



Optimal Use of New and Existing Drugs for Tuberculosis Control

The Harvard community has made this
article openly available. [Please share](#) how
this access benefits you. Your story matters

Citation	Kunkel, Amber. 2016. Optimal Use of New and Existing Drugs for Tuberculosis Control. Doctoral dissertation, Harvard T.H. Chan School of Public Health.
Citable link	http://nrs.harvard.edu/urn-3:HUL.InstRepos:32644531
Terms of Use	This article was downloaded from Harvard University's DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA

OPTIMAL USE OF NEW AND EXISTING DRUGS FOR
TUBERCULOSIS CONTROL

AMBER KUNKEL

A Dissertation Submitted to the Faculty of
The Harvard T.H. Chan School of Public Health
in Partial Fulfillment of the Requirements
for the Degree of Doctor of Science
in the Department of Epidemiology

Harvard University

Boston, Massachusetts.

November, 2016

Optimal use of new and existing drugs for tuberculosis control

ABSTRACT

Tuberculosis (TB) recently surpassed HIV as the world's leading infectious killer. Because antibiotic therapy forms the cornerstone of TB control, prevention, and treatment, it is important to apply TB drugs in a way that maximizes their potential benefits while minimizing the risks of resistance. Here, I present three modeling analyses intended to explore these tensions inherent in the use of TB drugs.

Preventive therapy involves the use of antimicrobials in asymptomatic and noninfectious individuals, and has been applied to diseases ranging from TB to HIV to malaria. In my first paper, I outline how population use of preventive therapy could increase, decrease, or have non-monotonic effects on the prevalence of drug resistance, depending on the relative contributions of resistance acquired as a result of preventive therapy, resistance acquired as a result of treatment for active disease, and transmitted resistance.

In my second paper, I consider the specific use of isoniazid preventive therapy (IPT) to prevent active TB among people living with HIV. Previous models have suggested that widespread IPT use could increase the prevalence of drug resistant TB by providing a selective pressure in favor of resistant strains. In this paper, I show that the impact of IPT on drug resistance is highly dependent on the projected TB/HIV epidemic trends, and that the risks of resistance are likely to remain low for even lifelong IPT durations as long as transmission is already declining.

Finally, in my third paper, I present a decision analytic model to determine the optimal targeting of the new TB drug bedaquiline for patients with pre-existing resistance to other available drugs. The optimal use strategy for this new drug depends on the outcome being considered; whereas more liberal strategies would likely decrease resistance to existing drugs as well as onward transmission, more restrictive strategies would decrease resistance to bedaquiline. More research is needed to confirm that more liberal bedaquiline use strategies would improve life expectancy.

Overall, these papers illustrate the complexity of the decisions surrounding optimal TB drug use. Thoughtful antibiotic policies, coupled with continued innovation, are needed to effectively combat the global burden of TB.

TABLE OF CONTENTS

List of figures with captions.....	v
List of tables with captions.....	vii
Acknowledgements.....	viii
Preface.....	1
Paper 1: How could preventive therapy affect the prevalence of drug resistance? Causes and consequences.....	6
Appendix S1.....	28
Paper 2: Benefits of continuous isoniazid preventive therapy may outweigh resistance risks in a declining TB/HIV co-epidemic.....	33
Appendix S2.....	55
Paper 3: Tradeoffs in new anti-tuberculosis drug introduction policies: A model based analysis.....	115
Appendix S3.....	137

LIST OF FIGURES WITH CAPTIONS

Figure 1.1: Model states and transitions.....	11
Figure 1.2: Subset of the model representing the rates at which individuals with latent or active DS disease receiving preventive therapy acquire resistance and the transitions leading to these potentially at-risk states.....	16
Figure 1.3: The relationship between PT start rate and the rate at which resistance is acquired through PT at equilibrium.....	16
Figure 1.4: The relationship between PT start rate and the rate at which resistance is acquired through treatment for DS disease at equilibrium.....	17
Figure 1.5: The relationship between PT start rate and the effective reproductive number of the DR strain at equilibrium.....	19
Figure 1.6: Relationship between PT start rate and DR prevalence at equilibrium.....	21
Figure S1.1: The relationship between PT start rate and the proportion of people infected with the DR strain who progress to active DR infection.....	31
Figure S1.2: The relationship between PT start rate f and proportion of DR uninfected persons susceptible to the DR strain.....	32
Figure 2.1: Model structure.....	37
Figure 2.2: The effect of IPT duration on TB incidence by resistance phenotype under our baseline Botswana scenario.....	42
Figure 2.3: The composite effects of IPT duration on overall TB incidence, mortality rate among PLHIV, and cumulative mortality among PLHIV (relative to no IPT)	43
Figure 2.4: The effects of IPT duration on the incidence of isoniazid resistant and overall TB when the transmission parameter post-2017 is increased 1.25x, 1.5x, and 1.75x compared to our baseline scenario.....	45
Figure 2.5: The effects of IPT duration on the mortality rate and cumulative mortality relative to no IPT per 1,000 PLHIV when the transmission parameter post-2017 is increased 1.25x, 1.5x, and 1.75x compared to our baseline scenario.....	46
Figure S2.1: Comparison of model output to UNAIDS estimates of HIV prevalence from 1990-2013.....	56
Figure S2.2: Comparison of model output to UNAIDS AIDInfo estimates of ARV coverage from 2010-2014	57

Figure S2.3: Comparison of model output to WHO global TB program estimates of HIV prevalence in TB cases from 1990-2013.....	57
Figure S2.4: Comparison of model output to WHO global TB program estimates of TB incidence from 1990-2013.....	58
Figure S2.5: Comparison of model output to WHO global TB program estimates of TB prevalence from 1990-2013.....	58
Figure S2.6: Comparison of model output to the results of the TB drug resistance surveys from 1995, 1999, 2002, and 2008 in Botswana.....	59
Figure S2.7: Marginal prior and posterior distributions.....	71
Figure S2.8: Incidence of isoniazid resistant and overall TB by assumed susceptibility to reinfection.....	93
Figure S2.9: Incidence of isoniazid resistant and overall TB by assumed susceptibility to reinfection, assuming greater transmission.....	95
Figure 3.1: Optimal bedaquiline use strategy for different outcomes based on 5,000 simulation runs.....	123
Figure S3.1: Transitions between resistance levels.....	137
Figure S3.2: Transitions between TB health states and regimen type.....	138

LIST OF TABLES WITH CAPTIONS

Table 1.1: Model states and parameters.....	12
Table 1.2: Summary of mechanisms through which PT may affect the prevalence of drug resistance.....	18
Table S2.1: Description of TB latency states.....	63
Table S2.2: Prior distributions on variable parameters.....	67
Table S2.3: Fixed and derived parameters.....	74
Table 3.1: Bedaquiline-associated parameter ranges.....	121
Table 3.2: Life expectancy comparing bedaquiline use strategies when under our baseline scenario (conventional DST to identify PreXDR and XDR cases) and a scenario with rapid DST for fluoroquinolones and injectables.....	124
Table 3.3: Expected increase in life expectancy (in years) if perfect information was available for all or particular bedaquiline-related parameters.....	125
Table 3.4: Proportion of the initial cohort acquiring different resistance patterns.....	126
Table 3.5: Impact of different bedaquiline use strategies on the number and health outcomes of secondary TB cases.....	127
Table S3.1: Detailed description of model parameters.....	144

ACKNOWLEDGEMENTS

This work would not have been possible without the guidance of my advisor, Ted Cohen, whose innovative thinking and dedication to tuberculosis research I very much admire. It has certainly been strengthened by the support and assistance of my committee members Megan Murray and Marc Lipsitch. A number of other individuals also contributed directly to this work, including Caroline Colijn, Forrest Crawford, Frank Cobelens, and James Shepherd. I am grateful for all their insights and advice.

I greatly appreciate the funding that I have received for this work through the Infectious Disease Epidemiology NIH Training Grant as well as the Gates Foundation/TB Modelling and Analysis Consortium.

I would like to thank Ted, as well as Valeriu Crudu, for giving me the opportunity to learn more about the on-the-ground realities of tuberculosis control and the impact of drug resistant tuberculosis on patients and their families in Moldova. This experience strongly enhanced my motivation for and understanding of this work.

I am very grateful for the close friendships I have made in both Boston and New Haven, with fellow students and researchers as well as outside the university setting. These friendships have been a great source of support and encouragement for me.

I would especially like to thank my family, including Nancy, Joe, David, Will, Faith, and Meaghan, for cheering me on since Day 1 and keeping me going all along the way.

Finally, I would like to thank God, the source of all knowledge and goodness, for leading and providing for me all throughout this sometimes-challenging process. “In your book were written, every one of them, the days that were formed for me, when as yet there was none of them” (Psalm 139).

PREFACE

An estimated 1.5 million people were killed by tuberculosis (TB) in 2014, exceeding the number of deaths due to HIV [1]. These deaths represent only a fraction of the health and economic impact of the 9.6 million estimated new cases of TB disease [1]. Because only 5-10% of immunocompetent individuals infected with *Mycobacterium tuberculosis* ever develop disease, the global prevalence of latent TB infection is much greater still [2].

Antibiotic therapy forms the basis of the global TB control strategy. Individuals with uncomplicated active TB disease rapidly lose infectiousness after starting treatment, and cure rates approach 95% in some settings [1, 3-5]. Antibiotics can also prevent the progression from latent to active TB disease, and this intervention may be particularly attractive among individuals at highest risk of progression, such as children and people living with HIV [2, 6].

However, the reliance on antibiotics for TB prevention and treatment poses several challenges at both the individual and population levels. First-line treatment requires four drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol) daily for two months, and daily isoniazid and rifampicin therapy for the following four months; this long course of combination therapy places a heavy burden on both patients and healthcare systems [7]. Suboptimal use of these drugs, combined with ongoing transmission, has resulted in global spread of multi-drug resistant (MDR) TB, defined as resistance to both isoniazid and rifampicin. In 2014, the World Health Organization estimated that nearly 500,000 individuals developed MDR TB, with only a quarter of these cases being detected and reported [1]. Existing treatments for MDR TB are long (up to two years), poorly tolerated, and ineffective; even among those diagnosed, global rates of successful treatment hover

around 50% [1]. The remaining patients experience high risks of dying or acquiring additional resistance to second-line drugs.

The use of antibiotics for prevention also poses several potential issues when the same drugs are needed for treatment of active disease. Daily isoniazid reduces the risk of TB disease among people living with HIV, who are otherwise at very high risk of progressing from latent to active TB. However, accumulating data suggest that the standard 6-9 month regimen of isoniazid preventive therapy (IPT) is insufficient to reduce long-term TB risks at both the individual and population levels in some settings [8-10]. Additionally, previous mathematical modeling studies have suggested that widespread IPT use could dramatically increase the incidence of isoniazid resistant TB, thereby eroding the effectiveness of this drug as a treatment for active disease [11, 12].

This question of using versus losing key antibiotics arises again when considering how best to use new drugs for TB. The conditional approval of bedaquiline by the US FDA marked the first new drug available for treatment of TB in over 40 years [13, 14]. However, physicians and policymakers have struggled to decide which patients should receive this drug - in particular, whether it should be made available to all patients with MDR TB, or reserved for patients with additional resistance [15-17].

My thesis aims to address questions related to optimal population-level of use of anti-TB drugs. First, I consider the general mechanisms through which preventive or prophylactic antimicrobial therapies could affect the population prevalence of drug resistance. Second, I apply these considerations specifically to the issue of optimal IPT duration and use among people living with HIV in Botswana. Finally, I outline the potential

risks and benefits associated with different potential bedaquiline use strategies for patients with MDR TB.

These analyses are all based on mathematical models that allow me to formalize an understanding of disease dynamics and natural history derived from previous studies. The first two papers of my thesis use transmission dynamic models to project the population-level impacts of preventive therapy, while my third paper uses a decision analytic model to estimate the direct impact of bedaquiline on a single generation of MDR TB patients and their immediate contacts. Taken together, these papers demonstrate the utility of mathematical modeling in determining the emergent properties of the complex systems that govern optimal TB drug use at the population level.

References

1. World Health Organization. Global Tuberculosis Report 2015. Geneva: 2015.
2. World Health Organization. Guidelines on the management of latent tuberculosis infection. Geneva 2015.
3. Riley RL, Mills CC, O'Grady F, Sultan LU, Wittstadt F, Shivpuri DN. Infectiousness of air from a tuberculosis ward. Ultraviolet irradiation of infected air: comparative infectiousness of different patients. *The American review of respiratory disease*. 1962;85:511-25. doi:10.1164/arrd.1962.85.4.511.
4. Rouillon A, Perdrizet S, Parrot R. Transmission of tubercle bacilli: The effects of chemotherapy. *Tubercle*. 1976;57(4):275-99.
5. Shin HJ, Kwon YS. Treatment of Drug Susceptible Pulmonary Tuberculosis. *Tuberculosis and respiratory diseases*. 2015;78(3):161-7. doi:10.4046/trd.2015.78.3.161.

6. World Health Organization. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Geneva: 2011.
7. World Health Organization. Treatment of tuberculosis guidelines: fourth edition. Geneva: 2010.
8. Samandari T, Agizew TB, Nyirenda S, Tedla Z, Sibanda T, Shang N et al. 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial. *Lancet (London, England)*. 2011;377(9777):1588-98. doi:10.1016/s0140-6736(11)60204-3.
9. Johnson JL, Okwera A, Hom DL, Mayanja H, Mutuluza Kityo C, Nsubuga P et al. Duration of efficacy of treatment of latent tuberculosis infection in HIV-infected adults. *AIDS (London, England)*. 2001;15(16):2137-47.
10. Churchyard GJ, Fielding KL, Lewis JJ, Coetzee L, Corbett EL, Godfrey-Faussett P et al. A trial of mass isoniazid preventive therapy for tuberculosis control. *The New England journal of medicine*. 2014;370(4):301-10. doi:10.1056/NEJMoa1214289.
11. Cohen T, Lipsitch M, Walensky RP, Murray M. Beneficial and perverse effects of isoniazid preventive therapy for latent tuberculosis infection in HIV-tuberculosis coinfecting populations. *Proceedings of the National Academy of Sciences of the United States of America*. 2006;103(18):7042-7. doi:10.1073/pnas.0600349103.
12. Mills HL, Cohen T, Colijn C. Community-wide isoniazid preventive therapy drives drug-resistant tuberculosis: a model-based analysis. *Science translational medicine*. 2013;5(180):180ra49. doi:10.1126/scitranslmed.3005260.

13. Lienhardt C, Raviglione M, Spigelman M, Hafner R, Jaramillo E, Hoelscher M et al. New drugs for the treatment of tuberculosis: needs, challenges, promise, and prospects for the future. *The Journal of infectious diseases*. 2012;205 Suppl 2:S241-9. doi:10.1093/infdis/jis034.
14. Brigden G, Hewison C, Varaine F. New developments in the treatment of drug-resistant tuberculosis: clinical utility of bedaquiline and delamanid. *Infection and drug resistance*. 2015;8:367-78. doi:10.2147/idr.s68351.
15. Cox E, Laessig K. FDA approval of bedaquiline--the benefit-risk balance for drug-resistant tuberculosis. *The New England journal of medicine*. 2014;371(8):689-91. doi:10.1056/NEJMp1314385.
16. Mingote LR, Namutamba D, Apina F, Barnabas N, Contreras C, Elnour T et al. The use of bedaquiline in regimens to treat drug-resistant and drug-susceptible tuberculosis: a perspective from tuberculosis-affected communities. *Lancet (London, England)*. 2015;385(9966):477-9. doi:10.1016/s0140-6736(14)60523-7.
17. World Health Organization. The use of bedaquiline in the treatment of multidrug-resistant tuberculosis: interim policy guidance. Geneva2013.

Paper 1: Kunkel, A., Colijn, C., Lipsitch, M. & Cohen, T. (2015). How could preventive therapy affect the prevalence of drug resistance? Causes and consequences. *Phil Trans R Soc B 370*(1670): 20140306

Abstract

Various forms of preventive and prophylactic antimicrobial therapies have been proposed to combat HIV (e.g. pre-exposure prophylaxis), tuberculosis (e.g. isoniazid preventive therapy), and malaria (e.g. intermittent preventive treatment). However, the potential population-level effects of preventive therapy on the prevalence of drug resistance are not well understood. Preventive therapy can directly affect the rate at which resistance is acquired among those receiving preventive therapy. It can also indirectly affect resistance by altering the rate at which resistance is acquired through treatment for active disease and by modifying the level of competition between transmission of drug-resistant and drug-sensitive pathogens. We propose a general mathematical model to explore the ways in which preventive therapy can affect the long-term prevalence of drug resistance. Depending on the relative contributions of these three mechanisms, we find that increasing the level of coverage of preventive therapy may result in increases, decreases, or non-monotonic changes in the overall prevalence of drug resistance. These results demonstrate the complexity of the relationship between preventive therapy and drug resistance in the population. Care should be taken when predicting population-level changes in drug resistance from small pilot studies of preventive therapy or estimates based solely on its direct effects.

Introduction

Preventive and prophylactic infectious disease therapies (we will refer to both collectively as preventive therapy, PT) involve the use of chemotherapeutic agents in asymptomatic and noninfectious individuals, with the goal of preventing future symptoms and infectiousness. PT may be applied to individuals who are either uninfected or latently infected with a given pathogen. For example, whereas isoniazid preventive therapy for TB can prevent disease progression in latently infected individuals [1][2], pre-exposure prophylaxis for HIV is intended solely for use in uninfected individuals [3]. Some interventions may include aspects of both treatment and preventive therapy; for example, intermittent preventive treatment for malaria involves a full course of antimalarial treatment applied irrespective of infection status [4].

Because PT prevents development of infectiousness as well as symptoms, PT has been proposed as an element of public health strategies aimed at reducing the burden of TB, HIV, and malaria [4][5][6]. However, such strategies have often been controversial, with concerns about drug resistance forming one major barrier to implementation [7][8]. When the chemotherapeutic agents that are used for prevention are also needed for treatment, any drug resistance produced or amplified as a result of PT may undermine future control efforts. Simulation models intended to assess the potential effects of PT on the prevalence of drug resistance have produced sometimes inconsistent results [9]. For example, Supervie *et al.* [10][11] predicted that rolling out pre-exposure prophylaxis in Botswana would reduce the prevalence of drug resistant HIV, whereas Abbas *et al.* [12][13] predicted that a similar programme in South Africa would increase the prevalence of drug resistant HIV.

Models intended to predict the effects of specific PT programmes tend to be fairly complex, with states and parameters chosen to reflect the natural history of the disease of interest, the operational details of the proposed intervention, and the efficacy of the available drug. While this complexity may improve the predictive accuracy of each individual model, it can complicate attempts to explain differences in their predictions [9][11][13]. In this paper, we create a simplified, general model of PT with the goal of better understanding the ways in which PT could alter the population prevalence of drug resistance. We show that increasing PT coverage can have qualitatively different effects on the prevalence of drug resistance depending on the relative importance of resistance acquired

as a result of preventive therapy, resistance acquired as a result of treatment, and the competitive fitness of drug resistant strains.

Methods

We developed a simple mathematical model to demonstrate the ways in which preventive therapy may alter the prevalence of drug resistance. Mathematical modelling provides a way to formally encode our understanding of the individual-level effects of preventive therapy, some of which may lead to drug resistance. Furthermore, mathematical modelling creates a conceptual framework to explore how the effects of preventive therapy on drug resistance in the population may extend beyond its immediate recipients.

Model Structure: Disease Course

A description of the states and parameters used in our model is given in Table 1.1. Figure 1.1 displays the structure of this compartmental model, with the health states and transitions among individuals not receiving PT on the left-hand side and among individuals receiving PT on the right-hand side. We focus first on individuals not receiving PT, shown on the left. Although this portion of the figure shows the rates at which individuals may begin and end preventive therapy (PT states shown in dotted boxes), it does not display transitions between PT states.

Within the model, an individual may be infected by pathogen phenotypes that are either drug sensitive (DS, indicated in the diagram by a subscript S) or drug resistant (DR, indicated in the diagram by a subscript R), but not by both simultaneously. Not allowing for mixed infections greatly simplifies our model, but introduces strong assumptions about competition between strains, the implications of which are considered in the Discussion. Susceptible (S) persons who are infected enter latency with either the DS strain (L_S) or the DR strain (L_R), depending on the source of the infection. Latently infected individuals may be superinfected and move to the latent state characterized by the drug sensitivity pattern of the most recently infecting strain. We assume the degree of susceptibility to reinfection x does not depend on the identity of the initial or reinfecting strain. We do allow the risks of infection and progression to active disease to differ based on the drug sensitivity of the infecting strain, reflecting the potential fitness costs of resistance.

All actively infected individuals within our model, including those on treatment, contribute to the overall force of infection. We assume that infectious individuals cannot be reinfected and cannot

recover except by treatment. We allow individuals receiving treatment for DS disease to acquire resistance at rate a . We assume such acquired resistant cases are immediately detected and started on treatment for DR disease, which we assume has a lower cure rate than treatment for DS disease. We do not allow for disease-induced mortality or explicitly encode for treatment failure, though the latter may be incorporated into the treatment cure rate. Once cured, individuals revert to a recovered (R) state exhibiting the same level of immunity as that experienced by latently infected individuals.

Though we omit arrows representing mortality from Fig 1.1, we assume a constant mortality rate from each compartment and a constant population size. All individuals enter the model susceptible to infection and not on PT. Because we assume a fixed population size, we express all states in terms of proportion of the population.

Model Structure: Preventive Therapy

The right-hand side of Fig 1.1 displays the portion of our model pertaining to individuals receiving preventive therapy. This portion of the figure again displays the rates at which individuals may begin or end preventive therapy (non-PT states shown in dotted boxes), but omits arrows indicating the transitions between states of individuals not receiving PT. We allow for individuals who are uninfected, latently infected, or actively infected to potentially receive PT. Uninfected individuals begin PT at rate f and cease therapy at rate w . Latently infected individuals begin PT at rate f_l and cease therapy at rate w . We allow the rates at which uninfected and latently infected individuals initiate PT to differ, as the specific targeting of PT depends on the disease and drug of interest. Pre-exposure prophylaxis for HIV, for example, is intended solely for uninfected individuals [3], whereas isoniazid preventive therapy is typically targeted to individuals with latent TB infection [1][2]. We assume that the PT initiation rate is the same for both DS and DR latently infected individuals, assuming that the resistance phenotype of the infecting strain is not known during latency. Actively infected individuals may also receive PT within our model. Though PT is generally not intended for such individuals (except when the same drug is applied as both treatment and prevention, e.g. intermittent preventive treatment for malaria [4]), individuals may progress from latent to active infection while receiving PT (rate k_S^{PT}) or initiate PT during active disease as a result of imperfect screening (rate f_i). We assume that the PT start rate is the same for both DS and DR actively infected individuals, assuming the infection is not recognized prior to PT

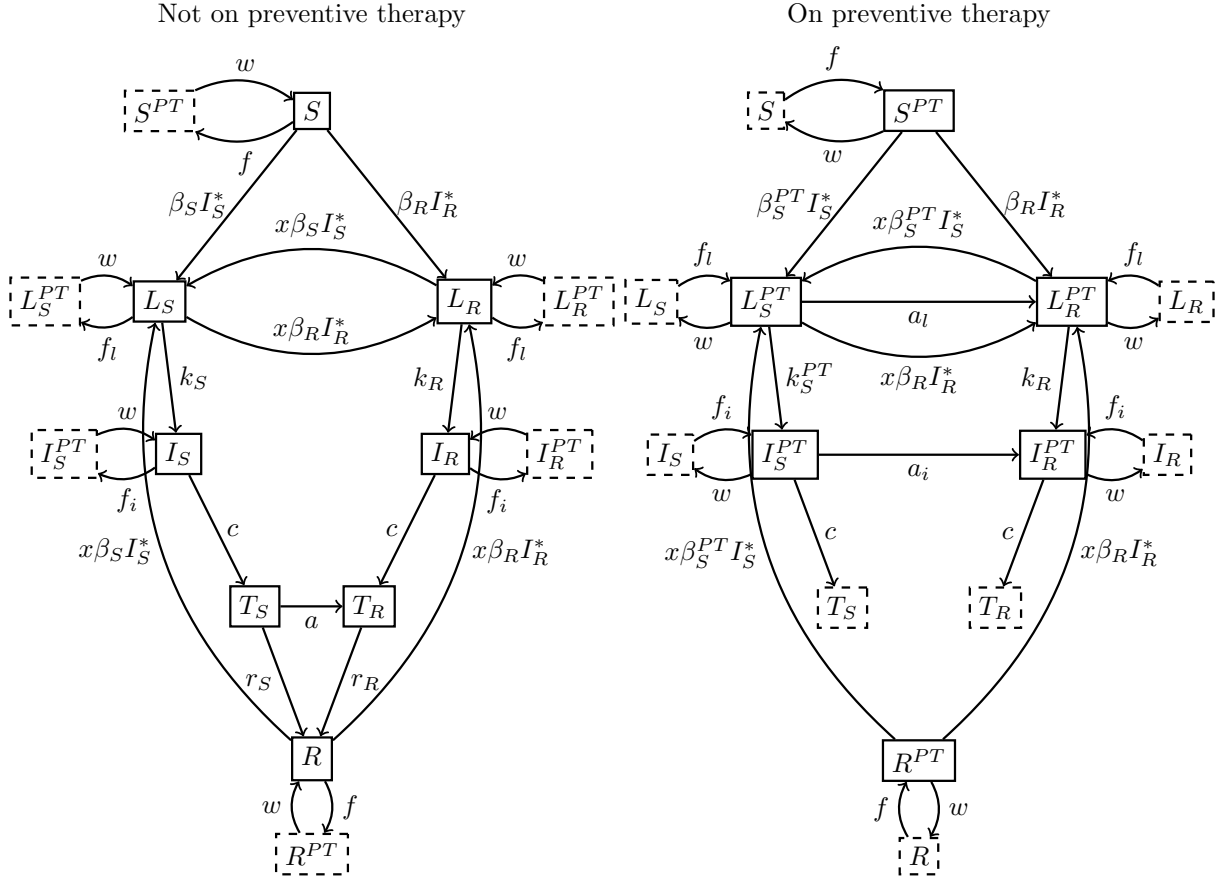


Figure 1.1: **Left:** All states and transitions involving individuals not on preventive therapy (solid boxes), with transitions on and off PT shown via links to on-PT states (dashed boxes). **Right:** All states and transitions involving individuals on preventive therapy (solid boxes), with transitions off and on PT shown via links to off-PT states (dashed boxes).

Table 1.1: Model states and parameters

State	Name	Description (All States: Proportion of Population)
S	Susceptible	Uninfected, negative infection history
L_S	DS Latent	Latently infected with DS strain
L_R	DR Latent	Latently infected with DR strain
I_S	DS Actively Infected	Infectious with DS strain, not on treatment
I_R	DR Actively Infected	Infectious with DR strain, not on treatment
T_S	DS Treated	Infectious with DS strain, on treatment
T_R	DR Treated	Infectious with DR strain, on treatment
I_S^*	Total DS Infectious	Sum of DS infectious states: $I_S + I_S^{PT} + T_S$
I_R^*	Total DR Infectious	Sum of DR infectious states: $I_R + I_R^{PT} + T_R$
R	Recovered	Uninfected, positive infection history
Parameter	Name	Description
β_S	DS transmission parameter	# DS effective contacts per susceptible per unit time
β_R	DR transmission parameter	# DR effective contacts per susceptible per unit time
k_S	DS progression rate	Rate of progression from DS latent to DS actively infected
k_R	DR progression rate	Rate of progression from DR latent to DR actively infected
c	Case detection rate	Rate at which actively infected individuals begin treatment
r_S	DS recovery rate	Rate of recovery from DS treated to recovered
r_R	DR recovery rate	Rate of recovery from DR treated to recovered
a	Treated resistance rate	Rate resistance is acquired due to treatment
a_l	PT latent resistance rate	Rate resistance is acquired by DS latents on PT
a_i	PT active resistance rate	Rate resistance is acquired by DS actively infecteds on PT
x	Reinfection susceptibility	Susceptibility retained after initial infection
w	PT exit rate	Reciprocal of average duration of PT
f	PT uninfected start rate	Start rate of PT for uninfected individuals
f_l	PT latent start rate	Start rate of PT for latently infected individuals
f_i	PT active start rate	Start rate of PT for actively infected individuals
Superscript	Name	Description
PT	Preventive therapy	State/parameter refers to individuals receiving PT

initiation. We assume that actively infected individuals cease preventive therapy routinely, at rate w , or upon initiation of treatment, at the same case detection rate c as for individuals not receiving PT.

The health states for individuals receiving PT are similar to those described for individuals not receiving PT. We assume PT reduces the rate at which uninfected and latently infected individuals are infected with the DS strain ($\beta_S^{PT} < \beta_S$), the rate at which DS latently infected individuals progress to active disease ($k_S^{PT} < k_S$), or the rates of both infection and progression with the DS strain. Although we assume that preventive therapy has no direct effect on infection or progression with the DR strain, it may affect the probability of progression with the DR strain by changing the probability of reinfection with the DS strain. We allow DS latently infected individuals to acquire resistance as a result of preventive therapy at rate a_l and DS actively infected individuals at rate a_i . We assume PT does not cure or reduce the infectiousness of individuals with active infection. We also assume that individuals cannot receive PT and treatment simultaneously, but treated individuals again become eligible for PT upon recovery. Throughout our analysis, we do not track which individuals receive PT and thus assume that the same individuals may receive multiple courses of PT.

Outcome Measures

Throughout our analysis, we focus on the equilibrium behaviour of the model. Doing so simplifies our analysis by removing its dependence on the initial model conditions. We begin each of our analyses in the absence of PT (setting the PT start rates $f = f_l = f_i = 0$). For each of our analyses, we choose a parameter set such that, in the absence of PT, the equilibrium prevalence of the DS strain is nonzero and the basic reproductive number of the DR strain exceeds 1. Because we allow for acquired resistance, the former requirement implies that the equilibrium prevalence of the DR strain is also nonzero in the absence of PT (i.e. there is no DS only equilibrium). The latter implies that the equilibrium prevalence of the DR strain will remain nonzero even if the equilibrium prevalence of the DS strain does not.

Holding this parameter set fixed, including the rates of case detection and treatment for active disease, we run a series of simulations at progressively higher values of the PT initiation rate. For the purpose of our simulations, we assume the PT start rates among uninfected, latently infected, and infectious individuals are proportional throughout, with $f_l = f$ and $f_i = f/10$, and thus

refer to the PT start rate using the single parameter f . For each individual simulation, we fix the value of the PT initiation rate, run the model to equilibrium (i.e. until changes in population composition between time steps become negligible), and record the resulting prevalence of the DR strain. We repeat the simulation process for incrementally increasing values of f until the DS strain is eliminated (the equilibrium prevalence of the DS strain equals 0), still holding the PT initiation rate constant within each individual simulation. Because we do not allow DR strains to revert to DS, such elimination of the DS strain is possible in our model even when the equilibrium prevalence of the DR strain remains nonzero.

All of the results provided are based on model simulations created using the R differential equation solver “ode” within package deSolve.

Results

In our model, increasing the intensity of preventive therapy directly affects the amount of resistance acquired through preventive therapy. It also indirectly affects the amount of resistance acquired through treatment for active disease and the competitive transmission advantage afforded to DR strains. We find that the combined effects of these mechanisms can result in increasing, decreasing, and non-monotonic relationships between the intensity of PT coverage and DR prevalence. Throughout the results, we use the word “treatment” to refer solely to treatment for active disease.

PT coverage and resistance acquired through PT

In our model, preventive therapy may lead directly to acquired resistance among individuals latently or actively infected with the DS strain. To demonstrate how it may do so, Fig 1.2 provides a focused view of the relevant states and transitions from Fig 1.1. Unbolded arrows in Fig 1.2 show the transitions that may lead to individuals latently or actively infected with the DS strain receiving PT. Bolded arrows show the acquisition of resistance among such individuals as a result of PT. If no individuals are to acquire resistance as a result of preventive therapy, one of the following scenarios must apply: 1) no individuals with active or latent infection ever receive PT, 2) no individuals with active infection ever receive PT, and PT never results in acquired resistance among latently infected individuals, or 3) PT never results in acquired resistance among latently or actively infected individuals. The first scenario assumes that PT is intended only for uninfected

individuals, that screening for latent and active infection prior to PT initiation is perfect ($f_i = 0$ and $f_l = 0$), and that adherence and drug efficacy are sufficiently high that individuals receiving PT never become infected ($\beta_S^{PT} = 0$). The second scenario assumes that PT never selects for sporadically occurring resistant mutants among individuals with latent infection ($a_l = 0$), that screening for active infection prior to PT initiation is perfect ($f_i = 0$), and that adherence and drug efficacy are sufficiently high that individuals receiving PT never progress from latent to active infection ($k_S^{PT} = 0$). The third scenario assumes that PT is incapable of selecting for resistance at the individual level among both latently and actively infected individuals ($a_l = 0$ and $a_i = 0$). Even well-functioning preventive therapy programmes are unlikely to meet these stringent criteria, and thus it is reasonable to expect that some individuals will directly acquire resistance as a result of preventive therapy.

When we assume that some or all of these parameters are nonzero, reflecting the vast majority of real-world PT applications, the relationship between PT coverage and resistance acquired as a result of PT is shown in Fig 1.3. The level of resistance acquired through PT is a function of the number of DS actively and latently infected individuals receiving PT ($a_i I_S^{PT} + a_l L_S^{PT}$). When PT coverage is low and insufficiently able to control the epidemic, increasing PT coverage increases the number of latently and actively infected individuals receiving PT and thus the number of people who acquire resistance as a result of preventive therapy. When PT coverage is high and better able to control the epidemic, increasing PT coverage decreases the number of people who acquire resistance as a result of preventive therapy (similar to an effect described in [14]). Under such scenarios, although increasing the PT initiation rate still increases the total number of people receiving PT, the resulting reduction in the force of DS infection is sufficient to decrease the number of people receiving PT who have latent or active DS infection. Because only DS infected individuals are at risk of acquiring resistance as a result of PT, this results in a reduction of the rate at which resistance is acquired as a result of PT.

PT coverage and resistance acquired through treatment

As is seen in Fig 1.1, our model allows individuals receiving treatment for active DS disease (T_S) to acquire resistance at rate a . Increasing the coverage of PT in the population decreases the number of people infected with the DS strain, and thus decreases the number of people who acquire resistance through treatment for active disease. This relationship is shown in Fig 1.4.

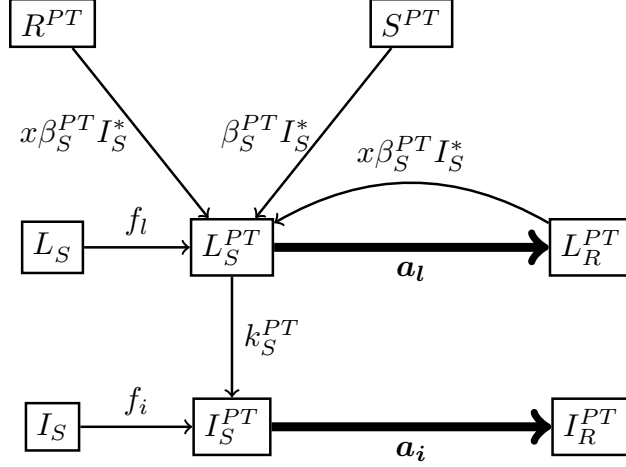


Figure 1.2: Subset of the model representing the rates at which individuals with latent or active DS disease receiving preventive therapy (L_S^{PT} and I_S^{PT} , respectively) acquire resistance (bold) and the transitions leading to these potentially at-risk states

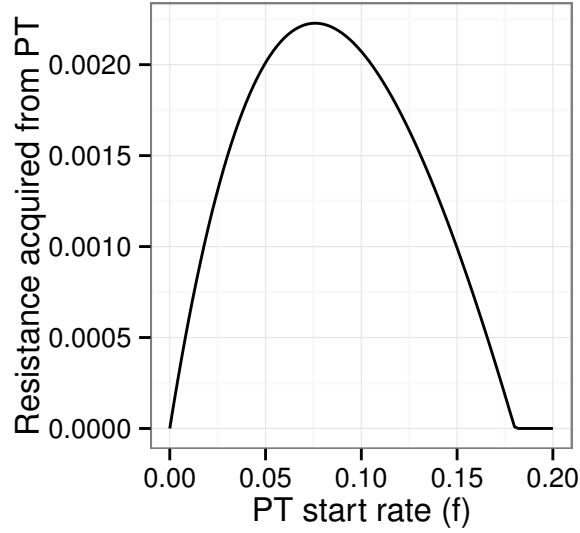


Figure 1.3: The relationship between PT start rate f and the rate at which resistance is acquired through PT ($a_i I_S^{PT} + a_l L_S^{PT}$) at equilibrium. Parameters for this figure: $\mu = 0.02, r_R = 1, r_S = 2, c = 1, k_R = 1, k_S = 1.5, \beta_S = 2, \beta_R = 1, x = 1, a = 0.3, a_i = 0.5, a_l = 0.1, w = 0.1, \beta_S^{PT} = 0, k_S^{PT} = 0$.

PT coverage and transmission of the DR strain

Our model assumes high levels of competition for susceptible hosts between strains, as we do not allow for latent or active coinfection. As a result, increasing PT coverage may provide a selective

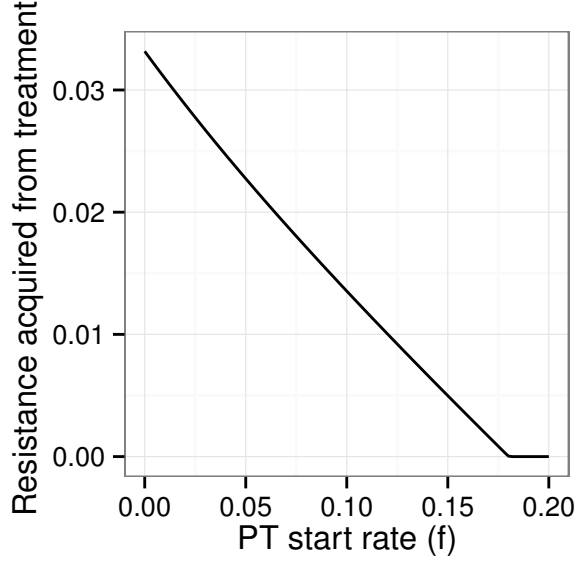


Figure 1.4: The relationship between PT start rate f and the rate at which resistance is acquired through treatment for DS disease (aT_S) at equilibrium. Parameters for this figure are the same as those for Fig 1.3.

advantage to DR strains through two distinct mechanisms. First, increasing PT coverage increases the probability that an individual latently infected with the DR strain will progress to active DR infection. This relationship is a result of our assumption that DR latently infected individuals could potentially be “rescued” from progressing to DR disease by superinfection with the DS strain. As PT coverage increases, DR latently infected individuals are increasingly protected from such superinfection and are therefore more likely to progress with their DR strain. Second, increasing PT coverage increases the proportion of DR uninfected individuals who are susceptible to the DR strain. In our model, the proportion of all individuals who are susceptible to the DR strain is given by $S + xL_S + xR + S^{PT} + xL_S^{PT} + xR^{PT}$, which depends on the proportion of people uninfected by the DR strain, the proportion of people with active DS infection, and the level of immunity afforded by initial infection. To obtain the proportion of DR uninfected individuals who are susceptible to DR infection, we divide this by the total proportion of individuals not actively or latently infected with the DR strain ($S + R + L_S + S^{PT} + R^{PT} + L_S^{PT} + I_S + I_S^{PT} + T_S$). Increasing PT coverage reduces the number of persons with active DS infection, and therefore increases the proportion of DR uninfected individuals who are susceptible to the DR strain. These two effects are discussed in more detail in the appendix.

The effective reproductive number of the DR strain is a composite measure that allows us to assess the combined effects of these mechanisms on the competitive fitness of the DR strain. The effective reproductive number shows the number of secondary infectious cases produced by a single infectious individual over the course of their infectious period. As opposed to the basic reproductive number R_0 , which assumes a wholly susceptible population, the effective reproductive number at a given time point depends on the susceptibility pattern of the population at that point in time. In a single strain model, the effective reproductive number at equilibrium is equal to 1. In our model, however, the number of DR infected individuals is boosted by acquired resistance, and therefore the DR strain may coexist with the DS strain in the population even when the effective reproductive number of the DR strain is below 1.

Fig 1.5 shows how the effective reproductive number of the DR strain at equilibrium changes as PT coverage increases. At low PT coverage levels, the DR effective reproductive number is less than 1, indicating that acquired resistance is necessary for the persistence of the DR strain in the population. As PT coverage increases, the reproductive fitness of the DR strain increases as well. When PT coverage is sufficiently high, the DR effective reproductive number reaches 1, indicating that resistance has become self-sustaining and the DR strain has overtaken the DS strain in the population.

Composite effects of PT coverage on DR prevalence

Table 1.2: Summary of mechanisms through which PT may affect the prevalence of drug resistance. The proportion susceptible to the DR strain and the reproductive number of the DR strain are discussed in more detail in the appendix.

Source of Resistance	Influence Driven by		Effect on DR Prevalence for	
	Health States	Parameters	Low PT Coverage	High PT Coverage
PT	DS infected on PT (L_S^{PT}, I_S^{PT})	Rate resistance acquired on PT (a_l, a_i)	↑	↓
Treatment	DS Treated (T_S)	Rate resistance acquired on treatment (a)	↓	↓
Transmission	Susceptible to DR strain	Reproductive number of DR strain	↑	↑

Table 1.2 summarises the ways in which each of the resistance mechanisms outlined above will tend to alter DR prevalence. While increasing PT coverage can decrease the rate of resistance

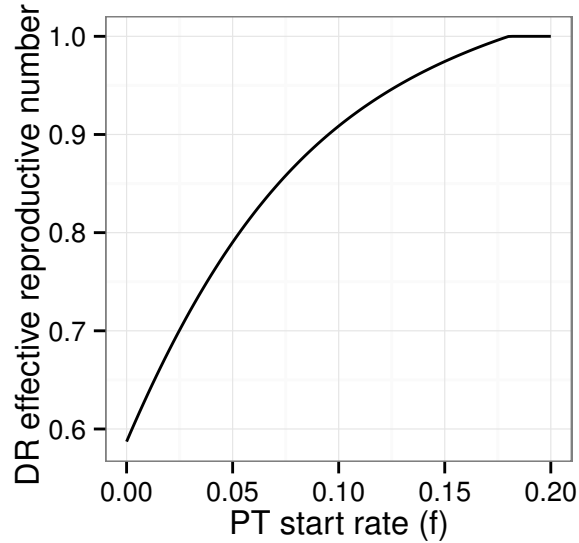


Figure 1.5: The relationship between PT start rate f and the effective reproductive number of the DR strain at equilibrium. Calculations are given in the appendix. Parameters for this figure are the same as those for Fig 1.3.

acquired due to treatment, it can also increase the competitive transmission advantage of circulating DR strains, and its effects on the rate of resistance acquired due to PT are non-monotonic. Furthermore, in our model as in reality, none of these mechanisms exist in isolation. Rather, increasing PT coverage acts simultaneously on the rate at which resistance is acquired through PT, the rate at which resistance is acquired through treatment, and the competitive fitness of the DR strain. In Fig 1.6 we show that the interactions between these mechanisms are sufficient to produce a range of qualitatively distinct relationships between PT coverage and equilibrium DR prevalence. Though the behaviours shown in this figure occur with varying frequencies and are not necessarily exhaustive, they demonstrate the complexity of the changes in DR prevalence that may result from PT.

All of the subplots in Fig 1.6 were created using the same model of preventive therapy under different sets of parameters. The parameters used for each subplot are shown in the figure caption. In Subplot A, DR prevalence increases monotonically with PT coverage. The parameters used to produce this subplot were the same as those used to create the figures for the previous sections. In Subplot B, DR prevalence increases with PT coverage when PT coverage is low, but decreases with

increasing PT coverage if PT coverage exceeds a threshold value. To create this subplot, we lowered the transmission parameter for the DR strain β_R . This decrease in the transmissibility of the DR strain allows acquisition of resistance through PT and treatment to play a larger role in changing DR prevalence. In Subplot C, DR prevalence decreases monotonically with increasing PT coverage. To create this subplot, we lowered the transmission parameter of the DR strain as in subplot B and assumed that no resistance was acquired as a result of preventive therapy, allowing acquisition of resistance by treatment alone to become the major driver of DR prevalence. Finally, in Subplot D, DR prevalence decreases with increasing PT coverage when PT coverage is low, but increases with increasing PT coverage if PT coverage exceeds a threshold value. To create this subplot, we lowered the reinfection susceptibility of latently infected and recovered individuals, assumed no resistance acquired as a result of preventive therapy, and assumed PT did not affect infection with the DS strain (i.e. that it only affected disease progression). The resulting U-shaped curve indicates that, at low coverage levels, PT primarily influences resistance acquired due to treatment for active disease, whereas at high coverage levels, PT exerts more influence by allowing greater transmission of the DR strain. This relationship may reflect the fact that lowering the progression rate affects the prevalence of latent DS infection differently than the rate of active DS infection, complicating the association between the prevalence of DS disease and the number of people susceptible to infection with the DR strain. Note that the absolute changes in DR prevalence in this subplot are small; nevertheless, this shape further reflects the complexity of the ways in which PT may cause changes in DR prevalence.

Discussion

Mathematical models of varying complexity have been constructed to predict the effects of pre-exposure prophylaxis for HIV [15][12][10], isoniazid preventive therapy for TB [16][17][18], and intermittent preventive treatment for malaria [19][20] on the prevalence of drug resistance. Here, we have used a more general model to provide an overall view of the ways in which preventive therapy may influence the prevalence of drug resistance and the anticipated directions of these effects.

First, we have described the relationship between PT coverage and the amount of resistance acquired directly as a result of PT. Previous models have demonstrated particular sensitivity to assumptions surrounding the use of PT in infected individuals [21]. Our model shows that when

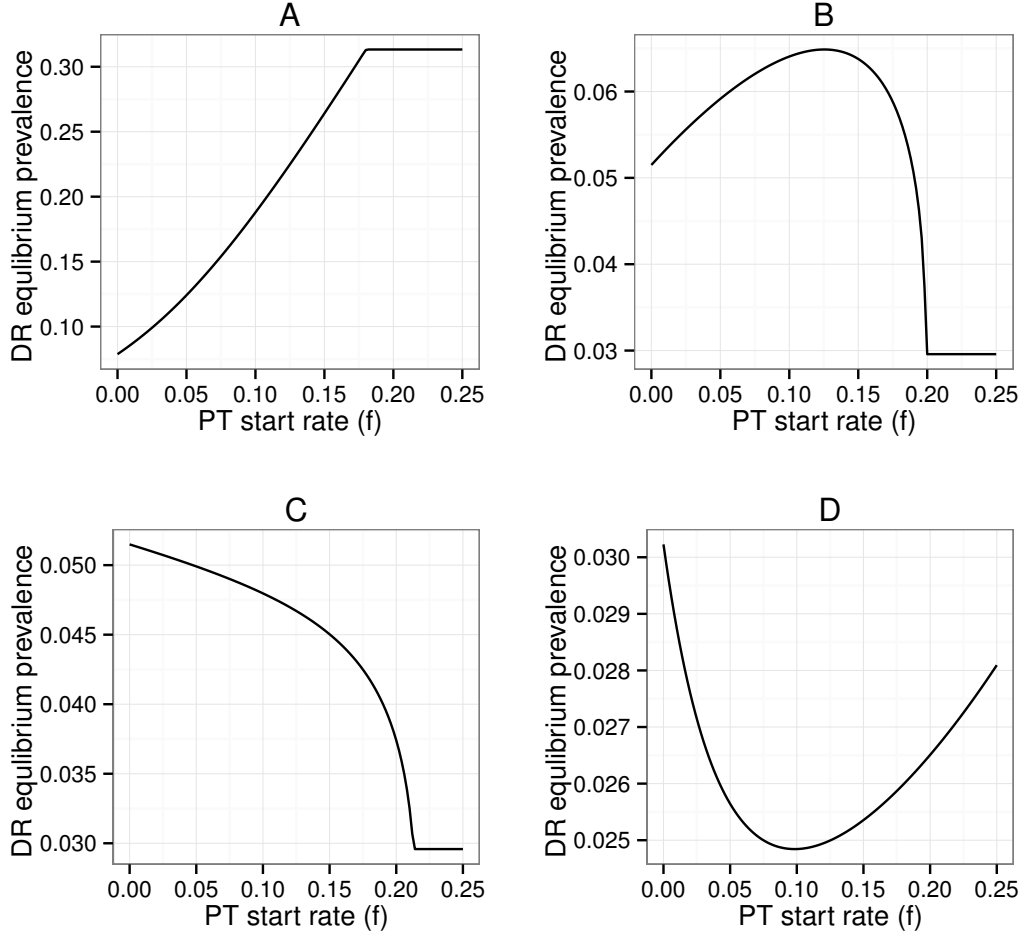


Figure 1.6: Relationship between PT start rate f and DR prevalence ($I_R + I_R^{PT} + T_R$) at equilibrium. Parameters for Subplot A are the same as those from Figs 1.3, 1.4, and 1.5: $\mu = 0.02, r_R = 1, r_S = 2, c = 1, k_R = 1, k_S = 1.5, \beta_S = 2, \beta_R = 1, x = 1, a = 0.3, a_i = 0.5, a_l = 0.1, w = 0.1, \beta_S^{PT} = 0, k_S^{PT} = 0$. Parameters for Subplot B: same as for Subplot A, except $\beta_R = 0.55$. Parameters for Subplot C: same as for Subplot A, except $\beta_R = 0.55, a_i = 0, a_l = 0$. Parameters for Subplot D: same as for Subplot A, except $x = 0.4, a_i = 0, a_l = 0, \beta_S^{PT} = 2$. The same range of PT start rates is shown for each subplot, though this range is insufficient to cause elimination of the DS strain in subplot D.

PT coverage is low, increasing PT coverage increases the amount of resistance acquired as a result of PT. When PT coverage is high, however, further increasing PT coverage decreases the amount of resistance acquired as a result of PT, resulting in an inverted U-shaped curve between PT coverage and resistance acquired from PT. A similar relationship has been described between drug pressure and the rate of resistance in the setting of treatment for active disease [14]. Notably, this resistance mechanism is not a necessary consequence of the beneficial effects of PT. The number of people who acquire resistance as a result of PT may be reduced by limiting the number of infected individuals started on PT (e.g. through better screening programmes), the number of individuals receiving PT who develop latent or active infection (e.g. through better adherence or more effective PT drugs), and the rate at which infected individuals on PT acquire resistance (e.g. through drugs or drug combinations more similar to those used for treatment).

Second, we have shown that increasing PT coverage decreases the amount of resistance acquired as a result of treatment for active disease. This relationship occurs because PT decreases the number of individuals with active DS disease. We would expect a similar relationship to hold for non-therapeutic interventions that do not exclusively target DS disease, such as condom use in the setting of HIV.

Third, we have demonstrated that increasing PT coverage provides a selective advantage to circulating DR strains. We have found that increasing PT coverage increases the effective reproductive number of the DR strain, which is consistent with predictions and observations for vaccines targeting specific disease strains [22][23] and previous PT modelling papers that have used strain competition to explain predicted increases in DR prevalence [17][18]. Increasing the intensity of PT coverage increases the effective reproductive number of the DR strain by increasing the probability that a DR latently infected individual will progress to active DR infection (before reinfection with the DS strain) and by increasing the proportion of the DR uninfected population that is susceptible to infection with the DR strain.

Finally, we have shown that PT may have a wide range of effects on overall DR prevalence, depending on the interaction of these three mechanisms. Specifically, we have provided examples of increasing, decreasing, U-shaped, and inverted U-shaped relationships between PT intensity and equilibrium DR prevalence resulting from our model. These four shapes are not necessarily exhaustive, but demonstrate that the relationship between PT coverage and DR prevalence may

differ qualitatively depending on the disease and drug in question. In particular, predictions of the effects of PT on drug resistance are sensitive to a number of properties of the system: the rate at which resistance is acquired as a result of PT, the rate at which resistance is acquired as a result of treatment, the fitness costs of resistance on disease transmissibility, the mechanisms of PT, and the rate of reinfection. Reliable estimates of these parameters are needed to accurately predict the effects of proposed PT programmes on DR prevalence. Our estimates are also sensitive to the assumption that individuals cannot be reinfected throughout their infectious periods, illustrating the importance of understanding within-host strain competition when predicting the population-level effects of PT.

Understanding how each of these factors contribute to the relationship between preventive therapy and drug resistance may aid in the interpretation of models with differing predictions about the effects of PT on drug resistance. For example, our analysis sheds some additional light on the observations made by Abbas *et al.* [13] on the sources of difference in the model predictions of Supervie *et al.* [10] and Abbas *et al.* [12]. Abbas *et al.* [13] re-created both models to explore the reasons for contrasting conclusions about the potential relationship between PrEP and HIV drug resistance in sub-Saharan Africa. They suggest that a low value of R_0 contributed to PrEP decreasing the prevalence of drug resistance in [10], which accords with our demonstration that although preventive therapy provides a competitive advantage to DR strains, it may still reduce the overall prevalence of drug resistance when the transmissibility of the DR strain is low and resistance is driven primarily by acquisition. Similarly, their observation that the differences between the two models could be partially explained by differing PrEP coverage rates is supported by our finding that the effects of increasing PT coverage may be non-monotonic. The authors also acknowledge that resistance in the population occurs as a result of transmission and treatment (i.e. antiretroviral therapy) as well as PrEP; as we have shown, the effects of preventive therapy on drug resistance cannot be distilled to its effects on resistance acquired through PT alone.

We have presented a general model that may not perfectly reflect the natural history of any particular infection. Though in reality the specific action and targeting of PT varies depending on the disease and drug of interest, we assume PT protects both susceptible and latently infected individuals from active DS disease. Our assumption of no latent or active mixed infections encodes a high level of competition between strains for susceptible hosts, the biological plausibility

of which will depend on the disease of interest. Other models have demonstrated that allowing for mixed infections may either heighten or mitigate the effective degree of competition between strains depending on assumptions of how strains compete within and between hosts [24][25][26][27]. If we could assume DS and DR strains are perfectly non-competing, changing PT coverage may not affect the effective reproductive number of the DR strain; however, we expect most pathogens to exhibit some level of within-strain competition and therefore qualitative behaviours similar to those described here. In addition to the assumption of no mixed infections, we assume a binary designation of drug resistance that may not accurately represent the accumulation of resistance mutations within a single host. Furthermore, we do not allow DR strains to revert to DS, though this behaviour has been demonstrated for pathogens including HIV [28]. We assume that the effects of PT on disease progression cease immediately after PT is removed, and do not allow PT to increase the cure rate or reduce the infectiousness of infectious individuals (as might occur if the drugs used for PT are similar to those used for treatment). Similarly, we assume that PT has no direct effects on immunity to future infection. Finally, we focus our analysis on the effects of PT on drug resistance at equilibrium, even though policymakers may be most interested in its short-term effects.

Nevertheless, we have provided a systematic account of both direct and indirect mechanisms through which PT may affect DR prevalence. Depending on the relative contributions of these resistance mechanisms, raising PT coverage could have increasing, decreasing, or non-monotonic effects on long-term DR prevalence. Because these relationships may be non-monotonic, care should be taken when extrapolating the effects of small PT programmes to larger efforts.

References

- [1] Smieja, M. J., Marchetti, C. A., Cook, D. J. & Smaill, F. M., 2000 Isoniazid for preventing tuberculosis in non-HIV infected persons. *Cochrane Database Syst Rev* p. CD001363. (doi:10.1002/14651858.CD001363).
- [2] Akolo, C., Adetifa, I., Shepperd, S. & Volmink, J., 2010 Treatment of latent tuberculosis infection in HIV infected persons. *Cochrane Database Syst Rev* p. CD000171. (doi:10.1002/14651858.CD000171.pub3).
- [3] Okwundu, C. I., Uthman, O. A. & Okoromah, C. A., 2012 Antiretroviral pre-exposure pro-

- phylaxis (PrEP) for preventing HIV in high-risk individuals. *Cochrane Database Syst Rev* **7**, CD007189. (doi:10.1002/14651858.CD007189.pub3).
- [4] Greenwood, B., 2010 Anti-malarial drugs and the prevention of malaria in the population of malaria endemic areas. *Malar J* **9 Suppl 3**, S2. (doi:10.1186/1475-2875-9-S3-S2).
- [5] Churchyard, G. J., Chaisson, R. E., Maartens, G. & Getahun, H., 2014 Tuberculosis preventive therapy: an underutilised strategy to reduce individual risk of TB and contribute to TB control. *S Afr Med J* **104**, 339–43.
- [6] Underhill, K., Operario, D., Skeer, M., Mimiaga, M. & Mayer, K., 2010 Packaging PrEP to prevent HIV: An integrated framework to plan for pre-exposure prophylaxis implementation in clinical practice. *J Acquir Immune Defic Syndr* **55**, 8–13.
- [7] Date, A. A., Vitoria, M., Granich, R., Banda, M., Fox, M. Y. & Gilks, C., 2010 Implementation of co-trimoxazole prophylaxis and isoniazid preventive therapy for people living with HIV. *Bull World Health Organ* **88**, 253–9. (doi:10.2471/BLT.09.066522).
- [8] Karris, M. Y., Beekmann, S. E., Mehta, S. R., Anderson, C. M. & Polgreen, P. M., 2014 Are we prepped for preexposure prophylaxis (PrEP)? Provider opinions on the real-world use of PrEP in the United States and Canada. *Clin Infect Dis* **58**, 704–12. (doi:10.1093/cid/cit796).
- [9] Dimitrov, D., Boily, M.-C., Brown, E. R. & Hallett, T. B., 2013 Analytic review of modeling studies of ARV based PrEP interventions reveals strong influence of drug-resistance assumptions on the population-level effectiveness. *PLoS One* **8**, e80927. (doi:10.1371/journal.pone.0080927).
- [10] Supervie, V., Barrett, M., Kahn, J. S., Musuka, G., Moeti, T. L., Busang, L. & Blower, S., 2011 Modeling dynamic interactions between pre-exposure prophylaxis interventions & treatment programs: predicting HIV transmission & resistance. *Sci Rep* **1**, 185. (doi:10.1038/srep00185).
- [11] Okano, J. T. & Blower, S., 2014 HIV treatment, preexposure prophylaxis, and drug resistance: reconciling conflicting predictions from mathematical models. *J Infect Dis* **209**, 163–4. (doi:10.1093/infdis/jit544).

- [12] Abbas, U. L., Glaubius, R., Mubayi, A., Hood, G. & Mellors, J. W., 2013 Antiretroviral therapy and pre-exposure prophylaxis: combined impact on HIV transmission and drug resistance in South Africa. *J Infect Dis* **208**, 224–34. (doi:10.1093/infdis/jit150).
- [13] Abbas, U. L., Glaubius, R., Hood, G. & Mellors, J. W., 2014 Antiretroviral treatment, preexposure prophylaxis, and drug resistance in sub-Saharan Africa: a consensus among mathematical models. *J Infect Dis* **209**, 164–6. (doi:10.1093/infdis/jit545).
- [14] Kouyos, R. D., Metcalf, C. J. E., Birger, R., Klein, E. Y., Abel zur Wiesch, P., Ankomah, P., Arinaminpathy, N., Bogich, T. L., Bonhoeffer, S., Brower, C. *et al.*, 2014 The path of least resistance: aggressive or moderate treatment? *Proc Biol Sci* **281**, 20140566. (doi:10.1098/rspb.2014.0566).
- [15] Supervie, V., García-Lerma, J. G., Heneine, W. & Blower, S., 2010 HIV, transmitted drug resistance, and the paradox of preexposure prophylaxis. *Proc Natl Acad Sci U S A* **107**, 12381–6. (doi:10.1073/pnas.1006061107).
- [16] Basu, S., Maru, D., Poolman, E. & Galvani, A., 2009 Primary and secondary tuberculosis preventive treatment in HIV clinics: simulating alternative strategies. *Int J Tuberc Lung Dis* **13**, 652–8.
- [17] Mills, H. L., Cohen, T. & Colijn, C., 2013 Community-wide isoniazid preventive therapy drives drug-resistant tuberculosis: a model-based analysis. *Sci Transl Med* **5**, 180ra49. (doi:10.1126/scitranslmed.3005260).
- [18] Cohen, T., Lipsitch, M., Walensky, R. P. & Murray, M., 2006 Beneficial and perverse effects of isoniazid preventive therapy for latent tuberculosis infection in HIV-tuberculosis coinfecting populations. *Proc Natl Acad Sci U S A* **103**, 7042–7. (doi:10.1073/pnas.0600349103).
- [19] Teboh-Ewungkem, M. I., Mohammed-Awel, J., Baliraine, F. N. & Duke-Sylvester, S. M., 2014 The effect of intermittent preventive treatment on anti-malarial drug resistance spread in areas with population movement. *Malar J* **13**, 428. (doi:10.1186/1475-2875-13-428).

- [20] O’Meara, W. P., Smith, D. L. & McKenzie, F. E., 2006 Potential impact of intermittent preventive treatment (IPT) on spread of drug-resistant malaria. *PLoS Med* **3**, e141. (doi:10.1371/journal.pmed.0030141).
- [21] Abbas, U. L., Hood, G., Wetzel, A. W. & Mellors, J. W., 2011 Factors influencing the emergence and spread of HIV drug resistance arising from rollout of antiretroviral pre-exposure prophylaxis (PrEP). *PLoS One* **6**, e18165. (doi:10.1371/journal.pone.0018165).
- [22] Lipsitch, M., 1997 Vaccination against colonizing bacteria with multiple serotypes. *Proc Natl Acad Sci U S A* **94**, 6571–6.
- [23] Martcheva, M., Bolker, B. M. & Holt, R. D., 2008 Vaccine-induced pathogen strain replacement: what are the mechanisms? *J R Soc Interface* **5**, 3–13. (doi:10.1098/rsif.2007.0236).
- [24] Hansen, J. & Day, T., 2014 Coinfection and the evolution of drug resistance. *J Evol Biol* **27**, 2595–604. (doi:10.1111/jeb.12518).
- [25] Lipsitch, M., Colijn, C., Cohen, T., Hanage, W. P. & Fraser, C., 2009 No coexistence for free: neutral null models for multistrain pathogens. *Epidemics* **1**, 2–13. (doi:10.1016/j.epidem.2008.07.001).
- [26] Colijn, C., Cohen, T. & Murray, M., 2009 Latent coinfection and the maintenance of strain diversity. *Bull Math Biol* **71**, 247–63. (doi:10.1007/s11538-008-9361-y).
- [27] Sergeev, R., Colijn, C. & Cohen, T., 2011 Models to understand the population-level impact of mixed strain *M. tuberculosis* infections. *J Theor Biol* **280**, 88–100. (doi:10.1016/j.jtbi.2011.04.011).
- [28] Devereux, H. L., Youle, M., Johnson, M. A. & Loveday, C., 1999 Rapid decline in detectability of HIV-1 drug resistance mutations after stopping therapy. *AIDS* **13**, F123–7.

APPENDIX S1

How could preventive therapy affect the prevalence of drug resistance? Causes and consequences

Amber Kunkel, Caroline Colijn, Marc Lipsitch, Ted Cohen

Equations

The states and parameters used here are the same as those described in Table 1.1 in the main text.

$$\begin{aligned}
 \dot{S}^{PT} &= fS - wS^{PT} - \beta_S^{PT}(I_S + I_S^{PT} + T_S)S^{PT} - \beta_R(I_R + I_R^{PT} + T_R)S^{PT} - \mu S^{PT} \\
 \dot{L}_S &= \beta_S(I_S + I_S^{PT} + T_S)(S + xL_R + xR) - x\beta_R(I_R + I_R^{PT} + T_R)L_S - (k_S + \mu + f_l)L_S + wL_S^{PT} \\
 \dot{L}_R &= \beta_R(I_R + I_R^{PT} + T_R)(S + xL_S + xR) - x\beta_S(I_S + I_S^{PT} + T_S)L_R - (k_R + \mu + f_l)L_R + wL_R^{PT} \\
 \dot{L}_S^{PT} &= \beta_S^{PT}(I_S + I_S^{PT} + T_S)(S^{PT} + xL_R^{PT} + xR^{PT}) - x\beta_R(I_R + I_R^{PT} + T_R)L_S^{PT} \\
 &\quad - (k_S^{PT} + \mu + w + a_l)L_S^{PT} + f_lL_S \\
 \dot{L}_R^{PT} &= \beta_R(I_R + I_R^{PT} + T_R)(S^{PT} + xL_S^{PT} + xR^{PT}) - x\beta_S^{PT}(I_S + I_S^{PT} + T_S)L_R^{PT} \\
 &\quad - (k_R + \mu + w)L_R^{PT} + f_lL_R + a_lL_S^{PT} \\
 \dot{I}_S &= k_S L_S - (c + \mu + f_i)I_S + wI_S^{PT} \\
 \dot{I}_R &= k_R L_R - (c + \mu + f_i)I_R + wI_R^{PT} \\
 \dot{I}_S^{PT} &= k_S^{PT} L_S^{PT} - (c + \mu + a_i + w)I_S^{PT} + f_i I_S \\
 \dot{I}_R^{PT} &= k_R L_R^{PT} + a_i I_S^{PT} - (c + \mu + w)I_R^{PT} + f_i I_R \\
 \dot{T}_S &= c(I_S + I_S^{PT}) - (r_S + \mu + a)T_S \\
 \dot{T}_R &= c(I_R + I_R^{PT}) - (r_R + \mu)T_R + aT_S \\
 \dot{R} &= wR^{PT} - fR + r_S T_S + r_R T_R - x\beta_S(I_S + I_S^{PT} + T_S)R - x\beta_R(I_R + I_R^{PT} + T_R)R - \mu R \\
 \dot{R}^{PT} &= fR - wR^{PT} - x\beta_S^{PT}(I_S + I_S^{PT} + T_S)R^{PT} - x\beta_R(I_R + I_R^{PT} + T_R)R^{PT} - \mu R^{PT} \\
 S &= 1 - T_S - T_R - I_S - I_R - I_S^{PT} - I_R^{PT} - L_S - L_R - L_S^{PT} - L_R^{PT} - R - R^{PT} - S^{PT}
 \end{aligned}$$

Calculating DR Effective Reproductive Number

This section refers to states and parameters described in Table 1.1 in the main text. The effective reproductive number is the number of secondary infectious cases produced by a single infectious individual over the course of their infectious period. We derived the effective reproductive number

of the DR strain R_{RE} at equilibrium from first principles using the following equation:

$$R_{RE} = \beta_R D (P^0 \theta_R^0 + P^{PT} \theta_R^{PT}).$$

We walk through each of the individual components of this equation below. β_R is the transmission parameter for the DR strain, as described in the main text.

D , the average duration of infectiousness with the DR strain, is the sum of two terms: 1) the average length of stay in the untreated infectious compartment and 2) the average length of stay in the treated infectious compartment given that the individual initiates treatment prior to death. This expression is given below:

$$D = \frac{1}{c + \mu} + \left(\frac{c}{c + \mu} \right) \left(\frac{1}{\mu + r_R} \right).$$

P^0 , the probability of progressing from latent to active disease for individuals not on preventive therapy at the time of infection, is the sum of the probability of progressing before leaving L_R , the probability of starting preventive therapy and then progressing before leaving L_R^{PT} , the probability of starting preventive therapy and then stopping preventive therapy and then progressing before leaving L_R , and so on:

$$P^0 = \frac{k_R}{D_0} + \frac{f_l}{D_0} \frac{k_R}{D_{PT}} + \frac{f_l}{D_0} \frac{w}{D_{PT}} \frac{k_R}{D_0} + \frac{f_l}{D_0} \frac{w}{D_{PT}} \frac{f_l}{D_0} \frac{k_R}{D_{PT}} + \dots$$

$$P^0 = \frac{k_R}{D_0} \sum_{i=0}^{\infty} \left(\frac{f_l}{D_0} \frac{w}{D_{PT}} \right)^i + \frac{f_l}{D_0} \frac{k_R}{D_{PT}} \sum_{j=0}^{\infty} \left(\frac{f_l}{D_0} \frac{w}{D_{PT}} \right)^j$$

where D_0 is the rate of exit from L_R

$$D_0 = k_R + \mu + \beta_S (I_S + I_S^{PT} + T_S) + f_l$$

and D_{PT} is the rate of exit from L_R^{PT}

$$D_{PT} = k_R + \mu + \beta_S^{PT} (I_S + I_S^{PT} + T_S) + w.$$

This expression for P^0 captures all of the possible paths from the latent state to the infectious

state and hence captures the total probability of progression from latency to active DR disease. If we let $z = wf_l/(D_0D_{PT})$ then the expression for P^0 simplifies to

$$P^0 = \frac{k_R}{D_0} \left(1 + \frac{z}{1-z}\right) + \frac{f_l}{D_0} \frac{k_R}{D_{PT}} \left(1 + \frac{z}{1-z}\right).$$

We can similarly derive the expression for P^{PT} , the probability of progressing from latent to active disease for individuals on preventive therapy at the time of infection, which simplifies to

$$P^{PT} = \frac{k_R}{D_{PT}} \left(1 + \frac{z}{1-z}\right) + \frac{w}{D_{PT}} \frac{k_R}{D_0} \left(1 + \frac{z}{1-z}\right).$$

Finally, θ_R^0 is the fraction of individuals who are susceptible to infection with the DR strain and not currently on PT:

$$\theta_R^0 = S + xR + xL_S$$

and θ_R^{PT} is the fraction of individuals on PT who are susceptible to infection with the DR strain:

$$\theta_R^{PT} = S^{PT} + xR^{PT} + xL_S^{PT}.$$

Individuals already infected with the DR strain are not included here, even though they may be reinfected with the DR strain, because they do not change states upon reinfection.

DR Effective Reproductive Number Components

Changing the coverage of preventive therapy changes the DR effective reproductive number in two ways: by affecting the proportion of people infected with the DR strain who progress to active DR disease, and by affecting the proportion of the population that is susceptible to the DR strain. Here we show how each of these components are affected by changing PT coverage, using notation defined earlier in the appendix and in Table 1.1 in the main text.

The proportion of people infected with the DR strain who progress to active DR infection depends on the DS infection rate, which itself depends on the proportion of the population receiving preventive therapy. To produce a population average, we used the formula

$$P = \frac{P^0\theta_R^0 + P^{PT}\theta_R^{PT}}{\theta_R^0 + \theta_R^{PT}}.$$

The results are shown in Supplemental Figure S1.1. The proportion of DR infected persons who progress to active infection with the DR strain increases with increasing PT coverage.

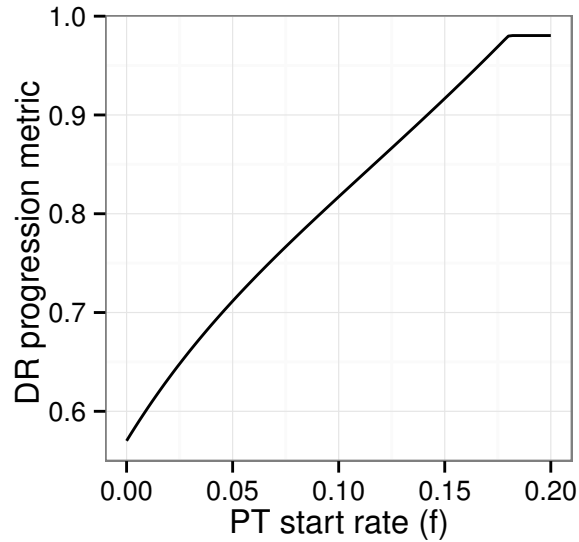


Figure S1.1: The relationship between PT start rate f and the proportion of people infected with the DR strain who progress to active DR infection. Parameters for this figure are the same as those for Fig 1.3 in the main text.

The proportion of people susceptible to the DR strain depends on the number of people uninfected with the DR strain without active DS infection and the level of immunity afforded by initial infection. To remove the effects of changing DR prevalence, we show here the proportion of DR uninfected persons who are susceptible to the DR strain:

$$\theta_R = \frac{\theta_R^0 + \theta_R^{PT}}{S + R + L_S + S^{PT} + R^{PT} + L_S^{PT} + I_S + I_S^{PT} + T_S}.$$

The results are shown in Supplemental Fig S1.2. The proportion of DR uninfected individuals who are susceptible to the DR strain increases with increasing PT coverage.

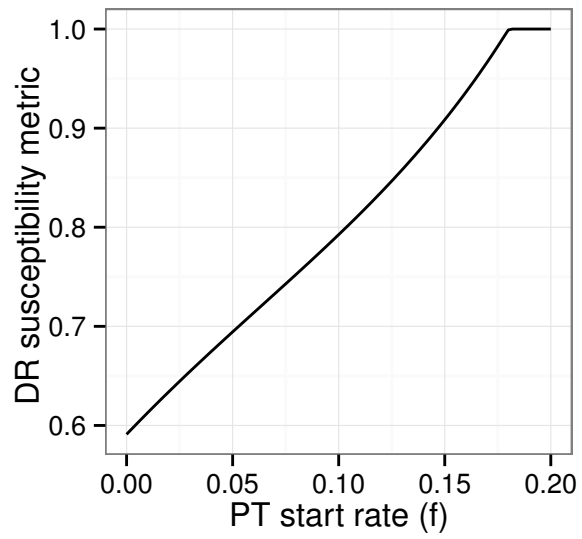


Figure S1.2: The relationship between PT start rate f and proportion of DR uninfected persons susceptible to the DR strain. Parameters for this figure are the same as those for Fig 1.3 in the main text.

Paper 2: Kunkel, A., Crawford, F.W., Shepherd, J. & Cohen, T. Benefits of continuous isoniazid preventive therapy may outweigh resistance risks in a declining TB/HIV co-epidemic.

Abstract

Objective: Extending the duration of isoniazid preventive therapy (IPT) among people living with HIV (PLHIV) may improve its effectiveness at both the individual and population level, but could also increase selective pressure in favor of isoniazid resistant tuberculosis (TB) strains. The objective of this study was to determine the relative importance of these two effects.

Methods: Transmission dynamic model

Design: We created a mathematical model of TB transmission incorporating HIV incidence and treatment, mixed strain latent TB infections, and four different phenotypes of TB drug resistance (pan-susceptible, isoniazid mono-resistant, rifampicin mono-resistant, and multi-drug resistant). We used this model to project the effects of IPT duration on the incidence of isoniazid-sensitive and -resistant TB as well as mortality among PLHIV. We evaluated the sensitivity of our baseline model, which was calibrated to data from Botswana, to different assumptions about the future trajectory of the TB epidemic.

Results: Our model suggests that, in the context of a declining TB epidemic such as that currently observed in Botswana, the incidence and mortality benefits of continuous IPT for PLHIV are likely to outweigh the potential resistance risks associated with long duration IPT. However, in less well-controlled epidemics, the selective pressure imposed by widespread use of continuous IPT on isoniazid resistant TB incidence may erode its initial benefits.

Conclusions: Continuous IPT should be coupled with strong and effective HIV control, TB case-finding and treatment, and drug resistance surveillance to maximize the expected benefits of preventive therapy.

Introduction

The World Health Organization currently recommends at least 6-9 months of isoniazid preventive therapy (IPT) for all people living with HIV (PLHIV) deemed unlikely to have active tuberculosis (TB) on the basis of symptom screening [1]. Several clinical trials have demonstrated an individual-level efficacy of IPT for preventing TB among PLHIV [2]. Longer follow-up studies on the risks of TB after stopping IPT, however, suggest that the duration of protection post-IPT varies based on setting and may be lost almost immediately [3-6]. Community-wide IPT was demonstrated to have no effect on TB incidence within the Thibela study, an observation that has been at least partly attributed to rapid loss of protection from re-infection after IPT and could also suggest that 9 months of IPT are insufficient to clear latent TB strains among PLHIV [7-10].

A continuous, lifelong course of IPT has been suggested as a potential way to increase the community-wide impact of IPT [7]. At the individual level, clinical trials have shown an increased efficacy of 36 months of IPT, intended as a proxy for lifelong treatment, compared to the standard 6-month regimen [11, 12]. Despite these potential benefits, prolonging the course of IPT could exacerbate concerns about the risk of side effects and potential for increased isoniazid resistance. Martinson *et al.* found a greater risk of serious adverse effects on continuous IPT as compared to shorter duration regimens [13]. While the analysis of published literature included in WHO IPT guidelines concluded that IPT does not increase the risk of isoniazid-resistant TB among IPT recipients (graded “strong recommendation, moderate quality of evidence”), this analysis was based on clinical trials of IPT that used stricter criteria to exclude active TB than the WHO recommended symptom-screening algorithm. Furthermore, the included studies were not powered to

assess risks of resistance [1, 14]. This analysis also did not consider the potential competitive advantage that community-wide IPT could confer to isoniazid resistant TB strains at the population level [15-17].

Several modeling studies have previously assessed the potential impact of widespread IPT use among PLHIV on the incidence of both isoniazid sensitive and isoniazid resistant TB [16, 18, 19]. However, these studies have not specifically investigated the impact of different IPT durations. They also have not accounted for multiple pathways to multi-drug resistant (MDR) TB and have typically offered little guidance as to the conditions under which the potential benefits of IPT are most likely to outweigh increased risks of resistance. For this analysis, we created a mathematical model to assess the potential impact of variable durations of IPT on overall mortality among PLHIV over a range of epidemic scenarios. Unlike previous models, our analysis explicitly explores the potential multi-faceted effects of IPT on the incidence of pan-sensitive, isoniazid mono-resistant, rifampicin mono-resistant, and MDR TB. Our baseline scenario was chosen and the most uncertain parameters were estimated based on historical trends and future projections of the TB-HIV co-epidemic in Botswana.

Methods

To assess the potential impact of continuous vs. 6-month IPT on the incidence of isoniazid resistant TB in Botswana, we created a compartmental transmission model accounting for the natural history of TB, the incidence of HIV and uptake of antiretroviral therapy (ART), and the acquisition and transmission of TB drug resistance in this setting. Our modeling strategy is described briefly below and in more detail in the Appendix. The

model was implemented in R version 3.2.0 as a series of delay differential equations numerically integrated using package deSolve.

Model Overview

The basic structure of our model is shown in Fig 1. With respect to TB, individuals in the model may be fully susceptible, latently infected, actively infected, or receiving treatment. Initial infection moves individuals from the susceptible compartment to either the active TB (fast progression) or latently infected (slow progression) compartment. People who are latently infected may become actively infected via either reactivation or reinfection. We assume that initial infection affords partial but incomplete protection against future reinfection.

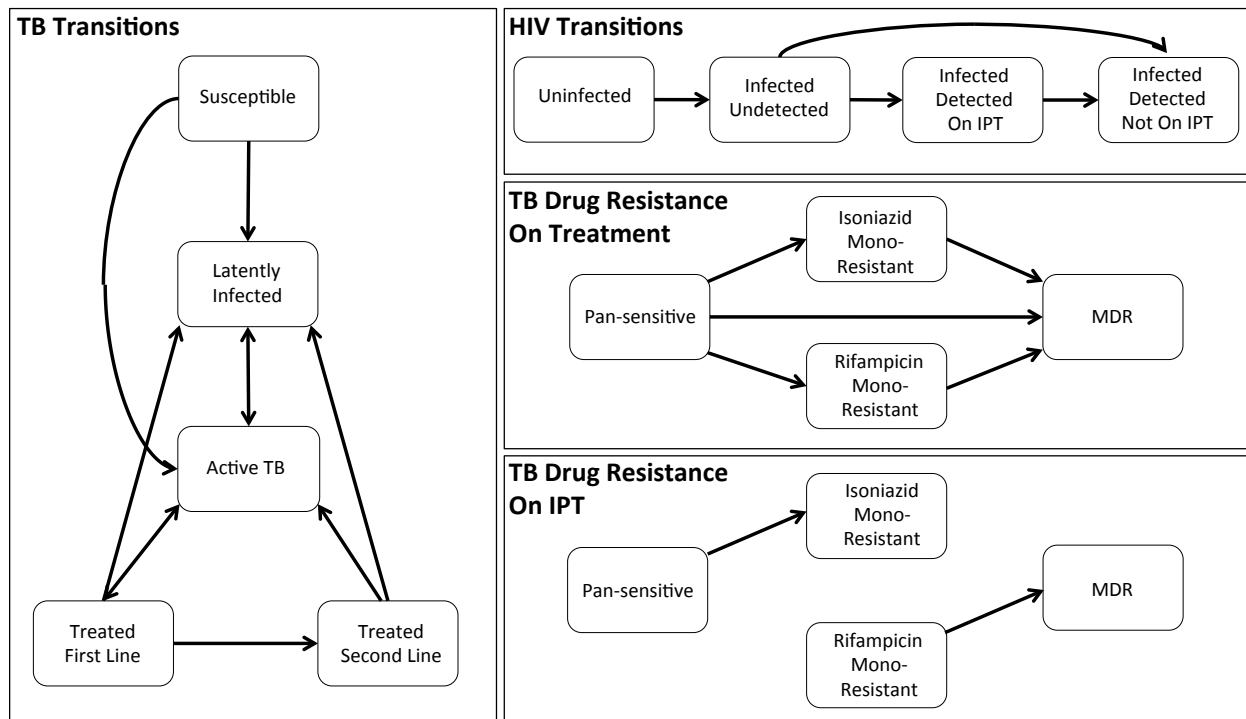


Figure 2.1: Model structure

Episodes of active TB in the model may result in death, spontaneous cure, or initiation on treatment. Treatment episodes may result in successful cure, leading to return to latent infection, or in treatment failure, resulting in relapse to active disease either with or without acquired resistance. The treatment a patient receives depends on their drug susceptibility profile and whether drug resistance is detected by their healthcare provider. We assume that all newly diagnosed patients initially receive first-line TB treatment, but starting in 2008 allow a proportion of individuals failing their initial treatment course to receive drug susceptibility testing and appropriate retreatment [20].

With respect to HIV, individuals in the model may be uninfected, infected and undetected (i.e. not receiving ART), or infected and detected (i.e. receiving ART if eligible). Individuals with detected HIV are also eligible for IPT. Our model of HIV is not a transmission model in that the number of new HIV infections does not reflect the interaction between susceptible and infected individuals in the model, but is instead based on UNAIDS Botswana HIV incidence projections (UNAIDS 2015, unpublished data).

We account for four phenotypes of drug resistant TB in this model: pan-sensitive, isoniazid mono-resistant, rifampicin mono-resistant, and multi-drug resistant (MDR, resistant to both isoniazid and rifampicin). We assume that patients receiving treatment are at risk of developing resistance to both isoniazid and rifampicin. We also assume that patients receiving IPT are at risk of developing resistance to isoniazid, with rates depending on whether they are latently infected or have active TB disease (we assume imperfect sensitivity of symptom screening such that a small number of individuals with active disease may be initiated on IPT [21]). During the latent stage, individuals in the model may be infected by multiple strains with the same or varying resistant types;

however, we assume that progression to active infection acts as a bottleneck, with only one strain dominating (as in [16]). Specifically, we assume that the dominant strain is determined at the time of each (re)infection event, but may switch if IPT is applied to a latently infected individual with a dominant strain that is isoniazid sensitive and non-dominant strain that is isoniazid resistant.

All individuals are assumed to enter the model HIV susceptible at age 15. We allow individuals to be latently infected with at most one TB strain at the time of model entry, with rates determined by the annual risk of infection over the previous 15 years. We do not include a detailed demographic model, and instead allow for a rate of entry that maintains a fairly consistent population size throughout our predictions.

Historical IPT use in Botswana is incorporated from 2004-2008 by allowing patients started on ARVs during that time to receive IPT for a mean duration of 3 months [22, 23]. Otherwise we assume no individuals receive IPT until 2017. We focus our analysis on the potential impact of different IPT strategies from 2017 onwards.

Parameterization

We allow the rates of TB infection, progression, and other natural history parameters to vary depending on whether a person is HIV uninfected, HIV infected and undetected, or HIV infected and detected. Treatment success is also allowed to vary based on both HIV status and resistance pattern. We assume that the majority of these parameters are known with certainty, with values chosen based on a review of the literature. The remaining 18 parameters were assigned prior distributions based on this literature review. Our estimates of these parameters were then refined using Bayesian melding [24, 25] by comparing model outputs to published estimates of TB incidence, TB

prevalence, HIV prevalence, HIV prevalence in TB cases, and the coverage of antiretroviral therapy in Botswana from 1990-2013, as well as data from four TB drug resistance surveys conducted over the same time period [26-28].

Several of our parameters were allowed to vary over time to reflect observed trends in TB and HIV control in Botswana. These parameters include the rate of HIV infection, the rate at which PLHIV are started on ART, the TB case detection rate, and the rate of second-line treatment, and are discussed in more detail in the Appendix.

IPT Implementation & Impact

Individuals receiving IPT experience several different effects. First, we assume that individuals cannot be infected or reinfected by isoniazid sensitive TB strains while receiving IPT. Second, we assume that the reactivation rate of pre-existing isoniazid sensitive infections is reduced for individuals receiving IPT. IPT may either clear these strains completely or suppress them only during the time that the individual is receiving IPT [8, 9]. If IPT is able to clear these strains, individuals may either retain or lose partial immunity to reinfection. Latently infected individuals may acquire resistance to isoniazid at a low rate; this rate is much higher for individuals with active TB inadvertently receiving IPT. Actively infected individuals receiving IPT may also be cured at low rates reflecting those of the initial trials of isoniazid alone [29, 30]. We allow individuals receiving IPT to experience a small excess mortality rate due to adverse effects.

Beginning in 2017, we implement and compare four different IPT scenarios: no IPT, short-term IPT (mean duration 6 months plus additional dropout), realistic continuous IPT accounting for dropout (median duration 4.7 years, similar to [13]), and perfect continuous IPT assuming no dropout. We introduce a brief catch-up period in the beginning of 2017 to

allow individuals already started on ART to receive IPT; from that point forward, people may only receive IPT upon HIV detection. Individuals may choose not to receive IPT, and those with active TB may be detected by symptom screening prior to IPT initiation and instead started on treatment for active TB. We do not model the effect of secondary IPT after completion of treatment for active disease.

Outcomes

The outcomes we investigated included TB incidence (both overall and by resistance type), mortality rate among PLHIV, and cumulative mortality among PLHIV.

Results

Here we describe the results of our analysis both for our baseline Botswana scenario, in which transmission is declining based on WHO estimates and our model predictions, and for scenarios with higher transmission post-2017.

Baseline Botswana Results

Figure 2.2 shows the projected incidence of pan-sensitive, rifampicin mono-resistant, isoniazid mono-resistant, and MDR TB in Botswana for the range of IPT durations. Our model projects that longer IPT durations will decrease the incidence of pan-sensitive and rifampicin mono-resistant TB through 2050. We also predict that longer durations of IPT will increase the incidence of isoniazid mono-resistant and MDR TB.

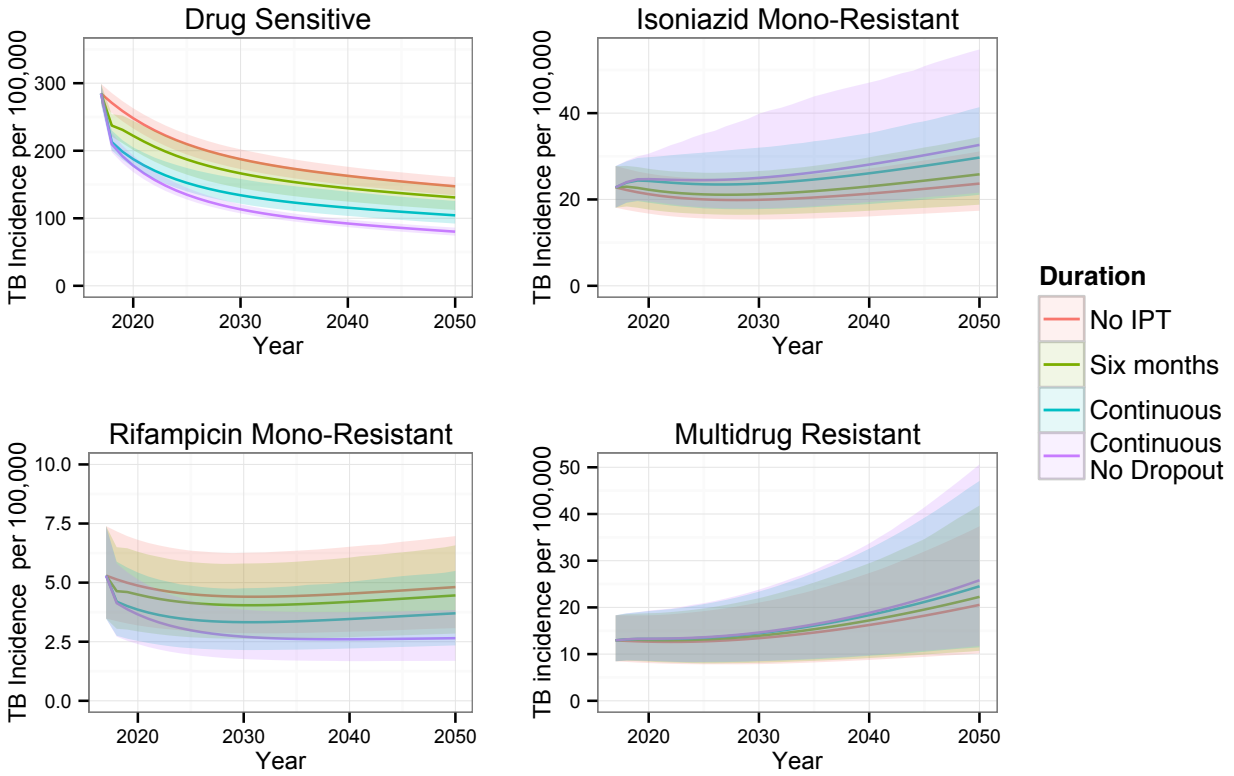


Figure 2.2: The effect of IPT duration on TB incidence by resistance phenotype under our baseline Botswana scenario. Solid lines display means and shaded regions display 95% quantiles of our posterior predictions.

IPT has the greatest impact in absolute terms on the incidence of drug sensitive TB. Figure 2.3 shows projections of different IPT durations on overall TB incidence, mortality rate among PLHIV, and cumulative mortality among PLHIV relative to no IPT. Under our baseline scenario, we predict that longer durations of IPT will decrease the overall incidence of TB through 2050 despite increases in the incidence of isoniazid mono-resistant and MDR TB. We similarly predict that longer durations of IPT will provide overall mortality benefits to our population through at least 2050, suggesting that the

projected increases in isoniazid resistance are not sufficient to outweigh the benefits of decreased overall TB incidence under this scenario.

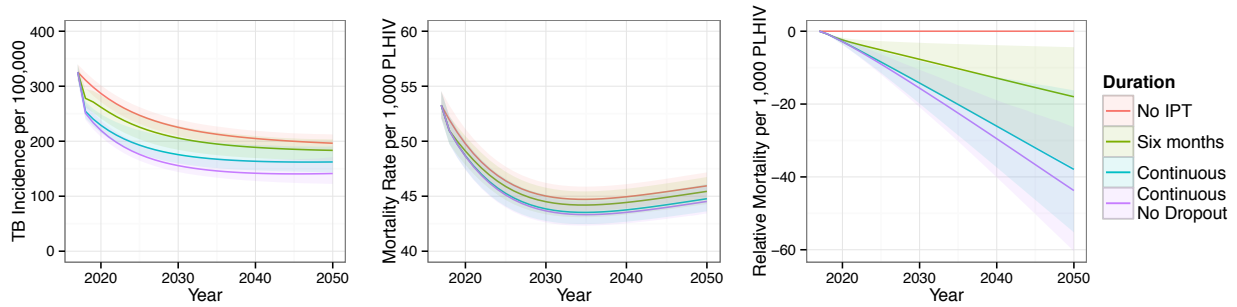


Figure 2.3: The composite effects of IPT duration on overall TB incidence, mortality rate among PLHIV, and cumulative mortality among PLHIV (relative to no IPT). Solid lines display means and shaded regions display 95% quantiles of our posterior predictions.

The initial program providing IPT to PLHIV in Botswana beginning in 2004 was stopped in 2008 after an observed increase in isoniazid resistance between the 2002 and 2008 drug resistance surveys; it was unclear, however, how much of this increase could be attributed to the IPT program [22, 23, 26]. By comparing our baseline model results from these two time periods with a counterfactual scenario under which no IPT was provided, we estimate that 12.8% (95% quantiles 9.2%, 16.9%) of the increase in drug resistance from 2002 to 2008 was a result of the IPT program, with the remainder reflecting trends in treatment and transmission.

Sensitivity of Findings to Projected Epidemic Trajectory

Under our baseline scenario, we predict substantial decreases in overall TB incidence through 2050 even in the absence of IPT, reflecting UNAIDS HIV incidence

projections and expanded access to antiretroviral therapy. However, these observed trends could be subject to unforeseen events or changes, whether technological, medical, or political; they also may limit the generalizability of our results to other settings. Therefore, we also explored the effect of IPT duration on the incidence of both isoniazid sensitive and isoniazid resistant TB under assumptions of constant or increasing TB transmission after 2017.

Figure 2.4 shows the incidence of isoniazid resistant (mono-resistant plus MDR) and overall TB under different durations of IPT when the transmission parameter is increased 1.25x, 1.5x, or 1.75x that of our baseline scenario beginning in 2017. Longer durations of IPT have a stronger effect on the incidence of isoniazid resistant TB under these higher transmission scenarios. When transmission is sufficiently high, the expected increase in isoniazid resistant TB outpaces the decrease in isoniazid sensitive TB within 25 years or less. Figure 2.5 shows the impact of IPT duration on the mortality rate and cumulative mortality (relative to no IPT) per 1,000 PLHIV under these higher transmission scenarios. For all scenarios, longer IPT durations initially decrease the mortality rate among PLHIV, yet for the highest transmission scenario this initial difference in mortality rates is lost within the first 25 years of the applied IPT policy. The average cumulative mortality remains lowest for the longest IPT duration scenario through 2050 even for the highest transmission scenario; however, by 2050 the differences between the IPT policies are beginning to close and there is considerable uncertainty in our mortality estimates.

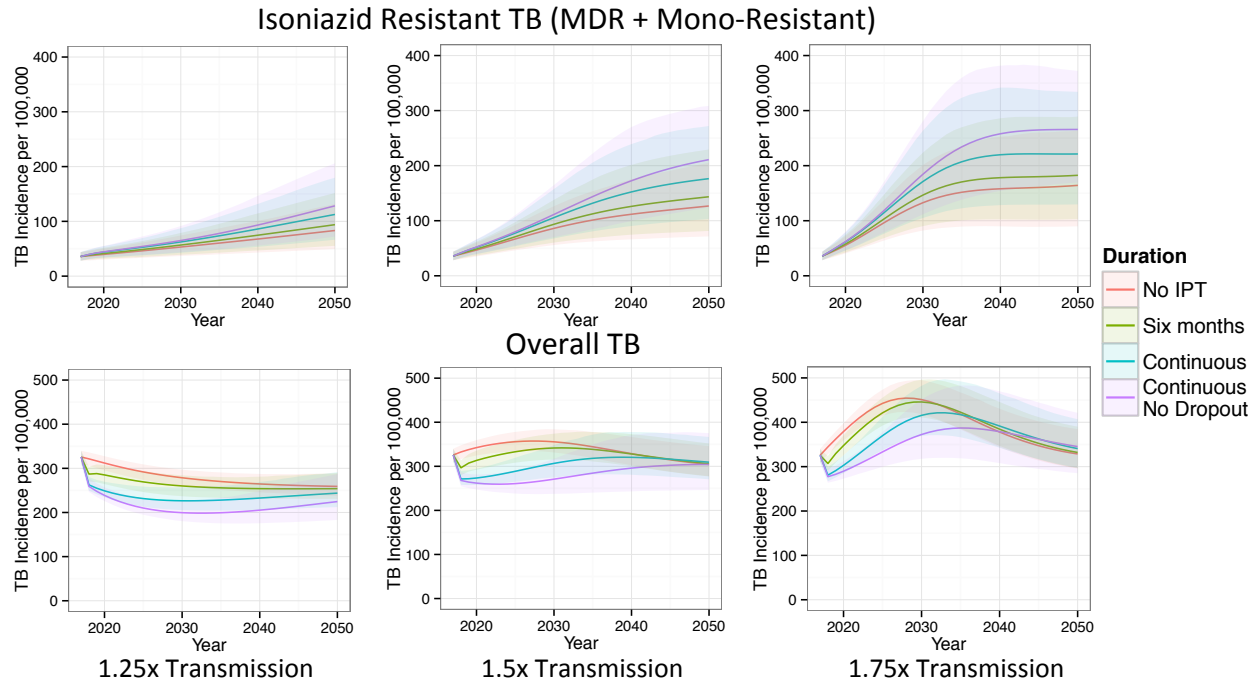


Figure 2.4: The effects of IPT duration on the incidence of isoniazid resistant and overall TB when the transmission parameter post-2017 is increased 1.25x, 1.5x, and 1.75x compared to our baseline scenario. When transmission is relatively high, longer durations of IPT can produce large increases in the incidence of isoniazid resistant TB, eroding their initial overall incidence benefits. Solid lines display means and shaded regions display 95% quantiles of our posterior predictions.

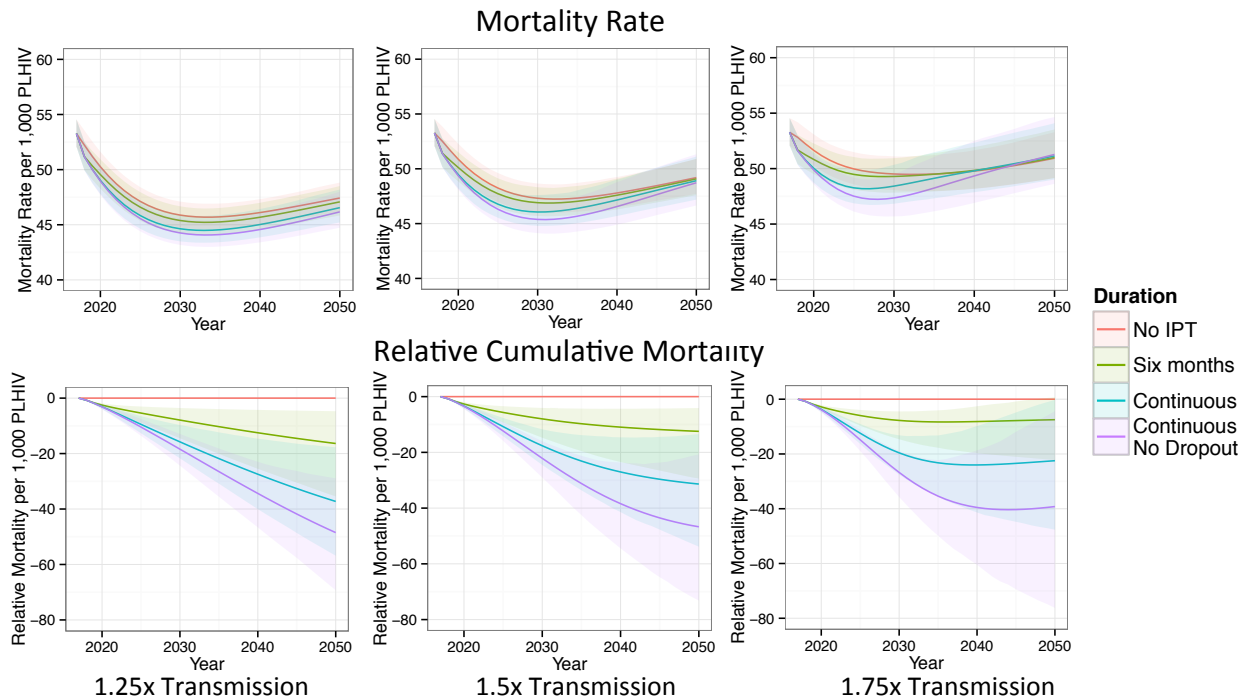


Figure 2.5: The effects of IPT duration on the mortality rate and cumulative mortality relative to no IPT per 1,000 PLHIV when the transmission parameter post-2017 is increased 1.25x, 1.5x, and 1.75x compared to our baseline scenario. When transmission is relatively high, the mortality benefits of continuous IPT among PLHIV may be short-lived. Solid lines display means and shaded regions display 95% quantiles of our posterior predictions.

Discussion

We created a mathematical model to examine the potential impact of implementing IPT programs of varying durations among PLHIV in Botswana and explored the sensitivity of these results to assumptions about future TB transmission trends. Our model consistently predicts longer durations of IPT to decrease incidence of isoniazid sensitive TB and increase incidence of isoniazid resistant TB. However the relative importance of these

two effects varies depending on the future trajectory of the epidemic. In a declining epidemic such as our baseline Botswana scenario, we predict the benefits of continuous IPT for PLHIV to outweigh the risks of increases in isoniazid resistance through at least 2050. In higher transmission settings or scenarios, however, the initial incidence and mortality benefits of longer IPT durations may subsequently be eroded by substantial increases in the incidence of isoniazid resistant TB, reflecting an increased importance of the selective pressure imposed by IPT relative to other resistance mechanisms [17].

TB transmission trends may be affected by a large range of underlying parameters, including potential changes in HIV transmission, population structure, and standards of living, as well as the structural assumptions of our model. As a result, it is not possible to predict future TB transmission trends in Botswana with certainty. Our initial assumption was that the transmission parameter would remain fixed from 2017-2050, reflecting continued projected advances in HIV diagnosis and treatment as well as TB case detection and treatment policies that were assumed to be fairly well-functioning. If these assumptions do not hold, or in other settings that are not yet reporting similar declines in TB and HIV incidence, our higher transmission scenarios may provide more realistic projections.

These results suggest that continuous IPT is likely to be most effective in preventing future TB transmission when coupled with strong TB and HIV control programs. Using continuous IPT in the absence of highly-effective TB and HIV case-finding and treatment, however, may result in substantial increases in the incidence of isoniazid resistant TB. Continuous IPT should be considered as one of a suite of tools that could be useful for more rapidly reducing the burden of HIV-associated TB, and does not decrease the importance of

other interventions. We also suggest that IPT programs providing widespread and/or continuous IPT be accompanied by robust drug resistance surveillance, especially in settings with a high prevalence of HIV or where TB transmission is believed to be stable or increasing. Such surveillance programs should focus on the absolute incidence of isoniazid resistant TB, rather than the proportion of TB cases that are isoniazid resistant, as increases in the latter could also reflect expected declines in incidence of isoniazid sensitive TB.

Even under our most pessimistic high transmission scenario, however, the risks of increased isoniazid resistance seen in this analysis are not immediate. Longer durations of IPT are predicted to lower overall TB incidence and the mortality rate among PLHIV for at least 20 years on average, and the cumulative mortality advantage of continuous IPT could last much longer. The risks of resistance driven by widespread, long duration IPT should therefore be weighed against its potential immediate benefits. These future risks could be mitigated by future trends in TB research and treatment, particularly in the area of TB drug development. Though the use of different drugs for prevention and treatment may not currently be possible given the limited number of TB drugs available, continued drug development could make this a highly appealing option, either through the development of an effective alternative first-line regimen without isoniazid or perhaps even the targeted use of a new drug for prevention only [31, 32].

Our analysis has several limitations. Because IPT is a complicated intervention, with population-level impacts potentially affected by trends in TB, HIV, and drug resistance, we have presented a complex model with many parameters for which there is limited data to inform their values. The detailed structure of our model afforded us the opportunity to

account for complexities avoided in previous models, such as the stepwise accumulation of mutations for resistance to isoniazid and rifampicin [16, 18, 19]. However, it also reduces its transparency, and many of the parameters assumed fixed may not actually be known with certainty. Similarly, the data used to estimate the most uncertain parameters were both limited in scope and based primarily on country-wide estimates rather than actual data points. Despite the complexity of the model, it also incorporates a number of strong simplifying assumptions and structural elements that may constrain the sorts of predictions we can make. In particular, this analysis does not incorporate a detailed model of demographic trends in Botswana. The HIV model is also simplified and does not fully account for the natural history of HIV infection. Furthermore, we relied on UNAIDS HIV incidence estimates rather than creating a full transmission model of HIV. These limitations suggest caution should be used in relying on the quantitative projections provided in this paper, but are less likely to affect the qualitative trends we report here. s

In summary, our results suggest that if interventions using longer duration IPT among PLHIV could be brought to scale in Botswana, we would observe a decrease the incidence of isoniazid sensitive (including rifampicin mono-resistant) TB through at least 2050. However, the projected effects of widespread continuous IPT on the incidence of isoniazid resistant TB vary depending on future transmission trends. In settings with declining transmission of TB and HIV, we predict the impact of IPT on isoniazid resistant TB to be fairly small. In higher transmission settings, however, IPT could result in large increases in the incidence of isoniazid resistant TB. Under such a scenario, the benefits of IPT may be eroded such that the initial reductions in TB incidence may be lost within two decades. The benefits of continuous IPT are most likely to outweigh the costs when

coupled with strong HIV and TB case-finding and treatment programs, continued TB drug development, and robust TB drug resistance surveillance.

References

1. World Health Organization. *Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings*. Geneva; 2011.
2. Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. *Cochrane Database Syst Rev* 2010:Cd000171.
3. Johnson JL, Okwera A, Hom DL, Mayanja H, Mutuluuza Kityo C, Nsubuga P, *et al*. Duration of efficacy of treatment of latent tuberculosis infection in HIV-infected adults. *Aids* 2001,**15**:2137-2147.
4. Quigley MA, Mwinga A, Hosp M, Lisse I, Fuchs D, Porter JDH, *et al*. Long-term effect of preventive therapy for tuberculosis in a cohort of HIV-infected Zambian adults. *Aids* 2001,**15**:215-222.
5. Golub JE, Cohn S, Saraceni V, Cavalcante SC, Pacheco AG, Moulton LH, *et al*. Long-term protection from isoniazid preventive therapy for tuberculosis in HIV-infected patients in a medium-burden tuberculosis setting: the TB/HIV in Rio (THRio) study. *Clin Infect Dis* 2015,**60**:639-645.
6. Samandari T, Agizew TB, Nyirenda S, Tedla Z, Sibanda T, Mosimaneotsile B, *et al*. Tuberculosis incidence after 36 months' isoniazid prophylaxis in HIV-infected adults in Botswana: a posttrial observational analysis. *Aids* 2015,**29**:351-359.
7. Churchyard GJ, Fielding KL, Lewis JJ, Coetzee L, Corbett EL, Godfrey-Faussett P, *et al*. A trial of mass isoniazid preventive therapy for tuberculosis control. *N Engl J Med* 2014,**370**:301-310.

8. Vynnycky E, Sumner T, Fielding KL, Lewis JJ, Cox AP, Hayes RJ, *et al.* Tuberculosis control in South African gold mines: mathematical modeling of a trial of community-wide isoniazid preventive therapy. *Am J Epidemiol* 2015,**181**:619-632.
9. Houben RM, Sumner T, Grant AD, White RG. Ability of preventive therapy to cure latent *Mycobacterium tuberculosis* infection in HIV-infected individuals in high-burden settings. *Proc Natl Acad Sci U S A* 2014,**111**:5325-5330.
10. Sumner T, Houben RM, Rangaka MX, Maartens G, Boulle A, Wilkinson RJ, *et al.* Post-Treatment Effect of Isoniazid Preventive Therapy on Tuberculosis Incidence in HIV-Infected Individuals on Antiretroviral Therapy. *Aids* 2016.
11. Samandari T, Agizew TB, Nyirenda S, Tedla Z, Sibanda T, Shang N, *et al.* 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial. *Lancet* 2011,**377**:1588-1598.
12. Boon SD, Matteelli A, Ford N, Getahun H. Continuous isoniazid for the treatment of latent tuberculosis infection in people living with HIV: a systematic review and meta-analysis. *Aids* 2016.
13. Martinson NA, Barnes GL, Moulton LH, Msandiwa R, Hausler H, Ram M, *et al.* New regimens to prevent tuberculosis in adults with HIV infection. *N Engl J Med* 2011,**365**:11-20.
14. Balcells ME, Thomas SL, Godfrey-Faussett P, Grant AD. Isoniazid preventive therapy and risk for resistant tuberculosis. *Emerg Infect Dis* 2006,**12**:744-751.
15. Lipsitch M, Samore MH. Antimicrobial use and antimicrobial resistance: a population perspective. *Emerg Infect Dis* 2002,**8**:347-354.

16. Mills HL, Cohen T, Colijn C. Community-wide isoniazid preventive therapy drives drug-resistant tuberculosis: a model-based analysis. *Sci Transl Med* 2013,**5**:180ra149.
17. Kunkel A, Colijn C, Lipsitch M, Cohen T. How could preventive therapy affect the prevalence of drug resistance? Causes and consequences. *Philos Trans R Soc Lond B Biol Sci* 2015,**370**:20140306.
18. Cohen T, Lipsitch M, Walensky RP, Murray M. Beneficial and perverse effects of isoniazid preventive therapy for latent tuberculosis infection in HIV-tuberculosis coinfecting populations. *Proc Natl Acad Sci U S A* 2006,**103**:7042-7047.
19. Basu S, Maru D, Poolman E, Galvani A. Primary and secondary tuberculosis preventive treatment in HIV clinics: simulating alternative strategies. *Int J Tuberc Lung Dis* 2009,**13**:652-658.
20. Botswana National Tuberculosis Program. *National Tuberculosis Program Annual Report 2012*; 2012.
21. Getahun H, Kittikraisak W, Heilig CM, Corbett EL, Ayles H, Cain KP, *et al*. Development of a standardized screening rule for tuberculosis in people living with HIV in resource-constrained settings: individual participant data meta-analysis of observational studies. *PLoS Med* 2011,**8**:e1000391.
22. Ministry of Health Botswana. *Isoniazid preventive therapy programme (IPT) evaluation report*; 2008.
23. Ministry of Health Botswana. *Isoniazid preventive therapy (IPT) progress report 2002-009*; 2009.

24. Poole D, Raftery AE. Inference for Deterministic Simulation Models: The Bayesian Melding Approach. *Journal of the American Statistical Association* 2000,**95**:1244-1255.
25. Alkema L, Raftery AE, Brown T. Bayesian melding for estimating uncertainty in national HIV prevalence estimates. *Sex Transm Infect* 2008,**84 Suppl 1**:i11-i16.
26. Menzies HJ, Moalosi G, Anisimova V, Gammino V, Sentle C, Bachhuber MA, *et al*. Increase in anti-tuberculosis drug resistance in Botswana: results from the fourth National Drug Resistance Survey. *Int J Tuberc Lung Dis* 2014,**18**:1026-1033.
27. UNAIDS. *AIDSinfo*. <http://aidsinfo.unaids.org>. Accessed September 19, 2015.
28. World Health Organization. *TB burden estimates*. <http://www.who.int/tb/country/data/download/en/>. Accessed September 19, 2015.
29. Sita Lumsden EG, Swoboda JA. Isoniazid in the treatment of pulmonary tuberculosis. *Tubercle* 1952,**33**:322-329.
30. Treatment of pulmonary tuberculosis with isoniazid; an interim report to the Medical Research Council by their Tuberculosis Chemotherapy Trials Committee. *Br Med J* 1952,**2**:735-746.
31. Diacon AH, Dawson R, von Groote-Bidlingmaier F, Symons G, Venter A, Donald PR, *et al*. 14-day bactericidal activity of PA-824, bedaquiline, pyrazinamide, and moxifloxacin combinations: a randomised trial. *Lancet* 2012,**380**:986-993.
32. Churchyard GJ, Friedland G, Fielding K, Nardell E. Opportunities afforded by new drugs for tuberculosis. *Lancet Infect Dis* 2010,**10**:368-369.

APPENDIX S2

Benefits of continuous isoniazid preventive therapy may outweigh resistance risks in a declining TB/HIV co-epidemic

Amber Kunkel, Forrest W. Crawford, James Shepherd, Ted Cohen

Contents Overview

1. Plots of model output and data used to inform likelihoods
2. Detailed methods narrative
3. Table of prior distributions on variable parameters
4. Plots of marginal prior and posterior distributions
5. Table of fixed and derived parameters
6. Effects of reinfection on relationship between IPT and drug resistance
7. Model equations (as R code)
8. Supplemental references

Comparisons of Data and Model Output

Here, we compare our model performance prior to IPT implementation in 2017 with the data used to inform the likelihoods for our posterior predictions. Plots were created by running the model forwards from 1980 over the range of considered parameter sets (see Detailed Methods below for more details).

HIV Plots

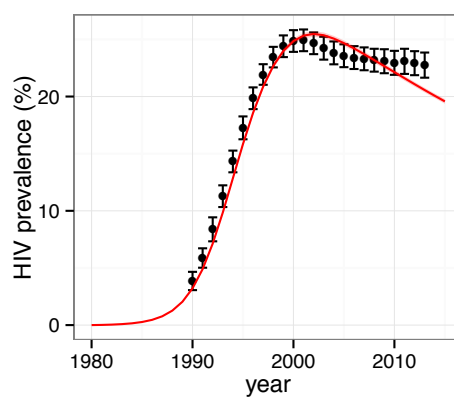


Figure S2.1: Comparison of model output (red) to UNAIDS (UNAIDS 2015, unpublished data) estimates of HIV prevalence (black) from 1990-2013. Uncertainty in the estimates was assumed to be the same as from UNAIDS AIDSinfo estimates of HIV prevalence [1]. Solid lines display means and shaded regions display 95% quantiles of our posterior predictions.

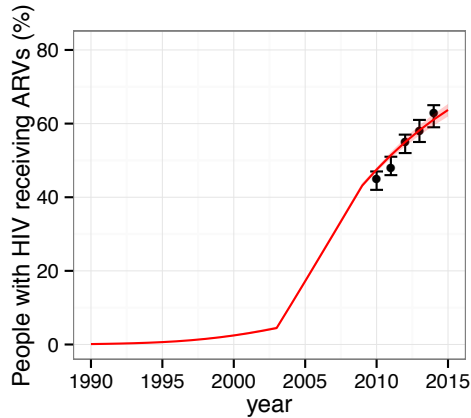


Figure S2.2: Comparison of model output (red) to UNAIDS AIDSinfo estimates of ARV coverage (black) from 2010-2014 [1]. Solid lines display means and shaded regions display 95% quantiles of our posterior predictions. ARVs were assumed to be unavailable prior to 2003, except for individuals with active TB.

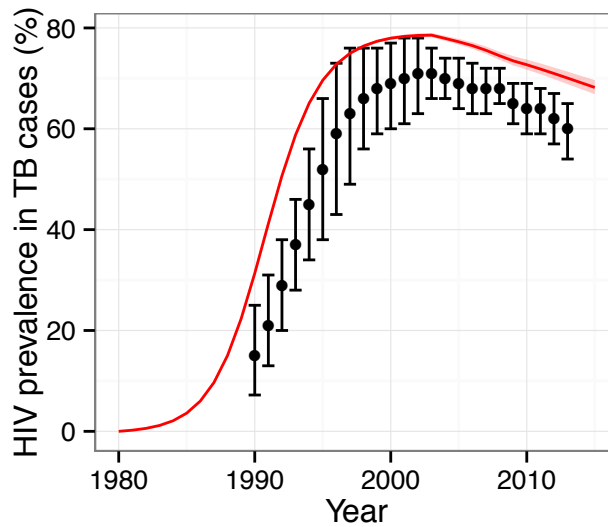


Figure S2.3: Comparison of model output (red) to WHO global TB program estimates of HIV prevalence in TB cases (black) from 1990-2013 [2]. Solid lines display means and shaded regions display 95% quantiles of our posterior predictions.

TB Plots

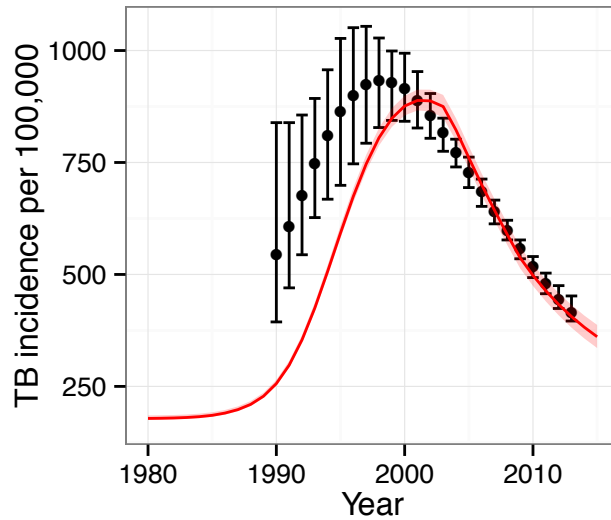


Figure S2.4: Comparison of model output (red) to WHO global TB program estimates of TB incidence (black) from 1990-2013 [2]. Solid lines display means and shaded regions display 95% quantiles of our posterior predictions.

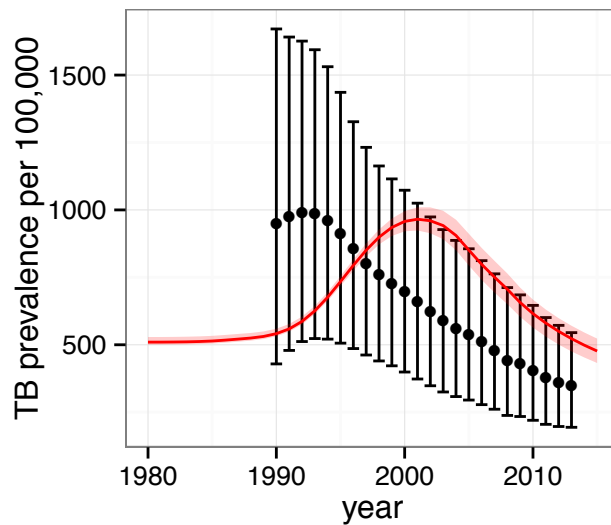


Figure S2.5: Comparison of model output (red) to WHO global TB program estimates of TB prevalence (black) from 1990-2013 [2]. Solid lines display means and shaded regions display 95% quantiles of our posterior predictions.

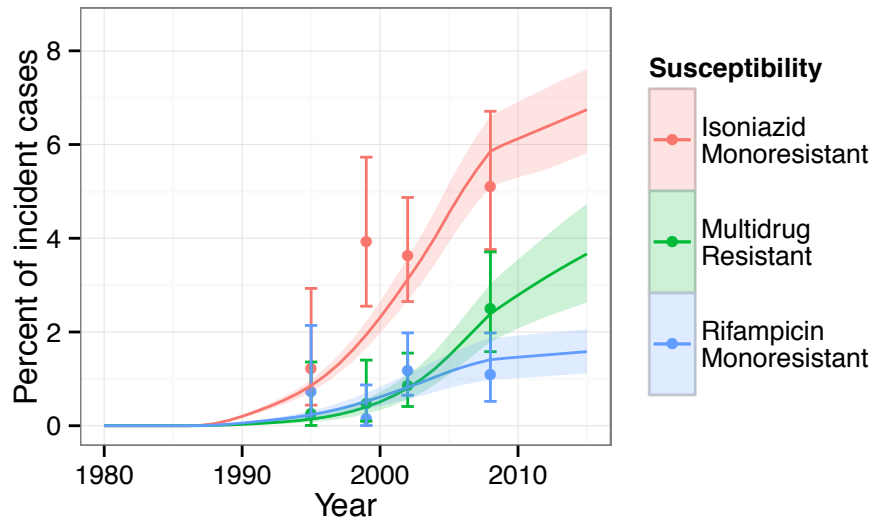


Figure S2.6: Comparison of model output (solid and shaded lines) to the results of the TB drug resistance surveys from 1995, 1999, 2002, and 2008 in Botswana [3]. Solid lines display means and shaded regions display 95% quantiles of our posterior predictions.

Detailed Methods Narrative

To assess the effects of varying IPT duration, we created a deterministic delay differential equation model with compartments representing both TB and HIV states. The model was parameterized to the TB and HIV epidemics in Botswana using Bayesian melding [4, 5].

HIV Model States

The model includes four distinct HIV states: HIV susceptible, infected with undetected HIV, infected with detected HIV and on IPT, and infected with detected HIV, not on IPT (here on, “HIV susceptible,” “HIV undetected,” “on IPT,” and “HIV detected”). The HIV undetected state represents individuals whose HIV status is unknown and who cannot access antiretroviral treatment. To simplify the model, we combine the effects of HIV detection and antiretroviral treatment, such that people with detected HIV experience better outcomes than those whose HIV remains undetected. Within the model, HIV increases the mortality rate, the probability of fast progression among individuals newly infected with TB, and the TB reactivation rate, and reduces the immunity produced by previous TB infection, rate of self cure from active TB, and infectiousness of TB cases per unit time. We assume that the proportion of TB cases detected prior to death or self cure is independent of HIV status; as a result, TB cases with HIV infection are detected faster on average than those without HIV infection.

All individuals enter the model HIV susceptible and are infected with rates reflecting UNAIDS estimates of historical HIV incidence in Botswana (UNAIDS 2015, unpublished data). If infected, they first enter the HIV undetected compartment. Their HIV may be detected either through routine testing or upon presentation for treatment of active TB. We

assume that all people will receive symptom screening for TB upon routine HIV detection and that actively infected individuals detected through such screening will receive treatment. Otherwise, individuals either begin IPT or move directly into the HIV detected class. No individuals revert from detected to undetected HIV. A brief catch-up IPT campaign in the first 6 months of 2017 is modeled to allow 75% of people already receiving ARVs to receive IPT; thereafter, only people initiating ARV treatment are eligible for IPT.

TB Model States

The TB portion of the model includes states for individuals who are TB susceptible, latently infected, actively infected, and on TB treatment. Infections may be fast-progressing, moving individuals from the susceptible class directly to active disease, or slow-progressing, moving individuals from the susceptible class into latency. Latent infections may lead to active infection through reactivation or reinfection. Latency provides partial immunity against reinfection. Individuals with active TB experience increased mortality rates, and may return to latency either through self-cure or treatment. People may receive either first-line treatment or appropriate treatment tailored to their resistance pattern. We assume only first-line treatment is available prior to 2008, and that after 2008 alternative treatments are only available to individuals who have failed their initial treatment course [6]. Both actively infected, untreated individuals and the proportion of treated individuals who fail to achieve treatment success despite surviving therapy contribute to the force of TB infection.

We assume individuals enter the model at age 15. We allow them to have been previously latently infected during childhood with at most 1 TB strain based on the annual risk of infection over the 15 years prior to model entry. The calculations used to estimate

the proportion of individuals entering the model in each latently infected compartments are provided in the parameter table below.

TB Drug Resistance

We include four TB resistance phenotypes: drug susceptible (DS), isoniazid (INH) mono-resistant, rifampicin (RMP) mono-resistant, and multi-drug resistant (MDR). Our model allows for mixed infections with an unlimited number of TB strains during latency, but assumes that progression to active infection acts as a bottleneck with only a single dominant strain surviving and progressing to active disease.

Within the model, each individual is initially infected with only one TB strain, and may be reinfected from the latent compartment with any strain. Upon reinfection, the individual either immediately transitions to active disease with the infecting strain, or enters a latent state in which both strains are present. Theoretically, this process may be repeated any number of times, so that a single latently infected person could contain any number of strains with any pattern of resistance. We simplify the analysis by assuming the progression to active disease acts as a bottleneck, with only the dominant strain surviving and causing disease (similar to [7]). The dominant strain may be probabilistically determined at the time of each infecting event; for this analysis, we assume that the newly infecting strain always dominates any previously existing strains. We also assume that IPT is the only condition under which a non-dominant strain may become dominant, and that this will only occur in individuals with both dominant isoniazid sensitive and non-dominant isoniazid resistant strains. At any given time, each person has at most two strains of interest: the strain that will dominate under normal conditions, and (potentially) a second strain that will dominate under the selective pressure of IPT. We therefore restrict

our latent states to eight resistance classes (see Table 1) and our active states to four resistance classes representing the four strain types. We assume individuals with active infection cannot be reinfected until they are cured and return to latency.

Table S2.1: Description of TB Latency States

		Dominant strain resistance (no IPT)			
		DS	INH-r	RMP-r	MDR
Dominant strain (IPT)	DS	L_s	-	-	-
	INH-r	L_{si}	L_i	L_{ri}	-
	RMP-r	-	-	L_r	-
	MDR	L_{sm}	-	L_{rm}	L_m

Parameter Inference Summary

Uncertain model parameters (see Table 2 below) were inferred using data from the HIV and TB epidemics in Botswana using Bayesian melding [4, 5]. The posterior probability of each parameter set is proportional to the product of the prior probability of each parameter set and the likelihood of the observed data given those parameters. Prior distributions for each parameter were determined based on a review of the literature and are described in more detail in Table 2. We assumed that these parameters were independent except as otherwise specified. The data used to define likelihoods are described in more detail below. We used importance sampling to derive an estimate of the posterior probability distribution for each of the variable parameters.

Likelihoods

This section describes the data and procedures used to define likelihood functions for our calibration procedure.

TB prevalence and incidence

We compared model outputs for TB prevalence with WHO global TB program estimates of TB prevalence per 100,000 in Botswana from 1990-2013 [2]. Following [8], we assumed that the uncertainty around the TB prevalence estimates was distributed normally, with standard deviation estimated from the width of the reported confidence intervals. These standard deviations were used to calculate the likelihood of observing the WHO prevalence estimates given the model parameters. The same procedure was used to derive the likelihood of observing WHO TB incidence estimates for the same years.

HIV parameters

Model estimates of HIV prevalence in TB patients were calculated for 1990-2013 and compared with WHO global TB program estimates [2]. As for TB incidence and prevalence, we assumed uncertainty around these estimates was normally distributed.

Model estimates of HIV prevalence in the general population were calculated for 1990-2013 and compared to UNAIDS estimates of HIV prevalence age 15+ (UNAIDS 2015, unpublished data). The uncertainty was again assumed to be normally distributed and estimated based on the uncertainty from UNAIDS AIDSinfo estimates of HIV prevalence for the same years [1].

We estimated the rate at which people with HIV were started on ARVs from 2003-2009 based on the data reported in [9]. From 2010-2014, we compared model estimates to UNAIDS AIDSinfo estimates of adult coverage of antiretrovirals in Botswana, assuming the uncertainty was normally distributed as above [1].

Drug resistance

The prevalence of rifampicin mono-resistance, isoniazid mono-resistance, and multi-drug resistance among treatment-naive patients were obtained from four drug

resistance surveys among new TB cases in Botswana (from 1995, 1999, 2002, and 2008) [3]. We assumed that survey observations were drawn from a multinomial distribution, with the number of observations given by the number of individuals sampled in each survey. The likelihood of the model parameters was calculated by comparing the proportion of each resistance level among incident TB cases in the model at the time of each survey and the observed probabilities of isoniazid resistance (except MDR), rifampicin resistance (except MDR), and multi-drug resistance from each survey.

Model Initialization

We assume that TB prevalence had reached an equilibrium value in the pre-treatment, pre-HIV era. The inferred parameter “equil_prev” represents the equilibrium prevalence of active TB that we would expect in the absence of TB treatment and HIV. This parameter is then used to derive both the TB transmission parameter and the prevalence of latent TB for a given parameter set. The model is started in 1980 with initial conditions given by these pre-HIV, pre-treatment equilibrium values.

The equations used to relate the equilibrium prevalence of TB to the transmission parameter and prevalence of latent TB are as follows (with parameters as defined in the following parameter tables):

$$\begin{aligned} \dot{S} &= \Lambda e^{-15\beta\left(\frac{I}{N}\right)} - \mu_0 S - \beta S \left(\frac{I}{N}\right) = 0 \\ \dot{L} &= \Lambda \left(1 - e^{-15\beta\left(\frac{I}{N}\right)}\right) + (1 - \rho_0)\beta S \left(\frac{I}{N}\right) - m_0 q_0 \rho_0 \beta L \left(\frac{I}{N}\right) - \tau_0 L - \mu_0 L + \sigma I = 0 \\ \dot{I} &= \rho_0 \beta S \left(\frac{I}{N}\right) + m_0 q_0 \rho_0 \beta L \left(\frac{I}{N}\right) + \tau_0 L - \mu_t I - \sigma I = 0 \\ N &= S + L + I \end{aligned}$$

Implementation

The model was numerically integrated forward from the initial conditions above in R using the function “dede” for delay differential equations in package deSolve.

Initial importance sampling distributions were derived based on the conditional distributions along each variable parameter near the mode of the posterior. These distributions were refined based on the shape of the resulting marginal posterior distributions. Our final results are based on 100,000 initial samples of the importance distributions, followed by 10,000 parameter sets resampled (with replacement) according to the importance weights. Our final marginal posterior distributions for each parameter are provided below. Throughout the paper, we report mean projected outcomes for these 10,000 parameter sets as well as 2.5th and 97.5th percentiles.

Table S2.2: Prior distributions on variable parameters

Parameter	Description	Distribution	Lower (bound if uniform, else 2.5th percentile)	Upper (bound if uniform, else 97.5th percentile)	Median	Citations
<u>General TB and HIV parameters</u>						
equil_prev	TB prevalence at equilibrium before treatment and HIV	uniform(0.005, 0.02)	500/100,000	2000/100,000	1250/100,000	[10, 11]
ac	ARV effectiveness parameter. ac=1: ARVs have no effect ac=0: On ARVs, functionally HIV-	logitnormal(0, 0.707)	0.2	0.8	0.5	[12-15]
z_fixed	rate starting ARVs post-2008	lognormal(-1.092, 0.411)	0.15	0.75	0.34	-
h_m	multiplier on HIV incidence	lognormal(0, 0.114)	0.8	1.25	1	-
<u>TB Treatment Parameters</u>						

Table S2.2 (Continued)

c_{max}	maximum proportion of TB cases entering TB treatment prior to death or self-cure (see c_p in Table 3)	logitnormal(0.793, 0.302)	0.55	0.8	0.69	[2]
ϵ	proportion of treatment failures receiving immediate retreatment	before 2008: 0 from 2008: logitnormal(0, 0.707)	0.2	0.8	0.5	[6]
<u>Resistance Parameters</u>						
a_{sj}	proportion of DS treatment failures who acquire INH mono-resistance	logitnormal(-2.165, 0.397)	0.05	0.2	0.1	[16-18]
a_{sr}	proportion of DS treatment failures who acquire RMP mono-resistance	logitnormal(-3.165, 0.73)	0.01	0.15	0.04	[16-18]
a_{sm}	proportion of DS treatment failures who acquire MDR	logitnormal(-3.165, 0.73)	0.01	0.15	0.04	[16-18]
a_{im}	proportion of INH mono-resistant, 1st line treatment failures who acquire MDR	logitnormal(-0.490, 0.457)	0.2	0.6	0.38	[17, 19]

Table S2.2 (Continued)

a_{rm}	proportion of RMP mono-resistant, 1 st line treatment failures who acquire MDR	logitnormal(1.738, 0.887)	0.5	0.97	0.85	[20]
x_i	transmission fitness of INH-resistant TB strains (relative to DS)	lognormal(-0.081, 0.041)	0.85	1	0.92	[8, 21]
$x_{r,m}$	transmission fitness of RMP mono-resistant TB strains (relative to INH mono-resistant)	logitnormal(1.896, 0.535)	0.7	0.95	0.87	[8, 22, 23]
$x_{m,m}$	transmission fitness of MDR TB strains (relative to RMP mono-resistant)	logitnormal(1.472, 0.751)	0.5	0.95	0.81	[8, 21, 22, 24, 25]
<u>IPT Parameters</u>						
v	Risk ratio: DS reactivations allowed while on IPT	lognormal(-1.263, 0.530)	0.1	0.8	0.28	[26] (positive TST)
a_{lipt}	rate of INH resistance on IPT among people with latent TB	uniform(0, 0.05)	0	0.05	0.025	[27]; smaller than rate of acquired resistance on first line therapy

Table S2.2 (Continued)

γ_{ipt}	Rate of removal of latent TB strains on IPT	uniform(0, 5)	0	5	2.5	[28] 0.5-70% of people are cured by the end of 6 mo therapy
m_{ipt_m}	Susceptibility to reinfection after removal of latent TB strains 1: same as susceptible 0: same as latently infected	uniform(0, 1)	0	1	0.5	

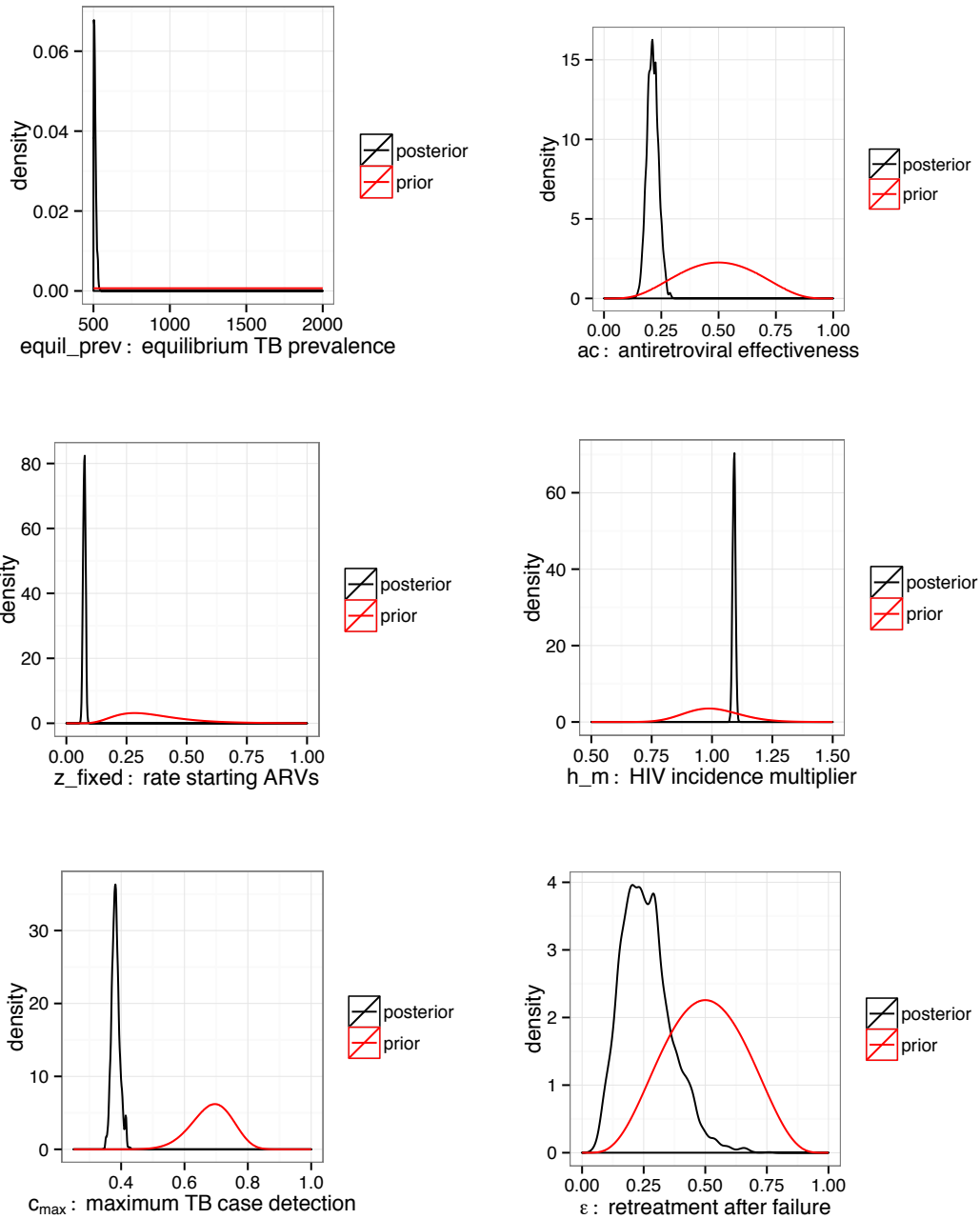


Figure S2.7: Marginal prior and posterior distributions (see also Table 2)

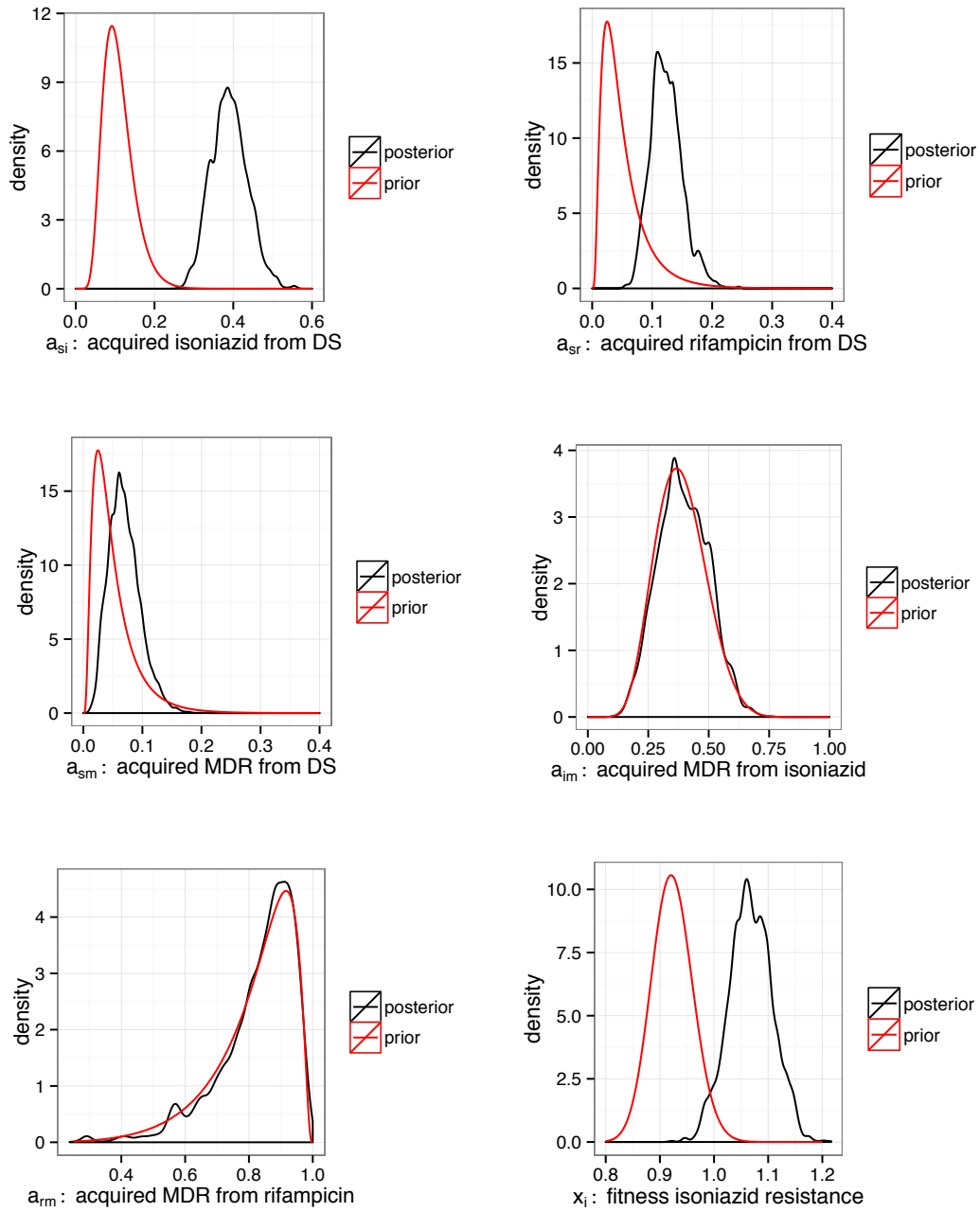


Figure S2.7 (Continued)

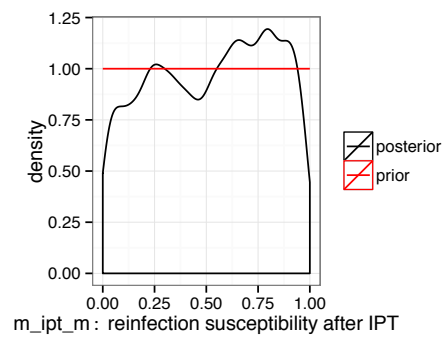
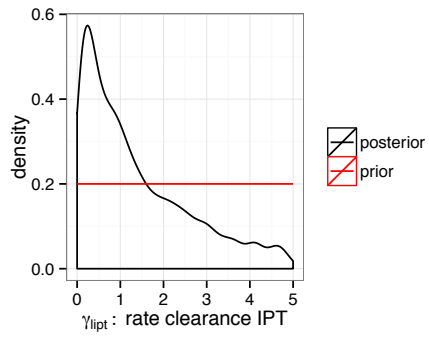
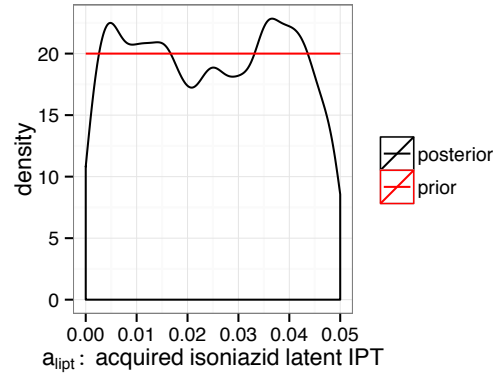
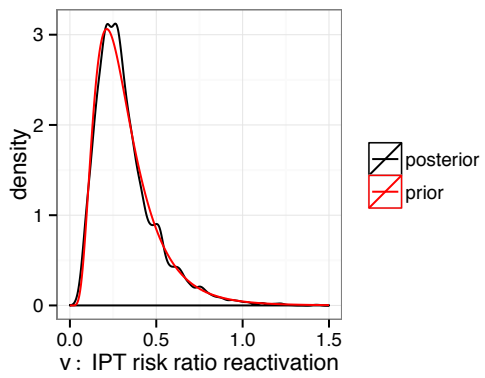
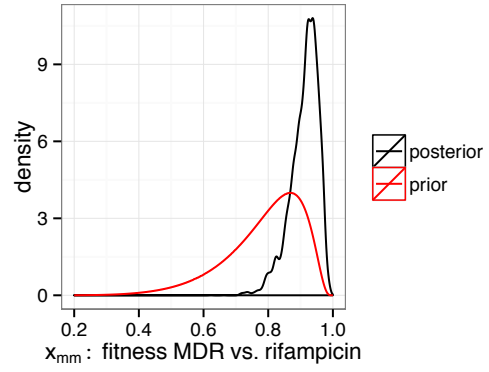
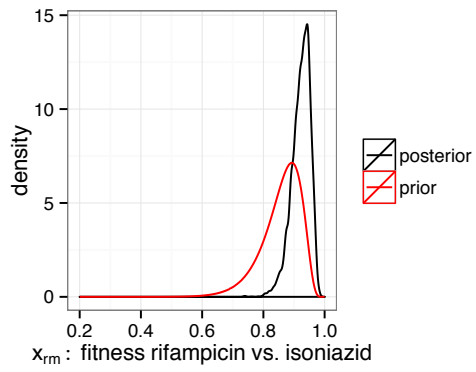


Figure S2.7 (Continued)

Table S2.3: Fixed and derived parameters

Parameter	Description	Value or Calculation	Citations
<u>Transmission Parameters</u>			
β_0	TB transmission parameter (infections per HIV- active TB case per year)	calculated from $equil_prev$	-
b	see β_h	0.65	[29]
β_h	TB transmission parameter (infections per HIV+ active TB case per year)	$b * \beta_0$	-
$\lambda_j(t)$	Force of infection with strain j at time t - see equations for details	-	-
<u>Treatment Success Parameters</u>			

Table S2.3 (Continued)

γ_s	Proportion of DS TB cases cured by 1 st line therapy (conditional on survival)	0.85	[6]
γ_{i1}	Proportion of INH resistant TB cases cured by 1 st line therapy (conditional on survival)	$\gamma_{i1_m} * \gamma_s$	-
γ_{i1_m}	see γ_{i1}	0.85	[19, 30, 31]
γ_{i2}	Proportion of INH resistant TB cases cured by appropriate therapy (conditional on survival)	$rc * \gamma_{i1} + (1-rc) * \gamma_s$	Between treatment success of DS TB and INH resistant TB on 1 st line therapy
rc	see γ_{i2} , γ_{r2} , γ_{m2}	0.25	[19, 32, 33]

Table S2.3 (Continued)

γ_{r1}	Proportion of RMP resistant TB cases cured by 1 st line therapy (conditional on survival)	$\gamma_{r1_m} * \gamma_s$	-
γ_{r1_m}	see γ_{r1}	0.6	[20]; based on use of isoniazid alone
γ_{r2}	Proportion of RMP resistant TB cases cured by appropriate therapy (conditional on survival)	$rc * \gamma_{r1} + (1-rc) * \gamma_s$	Between treatment success of DS TB and RMP-resistant TB on 1 st line therapy
γ_{m1}	Proportion of MDR TB cases cured by 1 st line therapy (conditional on survival)	$\gamma_{m1_m} * \gamma_s$	-
γ_{m1_m}	see γ_{m1}	0.4	[30, 34]

Table S2.3 (Continued)

Y_{m2}	Proportion of INH resistant TB cases cured by appropriate therapy (conditional on survival)	$rc * Y_{m1} + (1-rc) * Y_s$	Between treatment success of DS TB and MDR TB on 1 st line therapy
<u>General HIV parameters</u>			
$h(t)$	HIV infection rate	$h_{-m} \left(\frac{e^{0.55(t-1992.8)}}{1 + e^{0.55(t-1992.8)}} \right) \left(0.0048 + \frac{0.141e^{-0.181(t-1992.8)}}{1 + e^{-0.181(t-1992.8)}} \right)$	double logistic curve fit (by hand) to UNAIDS incidence estimates (2015, unpublished)
z	HIV detection rate	Before 2003: 0 2003-2009: 20,000 people/year After 2009: constant at 80% treated before (non-TB) death	[9]
<u>Model Entry Parameters</u>			
Λ	rate of entry into population age 15+	$1.15 * N(0) * \mu_0$	chosen to keep population size relatively stable

Table S2.3 (Continued)

Λ_s	rate of entry into TB susceptible population	$\Lambda - \Lambda_l$	all who do not enter with latent infection
Λ_l	rate of entry into latently infected	$\Lambda * \left(1 - e^{-\int_{t-15}^t \lambda(w) / N(w) dw} \right)$	entry rate * probability of escaping infection over previous 15 years
Λ_{ls}	rate of entry into population latently infected with DS TB	$\Lambda_l * \left(\frac{\int_{t-15}^t \lambda_s(w) / N(w) dw}{\sum_{j \in \{s,i,r,m\}} \left(\int_{t-15}^t \lambda_j(w) / N(w) dw \right)} \right)$	approximation; based on relative force of infection by each strain
Λ_{li}	rate of entry into population latently infected with INH-resistant TB	$\Lambda_l * \left(\frac{\int_{t-15}^t \lambda_i(w) / N(w) dw}{\sum_{j \in \{s,i,r,m\}} \left(\int_{t-15}^t \lambda_j(w) / N(w) dw \right)} \right)$	approximation; based on relative force of infection by each strain
Λ_{lr}	rate of entry into population latently infected with RMP-resistant TB	$\Lambda_l * \left(\frac{\int_{t-15}^t \lambda_r(w) / N(w) dw}{\sum_{j \in \{s,i,r,m\}} \left(\int_{t-15}^t \lambda_j(w) / N(w) dw \right)} \right)$	approximation; based on relative force of infection by each strain

Table S2.3 (Continued)

Λ_{in}	rate of entry into population latently infected with MDR TB	$\Lambda_l^* \left(\frac{\int_{r-15}^r \lambda_m(w) / N(w) dw}{\sum_{j \in \{s, i, r, m\}} \left(\int_{r-15}^r \lambda_j(w) / N(w) dw \right)} \right)$	approximation; based on relative force of infection by each strain
$N(0)$	initial population size	1,200,000	adult population mid-2000s [35]
<u>Treatment Duration Parameters</u>			
k_1	rate completing first line treatment	12/6	[36]
k_i	rate completing appropriate treatment for INH-resistant disease	12/9	[36]
k_r	rate completing appropriate treatment for RMP-resistant disease	12/18	[36]

Table S2.3 (Continued)

k_m	rate completing appropriate treatment for MDR disease	12/21	[36]
<u>Mortality Parameters</u>			
μ_0	background mortality rate without HIV	0.025	Average life expectancy = 40 years after model entry (55 years old)
μ_u	background mortality rate with undetected HIV	0.085	[37-39]
μ_d	background mortality rate with detected HIV	0.0285	average 35 years, or 5 years shorter than HIV- [12, 40]
μ_t	mortality with active TB, without HIV	0.21	[41]

Table S2.3 (Continued)

μ_{tu}	mortality rate with active TB, with undetected HIV	1	[42, 43]
μ_{td}	mortality rate with active TB, with detected HIV	$ac * \mu_{tu} + (1-ac) * \mu_t$	between no HIV and undetected HIV
μ_{ts_p}	proportion of HIV- people with DS TB who die during 1 st line therapy	0.032	[44]
μ_{ts}	HIV- mortality rate on 1 st line treatment with DS TB	$-\log(1-\mu_{ts_p}) * k_1$	converting proportion to rate
$\mu_{ti1_p_m}$	DS multiplier: HIV- mortality rate with INH-resistant TB	1.15	assumed
μ_{ti1}	HIV- mortality rate on 1 st line treatment with INH-resistant TB	$-\log(1-\mu_{ts_p} * \mu_{ti1_p_m}) * k_1$	converting proportion to rate

Table S2.3 (Continued)

μ_{ti2}	HIV- mortality rate on appropriate therapy for INH-resistant TB	$-\log(1-\mu_{ts_p} * \mu_{tr1_p_m}) * k_i$	assumed same proportion as 1 st line therapy (longer duration, so lower rate)
$\mu_{tr1_p_m}$	DS multiplier: HIV- mortality rate with RMP-resistant TB	2	assumed
μ_{tr1}	HIV- mortality rate on 1 st line treatment with RMP-resistant TB	$-\log(1-\mu_{ts_p} * \mu_{tr1_p_m}) * k_1$	converting proportion to rate
μ_{tr2}	HIV- mortality rate on appropriate therapy for RMP-resistant TB	$-\log(1-\mu_{ts_p} * \mu_{tr1_p_m}) * k_r$	assumed same proportion as 1 st line therapy (longer duration, so lower rate)
$\mu_{tm2_p_m}$	DS multiplier: HIV- mortality rate on appropriate therapy for MDR TB	3	[32, 33]

Table S2.3 (Continued)

μ_{tm2}	HIV- mortality rate on appropriate therapy for MDR TB	$-\log(1-\mu_{ts_p} * \mu_{tm2_p_m}) * k_m$	converting proportion to rate
μ_{ths_p}	proportion of HIV+ people with DS TB who die during 1 st line therapy	0.053	[44-46]
μ_{ths}	HIV+ mortality rate on 1 st line treatment with DS TB	$-\log(1-\mu_{ths_p}) * k_1$	converting proportion to rate
μ_{thi1}	mortality with active INH-resistant TB, on 1 st line treatment, with HIV	$-\log(1-\mu_{ths_p} * \mu_{ti1_p_m}) * k_1$	same multipliers, duration as applied to HIV-
μ_{thi2}	mortality with active INH-resistant TB, on appropriate treatment, with HIV	$-\log(1-\mu_{ths_p} * \mu_{ti1_p_m}) * k_i$	same multipliers, duration as applied to HIV-
μ_{thr1}	mortality with active RMP-resistant TB, on 1 st line treatment, with HIV	$-\log(1-\mu_{ths_p} * \mu_{tr1_p_m}) * k_1$	same multipliers, duration as applied to HIV-

Table S2.3 (Continued)

μ_{thr2}	mortality with active RMP-resistant TB, on appropriate treatment, with HIV	$-\log(1 - \mu_{this_p} * \mu_{tr1_p_m}) * K_r$	same multipliers, duration as applied to HIV-
μ_{tm2}	mortality with active MDR TB, on appropriate treatment, with HIV	$-\log(1 - \mu_{this_p} * \mu_{tm2_p_m}) * K_m$	same multipliers, duration as applied to HIV-
<u>TB Natural History Parameters</u>			
ρ_0	proportion of HIV- people with fast progressing TB upon infection	0.11	[47-50]
ρ_m	HIV- multiplier: proportion of TB fast progressors among people with undetected HIV	2.65	[51-53]
ρ_u	proportion of TB fast progressors among people with undetected HIV	$\rho_m * \rho_0$	-
ρ_d	proportion of TB fast progressors among people with detected HIV	$ac * \rho_u + (1-ac) * \rho_0$	between no HIV and undetected HIV

Table S2.3 (Continued)

q_0	probability the new infecting strain dominates in people who are HIV-	1	assumed; immunity affects transmission not progression
q_u	probability the new infecting strain dominates in people with undetected HIV	1	assumed
q_d	probability the new infecting strain dominates in people with detected HIV	1	assumed
r	probability infecting strain replaces subdominant strain, given it does not dominate	0.5	assumed (no effect when $q=1$)
τ_0	TB reactivation rate, among people without HIV	0.0003	[47-50]
τ_u	TB reactivation rate, among people with undetected HIV	0.03	[14, 43, 54]

Table S2.3 (Continued)

τ_d	TB reactivation rate, among people with detected HIV	$ac*\tau_u + (1-ac)*\tau_0$	between no HIV and undetected HIV
σ	rate of TB self-cure among people without HIV	0.14	[41]
σ_d	rate of TB self-cure among people with detected HIV	$(1-ac)*\sigma$	assuming self cure rate is 0 for undetected HIV
m_u	susceptibility to reinfection, undetected HIV	0.35	[15, 55-57]
m_0_m	relative susceptibility to reinfection, HIV- (multiplier to m_u)	0.75	[47, 49, 50, 57, 58]
m_0	relative susceptibility to TB infection after first infection, among HIV- people	$m_0_m*m_u$	-

Table S2.3 (Continued)

m_d	relative susceptibility to TB infection after first infection, with detected HIV	$ac * m_u + (1-ac) * m_0$	between no HIV and undetected HIV
<u>TB case detection rates</u>			
c_{first}	date TB treatment started	1986	[6] introduction of short-course chemotherapy
c_p	proportion entering TB treatment before death or self-cure	Before c_{first} : 0 c_{first} -2005: $c_{max}/(2005 - c_{first}) * (t - c_{first})$ After 2005: c_{max}	[2] linear trend line fit to Botswana CDR before plateau in 2005
c_0	rate entering TB treatment for people without HIV	$c_p(\mu_t + \sigma)/(1 - c_p)$	converting to rate
c_u	rate entering TB treatment for people with undetected HIV (not from HIV detection)	$c_p * \mu_{tu}/(1 - c_p) - \epsilon_i * z$	converting to rate

Table S2.3 (Continued)

c_d	rate entering TB treatment for people with detected HIV (including on IPT)	$c_p(\mu_{td} + \sigma_d)/(1 - c_p)$	converting to rate
ϵ_i	proportion of active TB disease that is detected upon HIV detection	0.79	sensitivity of symptom screening from [59]
f_i	proportion of patients whose INH resistance is undetected prior to initial treatment	1	assumed
f_r	proportion of patients whose RMP resistance is undetected prior to initial treatment	1	assumed
f_m	proportion of patients whose multi-drug resistance is undetected prior to initial treatment	1	assumed
g_i	proportion of patients whose INH resistance is not detected prior to immediate retreatment after initial failure	0	assumed

Table S2.3 (Continued)

g_r	proportion of patients whose RMP resistance is not detected prior to immediate retreatment after initial failure	0	assumed
g_m	proportion of patients whose multi-drug resistance is not prior to immediate retreatment after initial failure	0	assumed
<u>Resistance Parameters</u>			
x_r	transmission fitness of RMP-resistant TB strains (relative to DS)	$x_r * x_{r,m}$	-
x_m	transmission fitness of MDR TB strains (relative to DS)	$x_r * x_{m,m}$	-
<u>IPT parameters</u>			
μ_i	mortality rate with detected HIV, on IPT	$0.0006 + \mu_d$	[26]

Table S2.3 (Continued)

μ_{ti}	mortality rate with active TB, with detected HIV, on IPT	μ_{thr1}	assumed same as 1 st line treatment of RMP-resistant TB
θ_s	proportion of TB susceptibles who receive IPT upon HIV detection (>1 dose)	θ_i	WHO recommends not requiring TST prior to IPT initiation [60]
θ_l	proportion of people with latent TB who receive IPT upon HIV detection (>1 dose)	Before 2004: 0 2004-2008: 0.9 2008-2017: 0 2017 on (IPT scenarios): 0.9	assumed
ϕ	proportion of people who start IPT after successfully finishing treatment	0	assumed
w	rate of IPT completion/dropout	2.147 (6 month), 0.147 (realistic continuous), or 0 (ideal continuous)	dropout based on [61]

Table S2.3 (Continued)

e	Rate allowed to start IPT from detected HIV compartment	Pre-2017: 0 2017-2017.5: 2.77 Post 2017.5: 0 (75% people already detected may start IPT)	assumed
---	---	---	---------

Effect of assumed susceptibility to reinfection on the relationship between IPT and drug resistance

As a secondary analysis, we explored how the assumed susceptibility to TB reinfection might affect the projected relationship between IPT and drug resistance. Previous papers have shown that competition between drug sensitive and drug resistant strains is the major mechanism through which IPT might increase the prevalence of drug resistance [7, 62]. The degree of immunity after initial TB infection is a likely major driver of competition, and unlike other parameters such as fitness costs of resistance [57], its potential impact on resistance resulting from IPT has not yet been explored.

For Figure S2.8, we set the susceptibility to TB reinfection to 30%, 60%, or 90% among people uninfected with HIV, and 90% for PLHIV. All other parameters were re-estimated for these different reinfection values. The incidence of isoniazid resistant TB is given as isoniazid mono-resistant plus MDR. In the absence of IPT, overall TB incidence continues to decline for all values of assumed susceptibility to reinfection, following the trends seen in Figure 2.2 of the main text. Increasing durations of IPT do appear to increase the incidence of isoniazid resistant TB. However, the extent to which this occurs varies depending on the assumed susceptibility to reinfection. If we assume susceptibility to reinfection is high (90%), the increase in incidence of isoniazid resistance resulting from IPT is negligible even for perfect lifelong IPT. If we assume susceptibility to reinfection is low (30%), the effect of IPT duration on the incidence of isoniazid resistant TB is more noticeable. However, in this context of declining transmission, the increase in

isoniazid resistant TB resulting from IPT is still minor compared to the corresponding decrease in isoniazid sensitive TB. As a result, the incidence of overall TB through 2050 decreases with increasing IPT duration regardless of the assumed susceptibility to reinfection.

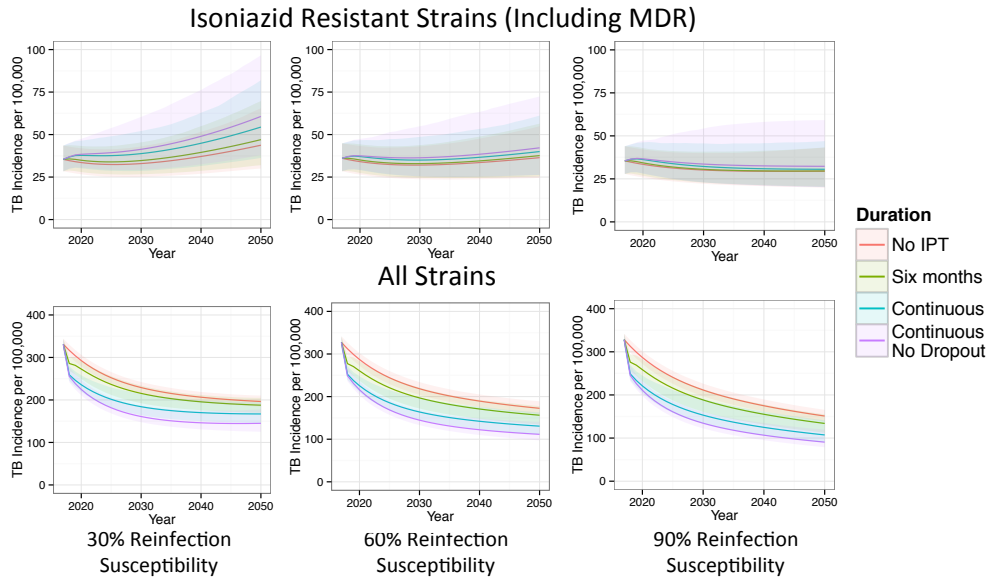


Figure S2.8: Incidence of isoniazid resistant and overall TB by assumed susceptibility to reinfection

Figure S2.9 shows how the effect of varying IPT duration depends on the assumed susceptibility to reinfection in the context of higher transmission. To create this figure, we added a multiplier to the transmission parameter after 2017 that would result in a prevalence of isoniazid resistant TB of approximately 150 per 100,000 in the absence of IPT. The applied multipliers were 1.85 for 30% susceptibility to reinfection, 1.4 for 60% susceptibility to reinfection, and 1.35 for 90% susceptibility to reinfection, reflecting the differences in the inferred parameters for each value.

As in the low transmission scenario, longer IPT durations increase the prevalence of isoniazid resistance for low and moderate values of susceptibility to reinfection. There is no observable effect of IPT duration on resistance of isoniazid when the assumed susceptibility to reinfection is high (90%). For all values of the susceptibility to reinfection, IPT produces an initial decrease in the overall incidence of TB, again as seen in the low transmission setting. However, when susceptibility to reinfection is low (30%), this drop in overall TB incidence is short-lived. In this relatively high immunity, high transmission scenario, the decline in isoniazid sensitive TB cases resulting from IPT is quickly counteracted by the corresponding increase in isoniazid resistant cases, such that by 2035 the overall incidence of TB is the same or slightly higher for longer durations of IPT.

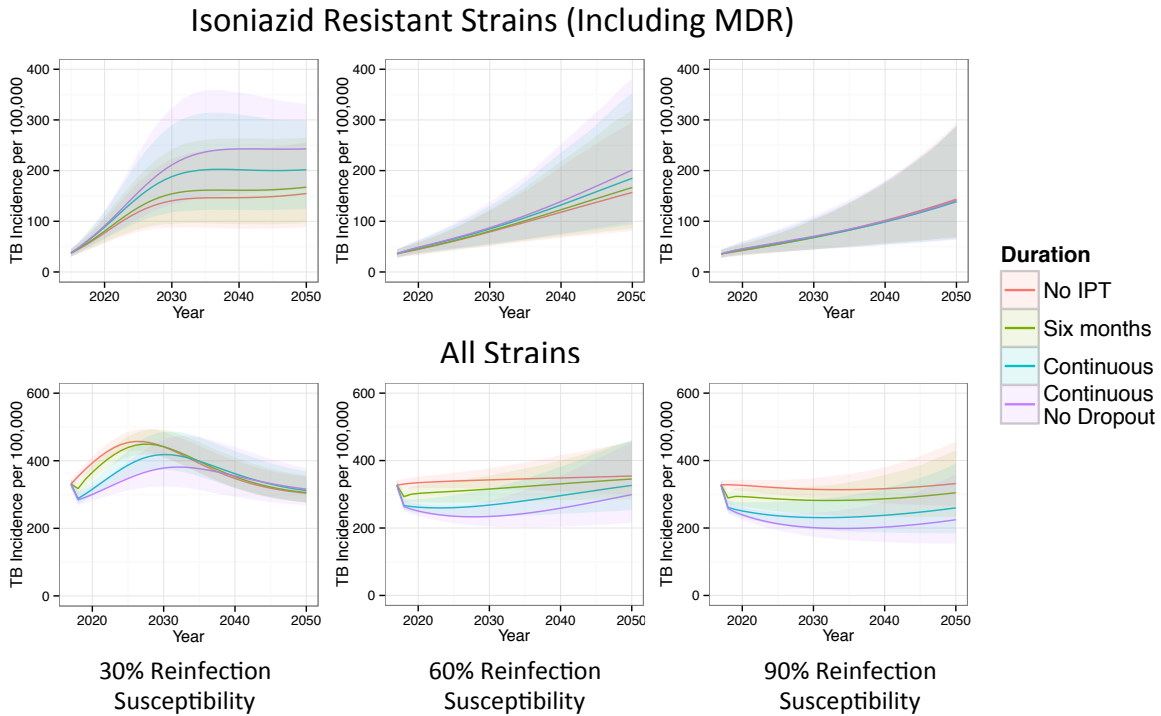


Figure S2.9: Incidence of isoniazid resistant and overall TB by assumed susceptibility to re-infection, assuming greater transmission

In summary, IPT is predicted to have a greater impact on the incidence of isoniazid resistant TB when initial TB infection provides strong protection against future infection. This difference is less likely to be clinically relevant in the context of a declining epidemic.

Model equations

```
# R code containing model equations
# Does not include time dependent parameters
# Can be run via R function "dede" from package deSolve

IPT_model_mixed <- function(times, yinit, pars) {
  with(as.list(c(yinit,pars)), {

    #####
    # Sums
    #####

    Ln = Ln_s + Ln_si + Ln_sm + Ln_r + Ln_ri + Ln_rm + Ln_i + Ln_m;
    Lu = Lu_s + Lu_si + Lu_sm + Lu_r + Lu_ri + Lu_rm + Lu_i + Lu_m;
    Lipt = Lipt_s + Lipt_i + Lipt_r + Lipt_m;
    Ld = Ld_s + Ld_si + Ld_sm + Ld_r + Ld_ri + Ld_rm + Ld_i + Ld_m;

    ln = ln_s + ln_r + ln_i + ln_m;
    lu = lu_s + lu_r + lu_i + lu_m;
    lipt = lipt_s + lipt_r + lipt_i + lipt_m;
    ld = ld_s + ld_r + ld_i + ld_m;

    T1n = T1n_s + T1n_r + T1n_i + T1n_m;
    T1d = T1d_s + T1d_r + T1d_i + T1d_m;

    T2n = T2n_r + T2n_i + T2n_m;
    T2d = T2d_r + T2d_i + T2d_m;

    N = Sn + Su + Sipt + Sd + Ln + Lu + Lipt + Ld +
        ln + lu + lipt + ld +
        T1n + T1d + T2n + T2d + Sipt_postipt + Sd_postipt;

    N_hiv = Su + Sipt + Sd + Lu + Lipt + Ld +
        lu + lipt + ld +
        T1d + T2d + Sipt_postipt + Sd_postipt;

    #####
    # Force of infection by resistance type
    #####

    beta_h = b*beta_0;

    lambda_s = (beta_h*(lu_s + lipt_s + ld_s + (1-gamma_s)*T1d_s) +
beta_0*(ln_s + (1-gamma_s)*T1n_s))/N;

    lambda_i = x_i*(beta_h*(lu_i + lipt_i + ld_i + (1-gamma_i1)*T1d_i +
(1-gamma_i2)*T2d_i) + beta_0*(ln_i + (1-gamma_i1)*T1n_i +
(1-gamma_i2)*T2n_i))/N;

    lambda_r = x_r*(beta_h*(lu_r + lipt_r + ld_r + (1-gamma_r1)*T1d_r +
(1-gamma_r2)*T2d_r) + beta_0*(ln_r + (1-gamma_r1)*T1n_r +
(1-gamma_r2)*T2n_r))/N;
```

```

lambda_m = x_m*(beta_h*(lu_m + lipt_m + ld_m +
(1-gamma_m1)*T1d_m + (1-gamma_m2)*T2d_m) +
beta_0*(ln_m + (1-gamma_m1)*T1n_m + (1-gamma_m2)*T2n_m ))/N;

lambda = lambda_s + lambda_i + lambda_r + lambda_m;

#####
# Recruitment rate (age 15+)
#####

dCum_ARI = lambda; # force of infection per capita
dCum_ARI_s = lambda_s;
dCum_ARI_r = lambda_r;
dCum_ARI_i = lambda_i;
dCum_ARI_m = lambda_m;

year_15 = 1995 # assume starting code in 1980

# Cum_ARI is variable 54
if (times>year_15) { # if have run model for >15 years
  # latent infections determined by force of infection over previous 15 years
  Lambda_l = Lambda*(1-exp(-(Cum_ARI - lagvalue(times-15,54))))
  Lambda_s = Lambda-Lambda_l
  prop_s = Cum_ARI_s - lagvalue(times-15,55)
  prop_r = Cum_ARI_r - lagvalue(times-15,56)
  prop_i = Cum_ARI_i - lagvalue(times-15,57)
  prop_m = Cum_ARI_m - lagvalue(times-15,58)
} else {
  # assume were at equilibrium prevalence before starting code in 1980
  Lambda_l = Lambda*(1-exp(-(Cum_ARI +
(year_15-times)*equil_prev*beta_0)))
  Lambda_s = Lambda-Lambda_l
  prop_s = Cum_ARI_s + (year_15-times)*equil_prev*beta_0
  prop_r = Cum_ARI_r # no resistance prior to 1980
  prop_i = Cum_ARI_i
  prop_m = Cum_ARI_m
}

tot_prop <- prop_s + prop_r + prop_i + prop_m

# Assume everyone enters with only one strain, proportional to the
# amount that they have seen each
if (prop_s > 0) {
  Lambda_ls <- prop_s/tot_prop*Lambda_l
} else {Lambda_ls<-0
}
if (prop_i > 0) {
  Lambda_li <- prop_i/tot_prop*Lambda_l
} else {Lambda_li=0
}
if (prop_r > 0) {
  Lambda_lr <- prop_r/tot_prop*Lambda_l
} else {Lambda_lr=0
}

```

```

}
  if (prop_m > 0) {
    Lambda_lm <- prop_m/tot_prop*Lambda_l
      } else {Lambda_lm=0
}

#####
# TB susceptibles
#####

dSn = Sn*(-lambda - mu_0 - h) + Lambda_s

dSu = Su*(-lambda - mu_u - z) + h*Sn;

dSipt = Sipt*(-lambda_i - lambda_m - mu_i - w) +
theta_s*z*Su + theta_s*e*Sd;

dSd = Sd*(-lambda - mu_d) + (1 - theta_s)*z*Su +
w*Sipt - theta_s*e*Sd;

# Strains cleared through IPT - also calling "S"

dSipt_postipt = gamma_lipt*(Lipt_s+Lipt_r) +
Sipt_postipt*(-m_ipt*lambda_i - m_ipt*lambda_m - mu_i - w) +
theta_s*e*Sd_postipt;

dSd_postipt = Sd_postipt*(-m_ipt*lambda - mu_d) +
w*Sipt_postipt - theta_s*e*Sd_postipt;

#####
# TB latently infected
#####

# HIV uninfected

dLn_s = Lambda_ls + (1-rho_0)*Sn*lambda_s +
m_0*q_0*(Ln_s*(-lambda_r - rho_0*lambda_s) +
(1-rho_0)*Ln_r*lambda_s) + gamma_s*k_1*T1n_s + sigma*ln_s +
Ln_s*(-tau_0 - mu_0 - h - m_0*(lambda_m + lambda_i));

dLn_si = Ln_si*(-tau_0 - mu_0 - h) +
m_0*q_0*(Ln_si*(-lambda_r - lambda_i - lambda_m - rho_0*lambda_s) +
(1-rho_0)*(Ln_i + Ln_ri)*lambda_s) +
m_0*(1-q_0)*(-r*Ln_si*lambda_m + lambda_i*(Ln_s + r*Ln_sm));

dLn_sm = Ln_sm*(-tau_0 - mu_0 - h) +
m_0*q_0*(Ln_sm*(-lambda_r - lambda_i - lambda_m - rho_0*lambda_s) +
(1-rho_0)*(Ln_m + Ln_rm)*lambda_s) +
m_0*(1-q_0)*(-r*Ln_sm*lambda_i + lambda_m*(Ln_s + r*Ln_si));

dLn_r = Lambda_lr + (1-rho_0)*Sn*lambda_r + gamma_r2*k_r*T2n_r -
m_0*Ln_r*(lambda_m + lambda_i) +
m_0*q_0*(Ln_r*(-lambda_s - rho_0*lambda_r) + (1-rho_0)*Ln_s*lambda_r) +

```

$$Ln_r*(-tau_0 - mu_0 - h) + sigma*ln_r + gamma_r1*k_1*T1n_r;$$

$$dLn_{ri} = Ln_{ri}*(-tau_0 - mu_0 - h) + m_0*q_0*(Ln_{ri}*(-lambda_s - lambda_i - lambda_m - rho_0*lambda_r) + (1-rho_0)*(Ln_i + Ln_{si})*lambda_r) + m_0*(1-q_0)*(-r*Ln_{ri}*lambda_m + lambda_i*(Ln_r + r*Ln_{rm}));$$

$$dLn_{rm} = Ln_{rm}*(-tau_0 - mu_0 - h) + m_0*q_0*(Ln_{rm}*(-lambda_s - lambda_i - lambda_m - rho_0*lambda_r) + (1-rho_0)*(Ln_m + Ln_{sm})*lambda_r) + m_0*(1-q_0)*(-r*Ln_{rm}*lambda_i + lambda_m*(Ln_r + r*Ln_{ri}));$$

$$dLn_i = Lambda_{li} + (1-rho_0)*Sn*lambda_i + m_0*q_0*((1-rho_0)*(Ln - Ln_i)*lambda_i + gamma_{i2}*k_i*T2n_i + Ln_i*(-lambda_s - lambda_r - lambda_m - rho_0*lambda_i)) + Ln_i*(-tau_0 - mu_0 - h) + sigma*ln_i + gamma_{i1}*k_1*T1n_i;$$

$$dLn_m = Lambda_{lm} + (1-rho_0)*Sn*lambda_m + m_0*q_0*((1-rho_0)*(Ln - Ln_m)*lambda_m + Ln_m*(-lambda_s - lambda_i - lambda_r - rho_0*lambda_m)) + Ln_m*(-tau_0 - mu_0 - h) + sigma*ln_m + gamma_{m1}*k_1*T1n_m + gamma_{m2}*k_m*T2n_m;$$

HIV undetected

$$dLu_s = (1-rho_u)*Su*lambda_s - m_u*Lu_s*(lambda_i + lambda_m) + m_u*q_u*(Lu_s*(-lambda_r - rho_u*lambda_s) + (1-rho_u)*Lu_r*lambda_s) + Lu_s*(-tau_u - mu_u - z) + h*Ln_s;$$

$$dLu_{si} = Lu_{si}*(-tau_u - mu_u - z) + h*Ln_{si} + m_u*q_u*(Lu_{si}*(-lambda_r - lambda_i - lambda_m - rho_u*lambda_s) + (1-rho_u)*(Lu_i + Lu_{ri})*lambda_s) + m_u*(1-q_u)*(-r*Lu_{si}*lambda_m + lambda_i*(Lu_s + r*Lu_{sm}));$$

$$dLu_{sm} = Lu_{sm}*(-tau_u - mu_u - z) + h*Ln_{sm} + m_u*q_u*(Lu_{sm}*(-lambda_r - lambda_i - lambda_m - rho_u*lambda_s) + (1-rho_u)*(Lu_m + Lu_{rm})*lambda_s) + m_u*(1-q_u)*(-r*Lu_{sm}*lambda_i + lambda_m*(Lu_s + r*Lu_{si}));$$

$$dLu_r = (1-rho_u)*Su*lambda_r - m_u*Lu_r*(lambda_m + lambda_i) + m_u*q_u*(Lu_r*(-lambda_s - rho_u*lambda_r) + (1-rho_u)*Lu_s*lambda_r) + Lu_r*(-tau_u - mu_u - z) + h*Ln_r;$$

$$dLu_{ri} = Lu_{ri}*(-tau_u - mu_u - z) + m_u*q_u*(Lu_{ri}*(-lambda_s - lambda_i - lambda_m - rho_u*lambda_r) + (1-rho_u)*(Lu_i + Lu_{si})*lambda_r) + h*Ln_{ri} + m_u*(1-q_u)*(-r*Lu_{ri}*lambda_m + lambda_i*(Lu_r + r*Lu_{rm}));$$

$$dLu_{rm} = Lu_{rm}*(-tau_u - mu_u - z) + m_u*q_u*(Lu_{rm}*(-lambda_s - lambda_i - lambda_m - rho_u*lambda_r) + (1-rho_u)*(Lu_m + Lu_{sm})*lambda_r) + h*Ln_{rm} + m_u*(1-q_u)*(-r*Lu_{rm}*lambda_i + lambda_m*(Lu_r + r*Lu_{ri}));$$

$$dLu_i = (1-rho_u)*Su*lambda_i + Lu_i*(-tau_u - mu_u - z) + h*Ln_i + m_u*q_u*((1-rho_u)*(Lu - Lu_i)*lambda_i +$$

```

Lu_i*(-lambda_s - lambda_r - lambda_m - rho_u*lambda_i));

dLu_m = (1-rho_u)*Su*lambda_m + Lu_m*(-tau_u - mu_u - z) + h*Ln_m +
m_u*q_u*((1-rho_u)*(Lu - Lu_m)*lambda_m +
Lu_m*(- lambda_s - lambda_i - lambda_r - rho_u*lambda_m)) ;

# on IPT
dLipt_s = -m_d*Lipt_s*(lambda_m +lambda_i) -
v*tau_d*Lipt_s - mu_i*Lipt_s + gamma_ipt*lipt_s -
a_lipt*Lipt_s + phi*gamma_s*k_1*T1d_s +
theta_l*z*Lu_s - w*Lipt_s - gamma_lipt*Lipt_s + theta_l*e*Ld_s;

dLipt_r = -m_d*Lipt_r*(lambda_m +lambda_i) - v*tau_d*Lipt_r -
mu_i*Lipt_r + gamma_ipt*lipt_r - a_lipt*Lipt_r +
phi*gamma_r1*k_1*T1d_r + theta_l*z*Lu_r - w*Lipt_r -
gamma_lipt*Lipt_r + phi*gamma_r2*k_r*T2d_r + theta_l*e*Ld_r;

dLipt_i = (1-rho_d)*Sipt*lambda_i +
(1-rho_d)*m_ipt*Sipt_postipt*lambda_i +
m_d*q_d*(1-rho_d)*(Lipt_r + Lipt_s + Lipt_m)*lambda_i +
m_d*(1-q_d)*(Lipt_r + Lipt_s)*lambda_i - m_d*q_d*Lipt_i*lambda_m -
m_d*q_d*rho_d*Lipt_i*lambda_i - tau_d*Lipt_i - mu_i*Lipt_i +
sigma_d*lipt_i + a_lipt*Lipt_s + phi*gamma_i1*k_1*T1d_i +
theta_l*z*(Lu_i + Lu_si + Lu_ri) - w*Lipt_i + theta_l*e*(Ld_i + Ld_si + Ld_ri);

dLipt_m = (1-rho_d)*Sipt*lambda_m +
(1-rho_d)*m_ipt*Sipt_postipt*lambda_m +
m_d*q_d*(1-rho_d)*(Lipt_r + Lipt_s + Lipt_i)*lambda_m +
m_d*(1-q_d)*(Lipt_r + Lipt_s)*lambda_m - m_d*q_d*Lipt_m*lambda_i -
m_d*q_d*rho_d*Lipt_m*lambda_m - tau_d*Lipt_m - mu_i*Lipt_m +
sigma_d*lipt_m + a_lipt*Lipt_r + phi*gamma_m1*k_1*T1d_m +
theta_l*z*(Lu_m + Lu_sm + Lu_rm) -
w*Lipt_m + theta_l*e*(Ld_m + Ld_sm + Ld_rm);

# HIV detected

dLd_s = (1-rho_d)*Sd*lambda_s - m_d*Ld_s*(lambda_i+lambda_m) +
(1-rho_d)*m_ipt*Sd_postipt*lambda_s + w*Lipt_s - theta_l*e*Ld_s +
m_d*q_d*(Ld_s*(-lambda_r - rho_d*lambda_s) +
(1-rho_d)*Ld_r*lambda_s) + Ld_s*(-tau_d - mu_d) +
sigma_d*ld_s + k_1*(1-phi)*gamma_s*T1d_s + (1 - theta_l)*z*Lu_s;

dLd_si = (1 - theta_l)*z*Lu_si - theta_l*e*Ld_si +
m_d*q_d*(Ld_si*(-lambda_r - lambda_i - lambda_m - rho_d*lambda_s) +
(1-rho_d)*(Ld_i+Ld_ri)*lambda_s) + Ld_si*(-tau_d - mu_d) +
m_d*(1-q_d)*(-r*Ld_si*lambda_m + lambda_i*(Ld_s + r*Ld_sm)) ;

dLd_sm = (1 - theta_l)*z*Lu_sm - theta_l*e*Ld_sm +
m_d*q_d*(Ld_sm*(-lambda_r - lambda_i - lambda_m - rho_d*lambda_s) +
(1-rho_d)*(Ld_m+Ld_rm)*lambda_s) + Ld_sm*(-tau_d - mu_d) +
m_d*(1-q_d)*(-r*Ld_sm*lambda_i + lambda_m*(Ld_s + r*Ld_si)) ;

dLd_r = (1-rho_d)*Sd*lambda_r - m_d*Ld_r*(lambda_m+lambda_i) +
(1-rho_d)*m_ipt*Sd_postipt*lambda_r +
m_d*q_d*(Ld_r*(-lambda_s - rho_d*lambda_r) +

```

$$(1-\rho_d)*Ld_s*\lambda_r) + (1-\phi)*\gamma_{r2}*k_r*T2d_r + \\ Ld_r*(-\tau_d - \mu_d) + \sigma_d*Id_r + k_1*(1-\phi)*\gamma_{r1}*T1d_r + \\ (1 - \theta_l)*z*Lu_r + w*Lipt_r - \theta_l*e*Ld_r;$$

$$dLd_{ri} = (1 - \theta_l)*z*Lu_{ri} - \theta_l*e*Ld_{ri} + \\ m_d*q_d*(Ld_{ri}*(-\lambda_s - \lambda_i - \lambda_m - \rho_d*\lambda_r) + \\ (1-\rho_d)*(Ld_i+Ld_{si})*\lambda_r) + Ld_{ri}*(-\tau_d - \mu_d) + \\ m_d*(1-q_d)*(-r*Ld_{ri}*\lambda_m + \lambda_i*(Ld_r + r*Ld_{rm}));$$

$$dLd_{rm} = (1 - \theta_l)*z*Lu_{rm} - \theta_l*e*Ld_{rm} + \\ m_d*q_d*(Ld_{rm}*(-\lambda_s - \lambda_i - \lambda_m - \rho_d*\lambda_r) + \\ (1-\rho_d)*(Ld_m+Ld_{sm})*\lambda_r) + Ld_{rm}*(-\tau_d - \mu_d) + \\ m_d*(1-q_d)*(-r*Ld_{rm}*\lambda_i + \lambda_m*(Ld_r + r*Ld_{ri}));$$

$$dLd_i = (1-\rho_d)*Sd*\lambda_i + (1 - \theta_l)*z*Lu_i + \\ (1-\rho_d)*m_{ipt}*Sd_{postipt}*\lambda_i + \\ m_d*q_d*((1-\rho_d)*(Ld - Ld_i)*\lambda_i + \\ Ld_i*(-\lambda_s - \lambda_r - \lambda_m - \rho_d*\lambda_i)) + \\ Ld_i*(-\tau_d - \mu_d) + \sigma_d*Id_i + k_1*(1-\phi)*\gamma_{i1}*T1d_i + \\ w*Lipt_i + \gamma_{i2}*k_i*T2d_i - \theta_l*e*Ld_i;$$

$$dLd_m = (1-\rho_d)*Sd*\lambda_m + (1 - \theta_l)*z*Lu_m + \\ (1-\rho_d)*m_{ipt}*Sd_{postipt}*\lambda_m + \\ m_d*q_d*((1-\rho_d)*(Ld - Ld_m)*\lambda_m + \\ Ld_m*(-\lambda_s - \lambda_i - \lambda_r - \rho_d*\lambda_m)) + \\ Ld_m*(-\tau_d - \mu_d) + \sigma_d*Id_m + k_1*(1-\phi)*\gamma_{m1}*T1d_m + \\ w*Lipt_m + \gamma_{m2}*k_m*T2d_m - \theta_l*e*Ld_m;$$

Infectious
#####

HIV negative

$$dln_s = \lambda_s*\rho_0*(S_n + m_0*q_0*Ln) + \\ \tau_0*(Ln_s + Ln_{si} + Ln_{sm}) + ln_s*(-\mu_t - c_0 - \sigma - h) + \\ (1-\epsilon)*k_1*(1-a_{si}-a_{sr}-a_{sm})*(1-\gamma_s)*T1n_s;$$

$$dln_r = \lambda_r*\rho_0*(S_n + m_0*q_0*Ln) + \\ \tau_0*(Ln_r + Ln_{ri} + Ln_{rm}) + ln_r*(-\mu_t - c_0 - \sigma - h) + \\ (1-\epsilon)*k_1*(a_{sr}*(1-\gamma_s)*T1n_s + \\ (1-a_{rm})*(1-\gamma_{r1})*T1n_r) + \\ (1-\epsilon)*(1-a_{si})*(1-\gamma_{r2})*k_r*T2n_r;$$

$$dln_i = \lambda_i*\rho_0*(S_n + m_0*q_0*Ln) + \tau_0*Ln_i + \\ ln_i*(-\mu_t - c_0 - \sigma - h) + \\ (1-\epsilon)*k_1*(a_{si}*(1-\gamma_s)*T1n_s + \\ (1-a_{im})*(1-\gamma_{i1})*T1n_i) + \\ (1-\epsilon)*(1-a_{sr})*(1-\gamma_{i2})*k_i*T2n_i;$$

$$dln_m = \lambda_m*\rho_0*(S_n + m_0*q_0*Ln) + \tau_0*Ln_m + \\ ln_m*(-\mu_t - c_0 - \sigma - h) + \\ (1-\epsilon)*k_1*((1-\gamma_{m1})*T1n_m + a_{sm}*(1-\gamma_s)*T1n_s + \\ a_{rm}*(1-\gamma_{r1})*T1n_r + a_{im}*(1-\gamma_{i1})*T1n_i) + \\ (1-\epsilon)*a_{sr}*(1-\gamma_{i2})*k_i*T2n_i +$$

$$(1-\epsilon)*a_{si}*(1-\gamma_{r2})*k_r*T2n_r +$$

$$(1-\epsilon)*(1-\gamma_{m2})*k_m*T2n_m;$$

HIV undetected

$$d_{lu_s} = \lambda_s * \rho_u * (S_u + m_u * q_u * Lu) +$$

$$\tau_u * (Lu_s + Lu_{si} + Lu_{sm}) + lu_s * (-\mu_{tu} - c_u - z) + h * \ln_s;$$

$$d_{lu_r} = \lambda_r * \rho_u * (S_u + m_u * q_u * Lu) +$$

$$\tau_u * (Lu_r + Lu_{ri} + Lu_{rm}) + lu_r * (-\mu_{tu} - c_u - z) + h * \ln_r;$$

$$d_{lu_i} = \lambda_i * \rho_u * (S_u + m_u * q_u * Lu) + \tau_u * Lu_i +$$

$$lu_i * (-\mu_{tu} - c_u - z) + h * \ln_i;$$

$$d_{lu_m} = \lambda_m * \rho_u * (S_u + m_u * q_u * Lu) + \tau_u * Lu_m +$$

$$lu_m * (-\mu_{tu} - c_u - z) + h * \ln_m;$$

on IPT

$$d_{lipt_s} = v * \tau_d * Lipt_s - \mu_{ti} * lipt_s - c_d * lipt_s -$$

$$\gamma_{ipt} * lipt_s - a_{ipt} * lipt_s +$$

$$(1-\epsilon_i) * \theta_l * z * lu_s - w * lipt_s +$$

$$\phi * (1-\epsilon) * (1-a_{si}-a_{sr}-a_{sm}) * (1-\gamma_s) * k_1 * T1d_s +$$

$$(1-\epsilon_i) * \theta_l * e * Id_s;$$

$$d_{lipt_r} = v * \tau_d * Lipt_r - \mu_{ti} * lipt_r - c_d * lipt_r -$$

$$\gamma_{ipt} * lipt_r - a_{ipt} * lipt_r + (1-\epsilon_i) * \theta_l * z * lu_r -$$

$$w * lipt_r + \phi * (1-\epsilon) * a_{sr} * (1-\gamma_s) * k_1 * T1d_s +$$

$$\phi * (1-\epsilon) * (1-a_{rm}) * (1-\gamma_{r1}) * k_1 * T1d_r +$$

$$\phi * (1-\epsilon) * (1-a_{si}) * (1-\gamma_{r2}) * k_r * T2d_r +$$

$$(1-\epsilon_i) * \theta_l * e * Id_r;$$

$$d_{lipt_i} = \rho_d * Sipt * \lambda_i + \rho_d * m_{ipt} * Sipt_{postipt} * \lambda_i +$$

$$m_d * q_d * \rho_d * Lipt * \lambda_i + \tau_d * Lipt_i -$$

$$\mu_{td} * lipt_i - c_d * lipt_i - \sigma_d * lipt_i + a_{ipt} * lipt_s +$$

$$(1-\epsilon_i) * \theta_l * z * lu_i - w * lipt_i +$$

$$\phi * (1-\epsilon) * a_{si} * (1-\gamma_s) * k_1 * T1d_s +$$

$$\phi * (1-\epsilon) * (1-a_{im}) * (1-\gamma_{i1}) * k_1 * T1d_i +$$

$$(1-\epsilon_i) * \theta_l * e * Id_i;$$

$$d_{lipt_m} = \rho_d * Sipt * \lambda_m + \rho_d * m_{ipt} * Sipt_{postipt} * \lambda_m +$$

$$m_d * q_d * \rho_d * Lipt * \lambda_m + \tau_d * Lipt_m -$$

$$\mu_{td} * lipt_m - c_d * lipt_m - \sigma_d * lipt_m + a_{ipt} * lipt_r +$$

$$(1-\epsilon_i) * \theta_l * z * lu_m - w * lipt_m +$$

$$\phi * (1-\epsilon) * (1-\gamma_{m1}) * k_1 * T1d_m +$$

$$\phi * (1-\epsilon) * a_{sm} * (1-\gamma_s) * k_1 * T1d_s +$$

$$\phi * (1-\epsilon) * a_{rm} * (1-\gamma_{r1}) * k_1 * T1d_r +$$

$$\phi * (1-\epsilon) * a_{im} * (1-\gamma_{i1}) * k_1 * T1d_i +$$

$$\phi * (1-\epsilon) * a_{si} * (1-\gamma_{r2}) * k_r * T2d_r +$$

$$(1-\epsilon_i) * \theta_l * e * Id_m;$$

HIV detected

$$\begin{aligned} dld_s = & \lambda_s \rho_d (S_d + m_d q_d L_d + m_{ipt} S_{d_postipt}) + \\ & \tau_d (L_{d_s} + L_{d_si} + L_{d_sm}) + l_{d_s} (-\mu_{td} - c_d - \sigma_d) + \\ & (1-\phi)(1-\epsilon) k_1 (1-a_{si}-a_{sr}-a_{sm}) (1-\gamma_s) T1d_s + \\ & (1-\epsilon_i)(1-\theta_l) z^* l_{u_s} + w_{lipt_s} - \\ & (1-\epsilon_i) \theta_l e^* l_{d_s} - \epsilon_i e^* l_{d_s}; \end{aligned}$$

$$\begin{aligned} dld_r = & \lambda_r \rho_d (S_d + m_d q_d L_d + m_{ipt} S_{d_postipt}) + \\ & \tau_d (L_{d_r} + L_{d_ri} + L_{d_rm}) + l_{d_r} (-\mu_{td} - c_d - \sigma_d) + \\ & (1-\phi)(1-\epsilon) k_1 (a_{sr} (1-\gamma_s) T1d_s + \\ & (1-a_{rm}) (1-\gamma_{r1}) T1d_r) + (1-\epsilon_i)(1-\theta_l) z^* l_{u_r} + \\ & (1-\phi)(1-\epsilon) (1-a_{si}) (1-\gamma_{r2}) k_r T2d_r - \\ & (1-\epsilon_i) \theta_l e^* l_{d_r} - \epsilon_i e^* l_{d_r} + w_{lipt_r}; \end{aligned}$$

$$\begin{aligned} dld_i = & \lambda_i \rho_d (S_d + m_d q_d L_d + m_{ipt} S_{d_postipt}) + \\ & \tau_d L_{d_i} + l_{d_i} (-\mu_{td} - c_d - \sigma_d) + \\ & (1-\phi)(1-\epsilon) k_1 (a_{si} (1-\gamma_s) T1d_s + \\ & (1-a_{im}) (1-\gamma_{i1}) T1d_i) + \\ & (1-\epsilon_i)(1-\theta_l) z^* l_{u_i} + w_{lipt_i} + \\ & (1-\epsilon) (1-a_{sr}) (1-\gamma_{i2}) k_i T2d_i - \\ & (1-\epsilon_i) \theta_l e^* l_{d_i} - \epsilon_i e^* l_{d_i}; \end{aligned}$$

$$\begin{aligned} dld_m = & \lambda_m \rho_d (S_d + m_d q_d L_d + m_{ipt} S_{d_postipt}) + \\ & \tau_d L_{d_m} + l_{d_m} (-\mu_{td} - c_d - \sigma_d) + \\ & (1-\phi)(1-\epsilon) k_1 ((1-\gamma_{m1}) T1d_m + \\ & a_{sm} (1-\gamma_s) T1d_s + a_{rm} (1-\gamma_{r1}) T1d_r + \\ & a_{im} (1-\gamma_{i1}) T1d_i) + (1-\epsilon_i)(1-\theta_l) z^* l_{u_m} + \\ & w_{lipt_m} + (1-\epsilon) a_{sr} (1-\gamma_{i2}) k_i T2d_i + \\ & (1-\phi)(1-\epsilon) a_{si} (1-\gamma_{r2}) k_r T2d_r + \\ & (1-\epsilon) (1-\gamma_{m2}) k_m T2d_m - \\ & (1-\epsilon_i) \theta_l e^* l_{d_m} - \epsilon_i e^* l_{d_m}; \end{aligned}$$

 # Treated First-Line
 #####

HIV negative

$$dT1n_s = T1n_s (-\mu_{ts} - k_1) + c_0 l_{n_s} + \epsilon k_1 (1-a_{si}-a_{sr}-a_{sm}) (1-\gamma_s) T1n_s;$$

$$dT1n_r = T1n_r (-\mu_{tr1} - k_1) + f_r c_0 l_{n_r} + g_r \epsilon k_1 (a_{sr} (1-\gamma_s) T1n_s + (1-a_{rm}) (1-\gamma_{r1}) T1n_r);$$

$$dT1n_i = T1n_i (-\mu_{ti1} - k_1) + f_i c_0 l_{n_i} + g_i \epsilon k_1 (a_{si} (1-\gamma_s) T1n_s + (1-a_{im}) (1-\gamma_{i1}) T1n_i);$$

$$dT1n_m = T1n_m (-\mu_t - k_1) + f_m c_0 l_{n_m} + g_m \epsilon k_1 ((1-\gamma_{m1}) T1n_m + a_{sm} (1-\gamma_s) T1n_s + a_{rm} (1-\gamma_{r1}) T1n_r + a_{im} (1-\gamma_{i1}) T1n_i)$$

HIV detected


```

dT1d_s = T1d_s*(-mu_ths - k_1 +
epsilon*(1-a_si-a_sr-a_sm)*(1-gamma_s)*k_1) +
c_d*(ld_s + lipt_s) + c_u*lu_s + epsilon_i*z*lu_s +
epsilon_i*e*ld_s;

dT1d_r = T1d_r*(-mu_thr1 - k_1) +
f_r*(c_d*(ld_r + lipt_r) + c_u*lu_r) + f_r*epsilon_i*z*lu_r +
g_r*epsilon*k_1*(a_sr*(1-gamma_s)*T1d_s +
(1-a_rm)*(1-gamma_r1)*T1d_r) + f_r*epsilon_i*e*ld_r;

dT1d_i = T1d_i*(-mu_thi1 - k_1) +
f_i*(c_d*(ld_i + lipt_i) + c_u*lu_i) + f_i*epsilon_i*z*lu_i +
g_i*epsilon*k_1*(a_si*(1-gamma_s)*T1d_s +
(1-a_im)*(1-gamma_i1)*T1d_i) + f_i*epsilon_i*e*ld_i;

dT1d_m = T1d_m*(-mu_td - k_1) +
f_m*(c_d*(ld_m + lipt_m) + c_u*lu_m) + f_m*epsilon_i*z*lu_m +
g_m*epsilon*k_1*((1-gamma_m1)*T1d_m +
a_sm*(1-gamma_s)*T1d_s + a_rm*(1-gamma_r1)*T1d_r +
a_im*(1-gamma_i1)*T1d_i) + f_m*epsilon_i*e*ld_m;

#####
# Treated Second-Line
#####

# HIV negative

dT2n_r = -mu_tr2*T2n_r + (1-f_r)*c_0*ln_r - k_r*T2n_r +
(1-g_r)*epsilon*a_sr*(1-gamma_s)*k_1*T1n_s +
(1-g_r)*epsilon*(1-a_rm)*(1-gamma_r1)*k_1*T1n_r +
epsilon*(1-a_si)*(1-gamma_r2)*k_r*T2n_r;

dT2n_i = -mu_ti2*T2n_i + (1-f_i)*c_0*ln_i - k_i*T2n_i +
(1-g_i)*epsilon*a_si*(1-gamma_s)*k_1*T1n_s +
(1-g_i)*epsilon*(1-a_im)*(1-gamma_i1)*k_1*T1n_i +
epsilon*(1-a_sr)*(1-gamma_i2)*k_i*T2n_i;

dT2n_m = -mu_tm2*T2n_m + (1-f_m)*c_0*ln_m - k_m*T2n_m +
(1-g_m)*epsilon*(1-gamma_m1)*k_1*T1n_m +
(1-g_m)*epsilon*a_sm*(1-gamma_s)*k_1*T1n_s +
(1-g_m)*epsilon*a_rm*(1-gamma_r1)*k_1*T1n_r +
(1-g_m)*epsilon*a_im*(1-gamma_i1)*k_1*T1n_i +
epsilon*a_sr*(1-gamma_i2)*k_i*T2n_i +
epsilon*a_si*(1-gamma_r2)*k_r*T2n_r +
epsilon*(1-gamma_m2)*k_m*T2n_m;

# HIV detected

dT2d_r = -mu_thr2*T2d_r - k_r*T2d_r +
(1-f_r)*(c_d*ld_r + c_d*lipt_r + c_u*lu_r) +
(1-g_r)*epsilon*a_sr*(1-gamma_s)*k_1*T1d_s +
(1-g_r)*epsilon*(1-a_rm)*(1-gamma_r1)*k_1*T1d_r +
epsilon*(1-a_si)*(1-gamma_r2)*k_r*T2d_r +

```

```

(1-f_r)*epsilon_i*z*lu_r + (1-f_r)*epsilon_i*e*ld_r;

dT2d_i = -mu_thi2*T2d_i - k_i*T2d_i +
(1-f_i)*(c_d*ld_i + c_d*lipt_i + c_u*lu_i) +
(1-g_i)*epsilon*a_si*(1-gamma_s)*k_1*T1d_s +
(1-g_i)*epsilon*(1-a_im)*(1-gamma_i1)*k_1*T1d_i +
epsilon*(1-a_sr)*(1-gamma_i2)*k_i*T2d_i +
(1-f_i)*epsilon_i*z*lu_i + (1-f_i)*epsilon_i*e*ld_i;

dT2d_m = -mu_thm2*T2d_m - k_m*T2d_m +
(1-f_m)*(c_d*ld_m + c_d*lipt_m + c_u*lu_m) +
(1-g_m)*epsilon*(1-gamma_m1)*k_1*T1d_m +
(1-g_m)*epsilon*a_sm*(1-gamma_s)*k_1*T1d_s +
(1-g_m)*epsilon*a_rm*(1-gamma_r1)*k_1*T1d_r +
(1-g_m)*epsilon*a_im*(1-gamma_i1)*k_1*T1d_i +
epsilon*a_sr*(1-gamma_i2)*k_i*T2d_i +
epsilon*a_si*(1-gamma_r2)*k_r*T2d_r +
epsilon*(1-gamma_m2)*k_m*T2d_m +
(1-f_m)*epsilon_i*z*lu_m + (1-f_m)*epsilon_i*e*ld_m;

#####
# Mortality
#####
# HIV deaths
# ALL deaths to people with HIV
# Per 1000 people with HIV
if (N_hiv > 1) {
dM_hiv = (mu_u*(Su + Lu) + mu_i*(Sipt + Sipt_postipt + Lipt) +
mu_d*(Sd + Sd_postipt + Ld) + mu_tu*lu +
mu_ti*(lipt_s + lipt_r) + mu_td*(lipt_m + lipt_i + ld + T1d_m) +
mu_ths*T1d_s + mu_thi1*T1d_i + mu_thr1*T1d_r +
mu_thr2*T2d_r + mu_thi2*T2d_i + mu_thm2*T2d_m)/N_hiv*1000
} else {
dM_hiv = 0
}
}

return(list(c(dSn, dSu, dSd, #3
dLn_s, dLn_si, dLn_sm, dLn_i, dLn_r, dLn_ri, dLn_rm, dLn_m, #11
dLu_s, dLu_si, dLu_sm, dLu_i, dLu_r, dLu_ri, dLu_rm, dLu_m, #19
dLd_s, dLd_si, dLd_sm, dLd_i, dLd_r, dLd_ri, dLd_rm, dLd_m, #27
dln_s, dln_r, dln_i, dln_m, #31
dlu_s, dlu_r, dlu_i, dlu_m, #35
dld_s, dld_r, dld_i, dld_m, #39
dT1n_s, dT1n_r, dT1n_i, dT1n_m, #43
dT1d_s, dT1d_r, dT1d_i, dT1d_m, #47
dT2n_r, dT2n_i, dT2n_m, #50
dT2d_r, dT2d_i, dT2d_m, #53
dCum_ARI, dCum_ARI_s, dCum_ARI_r, dCum_ARI_i, dCum_ARI_m, #58
dSipt, dLipt_s, dLipt_i, dLipt_r, dLipt_m,
dlipt_s, dlipt_r, dlipt_i, dlipt_m,
dSipt_postipt, dSd_postipt, dM_hiv)))
})
}

```

References

1. UNAIDS. *AIDSinfo*. <http://aidsinfo.unaids.org>. Accessed September 19, 2015.
2. World Health Organization. *TB burden estimates*.
<http://www.who.int/tb/country/data/download/en/>. Accessed September 19, 2015.
3. Menzies HJ, Moalosi G, Anisimova V, Gammino V, Sentle C, Bachhuber MA, *et al*. Increase in anti-tuberculosis drug resistance in Botswana: results from the fourth National Drug Resistance Survey. *Int J Tuberc Lung Dis* 2014,**18**:1026-1033.
4. Poole D, Raftery AE. Inference for Deterministic Simulation Models: The Bayesian Melding Approach. *Journal of the American Statistical Association* 2000,**95**:1244-1255.
5. Alkema L, Raftery AE, Brown T. Bayesian melding for estimating uncertainty in national HIV prevalence estimates. *Sex Transm Infect* 2008,**84 Suppl 1**:i11-i16.
6. Botswana National Tuberculosis Program. *National Tuberculosis Program Annual Report 2012*; 2012.
7. Mills HL, Cohen T, Colijn C. Community-wide isoniazid preventive therapy drives drug-resistant tuberculosis: a model-based analysis. *Sci Transl Med* 2013,**5**:180ra149.
8. Menzies NA, Cohen T, Lin HH, Murray M, Salomon JA. Population health impact and cost-effectiveness of tuberculosis diagnosis with Xpert MTB/RIF: a dynamic simulation and economic evaluation. *PLoS Med* 2012,**9**:e1001347.

9. Farahani M, Vable A, Lebelonyane R, Seipone K, Anderson M, Avalos A, *et al.* Outcomes of the Botswana national HIV/AIDS treatment programme from 2002 to 2010: a longitudinal analysis. *Lancet Glob Health* 2014,**2**:e44-50.
10. Styblo K. *Epidemiology of Tuberculosis: Selected Papers*. The Hague: Royal Netherlands Tuberculosis Foundation (KNCV); 1991.
11. World Health Organization. *Global Tuberculosis Report 2015*. Geneva; 2015.
12. May M, Gompels M, Delpech V, Porter K, Post F, Johnson M, *et al.* Impact of late diagnosis and treatment on life expectancy in people with HIV-1: UK Collaborative HIV Cohort (UK CHIC) Study. *Bmj* 2011,**343**:d6016.
13. Wang C, Vlahov D, Galai N, Bareta J, Strathdee SA, Nelson KE, *et al.* Mortality in HIV-seropositive versus -seronegative persons in the era of highly active antiretroviral therapy: implications for when to initiate therapy. *J Infect Dis* 2004,**190**:1046-1054.
14. Antonucci G, Girardi E, Raviglione MC, Ippolito G. Risk factors for tuberculosis in HIV-infected persons. A prospective cohort study. The Gruppo Italiano di Studio Tuberculosis e AIDS (GISTA). *Jama* 1995,**274**:143-148.
15. Houben RM, Glynn JR, Mboma S, Mzemba T, Mwaungulu NJ, Mwaungulu L, *et al.* The impact of HIV and ART on recurrent tuberculosis in a sub-Saharan setting. *Aids* 2012,**26**:2233-2239.
16. Dye C, Espinal MA. Will tuberculosis become resistant to all antibiotics? *Proc Biol Sci* 2001,**268**:45-52.

17. Lew W, Pai M, Oxlade O, Martin D, Menzies D. Initial drug resistance and tuberculosis treatment outcomes: systematic review and meta-analysis. *Ann Intern Med* 2008,**149**:123-134.
18. Murray J, Sonnenberg P, Shearer S, Godfrey-Faussett P. Drug-resistant pulmonary tuberculosis in a cohort of southern African goldminers with a high prevalence of HIV infection. *S Afr Med J* 2000,**90**:381-386.
19. Menzies D, Benedetti A, Paydar A, Royce S, Madhukar P, Burman W, *et al*. Standardized treatment of active tuberculosis in patients with previous treatment and/or with mono-resistance to isoniazid: a systematic review and meta-analysis. *PLoS Med* 2009,**6**:e1000150.
20. A concurrent comparison of isoniazid plus PAS with three regimens of isoniazid alone in the domiciliary treatment of pulmonary tuberculosis in South India. *Bull World Health Organ* 1960,**23**:535-585.
21. Dye C, Williams BG, Espinal MA, Raviglione MC. Erasing the world's slow stain: strategies to beat multidrug-resistant tuberculosis. *Science* 2002,**295**:2042-2046.
22. Bottger EC, Springer B. Tuberculosis: drug resistance, fitness, and strategies for global control. *Eur J Pediatr* 2008,**167**:141-148.
23. Gagneux S, Long CD, Small PM, Van T, Schoolnik GK, Bohannan BJ. The competitive cost of antibiotic resistance in *Mycobacterium tuberculosis*. *Science* 2006,**312**:1944-1946.

24. Luciani F, Sisson SA, Jiang H, Francis AR, Tanaka MM. The epidemiological fitness cost of drug resistance in *Mycobacterium tuberculosis*. *Proc Natl Acad Sci U S A* 2009,**106**:14711-14715.
25. Grandjean L, Gilman RH, Martin L, Soto E, Castro B, Lopez S, *et al.* Transmission of Multidrug-Resistant and Drug-Susceptible Tuberculosis within Households: A Prospective Cohort Study. *PLoS Med* 2015,**12**:e1001843; discussion e1001843.
26. Samandari T, Agizew TB, Nyirenda S, Tedla Z, Sibanda T, Shang N, *et al.* 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial. *Lancet* 2011,**377**:1588-1598.
27. Balcells ME, Thomas SL, Godfrey-Faussett P, Grant AD. Isoniazid preventive therapy and risk for resistant tuberculosis. *Emerg Infect Dis* 2006,**12**:744-751.
28. Vynnycky E, Sumner T, Fielding KL, Lewis JJ, Cox AP, Hayes RJ, *et al.* Tuberculosis control in South African gold mines: mathematical modeling of a trial of community-wide isoniazid preventive therapy. *Am J Epidemiol* 2015,**181**:619-632.
29. Gupta RK, Lawn SD, Bekker LG, Caldwell J, Kaplan R, Wood R. Impact of human immunodeficiency virus and CD4 count on tuberculosis diagnosis: analysis of city-wide data from Cape Town, South Africa. *Int J Tuberc Lung Dis* 2013,**17**:1014-1022.

30. Espinal MA, Kim SJ, Suarez PG, Kam KM, Khomenko AG, Migliori GB, *et al.* Standard short-course chemotherapy for drug-resistant tuberculosis: treatment outcomes in 6 countries. *Jama* 2000,**283**:2537-2545.
31. Seung KJ, Gelmanova IE, Peremitin GG, Golubchikova VT, Pavlova VE, Sirotkina OB, *et al.* The effect of initial drug resistance on treatment response and acquired drug resistance during standardized short-course chemotherapy for tuberculosis. *Clin Infect Dis* 2004,**39**:1321-1328.
32. Orenstein EW, Basu S, Shah NS, Andrews JR, Friedland GH, Moll AP, *et al.* Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. *Lancet Infect Dis* 2009,**9**:153-161.
33. Johnston JC, Shahidi NC, Sadatsafavi M, Fitzgerald JM. Treatment outcomes of multidrug-resistant tuberculosis: a systematic review and meta-analysis. *PLoS One* 2009,**4**:e6914.
34. Migliori GB, Espinal M, Danilova ID, Punga VV, Grzemska M, Raviglione MC. Frequency of recurrence among MDR-tB cases 'successfully' treated with standardised short-course chemotherapy. *Int J Tuberc Lung Dis* 2002,**6**:858-864.
35. World Bank. *Botswana Health Indicators*. <http://data.worldbank.org>. Accessed September 15, 2015.
36. World Health Organization. *Guidelines for the programmatic management of drug-resistant tuberculosis: emergency update 2008*. Geneva; 2008.
37. Time from HIV-1 seroconversion to AIDS and death before widespread use of highly-active antiretroviral therapy: a collaborative re-analysis. Collaborative

- Group on AIDS Incubation and HIV Survival including the CASCADE EU Concerted Action. Concerted Action on SeroConversion to AIDS and Death in Europe. *Lancet* 2000,**355**:1131-1137.
38. Munoz A, Wang MC, Bass S, Taylor JM, Kingsley LA, Chmiel JS, *et al*. Acquired immunodeficiency syndrome (AIDS)-free time after human immunodeficiency virus type 1 (HIV-1) seroconversion in homosexual men. Multicenter AIDS Cohort Study Group. *Am J Epidemiol* 1989,**130**:530-539.
39. Medley GF, Anderson RM, Cox DR, Billard L. Incubation period of AIDS in patients infected via blood transfusion. *Nature* 1987,**328**:719-721.
40. Farnham PG, Gopalappa C, Sansom SL, Hutchinson AB, Brooks JT, Weidle PJ, *et al*. Updates of lifetime costs of care and quality-of-life estimates for HIV-infected persons in the United States: late versus early diagnosis and entry into care. *J Acquir Immune Defic Syndr* 2013,**64**:183-189.
41. Tiemersma EW, van der Werf MJ, Borgdorff MW, Williams BG, Nagelkerke NJ. Natural history of tuberculosis: duration and fatality of untreated pulmonary tuberculosis in HIV negative patients: a systematic review. *PLoS One* 2011,**6**:e17601.
42. Corbett EL, Charalambous S, Moloji VM, Fielding K, Grant AD, Dye C, *et al*. Human immunodeficiency virus and the prevalence of undiagnosed tuberculosis in African gold miners. *Am J Respir Crit Care Med* 2004,**170**:673-679.
43. Dowdy DW, Chaisson RE, Maartens G, Corbett EL, Dorman SE. Impact of enhanced tuberculosis diagnosis in South Africa: a mathematical model of

- expanded culture and drug susceptibility testing. *Proc Natl Acad Sci U S A* 2008,**105**:11293-11298.
44. Straetemans M, Glaziou P, Bierrenbach AL, Sismanidis C, van der Werf MJ. Assessing tuberculosis case fatality ratio: a meta-analysis. *PLoS One* 2011,**6**:e20755.
45. Abdool Karim SS, Naidoo K, Grobler A, Padayatchi N, Baxter C, Gray A, *et al.* Timing of initiation of antiretroviral drugs during tuberculosis therapy. *N Engl J Med* 2010,**362**:697-706.
46. Churchyard GJ, Kleinschmidt I, Corbett EL, Murray J, Smit J, De Cock KM. Factors associated with an increased case-fatality rate in HIV-infected and non-infected South African gold miners with pulmonary tuberculosis. *Int J Tuberc Lung Dis* 2000,**4**:705-712.
47. Vynnycky E, Fine PE. The natural history of tuberculosis: the implications of age-dependent risks of disease and the role of reinfection. *Epidemiol Infect* 1997,**119**:183-201.
48. Dye C, Garnett GP, Sleeman K, Williams BG. Prospects for worldwide tuberculosis control under the WHO DOTS strategy. Directly observed short-course therapy. *Lancet* 1998,**352**:1886-1891.
49. Sutherland I, Svandova E, Radhakrishna S. The development of clinical tuberculosis following infection with tubercle bacilli. 1. A theoretical model for the development of clinical tuberculosis following infection, linking from data on the risk of tuberculous infection and the incidence of clinical tuberculosis in the Netherlands. *Tubercle* 1982,**63**:255-268.

50. Sutherland I. Recent studies in the epidemiology of tuberculosis, based on the risk of being infected with tubercle bacilli. *Adv Tuberc Res* 1976,**19**:1-63.
51. Daley CL, Small PM, Schechter GF, Schoolnik GK, McAdam RA, Jacobs WR, Jr., *et al.* An outbreak of tuberculosis with accelerated progression among persons infected with the human immunodeficiency virus. An analysis using restriction-fragment-length polymorphisms. *N Engl J Med* 1992,**326**:231-235.
52. Di Perri G, Cruciani M, Danzi MC, Luzzati R, De Checchi G, Malena M, *et al.* Nosocomial epidemic of active tuberculosis among HIV-infected patients. *Lancet* 1989,**2**:1502-1504.
53. Coronado VG, Beck-Sague CM, Hutton MD, Davis BJ, Nicholas P, Villareal C, *et al.* Transmission of multidrug-resistant *Mycobacterium tuberculosis* among persons with human immunodeficiency virus infection in an urban hospital: epidemiologic and restriction fragment length polymorphism analysis. *J Infect Dis* 1993,**168**:1052-1055.
54. Gilks CF, Godfrey-Faussett P, Batchelor BI, Ojoo JC, Ojoo SJ, Brindle RJ, *et al.* Recent transmission of tuberculosis in a cohort of HIV-1-infected female sex workers in Nairobi, Kenya. *Aids* 1997,**11**:911-918.
55. Sonnenberg P, Murray J, Glynn JR, Shearer S, Kambashi B, Godfrey-Faussett P. HIV-1 and recurrence, relapse, and reinfection of tuberculosis after cure: a cohort study in South African mineworkers. *Lancet* 2001,**358**:1687-1693.
56. Narayanan S, Swaminathan S, Supply P, Shanmugam S, Narendran G, Hari L, *et al.* Impact of HIV infection on the recurrence of tuberculosis in South India. *J Infect Dis* 2010,**201**:691-703.

57. Cohen T, Lipsitch M, Walensky RP, Murray M. Beneficial and perverse effects of isoniazid preventive therapy for latent tuberculosis infection in HIV-tuberculosis coinfecting populations. *Proc Natl Acad Sci U S A* 2006,**103**:7042-7047.
58. Andrews JR, Noubary F, Walensky RP, Cerda R, Losina E, Horsburgh CR. Risk of progression to active tuberculosis following reinfection with *Mycobacterium tuberculosis*. *Clin Infect Dis* 2012,**54**:784-791.
59. Getahun H, Kittikraisak W, Heilig CM, Corbett EL, Ayles H, Cain KP, *et al*. Development of a standardized screening rule for tuberculosis in people living with HIV in resource-constrained settings: individual participant data meta-analysis of observational studies. *PLoS Med* 2011,**8**:e1000391.
60. World Health Organization. *Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings*. Geneva; 2011.
61. Martinson NA, Barnes GL, Moulton LH, Msandiwa R, Hausler H, Ram M, *et al*. New regimens to prevent tuberculosis in adults with HIV infection. *N Engl J Med* 2011,**365**:11-20.
62. Kunkel A, Colijn C, Lipsitch M, Cohen T. How could preventive therapy affect the prevalence of drug resistance? Causes and consequences. *Philos Trans R Soc Lond B Biol Sci* 2015,**370**:20140306.

Paper 3: Kunkel, A., Cobelens, F.G., & Cohen, T. Tradeoffs in new anti-tuberculosis drug introduction policies: a model based analysis.

Abstract

Background: New drugs for the treatment of tuberculosis (TB) are becoming available for the first time in over 40 years. Optimal strategies for introducing these drugs have not yet been established. The objective of this study was to compare different strategies for introducing the new TB drug bedaquiline based on patients' resistance patterns.

Methods and Findings: We created a Markov decision model to follow a hypothetical cohort of multidrug resistant (MDR) TB patients under different bedaquiline use strategies. The explored strategies included making bedaquiline available to all patients with MDR TB, restricting bedaquiline usage to patients with MDR plus additional resistance, and withholding bedaquiline introduction completely. We compared these strategies according to life expectancy, risks of acquired resistance, and the expected number and health outcomes of secondary cases. Providing bedaquiline to all MDR patients maximized the life expectancy of our initial cohort in 76·8% of 5,000 simulations. In 22·6% of simulations, however, life expectancy was maximized by withholding bedaquiline completely, reflecting assumed uncertainty in bedaquiline safety and efficacy. The most liberal bedaquiline use strategies consistently increased the risk of bedaquiline resistance, but decreased the risk of resistance to other MDR drugs. In almost all cases, more liberal bedaquiline use strategies reduced the expected number of and life years lost to secondary cases.

Conclusions: Continued research on bedaquiline is necessary to verify an overall mortality benefit in programmatic settings. Once established, the desire to prevent bedaquiline resistance by restricting its use should be weighed against the possibility of extending current patients' lives and protecting existing drugs through expanded use.

Introduction

Only approximately 50% of the 111,000 people started on treatment for multidrug resistant tuberculosis (MDR TB) in 2014 are likely to be successfully treated [1]. The remainder will experience high mortality, risk acquisition of extensively drug resistant (XDR) TB, and may continue to infect others. New antibiotics have the potential to revolutionize both prevention and treatment of highly drug resistant TB. Bedaquiline and delamanid recently became the first new drugs approved for TB treatment in over 40 years [2, 3], and other promising drugs such as pretomanid are in development [4]. Effective drug use policies will be necessary to obtain maximal benefit from these new drugs while also managing risks of resistance.

Although clinical management of TB relies on strong multidrug regimens, the initial discovery and development of new TB drugs often occur in isolation. Optimizing multidrug regimens is complicated in both theory (e.g. by the number of drugs, limited data on drug efficacy and interactions, and the prevalence of existing resistance) and practice (e.g. by lack of access to patients' full drug susceptibility profiles and limited opportunity for controlled trials) [5, 6]. Thus, decisions about how best to introduce and combine new TB drugs have relied heavily on expert opinion. Limited guidance exists beyond common-sense strategies, such as never to add a single drug to a failing regimen, and broad considerations, such as the number of drugs and their side-effect profiles [5, 7].

Here, we present a Markov decision model to begin formalizing a rational basis for decisions about drug introduction. Using the model, we outline the tradeoffs involved in deciding which patients should receive a new anti-TB drug, based on both their outcomes and those of their immediate contacts. We explore a continuum of policies ranging from

most conservative (i.e. restricting the new drug entirely or for use only among the most highly resistant patients) to most liberal (i.e. allowing all patients with MDR TB to receive the new drug). Though the general framework of our analysis is broadly generalizable, we focus this paper specifically on the new TB drug bedaquiline. Bedaquiline was approved by the FDA in 2012 for use in MDR TB patients without other treatment options on the basis of its Phase IIb trial culture conversion results. However, concerns about resistance and a mortality imbalance observed in the pivotal Phase IIb trial have generated controversy about the appropriate role of this new drug [8-11]. A formal approach to assessing potential bedaquiline use strategies is therefore especially appropriate.

Methods

To evaluate the impact and potential tradeoffs of different bedaquiline introduction strategies, we created a Markov decision model following a hypothetical cohort of patients initiating MDR TB treatment and their immediate contacts. A model description is provided below, with full details available in the S1 Appendix.

Population

Our assumed population was a cohort of European men initiating MDR TB treatment at age 30. All men were assumed to be bedaquiline susceptible at baseline and have either MDR TB without additional resistance (“MDR” from here), MDR TB with additional resistance to either at least one fluoroquinolone or at least one second-line injectable, but not both (“PreXDR”), or MDR TB with additional resistance to at least one fluoroquinolone and at least one second-line injectable (“XDR”). The distributions of patients’ initiating resistance patterns were informed by a published cohort [12].

Health States and Transitions

Modeled health states were defined based on TB culture status (positive, negative, or stable cure), treatment regimen (optimized background regimen, OBR; OBR plus bedaquiline; or no treatment), and resistance pattern (to bedaquiline and background drugs). Transitions between these states included culture conversion, relapse, routine or premature cessation of treatment, treatment re-initiation after cessation, regimen change, resistance acquisition, and death. We assumed that resistance was acquired in a stepwise fashion (i.e. to one drug at a time) and that patients could only relapse after treatment (i.e. culture conversions were only modeled if sustained through the end of treatment). We also assumed that TB-related mortality and acquired resistance rates applied only to patients who were culture-positive, and that some patients self-cured even in the absence of TB treatment.

Cycle Length

We used a cycle length of one week within our model to capture potentially rapid changes in infectiousness, prognosis, and resistance patterns.

Treatment Strategies

We considered the following treatment strategies: withholding bedaquiline from all patients, providing bedaquiline to patients with XDR TB only, providing bedaquiline to patients with PreXDR or XDR TB, or providing bedaquiline to all patients with at least MDR TB. We did not allow treatment to differ based on bedaquiline resistance patterns, reflecting the current lack of a validated test with breakpoints defining clinically relevant bedaquiline resistance [5].

For the strategy in which all patients with MDR TB were eligible for bedaquiline, we assumed that all patients received bedaquiline from the beginning of treatment. For the

more conservative strategies, we assumed a 13 week average lag time after acquisition of or treatment initiation with the relevant resistance pattern to account for a delay in obtaining results of second-line drug susceptibility testing (DST). We compared these results to an analysis assuming no lag time, reflecting the potential impact of widespread rapid second-line DST availability.

Secondary cases were subjected to the same treatment strategy as the initial cohort. We assumed secondary cases were initially undetected at the time of disease initiation, but recognized as MDR TB upon presentation to the health system. Detection of additional resistance was subject to the same delays as for the index patients.

Outcomes

We considered mortality, resistance, and transmission outcomes. To assess mortality, we compared the average life expectancy from initiation of MDR TB treatment across the different bedaquiline use strategies, and to assess resistance, we recorded the number of patients who acquired particular resistance patterns under each treatment strategy. To assess transmission, we calculated the number of secondary cases infected by our initial cohort based on the expected number of transmission events per year (accounting for treatment status, fitness costs of resistance, and the duration of infectiousness) and the probability of progressing to active disease. The life expectancy of each secondary case was calculated based on the resistance pattern of the index case at the time of the infection event. These estimates were combined to give the expected number of life years lost to secondary cases under each treatment scenario.

Parameterization

Parameters describing TB natural history and outcomes in the absence of bedaquiline were taken from published cohorts, clinical trials, and meta-analyses [13-15]. These parameters were held fixed throughout our analysis. Parameters describing the effect of bedaquiline were derived from the bedaquiline pivotal trials [8, 16] and more recent cohorts [3, 17, 18]. Because only small numbers of patients receiving bedaquiline-containing regimens had completed treatment at the time of this analysis, we explored wide ranges of values for key bedaquiline associated parameters as described in Table 3.1.

Table 3.1: Bedaquiline-associated parameter ranges

Parameter	Distribution	References/Explanation
Default rate on bedaquiline (vs. OBR)	Unif(-10%,+10%)	[19, 20]
Risk of relapse on bedaquiline (ratio to OBR)	Unif(0.4,1)	[15, 21, 16]
Median time to culture conversion on bedaquiline (ratio to OBR)	Unif(0.4,1)	[8, 16-18, 22, 23]
Bedaquiline-associated mortality rate (addition to TB or background mortality)	Unif(0, 5 per 100 person-years)	[8]: 3 deaths in BDQ arm in overall treatment phase. 79 people assigned to BDQ, 50 completed treatment (~2 years); [18, 17, 24]
Risk of acquired bedaquiline resistance	Unif(0.1,0.5) for XDR 4x lower for PreXDR 16x lower for MDR	[13, 8, 16]
Risk of acquired resistance to background drugs on OBR (ratio to on bedaquiline)	Unif(1.05,8)	[13, 8, 16]
Transmission fitness of bedaquiline resistance (ratio to bedaquiline sensitive)	Unif(0.7,1)	Similar to other TB drugs [25-28]

Calculation & Value of Information

All analyses were performed in TreeAge Pro 2015 R2.2. Monte Carlo probabilistic sensitivity analyses with 5,000 samples were performed to estimate the life expectancy, resistance acquisition patterns, and number and outcomes of secondary cases expected under each treatment scenario. For our life expectancy outcome, we calculated the expected value of perfect information, or the additional life expectancy that one would expect to gain on average if there was no uncertainty in our bedaquiline-related parameters. We also calculated the expected value of partial perfect information separately for each of the bedaquiline parameters, sampling 200 values in the outer loop of the parameter of interest and 1000 values in the inner loop of the remaining parameters.

Results

Figure 3.1 summarizes the optimal bedaquiline use strategies from each simulation for a range of mortality, resistance, and transmission outcomes. An overview of these results and additional analyses for each outcome are provided below.

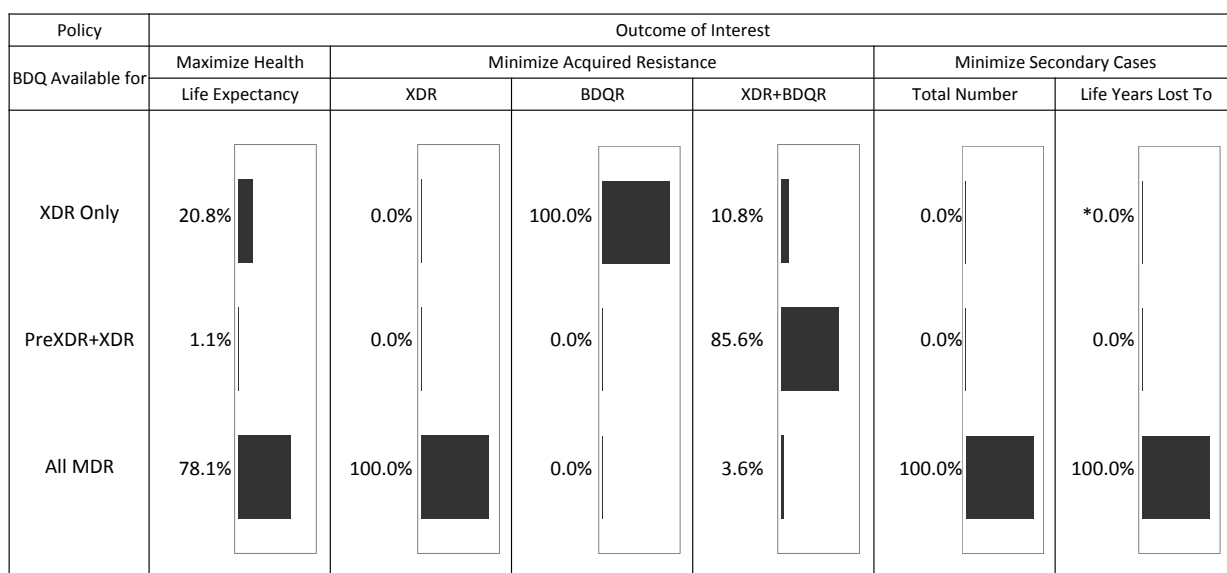
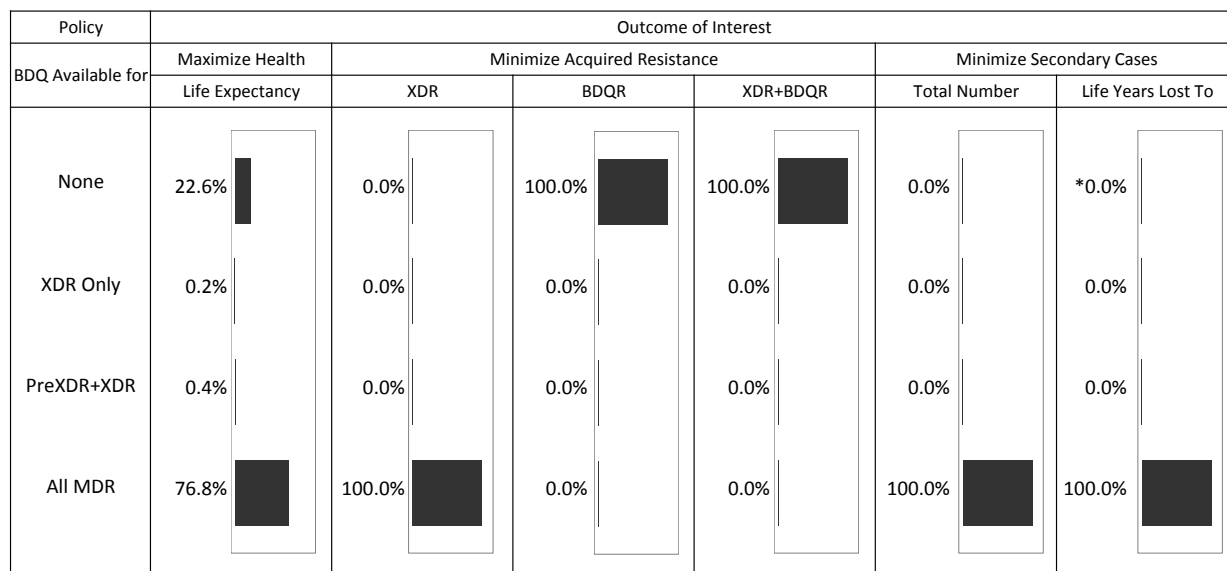


Figure 3.1: Optimal bedaquiline use strategy for different outcomes based on 5,000 simulation runs. The top half of the figure shows the results across all four potential bedaquiline use strategies. The bottom half shows results assuming bedaquiline is made available for at least some patients (i.e. no “none” strategy). The * indicates that one simulation run resulted in this simulation being optimal

Life Expectancy

Providing bedaquiline to all patients with MDR TB maximized the life expectancy of our initial cohort in 76·8% of 5,000 simulations (Figure 3.1). In nearly all remaining simulations, the optimal strategy was to withhold bedaquiline from all patients, suggesting that the benefits of bedaquiline did not outweigh potential added mortality risks.

Intermediate bedaquiline use strategies were optimal in fewer than 1% of simulations. The average difference in life expectancy between the best and worst strategies was 1·45 years.

Table 3.2 displays the effect of the DST methods available to detect PreXDR and XDR TB on life expectancy under the different bedaquiline use strategies. The rapid DST method, which shortens the lag time for eligible individuals to receive bedaquiline, increased the average life expectancy for both the “XDR only” and “PreXDR+XDR” strategies. However, the average life expectancies for these two scenarios remained smaller than that of the “all MDR” scenario, suggesting that the potential benefits of making bedaquiline available for all patients with MDR TB extend beyond simply shortening the time to bedaquiline initiation for patients with more extensive resistance.

Table 3.2: Life expectancy comparing bedaquiline use strategies when under our baseline scenario (conventional DST to identify PreXDR and XDR cases) and a scenario with rapid DST for fluoroquinolones and injectables. Results are given as simulation mean (2·5 percentile, 97·5 percentile)

DST Method	Life Expectancy when BDQ Available for			
	All MDR	PreXDR+XDR	XDR Only	None
Conventional (Baseline)	36·0 (33·5, 38·7)	35·1 (34·4, 35·8)	34·9 (34·6, 35·2)	34·8
Rapid	36·0 (33·5, 38·7)	35·5 (34·5, 36·7)	35·0 (34·6, 35·5)	34·8

The results of our value of information analysis are provided in Table 3.3. The expected value of perfect information for all parameters is 0.153 life years (per patient). The expected value of partial perfect information was 0 for all parameters except the ratio of median time to culture conversion on vs. off bedaquiline (0.074) and the bedaquiline-associated mortality rate (0.006). These results indicate that uncertainty in the estimated mortality benefits of bedaquiline reflects assumptions about efficacy and (possible) drug-related mortality, but not resistance.

Table 3.3: Expected increase in life expectancy (in years) if perfect information was available for all or particular bedaquiline-related parameters

Expected Value of Perfect Information	
Overall	0.153
Expected Value of Partial Perfect Information (BDQ Parameters)	
Default rate on BDQ	0
Relapse risk on BDQ	0
Time to culture conversion on BDQ	0.074
BDQ-Related Mortality	0.006
Protection from Resistance to OBR	0
Rate of Resistance to BDQ	0

Acquired Resistance

Figure 3.1 and Table 3.4 show the impact of different drug use strategies on acquired resistance to the new and existing drugs in our initial cohort. The best strategy to avoid resistance to bedaquiline was to strictly constrain bedaquiline availability. The simulation mean percentage of people acquiring resistance to bedaquiline was 5.88% (2.5th percentile 2.18%, 97.5th percentile 9.45%) in the scenario providing bedaquiline to all patients with MDR TB, compared with 3.50% (1.30%, 5.62%) when restricting

bedaquiline for patients with XDR TB only. However, expanding bedaquiline availability is predicted to reduce the rate of acquired XDR TB by providing additional protection to the existing drugs. The percentage of people acquiring XDR TB was 2.56% (1.09%, 7.68%) in the scenario providing bedaquiline to all patients with MDR TB, compared with 9.82% (no variability, as non-bedaquiline parameters are assumed fixed) when restricting bedaquiline for patients with XDR TB only.

Table 3.4: Proportion of the initial cohort acquiring different resistance patterns. We only count patients who did not begin with the listed resistance pattern (e.g. patients who are initially XDR may be counted as acquiring “XDR+BDQR” but not “XDR”). Resistance patterns that are unspecified may have any value (e.g. “BDQR” identifies resistance to bedaquiline in combination with any pattern of OBR resistance). Results are given as simulation mean (2.5 percentile, 97.5 percentile)

% Acquiring	BDQ Available for			
	All MDR	PreXDR+XDR	XDR Only	None
BDQR	5.88 (2.18, 9.45)	3.91 (1.44, 6.29)	3.50 (1.30, 5.62)	0
PreXDR	2.50 (1.16, 6.43)	7.66	7.66	7.66
PreXDR+BDQR	1.93 (0.39, 3.69)	1.00 (0.16, 1.99)	0	0
XDR	2.56 (1.09, 7.68)	6.59 (5.84, 8.94)	9.82	9.82
XDR+BDQR	3.44 (1.29, 6.15)	3.20 (1.20, 5.23)	3.50 (1.65, 5.62)	0

When we only consider scenarios in which at least some patients are eligible for bedaquiline, complete resistance to the new and existing drugs (XDR+BDQR) was minimized most often by the intermediate strategy of providing bedaquiline to patients with PreXDR and XDR TB only. However, the “XDR only” strategy is preferred in 10.8% of the 5,000 simulation runs and the “all MDR” strategy in 3.6% of runs, indicating that the optimal decision for this outcome is parameter-dependent. This pattern reflects the

differential effects of the bedaquiline use strategies on patients with different initial resistance patterns. For many (though not all) parameter sets, providing bedaquiline to all patients with MDR TB minimized the number of cases of acquired XDR+BDQR among patients with initial MDR or PreXDR TB, but maximized the number of cases of acquired XDR+BDQR among patients with initial XDR TB. However, the absolute differences in the number of cases of acquired XDR+BDQR across scenarios are small when bedaquiline is provided to at least some categories of patients, indicating that the costs of making a suboptimal decision with respect to this variable may be limited.

Secondary Cases

The total number of secondary cases produced from the time of MDR TB treatment initiation was low (<1 per person) across all treatment strategies, as shown in Table 3.5. This number was higher but remained below 1 if we assumed individuals were initially untreated, reflecting the high mortality rate and lack of diagnostic delay in our model. Making bedaquiline available to all patients with MDR TB was the preferred strategy to minimize the number of secondary cases for all 5,000 simulation parameter sets, and the years of life lost amongst secondary cases for all but one.

Table 3.5: Impact of different bedaquiline use strategies on the number and health outcomes of secondary TB cases. Results are given as simulation mean (2.5 percentile, 97.5 percentile)

Outcome per 100 Initial Patients	BDQ Available for			
	All MDR	PreXDR+XDR	XDR Only	None
Number of Secondary Cases	14 (10, 17)	17 (16, 18)	18 (18, 19)	19
Life Years Lost to Secondary Cases	243 (164, 317)	315 (290, 336)	333 (320, 343)	346

Discussion

New anti-TB drugs such as bedaquiline hold much promise to reduce morbidity and mortality associated with drug resistance. In this paper, we performed a decision analysis to explore the potential impact of different bedaquiline use strategies on a range of individual and public health outcomes. Different strategies may be preferred based on the outcome of primary interest (e.g. minimize resistance, minimize years of life lost), illustrating the tradeoffs involved in decision-making for the introduction of new antibiotics.

When considering whether and how to introduce a new drug, we assert that individual patient health considerations should prevail. Drugs for which the risk of mortality due to adverse events exceeds expected reductions in mortality should not be used regardless of their potential public health benefits. Our model predicted the risks of bedaquiline to outweigh the benefits of its use in any patients for 22.6% of parameter sets tested. For 76.8% of parameter sets, we predicted that the optimal strategy would be to provide bedaquiline for all patients with MDR TB. These results primarily reflect the assumed uncertainty in rates of mortality and culture conversion associated with bedaquiline and demonstrate the vital importance of continued research into bedaquiline safety and efficacy. Thus far, interim cohort analyses of patients receiving bedaquiline outside of trial settings have not identified excess bedaquiline-associated mortality [17, 18]; however, continued research and in particular Phase III trial results are needed to verify that the unexplained mortality imbalance of the pivotal phase IIb trial was not drug related.

Antibiotic introduction strategies may affect rates of acquired resistance to the new drug, existing drugs, or both. In general, we would expect more expansive access to a new drug to promote resistance to the new drug, while preventing resistance to existing drugs. These expectations are reflected in our results. Acquired bedaquiline resistance occurred most often under the most liberal bedaquiline use policy (providing bedaquiline to all patients with MDR TB); however, this same policy was most effective at preventing new cases of PreXDR and XDR TB. The effects of expanding access to a new drug on composite resistance to new and existing drugs are less clear-cut. When considering only strategies providing bedaquiline to at least some categories of patients, the majority of our simulations predicted an intermediate strategy targeting bedaquiline to patients with PreXDR and XDR TB only to minimize the combination of XDR plus bedaquiline resistance. However, both the “All MDR” and “XDR only” strategies were preferred for some combinations of parameter values, and differences in the proportions of people acquiring XDR+BDQR across different strategies were small.

From a public health perspective, optimal use of a new antibiotic should also account for future transmission. For this paper, we limited our attention to the second generation of infected patients. We found that, for all but one of the 5,000 parameter sets tested, making bedaquiline available to all patients with MDR TB would minimize the total number of and expected number of life years lost to secondary cases. This relationship can be explained by the correlation between severe and highly infectious disease within our model. For diseases and treatments for which this assumption does not hold, associations may appear in the opposite direction [29]. Future drug development and policy changes may also affect the relationship between new drug use strategies and outcomes among

potential secondary cases. Bedaquiline use strategies chosen now could alter the effectiveness of potential future TB regimens incorporating both bedaquiline (e.g. the NC-005 trial of bedaquiline, pyrazinamide, and pretomanid) and background drugs such as pyrazinamide and the fluoroquinolones (e.g. the STAND trial of pretomanid, moxifloxacin, and pyrazinamide) [3]. Of course, the desire to be prepared for the range of outcomes that could result from these trials must be weighed against the need to provide the best available care to patients presenting today. A full modeling analysis of these costs and benefits would require a transmission dynamic structure not included here.

This study has several limitations. We have not explored the full range of potential bedaquiline use strategies, for example as an early drug substitution method to prevent hearing loss during MDR TB treatment. For simplicity, we held the natural history and treatment parameters unrelated to bedaquiline fixed throughout our analysis, which does not reflect the potential uncertainty and heterogeneity in these parameters. Many of these estimates were based on large meta-analyses with data from multiple countries, allowing us to average over but not fully address the variability expected in e.g. settings with standardized vs. individualized treatment regimes. We assumed that our initial cohort was comprised of 30-year-old European men, which may differ from the target population of bedaquiline in many settings; however, as this assumption was used only in defining background mortality rates, it is most likely to affect the magnitude rather than the direction of the observed effects. Similarly, the effects of our particular background distribution of resistance are likely mitigated by the range of explored scenarios, which incrementally account for expanded access of bedaquiline to patients with XDR, then PreXDR+XDR, and finally all MDR. Changing the HIV status of this cohort could have greater

effects if bedaquiline is found to have differential impact on HIV-positive and negative individuals. Similarly, we may see differential effects of bedaquiline if the background regimen varies substantially from the data on which our model was based, as in the STREAM II trial of shorter MDR regimens [3].

Overall, we have used a common-sense decision-analytic framework to outline the types of tradeoffs involved in the introduction of new TB drugs such as bedaquiline. Though our quantitative predictions are limited by the available data, our results demonstrate the range of considerations involved in deciding whether to provide a drug to or beyond patients with the most highly resistant TB strains. These results may be used to guide future discussion around the appropriate use of new antibiotics, particularly about the relative costs and benefits of more restrictive policies that may protect a new drug at the cost of promoting existing background resistance.

References

1. World Health Organization. Global Tuberculosis Report 2015. Geneva2015.
2. Lienhardt C, Raviglione M, Spigelman M, Hafner R, Jaramillo E, Hoelscher M et al. New drugs for the treatment of tuberculosis: needs, challenges, promise, and prospects for the future. *The Journal of infectious diseases*. 2012;205 Suppl 2:S241-9. doi:10.1093/infdis/jis034.
3. Brigden G, Hewison C, Varaine F. New developments in the treatment of drug-resistant tuberculosis: clinical utility of bedaquiline and delamanid. *Infection and drug resistance*. 2015;8:367-78. doi:10.2147/idr.s68351.
4. Olaru ID, von Groote-Bidlingmaier F, Heyckendorf J, Yew WW, Lange C, Chang KC. Novel drugs against tuberculosis: a clinician's perspective. *The European respiratory journal*. 2014. doi:10.1183/09031936.00162314.
5. World Health Organization. The use of bedaquiline in the treatment of multidrug-resistant tuberculosis: interim policy guidance. Geneva2013.
6. Zumla A, Nahid P, Cole ST. Advances in the development of new tuberculosis drugs and treatment regimens. *Nature reviews Drug discovery*. 2013;12(5):388-404. doi:10.1038/nrd4001.
7. Brigden G, Nyang'wa BT, du Cros P, Varaine F, Hughes J, Rich M et al. Principles for designing future regimens for multidrug-resistant tuberculosis. *Bulletin of the World Health Organization*. 2014;92(1):68-74. doi:10.2471/blt.13.122028.
8. Diacon AH, Pym A, Grobusch MP, de los Rios JM, Gotuzzo E, Vasilyeva I et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. *The New England journal of medicine*. 2014;371:723-32. doi:10.1056/NEJMoa1313865.

9. Cox E, Laessig K. FDA approval of bedaquiline--the benefit-risk balance for drug-resistant tuberculosis. *The New England journal of medicine*. 2014;371(8):689-91. doi:10.1056/NEJMp1314385.
10. Mingote LR, Namutamba D, Apina F, Barnabas N, Contreras C, Elnour T et al. The use of bedaquiline in regimens to treat drug-resistant and drug-susceptible tuberculosis: a perspective from tuberculosis-affected communities. *Lancet*. 2015;385(9966):477-9. doi:10.1016/s0140-6736(14)60523-7.
11. Kakkar AK, Dahiya N. Current issues with the use of bedaquiline. *The Annals of pharmacotherapy*. 2014;48(5):666. doi:10.1177/1060028014521589.
12. Dalton T, Cegielski P, Akksilp S, Asencios L, Campos Caoili J, Cho SN et al. Prevalence of and risk factors for resistance to second-line drugs in people with multidrug-resistant tuberculosis in eight countries: a prospective cohort study. *Lancet*. 2012;380(9851):1406-17. doi:10.1016/s0140-6736(12)60734-x.
13. Cegielski JP, Dalton T, Yagui M, Wattanaamornkiet W, Volchenkov GV, Via LE et al. Extensive drug resistance acquired during treatment of multidrug-resistant tuberculosis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2014;59(8):1049-63. doi:10.1093/cid/ciu572.
14. Falzon D, Gandhi N, Migliori GB, Sotgiu G, Cox H, Holtz TH et al. Resistance to fluoroquinolones and second-line injectable drugs: impact on MDR-TB outcomes. *The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology*. 2012;1-24. doi:10.1183/09031936.00134712.

15. Chiang CY, Enarson DA, Yu MC, Bai KJ, Huang RM, Hsu CJ et al. Outcome of pulmonary multidrug-resistant tuberculosis: a 6-yr follow-up study. *The European respiratory journal*. 2006;28(5):980-5. doi:10.1183/09031936.06.00125705.
16. Pym AS, Diacon AH, Tang SJ, Conradie F, Danilovits M, Chuchottaworn C et al. Bedaquiline in the treatment of multidrug- and extensively drug-resistant tuberculosis. *The European respiratory journal*. 2015. doi:10.1183/13993003.00724-2015.
17. Guglielmetti L, Le Dû D, Jachym M, Henry B, Martin D, Caumes E et al. Compassionate use of bedaquiline for the treatment of multidrug-resistant and extensively drug-resistant tuberculosis: interim analysis of a French cohort. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2015;60:188-94. doi:10.1093/cid/ciu786.
18. Ndjeka N, Conradie F, Schnippel K, Hughes J, Bantubani N, Ferreira H et al. Treatment of drug-resistant tuberculosis with bedaquiline in a high HIV prevalence setting: an interim cohort analysis. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease*. 2015;19(8):979-85. doi:10.5588/ijtld.14.0944.
19. Franke MF, Appleton SC, Bayona J, Arteaga F, Palacios E, Llaro K et al. Risk factors and mortality associated with default from multidrug-resistant tuberculosis treatment. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2008;46(12):1844-51. doi:10.1086/588292.
20. Sanchez-Padilla E, Marquer C, Kalon S, Qayyum S, Hayrapetyan A, Varaine F et al. Reasons for defaulting from drug-resistant tuberculosis treatment in Armenia: a quantitative and qualitative study. *The international journal of tuberculosis and lung*

disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2014;18(2):160-7. doi:10.5588/ijtld.13.0369.

21. Gelmanova IY, Ahmad Khan F, Becerra MC, Zemlyanaya NA, Unakova IA, Andreev YG et al. Low rates of recurrence after successful treatment of multidrug-resistant tuberculosis in Tomsk, Russia. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2015;19(4):399-405. doi:10.5588/ijtld.14.0415.

22. Kurbatova E, Gammino VM, Bayona J, Becerra MC, Danilovitz M, Falzon D et al. Predictors of sputum culture conversion among patients treated for multidrug-resistant tuberculosis. International Journal of Tuberculosis and Lung Disease. 2012;16:1335-43. doi:10.5588/ijtld.11.0811.

23. Shah NS, Pratt R, Armstrong L, Robison V, Castro KG, Cegielski JP. Extensively drug-resistant tuberculosis in the United States, 1993-2007. *Jama*. 2008;300(18):2153-60. doi:10.1001/jama.300.18.2153.

24. Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. *PLoS medicine*. 2012;9:e1001300. doi:10.1371/journal.pmed.1001300.

25. Gagneux S, Long CD, Small PM, Van T, Schoolnik GK, Bohannan BJ. The competitive cost of antibiotic resistance in *Mycobacterium tuberculosis*. *Science (New York, NY)*. 2006;312(5782):1944-6. doi:10.1126/science.1124410.

26. Grandjean L, Gilman RH, Martin L, Soto E, Castro B, Lopez S et al. Transmission of Multidrug-Resistant and Drug-Susceptible Tuberculosis within Households: A Prospective

Cohort Study. PLoS medicine. 2015;12(6):e1001843; discussion e.

doi:10.1371/journal.pmed.1001843.

27. Luciani F, Sisson SA, Jiang H, Francis AR, Tanaka MM. The epidemiological fitness cost of drug resistance in *Mycobacterium tuberculosis*. Proceedings of the National Academy of Sciences of the United States of America. 2009;106(34):14711-5.

doi:10.1073/pnas.0902437106.

28. Bottger EC, Springer B. Tuberculosis: drug resistance, fitness, and strategies for global control. European journal of pediatrics. 2008;167(2):141-8. doi:10.1007/s00431-007-0606-9.

29. Dodd PJ, Knight GM, Lawn SD, Corbett EL, White RG. Predicting the long-term impact of antiretroviral therapy scale-up on population incidence of tuberculosis. PloS one.

2013;8(9):e75466. doi:10.1371/journal.pone.0075466.

APPENDIX S3

Tradeoffs in new anti-tuberculosis drug introduction policies: a model based analysis

Amber Kunkel, Frank G. Cobelens, Ted Cohen

Partial Model Diagrams

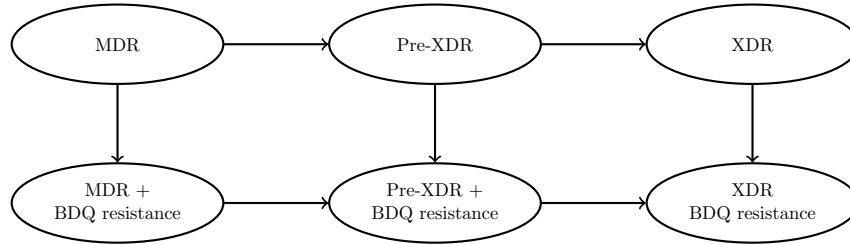


Figure S3.1: Transitions between resistance levels. We assume individuals can only acquire resistance while culture positive and receiving the drug of interest.

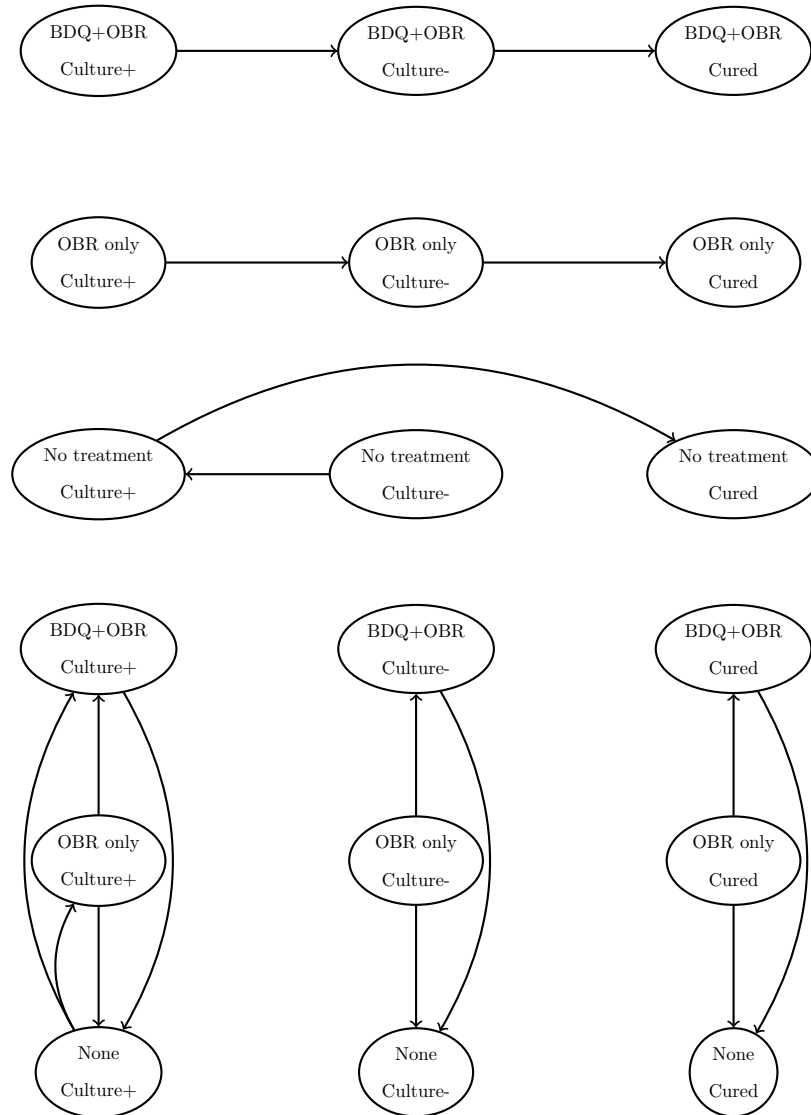


Figure S3.2: Transitions between TB health states (top) and regimen type (bottom). In the top figure, movements right indicate culture conversion or cure, while movements left indicate relapse. Only individuals who are untreated and culture negative are at risk of relapse. Untreated individuals may self-cure from active disease, but only long-term stable cures are counted. In the bottom figure, movements down indicate stopping treatment (routinely or default). Movements up indicate starting treatment (if untreated) or starting bedaquiline (if eligible and untreated or on OBR only). Changes in health status and regimen may occur simultaneously within one time step.

General Calculation Principles

Accounting for conditional probabilities

In constructing the model, the potential events for each week were modeled in sequence. For each weekly cycle we gave priority to events in an order that reflected the way they would be recorded as treatment outcomes. For example, for people receiving treatment we first recorded all deaths. Those people who did not die could end treatment routinely, or if not they could end treatment prematurely (default). We assumed only patients who remained on treatment could have culture converted, and only those who did not culture convert could have acquired resistance (to at most one drug per week). To account for ordering, we input the probability of each event conditional on not experiencing any of the events earlier in the calculation sequence that week.

Examples:

- Weekly probability of culture conversion - input conditional on not dying, defaulting, or finishing treatment that week
- Weekly probability of stopping treatment routinely - conditional on not dying that week
- Weekly probability of default - conditional on not dying or stopping treatment routinely that week

Converting rates to weekly probabilities

To convert rates to weekly probabilities (p), we first converted them to rates per week. We then used the following formula:

$$p = 1 - \exp(-rate)$$

Examples:

- Added mortality BDQ (rate 5 per 100 person-years, weekly probability 0.00096)

Resistance and relapse probabilities

To convert the probability of acquiring resistance prior to death, conversion, default, or stopping treatment (Q) into weekly probabilities, we used the following equation with the weekly probabilities of each event (p):

$$Q_{res} = \frac{p_{res}}{p_{die} + p_{default} + p_{stop} + p_{convert} + p_{res}}$$

Examples:

- Probability acquired BDQ resistance given XDR
- Probability acquired XDR given pre-XDR, not on BDQ
- All other acquired resistance parameters (but may include additional considerations below)

A similar equation was used to relate the weekly cure rate to the probability of moving from “culture negative” (high risk of relapse immediately after treatment) to “stable cure” prior to death, default, or stopping treatment.

Median time to culture conversion

Based on our literature review, we estimated the median time to culture conversion (if no one had died or stopped treatment) to be approximately 13 weeks for people initially MDR, 18 weeks for people initially pre-XDR, and 26 weeks for people initially XDR. We used TreeAge to estimate a weekly probability of conversion based on these targets and our fixed weekly probabilities of acquiring pre-XDR and XDR TB.

To simplify our sensitivity analyses, we chose to consider the effect of BDQ on the median time to culture conversion if no one had died, stopped treatment, or acquired resistance. We did this by calculating the weekly probabilities of conversion from above to the median time of culture conversion if no one had died, stopped treatment, or acquired resistance. Our bedaquiline multiplier was then applied to these values.

We converted median time to event parameters (in weeks) to weekly probabilities using the geometric distribution:

$$P = 1 - 2^{-1/M}$$

Probability acquiring pre-XDR without BDQ

From the literature, we estimated that the probability of acquiring resistance to any fluoroquinolone given initial MDR was approximately 0.065, and that the probability of acquiring resistance to any second-line injectable was similar. We also determined that the risk of XDR given pre-XDR was approximately 0.26. Note the informal notation: $P(\text{PreXDR}|\text{MDR})$ is the probability of developing at least PreXDR for an individual who is initially MDR, and not receiving bedaquiline.

$$P(\text{PreXDR}|\text{MDR}) = P(\text{FQR}|\text{MDR}) + P(\text{2LIR}|\text{MDR}) - P(\text{XDR}|\text{MDR})$$

$$P(\text{PreXDR}|\text{MDR}) = P(\text{FQR}|\text{MDR}) + P(\text{2LIR}|\text{MDR}) - P(\text{PreXDR}|\text{MDR})P(\text{XDR}|\text{PreXDR})$$

$$P(\text{PreXDR}|\text{MDR}) = .065 * 2 - 0.26 * P(\text{PreXDR}|\text{MDR})$$

$$P(\text{PreXDR}|\text{MDR}) = 0.103$$

Probability acquiring pre-XDR with BDQ

This is similar to the section above, except we also need to account for the potential to acquire resistance to bedaquiline. Note the informal notation: $P(\text{PreXDR}|\text{MDR})$ is the probability of developing at least PreXDR for an individual who is initially MDR (and BDQ sensitive), on bedaquiline.

$$P(\text{PreXDR}|\text{MDR}) = P(\text{FQR}|\text{MDR}) + P(\text{2LIR}|\text{MDR}) - P(\text{XDR}|\text{MDR})$$

$$P(\text{PreXDR}|\text{MDR}) = P(\text{FQR}|\text{MDR}) + P(\text{2LIR}|\text{MDR}) - P(\text{PreXDR}|\text{MDR})P(\text{XDR}|\text{develop PreXDR})$$

The issue here is that $P(\text{XDR}|\text{develop PreXDR})$ depends on whether the individual already has resistance to BDQ at the time they become PreXDR or not.

$$\begin{aligned} P(\text{XDR}|\text{develop PreXDR}) &= P(\text{already BDQR}|\text{develop PreXDR})P(\text{XDR}|\text{PreXDR}, \text{BDQR}) \\ &+ (1 - P(\text{already BDQR}|\text{develop PreXDR}))P(\text{XDR}|\text{PreXDR}, \text{BDQS}) \end{aligned}$$

To solve for $P(\text{already BDQR}|\text{develop PreXDR})$, we can use our knowledge of the risk of resistance to bedaquiline for people who are initially MDR vs preXDR.

$$\begin{aligned} P(\text{BDQR}|\text{MDR}) &= P(\text{BDQR prior to/without PreXDR}) \\ &+ (1 - P(\text{already BDQR}|\text{develop PreXDR}))P(\text{PreXDR}|\text{BDQS}, \text{MDR})P(\text{BDQR}|\text{PreXDR}, \text{BDQS}) \end{aligned}$$

$$P(\text{already BDQR}|\text{develop PreXDR}) = \frac{P(\text{BDQR prior to/without PreXDR})P(\text{PreXDR}|\text{MDR}, \text{BDQR})}{P(\text{PreXDR}|\text{MDR})}$$

Let X be the probability of developing bedaquiline resistance either prior to or without developing pre-XDR for people initially MDR on BDQ. Let Y be the probability of ever developing pre-XDR for people initially MDR on BDQ.

Let Q_{fm} be the probability of ever developing FQ resistance given MDR on BDQ. Let Q_{xpb} be the probability of ever developing XDR given pre-XDR and BDQ resistance. Let Q_{xp} be the probability of ever developing XDR given pre-XDR and BDQ sensitivity. Let Q_{bm} be the probability of developing bedaquiline resistance given initially MDR and BDQ sensitive. Let Q_{bp} be the probability of developing bedaquiline resistance given initially pre-XDR and BDQ sensitive. Let Q_{pmb} be the probability of developing pre-XDR

given initially MDR and bedaquiline resistant.

$$Y = 2Q_{fm} - Y \left(\frac{XQ_{xpb}Q_{pmb}}{Y} + \left(1 - \frac{XQ_{pmb}}{Y}\right)Q_{xp} \right)$$

$$Q_{bm} = X + \left(1 - \frac{XQ_{pmb}}{Y}\right)YQ_{bp}$$

Solving the first equation for X:

$$Q_{bm} - YQ_{bp} = X - XQ_{pmb}Q_{bp}$$

$$Q_{bm} - YQ_{bp} = X(1 - Q_{pmb}Q_{bp})$$

$$\frac{Q_{bm} - YQ_{bp}}{1 - Q_{pmb}Q_{bp}} = X$$

Substituting into the first equation:

$$Y = 2Q_{fm} - Y \left(\frac{XQ_{xpb}Q_{pmb}}{Y} + \left(1 - \frac{XQ_{pmb}}{Y}\right)Q_{xp} \right)$$

$$Y = 2Q_{fm} - XQ_{xpb}Q_{pmb} - YQ_{xp} + XQ_{xp}Q_{pmb}$$

$$Y = 2Q_{fm} - XQ_{pmb}(Q_{xpb} - Q_{xp}) - YQ_{xp}$$

$$Y = 2Q_{fm} - \frac{Q_{bm} - YQ_{bp}}{1 - Q_{pmb}Q_{bp}}Q_{pmb}(Q_{xpb} - Q_{xp}) - YQ_{xp}$$

We used Matlab's symbolic toolbox to solve this equation for Y. We checked this equation by verifying that our TreeAge model gave similar results for X and the probability of developing XDR given initially MDR and BDQ sensitive for a typical parameter set.

Probability acquiring XDR or BDQ resistance - from pre-XDR receiving BDQ

People can develop XDR without or prior to developing BDQ resistance, or they can acquire BDQ resistance first, increasing their chances of developing XDR. Similarly people can develop BDQ resistance without, prior to, or after developing XDR.

Let X be the weekly probability of developing BDQ resistance given pre-XDR. Let Y be the weekly probability of developing XDR given pre-XDR. Let A be the weekly probability of any other possible event (probability of dying or defaulting or finishing treatment or culture converting).

Let Q_{bp} be the probability of ever developing BDQ resistance starting pre-XDR, on BDQ. Let Q_{xp} be the probability of ever developing XDR starting pre-XDR, BDQ-sensitive, on BDQ. Let Q_{bx} be the probability

of ever developing BDQ resistance starting XDR. Let Q_{xpb} be the proportion of people with pre-XDR and BDQ resistance who acquire XDR prior to death, default, finishing treatment, or culture conversion.

We can then use the following equations to solve for X and Y .

$$Q_{bp} = \frac{X}{X + Y + A} + Q_{bx} \frac{Y}{X + Y + A}$$

$$Q_{xp} = \frac{Y}{X + Y + A} + Q_{xbp} \frac{X}{X + Y + A}$$

Therefore

$$Q_{bp}(X + Y + A) = X + Q_{bx}Y$$

$$Q_{xp}(X + Y + A) = Y + Q_{xbp}X$$

Solving for X first:

$$(Q_{bp} - 1)X = Q_{bx}Y - Q_{bp}(Y + A)$$

$$X = \frac{(Q_{bx} - Q_{bp})Y - Q_{bp}A}{Q_{bp} - 1}$$

Plugging into the equation for Y:

$$Q_{xp}(X + Y + A) = Y + Q_{xbp}X$$

$$(Q_{xp} - Q_{xbp})X + Q_{xp}A = Y - Q_{xp}Y$$

$$(Q_{xp} - Q_{xbp}) \left(\frac{(Q_{bx} - Q_{bp})Y - Q_{bp}A}{Q_{bp} - 1} \right) + Q_{xp}A = Y - Q_{xp}Y$$

$$Q_{xp}A - (Q_{xp} - Q_{xbp}) \left(\frac{Q_{bp}A}{Q_{bp} - 1} \right) = Y - Q_{xp}Y - (Q_{xp} - Q_{xbp}) \left(\frac{(Q_{bx} - Q_{bp})Y}{Q_{bp} - 1} \right)$$

$$Q_{xp}A - \frac{(Q_{xp} - Q_{xbp})Q_{bp}A}{Q_{bp} - 1} = Y \left(1 - Q_{xp} - \frac{(Q_{xp} - Q_{xbp})(Q_{bx} - Q_{bp})}{Q_{bp} - 1} \right)$$

$$Y = \frac{Q_{xp}A(Q_{bp} - 1) - (Q_{xp} - Q_{xbp})Q_{bp}A}{(Q_{bp} - 1)(1 - Q_{xp}) - (Q_{xp} - Q_{xbp})(Q_{bx} - Q_{bp})}$$

Table S3.1: Detailed description of model parameters

Name	Description	Calculation & Units	Value	Explanation
Age	Age starting treatment	Years	30	
InitMDR	Proportion of people initiating MDR treatment without pre-XDR or XDR TB	Proportion	0.671	[1]
InitPreXDR	Proportion of people initiating MDR treatment with pre-XDR TB	Proportion	0.262	[1]
InitXDR	Proportion of people initiating MDR treatment with XDR TB	Proportion	0.067	[1]
MedianCCMDR	Median time to culture conversion - MDR, not on BDQ	median time in weeks, assuming no death, default, or acquired resistance	12.82 (13 allowing for acquired resistance)	[2] (13 weeks for all patients), [3] (13 weeks for MDR only), [4]
MedianCCPreXDR	Median time to culture conversion - pre-XDR, not on BDQ	median time in weeks, assuming no death, default, or acquired resistance	16.85 (18 allowing for acquired resistance)	[2] (HR 0.6 FQ-res, 0.8 2LI-res), [4]
MedianCCXDR	Median time to culture conversion - XDR, not on BDQ	median time in weeks, assuming no death, default, or acquired resistance	26	[3] (183 days), [2] (HR 0.52)
pAcquireBDQ_MDR	Weekly probability of acquiring BDQ resistance from MDR	Probability of ever acquiring BDQ resistance (initially MDR) is RiskResBDQXDR/16	See calculation page	Assuming each new drug reduces the risk of resistance 4-fold, similar to [5]
pAcquireBDQ_PreXDR	Weekly probability of acquiring BDQ resistance from pre-XDR	Probability of acquiring BDQ resistance (initially pre-XDR) is RiskResBDQXDR/4	See calculation page	[5]
pAcquireBDQ_XDR	Weekly probability of acquiring BDQ resistance from XDR	Probability of ever acquiring BDQ resistance (initially XDR) is RiskResBDQXDR	See calculation page	[5]

Table S3.1 (Continued)

pAcquirePreXDR	Weekly probability of acquiring pre-XDR (from MDR, not on BDQ)	Probability of ever acquiring FQ-R or 2LI-R (initially MDR, not on BDQ) prior to death, default, stopping treatment, or conversion is 0.065	See calculation page	[5]
pAcquirePreXDR_BDQ	Weekly probability of acquiring pre-XDR (from MDR, while on BDQ)	Probability of ever acquiring FQ-R or 2LI-R (initially MDR, on BDQ) prior to death, default, stopping treatment, or conversion is 0.065/ResProtectionBDQ	See calculation page	[5]
pAcquireXDR	Weekly probability of acquiring XDR (from pre-XDR, not on BDQ)	Probability of ever acquiring XDR (initially pre-XDR, not on BDQ) prior to death, default, stopping treatment, or conversion is 0.26	See calculation page	[5]
pAcquireXDR_BDQ	Weekly probability of acquiring XDR (from pre-XDR, while on BDQ)	Probability of ever acquiring XDR (initially pre-XDR, on BDQ) prior to death, default, stopping treatment, or conversion is 0.26/ResProtectionBDQ	See calculation page	[5]
pConvertMDR	Weekly probability of culture conversion - MDR on BR	Assuming median time to culture conversion in the absence of death, default, or acquired resistance would be MedianCCMDR	See calculation page	NA
pConvertMDR_BDQ	Weekly probability of culture conversion - MDR on BDQ	Assuming median time to culture conversion in the absence of death, default, or acquired resistance would be MedianCCMDR*BDQMedianCCRR	See calculation page	NA
pConvertPreXDR	Weekly probability of culture conversion - PreXDR on BR	Assuming median time to culture conversion in the absence of death, default, or acquired resistance would be MedianCCPreXDR	See calculation page	NA
pConvertPreXDR_BDQ	Weekly probability of culture conversion - PreXDR on BDQ	Assuming median time to culture conversion in the absence of death, default, or acquired resistance would be MedianCCPreXDR*BDQMedianCCRR	See calculation page	NA
pConvertXDR	Weekly probability of culture conversion - XDR on BR	Assuming median time to culture conversion in the absence of death, default, or acquired resistance would be MedianCCXDR	See calculation page	NA
pConvertXDR_BDQ	Weekly probability of culture conversion - XDR on BDQ	Assuming median time to culture conversion in the absence of death, default, or acquired resistance would be MedianCCXDR*BDQMedianCCRR	See calculation page	NA

Table S3.1 (Continued)

pCure	Weekly probability of moving from "culture negative" (high relapse risk post-treatment) to "cure"	Reflects relapse probabilities that depend on regimen and resistance pattern	NA	
pCureUntreated	Weekly probability of moving from "culture positive" to "cure" for untreated individuals	Assumes a case fatality rate of 60% for untreated TB	[6]	.0057/(1-pDie)
pDieBDQ	Weekly probability of dying from adverse effects related to BDQ administration	Assume constant throughout treatment for all patients who have ever received BDQ, reflecting long half-life	NA	See calculation page
pDieTreatedTB	Weekly excess probability of dying from TB while culture positive on treatment	Chosen such that 16% of people with XDR on BR die prior to default or treatment completion. Excess mortality only applies while culture positive	[7] (15% of patients with XDR TB die, sums to 95%)	.0075+pDieWell
pDieUntreatedTB	Weekly excess probability of dying from TB while culture positive not on treatment	Assumed to be equal to pDieTreatedTB (case fatality of untreated TB still >> treated TB because excess mortality only applies while culture positive)	[7]	.0075+pDieWell
pDieWell	Weekly probability of dying - background mortality	Varies according to age	[8]	Taken from WHO European region male life tables from 2013
pEnd	Probability of stopping treatment routinely	Assume average treatment duration of 21 months regardless of resistance pattern	[9]	.011/(1-pDie)
pRelapse	Weekly probability of relapse after treatment (for individuals stopping treatment not fully cured)	Assume 75% of relapses occur within one year	[10-13]	0.0263
pStartBDQPreXDR	Weekly probability of starting bedaquiline for patients with Pre-XDR TB receiving BR	0 if ineligible for BDQ; otherwise assume takes an average of 13 weeks for DST results	[9]	0.077/((1-pDie)*(1-pDefault)*(1-pEnd))
pStartBDQXDR	Weekly probability of starting bedaquiline for patients with XDR TB receiving BR	0 if ineligible for BDQ; otherwise assume takes an average of 13 weeks for DST results	[9]	0.077/((1-pDie)*(1-pDefault)*(1-pEnd))

Table S3.1 (Continued)

pStartTreat	Weekly probability of starting treatment for untreated, culture positive individuals	Assume average 1.5 years (78 weeks) prior to starting treatment	$0.0128 / ((1 - pDie) * (1 - pCureUntreated))$	[14] (1.15 years smear+, 2.39 years all confirmed TB among HIV- individuals. We have chosen an intermediate value)
pStartTreatBDQ	Probability of receiving BDQ from the initiation of MDR TB treatment	1 if all people with MDR are eligible for BDQ; 0 otherwise	GetBDQMDR	NA
pStartTreatBR	Probability of receiving BR only from initiation of MDR TB treatment	0 if all people with MDR are eligible for BDQ; 1 otherwise	1-GetBDQMDR	NA
RelapsePropMDR	Proportion of people with MDR TB only who ever relapse	NA	0.04	[15-17]
RelapsePropPreXDR	Proportion of people with PreXDR TB only who ever relapse	NA	0.08	[15]
RelapsePropXDR	Proportion of people with XDR TB only who ever relapse	NA	0.16	[15, 18]
RiskPreXDRBDQ	Risk of ever developing PreXDR for individuals with MDR TB receiving BDQ	Assuming BDQ reduces the risk of resistance to any fluoroquinolone or any second-line injectable by ResProtectionBDQ	See calculation page	NA
SecMultiUntreated	Ratio of infectiousness of untreated to treated individuals with culture positive TB	Assuming similar to the infectiousness of smear-positive vs. smear-negative individuals	5	[19-21]
uLE	Weekly utility when calculating life expectancy	Fraction of a year	1/52	NA
uSec_MDR	Weekly utility when calculating secondary MDR cases (on treatment, culture positive)	10 persons infected per year if smear positive*0.1 chance of progressing to active TB*.7 fitness MDR*(1/SecMultiUntreated)	0.14/52	[21-27]

Table S3.1 (Continued)

uSec_MDR_BDQ	Weekly utility when calculating secondary MDR+BDQR cases (on treatment, culture positive)	10 persons infected per year if smear positive*0.1 chance of progressing to active TB* 7 fitness MDR*FitCostBDQR* (1/SecMultiUntreated)	0.14*FitCostBDQR/52	[21-27]
uSec_PreX_BDQ	Weekly utility when calculating secondary PreXDR+BDQR cases (on treatment, culture positive)	10 persons infected per year if smear positive*0.1 chance of progressing to active TB* .63 fitness PreXDRDR* FitCostBDQR* (1/SecMultiUntreated)	.126*FitCostBDQR/52	[21-27]
uSec_PreXDR	Weekly utility when calculating secondary PreXDR cases (on treatment, culture positive)	10 persons infected per year if smear positive*0.1 chance of progressing to active TB* .63 fitness PreXDR* (1/SecMultiUntreated)	.126/52	[21-27]
uSec_XDR	Weekly utility when calculating secondary XDR cases (on treatment, culture positive)	10 persons infected per year if smear positive*0.1 chance of progressing to active TB* .51 fitness XDR*(1/SecMultiUntreated)	0.113/52	[21-27]
uSec_XDR_BDQR	Weekly utility when calculating secondary XDR+BDQR cases (on treatment, culture positive)	10 persons infected per year if smear positive*0.1 chance of progressing to active TB* .51 fitness XDR*FitCostBDQR* (1/SecMultiUntreated)	0.113*FitCostBDQR/52	[21, 22, 27-30]
GetBDQMDR	Whether people with MDR TB are eligible for BDQ	Varies depending on treatment scenario	1 if yes, 0 if no	NA
GetBDQPreXDR	Whether people with PreXDR TB are eligible for BDQ	Varies depending on treatment scenario	1 if yes, 0 if no	NA
GetBDQXDR	Whether people with XDR TB are eligible for BDQ	Varies depending on treatment scenario	1 if yes, 0 if no	NA
pDefault	Weekly default probability	Constant throughout treatment, value depends on regimen. Baseline is chosen such that 17.3% of people with XDR on BR default prior to death or stopping treatment.	See TreeAge file	[7]
pDie	Weekly probability of death	Depends on whether the individual is culture positive or receiving bedaquiline and their age	Sum of relevant probabilities	NA
RelapseProp	Proportion of people who would relapse post-treatment	Depends on the individual's regimen and resistance pattern	See TreeAge file	NA

References

1. Dalton T, Cegielski P, Akksilp S, Asencios L, Campos Caoili J, Cho SN et al. Prevalence of and risk factors for resistance to second-line drugs in people with multidrug-resistant tuberculosis in eight countries: a prospective cohort study. *Lancet*. 2012;380(9851):1406-17. doi:10.1016/s0140-6736(12)60734-x.
2. Kurbatova E, Gammino VM, Bayona J, Becerra MC, Danilovitz M, Falzon D et al. Predictors of sputum culture conversion among patients treated for multidrug-resistant tuberculosis. *International Journal of Tuberculosis and Lung Disease*. 2012;16:1335-43. doi:10.5588/ijtld.11.0811.
3. Shah NS, Pratt R, Armstrong L, Robison V, Castro KG, Cegielski JP. Extensively drug-resistant tuberculosis in the United States, 1993-2007. *Jama*. 2008;300(18):2153-60. doi:10.1001/jama.300.18.2153.
4. Diacon AH, Lounis N, Dannemann B. Multidrug-resistant tuberculosis and bedaquiline. *The New England journal of medicine*. 2014;371(25):2436. doi:10.1056/NEJMc1412235.
5. Cegielski JP, Dalton T, Yagui M, Wattanaamornkiet W, Volchenkov GV, Via LE et al. Extensive drug resistance acquired during treatment of multidrug-resistant tuberculosis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2014;59(8):1049-63. doi:10.1093/cid/ciu572.
6. Tiemersma EW, van der Werf MJ, Borgdorff MW, Williams BG, Nagelkerke NJD. Natural history of tuberculosis: duration and fatality of untreated pulmonary tuberculosis in HIV negative patients: a systematic review. *PloS one*. 2011;6:e17601. doi:10.1371/journal.pone.0017601.
7. Falzon D, Gandhi N, Migliori GB, Sotgiu G, Cox H, Holtz TH et al. Resistance to fluoroquinolones and second-line injectable drugs: impact on MDR-TB outcomes. *The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology*. 2012;1-24. doi:10.1183/09031936.00134712.
8. World Health Organization. Life tables by WHO region: Europe. In: *Global Health Observatory data repository*. 2015. Accessed June 11 2015.
9. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. Geneva 2011.
10. Glynn JR, Murray J, Bester A, Nelson G, Shearer S, Sonnenberg P. High rates of recurrence in HIV-infected and HIV-uninfected patients with tuberculosis. *The Journal of infectious diseases*. 2010;201(5):704-11. doi:10.1086/650529.

11. Guerra-Assuncao JA, Houben RM, Crampin AC, Mzembe T, Mallard K, Coll F et al. Recurrence due to relapse or reinfection with *Mycobacterium tuberculosis*: a whole-genome sequencing approach in a large, population-based cohort with a high HIV infection prevalence and active follow-up. *The Journal of infectious diseases*. 2015;211(7):1154-63. doi:10.1093/infdis/jiu574.
12. Marx FM, Dunbar R, Enarson DA, Williams BG, Warren RM, van der Spuy GD et al. The temporal dynamics of relapse and reinfection tuberculosis after successful treatment: a retrospective cohort study. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2014;58(12):1676-83. doi:10.1093/cid/ciu186.
13. Nunn AJ, Phillips PP, Mitchison DA. Timing of relapse in short-course chemotherapy trials for tuberculosis. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease*. 2010;14(2):241-2.
14. Corbett EL, Charalambous S, Moloji VM, Fielding K, Grant AD, Dye C et al. Human immunodeficiency virus and the prevalence of undiagnosed tuberculosis in African gold miners. *American journal of respiratory and critical care medicine*. 2004;170(6):673-9. doi:10.1164/rccm.200405-590OC.
15. Chiang CY, Enarson DA, Yu MC, Bai KJ, Huang RM, Hsu CJ et al. Outcome of pulmonary multidrug-resistant tuberculosis: a 6-yr follow-up study. *The European respiratory journal*. 2006;28(5):980-5. doi:10.1183/09031936.06.00125705.
16. Johnston JC, Khan FA, Dowdy DW. Reducing relapse in tuberculosis treatment: is it time to reassess WHO treatment guidelines? *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease*. 2015;19(6):624. doi:10.5588/ijtld.15.0224.
17. Gelmanova IY, Ahmad Khan F, Becerra MC, Zemlyanaya NA, Unakova IA, Andreev YG et al. Low rates of recurrence after successful treatment of multidrug-resistant tuberculosis in Tomsk, Russia. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease*. 2015;19(4):399-405. doi:10.5588/ijtld.14.0415.
18. Menzies D, Benedetti A, Paydar A, Martin I, Royce S, Pai M et al. Effect of duration and intermittency of rifampin on tuberculosis treatment outcomes: a systematic review and meta-analysis. *PLoS medicine*. 2009;6(9):e1000146. doi:10.1371/journal.pmed.1000146.

19. Tostmann A, Kik SV, Kalisvaart NA, Sebek MM, Verver S, Boeree MJ et al. Tuberculosis transmission by patients with smear-negative pulmonary tuberculosis in a large cohort in the Netherlands. *Clinical infectious diseases* : an official publication of the Infectious Diseases Society of America. 2008;47(9):1135-42. doi:10.1086/591974.
20. Behr MA, Warren SA, Salamon H, Hopewell PC, Ponce de Leon A, Daley CL et al. Transmission of *Mycobacterium tuberculosis* from patients smear-negative for acid-fast bacilli. *Lancet*. 1999;353(9151):444-9.
21. Styblo K. *Epidemiology of Tuberculosis: Selected Papers*. The Hague: Royal Netherlands Tuberculosis Foundation (KNCV); 1991.
22. Trunz BB, Fine P, Dye C. Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: a meta-analysis and assessment of cost-effectiveness. *Lancet*. 2006;367(9517):1173-80. doi:10.1016/s0140-6736(06)68507-3.
23. Gagneux S, Long CD, Small PM, Van T, Schoolnik GK, Bohannon BJ. The competitive cost of antibiotic resistance in *Mycobacterium tuberculosis*. *Science (New York, NY)*. 2006;312(5782):1944-6. doi:10.1126/science.1124410.
24. Luciani F, Sisson SA, Jiang H, Francis AR, Tanaka MM. The epidemiological fitness cost of drug resistance in *Mycobacterium tuberculosis*. *Proceedings of the National Academy of Sciences of the United States of America*. 2009;106(34):14711-5. doi:10.1073/pnas.0902437106.
25. Bottger EC, Springer B. Tuberculosis: drug resistance, fitness, and strategies for global control. *European journal of pediatrics*. 2008;167(2):141-8. doi:10.1007/s00431-007-0606-9.
26. Grandjean L, Gilman RH, Martin L, Soto E, Castro B, Lopez S et al. Transmission of Multidrug-Resistant and Drug-Susceptible Tuberculosis within Households: A Prospective Cohort Study. *PLoS medicine*. 2015;12(6):e1001843; discussion e. doi:10.1371/journal.pmed.1001843.
27. Vynnycky E, Fine PE. The natural history of tuberculosis: the implications of age-dependent risks of disease and the role of reinfection. *Epidemiology and infection*. 1997;119(2):183-201.
28. Becerra MC, Appleton SC, Franke MF, Chalco K, Arteaga F, Bayona J et al. Tuberculosis burden in households of patients with multidrug-resistant and extensively drug-resistant tuberculosis: a retrospective cohort study. *Lancet*. 2011;377(9760):147-52. doi:10.1016/s0140-6736(10)61972-1.

29. Naidoo CC, Pillay M. Increased in vitro fitness of multi- and extensively drug-resistant F15/LAM4/KZN strains of *Mycobacterium tuberculosis*. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases*. 2014;20(6):O361-9. doi:10.1111/1469-0691.12415.
30. Smith KL, Saini D, Bardarov S, Larsen M, Frothingham R, Gandhi NR et al. Reduced virulence of an extensively drug-resistant outbreak strain of *Mycobacterium tuberculosis* in a murine model. *PloS one*. 2014;9(4):e94953. doi:10.1371/journal.pone.0094953.