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Comparing epidemic tuberculosis in demographically distinct heterogeneous populations

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Abstract

There is wide variation in endemic tuberculosis (TB) levels between countries and we seek to identify possible causes of these differences. In this study we present an epidemiological model of *Mycobacterium tuberculosis* infection to investigate the effects of host genetics and demographic factors on epidemic TB. We discuss the general framework for this approach and present analytical results to identify important parameters affecting steady-state prevalence and incidence rate of TB disease. We then use numerical simulations of our model to observe the effects of a genetically susceptible subpopulation on TB disease dynamics at the population level. Finally, we simulate infection within a genetically heterogeneous population in two demographic settings: India (a typical population with high TB prevalence) and the USA (a typical population with low TB prevalence). Results show that changes in transmission parameters, the fraction of the population genetically susceptible to infection, and demographic factors strongly affect TB prevalence and incidence rates.

Keywords: Tuberculosis; Genetic susceptibility; SIR mathematical model; Prevalence; Incidence rate; Next generation operator

1. Introduction

Tuberculosis (TB) is caused by infection with the bacterium *Mycobacterium tuberculosis*, which is estimated to infect roughly one-third of the world's population resulting in 2–3 million deaths each year [1]. Although between 90% and 95% of infections occur in developing countries [1], the

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emergence of HIV as well as multi-drug-resistant (MDR) strains of *M. tuberculosis* will dramatically change the dynamics of infection world-wide [2]. Other factors may contribute to the TB epidemic including elimination of TB control programs, IV drug use, poverty, and immigration [3,4].

TB is an ancient disease whose world-wide prevalence had been declining long before vaccination and protective strategies were implemented [5–7], but its recent reappearance in developing countries and the high burden of infection in regions of Southeast Asia have sparked renewed interest in TB. The current world estimate of prevalence is 33% while the incidence rate of active (infectious) TB is estimated to be 140 per 100 000 per year (/100k/yr) [8]. Wide variation exists in the severity of TB between countries. For example, prevalence and incidence in the U.S. are roughly 5% and 6/100k/yr, respectively [9], while in India and other Southeast Asian regions, prevalence and incidence may be as high as 50% and 200–400/100k/yr, respectively [8,10,11].

Humans are the natural reservoir for *M. tuberculosis*, which is spread from person to person via airborne droplets [12]. *M. tuberculosis* may need only a low infectious dose to establish infection ($ID_{50} \approx 10$) [13]. Factors that affect transmission of *M. tuberculosis* include the number, viability, and virulence of organisms within sputum droplet nuclei, and most importantly, time spent in close contact with an infectious person [14–17]. Socio-economic status, family size, crowding, malnutrition, and limited access to health care or effective treatment also influence transmission [18,19]. Consistent estimates of *M. tuberculosis* transmission rates do not exist; however, it is known that transmission is rather inefficient for most strains [20]. Infection with *M. tuberculosis* is dependent on non-linear contact processes that are determined by population size and density, as well as other factors. Demographic characteristics of a population, therefore, play a significant role in the development and progression of a TB epidemic.

The type and strength of immune response that develops following initial infection with *M. tuberculosis* results in either latent infection, in which the bacteria are contained, or active disease, where the host suffers clinical symptoms and can transmit bacteria [21,22]. Estimating the risk of developing these various outcomes is difficult and varies greatly between studies [23]. It is generally accepted that only 5–10% of initial infections produce primary active TB [21,22], although one study reports percentages as high as 40% [24]. There is a 5–10% lifetime risk of a latent infection reactivating to active TB disease [14,15]. A loss (or reduction) of immunity in a latently infected individual, due to HIV for example, may increase the probability of reactivation up to 10% per year [24].

A key question for researchers then is what allows for different disease outcomes following infection with *M. tuberculosis*. A number of factors contribute, ranging over environmental, microbial and host characteristics [25]. In this paper we present a mathematical model of epidemic TB in a population that is heterogeneous regarding susceptibility to infection with *M. tuberculosis*. Our model is an extension of standard susceptible, infected, and removed (SIR) epidemic models, yet is novel because we account for genetic heterogeneity (susceptibility or resistance) to infection with *M. tuberculosis*.

The paper is organized in the following manner. We first discuss the general framework of the model, then determine the basic reproduction number for epidemic TB in a population with known susceptibility to infection. We identify major parameters affecting prevalence and incidence rates of TB infection in the heterogeneous population. Next, we present numerical simulations of our model and compare two case studies. First, we illustrate the effects of a particular

host susceptibility genotype/phenotype on population-level TB disease dynamics. Parameter values for this example reflect a setting such as India, where specific evidence suggests a link between underlying susceptibility to active TB with a genetic component of the immune system. Second, we investigate heterogeneity to infection in two demographically different populations with extremely different TB prevalence levels, one with high birth and death rates (similar to those of India) and one with low birth and death rates (similar to those of the USA). Our overall goals are to determine which parameters significantly affect prevalence and incidence of TB in the general population and to make predictions regarding relative roles of inherent susceptibility versus population demographics.

2. Genetic factors associated with tuberculosis

Several studies have found that genetic factors influence susceptibility and resistance to *M. tuberculosis* infection [25–32]. These studies employ a variety of methods including large-scale association-based population case/control studies of candidate genes, family-based linkage analysis, investigation of rare individuals with exceptional mycobacteria susceptibility, and comparison with murine models of disease. Such studies enable identification of particular host genes that influence susceptibility to TB disease.

The major components of susceptibility and resistance to TB appear to be linked directly to the immune response, and in particular, the major histocompatibility (MHC) molecules responsible for antigen presentation to immune effector cells. Two types of MHC molecules, class I and class II, play different roles in an immune response to foreign pathogens. Human MHC molecules are termed human leukocyte antigen (HLA) molecules. Increased susceptibility and resistance to more than 500 diseases has been shown to be associated with various HLA antigens, alleles, or haplotypes (sets of genes that are typically inherited as a unit) [33]. In some diseases, the HLA expression may influence the balance and strength of the immune response [34]. The level and type of immune response to a particular pathogen may vary among populations that have different distributions of HLA molecules.

Many HLA genotypes are implicated in susceptibility to *M. tuberculosis* infection [26–28,35]. Variable binding of mycobacterial antigens to the various HLA molecules may affect the intensity of the adaptive immune response and thus influence susceptibility to TB [36,37]. Table 1 sum-

Table 1
HLA genes that correlate with susceptibility to active TB in the Indian population

HLA allele	Association with active TB	References
HLA-DR2	+++	[28,44–46]
HLA-DRw6	+	[44]
HLA-DQ1	+	[28]
HLA-DQw1	+	[45]
HLA-A10	+	[46]
HLA-B8	+	[46,75]
HLA-B15	+	[76]

A positive association (+) indicates that the presence of the particular allele correlates with active TB disease. The HLA-DR2 allele is more commonly and strongly associated (+++) with active TB disease.

marizes associations of HLA with active TB within India, although studies have been conducted in other countries and even within specific ethnic groups (see [38–43]).

HLA-DR2. Expression of HLA-DR2 is strongly and consistently linked to pulmonary TB and the severe multi-bacillary form of TB in India [28,44–47] (see Table 1). HLA-DR2 correlates with increased levels of serum antibody levels [26,28,45], indicating an elevated humoral immune response, associated with active disease. The presence of the HLA-DR2 allele may induce tolerance to *M. tuberculosis*, leading to uncontrolled growth of the bacilli [47]. In addition, HLA-DR2 correlates with decreased production of key proteins that play crucial roles in granuloma formation and subsequent containment of bacteria [48,49].

3. Modeling epidemic TB

Our goal is to develop a mathematical model of epidemic TB that allows us to investigate effects of demographics on epidemic TB in a population with inherently susceptible and/or resistant subpopulations. Without loss of generality, we present our model in the context of genetic susceptibility to *M. tuberculosis* infection.

We are motivated by previous work from our group which presents one of the first models of HIV infection within a genetically heterogeneous population (see [50]). In that work, epidemic HIV is characterized within three subpopulations (wild type, heterozygotes, or homozygotes) according to a protective 32-bp deletion in the CCR5 chemokine receptor, denoted CCR5Δ32. To incorporate the role(s) of genetic heterogeneity in this model, phenotypic differences are accounted for through both parameter values and dynamic birth processes. Simulation results show that prevalence of HIV/AIDS is greater in populations lacking the CCR5Δ32 allele. In addition, HIV is shown to provide selective pressure for CCR5Δ32, thus increasing the frequency of the allele.

We develop a mathematical model of epidemic TB using a modified SIR model with mutually exclusive groups of individuals who are uninfected, $U(t)$, latently infected, $L(t)$ (those infected with *M. tuberculosis* but *not* infectious), or actively infected with *M. tuberculosis*, $T(t)$ (those infected *and* infectious). Our goal is to study the effects of a genetically susceptible subpopulation on the dynamics of epidemic TB at the population level, so we further subdivide each of these three groups to include individuals carrying a susceptibility allele, resulting in the six mutually exclusive populations: $U_N(t)$, $L_N(t)$, $T_N(t)$, and $U_S(t)$, $L_S(t)$, $T_S(t)$, where the subscript N (neutral) denotes those without a susceptibility genotype and S (susceptible) denotes those with a susceptible genotype. Due to extensive diversity in the HLA genetic system, we examine disease relationships based upon the presence of susceptibility with no distinction between homozygotes and heterozygotes. Fig. 1 shows interactions of the six subpopulations.

3.1. The model

A system of non-linear, ordinary differential equations are used to model the dynamics of individuals within the population. Setting $P(t) = U_N(t) + U_S(t) + L_N(t) + L_S(t) + T_N(t) + T_S(t)$ and suppressing time-dependence, t, for each variable, the six model equations are

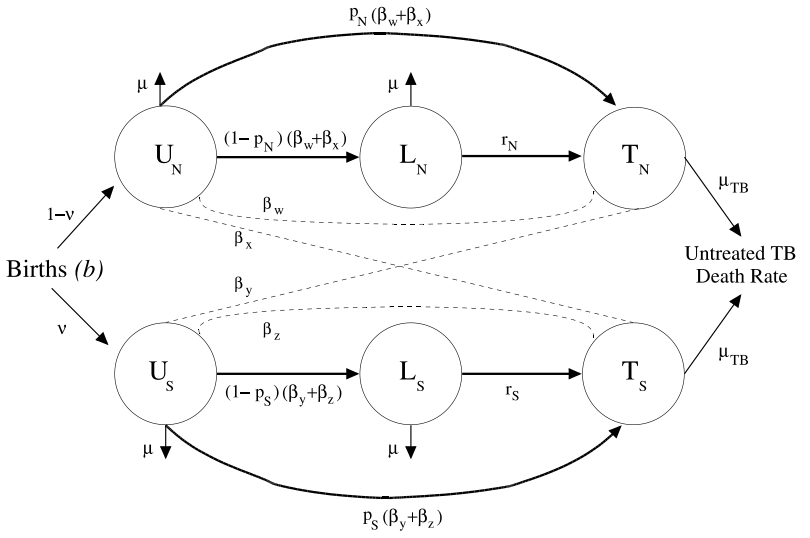

Fig. 1. A TB epidemic model including genetically neutral (U_N, L_N, T_N) and genetically susceptible (U_S, L_S, T_S) populations. Births (b) occur at a constant rate with a fraction (v) being genetically susceptible to infection. Transmission/receipt of *M. tuberculosis* depends on β_j $(j = w, x, y,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

$$\frac{\mathrm{d}U_N}{\mathrm{d}t} = b(1-v) - \beta_w U_N \frac{T_N}{P} - \beta_x U_N \frac{T_S}{P} - \mu U_N, \tag{1}$$

$$\frac{\mathrm{d}U_S}{\mathrm{d}t} = bv - \beta_y U_S \frac{T_N}{P} - \beta_z U_S \frac{T_S}{P} - \mu U_S, \tag{2}$$

$$\frac{\mathrm{d}L_N}{\mathrm{d}t} = (1-p_N)\beta_w U_N \frac{T_N}{P} + (1-p_N)\beta_x U_N \frac{T_S}{P} - r_N L_N - \mu L_N, \tag{3}$$

$$\frac{\mathrm{d}L_S}{\mathrm{d}t} = (1-p_S)\beta_y U_S \frac{T_N}{P} + (1-p_S)\beta_z U_S \frac{T_S}{P} - r_S L_S - \mu L_S, \tag{4}$$

$$\frac{\mathrm{d}T_N}{\mathrm{d}t} = p_N \beta_w U_N \frac{T_N}{P} + p_N \beta_x U_N \frac{T_S}{P} + r_N L_N - \mu_{\mathrm{TB}} T_N, \tag{5}$$

$$\frac{\mathrm{d}T_S}{\mathrm{d}t} = p_S \beta_y U_S \frac{T_N}{P} + p_S \beta_z U_S \frac{T_S}{P} + r_S L_S - \mu_{\mathrm{TB}} T_S, \tag{6}$$

Eqs. (1) and (2) describe the rate of change in uninfected populations U_N and U_S. There is a gain in each population from constant birth rates $b(1-v)$ (into U_N) and bv (into U_S). A loss in each population occurs as a result of infection with *M. tuberculosis* at rate $\beta_j U_i T_k / P$ (where $i, k \in \{N, S\}$ and $j \in \{w, x, y, z\}$), and constant death (μ). Eqs. (3) and (4) represent the rate of change in the latently infected populations. The rate of change in L_N and L_S increases due to *M. tuberculosis* infections which result in latent infection (at rate $(1-p_i)\beta_j U_i T_k / P$, where $i, k \in \{N, S\}$ and

$j \in \{w,x,y,z\}$) and decrease from reactivation of latent infection at rate r_iL_i ($i \in \{N,S\}$), and natural death (μ). The rate of change of the actively infected populations T_N and T_S are described in Eqs. (5) and (6). *M. tuberculosis* infections which progress directly to active disease are source terms at rate $p_i\beta_jU_iT_k/P$ ($i,k \in \{N,S\}$ and $j \in \{w,x,y,z\}$). They also increase due to reactivation of latent disease (at rate r_iL_i, where $i \in \{N,S\}$). Finally, the rate of change of T_N and T_S are reduced by disease-related death (at rate μ_{TB}).

3.2. Prevalence and incidence rate

Models of infectious diseases typically describe prevalence and incidence rates of infection. Here we define *prevalence* as the fraction of the population with either latent or active TB. We calculate prevalence using the formula:

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

The *incidence rate* of an infectious disease is defined as the number of new, infectious cases of disease per unit time. In our model, only members of the T_N and T_S classes are infectious. Therefore, we calculate incidence as the number of new cases of infectious TB per 100 000 population per year, and we use the formula:

$$\text{Incidence}(t) = \frac{100\,000}{P(T)} \times \left[\left(p_N\beta_wU_N(t)\frac{T_N(t)}{P(t)}\right) + \left(p_N\beta_xU_N(t)\frac{T_S(t)}{P(t)}\right) + (r_NL_N(t)) + \left(p_S\beta_yU_S(t)\frac{T_N(t)}{P(t)}\right) + \left(p_S\beta_zU_S(t)\frac{T_S(t)}{P(t)}\right) + (r_SL_S(t))\right],$$

where $P(t)$ indicates the total population size at time t.

4. Definitions and assumptions

4.1. Vital dynamics

All individuals born into the population are uninfected. For this paper, we assume a constant birth rate, b, although this assumption will be modified in a subsequent paper to account for changes in the birth rate over time (in a similar manner as in [50]). Our model analysis and simulations rely on the constant birth rate assumption; however, this is an initial simplification necessary for isolating and identifying affects of genetic susceptibility on present-day TB disease dynamics.

Death rates in the model are dependent on disease status. We assume that individuals in the uninfectious populations U_N, U_S, L_N, and L_S die from all-cause death at constant rate μ. Due to the different time scales of all-cause death and active disease death rates, and that initially we do not account for treatment, we assume individuals with active TB die only from disease at constant rate μ_{TB}. Parameter estimates for b and μ are readily available from population vital studies or census data.

4.2. Host genetic factors

Individuals entering uninfected classes (at rate b) are divided between neutral and susceptible populations, with a proportion v entering the susceptible group. Within the model framework, v represents the fraction of the general population exhibiting a susceptible phenotype. If we consider a specific genotype underlying this phenotype, then v must be derived from the allelic frequency according to dominance patterns for that allele. In the current model implementation, we hold v constant under the assumption that we are examining model steady-state values rather than evolution over time. We do not consider selection for or against neutral or susceptible genotypes as in [50], although these processes are presently being explored.

Model parameters within the susceptible subpopulation may represent both genetic and non-genetic factors. To account for this within the modeling framework, we introduce the parameter ϵ_S to describe the possible influence(s) of genetic susceptibility on baseline (genetically neutral) parameters (ϵ_S, susceptibility factor). In this work, we do not report specific values for ϵ_S, as they have not yet been identified; rather we use ϵ_S as a notational parameter to indicate where we include influences of genetic susceptibility in the model.

Based on the observed significant correlation of HLA-DR2 with active TB (Table 1) we hypothesize three possible ways that the HLA-DR2 susceptibility allele may affect the dynamics of epidemic TB:

1. HLA-DR2$^+$ individuals have an increased probability of direct progression to active TB upon initial infection; in this case, the susceptibility factor is represented by ϵ_{p}.
2. HLA-DR2$^+$ individuals exhibit an increased reactivation rate from latent to active TB; in this case, the susceptibility factor is represented by ϵ_{r}.
3. HLA-DR2$^+$ individuals are more likely to transmit and/or receive *M. tuberculosis*; in this case, the susceptibility factors are represented by ϵ_x, ϵ_y, and ϵ_z.

We assume $\epsilon_S \geqslant 1$ in each case to satisfy our susceptibility phenotype hypotheses. We would use $\epsilon_{\mathrm{r}} \leqslant 1$ (ϵ_{r}, resistance factor) if we were investigating a resistance phenotype instead.

Direct progression to active TB. When transmission of *M. tuberculosis* is successful, newly infected individuals will develop either latent infection or active TB with differing probabilities. We denote the probability of direct progression to active TB by p_i $(i = N, S)$; thus $(1 - p_i)$ is the probability of developing latent infection. By hypothesis (1), we assume $p_N \leqslant p_S$. In other words, $p_S = \epsilon_{\mathrm{p}} p_N$, where $\epsilon_{\mathrm{p}} \geqslant 1$.

Reactivation of latent TB. The parameter r_i $(i = N, S)$ denotes the average annual reactivation rate from latent to active TB, and may be interpreted as the lifetime risk (probability) of reactivation divided by the average duration of latent infection. We assume $r_N \leqslant r_S$ to satisfy hypothesis (2). Again, we take $r_S = \epsilon_{\mathrm{r}} r_N$, where $\epsilon_{\mathrm{r}} \geqslant 1$.

Disease transmission parameters. Although some studies have demonstrated that TB transmission can result from latently infected individuals whose sputum tests negative for *M. tuberculosis* bacteria [51], we assume that latently infected individuals are not infectious. Furthermore, we assume that latently infected individuals cannot be reinfected by actively infected individuals. Reinfection is a controversial topic in TB epidemiology, and it is currently unclear whether it

occurs, or to what extent [52,53]. In our model framework, transmission of *M. tuberculosis* occurs when there is adequate contact between an infectious and a susceptible individual.

Contact and transmission rates for TB are subject to a number of environmental and host-specific conditions. Contact rates may increase dependent on demographic conditions such as population density and crowding, or social patterns [19,52]. Furthermore, the probability of successful transmission once contact occurs likely depends on characteristics of both the transmitter and recipient (i.e., the number, viability, and virulence of the organisms within sputum droplet nuclei, immune status of the recipient, etc.). Therefore, we assume that transmission rates in our model are determined by broad demographic and social contexts, as well as by phenotypes of neutral and susceptible subpopulations in the model. For additional discussion of various forms and interpretations of transmission rates, see [54,55].

We assume non-linear contact dynamics in large populations and use the standard incidence expression $(\beta U)T/P$ (represented by $U \otimes T$) to model successful transmission of *M. tuberculosis* [54,56]. We use four different transmission rates to separate demographic from genetic influences. We define β_w as the average number of contacts per unit time resulting in successful transmission of *M. tuberculosis* due to contact between members of the phenotypically neutral subpopulation. Thus, β_w represents contact between an individual from the U_N compartment and an individual from the T_N compartment (represented by $U_N \otimes T_N$). We next define $\beta_x = \epsilon_x \beta_w$ for $U_N \otimes T_S$, $\beta_y = \epsilon_y \beta_w$ for $U_S \otimes T_N$, and $\beta_z = \epsilon_z \beta_w$ for $U_S \otimes T_S$. To reflect hypothesis (3), we assume $\beta_w \leqslant \beta_x \leqslant \beta_y \leqslant \beta_z$, or more generally, we require $1 \leqslant \epsilon_x \leqslant \epsilon_y \leqslant \epsilon_z$.

5. Analytical results

Initial analysis of the model in *Mathematica* [57] reveals four possible steady-state solutions of which only two are biologically relevant to the model. One steady state depends only on the vital dynamics of the susceptible populations ($U_N(t)$, $U_S(t)$), and can be found analytically to be

$$(\overline{U}_N^*, \overline{U}_S^*, \overline{L}_N^*, \overline{L}_S^*, \overline{T}_N^*, \overline{T}_S^*) = \left(\frac{b(1-v)}{\mu}, \frac{bv}{\mu}, 0, 0, 0, 0\right). \tag{7}$$

This represents an uninfected steady state, as there are no latently or actively infected individuals. The infectious steady state, representing epidemic or endemic infection, $(\overline{U}_N^{\mathrm{I}}, \overline{U}_S^{\mathrm{I}}, \overline{L}_N^{\mathrm{I}}, \overline{L}_S^{\mathrm{I}}, \overline{T}_N^{\mathrm{I}}, \overline{T}_S^{\mathrm{I}})$ is also observed, but is more complicated to compute directly.

One of the primary goals of constructing a model of TB infection is to determine under what conditions the disease will reach an endemic state. Mathematically this question is answered by identifying bifurcation points in the parameter space of the model. Epidemiologically this question is answered by determining the basic reproduction number of an infection, represented by R_0, for the population [58,55]. R_0 is a normalized bifurcation condition for an SIR model, such that $R_0 > 1$ implies that the endemic steady state is stable, and $R_0 \leqslant 1$ implies that the uninfected steady state is stable.

For SIR models which track homogeneous populations, the definition and construction of R_0 is well understood. For a single population, the value is given by the product of (1) the effective contact rate, (2) the average duration of an infectious case, and (3) the probability that an infected individual will become infectious (e.g. [59]). For the present model, we have two such R_0 values for

the mutually exclusive scenarios: (1) R_0^N, where the entire population is genetically neutral (i.e. $v = 0$), or (2) R_0^S, where the entire population is genetically susceptible (i.e. $v = 1$); we calculate

$$R_0^N = (\beta_w(1-v))\left(\frac{1}{\mu_{tn}}\right)\left(p_n + \frac{r_n(1-p_n)}{r_n+\mu}\right) \text{ or}$$
$$R_0^S = (\beta_z v)\left(\frac{1}{\mu_{ts}}\right)\left(p_s + \frac{r_s(1-p_s)}{r_s+\mu}\right).$$

These values, however, fail to predict the behavior of the heterogeneous population in any meaningful way. Infection dynamics in heterogeneous populations are sufficiently different from those of a homogeneous population such that the standard formulation of R_0 does not apply. Determination of R_0 for the mixed population must be done analytically.

5.1. Implicit determination of R_0

Model Eqs. (1)–(6) are sufficiently complicated to make analytic determination of the eigenvalues for either the infected or uninfected steady states an impractical approach to the problem of predicting bifurcation behavior. We present an implicit method to determine conditions under which a bifurcation may occur in the model. Although the method of Next Generation Operators (see [60,61]) does not work for the full model (1)–(6), it can be used to verify our formulation of R_0 under the case of separable (proportionate) infectivity, i.e., $\beta_x = \sigma\beta_w$ and $\beta_z = \sigma\beta_y$ (results not shown).

Using the criterion that at least one eigenvalue is equal to zero at a bifurcation point, we transform the characteristic equation $\det(J - \lambda I) = 0$, where J is the Jacobian matrix of system (1)–(6), into the bifurcation condition $\det(J) = 0$. While this condition is *necessary* for a bifurcation to occur, it is not *sufficient*. However, we show through numerical analysis that this condition does indeed predict when a bifurcation occurs in this case.

Substituting the value of the uninfected steady state (Eq. (7)), into the Jacobian matrix J yields

$$\begin{vmatrix} -\mu & 0 & 0 & 0 & -(1-v)\beta_w & -(1-v)\beta_x \\ 0 & -\mu & 0 & 0 & -v\beta_y & -v\beta_z \\ 0 & 0 & -r_N-\mu & 0 & (1-v)(1-p_N)\beta_w & (1-v)(1-p_N)\beta_x \\ 0 & 0 & 0 & r_S-\mu & v(1-p_S)\beta_y & v(1-p_S)\beta_z \\ 0 & 0 & r_N & 0 & (1-v)p_N\beta_w - \mu_{\mathrm{TB}} & (1-v)p_N\beta_x \\ 0 & 0 & 0 & r_S & vp_S\beta_y & vp_S\beta_z - \mu_{\mathrm{TB}} \end{vmatrix} = 0,$$

where the order of the state variables is (U_N, U_S, L_N, L_S, T_N, T_S). After some algebra this reduces to the condition:

$$\mathscr{R} = \mathscr{W} + \mathscr{Z} + \mathscr{X}\mathscr{Y} - \mathscr{W}\mathscr{Z} = 1, \tag{8}$$

where

$$\mathscr{W} = (\beta_w(1-v))\left(\frac{1}{\mu_{\mathrm{TB}}}\right)\left(p_N + \frac{r_N(1-p_N)}{r_N+\mu}\right), \tag{9}$$

$$\mathscr{X} = (\beta_x(1-v))\left(\frac{1}{\mu_{\mathrm{TB}}}\right)\left(p_N + \frac{r_N(1-p_N)}{r_N+\mu}\right), \tag{10}$$

$$\mathscr{Y} = (\beta_y v)\left(\frac{1}{\mu_{\mathrm{TB}}}\right)\left(p_S + \frac{r_S(1-p_S)}{r_S+\mu}\right), \tag{11}$$

$$\mathscr{Z} = (\beta_z v\left(\frac{1}{\mu_{\mathrm{TB}}}\right)\left(p_S + \frac{r_S(1-p_S)}{r_S+\mu}\right). \tag{12}$$

Since the expression $\mathscr{R}$ is equal to 1 at the bifurcation point, we provisionally call $\mathscr{R}$ the R_0 value for the heterogeneous population and examine further. The condition $\det(J) = 0$ may not correspond to a transcritical bifurcation; it is possible that this condition also describes a point where the number of stable dimensions of a saddle point changes. In order to ensure that the expression we have derived represents a transcritical bifurcation condition, we independently vary each parameter numerically and observe the resulting bifurcation behavior (Fig. 2). In each case, numerical experiments show that for $\mathscr{R} < 1$ the uninfected steady state is stable and the endemic steady state is unstable, while for $\mathscr{R} > 1$, stabilities are reversed. At $\mathscr{R} = 1$, the steady states collide in a transcritical bifurcation; it is clear that the behavior is constrained such that the transcritical bifurcation is the only event during which eigenvalues change signs. Thus, $\mathscr{R} \equiv R_0$.

Just as the R_0 expression for a homogeneous population has a probabilistic interpretation, so does R_0 for a heterogeneous population. Eqs. (9) and (12) of the expression represent the contact rate, duration of infectiousness, and probability of becoming infected for cases involving only members within each subpopulation (for example, β_w is the contact rate for individuals within the genetically neutral subpopulation only). The product of Eqs. (10) and (11) accounts for cases that

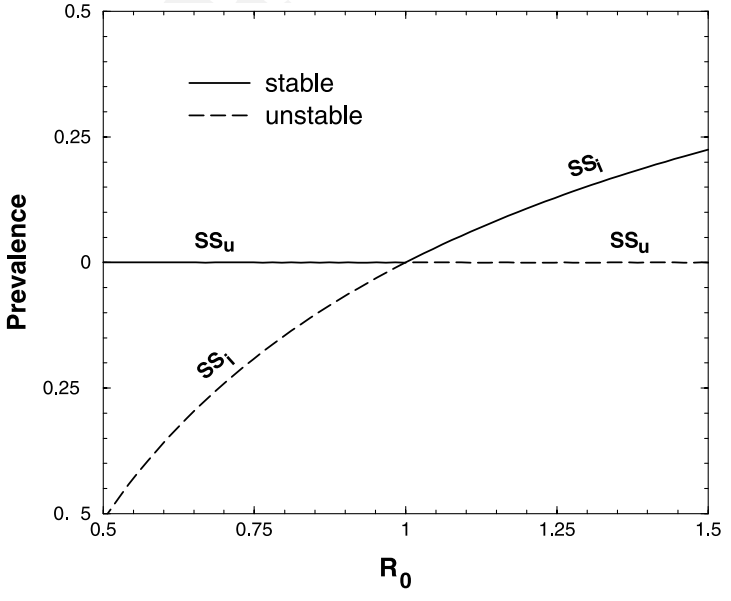

Fig. 2. Transcritical bifurcation at $\mathscr{R} \equiv R_0 = 1$.

involve contact (interaction) between members of the subpopulations. Finally, the product of Eqs. (9) and (12) must be subtracted, as these cases involve the homogeneous subpopulations and have already been accounted for in Eqs. (9) and (12).

5.2. Implications of R_0

The most basic demographic descriptions of a population are through its birth and death rates. In this model framework, the birth rate b does not appear in the expression for R_0, indicating that the control of epidemic TB is independent of birth rate. This fact is due to our choice of a constant birth rate instead of a birth rate that is a function of population size. All other parameters appear in the expression for R_0 (see Eq. (8)).

Variation in model parameters (due to measurement error, uncertainty, etc.) will influence the value of R_0 and thus the prevalence of TB. To investigate changes in R_0 due to variation in parameters, Blower has derived an alternative expression for R_0 from a simple SIR model of epidemic TB in a homogeneous population [62]. Sanchez and Blower then conduct a sensitivity and uncertainty analysis to identify the relative contribution of model parameters on the value of R_0 from their model [63]. Results show that the per capita natural death rate (μ) and the per capita death rate due to TB (μ_{TB}) are two of the most influential parameters in determining the magnitude of R_0. Although the numerical technique of Latin Hypercube Sampling (see [64–66]) was used to obtain these results, one can see from partial derivatives of Eq. (8) with respect to either μ or μ_{TB} that changes in these two parameters will provide the strongest contribution to changes in R_0.

6. Numerical simulation of genetic susceptibility

Numerically simulating a mathematical model of epidemic TB allows us to observe and quantify effects of host-specific genetic susceptibility factors on steady-state population-level prevalence and incidence rate values. To illustrate these effects, we present the following simulation results in a consistent format: baseline present-day distributions of steady-state prevalence and incidence rate values are shown and then compared with those resulting from changes in parameters representing hypotheses (1)–(3) associated with the genetically susceptible subpopulation.

We first use our mathematical model to investigate how the presence of a host susceptibility gene, specifically the HLA-DR2 allele, affects epidemic TB. We test the hypothesis that the enhanced susceptibility observed with this allele may partially explain why the prevalence of TB in India is roughly 50% (compared to a 33% world average and an estimated five percent in the USA, where the HLA-DR2 allele is far less prevalent) and an incidence rate between 200 and 400 /100k/yr (nearly 50 times the incidence rate in the USA) [8,10,11].

Parameter values used in the following experiments represent the genetic and epidemic TB situation in India and are summarized below, and a brief discussion of how they were estimated follows (see Table 2). 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 the parameters associated with genetic

Table 2
Variables and parameters

Variables	Definition	India initial condition	USA initial condition	References
$U_N(t)$	Uninfected, neutral	696 918 000 persons	250 780 000	[77] and calculated
$U_S(t)$	Uninfected, susceptible	298 679 000 persons	27 864 500	[77] and calculated
$L_N(t)$	Latent TB, neutral	344 288 000 persons	13 793 700	[77] and calculated
$L_S(t)$	Latent TB, susceptible	147 552 000 persons	1552 640	[77] and calculated
$T_N(t)$	Active TB, neutral	1 716 000 persons	30 466	[77] and calculated
$T_S(t)$	Active TB, susceptible	735 817 persons	3385	[77] and calculated
Parameter	**Definition**	**India values**	**USA values**	**References**
b	Birth rate	25 567 802 yr^{-1}	3 892 489 yr^{-1}	[78]
v	Frequency of susceptible phenotype	30%		[46,67,68]
			10%	[33,69]
μ	Non-TB death rate	0.01587 yr^{-1}	0.01314 yr^{-1}	[78]
μ_{tb}	TB death rate	0.8 yr^{-1}	0.8 yr^{-1}	[79]
β_w	# secondary infections ($UN \otimes TN$)	β_w^{I}: [5,7] yr^{-1}	β_w^{U}: [3,5] yr^{-1}	[22,80,81]
$\beta_x = \epsilon_x\beta_w$	# secondary infections ($UN \otimes TS$)	β_x^{I}: [7,9] yr^{-1}	β_x^{U}: [5,7] yr^{-1}	Estimate
$\beta_y = \epsilon_y\beta_w$	# secondary infections ($US \otimes TN$)	β_y^{I}: [7,9] yr^{-1}	β_y^{U}: [5,7] yr^{-1}	Estimate
$\beta_z = \epsilon_z\beta_w$	# secondary infections ($US \otimes TS$)	β_z^{I}: [9,11] yr^{-1}	β_z^{U}: [7,9] yr^{-1}	Estimate
p_N	Direct progression, neutral	5–10%	5–10%	[21,22]
$p_S = \epsilon_{\mathrm{p}}p_N$	Direct progression, susceptible	10–20%	10–20%	Estimate
r_N	Reactivation rate, neutral	0.00167–0.0033 yr^{-1}	0.00125–0.0025 yr^{-1}	[15,14]
$r_S = \epsilon_{\mathrm{r}}r_N$	Reactivation rate, susceptible	0.0033–0.0066 yr^{-1}	0.0025–0.0050 yr^{-1}	Estimate

susceptibility (ϵ_{p}, ϵ_{r}, ϵ_x, ϵ_y, and ϵ_z). Therefore we conduct a detailed sensitivity and uncertainty analysis on a range of values for all parameters (see [64–66] for similar methodology). Low values represent demographic and epidemiological data from the United States, while high values are taken from the Indian epidemic.

The frequency of HLA-DR2 allele in India is roughly 30% [28,44–47,67,68], while the frequency of HLA-DR2 allele in caucasoid populations of Western Europe and the United States is only 8–15% [33,69]. Therefore, initial conditions for the Indian population are calculated by distributing 30% of the population into the genetically susceptible subpopulation and ensuring that 33% of the population is infected with *M. tuberculosis*. Initial conditions for the USA are calculated by distributing 11% of the population into genetic susceptibility categories and starting with a prevalence of 5%.

Negative control simulations. We perform two negative control experiments to test the well-posedness of our model. Define $L(t) = L_N(t) + L_S(t)$ (total latent TB cases) and $T(t) = T_N(t) + T_S(t)$ (total active TB cases). First, to represent an infection-free population with no susceptible phenotype, we fix $v = 0$ and $L(t) = T(t) = 0$. Simulation results indicate that $U_N(t) = b/\mu$, while $U_S(t)$, $L(t)$, $T(t)$, prevalence, and the incidence rate are zero (data not shown).

Second, to represent an infection-free population with 30% frequency of the susceptibility phenotype, we fix $v = 0.30$ and $L(t) = T(t) = 0$. Simulations show $U_N(t) = b(1-v)/\mu$ and $U_S(t) = bv/\mu$, while $L(t)$, $T(t)$, prevalence, and the incidence rate are zero (data not shown).

6.1. Baseline simulation

Recall that current WHO estimates of prevalence and the incidence rate are 33% and 140/100k/yr, respectively. We now fix $v = 0.30$ and allow parameters to vary within their respective baseline ranges ($p_N = p_S \in [0.05, 0.10]$, $r_N = r_S \in [0.00167, 0.0033]$/yr, and $\beta_j \in [5.0, 7.0]$/yr ($j = w, x, y, z$)). This scenario represents a population with 30% frequency of susceptibility but assumes no ill-effects of being genetically susceptible. In other words, parameter variation is due only to natural uncertainty in parameter estimation and includes no detrimental effects of a susceptible phenotype. Fig. 3 shows the baseline distributions for prevalence and incidence rate values. Baseline prevalence has mean 32% and standard deviation (S.D.) 8%. The baseline incidence rate has mean 130.83/100k/yr and S.D. 42.45. Baseline prevalence and incidence rate results are consistent with present-day world averages of 33% and 140/100k/yr, respectively [8].

One might consider that the variation seen here could account for the differences in world-wide endemic TB levels. However, comparing countries like India and the USA, two countries whose prevalence and incidence rates are dramatically different, there may indeed be other factors that shift the distributions for those countries around a different mean. Therefore, we examine further.

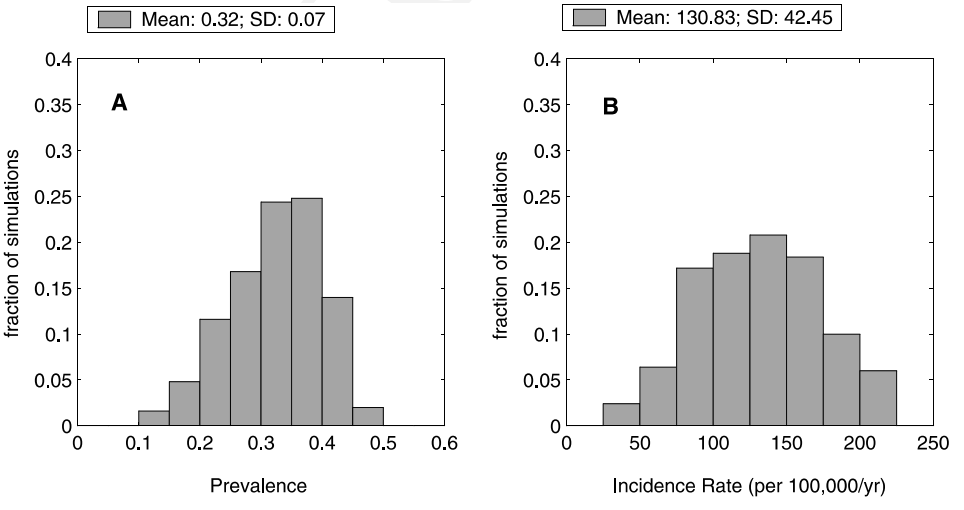

Fig. 3. Baseline simulation: present-day distributions for baseline prevalence (A) and incidence rate (B) with 30% HLA-DR2 allele in the population ($v = 0.30$), not accounting for detrimental effects on disease progression or transmission rates. Gray bars represent distributions for the fraction of simulations resulting in observed steady-state prevalence and incidence rates. Here $v = 0.30$ and $p_N = p_S \in [0.05, 0.10]$, $r_N = r_S \in [0.00167, 0.0033]$/yr, and $\beta_j \in [5.0, 7.0]$/yr ($j = w, x, y, z$) (see Table 2).

6.2. Effects of host genetic susceptibility on prevalence and incidence

Although it is known that the HLA-DR2 allele is associated with active TB disease, it is not known how the dynamics of TB infection at the population level are altered by the presence of a host-level susceptibility factor. Our model therefore serves as an experimental device to test hypothetical effects of a susceptibility phenotype and it can provide information that may be difficult to otherwise determine. We are attempting to explain, at least partially, why prevalence and incidence rate values of TB in India (up to 50% and 200–400/100k/yr, respectively [8,10,11]) are substantially higher than in other countries and WHO world-wide averages. In the following simulations, we allow for the three hypothetical effects of the HLA-DR2 susceptibility phenotype in our model, testing each hypothesis separately, then investigating their combined effects. Parameter values for the genetically neutral HLA-DR2$^-$ population are fixed at average values throughout (see Table 2).

6.2.1. Hypothesis 1: Increased direct progression to active TB (p_S)

Our first hypothesis is that HLA-DR2$^+$ individuals exhibit an increased risk of direct progression to active TB, relative to the average 5–10% progression rate [21,22]. We allow for the probability of direct progression to active TB, p_S, to range in the interval [0.10, 0.20]. In this scenario, the prevalence remains well below 50% (mean 39.6%, S.D. 2%) and the range on incidence rate is 145–205/100k/yr (mean 178/100k/yr, S.D. 17.86). Fig. 4 indicates that increasing p_S alone has only a minimal effect on prevalence and the incidence rate, as simulations produce a distribution whose mean is only slightly above baseline. This suggests that the HLA-DR2 allele likely has other effects on disease dynamics, either separate from or in addition to Hypothesis 1.

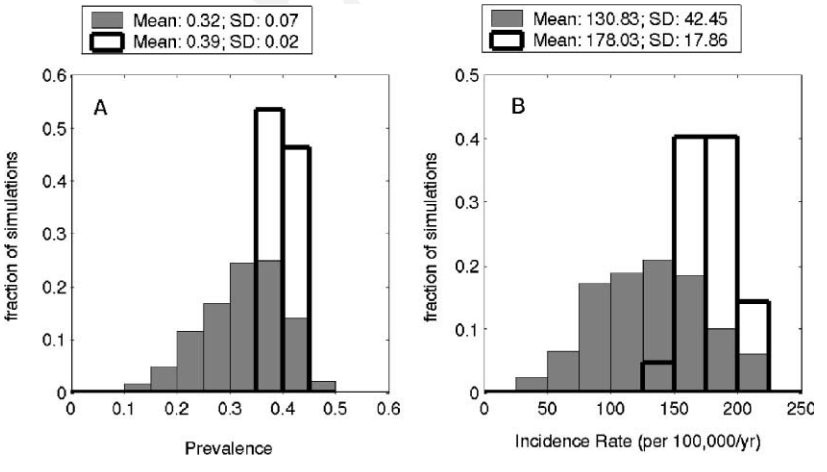

Fig. 4. Hypothesis 1: distributions of prevalence (A) and incidence rates (B) due only to the effects of an increase in direct progression to active TB in the HLA-DR2$^+$ population (p_S). Gray bars represent distributions for the fraction of baseline simulations resulting in observed steady-state prevalence and incidence rates. White bars represent distributions for the fraction of simulations resulting in observed steady-state prevalence and incidence rates due to increased p_S. Here $p_S \in [0.10, 0.20]$ while $v = 0.30$, $p_N \in [0.05, 0.10]$, $r_S = r_N = 0.002485$/yr and $\beta_w = \beta_x = \beta_y = \beta_z = 6.0$/yr.

399 *6.2.2. Hypothesis 2: Reactivation from latent TB to active TB (r_S)*
400 We now assume that the only effect of the HLA-DR2 susceptibility allele is to increase the rate
401 of reactivation. Under this hypothesis, HLA-DR2$^+$ individuals are capable of mounting an ap-
402 propriate immune response to initial infection with *M. tuberculosis*, and therefore initially develop
403 latent disease, but they exhibit an increased reactivation rate, r_S, perhaps due to waning immunity.
404 We allow r_S to vary within the interval [0.0033, 0.0066]/yr. In this scenario, the prevalence remains
405 below 50% (mean 41.9%, S.D. 2%) and the range on incidence rate is 156–236/100k/yr (mean 198/
406 100k/yr, S.D. 23.21) (see Fig. 5). Similar to Hypothesis 1, we find increasing r_S only has a minimal
407 affect on shifting prevalence and the incidence rates.

408 *6.2.3. Hypothesis 3: Transmission and receptive rates of infection (β_w, β_x, β_y, β_z)*
409 We next test the hypothesis that HLA-DR2$^+$ individuals experience only an increase in their
410 ability to transmit and/or receive *M. tuberculosis*. It is not known whether this trait is charac-
411 teristic of a HLA-DR2$^+$ transmitter (e.g. the organism exhibits greater virulence and/or viability
412 in susceptible individuals, or these individuals have a greater bacterial load in sputum, etc.) or a
413 HLA-DR2$^+$ receiver, or both. We choose $\beta_w \in [5.0, 7.0]$/yr, $\beta_x = \beta_y \in [7.0, 9.0]$/yr, and
414 $\beta_z \in [9.0, 11.0]$/yr, to reflect our assumptions that $\beta_w \leqslant \beta_x \leqslant \beta_y \leqslant \beta_z$, where the number of sec-
415 ondary infections caused by one infectious individual is greater for susceptible–susceptible in-
416 teractions (β_z) than for neutral–neutral interactions (β_w).
417 Results show that with variation in β_j $(j = w, x, y, z)$ values, prevalence of TB remains below
418 50% (mean 45.3%, S.D. 3%) and the incidence rate varies between 147 and 200/100k/yr (mean 179/
419 100k/yr, S.D. 11.29) (see Fig. 6). Variation in β_j values has a more marked effect on prevalence
420 levels than on the incidence rate. Although increased transmission/receipt of *M. tuberculosis* by

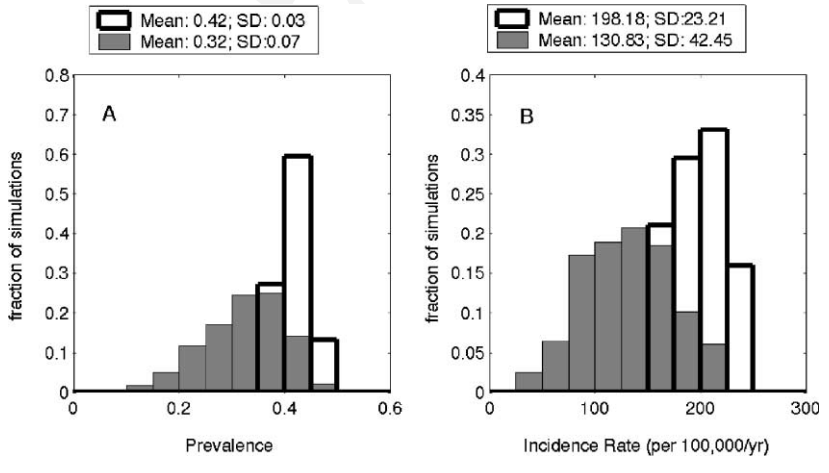

Fig. 5. Hypothesis 2: distributions of prevalence (A) and incidence rates (B) due only to the effects of an increase in the reactivation rate in the HLA-DR2$^+$ population (r_S). Gray bars represent distributions for the fraction of baseline simulations resulting in observed steady-state prevalence and incidence rates. White bars represent distributions for the fraction of simulations resulting in observed steady-state prevalence and incidence rates due to increased r_S. Here $r_S \in [0.0033, 0.0066]$/yr while $v = 0.30$, $p_S = p_N = 0.075$, $r_N \in [0.00167, 0.0033]$/yr and $\beta_w = \beta_x = \beta_y = \beta_z = 6.0$/yr.

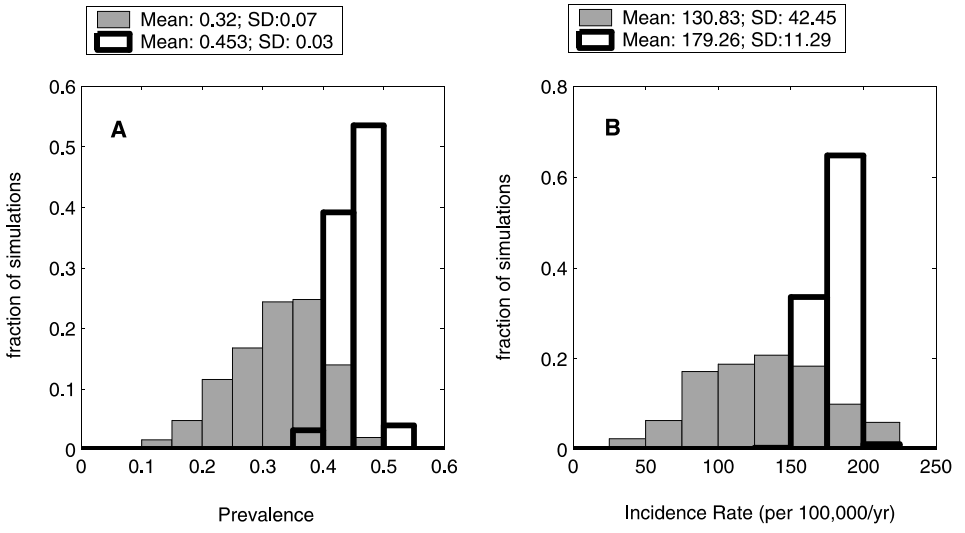

Fig. 6. Hypothesis 3: distributions of prevalence (A) and incidence rates (B) due only to the effects of an increase in the transmission/receipt rates of the HLA-DR2$^+$ population (β_x, β_y, β_z). Gray bars represent distributions for the fraction of baseline simulations resulting in observed steady-state prevalence and incidence rates. White bars represent distributions for the fraction of simulations resulting in observed steady-state prevalence and incidence rates due to increases in β_x, β_y, and β_z ranges. Here $\beta_w \in [5.0, 7.0]$/yr, $\beta_x = \beta_y \in [7.0, 9.0]$/yr, $\beta_z \in [9.0, 11.0]$/yr, while $v = 0.30$, $p_S = p_N = 0.075$ and $r_S = r_N = 0.002485$/yr.

HLA-DR2$^+$ individuals results in the high prevalence rates as in India, it cannot fully explain the high levels of both prevalence and the incidence rate as seen in India.

6.2.4. Combined effects of Hypotheses 1, 2, and 3

Biologically, the preceding experiments suggest that the presence of the HLA-DR2 allele likely affects the dynamics of epidemic TB in multiple ways. The minimal effects on prevalence and the incidence rate due to variation in p_S, r_S, or β_j $(j = w, x, y, z)$ values alone suggests that their combined effects may more realistically account for the effects of a susceptibility allele, allowing for the current state of TB within India. Therefore, we perform an experiment combining the mechanisms of action of the previous three experiments, simultaneously varying p_S, r_S, and the β_j values.

Simulation results for the combined effects indicate that both prevalence and the incidence rate are increased significantly over the baseline simulation, with prevalence ranging from 49.4% to 63.8% (mean 56.9%, S.D. 3%) and the incidence rate varying between 220 and 366/100k/yr (mean 299/100k/yr, S.D. 30.40) (see Fig. 7). These values of prevalence and the incidence rate are significantly higher than baseline and likely are more representative of the current state of TB in India, lending support to the fact that a susceptibility allele likely has multiple effects on *M. tuberculosis* infection dynamics.

To investigate the statistical relationship between each of the six parameters p_S, r_S, β_w, β_x, β_y and β_z and the outcome variable prevalence, we conduct a partial rank correlation of each input parameter (see [66] for similar methodology). The partial rank correlation coefficient, γ, indicates

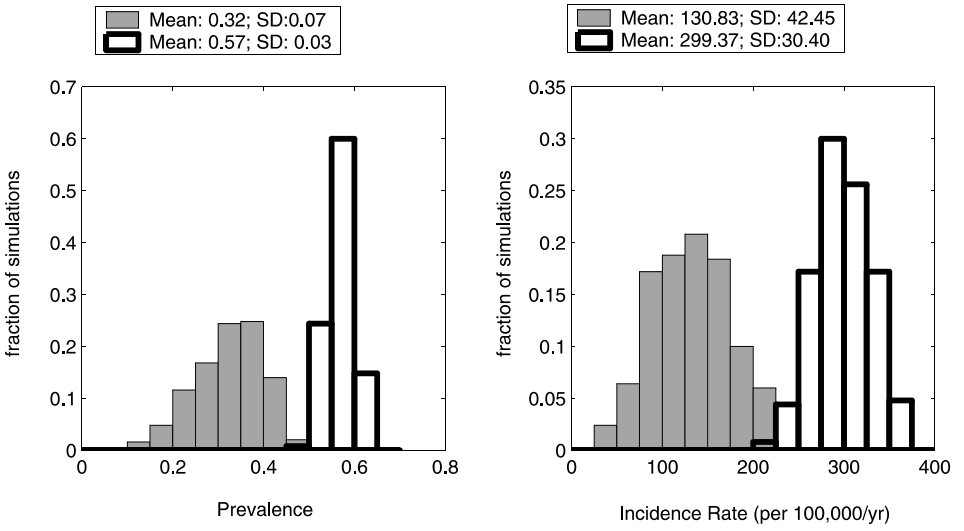

Fig. 7. Combined Hypotheses 1,2,3: distributions of prevalence (A) and incidence rates (B) due to the combined effects of increases in the direct progression (p_S), reactivation rate (r_S), and the transmission/receipt rates of the HLA-DR2$^+$ population (β_x, β_y, β_z). Gray bars represent distributions for the fraction of baseline simulations resulting in observed steady-state prevalence and incidence rates. White bars represent distributions for the fraction of simulations resulting in observed steady-state prevalence and incidence rates due to increases in p_S, r_S, β_x, β_y, and β_z. Here $p_S \in [0.10, 0.20]$, $r_S \in [0.0033, 0.0066]$/yr, $\beta_w \in [5.0, 7.0]$/yr, $\beta_x = \beta_y \in [7.0, 9.0]$/yr, $\beta_z \in [9.0, 11.0]$/yr, while $v = 0.30$, $p_N = 0.075$ and $r_N = 0.002485$/yr.

the degree of monotonicity between a parameter and an outcome (e.g. [66]). A partial rank correlation of the six parameters (p_S, r_S, β_w, β_x, β_y, β_z) indicates that p_S, r_S, β_w, and $\beta_x = \beta_y$ are key contributors to the variation from baseline prevalence (average $\gamma \approx 0.95$) while p_S and r_S are key elements for variation from the incidence rate baseline ($\gamma_{p_S} \approx 0.948, \gamma_{r_S} \approx 0.9713$).

6.3. Genetic susceptibility discussion

The ranges of prevalence and the incidence rate due to combined interactions of p_S, r_S, and β_j ($j = w, x, y, z$) contain simulations with prevalence values over 55% and incidence rates greater than 350/100k/yr, over-shooting what have been reported. This suggests two possibilities. First, susceptibility parameter value ranges may be too large, due to the fact that no data exist reporting the probability of direct progression to TB, the reactivation rate of latent TB infection, or the transmission rate of TB due to a susceptible genotype. However, these parameter ranges are a first approximation and still lend insight as to possible effects of a host susceptibility factor on epidemic TB. Second, the model uses only neutral and susceptible subpopulations; i.e., we do not account for a subpopulation with natural resistance in our model. This likely leads to overestimation of both prevalence and the incidence rate of TB within India. These inflated outcomes hint at the existence of a resistant subpopulation, which could decrease levels of both prevalence and the incidence rate (as seen in simulations, data not shown).

7. Demographic influences on *M. tuberculosis* infection in heterogeneous populations

There are four parameters within our model that may be influenced by demographics: birth rate (b), natural death rate (μ), transmission parameters ($\beta_j,\ j = w,x,y,z$), and the fraction of the population that is genetically susceptible to *M. tuberculosis* infection (v). Values for b, μ, and v are greater in India than in the USA (see Table 2).

Demographic factors such as crowding, closed environments, nutrition, and access to health care and treatment, likely affect the value of β_j [19]. 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 [52]. India has a population five times larger than the USA within an area one third the size. Therefore, 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.

As our goal is to determine the effects of demographic variations on prevalence, we simulate a baseline scenario where we allow for variation in demographic parameters while all other parameters are fixed at their median values. This creates a distribution for prevalence due to variation in demographics. Ranges for β_j^{U} and β_j^{I} ($j = w,x,y,z$) are noted in Table 2. Parameter ranges on b and μ for both countries were created by increasing and decreasing the fixed value in Table 2 by one factor of the countries' respective growth rates. For example, the range on b for India was created by calculating $b \pm 0.018b$ and the range on b for the USA was determined from $b \pm 0.009b$. See Fig. 8 for the baseline simulation.

In the rest of this section, we investigate changes in demographic parameters in pairs: b, μ and then $v, \beta_j^{\mathrm{I,U}}$. We do this to isolate parameters that were previously discovered to have strong effects on prevalence (see Section 6).

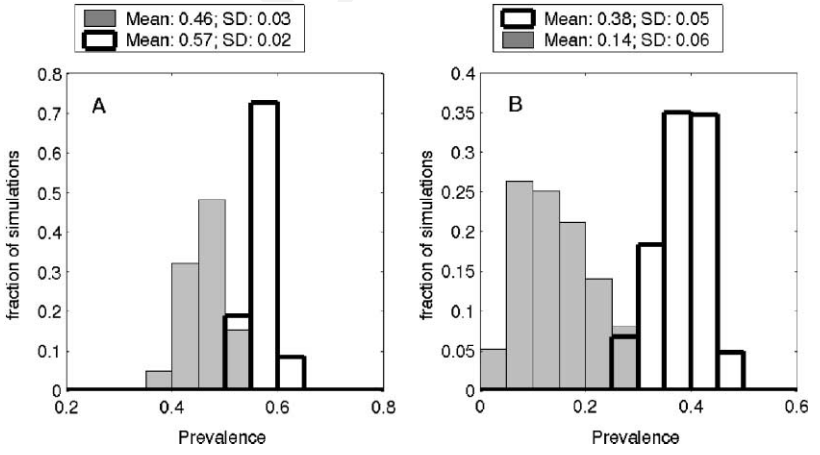

Fig. 8. Simulations for the distribution of prevalence for two populations under 2 scenarios. Panel A: India demographics with high genetic susceptibility ($v = 30\%$) to *M. tuberculosis* infection (white bars) and low genetic susceptibility ($v = 10\%$) to *M. tuberculosis* infection (gray bars). Panel B: USA demographics with high genetic susceptibility ($v = 30\%$) to *M. tuberculosis* infection (white bars) and low genetic susceptibility ($v = 10\%$) to *M. tuberculosis* infection (gray bars).

7.1. Birth (b) and death (μ) rates

Previously we discussed that, analytically, variations in the annual birth rate, b, have no influence on prevalence; numerical simulations agree with this result (data not shown). As discussed in [63], the per capita natural death rate μ is one of the most influential parameters in determining the magnitude of R_0, and thus the prevalence of TB. There is an inverse relationship between prevalence and death rate as an increase in death rate reduces the number of individuals at risk for infection. This relationship is observed regardless of the fraction of the susceptible subpopulation, v.

The per capita death rate due to TB disease, μ_{TB}, is even more strongly influential in determining the magnitude of R_0, and thus the prevalence of TB. This is clear since μ_{TB} indicates how long (on average) an individual remains infectious (capable of transmitting *M. tuberculosis*) in the absence of treatment. The longer an individual remains infectious (i.e., the smaller μ_{TB} is), the larger prevalence will be in the general population. Small changes in the value of μ_{TB} dominate variations in all other parameters, seen by the partial rank correlation coefficient $\gamma_{\mu_{\mathrm{TB}}} \approx -0.9483$. In fact, the correlation value for μ_{TB} indicates a significantly greater impact ($p = 0.0001$) on prevalence compared with any other parameter.

7.2. Transmission (β_j) and frequency of genetic susceptibility (v)

In Fig. 6 we see that, in addition to the frequency of genetic susceptibility, v, transmission rates β_j $(j = w, x, y, z)$ are the most important parameters influencing TB prevalence. It is difficult or impossible to gather reliable data on these rates. Thus, we perform additional experiments to determine whether the influence of v and β are modulated by demographic factors, and to examine further the relative dependence of prevalence on these two classes of parameters.

To examine the relative influence of transmission and HLA-DR2 frequency, we vary v in the range [0.0, 0.5] and perform three simulations:

1. vary only β_w in the range [3,7],
2. vary only $\beta_x = \beta_y$ in the range [7,11], and
3. vary only β_z in the range [11,15].

These simulations are duplicated for the two sets of demographic parameters reflecting both India and the USA. See Fig. 9 for contour plots of prevalence of TB versus both v and β for India (panels A, B, C) and the USA (panels D, E, F).

Results of these experiments show that in a population with a large genetically susceptible subpopulation (high values of v), prevalence is only marginally dependent on the transmission parameters β_j $(j = w, z, y, z)$. However, in a population with a small genetically susceptible subpopulation (low values of v), β_w is far more influential on prevalence than either β_x or β_z. This is due to the fact that the majority of the population is in the two compartments U_N and T_N. Even at low HLA-DR2 frequencies, varying v augments prevalence to a greater extent than varying the transmission parameters β_j $(j = w, z, y, z)$.

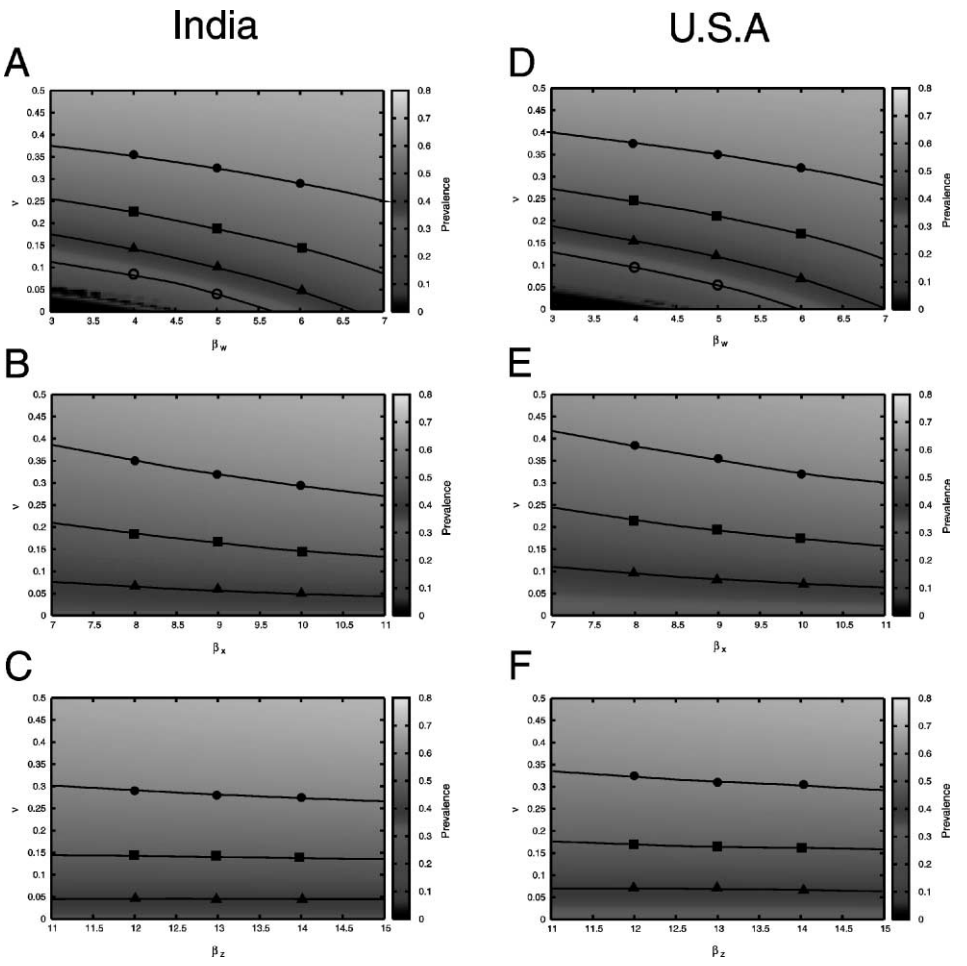

Fig. 9. Contour plots of TB prevalence versus v and β_j $(j = w, x = y, z)$ for Indian (panels A, B, C) and USA (panels D, E, F) demographics. Prevalence contours of 30%, 40%, 50%, and 60% are indicated by open circles, triangles, squares, and closed circles, respectively.

8. Discussion

In this study we have used an epidemiological model to investigate the effects of genetic susceptibility and demographic factors on epidemic tuberculosis. Wide variation in endemic TB levels between countries underlies the importance of identifying factors responsible for these differences, especially when designing treatment and public health strategies. This paper is novel as it investigates various explanations for differences in epidemic TB levels in distinct population settings. Mathematical models are powerful tools for studying the complex, non-linear dynamics of *M. tuberculosis* epidemics. In addition, mathematical models can provide clues to underlying mechanisms of disease dynamics that epidemiology studies alone cannot.

Specifically, we model two subpopulations, one with genetic susceptibility to *M. tuberculosis* infection and one that is genetically neutral. Our choice of modeling genetic susceptibility is arbitrary for this paper, and one could easily envision a similar approach to modeling a subpopulation that is genetically resistant to infection. A model that accounts for all three subpopulations, genetic resistance, neutrality, and susceptibility, is more realistic and is currently being investigated.

There are limitations to our initial approach, however, mainly due to the complex nature of modeling infectious disease in heterogeneous populations. One inherent difficulty is that many parameters incorporate both genetic as well as demographic (or social) components, in particular the disease transmission parameters β_j $(j = w, x, y, z)$. These limitations require a number of simplifications, which we are careful to point out in our assumptions (Section 4). Current and future research projects will investigate relaxing these.

We also do not attempt to model temporal TB epidemic dynamics. Rather, we focus on the effects of particular parameters, especially those that relate to genetic susceptibility, on changes in the present-day steady-state levels of prevalence and incidence. Because of this approach, we do not account for genetic selection on v, the fraction of the population with a particular susceptible phenotype. Many papers have been written which account for populations that undergo genetic selection due to infectious diseases [50,70–72]. We are currently exploring selection for or against traits of the neutral and susceptible populations in extensions of this work.

As a necessary simplification, we also do not account for changes in demographic parameters (birth and death rates) over time (as in [50]). This again reflects our initial approach of analyzing steady-state values rather than demographic trends over time. Once we gain better understanding of parameter contributions, we can relax this simplification and follow the approach similar to [50,73] for estimating and using demographic parameters that evolve over time.

The basic reproduction number R_0 of an infectious disease indicates whether or not the disease will become established within the population. Determining an R_0 expression for many epidemic SIR models can be routine. For scenarios where multiple strains (subtypes) of an infectious disease exist, an R_0 number is calculated for each strain. However, our model tracks only one strain of *M. tuberculosis* in a population with multiple subpopulations. In this case, we must define a single R_0 for the population as a whole, rather than an R_0 for each subpopulation. This is a significantly more difficult task.

We used an implicit method for generating an expression for R_0 (see Eqs. (8)–(12)). This method is based on the idea that R_0 is a normalized bifurcation condition for the model. We validate our calculation of R_0 using the Next Generation Operator method under the limiting condition of proportionate infectivity (scalability of the transmission parameters β_j $(j = w, x, y, z)$); results not shown).

The roles of genetic susceptibility and resistance to infectious diseases are clearly important but not well understood. In this paper we first simulate epidemic TB in a population with known susceptibility to infection. Results show that the presence of a small genetically susceptible subpopulation can dramatically increase prevalence and incidence of TB in the general population. We then study epidemic TB in two demographically different populations, India and the USA, and explore how demographic factors impact TB prevalence.

Obvious demographic differences between the USA and India are birth and death rates. Our choice of assuming a constant birth rate b means that changes in the birth rate will have no effect

on prevalence of TB. This is reasonable as a constant birth rate simply scales the size of the population, and thus the sizes of the subpopulations, while keeping the ratio of infecteds to uninfecteds, i.e., prevalence, constant. Changes in the death rate μ and μ_{TB} dominate changes in all other parameters.

Two other parameters, disease transmission (β_j) and the fraction of the population genetically susceptible to active TB disease (v), also have strong influences on prevalence. Results of simulations varying these two parameters indicates that in populations with a high level of genetic susceptibility, prevalence is only slightly affected by changes in β_j. In a population with a small-genetically susceptible subpopulation, β_w is far more influential than β_x or β_z. This is expected, for when v is small, a greater proportion of the population is in the uninfected, genetically neutral classes (U_N and T_N). This follows since transmission of *M. tuberculosis* to individuals in the U_N population is governed by β_w.

We are presently investigating treatment strategies that compare treating an entire population or targeting a particular subpopulation [74]. Using our model, we can study trade-offs between therapy of active TB disease and chemoprophylaxis of latent disease in heterogeneous populations. The added effects of drug-resistance, treatment non-compliance, and co-infection with other diseases together with ideas on genetic susceptibility needs to be investigated further.

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