24.

Walensky RP, Wolf LL, Wood R, **Fofana MO**, Freedberg KA, Martinson NA, Paltiel AD, Anglaret X, Weinstein MC, Losina E (2009). When to start antiretroviral therapy in resource-limited settings. *Ann Intern Med*, 151(3):157–166.

Walensky RP, Wood R, Weinstein MC, Martinson NA, Losina E, **Fofana MO**, Goldie SJ, Divi N, Yazdanpanah Y, Wang B, Paltiel A, Freedberg KA (2008). Scaling up antiretroviral therapy in South Africa: the impact of speed on survival. *J Infect Dis*, 197(9):1324–1332. doi: 10.1086/587184.

BOOK CHAPTERS & MANUALS

Forrestel A, Peluso M, Dandu M, **Fofana MO** et al. (2014). "The global health landscape at US medical schools: Global health program structures, content, and examples". In: *Developing global health programming: a guidebook for medical and professional schools*, 2nd Edition. J Evert, P Drain and T Hall (Eds). San Francisco: Global Health Education Consortium.

Johns Hopkins School of Medicine Global Health Leadership Program. Pre-departure preparation for global health clinical and research experiences: a handbook for health professionals and trainees. Available at: `http://www.hopkinsglobalhealth.org/assets/documents/Predeparture_handbook-web_version.pdf`.

OTHER PUBLICATIONS

Fofana MO (2014). Hazardous intersections: race, ethnicity, and medicine. *Virtual Mentor*, 16(6):419–422.

Fofana MO (2013). 2012 winning essay. Joey knows best? Balancing conflicts and defending a child's best interest in difficult clinical decisions. *Virtual Mentor*, 15(8):653–659. doi: 10.1001/virtualmentor.2013.15.8.conl1-1308.

ABSTRACTS & PRESENTATIONS

INVITED PRESENTATIONS

Fofana MO. The future of drug-resistant TB: insights from a multi-strain model of TB transmission. Johns Hopkins Center for TB Research Annual Scientific Meeting. June 10 2015, Baltimore, MD.

Fofana MO. Population-level impact of shorter treatment duration: first-line regimens. Developing Novel Strategies to Optimize Design of TB Drug Combinations (NIH/NIAID workshop). June 16-17 2015, Rockville, MD.

Fofana MO. Resistance to pyrazinamide and moxifloxacin during scale-up of novel regimens: preliminary modeling results. Critical Path to TB Regimens Drug Susceptibility Testing Consortium Workshop. Sep 30-Oct 1 2013, Washington, DC.

Fofana MO. Population-level impact of shorter TB regimens: are we being too optimistic? 3rd TB Modeling and Analysis Consortium Meeting. Sep 11-12 2013, Beijing, China.

Fofana MO. "Subject to the same diseases, heal'd by the same means"? Race and American medicine. 3rd Annual Symposium of the Fellowships at Auschwitz for the Study of Professional Ethics. Jan 21 2013, New York, NY.

ORAL CONFERENCE PRESENTATIONS

Fofana MO, Shrestha S, Knight GM, Cohen T, White RG, Cobelens F, Dowdy DW. Emergence of drug resistance following introduction of novel first-line TB treatment regimens: a modeling analysis. 45th Union World Conference on Lung Health. Oct 28-Nov 1 2014, Barcelona, Spain.

Walensky RP, Wood R, Weinstein MC, Losina E, **Fofana MO**, Martinson NA, Divi N, Wang B, Mercincavage LM, Goldie SJ, Freedberg KA. Antiretroviral treatment rollout in South Africa: alternative scenarios and outcomes. 2007 PEPFAR HIV/AIDS Implementers' Meeting. June 16-19 2007, Kigali, Rwanda.

CONFERENCE POSTERS

Fofana MO, Shrestha S, Knight GM, Cohen T, White RG, Cobelens F, Dowdy DW. Investigating the role of specific drugs in the emergence of drug-resistant tuberculosis. 5th International Conference on Infectious Disease Dynamics. Dec 1-4 2015, Clearwater Beach, FL.

Fofana MO, Shrestha S, Knight GM, Cohen T, White RG, Cobelens F, Dowdy DW. Projecting the impact of alternative drug susceptibility testing strategies on future TB drug resistance. 46th Union World Conference on Lung Health. Dec 2-6 2015, Cape Town, South Africa.

Eavey A, Fields E, **Fofana M**, Harrison D, Henning P, Karan A, Liu T, Miller J, Perez W, Rhee J, Shen J, Simon L, Sizemore E, Tcholakov Y, Wiley E. CUGH trainee advisory committee: bringing the trainee perspective to global health leadership and education. 6th Annual Consortium of Universities for Global Health Conference. March 26-28 2015, Boston, MA.

Shrestha S, Knight GM, **Fofana MO**, Cohen T, White RG, Cobelens F, Dowdy DW. Drivers and trajectories of resistance to new first-line drug regimens for tuberculosis. 45th Union World Conference on Lung Health. Oct 28-Nov 1 2014, Barcelona, Spain.

Kironji AG, Aluri J, DeCamp M, Carroll BM, Cox JT, **Fofana M**, Lie E, Moran D, Tackett S, Chen CCG. Gaps in pre-departure training and post-experience debriefing in global health experiences: a survey of health professions students. 5th Annual Consortium of Universities for Global Health Conference. May 10-12 2014, Washington, DC.

Aluri J, Carroll BM, **Fofana M**, Kironji AG, Lie E, Moran D, Cox JT, Chen CCG. Student-led development of global health educational opportunities at the Johns Hopkins University School of Medicine. 5th Annual Consortium of Universities for Global Health Conference. May 10-12 2014, Washington , DC.

Fofana MO, Knight GM, Gomez GB, White RW, Dowdy DW. Population-level impact of shorter-course regimens for tuberculosis: a model-based analysis. American Thoracic Society International Conference 2013. May 17-22 2013, Philadelphia, PA.

Fofana MO. From fringe to core: integrating global health in medical education. 4th Annual Consortium of Universities for Global Health Conference. March 14-16 2013, Washington, DC.

Sheth S, Cannon T, Fenell JC, Althaus J, **Fofana MO**, Milio L, Keller J, Anderson J. A history of depression is associated with non-adherence to HAART in pregnant patients who themselves have congenitally acquired HIV. 33rd Annual Meeting of the Society for Maternal Fetal Medicine. February 11-16 2013, San Francisco, CA.

Fofana MO. Integrating global health in medical education. 39th Annual Conference on Medical Student Education. January 24-27 2013, San Antonio, TX.

Fofana MO, Ekouevi DK, Merritt MW. Father knows best? Ethical considerations of required paternal consent in pediatric HIV research in Côte d'Ivoire. 2011 Global Health Conference. November 13-15 2011, Montreal, Canada.

Fofana MO, Merritt MW. Ethical considerations of paternal consent requirement in pediatric HIV research in Côte d'Ivoire. 61st Convention of the American Medical Student Association. March 10-13 2011, Washington, DC.

Walensky R, Wood R, **Fofana M**, Martinson N, Losina E, Weinstein M, April M, Bassett I, Freedberg K, Paltiel D. The clinical effect and cost-effectiveness of routine, voluntary HIV testing: South Africa. 16th Conference on Retroviruses and Opportunistic Infections. February 8-11 2009, Montreal, Canada.

Walensky R, Wolf L, Wood R, **Fofana M**, Freedberg K, Martinson N, Paltiel D, Anglaret X, Weinstein M, Losina E. When to start ART—a policy evaluation while awaiting trial results: South Africa. 16th Conference on Retroviruses and Opportunistic Infections. February 8-11 2009, Montreal, Canada.

Walensky R, Wolf L, Wood R, Freedberg K, Martinson N, Paltiel A, Anglaret X, **Fofana M**, Ribaudo H, Losina E. When to start ART in resource-limited settings. 15th Conference on Retroviruses and Opportunistic Infections. February 3-6 2008, Boston, MA.

Walensky RP, Wood R, Weinstein MC, Martinson NA, Losina E, **Fofana MO**, Goldie SJ, Divi N, Yazdanpanah Y, Wang B, Paltiel AD, Freedberg KA. Scaling up antiretroviral treatment (ART) in South Africa: speed and survival. 29th Annual Meeting of the Society for Medical Decision Making. October 20-24 2007, Pittsburgh, PA.

Walensky RP, Wood R, Weinstein MC, Losina E, **Fofana MO**, Martinson NA, Paltiel AD, Yazdanpanah Y, Divi N, Wang B, Mercincavage LM, Goldie SJ, Freedberg KA. Antiretroviral treatment rollout in South Africa: alternative scenarios and outcomes. 14th Conference on Retroviruses and Opportunistic Infections. February 25-28 2007, Los Angeles, CA.

Lamming DW, Latorre-Esteves M, Chen F, **Fofana M**, Torella J, Sinclair DA. SIR2 homologues regulate aging in yeast. 35th Annual Meeting of the American Aging Association. June 2-5 2006, Boston, MA.