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On treatment of tuberculosis in heterogeneous populations

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Abstract

Global eradication of tuberculosis (TB) is an international agenda. Thus understanding effects of treatment of TB in different settings is crucial. In previous work, we introduced the framework for a mathematical model of epidemic TB in demographically distinct, heterogeneous populations. Simulations showed the importance of genetic susceptibility in determining endemic prevalence levels. In the work presented here, we include treatment and investigate different strategies for treatment of latent and active TB disease in heterogeneous populations. We illustrate how the presence of a genetically susceptible subpopulation dramatically alters effects of treatment in the same way a core population does in the setting of sexually transmitted diseases. In addition, we evaluate treatment strategies that focus specifically on this subpopulation, and our results indicate that genetically susceptible subpopulations should be accounted for when designing treatment strategies to achieve the greatest reduction in disease prevalence.

Keywords: Tuberculosis; Genetic susceptibility; Treatment; Chemoprophylaxis; Math model

1. Introduction

Tuberculosis (TB) is an infectious disease caused by the bacterium *Mycobacterium tuberculosis*. One-third of the world's population is estimated to be infected with *M. tuberculosis*, resulting in nearly 3 million deaths each year (Bleed et al., 2001; Bloom, 1994; Snider et al., 1994). The continual high burden of TB infection in regions of Southeast Asia, Africa, and Russia has renewed interest in global TB control (Floyd et al., 2002; Reichman and Tanne, 2002). The emergence of drug-resistant strains of *M. tuberculosis* (Reichman and Tanne, 2002) and TB/HIV co-infection (Kirschner, 1999; Porco et al., 2001; Toossi et al., 2001) will likely impact TB treatment and control strategies (American Thoracic Society, 1994; Floyd et al., 2002).

Treatment strategies for *M. tuberculosis* infection depend on disease status. Treatment of active disease (usually identified by the presence of bacteria in sputum) follows a 6–12 month course with a combination of 2 or more antibiotics (American Thoracic Society, 1994; Gittler, 1994; WHO, 1983). If compliance is maintained with this therapeutic approach and the *M. tuberculosis* strain is drug-sensitive, 85% of patients convert from sputum positive to sputum negative, becoming uninfectious within 2 months (American Thoracic Society, 1994). Nearly 95% of patients will convert to sputum negative by the completion of treatment (they remain PPD^+, however[1]) (American Thoracic Society, 1994; Blower and Gerberding, 1998; Kirschner, 1999). Unfortunately, there is no data to indicate whether successfully treated individuals (those who convert from sputum positive to sputum negative) enter a latent state of TB. If this is the case, then following immunosuppression or some other perturbation, these individuals may suffer reactive TB disease.

More than 90% of actively infected individuals receive effective therapy in developed countries, while in developing countries, up to only 50% of actively infected individuals may receive effective therapy (Bleed et al., 2001; Lietman and Blower, 1999). Treatment of actively infected individuals is the only option in most developing countries because it is difficult to identify latently infected individuals, especially in regions where the BCG vaccine is routinely used (vaccinated

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[1] PPD (purified protein derivative) is used in the skin test for responsiveness to TB.

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individuals report PPD^+). Treatment of latent infections, termed chemoprophylaxis or preventative therapy, may be administered to as few as 10% of latently infected individuals (Blower and Gerberding, 1998). Chemoprophylaxis typically consists of a 6–12 month course of a single antimicrobial agent. In the USA, where the BCG vaccine is not used, it is routine for scientists, individuals in hospital or clinical settings, and those at high risk of infection or reactive disease to be tested and, if results are positive, to receive chemoprophylaxis treatment.

Although antibiotics for both latent and active disease are available that could theoretically eliminate TB, noncompliance due to the long duration of treatment regimens (American Thoracic Society, 1994) and the inability of health organizations around the world to agree on effective treatment/control strategies (Floyd et al., 2002; Reichman and Tanne, 2002) have drastically hindered the success of TB treatment. A full understanding of the effectiveness of treatment and control strategies within different regions of the world is still needed. Mathematical models may be useful tools to investigate various treatment strategies in these settings. Model results can then suggest important factors that should be considered when designing treatment strategies for a given region.

In this paper we present a mathematical model of epidemic TB in demographically distinct, heterogeneous populations. We build upon the modeling framework presented in Murphy et al. (2002) by including treatment of both latent infections (chemoprophylaxis) and active TB disease (therapeutics). Our goal is to describe how the presence of a genetically susceptible subpopulation can alter the results of a given treatment strategy. Information gained from model simulations can then be used to assist health organizations by suggesting possible limitations of currently designed strategies. To our knowledge this is the first paper to investigate treatment strategies in genetically heterogeneous populations.

2. Background

Initial infection with *M. tuberculosis* occurs when bacteria within aerosol droplets are inhaled into the lung (Smith and Moss, 1994). Characteristics of the immune response to initial infection dictate whether an individual will suffer a latent infection, in which the bacteria are contained, or active disease, where the host suffers clinical symptoms and can transmit bacteria. Roughly 5–10% of initial infections produce primary active TB within 2 years (Comstock, 1982, Styblo, 1986) while the lifetime risk of a latent infection reactivating to active TB disease is 5–10% (Adler and Rose, 1996; Karus, 1983). A loss or reduction in immunity, due to co-infection with HIV for example, may increase the probability of reactivation up to 10% per year (Parrish et al., 1998). The risks of disease progression are difficult to estimate and vary greatly between studies (Parrish et al., 1998; Vynnycky and Fine, 1997).

Consistent estimates of *M. tuberculosis* transmission rates do not exist; aerosol transmission has been reported either as rather inefficient, requiring extended contact between individuals (Enarson, 1994), or extremely efficient, with multiple secondary infections arising from one source of infection (Castillo-Chávez and Feng, 1997; Styblo, 1991). In addition to bacterial virulence, it is likely that socio-economic status, family size, crowding, malnutrition, and limited access to health care or effective treatment influence transmission (Chapman and Dyerly, 1964; Nardell and Piessens, 2000).

Many genetic factors are implicated in susceptibility and resistance to *M. tuberculosis* infection (Bellamy and Hill, 1998; Bellamy et al., 1998; Bothamley et al., 1993; Goldfeld et al., 1998; Hill, 1998; Kramnik et al., 2000; Meyer et al., 1998; Rook et al., 1986; Selvaraj et al., 1998; Wilkinson et al., 1999). These factors include key elements of the immune system responsible for presenting antigen from foreign pathogens to immune effector cells (Bothamley et al., 1993; Goldfeld et al., 1998; Meyer et al., 1998; Selvaraj et al., 1998), the vitamin D receptor (Bellamy and Hill, 1998; Rook et al., 1986), and macrophage proteins associated with natural resistance (Bellamy et al., 1998; Hill, 1998). A particular allele (HLA-DR2) is highly correlated with susceptibility to TB disease in India and is present in 30% of that population (Bothamley et al., 1989; Brahmajothi et al., 1991; Mehra et al., 1986; Rajalingam et al., 1996; Selvaraj et al., 1998; Singh et al., 1983; Subramanian et al., 1995). In caucasoid populations of Western Europe and the USA, the allele is present in only 8–15% of the population (Awad et al., 1987; Zachary et al., 1996).

We have developed a mathematical model of epidemic TB in a population with genetic heterogeneity towards *M. tuberculosis* infection (Murphy et al., 2002). Our work is based largely on a model of HIV infection in a population stratified by genotype (Sullivan et al., 2001). Specifically, we focused on modeling TB in a population with an inherently susceptible subpopulation with the goal of partially explaining the wide variation in TB levels between countries. For example, prevalence of TB in the USA is less than 5% (CDC, 1999), while in India and other Southeast Asian regions prevalence may be near 50% (Bleed et al., 2001; Chakraborty, 1997; WHO, 1997). The world average of TB prevalence is currently estimated to be 33% (Bleed et al., 2001).

In Murphy et al. (2002) we identify key model parameters affecting prevalence and incidence rates of TB infection within heterogeneous populations. Parameters such as fraction of the population with a genetic

susceptibility phenotype, death rate of individuals with active TB and transmission parameters strongly affect steady-state levels of prevalence and incidence rates of TB.

We also present numerical simulations of the model in Murphy et al. (2002) to illustrate effects of a specific host susceptibility phenotype on population-level TB disease dynamics. Results show that prevalence of TB could double (from 33% to roughly 60%) if a genetically susceptible phenotype is present in only 30% of the population. We also use simulations to understand the role of genetic heterogeneity in two demographic settings: a high-growth population with high birth and death rates (similar to those of India) and a low-growth population with low birth and death rates (similar to those of the USA).

3. Modeling treatment in heterogeneous populations

In our previous model formulation we did not account for treatment of TB as a necessary simplification towards understanding the role of genetic susceptibility. We now conduct a study of TB treatment by including therapy into our baseline model of genetic susceptibility to *M. tuberculosis* infection (see Murphy et al., 2002). This allows us to explore treatment of particular subpopulations, and thus determine if treatment strategies should focus more on particular groups of individuals (i.e. genetic susceptible individuals) versus the general population as a whole. Specifically, if treating only susceptible individuals can significantly decrease the prevalence of TB or if the presence of a genetic susceptibility factor can reduce the effectiveness of a treatment strategy, then identifying the level of genetic susceptiblity present in the population may be a reasonable public health measure.

We use a system of six nonlinear, ordinary differential equations to model the dynamics of *M. tuberculosis* infection within a heterogeneous population. Suppressing time-dependence t for each variable and setting $P(t)=U_N(t)+U_S(t)+L_N(t)+L_S(t)+T_N(t)+T_S(t)$, the equations are:

$$\frac{dU_N}{dt} = b(1-v) - \beta_w U_N \frac{T_N}{P} - \beta_x U_N \frac{T_S}{P} - \mu U_N, \quad (1)$$

$$\frac{dU_S}{dt} = bv - \beta_y U_S \frac{T_N}{P} - \beta_z U_S \frac{T_S}{P} - \mu U_S, \quad (2)$$

$$\frac{dL_N}{dt} = (1-p_N)\beta_w U_N \frac{T_N}{P} + (1-p_N)\beta_x U_N \frac{T_S}{P} - (1-lt_N) r_N L_N + at_N T_N - \mu L_N, \quad (3)$$

$$\frac{dL_S}{dt} = (1-p_S)\beta_y U_S \frac{T_N}{P} + (1-p_S)\beta_z U_S \frac{T_S}{P} - (1-lt_s) r_S L_S + at_S T_S - \mu L_S, \quad (4)$$

$$\frac{dT_N}{dt} = p_N \beta_w U_N \frac{T_N}{P} + p_N \beta_x U_N \frac{T_S}{P} + (1-lt_N) r_N L_N - at_N T_N - \mu_{TB} T_N, \quad (5)$$

$$\frac{dT_S}{dt} = p_S \beta_y U_S \frac{T_N}{P} + p_S \beta_z U_S \frac{T_S}{P} + (1-lt_S) r_S L_S - at_S T_S - \mu_{TB} T_S. \quad (6)$$

3.1. Model assumptions

Fig. 1 shows the model diagram, which we briefly outline. A more detailed description can be found in Murphy et al. (2002). Births occur at a constant rate b into the uninfected classes U_N and U_S and a constant proportion v of new children are born genetically susceptible to *M. tuberculosis* infection while $(1-v)$ are genetically neutral. Death rates in the model depend on disease status: individuals in the susceptible and latently infected populations (U_N, U_S, L_N, L_S) die from all-cause death at constant per capita rate μ, while individuals with active TB (T_N, T_S) die only from disease at a per capita rate μ_{TB}. Based on the disparate time-scales of natural death versus death to due TB disease, we assume that $\mu < \mu_{TB}$.

Transmission of *M. tuberculosis* occurs following adequate contact between a susceptible and an infectious individual. We assume that latently infected individuals are not infectious, and thus not capable of transmitting bacteria. We use the standard incidence expression $\beta U(t)(T(t)/P(t))$ (represented by $U \otimes T$) to indicate successful transmission of *M. tuberculosis* due

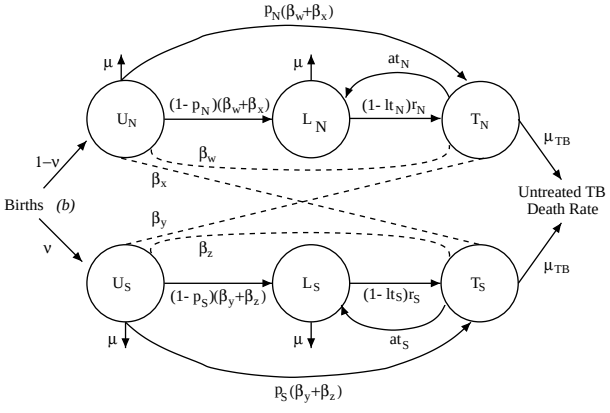

Fig. 1. TB epidemic model including genetically neutral (U_N, L_N, T_N) and genetically susceptible (U_S, L_S, T_S) populations. Births (b) occur at a constant rate with a fraction (v) being genetically more susceptible to infection. Transmission/receipt of *M. tuberculosis* is represented by β_j $(j = w, x, y, z)$, and potential interactions leading to infection are indicated by dashed lines. Direct progression to active TB and the reactivation rate of latent infections are represented by p_i and r_i, respectively. We account for all-cause death, μ, and death due to active TB, μ_{TB}. Treatment of latently and/or actively infected individuals is shown by lt_i and at_i, respectively. In all cases, $i = N, S$.

to nonlinear contact dynamics in large populations (Hethcote, 1976, 2000).

Four different transmission rates represent possible interactions that may occur among model subpopulations. β_w is the average number of contacts per unit time resulting in successful transmission of *M. tuberculosis* due to contact between individuals from phenotypically neutral subpopulations (represented by $U_N \otimes T_N$). Similarly, we use β_x for $U_N \otimes T_S, \beta_y$ for $U_S \otimes T_N$, and β_z for $U_S \otimes T_S$.

Following the standard disease progression discussed above, newly infected individuals progress either directly to active TB with probability p_i $(i = N, S)$ or develop latent TB with probability $(1 - p_i)$. The average reactivation rates from latent to active TB (r_i) can be interpreted as the lifetime risk of reactivation distributed over the average duration of latent infection (see also Blower et al., 1995). Once latently infected with *M. tuberculosis*, an individual will remain so for life unless reactivation occurs.

To account for treatment, we define lt_i as the fraction of the population receiving effective chemoprophylaxis, and at_i as the rate of effective per capita therapy $(i = N, S)$. We assume that chemoprophylaxis of latently infected individuals (L_N, L_S) reduces their reactivation rate (r_N, r_S) and that initiation of therapeutics immediately removes an individual from active status (T_N, T_S) and places them into a latent state (L_N, L_S). We thus modify our original system in Murphy et al. (2002) to include the terms $(1 - lt_i)r_iL_i$, representing effective chemoprophylaxis (see Eqs. (3) and (4)) and at_iT_i, tracking effective therapeutics (Eqs. (5) and (6)).

3.2. Determining the basic reproduction number, R_0

Many epidemiological models have a threshold condition which can be used to determine whether an infection will be eliminated from the population or become endemic (Brauer and Castillo-Chávez, 2001). The basic reproduction number, R_0, is defined as the average number of secondary infections produced by an infected individual in a completely susceptible population (Hethcote, 2000). As discussed in Murphy et al. (2002), R_0 is simply a normalized bifurcation (transcritical) condition for epidemiological models, such that $R_0 > 1$ implies that the endemic steady state is stable (i.e. the infection persists), and $R_0 \leqslant 1$ implies that the uninfected steady state is stable (i.e. the infection can be eliminated from the population).

In Murphy et al. (2002) we present an implicit method for calculating R_0 for a model of epidemic TB without treatment in a heterogeneous population. We verify that our formulation of R_0 is correct both numerically, through a bifurcation diagram, and analytically by comparing it with the R_0 generated using the next generation operator (NGO) method in the case of separable mixing (for a detailed discussion of the NGO method cf. (Diekmann et al., 1990; van den Driessche and Watmough, 2002)).

We now use our implicit method to determine the basic reproduction number for the model of epidemic TB with treatment in a heterogeneous population. We start by deriving the R_0 expression for a model of epidemic TB with treatment in a homogeneous population. Following the same methodology presented in Eqs. (1)–(6), such a simplified model has the form (collapsing the $N = S$ notation):

$$\frac{dU}{dt} = b - \beta U \frac{T}{P} - \mu U, \tag{7}$$

$$\frac{dL}{dt} = (1 - p)\beta U \frac{T}{P} - (1 - lt)rL + atT - \mu L, \tag{8}$$

$$\frac{dT}{dt} = p\beta U \frac{T}{P} + (1 - lt)rL - atT - \mu_{TB}T. \tag{9}$$

Using both our implicit method and the NGO method for calculating R_0, it is easy to show that

$$R_0 = \frac{\beta(\mu p + (1 - lt)r)}{at\mu + \mu_{TB}(\mu + (1 - lt)r)}. \tag{10}$$

The form of R_0 provides insight into how changes in treatment parameters affect the value of R_0. Increases in therapy of active disease, at, will cause values of R_0 to decrease. Therefore, theoretically, there always exists a therapy level that ensures $R_0 < 1$, implying ultimate elimination of TB is possible. The term for chemoprophylaxis of latent disease, lt, appears in both the numerator and denominator of Eq. (10); thus it is not obvious how changes in lt will affect the value of R_0.

We now calculate the basic reproduction number for the model of epidemic TB with treatment in a heterogeneous population. Using the implicit method (Murphy et al., 2002), we determine the Jacobian matrix J for Eqs. (1)–(6), then, assuming that (at least) one eigenvalue λ equals zero at a bifurcation condition, we calculate

$$det(J - \lambda I) = det(J) = 0$$

and as in Murphy et al. (2002) we arrive at the expression

$$R_0 = \mathscr{W} + \mathscr{Z} + \mathscr{X}\mathscr{Y} - \mathscr{W}\mathscr{Z} = 1, \tag{11}$$

where

$$\mathscr{W} = \frac{\beta_w(1 - v)(p_N\mu + (1 - lt_N)r_N)}{\mu at_N + \mu_{TB}(\mu + (1 - lt_N)r_N)}, \tag{12}$$

$$\mathscr{X} = \frac{\beta_x(1 - v)(p_N\mu + (1 - lt_N)r_N)}{\mu at_N + \mu_{TB}(\mu + (1 - lt_N)r_N)}, \tag{13}$$

$$\mathscr{Y} = \frac{\beta_y v(p_S\mu + (1 - lt_S)r_S)}{\mu at_S + \mu_{TB}(\mu + (1 - lt_S)r_S)}, \tag{14}$$

$$\mathscr{Z} = \frac{\beta_z v(p_S\mu + (1 - lt_S)r_S)}{\mu at_S + \mu_{TB}(\mu + (1 - lt_S)r_S)}. \quad (15)$$

The above formulation of R_0 (Eq. (11)) from the model of epidemic TB with treatment in a heterogeneous population is similar to the formulation of R_0 calculated from the model of epidemic TB without treatment in a heterogeneous population (see Murphy et al., 2002). Eqs. (12) and (15) represent the basic reproduction number for each subpopulation (i.e. $\mathscr{W}$ is the basic reproduction number for the genetically neutral subpopulation only). The product of Eqs. (13) and (14) accounts for the contact (interaction) between members of the subpopulations. Finally, the product of Eqs. (12) and (15) must be subtracted as the homogeneous subpopulations have already been accounted for in Eqs. (12) and (15).

In the case of no treatment ($lt_i = at_i = 0$), it is clear that the formulation of R_0 reduces to the basic reproduction number for a model of epidemic TB without treatment in a heterogeneous population (see Murphy et al., 2002). In addition, at the extreme conditions of either no genetic susceptibility ($v = 0$) or complete genetic susceptibility ($v = 1$) to infection, R_0 collapses to the expression in Eq. (10) for the model of epidemic TB in a homogeneous population. For example, if $v = 0$ (i.e. there is no genetically susceptible subpopulation), $\mathscr{Y} = \mathscr{Z} = 0$, and thus

$$R_0 = \mathscr{W} + \mathscr{Z} + \mathscr{X}\mathscr{Y} - \mathscr{W}\mathscr{Z} \quad (16)$$

$$= \mathscr{W} \quad (17)$$

$$= \frac{\beta_w(1 - v)(p_N\mu + (1 - lt_N)r_N)}{\mu at_N + \mu_{TB}(\mu + (1 - lt_N)r_N)} \quad (18)$$

which is precisely the expression for R_0 shown in Eq. (10). A similar result holds if $v = 1$.

The form of R_0 (Eq. (11)) is important and mirrors results discovered in our simulations. As therapy levels of active TB (at_i) increase, the denominator of R_0 become larger, and thus the value of R_0 becomes smaller. Thus, it is obvious that there are always values for at_i which can force $R_0 \leqslant 1$. This is less clear for chemoprophylaxis of latent disease (lt_i). Since lt_i appears in both numerator and denominator of R_0, increases in values of lt_i have much less of an effect on overall changes in R_0, and it is not obvious that R_0 can be forced less than 1 in all cases.

The implicit method for determining R_0 is an important technique that provides an accurate formulation of the basic reproduction number for epidemiological modes. The implicit method is a straightforward method which is likely to provide a result for most models, even in cases where the NGO method fails or produces multiple formulations for the basic reproduction number. For example, adding treatment terms to an epidemiological model introduces the issue of where to account for treatment terms within the NGO matrices $\mathscr{F}_i$ and $\mathscr{V}_i$. Different choices result in different formulations of the basic reproduction number (van den Driessche and Watmough, 2002) and this problem does not exist within the implicit method. In the appendix, we present the computation of R_0 by the NGO method, which agrees with our form of R_0 generated using the implicit method.

3.3. Parameter values and initial conditions

Parameter values used in the following experiments represent current genetic and epidemic TB data in two demographic settings: a high-growth setting with high genetic susceptibility, based on India, and a low-growth setting with low genetic susceptibility, based on the USA (see Table 1); we summarize below and provide a brief discussion of how estimates were obtained. Values for many parameters are determined from vital statistics and TB data available from the World Health Organization (WHO) and other recent literature.

Estimates for some parameters are scarce or unknown, specifically parameters associated with genetic susceptibility ($p_S, r_S, \beta_x, \beta_y, \beta_z$). In Murphy et al. (2002) we define a notational parameter $\varepsilon_S > 1$ to indicate influences of genetic susceptibility on baseline parameters of the genetically neutral subpopulations. We assume $p_S = \varepsilon_p p_N, r_S = \varepsilon_r r_N, \beta_x = \varepsilon_x\beta_w, \beta_y = \varepsilon_y\beta_w, \beta_z = \varepsilon_z\beta_w$ and hypothesize that $p_N \leqslant p_S$, $r_N \leqslant r_S$, and $\beta_w \leqslant \beta_x \leqslant \beta_y \leqslant \beta_z$ (see Murphy et al., 2002 and Table 1). We use a range of β_j values based on literature estimates of the number of secondary infections likely caused by an infectious source case in 1 year (Centre for International Cooperation in Health and Development, 2000; Murray and Salomon, 1998; Sanchez and Blower, 1997; Styblo, 1986). Regardless, we conduct a detailed sensitivity and uncertainty analysis on a range of values for all parameters (see (Blower and Dowlatabadi, 1994; Iman et al., 1981a, b) for similar methodology).

There are six parameters within our model that we assume are influenced by demographics: birth rate (b), natural death rate (μ), and the transmission parameters (β_j, $j = \{w, x, y, z\}$). Values for b and μ are greater in India than in the USA (see Table 1). Demographic factors such as crowding, closed environments, nutrition, and access to health care and treatment, likely affect the values of β_j (Nardell and Piessens, 2000). We choose transmission rates for the USA (β_j^U) to be less than or equal to rates for India (β_j^I) based on studies showing an increase in transmission of *M. tuberculosis* in crowded environments and closed spaces (Sepkowitz, 1996). The probability of encountering an infectious individual and the time spent in close contact with an infectious individual (the duration and intensity of exposure) are likely greater for more dense populations.

Table 1
Variables and parameters

Var.	Definition	HG initial cond.	LG initial cond.	Reference
$U_N(t)$	Uninfected, neutrals	696 918 000 persons	250 780 000	WHO (1999) & calc.
$U_S(t)$	Uninfected, susceptibles	298 679 000 persons	27 864 500	WHO (1999) & calc.
$L_N(t)$	Latent TB, neutrals	344 288 000 persons	13 793 700	WHO (1999) & calc.
$L_S(t)$	Latent TB, susceptibles	147 552 000 persons	1 552 640	WHO (1999) & calc.
$T_N(t)$	Active TB, neutrals	1 716 000 persons	30 466	WHO (1999) & calc.
$T_S(t)$	Active TB, susceptibles	735 817 persons	3 385	WHO (1999) & calc.
Param.	**Definition**	**HG values**	**LG values**	**Reference**
b	Birth rate	25 567 802 yr^{-1}	3 892 489 yr^{-1}	McDevitt (1999)
v	Frequency of suscept. phenotype	30%		Brahmajothi et al. (1991), Mehra et al. (1986), Subramanian et al. (1995)
			10%	Awad et al. (1987), Zachary et al. (1996)
μ	Non-TB death rate	0.01587 yr^{-1}	0.01314 yr^{-1}	McDevitt, (1999)
μ_{tb}	TB death rate	0.8 yr^{-1}	0.8 yr^{-1}	Pablos-Mendez et al. (1996)
β_w	# secondary infections ($U_N \otimes T_N$)	β_w^I: [5, 7] yr^{-1}	β_w^U: [3, 5] yr^{-1}	Centre for International Cooperation in Health and Development (2000), Murray and Salomon (1998), Styblo (1986)
$\beta_x = \varepsilon_x\beta_w$	# secondary infections ($U_N \otimes T_S$)	β_x^I: [7, 9] yr^{-1}	β_x^U: [5, 7] yr^{-1}	Estimate
$\beta_y = \varepsilon_y\beta_w$	# secondary infections ($U_S \otimes T_N$)	β_y^I: [7, 9] yr^{-1}	β_y^U: [5, 7] yr^{-1}	Estimate
$\beta_z = \varepsilon_z\beta_w$	# secondary infections ($U_S \otimes T_S$)	β_z^I: [9, 11] yr^{-1}	β_z^U: [7, 9] yr^{-1}	Estimate
p_N	Direct progression, neutrals	5–10%	5–10%	Comstock (1982), Styblo (1986)
$p_S = \varepsilon_p p_N$	Direct progression, susceptibles	10–20%	10—20%	Estimate
r_N	Reactivation rate, neutrals	0.00167–0.0033 yr^{-1}	0.00125–0.0025 yr^{-1}	Adler and Rose (1996), Karus (1983)
$r_S = \varepsilon_r r_N$	Reactivation rate, susceptibles	0.0033–0.0066 yr^{-1}	0.0025–0.0050 yr^{-1}	Estimate
lt_N, lt_S	Effective chemoprophylaxis	5–15%	5–15%	Bleed et al., 2001 Blower and Gerberding (1998)
at_N, at_S	Per capita therapy of active TB	0.3428570–3.2 yr^{-1}	0.342857–3.2 yr^{-1}	Bleed et al., 2001

For example, India has a population 5 times larger than the USA within an area one-third the size.

We calculate values for at_i in a manner similar to Blower and Gerberding (1998), where the fraction of infectious individuals treated at time t is defined by $\chi_t = at_i/(at_i + \mu_{TB})$. Knowing estimates for the fraction treated, we calculate $at_i = \chi_t\mu_{TB}/(1-\chi_t)$. As the fraction of individuals treated varies from zero to one, $at_i \in [0, \infty)$. Note that $lt_i \in [0, 1]$. In both cases, $lt_i = \chi_t = 0$ indicates no treatment while $lt_i = \chi_t = 1$ represents 100% effective treatment.

To model the current state of TB infection in the world, we calculate initial conditions for high-growth (HG) populations by distributing 30% of the population into the genetically susceptible subpopulation and ensuring an initial prevalence of 33%. Initial conditions for low-growth (LG) populations are calculated by distributing 10% of the population into genetic susceptibility categories and initiating with a prevalence of 5%.

4. Simulation results

A fundamental question regarding the efficacy of treatment is whether or not an effective treatment strategy exists for every epidemic situation; that is, are there always treatment levels (values of at_i and lt_i) that can significantly reduce the prevalence of disease? The ultimate goal of any treatment strategy should be eradication of disease from the population; however, a successful treatment strategy is one that induces a significant reduction in the burden of disease.

We perform three experiments to determine the effects of treatment in demographically distinct, heterogeneous populations. We are not interested in observing epidemic trends over time, rather how a particular treatment strategy affects present day levels of TB. In Section 4.1 we first investigate a treatment strategy that targets only individuals with active TB disease (therapy). Then in Section 4.2 we investigate a treatment strategy that targets only individuals with latent infection (chemoprophylaxis). In Section 4.3 we simulate a treatment strategy that allows for treatment of both latent and active disease. Finally, in Section 4.4 we investigate a treatment strategy that targets only genetically susceptible individuals.

In addition to performing experiments in both HG and LG populations, we conduct simulations with varying degrees of genetic susceptibility ($v \in [0–30\%]$) within these settings. Examining these different scenarios allows for cross comparisons. As mentioned previously, a particular allele is highly correlated with susceptibility to TB disease in India and is present in 30% of that population. In contrast, the allele is present in only 8–15% of caucasoid populations of Western Europe and the USA. We therefore designate $v = 30\%$

as a high level of genetic susceptibility and $v = 10\%$ as a low level of genetic susceptibility.

Each experiment consists of 250 simulations where treatment and genetic susceptibility parameters are varied within specified ranges; all other parameters remain fixed at their median values (see Table 1). The outcome of each experiment is a distribution of 250 steady-state prevalence values, where prevalence is the fraction of the population with either latent or active TB disease, i.e.

$$Prevalence(t) = \frac{L_N(t) + L_S(t) + T_N(t) + T_S(t)}{P(t)}.$$

4.1. Therapeutics: treatment of active disease only

We first study only therapeutics of individuals with active TB disease, where at_i $(i = N, S)$ is the effective per capita rate of treatment. We assume that treatment is administered to both the genetically neutral and genetically susceptible populations equally $(at_N = at_S)$. We fix $lt_i = 0$ and allow the fraction of infectious individuals treated $(\chi_t = at_i/(at_i + \mu_{TB}))$ to range between 0% and 100%. We are mainly interested in simulation results within two therapy ranges: low $(30\% \leqslant \chi_t \leqslant 50\%)$ and high $(50\% \leqslant \chi_t \leqslant 80\%)$. These two levels roughly represent therapy of active TB observed in developing and developed countries, respectively (Bleed et al., 2001). This implies for low therapeutic levels, $0.342857 \leqslant at_N = at_S \leqslant 0.8$ and for high therapeutic levels, $0.8 \leqslant at_N = at_S \leqslant 3.2$.

Low therapy levels. Fig. 2A shows the average of 250 steady-state prevalence values versus the fraction of individuals with active TB disease receiving therapy in four different demographic settings. In HG settings with $v = 30\%$ or 10% (dot–dash and dashed lines, respectively), prevalence decreases only slightly as the fraction treated increases from 30% to 50%. On the other hand, TB prevalence is reduced more rapidly in LG demographic settings with either $v = 10\%$ (bold line) or $v = 30\%$ (dotted line). In fact, if the fraction effectively treated exceeds 40% $(\chi_t > 40\%)$, our model shows that, theoretically, TB could be eliminated altogether. However, issues such as drug-resistant strains of *M. tuberculosis*, non-compliance with treatment directives, and co-infection with other diseases (i.e. HIV) likely maintain TB as endemic.

High therapy levels. Fig. 2A also shows the average steady-state prevalence levels associated with a high-level treatment program $(\chi_t \in [50\text{–}80\%])$. The reduction in TB prevalence is greater in both HG demographic settings ($v = 30\%$ or 10%; dot–dash and dashed lines, respectively) under high-level therapy of active TB disease compared to low-level therapy programs. Not accounting for the previously mentioned issues such as drug-resistance, treatment non-compliance, and co-infection with other diseases, our model indicates that TB could theoretically be eliminated if therapy of active TB disease reaches at least 70% of actively infected individuals $(\chi_t \geqslant 70\%)$, regardless of the demographic or genetic makeup of the population. This is currently an unlikely scenario for many developing countries.

4.2. Chemoprophylaxis: treatment of latent infection only

We next simulate exclusive treatment of latent infections in both demographic settings. Recall that lt_i $(i = N, S)$ is the fraction of the latently infected population receiving effective chemoprophylaxis. We assume that chemoprophylaxis is administered equally to the genetically neutral and genetically susceptible populations $(lt_N = lt_S)$. We fix $at_i = 0$ and vary lt_i

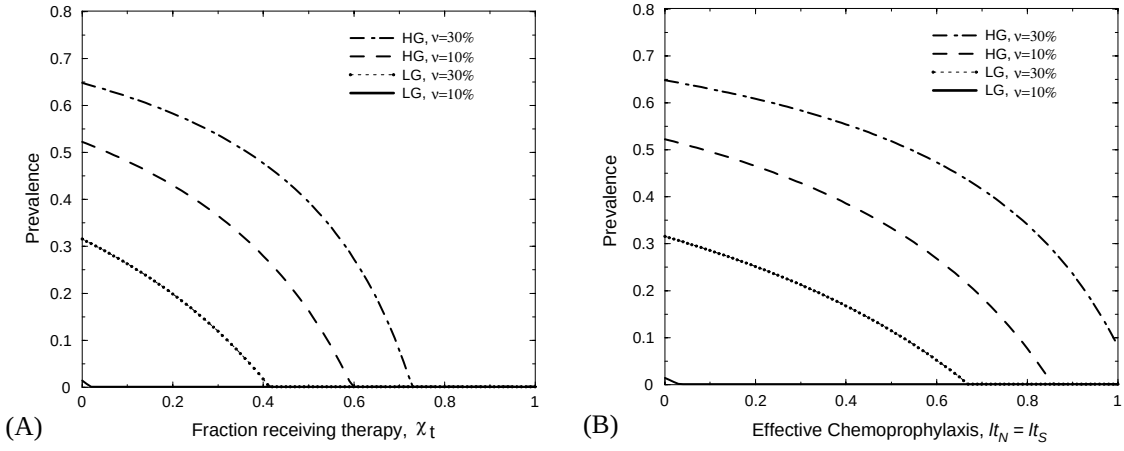

Fig. 2. Simulations showing average steady-state prevalence levels in four populations: HG with high genetic susceptibility (dot–dashed line), HG with low genetic susceptibility (dashed line), LG with high-genetic susceptibility (dotted line), and LG with low-genetic susceptibility (solid bold line). Panel A shows therapy of active disease only (i.e. $lt_N = lt_S = 0$) while Panel B shows chemoprophylaxis of latent infections only (i.e. $at_N = at_S = 0$).

between $0\% \leqslant lt_N = lt_S \leqslant 100\%$. Results are shown in Fig. 2B.

A treatment strategy utilizing only low chemoprohylaxis levels is not effective in reducing TB prevalence in HG demographic settings. Even if up to 50% of latent infections are effectively treated in the HG, $v = 30\%$ population (dot–dashed), TB prevalence will be reduced only by (roughly) 10 percentage points. A similar result is seen in the HG, $v = 10\%$ population (dashed line). Our model shows that for the HG, $v = 30\%$ population (dot–dashed line), chemoprophylaxis levels must reach more than 85% of the latently infected population in order to reduce prevalence to the present day world average (33%). A chemoprophylaxis-only treatment strategy is slightly more effective in a LG, $v = 30\%$ population (dotted line).

Results from Sections 4.1 and 4.2 show that exclusive treatment of latently infected individuals is not nearly as effective as a treatment strategy consisting of therapeutics of actively infected individuals alone, which produces a more rapid reduction in TB prevalence. This can be seen by comparing the steepness of the curves in Figs. 2A and B as treatment levels increase. Our model thus suggests that an effective treatment strategy should consider therapeutics of actively infected individuals alone or together with chemoprophylaxis.

4.3. The roles of demographics and genetics in treatment strategies

The influences of demographics on treatment strategies are well illustrated in the previous example. In the case where only active disease is treated (Fig. 2A), a greater reduction in TB prevalence occurs for lower therapy levels in the LG versus the HG populations. In fact, therapy within the 30–50% range has little effect on reducing prevalence in the HG populations. A chemoprophylaxis-only treatment strategy requires unrealistic levels of treatment in the HG demographic settings to achieve even a minimal reduction in TB prevalence (dot–dashed and dashed lines, Fig. 2B), whereas this strategy is more beneficial (and more likely to be plausible) in LG demographic settings (dotted and solid lines, Fig. 2B).

To further illustrate demographic effects, we now simulate a treatment strategy that combines both chemoprophylaxis and therapy. We conduct these simulations in two demographic settings with varying levels of genetic susceptibility ($v = 0\%, 10\%, 20\%, 30\%$). Our goal is to illustrate how demographics, combined with genetic susceptibility, can result in wide differences in treatment outcomes. Recall that birth rate (b), natural death rate (μ), and transmission of infection ($\beta_j, \{j = w, x, y, z\}$) are parameters influenced by demographics (See Table 1 or refer to Murphy et al., 2002).

Simulation results are shown in Figs. 3A–H. Two distributions of prevalence values are shown in each panel of Fig. 3: a baseline distribution, indicating prevalence in a population receiving no treatment (gray bars), and a distribution of prevalence values from a population receiving a specific treatment strategy (white bars). Each distribution consists of 250 steady-state prevalence values calculated from model simulations. In all cases, the treatment strategy consists of 30–50% therapy of active disease and 5–15% chemoprophylaxis of latent infection. These minimal treatment levels likely represent present treatment efforts in many developing countries.

The effects of both demographics and genetic susceptibility are well illustrated in Figs. 3A–H. In each case, the minimal treatment strategy significantly reduces prevalence from baseline (statistical significance of the difference between the mean baseline prevalence and the mean of prevalence following treatment verified by the Student's t test; $p \ll 0.001$).

The effects of genetic susceptibility in altering the outcome of a given treatment strategy are show by the four graphs in a given demographic setting (column). For example, Figs. 3A, C, E, and G show distributions of prevalence before and after the minimal treatment strategy in a HG population with 0, 10%, 20% or 30% genetic susceptibility, respectively. The ability of a treatment strategy to reduce prevalence to low levels is abrogated as the level of genetic susceptibility increases. Compare this to Figs. 3B, D, F, and G, which shows treatment in a LG setting with 0, 10%, 20% or 30% genetic susceptibility. In all cases the minimal treatment strategy reduces TB to near-zero levels. Finally, the combined effects of demographics and genetic susceptibility are illustrated by comparing Figs. 3A (HG, $v = 0\%$) and F (LG, $v = 20\%$). The minimal treatment strategy provides similar prevalence reduction in both settings. This indicates that a HG demographic setting with no known genetic susceptibility is similar to a LG population with 20% genetic susceptibility.

4.4. Treatment of genetically susceptible subpopulations

Finally, we investigate a treatment strategy that targets a specific subpopulation, in particular the genetically susceptible subpopulations L_S and T_S. We perform these experiments only in the HG, high genetic susceptibility population as the higher proportion of individuals susceptible to active TB in this population will likely provide more pronounced results. Simulation results are shown in Figs. 4A–D and again consist of two distributions of prevalence: a baseline distribution (prevalence with no treatment; gray bars), and a distribution showing prevalence following a specific treatment strategy (white bars). Each distribution consists of 250 steady-state prevalence values calculated from model simulations. We fix $lt_N = at_N = 0$ and allow

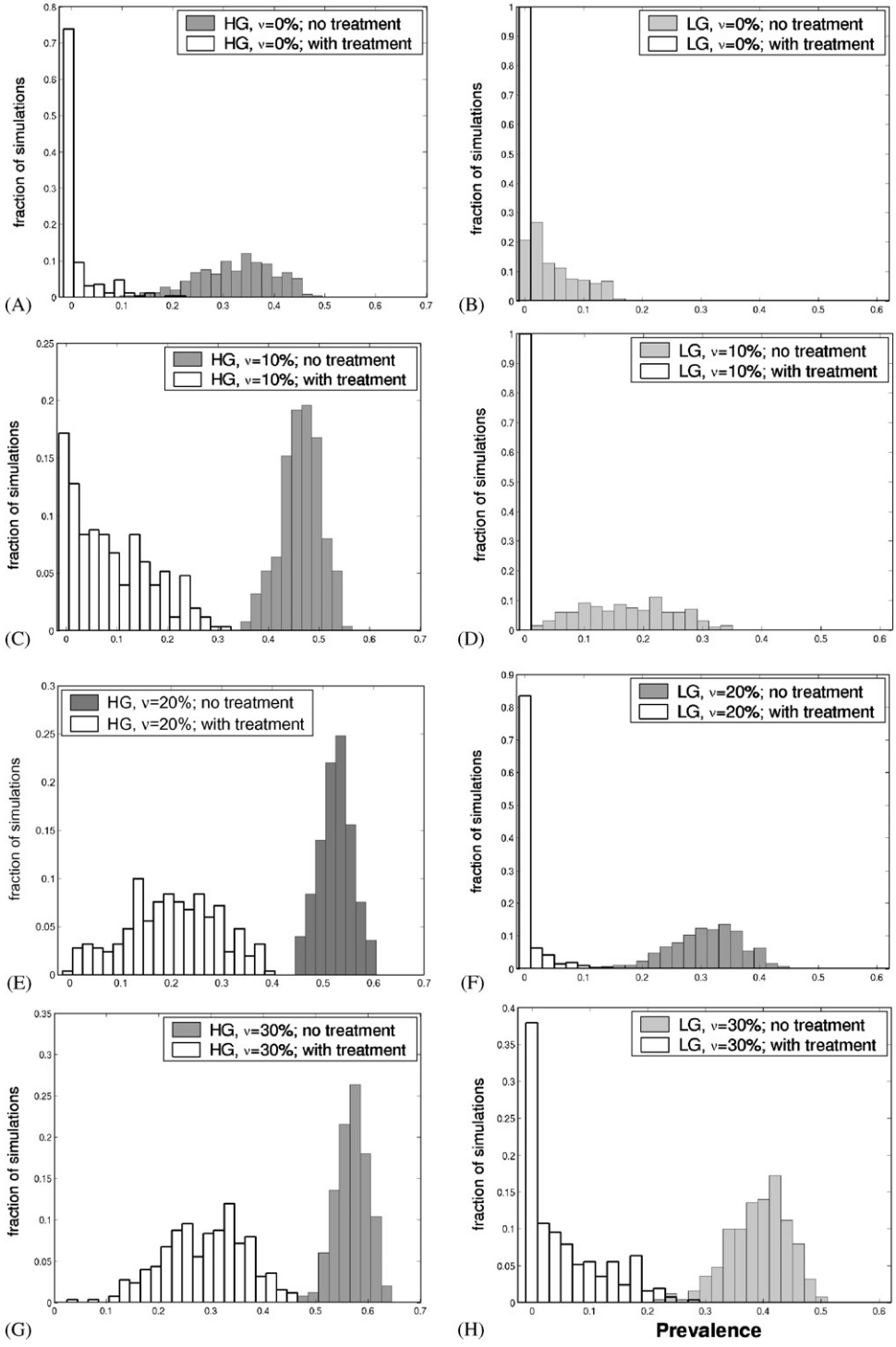

Fig. 3. Simulations of prevalence of tuberculosis in both untreated (gray bars) and treated (white bars) populations in two demographic settings (HG and LG) with varying levels of genetic susceptibility (A, B: $v = 0\%$; C, D: $v = 10\%$; E, F: $v = 20\%$; G, H: $v = 30\%$). In all cases, the treatment strategy consists of 30–50% therapy of active disease and 5–15% chemoprophylaxis of latent infection.

for two different levels of therapy: low ($at_S \in [30–50\%]$) and high ($at_S \in [50–80\%]$).

Results shown in Figs. 4A–D suggest that a treatment strategy targeting only genetically susceptible individuals can significantly reduce prevalence in the general population (statistical significance of the difference between the mean baseline distribution of prevalence and the mean distribution of prevalence following treatment was verified by the Student's t test; $p \ll 0.001$ for the distributions in Figs. 4A–D).

Therapy of the active susceptible group (T_S) only at either high or low levels does provide a significant

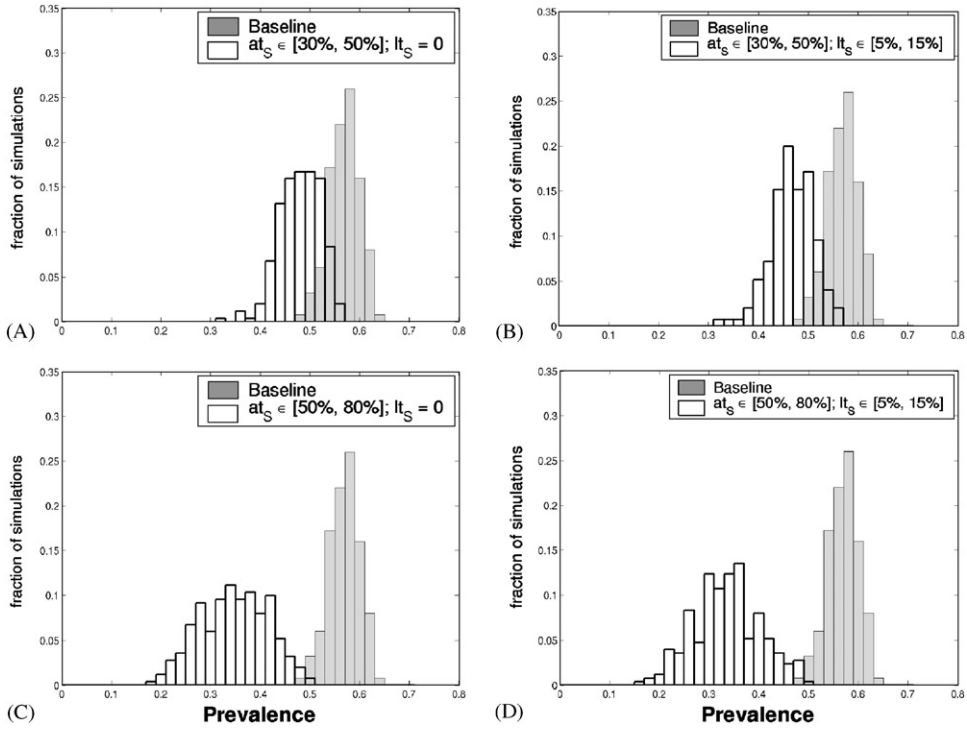

Fig. 4. Simulations of prevalence of TB in a high-growth setting when treatment strategies target genetically susceptible individuals only. Each graph shows the baseline distribution of steady-state values (gray bars) when no treatment is administered ($ln_N = lt_S = 0$ and $\chi_t = 0$) and the resulting distribution of steady-state values following a particular treatment strategy (white bars). Panels A and C show therapy of genetically susceptible individuals with active TB (T_S) only, at low (30–50%) and high (50–80%) levels, respectively. Panels B and D show treatment strategies that combine chemoprophylaxis and therapy of genetically susceptible individuals with latent and active TB (L_S and T_S). In both Panels B and D, effective chemoprophylaxis levels range between 5% and 15%.

reduction in prevalence of TB in the general population (Figs. 4A, C). However, high levels of therapy administered to only the T_S class cannot eliminate TB from the population as expected when treating active TB in the general population at the same level (compare with dot–dashed line, Fig. 2A, 70–80% therapy level). Figs. 4B and D present the expected prevalence when chemoprophylaxis of genetically susceptible latent infections (L_S) at the low level (5–15%) is combined with therapy of genetically-susceptible active disease (T_S).

5. Discussion

Treatment of latent TB infections (chemoprophylaxis) and active TB disease (standard therapeutics) are not administered with any level of consistency between countries. Even though powerful drugs are available to treat TB, treatment strategies remain ineffective at eliminating, or even reducing, TB levels. In this study we use an epidemiological model to investigate treatment strategies of TB in demographically distinct, heterogeneous populations. This paper is novel as it investigates various treatment strategies comparing contributions of both demographic and host genetic affects.

In previous work (Murphy et al., 2002), we provided a model framework for exploring epidemic TB in a heterogeneous population. We then conducted numerical simulations of our model to illustrate the importance of understanding genetic susceptibility and demographics when studying epidemic TB. This study is the first to consider treatment in these heterogeneous settings.

Many mathematical models have been published that investigate the use of TB treatment for epidemic control strategies (Aparicio et al., 2000; Blower and Gerberding, 1998; Castillo-Chávez and Feng, 1997; Murray and Salomon, 1998; Ziv et al., 2001). However, many of these models operate under the assumptions that chemoprophylaxis of latent infections and therapy of active disease effectively removes treated individuals from the governing SIR dynamics. In other words, treated individuals are removed from the latent (L_N, L_S) or active (T_N, T_S) groups (cf. Aparicio et al., 2000; Blower and Gerberding, 1998). We believe that it is unlikely that treatment confers lifelong immunity to TB, although there are no studies which clarify the disease status of treated individuals. We assume that chemoprophylaxis of latent infection and therapeutics of active infections also does not confer immunity to the treated individuals. Rather, treated individuals remain in, or are

moved into (in the case of active disease therapy), the latent state where they follow similar dynamics of latently infected individuals.

Initially, we investigate a treatment strategy where individuals with active TB disease or individuals with latent infection are exclusively treated. When simulating the effects of therapy of active disease only, we are mainly interested in two ranges of treatment, low and high, which represent ranges of treatment levels of active TB observed in developing and developed countries, respectively. With low therapy levels (30–50% therapy of actively infected individuals), simulations show that TB cannot be eliminated from a high-growth population, regardless of the level of genetic susceptibility. However, TB could eventually be eliminated from low-growth populations. Under high therapy levels (50–80% therapy of actively infected individuals), simulations show that TB could be eliminated in all demographic and genetic susceptibility settings. Therefore, an epidemic can theoretically be controlled by effective treatment of only actively infected individuals.

For treatment strategies of latently infected individuals, results show that low chemoprophylaxis levels have almost no appreciable affect on reducing prevalence in either demographic setting, regardless of the genetic susceptibility level. Model simulations indicate that for HG demographics with high genetic susceptibility, chemoprophylaxis alone can never eliminate TB. Even with a genetic susceptibility level of only 10% in a HG population, chemoprophylaxis must be effectively administered to over 85% of the latent class to eliminate TB, a highly unlikely scenario.

We next simulate a treatment strategy that combines both therapy of active disease (within a 30–50% level) as well as chemoprophylaxis of latent infection (within a 5–15% level). These simulations highlight the powerful influence of demographics and genetics on treatment outcomes. This combination treatment strategy is effective in significantly reducing prevalence, but it becomes ineffective at reducing TB to near-zero levels in HG populations where a genetic susceptibility factor is present in greater than 10% of the population. In contrast, a combination treatment strategy is very effective at reducing TB prevalence to near-zero levels in LG settings, regardless of the presence of genetic susceptibility. However, due to issues that we do not account for in the model, such as drug-resistant strains of *M. tuberculosis*, non-compliance with treatment directives, and co-infection with other diseases, TB remains endemic, even in those countries where it could otherwise be eliminated.

Finally, we investigate treatment strategies that target a particular subpopulation. Using our model, we study the effects of therapy, with and without chemoprophylaxis, in genetically susceptible subpopulations only. In all scenarios of low or high therapy levels (30–50% versus 50–80%), TB prevalence in the general population is significantly reduced from baseline. And, as expected, the addition of chemoprophylaxis of latent infections at an effective level of only 5–15% has little appreciable effects on reducing prevalence.

In this paper we illustrate the powerful influences of genetic susceptibility and demographics on altering results of treatment strategies. We have also shown that a treatment strategy targeting particular subpopulations can significantly reduce prevalence of disease within the general population. Finally, results suggest that specific effects of factors which likely keep TB endemic in regions that could otherwise clear it (e.g. drug-resistance, treatment non-compliance, and co-infection with other diseases) should be investigated further within the framework of genetic susceptibility to disease.

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Appendix

To add validity to the formulation of R_0 using our implicit method, we outline the computation of R_0 for our model (Eqs. (1)–(6)) using the next generation operator (NGO) method (Diekmann et al., 1990; van den Driessche and Watmough, 2002).

The NGO method requires the definition of two vector functions which describe flow into and out of model compartments representing infected individuals (L_N, L_S, T_N, T_S). In standard fashion, we define $\mathscr{F}_i(x)$ as the rate of appearance of new infections in compartment i, and $\mathscr{V}_i(x)$ as all other transfer interactions into and out of compartment i. In general, we rewrite each equation as $x_i'(t) = \mathscr{F}_i - \mathscr{V}_i$ for $x_i \in \{L_N, L_S, T_N, T_S\}$. We then calculate Jacobian matrices F and V of $\mathscr{F}_i$ and $\mathscr{V}_i$, respectively, and evaluate each at U_{ss}, the uninfected steady state. The *next generation matrix* is formed from the product FV^{-1}. Finally, the spectral radius of the next generation matrix FV^{-1} is the basic reproduction number, R_0.

We first separate Eqs. (3)–(6), the infected compartments, into terms representing $\mathscr{F}_i(x)$ and $\mathscr{V}_i(x)$. For our TB model, where $i = \{L_N, L_S, T_N, T_S\} = \{3, 4, 5, 6\}$:

$$L_N' = \mathscr{F}_3(x) - \mathscr{V}_3(x),$$
$$L_S' = \mathscr{F}_4(x) - \mathscr{V}_4(x),$$
$$T_N' = \mathscr{F}_5(x) - \mathscr{V}_5(x),$$
$$T_S' = \mathscr{F}_6(x) - \mathscr{V}_6(x).$$

From model equations (1)–(6) we see:

$$\mathscr{F}_3(x) = (1-p_N)\beta_w U_N \frac{T_N}{P} + (1-p_N)\beta_x U_N \frac{T_S}{P},$$
$$\mathscr{V}_3(x) = (1-lt_N)r_N L_N - at_N T_N + \mu L_N,$$
$$\mathscr{F}_4(x) = (1-p_s)\beta_y U_S \frac{T_N}{P} + (1-p_S)\beta_z U_S \frac{T_S}{P},$$
$$\mathscr{V}_4(x) = (1-lt_S)r_S L_S - at_S T_S + \mu L_S,$$
$$\mathscr{F}_5(x) = p_N\beta_w U_N \frac{T_N}{P} + p_N\beta_x U_N \frac{T_S}{P}$$
$$\mathscr{V}_5(x) = -(1-lt_N)r_N L_N + at_N T_N + \mu_{TB} T_N$$
$$\mathscr{F}_6(x) = p_S\beta_y U_S \frac{T_N}{P} + p_N\beta_z U_S \frac{T_S}{P},$$
$$\mathscr{V}_6(x) = -(1-lt_S)r_S L_S + at_S T_S + \mu_{TB} T_S.$$

Calculating Jacobian matrices F and V then evaluating each Jacobian at the uninfectious steady state

$$U_{ss} = (U_N, U_S, L_N, L_S, T_N, T_S) = \left(\frac{b(1-v)}{\mu}, \frac{bv}{\mu}, 0, 0, 0, 0\right)$$

gives

$$F = \begin{bmatrix} 0 & 0 & \beta_w(1-p_N)(1-v) & \beta_x(1-p_N)(1-v) \\ 0 & 0 & \beta_y(1-p_S)v & \beta_z(1-p_S)v \\ 0 & 0 & \beta_w p_N(1-v) & \beta_x p_N(1-v) \\ 0 & 0 & \beta_y p_S v & \beta_z p_S v \end{bmatrix}$$

and

$$V = \begin{bmatrix} (1-lt_N)r_N + \mu & 0 & -at_N & 0 \\ 0 & (1-lt_S)r_S + \mu & 0 & -at_S \\ -(1-kt_N)r_N & 0 & at_N + \mu_{TB} & 0 \\ 0 & -(1-lt_S)r_S & 0 & at_S + \mu_{TB} \end{bmatrix}.$$

The next generation matrix FV^{-1} has only two eigenvalues: $e_1 = 0$ (a repeated eigenvalue of multiplicity three) and a non-zero eigenvalue e_2. The spectral radius of FV^{-1} is thus e_2, which when rearranged and simplified produces:

$$R_0^{NGO} = \underbrace{\frac{\beta_w(1-v)(p_N\mu + (1-lt_N)r_N)}{\mu at_N + \mu_{TB}(\mu + (1-lt_N)r_N)}}_{\mathscr{W}} + \underbrace{\frac{\beta_z v(p_S\mu + (1-lt_S)r_S)}{\mu at_S + \mu_{TB}(\mu + (1-lt_S)r_S)}}_{\mathscr{Z}} \tag{19}$$

$$+ \underbrace{\left(\frac{\beta_x(1-v)(p_N\mu + (1-lt_N)r_N)}{\mu at_N + \mu_{TB}(\mu + (1-lt_N)r_N)}\right)}_{\mathscr{X}} \times \underbrace{\left(\frac{\beta_y v(p_S\mu + (1-lt_S)r_S)}{\mu at_S + \mu_{TB}(\mu + (1-lt_S)r_S)}\right)}_{\mathscr{Y}} \tag{20}$$

$$- \underbrace{\left(\frac{\beta_w(1-v)(p_N\mu + (1-lt_N)r_N)}{\mu at_N + \mu_{TB}(\mu + (1-lt_N)r_N)}\right)}_{\mathscr{W}} \times \underbrace{\left(\frac{\beta_z v(p_S\mu + (1-lt_S)r_S)}{\mu at_S + \mu_{TB}(\mu + (1-lt_S)r_S)}\right)}_{\mathscr{Z}}, \tag{21}$$

where $\mathscr{W}$, $\mathscr{X}$, $\mathscr{Y}$ and $\mathscr{Z}$ are defined as before (see Eqs. (12)–(15)) when calculating R_0 using our implicit method.

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