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A mathematical model of tuberculosis transmission with heterogeneity in disease susceptibility and progression under a treatment regime for infectious cases

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ABSTRACT

The effect of difference in susceptibility on the dynamics of tuberculosis is an ongoing study. Several genes in TB co-receptors (e.g. HLA and non-HLA) have been correlated with susceptibility and resistance to tuberculosis and rate of progression to active TB. In this paper, we present a novel mathematical model that distinguishes between susceptibility amongst the population. The model classifies the susceptibles as having no, partial or full natural resistance to tuberculosis and the latently infecteds as rapid, normal or very slow (or no) progressors to active TB depending on the genes. The goal of this paper is to investigate the impact of such heterogeneity on the spread of tuberculosis and to identify key parameters that could be used in understanding these heterogeneities more fully. We derived the reproduction number $\mathcal{R}_T$ for the model and examine the relative contributions to $\mathcal{R}_T$ from the three latently infected classes as well as the infectious classes. The effect of treatment under the heterogeneity is also examined.

1. Introduction

Tuberculosis, a chronic bacterial, infectious disease caused by *Mycobacterium tuberculosis*, has re-emerged as a leading public health problem. With about one third of the world's population infected with *M. tuberculosis*, it is reported that these infections leads to nearly three million deaths each year [1–3]. Although between 90% and 95% of infections occur in developing countries [3], the emergence of HIV as well as multi-drug-resistance (MDR) strains of *M.tuberculosis* has dramatically changed the dynamics of infections worldwide [1,4]. Other factors that may contribute to the tuberculosis epidemic includes elimination of TB control programs, poor drug usage, poverty, poor case detection rates and immigration [1,5–7].

The continual high burden of TB infection in regions of Southeast Asia, Africa, and some European countries like Russia, has renewed interest in global TB control [2,4]. For example, Nigeria ranks fifth among the world's high burden countries, with a number of TB cases of 450,000 [8,9]. The TB incidence is at 311/100,000 and the rate of new sputum smear positive disease is approximately 137/100,000 [9].

Interestingly, not all individuals exposed to *M. tuberculosis* become infected. Moreover, progression toward clinical tuberculosis is far from an inevitable consequence of infection with *M. tuberculosis*, since only about 10% of the vast number of infected individuals actually develop clinical disease [10,11]. Both *M. tuberculosis* infection and clinical tuberculosis result from complex interactions between the infectious agent, environmental factors, and the host [10].

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A global control strategy adopted by the World Health Organisation (WHO) to help reduce the number of active TB cases as well as promote proper treatment of patients with tuberculosis is the Direct Observation Therapy Strategy (DOTS). Non-adherence to treatment of TB results in resurgence of resistance strains, making it even more difficult to cure. DOTS have evolved into a strategy that makes it compulsory for patients to complete their treatment. The DOTS program uses a nurse or surrogate who delivers and supervises the patients taking all the doses of their drugs rather than relying on the patients to take the drugs on their own [12]. The patients may choose either to come to a health facility (the clinic based DOT) [12,13], or to be visited wherever they are, e.g. at work, home or shelter (the community based DOT) [14].

Treatment strategies for tuberculosis infection depend on disease status. More than 90% of actively infected individuals receive effective therapy in developed countries, while up to only 50% of active cases receive effective therapy in developing countries in the late 1990's [2]. Of course these figures are increasing with increased funding of tuberculosis control strategies in several developing countries. 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 [2]. However, some developed countries like the USA, still provides treatment for latently infected persons, termed chemoprophylaxis or preventive therapy [2].

An important question that researchers have continually sought answers to is what allows for different disease outcomes following infection with *M. tuberculosis*. As was stated earlier, a number of factors contribute, ranging over environmental, microbial and host characteristics [1]. However, genetic heterogeneity (susceptibility and resistance) is being studied as another key factor that could go a long way in explaining the dynamics of tuberculosis in a population. Genetic susceptibility to tuberculosis refers to genes that make someone susceptible to developing TB when exposed to *M. tuberculosis*; although several millions of new cases of TB are reported each year, not everyone exposed to the bacterium becomes infected nor does everybody infected with it develop clinical symptoms of TB. What is the role of genetics in the dynamics of tuberculosis?

2. Host genetics and tuberculosis

Why do some people who are exposed to *M. tuberculosis* not become infected or, if infected, not develop to active tuberculosis? Several studies had gone into investigating the effect of certain genes on susceptibility or resistance to tuberculosis. For instance, in [15], it was reported that one or multiple genes might provide certain people with resistance to tuberculosis infection. The findings in [15] shows the existence of a chromosomal site, or a locus, that controls resistance to TB infection. Out of the 128 families studied, who come from an area in South Africa with high tuberculosis rates, after considering non genetic factors such as age, 20% of individuals show natural resistance. As explained by one of the researchers, "In other words, some people seem to have a particular genetic heritage that makes them naturally resistant to [*M.tuberculosis*] infection".

However, even before the study reported in [15], the involvement of human genes in tuberculosis has been suggested by numerous epidemiological observations [1,16–21]. These studies employed, amongst other methods, large scale control studies of target genes, family-based linkages including twin studies and investigation of rare individuals with exceptional mycobacteria susceptibility. The studies enable identification of the particular host gene that influences susceptibility to tuberculosis.

Several studies have shown that a person's resistance level to the bacterium infection correlates with the region of his or her ancestry and that the ancestors of more-susceptible persons tend to come from areas once free of tuberculosis [10,22]. Greenwood et.al. in [23] identified a major gene in a Canadian study that appears to control the progression from infected status (i.e. individuals with positive tuberculin skin test) to affected status (i.e. individuals with tuberculosis). The results of the study showed that in certain genetic epidemiological contexts, predisposition to tuberculosis results mostly from the major gene.

Susceptibility of tuberculosis is multifactorial. Host genetic factors such as the human leucocyte antigens (HLA) and non-HLA genes that are associated with susceptibility to tuberculosis usually serves as genetic markers to predispose or predetermine the development of the disease. These markers are useful in understanding the immune mechanism of susceptibility or resistance to tuberculosis [24]. Increased susceptibility and resistance to more than 500 diseases has been shown to be associated with various HLA antigens, alleles, or haplotypes [1,25]. The level and type of immune response to a particular pathogen may vary among populations that have different distributions of HLA molecules.

Several studies of HLA association with pulmonary tuberculosis have been carried out in populations in China, Indonesia and Russia (See Ref. in [24]). In fact, Selvaraj in [24] listed some important candidate gene variants of HLA and non-HLA genes with the susceptibility or resistance to tuberculosis in Indian population. Table 1 lists some of the common classifications and shows the allele that is strongly associated with the active stage and others that are commonly associated with active TB.

The effect of some non-HLA genes on susceptibility has also been reported in [24,20]. For instance, in the study in [20], it was shown that variation in the human homolog NRAMP1 is associated with altered susceptibility to smear-positive tuberculosis amongst some individuals in the Gambia, West Africa. It was then concluded that the NRAMP1 gene governs susceptibility to tuberculosis. Although the study design used in [20] did not distinguish between susceptibility to infection with *M. tuberculosis* and susceptibility to disease progression, it is possible that the NRAMP1 could affect susceptibility to disease progression especially for individuals with this gene who are already affected with the bacteria. The study in [20] concluded

Table 1
Some HLA and non-HLA genes associated with susceptibility and resistance to TB in Indian population with the (+) indicating the positive correlation between the particular allele with active tuberculosis while (+++) indicates that the allele is more commonly and strongly associated with active TB [24,1].

Candidate genes	Effect	Ref.
HLA		
HLA-DR2	Susceptibility (+++)	[18,26,27]
subtypes		
-DRB1 *1501, *1502	Susceptibility (+)	[28]
HLA-DQ1	Susceptibility (+)	[18,29]
HLA-DP	Susceptibility (+)	[29]
Haplotype		
DRB1 and 1501-DQB1 *0601	Susceptibility (+)	[29]
DRB1 *11(5), *10, *0501	Resistance	[29]
Some Non-HLA		
-Heterozygotes of MBL codon 57	Resistance to relapse	[30]
Vitamin D Receptor (VDR)	Differential suscept. and resist.	[31,32]
NRMAP1	No association with suscept. or resist.	[33]

that there are genetic variations in NRAMP1 that affects susceptibility to tuberculosis in West Africans. In a study carried out, also in The Gambia (West Africa) [34], on pulmonary TB patients, the *tt* genotype of *TaqI* polymorphism of VDR gene was found less frequently in cases of pulmonary TB, suggesting that this genotype may be associated with resistance to pulmonary TB whereas *ApaI* polymorphism of the VDR gene showed no association.

In a recent study on the genetic diversity of tuberculosis in Jos, Nigeria, reported in [8], several strains of *Mycobacterium tuberculosis* complex (MTC) species were isolated. Using the method of spoligotyping, the study showed that LAM10 (which is strongly associated with tuberculosis) isolates were abundant in the population of MTC isolates from Jos, Nigeria. The study then concluded that the extensive TB epidemic in the area under study was caused by one successful *M. tuberculosis* family, dominated by the LAM10 subfamily.

In summary, the information above clearly indicates the existence of heterogeneities in susceptibility and resistance to TB and its effect on the dynamics of tuberculosis; susceptibility to progression (from the latent stage to the active stage) can also be linked to some genetic markers. The identification of host genes with their functional alleles controlling the response to mycobacterial infection is fundamental to the definition of new prevention (e.g. early detection and prolonged follow-up of high risk individuals) and treatment (e.g. aimed at restoring partially deficient immune responses) strategies for tuberculosis [10].

The purpose of this paper is to investigate, using mathematical models, the impact of genetic heterogeneity on the spread of TB. We will consider genetic susceptibility to infection and susceptibility to disease progression. We will tailor our model in the light of the work done by S-F Hsu Schmitz on genetic heterogeneity and its impact on the dynamics of HIV/AIDS in a homosexual population [35,36]. In fact, Castillo-Chavez and Song in [37] listed the effect of genetics on the dynamics of tuberculosis as a challenging area worth investigating and suggested the fine leads found in [35,36].

There are interesting articles that discusses the issue of genetic heterogeneity on tuberculosis dynamics. For example, the articles by Murphy et al. in [1,2] examined this issue using a system of six ordinary differential equations, whereby the susceptible, latently infected and infectious classes were divided into two sub classes each: a sub class for individuals with a susceptible genotype and another for individuals with a neutral (without a susceptible) genotype. The work in [2] included the effect of treatment (of the infected classes) on the the overall dynamics of the disease on the population. However, both models did not take into cognisance the effect of exogenous reinfection on the dynamics of the disease, an effect that is generally accepted as very crucial on TB epidemics [38–40]. Also, with the above information on specific genes, classifications can be broadly made for the susceptibles as to having no, partial or full natural resistance to tuberculosis and the latently infected as to being rapid, normal or very slow (or no) progressors. With the above, we can deal with the fact that gene differentiability occurs with susceptibles becoming infected (latent) and the infected becoming infectious (having active tuberculosis) so that some susceptibles, due to the gene, can never become infected (latently) and some latent cases can never progress to becoming infectious (active). More so, we want to formulate a mathematical model that has separate classes for the treated individuals.

3. Mathematical model description

We will make use of the level of natural resistance to TB while incorporating genetic heterogeneity in the epidemiological models. To do this, we will classify the susceptibles into three groups: susceptibles with no resistance (S_1), those with partial resistance (S_2) and susceptibles with complete resistance (S_3). We assume that S_3-individuals never become infected. This assumption, of course, simplifies the overall dynamical system. Similarly, based on the TB pathogenesis, latently infected individuals are classified into three groups: latently infected individuals that are rapid progressors to active TB (E_1), normal

progressors (E_2) and no or very slow progressors (E_3). We will further assume that the E_3-individuals will have very little or no reactivation rate since they will rarely progress to having active TB; moreover exogenous reinfection will play no role in the dynamics of this class. These latent classes will be referred to as 'primary' latency ('primary' latency refers to those who are contracting TB for the first time and are in the latent stage and those who get infected again after effective treatment following their previous infection). We will assume that I_1 represents infectious individuals from the class of rapid progressors, E_1, while I_2 will represent the infectious individuals from the normal progressors as well as very slow (if any) progressors i.e. E_2 and E_3. Further, let us assume that T_1 represent the effectively treated individuals whose infections were generated by the rapid progressors while T_2 will stand for effectively treated individuals whose infections are generated by the normal or very slow (if any) progressors. The treated classes, T_1 and T_2 are considered susceptible still after effective treatment. Note that we are not including treatment for the latent individuals; this is reasonable as most countries, especially developing countries, expend their energies on treating infectious, active cases of tuberculosis.

In addition to the classes explained above, we will include a separate class $R(t)$ to monitor individuals who become latent (which we shall refer to as 'secondary' latency) after failed treatment and those who became latent due to self-cure from the infectious classes, I_1 and I_2. These individuals are not allowed to go back to the 'primary' latent classes E_1, E_2 or E_3 for new infections. Note that we have not assumed that the individuals in the R class can never become infectious. However, for modeling purposes, we do not consider this group to be a part of the infection process since they are actually individuals that are in some form of isolation, under close monitoring. Of course excluding the individuals in the R class from the infection process implies that the disease incidence is lower when most individuals fail treatment and/or have a high self cure rate since individuals in these conditions are out of the model. However reports from the WHO (such as that in [9]) have shown that, under DOTS (which is the main strategy for TB treatment in most countries especially developing ones like Nigeria), treatment success rates have been impressively high; the main issue has been case detection rates, which have been abysmally poor over the years. In Nigeria, for instance, there is a low treatment failure rate, under DOTS, and a small number of infectious individuals reverting to latency by self cure. In fact, clinical data on TB dynamics in Nigeria shows that only 1% of failed treated cases ever develop resistant TB and just 7.6% of these are treated [9], a vast majority of individuals in the 'secondary' latency class remains in such a state for a long time. Also creating this class helps us track the number of individuals in this category of latency and have an idea of the burden of latent TB. So in realistic terms, there are rare reports (if any) of high treatment failure rates in recent times since the implementation of DOTS in several countries, especially the high burden countries. Hence our implied assumption that the incidence rates of the disease is not significantly affected when we exclude the R class from the infection process can be sustained.

We will set $N = S_1 + S_2 + S_3 + E_1 + E_2 + E_3 + I_1 + I_2 + T_1 + T_2 + R$ as the total number of individuals involved in the dynamics.

We assume that Λ is the constant recruitment rate to replenish the three susceptible groups with respective fractions, $h_i (i = 1, 2, 3$ and $\sum_i h_i = 1)$; the fractions are related to the frequencies of relevant genotype. We assume, for convenience, that the h_i's are constants. Because frequencies of mutant alleles are relatively small, we expect that

$$h_1 > h_2 > h_3; \tag{1}$$

so that a large fraction of individuals has no resistance, a small fraction has partial resistance, and an even smaller fraction has complete resistance.

Let μ be the common per capita natural death rate; then $1/\mu$ is the average life span of individuals in the population. Also let the per capita transmission rate be $\beta_i (i = 1, 2)$ for the infectiousness of the $I_i (i = 1, 2)$ individuals. Since I_1 individuals are most infectious (by their definition), we hypothesize that

$$\beta_1 \geqslant \beta_2. \tag{2}$$

During the contact between an S_2-individual and an I_i-individual, the transmission rate β_i of the infected individual is reduced to $x_i\beta_i$, with $0 < x_i < 1$ to account for the partial resistance to TB in S_2-individuals. Newly infected S_i-individuals $(i = 1, 2)$ join the three latently infected classes (with subscript $j, j = 1, 2, 3$) with respective proportions f_{ij}, which satisfies

$$0 \leqslant f_{ij} \leqslant 1 \text{ and } \sum_{j=1}^{3} f_{ij} = 1. \tag{3}$$

We expect the new infecteds who come from S_1 to generate a larger fraction of rapid progressors (E_1) and a smaller fraction of slow progressors (if any), (E_3) than those coming from S_2; hence

$$f_{11} > f_{21} \text{ and } f_{13} < f_{23}. \tag{4}$$

Let the reactivation rate of latent infections for E_j-individuals be denoted by $k_j (j = 1, 2, 3)$. It is obvious that (from the definitions of the latent classes)

$$k_1 > k_2 \gg k_3 \text{ with } 0 \leqslant k_3 \ll 1. \tag{5}$$

Let the fraction of direct progressions to active tuberculosis from new infections be denoted by $p_i (i = 1, 2)$ where

$$0 \leqslant p_1 \leqslant 1, \quad 0 \leqslant p_2 \leqslant 1 \text{ with } p_1 > p_2 \tag{6}$$

with $(1-p_1)$ of these infections moving to the E_1 class while $(1-p_2)$ of these infections move to the E_2 class.

By the definition of E_3, we assume that there is no direct progression to active TB from this group, but reactivation is assumed possible, but rare since $0 \leqslant k_3 \ll 1$.

Since we are including exogenous reinfection into the system, let β^* be the effective transmission rate for individuals in the E_1 with a reduced effect for individuals in the E_2 group by $x_3\beta^*$ where $0 < x_3 < 1$.

Let us further assume that the disease induced death rates are d_1 and d_2 for the I_1 and I_2 classes, respectively while the self-cure rates are denoted by n_1 and n_2 for the I_1 and I_2 groups, respectively (We assume that those who 'self-cure' revert to the "secondary" latent state R after an average of two years [41–43]; we then expect that $n_1 \leqslant n_2$).

Let the treatment rates be r_1 and r_2 for the effectively treated classes, T_1 and T_2, respectively. We also assume that of those treated, m_1 denotes the fraction of successful treatments from the I_1 group while m_2 denotes the fraction of successful treatments from the I_2 group, so that

$$0 \leqslant m_1 \leqslant 1 \text{ and } 0 \leqslant m_2 \leqslant 1. \tag{7}$$

Those who fail treatments revert to the "secondary" latency group R.

The infectiousness of the $I_i (i = 1, 2)$ classes on the treated classes is assumed reduced by virtue of the treatment itself, so that the transmission of the disease on the treated individuals is reduced from β_i to $z_i\beta_i$ with $0 < z_i \leqslant 1 (i = 1, 2)$; the value 0 is not included in the range for the z_i's as there is no evidence that treatment does confer any life long immunity against infection. Analogous to the $x_i (i = 1, 2)$ parameter for the S_2-individuals, let $y_i (i = 1, 2)$ further reduce the infectiousness of the T_2-individuals (by virtue of their definition) to $y_i z_i \beta_i (i = 1, 2)$ with $0 < y_i < 1$ and

$$y_i \leqslant x_i \quad i = 1, 2. \tag{8}$$

With the above, we now have an equivalent version of the f_{ij}'s for the treated classes, namely: g_{ij} which satisfies

$$0 \leqslant g_{ij} \leqslant 1 \text{ and } \sum_{j=1}^{3} g_{ij} \leqslant 1 \tag{9}$$

Again, we assume that the new infecteds who come from T_1 will generate a larger fraction of rapid progressors (E_1) and a smaller fraction of slow progressors (if any), (E_3) than those coming from T_2; hence

$$g_{11} > g_{21} \text{ and } g_{13} < g_{23}. \tag{10}$$

The positive effect of treatment then makes

$$g_{ij} \leqslant f_{ij}, \quad i = 1, 2, \quad j = 1, 2, 3. \tag{11}$$

Before we state the model, let

$$\delta_1 = \sum_{i=1}^{2} \beta_i \frac{I_i}{N} \quad \delta_2 = \sum_{i=1}^{2} x_i \beta_i \frac{I_i}{N} \tag{12}$$

$$\delta_3 = \sum_{i=1}^{2} z_i \beta_i \frac{I_i}{N} \quad \delta_4 = \sum_{i=1}^{2} y_i z_i \beta_i \frac{I_i}{N} \quad \delta_5 = \sum_{i=1}^{2} \frac{I_i}{N} \tag{13}$$

The δ_i's are the forces of infection caused by the infectious classes.

We are now ready to present the mathematical model which is made up of a system of 11 nonlinear ordinary differential equations:

$$\begin{aligned}
\dot{S}_1(t) &= h_1\Lambda - S_1\delta_1 - \mu S_1 \\
\dot{S}_2(t) &= h_2\Lambda - S_2\delta_2 - \mu S_2 \\
\dot{S}_3(t) &= h_3\Lambda - \mu S_3 \\
\dot{E}_1(t) &= (1-p_1)[f_{11}S_1\delta_1 + f_{21}S_2\delta_2 + g_{11}T_1\delta_3 + g_{21}T_2\delta_4] - \beta^* E_1\delta_5 - (k_1+\mu)E_1 \\
\dot{E}_2(t) &= (1-p_2)[f_{12}S_1\delta_1 + f_{22}S_2\delta_2 + g_{12}T_1\delta_3 + g_{22}T_2\delta_4] - x_3\beta^* E_2\delta_5 - (k_2+\mu)E_2 \\
\dot{E}_3(t) &= f_{13}S_1\delta_1 + f_{23}S_2\delta_2 + g_{13}T_1\delta_3 + g_{23}T_2\delta_4 - (k_3+\mu)E_3 \\
\dot{I}_1(t) &= p_1[f_{11}S_1\delta_1 + f_{21}S_2\delta_2 + g_{11}T_1\delta_3 + g_{21}T_2\delta_4] + \beta^* E_1\delta_5 + k_1E_1 - (r_1+\mu+d_1+n_1)I_1 \\
\dot{I}_2(t) &= p_2[f_{12}S_1\delta_1 + f_{22}S_2\delta_2 + g_{12}T_1\delta_3 + g_{22}T_2\delta_4] + x_3\beta^* E_2\delta_5 + k_2E_2 + k_3E_3 - (r_2+\mu+d_2+n_2)I_2
\end{aligned} \tag{14}$$

$$\dot{T}_1(t) = m_1 r_1 I_1 - T_1\delta_3 - \mu T_1$$

$$\dot{T}_2(t) = m_2 r_2 I_2 - T_2\delta_4 - \mu T_2$$

$$\dot{R}(t) = (1-m_1)r_1 I_1 + (1-m_2)r_2 I_2 + n_1 I_1 + n_2 I_2 - \mu R$$

In order to make the model (14) analytically tractable, some simplifications are required.

Let us re-parameterize the transmission rates via $\beta := \beta_2$ so that

$$\beta_1 = b\beta. \tag{15}$$

The relation in (2) implies that the multiplier $b \geqslant 1$.

Obtaining data that could throw some light on whether or not the reduction factors x_i, y_i and z_i depend on the specific β_i is not easy. However we will assume that $x_i = x, y_i = y$ and $z_i = z$ for all i. Further, let $\epsilon = \frac{\beta^*}{\beta}$. With the above, we can define a new force of infection thus

$$\lambda = \frac{\beta(bI_1 + I_2)}{N} \tag{16}$$

so that the simplified model now becomes

$$\begin{aligned}
\dot{S}_1(t) &= h_1\Lambda - \lambda S_1 - \mu S_1\\
\dot{S}_2(t) &= h_2\Lambda - x\lambda S_2 - \mu S_2\\
\dot{S}_3(t) &= h_3\Lambda - \mu S_3\\
\dot{E}_1(t) &= (1-p_1)[\lambda(f_{11}S_1 + f_{21}xS_2 + g_{11}zT_1 + g_{21}yzT_2)] - \epsilon\lambda E_1 - a_{11}E_1\\
\dot{E}_2(t) &= (1-p_2)[\lambda(f_{12}S_1 + f_{22}xS_2 + g_{12}zT_1 + g_{22}yzT_2)] - \epsilon x_3\lambda E_2 - a_{22}E_2\\
\dot{E}_3(t) &= \lambda(f_{13}S_1 + f_{23}xS_2 + g_{13}zT_1 + g_{23}yzT_2) - a_{33}E_3\\
\dot{I}_1(t) &= p_1[\lambda(f_{11}S_1 + f_{21}xS_2 + g_{11}zT_1 + g_{21}yzT_2)] + (\epsilon\lambda + k_1)E_1 - a_{44}\\
\dot{I}_2(t) &= p_2[\lambda(f_{12}S_1 + f_{22}xS_2 + g_{12}zT_1 + g_{22}yzT_2)] + (\epsilon\lambda x_3 + k_2)E_2 + k_3E_3 - a_{55}I_2\\
\dot{T}_1(t) &= m_1 r_1 I_1 - zT_1\lambda - \mu T_1\\
\dot{T}_2(t) &= m_2 r_2 I_2 - yzT_2\lambda - \mu T_2\\
\dot{R}(t) &= a_{66}I_1 + a_{77}I_2 - \mu R
\end{aligned} \tag{17}$$

where $a_{11} = k_1 + \mu, a_{22} = k_2 + \mu, a_{33} = k_3 + \mu, a_{44} = r_1 + \mu + d_1 + n_1, a_{55} = r_2 + \mu + d_2 + n_2, a_{66} = ((1-m_1)r_1 + n_1)$ and $a_{77} = ((1-m_2)r_2 + n_2)$.

4. Positivity and boundedness of solutions

Consider the biologically-feasible domain:

$$\mathcal{D} = \{(S_1, S_2, S_3, E_1, E_2, E_3, I_1, I_2, T_1, T_2, R) \in \mathbb{R}^{11}_{\geqslant 0} : N \leqslant \Lambda/\mu\}. \tag{18}$$

We can establish the positive invariance of $\mathcal{D}$ and a global attractor of this system (i.e. any phase trajectory initiated anywhere in the non-negative region $\mathbb{R}^{11}_{\geqslant 0}$ of the phase space eventually enters $\mathcal{D}$ and remains in $\mathcal{D}$ for all time).

The rate of change of N, is given by

$$\frac{dN}{dt} = \Lambda - \mu N - d_1 I_1 - d_2 I_2. \tag{19}$$

Thus we can see that whenever $N > \Lambda/\mu$, then $dN/dt < 0$. Hence since the right hand side of the inequality (19), dN/dt, is bounded by $\Lambda - \mu N$, a standard comparison theorem [44] can be used to show that

$$N(t) \leqslant N(0)e^{-\mu t} + \frac{\Lambda}{\mu}(1 - e^{-\mu t}). \tag{20}$$

In particular, if $N(0) \leqslant \frac{\Lambda}{\mu}$, then $N(t) \leqslant \frac{\Lambda}{\mu}$. Thus, $\mathcal{D}$ is a positively invariant set under the flow described in (17). Hence no solution path leaves through any boundary of $\mathcal{D}$.

The right hand side of (17) is smooth, hence the initial value problem has a unique solution that exists on maximal intervals [45]. Since paths cannot leave $\mathcal{D}$, solutions remain non-negative for non-negative initial conditions; solutions exist for all positive time [45]. Thus, the model (17) is mathematically and epidemiologically well posed.

5. Reproduction number and local stability of disease-free equilibrium

The model (17) has a disease-free equilibrium (DFE), obtained by setting the right hand sides of the equations in the model to zero, given by

$$\xi_0 = (S_1^0, S_2^0, S_3^0, E_1^0, E_2^0, E_3^0, I_1^0, I_2^0, T_1^0, T_2^0, R) = \left(\frac{h_1\Lambda}{\mu}, \frac{h_2\Lambda}{\mu}, \frac{h_3\Lambda}{\mu}, 0, 0, 0, 0, 0, 0, 0, 0\right). \tag{21}$$

Hence the susceptible classes, at this steady state, depend on the product of the genotype frequencies and the asymptotic population size, Λ/μ.

The endemic equlibrium (if it exists) for the model in (17) is given in Appendix A.

The stability of ξ_0 can be established using the next generation operator method on the system (17). Using the notations in van den Driessche and Watmough [46], the matrices F and V, for the new infection terms and the remaining transfer terms respectively, are given by

$$F = \begin{pmatrix} 0 & 0 & 0 & b(1-p_1)\beta\tau_1 & (1-p_1)\beta\tau_1 \\ 0 & 0 & 0 & b(1-p_2)\beta\tau_2 & (1-p_2)\beta\tau_2 \\ 0 & 0 & 0 & b\beta\tau_3 & \beta\tau_3 \\ 0 & 0 & 0 & bp_1\beta\tau_1 & p_1\beta\tau_1 \\ 0 & 0 & 0 & bp_2\beta\tau_2 & p_2\beta\tau_2 \end{pmatrix}, \tag{22}$$

where $\tau_j = f_{1j}h_1 + xf_{2j}h_2, (j = 1, 2, 3)$, and

$$V = \begin{pmatrix} a_{11} & 0 & 0 & 0 & 0 \\ 0 & a_{22} & 0 & 0 & 0 \\ 0 & 0 & a_{33} & 0 & 0 \\ -k_1 & 0 & 0 & a_{44} & 0 \\ 0 & -k_2 & -k_3 & 0 & a_{55} \end{pmatrix} \tag{23}$$

In the calculation of matrices F and V, we took the infection variables to be E_1, E_2, E_3, I_1 and I_2 as explained in [46].

Thus

$$\mathcal{R}_T = \beta\left[\frac{bk_1\tau_1}{a_{11}a_{44}}(1-p_1) + \frac{b\tau_1}{a_{44}}p_1 + \frac{k_2\tau_2}{a_{22}a_{55}}(1-p_2) + \frac{\tau_2}{a_{55}}p_2 + \frac{k_3\tau_3}{a_{33}a_{55}}\right] \tag{24}$$

where $\mathcal{R}_T$ is obtained from $\rho(FV^{-1})$ with ρ being the spectral radius of the matrix FV^{-1} and $a_{11} = k_1 + \mu, a_{22} = k_2 + \mu, a_{33} = k_3 + \mu, a_{44} = r_1 + \mu + d_1 + n_1, a_{55} = r_2 + \mu + d_2 + n_2, a_{66} = ((1-m_1)r_1 + n_1)$ with $a_{77} = ((1-m_2)r_2 + n_2)$.

The following result follow from Theorem 2 in [46]:

Lemma 5.1. *The DFE of the model (17), ξ, is locally asymptotically stable if $\mathcal{R}_T < 1$ and unstable if $\mathcal{R}_T > 1$.*

The threshold quantity $\mathcal{R}_T$ is the effective reproduction number under treatment for the TB model. Biologically speaking, Lemma (5.1) implies that TB can be eliminated from the community (when $\mathcal{R}_T < 1$) if the initial sizes of the subpopulation of the model are in the basin of attraction of ξ in the presence of treatment and self cure.

We can prove the global stability of the DFE using the comparison theorem ([44, p. 31]) in the absence of exogenous reinfection i.e. $\beta^* = 0$. Re-writing the equations for the infected compartments in (17), we have

$$\begin{pmatrix} \frac{dE_1}{dt} \\ \frac{dE_2}{dt} \\ \frac{dE_3}{dt} \\ \frac{dI_1}{dt} \\ \frac{dI_2}{dt} \end{pmatrix} = (F-V)\begin{pmatrix} E_1 \\ E_2 \\ E_3 \\ I_1 \\ I_2 \end{pmatrix} - \left(1 - \frac{S}{N}\right)K\begin{pmatrix} E_1 \\ E_2 \\ E_3 \\ I_1 \\ I_2 \end{pmatrix} \tag{25}$$

where

$$K = \begin{pmatrix} 0 & 0 & 0 & b(1-p_1)\beta\tau_1 & (1-p_1)\beta\tau_1 \\ 0 & 0 & 0 & b(1-p_2)\beta\tau_2 & (1-p_2)\beta\tau_2 \\ 0 & 0 & 0 & b\beta\tau_3 & \beta\tau_3 \\ 0 & 0 & 0 & bp_1\beta\tau_1 & p_1\beta\tau_1 \\ 0 & 0 & 0 & bp_2\beta\tau_2 & p_2\beta\tau_2 \end{pmatrix}, \tag{26}$$

where $\tau_j = f_{1j}h_1 + xf_{2j}h_2, (j = 1, 2, 3)$ as before.

Since $S \leqslant N$ for all $t > 0$ in $\mathcal{D}$, it follows that

$$\begin{pmatrix} \frac{dE_1}{dt} \\ \frac{dE_2}{dt} \\ \frac{dE_3}{dt} \\ \frac{dI_1}{dt} \\ \frac{dI_2}{dt} \end{pmatrix} \leqslant (F-V) \begin{pmatrix} E_1 \\ E_2 \\ E_3 \\ I_1 \\ I_2 \end{pmatrix} \tag{27}$$

Using the fact that the eigenvalues of the matrix $F-V$ all have negative real parts (see local stability result, where $\rho(FV^{-1})<1$ if $\mathcal{R}_T<1$, which is equivalent to $F-V$ having eigenvalues with negative real parts when $\mathcal{R}_T<1$ [46]), it follows that the linearized differential inequality system (27) is stable whenever $\mathcal{R}_T<1$. Consequently, $(E_1,E_2,E_3,I_1,I_2)\to(0,0,0,0,0)$ as $t\to\infty$. Thus, by the comparison theorem, $(E_1,E_2,E_3,I_1,I_2)\to(0,0,0,0,0)$ as $t\to\infty$. Substituting $E_1=E_2=E_3=I_1=I_2=0$ in (17) gives $S_1(t)\to S_1^0, S_2(t)\to S_2^0$ and $S_3(t)\to S_3^0$ as $t\to\infty$. Thus,

$(S_1(t),S_2(t),S_3(t),E_1(t),E_2(t),E_3(t),I_1(t),I_2(t),T_1(t),T_2(t),R(t))\to(S_1^0,S_2^0,S_3^0,0,0,0,0,0,0,0,0)$ as $t\to\infty$ for $\mathcal{R}_T<1$. Thus, ξ_0 is globally asymptotically stable if $\mathcal{R}_T<1$ when $\beta^*=0$.

Theorem 5.1. *The DFE of the model (17) without exogenous reinfection ($\beta^*=0$) is globally asymptotically stable whenever $\mathcal{R}_T>1$.*

With the threshold conditions on $\mathcal{R}_T$ clearly stated in Lemma (5.1), it is therefore imperative to evaluate the relative contribution of some of the infected groups, determined by b,τ_j,k_j and p_i (for $j=1,2,3$ and $i=1,2$), to $\mathcal{R}_T$. Let us rewrite $\mathcal{R}_T$ as

$$\mathcal{R}_T = B_1[Q_1+Q_2+Q_3+1+Q_4] \tag{28}$$

with

$$\begin{aligned} B_1 &= \beta\frac{\tau_2}{a_{55}}p_2, \\ Q_1 &= b\frac{k_1a_{55}}{a_{11}a_{44}}\frac{1-p_1}{p_2}\frac{\tau_1}{\tau_2}, \\ Q_2 &= b\frac{p_1}{p_2}\frac{a_{55}}{a_{44}}\frac{\tau_1}{\tau_2}, \\ Q_3 &= \frac{k_2}{a_{22}}\frac{1-p_2}{p_2}, \text{ and} \\ Q_4 &= \frac{k_3}{a_{33}}\frac{\tau_3}{\tau_2}\frac{1}{p_2}. \end{aligned} \tag{29}$$

If $Q_1<1, Q_2<1, Q_3<1$ and $Q_4<1$, then the majority of new infections will be caused by the group of infectious individuals (I_2) made possible by individuals from the group of normal progresssors (E_2) (and the E_3 class, if any); I_2 is then contributing more of B_1 to $\mathcal{R}_T$. In this case, if $B_1>1$, then surely will $\mathcal{R}_T$; the disease will spread and may persist in the population. However, if $B_1<1$, it may still be possible to have $\mathcal{R}_T>1$ when $B_1,Q_1<1,Q_2<1,Q_3<1$ and $Q_4<1$ are not too small.

Assuming we let $r_1=r_2=r, n_1=n_2=n$ and $d_1=d_2=d$, then we could have some simplifications that could further help us study the behavior of the Q_i's $(i=1,\ldots,4)$. This assumption means that $a_{44}=a_{55}$. Also we should note that the other term τ_1/τ_2 may be larger or smaller than one, depending on f_{ij}. For the sake of this analysis, and with the definition of k_3, we can take it that $k_3\approx 0$, so that $Q_4\approx 0$. From the expression for Q_1, we observe that $k_1/a_{11}<1$ with $b\geqslant 1$. Also $(1-p_1)/p_2$ depends strongly on the values of p_1 and p_2, although we know that $p_1>p_2$. For Q_2, in addition to $b\geqslant 1$, we see that $p_1/p_2>1$ while τ_1/τ_2 is indeterminate. For Q_3, we see that $k_2/a_{22}<1$ while

$$\frac{1-p_2}{p_2}\begin{cases} >1, & \text{if } p_2<0.5 \\ =1, & \text{if } p_2=0.5 \\ <1, & \text{if } p_2>0.5 \end{cases}$$

This invariably enables us to fix a range of values for p_1 since $p_1>p_2$. Hence p_2 (the fraction of direct progression to active TB from the normal progresssors E_2) plays a very crucial role in determining the value of Q_3 and, by extension, the value of $\mathcal{R}_T$. In all, comparing the magnitude of Q_1 and Q_2 is difficult without knowing the precise value or range of values for τ_1 and τ_2 *a priori*.

Now, consider the case where the the majority of new infections are caused by the relative contribution of the normal progressors E_2 vis a viz the number of infectious individuals in the I_2 class with $1-p_2$ being the fraction of new infections that are normal progressors without direct progression to active TB. In this case, we will rewrite $\mathcal{R}_T$ as

$$\mathcal{R}_T = B_2[Q_5 + Q_6 + 1 + Q_7 + Q_8] \tag{30}$$

with

$$\begin{aligned} B_2 &= \beta\frac{k_2\tau_2}{a_{22}a_{55}}(1-p_2),\\ Q_5 &= b\frac{k_1}{k_2}\frac{\tau_1}{\tau_2}\frac{(1-p_1)}{(1-p_2)}\frac{a_{22}a_{55}}{a_{11}a_{44}},\\ Q_6 &= b\frac{\tau_1}{\tau_2}\frac{1}{k_2}\frac{p_1}{(1-p_2)}\frac{a_{22}a_{55}}{a_{44}},\\ Q_7 &= \frac{a_{22}}{k_2}\frac{p_2}{(1-p_2)}, \text{ and}\\ Q_8 &= \frac{k_3}{k_2}\frac{\tau_3}{\tau_2}\frac{1}{1-p_2}\frac{a_{22}}{a_{33}}. \end{aligned} \tag{31}$$

If $Q_5 < 1, Q_6 < 1, Q_7 < 1$ and $Q_8 < 1$, then the majority of new infections are caused by the infectious cases generated from the normal progressors, E_2. In other words, this group of latent cases, who ordinarily did not become infectious themselves through the direct means, are obviously via exogenous reinfection and reactivation, generating a number of infectious cases that are contributing so much to the majority of new infections afterwards. Hence, this group contributes the major part, B_2 to $\mathcal{R}_T$. In this case, if $B_2 > 1$, then certainly $\mathcal{R}_T > 1$.

Again, for the sake of this analysis, let $k_3 \approx 0$, so that $Q_8 \approx 0$. Looking at the expression for Q_7, one can see that

$$\frac{p_2}{1-p_2}\begin{cases} > 1, & \text{if } p_2 > 0.5\\ = 1, & \text{if } p_2 = 0.5\\ < 1, & \text{if } p_2 < 0.5 \end{cases}$$

Again, we are now able to fix a range of values for p_1 since $p_1 > p_2$. Hence $1 - p_2$ (the fraction of new infections that remain latent as a normal progresssor E_2) plays a very crucial role in determining the value of Q_7 and, by extension, the value of $\mathcal{R}_T$. However, the indeterminate nature of τ_1/τ_2 makes it difficult to compare the magnitude of Q_5 and Q_6, whether we assume $r_1 = r_2 = r, n_1 = n_2 = n$ and $d_1 = d_2 = d$ or not, as we have no precise value or range of values for τ_1 and τ_2 *a priori*.

The analysis above can be carried out to determine the effect of other contributors to the value of $\mathcal{R}_T$. However, we conjecture that our inability to get the magnitude of the τ_i's will hinder measuring the values of some of the terms in the expression for $\mathcal{R}_T$.

6. Effect of control strategies

There are really two control strategies inherent in the model: treatment and self cure (the latter contributes to the relative reduction in the overall number of infectious cases while still maintaining the number of 'secondary' latency); the latter could only have a smaller effect on the overall dynamics than the former. We assume that the word "control" would mean bringing down the number of *infectious* TB cases.

To see the effect of these interventions, we need to consider the basic reproduction number of the model without treatment and self cure. This is given by

$$\mathcal{R}_0 = \beta J_0 \tag{32}$$

where

$$J_0 = \left[\frac{bk_1\tau_1(1-p_1)}{(k_1+\mu)(\mu+d_1)} + \frac{b\tau_1 p_1}{\mu+d_1} + \frac{k_2\tau_2(1-p_2)}{(k_2+\mu)(\mu+d_2)} + \frac{\tau_2 p_2}{\mu+d_2} + \frac{k_3\tau_3}{(k_3+\mu)(\mu+d_2)}\right] \tag{33}$$

Let us re-write the effective reproduction number as

$$\mathcal{R}_T = \beta J_T \tag{34}$$

where

$$J_T = \left[\frac{bk_1\tau_1(1-p_1)}{(k_1+\mu)(r_1+\mu+d_1+n_1)} + \frac{b\tau_1 p_1}{r_1+\mu+d_1+n_1} + \frac{k_2\tau_2(1-p_2)}{(k_2+\mu)(r_2+\mu+d_2+n_2)} + \frac{\tau_2 p_2}{r_2+\mu+d_2+n_2} + \frac{k_3\tau_3}{(k_3+\mu)(r_2+\mu+d_2+n_2)}\right]. \tag{35}$$

6.1. Effects of treatment and self cure

With the application of treatment to the population and cases of self cure occurring as well, we see that the difference between $\mathcal{R}_0$ and $\mathcal{R}_T$ is

$$\triangle_{TS} = \mathcal{R}_0 - \mathcal{R}_T = \beta(J_0 - J_T) = \beta[K_1 b\tau_1(k_1(1-p_1)M_1 + p_1) + K_2(k_2\tau_2(1-p_2)M_2 + p_2\tau_2 + k_3\tau_3 M_3)] \tag{36}$$

Table 2
Parameter Information.

Param.	Description	Values	Sampl. range	Ref.
μ	natural death rate	0.02041	$(0.0143, 0.04)yr^{-1}$	[47]
Λ	recruitment rate	$\mu \times 10^5$		[5,7]
β	trans. rate	8.557	$(4.4769, 15.1347)yr^{-1}$	[5]
β^*	trans. rate	1.5	$(1.5, 3.5)yr^{-1}$	[5]
p_1	frac. of direct prog.	0.1	$(10\%, 20\%)yr^{-1}$	[1,2]
p_2	frac. of direct prog.	0.05	$(5\%, 10\%)yr^{-1}$	[1,2]
k_1	activation rate	0.0033	$(0.0033, 0.0066)yr^{-1}$	implied from [1,2]
k_2	activation rate	0.00167	$(0.00167, 0.0033)yr^{-1}$	implied from [1,2]
k_3	activation rate	0.0001	$(0, 0.001)yr^{-1}$	implied from [1,2]
n_1, n_2	self-cure rates	0.2	$(0.14, 0.25)yr^{-1}$	[41,39,48]
m_1, m_2	treat. success	0.75	$(0.5, 1)yr^{-1}$	[9]
r_1, r_2	recovery rate	1.5	$(0.3429, 3.24)yr^{-1}$	[1,2,40,43]
d_1, d_2	TB-induced death	0.365	$(0.22, 0.39)yr^{-1}$	[41,39,48,43]
h_1	genome freq.	0.76	$(0.76, 0.87)yr^{-1}$	implied from cases in [8,20]
h_2	genome freq.	0.23	$(0.11, 0.23)yr^{-1}$	implied from cases in [8,20]
h_3	genome freq.	0.01	$(0.01, 0.02)yr^{-1}$	implied from cases in [8,20]

where

$$M_j = \frac{1}{\mu + k_j}, \text{ and } K_i = \frac{1}{\mu + d_i} - \frac{1}{\mu + d_i + n_i + r_i} \tag{37}$$

for $j = 1, 2, 3$ and $i = 1, 2$.

If the treatment is effective at the population level (as it is expected at the individual level) so as to slow down the spread of the disease while having some cases of self cure, then we expect that $\triangle_{TS} > 0$. This requirement relies on the sign of the K_i's. However, careful inspection shows that all the K_i's are positive, so that we can conclude that $\triangle_{TS} > 0$ for all K_i and M_j ($j = 1, 2, 3$ and $i = 1, 2$).

Using the information in (36), we can calculate the critical values of the disease control parameters (i.e. r_i and n_i) to have $\mathcal{R}_T < 1$. Since we only have just one equation, we can only solve for one unknown parameter at a time. However it would be good we take a look at a joint effect of treatment and self cure on the dynamics of the disease.

For example, if $r_1 = r_2 = r$ and $n_1 = n_2 = n$, then we can write $\phi = r + n$. Also, let $d_1 = d_2 = d$. We then have that the critical common treatment and self cure rates combined into ϕ with a given $\mathcal{R}_0$ has to be

$$\phi > \phi^* := \frac{(\mu + d)^2(\mathcal{R}_0 - 1)}{\beta U - (\mu + d)(\mathcal{R}_0 - 1)} \tag{38}$$

where

$$U := b\tau_1(k_1(1 - p_1)M_1 + p_1) + k_2\tau_2(1 - p_2)M_2 + p_2\tau_2 + k_3\tau_3 M_3. \tag{39}$$

Clearly, we can see that $U > 0$. Hence, if $(100 \times \phi)\%$ of some newly infected individuals are effectively treated while the rest revert to 'secondary latency' through self cure and $\phi > \phi^*$, then the epidemic will eventually die out. The condition $\phi^* > 0$ requires that

$$\beta U > (\mu + d)(\mathcal{R}_0 - 1) \tag{40}$$

with $\mathcal{R}_0 > 1$. The condition that $\mathcal{R}_0 > 1$ is the usual case for the current TB epidemic in many lands. We obtain a negative ϕ^* if $\mathcal{R}_0 < 1$; apparently this implies that there will be no need for any interventionist program as the disease will die out on its own.

Consider the expression in (40). Clearly this holds, for a given $\mathcal{R}_0$, when

$$U > \frac{(\mu + d)(\mathcal{R}_0 - 1)}{\beta}. \tag{41}$$

If $U = \frac{(\mu+d)(\mathcal{R}_0-1)}{\beta}$, then the condition in (38) will fail.

Now, since $\phi = r + n > 0$ based on the positivity of the parameters, then the condition $\phi^* > 0$ (using (38)) implies that

$$U < \frac{(\mu + d)(\mu + d + 1)(\mathcal{R}_0 - 1)}{\beta}. \tag{42}$$

Hence, for $\phi^* > 0$ and given $\mathcal{R}_0 > 1$, we require that

$$\frac{(\mu + d)(\mathcal{R}_0 - 1)}{\beta} < U < \frac{(\mu + d)(\mu + d + 1)(\mathcal{R}_0 - 1)}{\beta}. \tag{43}$$

We can conveniently say that if U falls outside the range given in (43), then ϕ^* would lose its positivity which then impacts on ϕ which is generally expected to be greater than zero.

Since self cure is inherent in the dynamics of tuberculosis, whether this is observed or not, it is interesting to investigate the additional effect of treatment on the population in the presence of self cure. Hence, we are interested in

$$\triangle_{TT} = \mathcal{R}_{0S} - \mathcal{R}_T = \beta(J_S - J_T) = \beta[K_3 b\tau_1(k_1(1-p_1)M_1 + p_1) + K_4(k_2\tau_2(1-p_2)M_2 + p_2\tau_2 + k_3\tau_3 M_3)] \tag{44}$$

where

$$K_i = \frac{1}{\mu + d_i + n_i} - \frac{1}{\mu + d_i + n_i + r_i} \quad \text{for } i = 3,4 \tag{45}$$

and

$$\mathcal{R}_{0S} = \beta J_S \tag{46}$$

with

$$J_S = \left[\frac{bk_1\tau_1(1-p_1)}{(k_1+\mu)(\mu+d_1+n_1)} + \frac{b\tau_1 p_1}{\mu+d_1+n_1} + \frac{k_2\tau_2(1-p_2)}{(k_2+\mu)(\mu+d_2+n_2)} + \frac{\tau_2 p_2}{\mu+d_2+n_2} + \frac{k_3\tau_3}{(k_3+\mu)(\mu+d_2+n_2)}\right]. \tag{47}$$

In this case, $\mathcal{R}_{0S}$ is the reproduction number in a population with only self cure as a means of leaving the infectious subpopulation.

Let $r_1 = r_2 = r$ and $n_1 = n_2 = n$ with $d_1 = d_2 = d$. Therefore the critical value for the common treatment rate r that makes $\mathcal{R}_T < 1$ for a given $\mathcal{R}_{0S}$ and common self cure rate n has to be

$$r > r^* := \frac{(\mu+d+n)^2(\mathcal{R}_{0S}-1)}{\beta U - (\mu+d+n)(\mathcal{R}_{0S}-1)}. \tag{48}$$

In this case, for r^* to be positive (and invariably r) and given $\mathcal{R}_{0S} > 1$, we require that

$$\frac{(\mu+d+n)(\mathcal{R}_{0S}-1)}{\beta} < U < \frac{(\mu+d+n)(\mu+d+n+1)(\mathcal{R}_{0S}-1)}{\beta}. \tag{49}$$

6.2. Effect of treatment

If only treatment is applied to the population and there are no other intervention or control including self cure, then we will set $n_1 = n_2 = 0$ (where n_1 and n_2 are the self cure rates for the I_1 and I_2 classes, respectively), so that we will refer to the effective reproduction number as $\mathcal{R}_{TT}$. This is obtained from $\mathcal{R}_T$ by setting $n_1 = n_2 = 0$ in $\mathcal{R}_T$.

In this case,

$$\mathcal{R}_{TT} = \beta J_{TT} \tag{50}$$

where

$$J_{TT} = \left[\frac{bk_1\tau_1(1-p_1)}{(k_1+\mu)(\mu+d_1+r_1)} + \frac{b\tau_1 p_1}{\mu+d_1+r_1} + \frac{k_2\tau_2(1-p_2)}{(k_2+\mu)(\mu+d_2+r_2)} + \frac{\tau_2 p_2}{\mu+d_2+r_2} + \frac{k_3\tau_3}{(k_3+\mu)(\mu+d_2+r_2)}\right]. \tag{51}$$

Now, let $\triangle_T = \mathcal{R}_0 - \mathcal{R}_{TT}$. Of course, we need $\triangle_T > 0$ for effective treatment at the population level to translate to a slowing down of the spread of the disease. So for $r_1 = r_2 = r$, with a given $\mathcal{R}_0$, the critical common treatment rate that would make $\mathcal{R}_{TT} < 1$ is

$$r > r^* := \frac{(\mu+d)^2(\mathcal{R}_0-1)}{\beta U - (\mu+d)(\mathcal{R}_0-1)}. \tag{52}$$

Interestingly, but not surprisingly, the critical condition on r for $\mathcal{R}_{TT} < 1$, given in (52) is the same as that on $\phi = r + n$ given in (38).

Therefore, for $r^* > 0$ and given $\mathcal{R}_0 > 1$, we again require that

$$\frac{(\mu+d)(\mathcal{R}_0-1)}{\beta} < U < \frac{(\mu+d)(\mu+d+1)(\mathcal{R}_0-1)}{\beta}. \tag{53}$$

so that we can say that if U falls outside the range given in (53), then r^* would lose its positivity which then impacts on r which is generally expected to be greater than zero for any serious impact on the population.

From literature (see for example, [41–43]), we know that self cure rates are generally smaller than treatment rates; its effect alone on control would be expected to be small compared to a vigorous treatment campaign with a good detection rate.

Table 3
Computer generated values for the f_{ij}'s.

	f_{11}	f_{21}	f_{12}	f_{22}	f_{13}	f_{23}
F_1	0.1321	0.0810	0.8253	0.8774	0.0363	0.0365
F_2	0.1304	0.0800	0.6550	0.6276	0.0531	0.2924
F_3	0.1206	0.0348	0.6896	0.9644	0.0004	0.0008
F_4	0.1075	0.0830	0.6808	0.6050	0.1987	0.3150
F_5	0.1075	0.0800	0.6550	0.6050	0.0540	0.2248
F_6	0.1185	0.0800	0.6550	0.7758	0.1155	0.1442
F_7	0.1255	0.0198	0.6550	0.6549	0.2195	0.3254
F_8	0.1075	0.0451	0.6550	0.6050	0.2375	0.3499
F_9	0.0808	0.0728	0.7337	0.6050	0.1855	0.0051
F_{10}	0.0341	0.0189	0.9538	0.9691	0.0006	0.0051

7. Example

7.1. Background information on parameters

Much of the values for the 'genetic' parameters herein were obtained using the information from [1,2,20,8]. However, parameters such as b, x, y, x_3 and the f_{ij}'s as well as the g_{ij}'s are difficult to obtain; we will treat some of them as free parameters and use established conditions on the f_{ij}'s and the g_{ij}'s to generate values for them. For study purposes, we will set $1 \leqslant b \leqslant 5$. The upper bound for b is chosen for illustrative purpose. Sensitivity analysis are carried out using different values

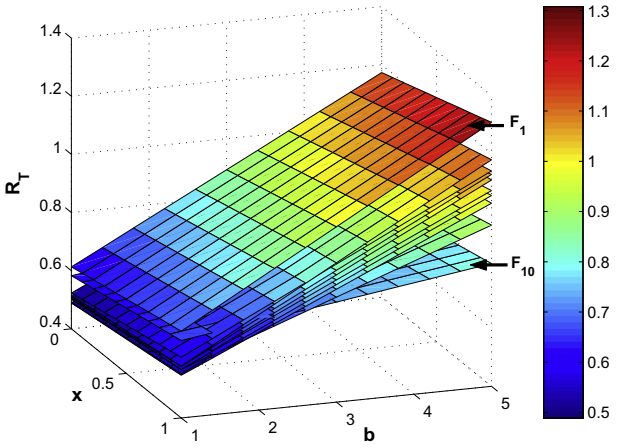

Fig. 1. Plot of $\mathcal{R}_T$ against b and x.

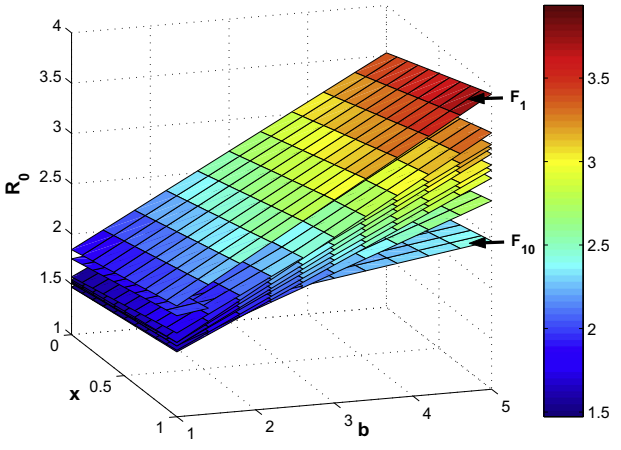

Fig. 2. Plot of $\mathcal{R}_0$ against b and x.

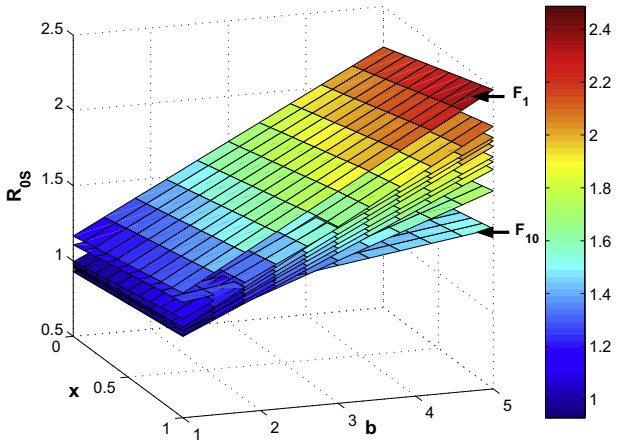

Fig. 3. Plot of $\mathcal{R}_{0S}$ against b and x.

of b and x since $0 < x < 1$ and $0 < y < 1$ with $y \leqslant x$. We fix $z = 0.9$ knowing that $0 < z < 1$. The exogenous reinfection reduction parameter x_3 is also set as a free parameter.

Table 2 gives the values of some of the parameters used in the model.

The values of the distributing fractions of infected groups, f_{ij}'s and g_{ij}'s, were obtained by means of a program using the relational and conditional operators in the software *Mathematica*; the operations were written so that these parameters satisfies the conditions in (3), (4), (9), (10) and (11). Also, based on intuition and what we feel are reasonable educative guesses, we expect that f_{12} and f_{22} (g_{12} and g_{22}) should be greater than 0.5 while f_{21} (g_{21}) should be less than or equal to 0.05.

Table 3 shows the different values of the f_{ij}'s; there are ten sets of values labelled F_1 to F_{10}.

Using the upper and the lower limits for the parameters given in Table 2 as well as the values of the f_{ij}'s, we were able to calculate values for the reproduction numbers as well as the Q_i's, B_i's and ϕ^*.

7.2. Simulations and discussions

We will now examine the effect of changes in the values of the parameters on some key variables including the reproduction numbers. Note that the minimum values of the variables to be considered occurred at $x = 0$ and $b = 1$ (which we will refer to as the 'good' case scenario or situation) while the maximum values occurred at $x = 1$ and $b = 5$ (which we will refer to as the 'worse' case scenario or situation).

Case 1: Using the lower limit values in the intervals of the parameters in Table 2

As shown in Figs. 1–3, we observe that the effective reproduction number $\mathcal{R}_T$, the basic reproduction number $\mathcal{R}_0$ and the reproduction number under the control of only self cure $\mathcal{R}_{0S}$, respectively, are more sensitive to b than to x regardless of the set of values for the f_{ij}'s. Of course, $\mathcal{R}_T$ had values less than both $\mathcal{R}_0$ and $\mathcal{R}_{0S}$, irrespective of the F_i's ($i = 1$ to 10) in Table 3. Figs. 4–6 shows the maximum and minimum values of the reproduction numbers for the different set of values of the f_{ij}'s indicated as F_1 to F_{10} in Table 3. We observe that, for a combination of effective treatment and cases of self cure, with

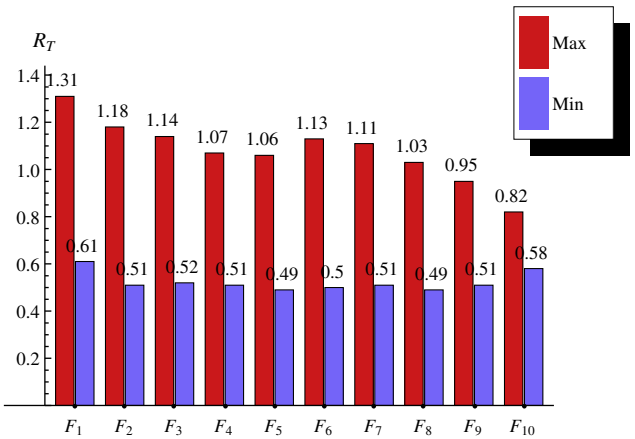

Fig. 4. Bar chart for $\mathcal{R}_T$ using lower limit values of parameters for different f_{ij}.

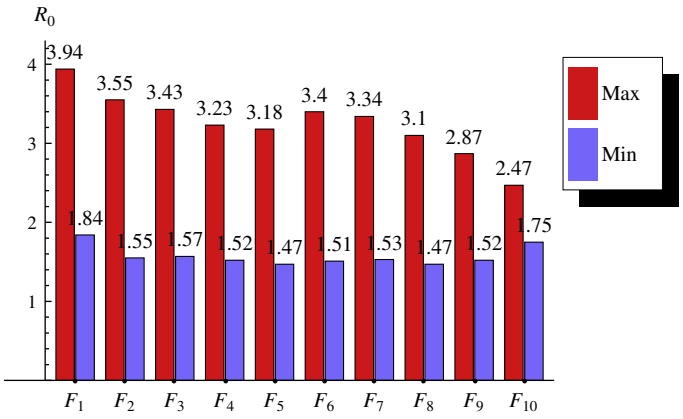

Fig. 5. Bar chart for $\mathcal{R}_0$ using lower limit values of parameters for different f_{ij}.

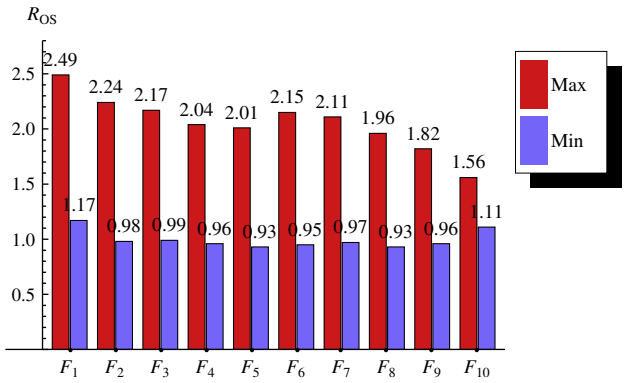

Fig. 6. Bar chart for $\mathcal{R}_{OS}$ using lower limit values of parameters for different f_{ij}.

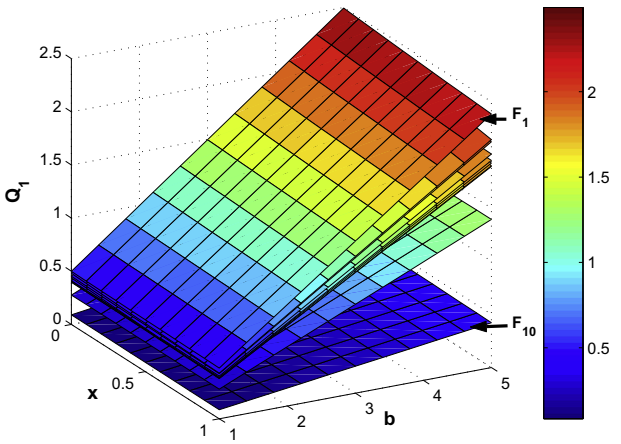

Fig. 7. Plot of Q_1 against b and x.

the f_{ij} values in F_9 and F_{10}, the maximum value for $\mathcal{R}_T$ is less than 1 ($\mathcal{R}_T = 0.82$) as seen in Fig. 4. In this case $b = 5$ and $x = 1$, the 'worse' case scenario, the set of values in F_{10} gave a better result though. Hence if a very large number of susceptible individuals with no resistance become infected and move to the class of normal progressors and susceptibles with partial resistance who became infected and also move to the class of normal progressors, even in this worse case scenario, it is still

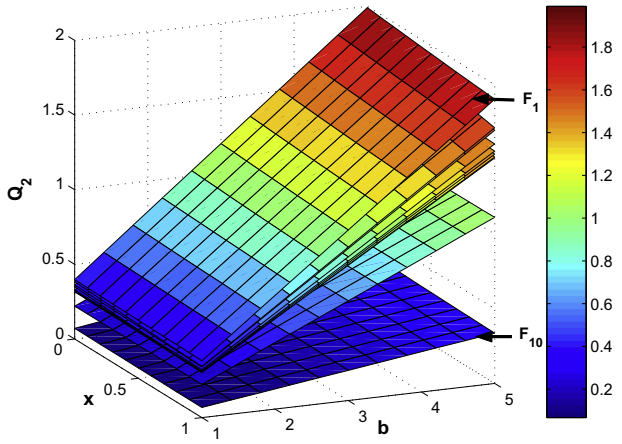

Fig. 8. Plot of Q_2 against b and x.

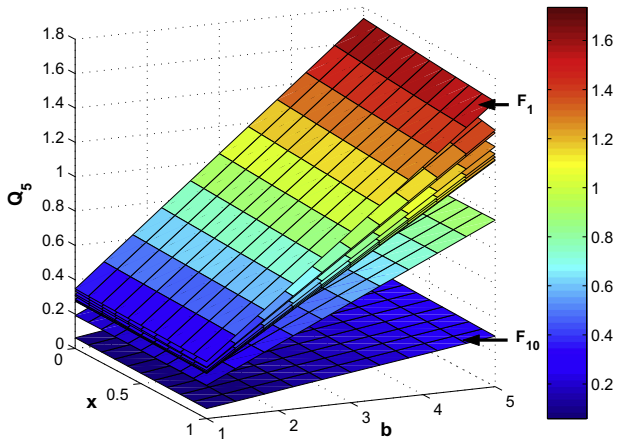

Fig. 9. Plot of Q_5 against b and x.

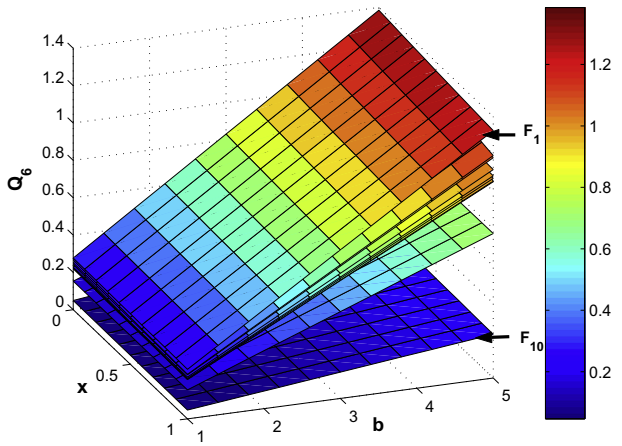

Fig. 10. Plot of Q_6 against b and x.

possible to drive down $\mathcal{R}_T$ to a value less than 1 in the presence of effective treatment and self cure; there should be fewer individuals moving from the S_1 and S_2 classes into the E_1 class.

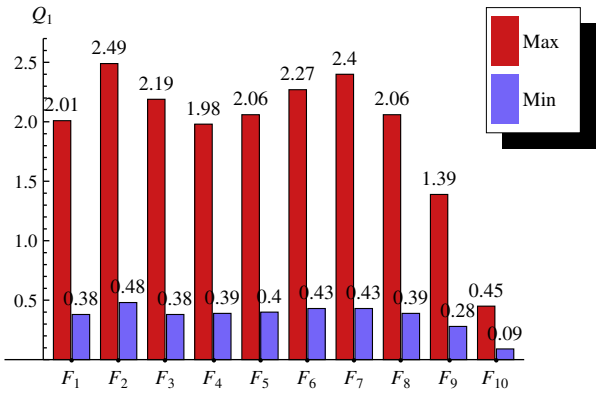

Fig. 11. Bar chart for Q_1 using lower limit values of parameters for different f_{ij}.

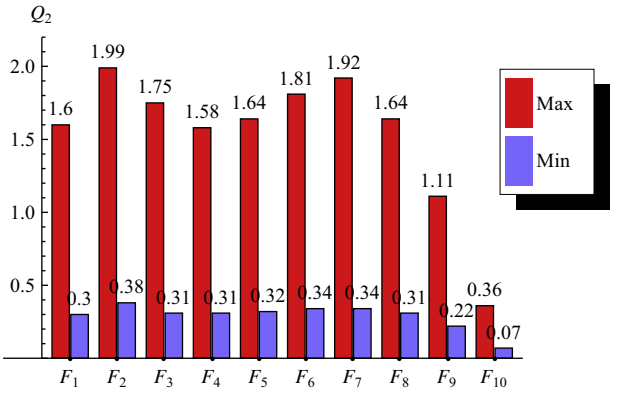

Fig. 12. Bar chart for Q_2 using lower limit values of parameters for different f_{ij}.

When $b = 1$ and $x = 0$, the 'good' situation, we observe that the minimum values of $\mathcal{R}_T$ were all less than 1, regardless of the combinations of the f_{ij}'s as seen from Fig. 4. The values of $\mathcal{R}_0$ are all greater than 1, regardless of the set of values in F_1 to F_{10} as can be seen from Fig. 2; if there is no intervention of any kind, the disease persist. As seen from the data in Fig. 5, in both the 'worse' case and 'good' case scenarios, the values of $\mathcal{R}_0$ were all greater than unity. It is interesting to note that in the presence of self cure alone, we still had some marginal values of $\mathcal{R}_{0S}$ that are less than 1, when considering the 'good' case situation of $b = 1$ and $x = 0$; the minimum values ranged from $0.93 < \mathcal{R}_{0S} < 0.99$ as seen from Fig. 6. This shows that self cure cannot positively impact on reducing the number of infectious cases in the population, even though the values of $\mathcal{R}_{0S}$ were marginally below unity at these instances.

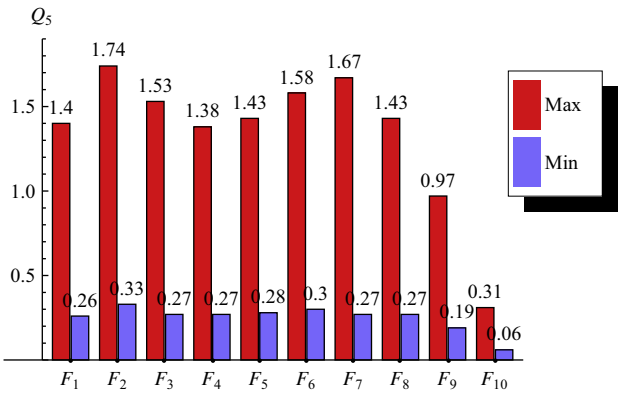

Fig. 13. Bar chart for Q_5 using lower limit values of parameters for different f_{ij}.

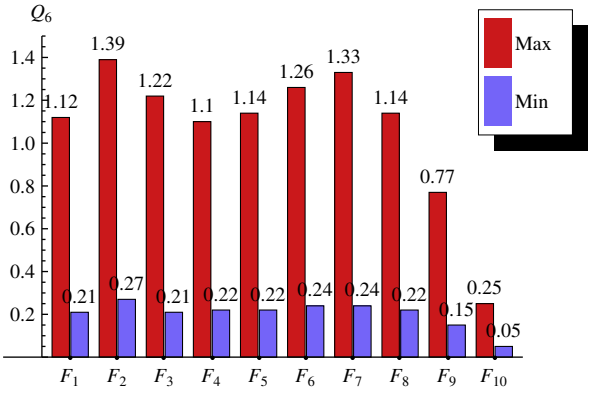

Fig. 14. Bar chart for Q_6 using lower limit values of parameters for different f_{ij}.

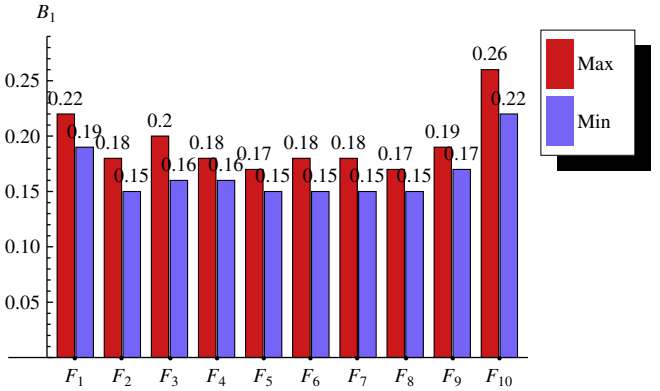

Fig. 15. Bar chart for B_1 using lower limit values of parameters for different f_{ij}.

In all, in the presence of effective treatment and cases of self cure, effort should be made to reduce the number of susceptibles with no or partial resistance from getting infected and moving into the class of rapid progressors; a large proportion of these susceptibles, when they become infected, should move into the class of normal progressors, as the introduced intervention will be effective, guaranteeing that the disease burden is reduced in the population. Recall that the above discussion is based on the use of lower limit values of the parameters shown in Table 2.

Fig. 7 shows the relative contribution of the rapid progressors, Q_1, vis a viz the effect of the number of infectious cases occasioned by the number of normal progressors. Again the set of values of the f_{ij}'s in F_{10} gave a value less than 1, $Q_1 = 0.45$, for the 'worse' case scenario of $b = 5$ and $x = 1$; other F_i's gave values of Q_1 that were greater than 1. The 'good' case scenario

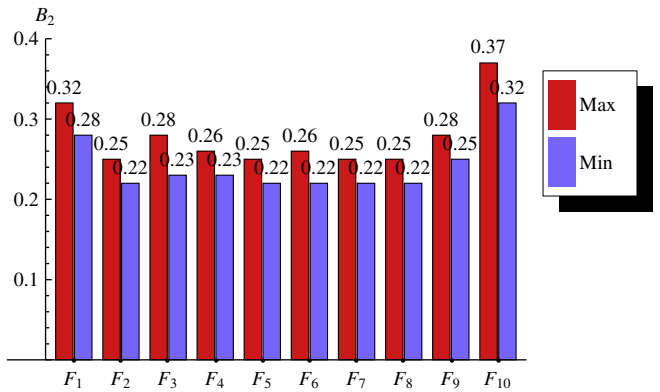

Fig. 16. Bar chart for B_2 using lower limit values of parameters for different f_{ij}.

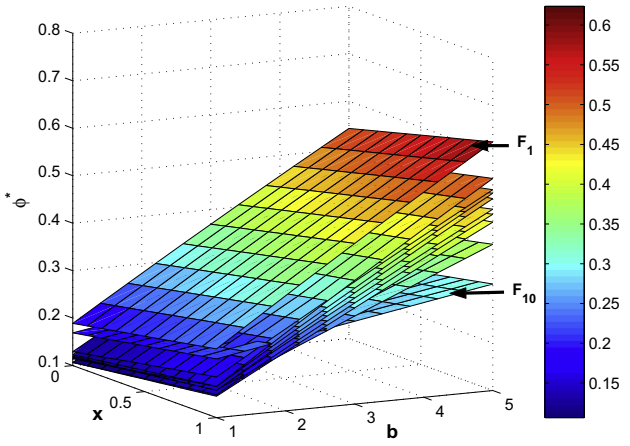

Fig. 17. Plot of ϕ^* against b and x. Here, $n = 0.14, r_1 = 0.3429$. Also, the values of ϕ^* shows the minimum requirements on ϕ for $\mathcal{R}_{TT} < 1$.

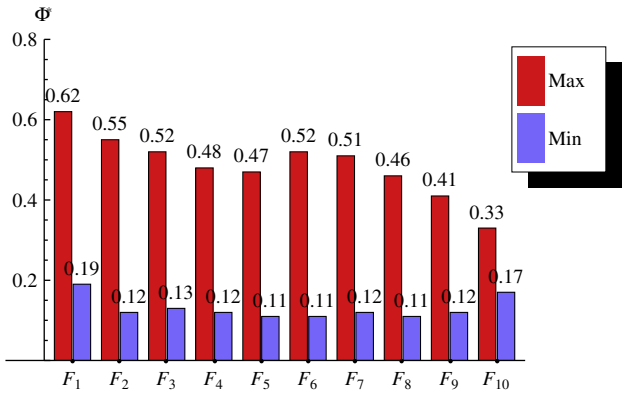

Fig. 18. Bar chart for ϕ^* using lower limit values of parameters for different f_{ij}. The maximum values were obtained when $b = 5, x = 1$ while the minimum values were obtained when $b = 1, x = 0$.

of $x = 0$ and $b = 1$ yielded small values for Q_1, ranging from 0.09 to 0.45, with the F_{10} set of f_{ij} values giving us the fine result of $Q_1 = 0.09$ as seen from Fig. 11. This then means that the contribution of the rapid progressors is very small in relation to the overall effect of the number of infectious cases generated by the normal progressors when considering the good case scenario for any set of values of the f_{ij}'s.

Fig. 8 shows the relative contribution of the infectious individuals who came from the rapid progressors, Q_2, vis a viz the effect of the number of infectious cases occasioned by the number of normal progressors for all the sets of values of f_{ij}'s. For the set in $F_{10}, Q_2 = 0.36$ for the 'worse' case scenario of $b = 5$ and $x = 1$; other sets of values of the f_{ij}'s in F_1 to F_9 as seen from Table 3 had Q_2 values that were greater than 1 as seen in Fig. 12. For the 'good' case scenario of $b = 1$ and $x = 0$, all values of Q_2 were less than 1, ranging from 0.07 to 0.38 with $Q_2 = 0.07$ obtained with values from F_{10}.

For the 'good' case scenario, The set of values in F_{10} gave better results for Q_1 and Q_2; and it is easily seen that Q_1 and Q_2 are more sensitive to b than to x. Their contribution is relatively small to the overall dynamics with the set of values in F_{10} when considering the worse case scenario. However for the good case scenario, irrespective of the f_{ij}'s, both Q_1 and Q_2 contributed relatively small values to the overall dynamics of the disease. For both scenarios, Q_1 was contributing more to $\mathcal{R}_T$ than Q_2.

Note that in all cases, references to worse case scenario is shown as the maximum values in all the concerned figures while references to 'good' case scenario is shown as the minimum values in the figures concerned.

Figs. 9 and 10 shows the relative contributions of the rapid progressors (now Q_5), and the infectious individuals who came from the class of rapid progressors (now Q_6), respectively, vis a viz the effect of the number of normal progressors on the overall dynamics of tuberculosis in the population.Observe that for the 'worse' case scenario of $b = 5$ and $x = 1, Q_5$ and Q_6 had values less than 1 for the set of values of the f_{ij}'s in F_9 and F_{10}, with the F_{10} values giving us a better result of $Q_5 = 0.31$ and $Q_6 = 0.25$. With the other set of values in F_1 to F_8, the contributions of Q_5 and Q_6 are relatively large as seen from Figs. 13 and 14, respectively; these are for the maximum values.

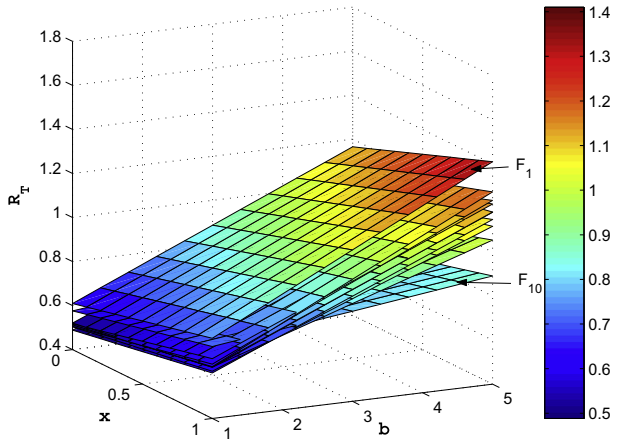

Fig. 19. Plot of $\mathcal{R}_T$ against b and x with upper limit values for the parameters.

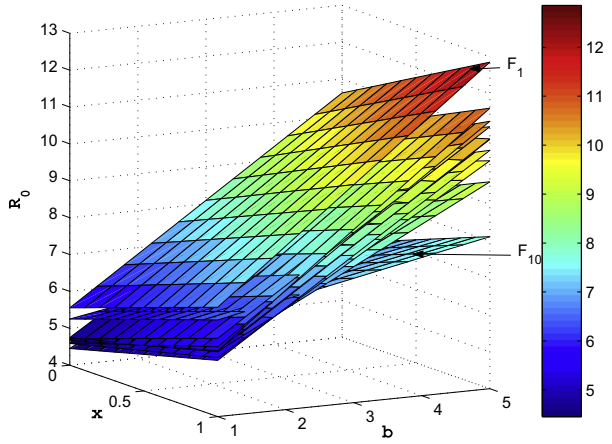

Fig. 20. Plot of $\mathcal{R}_0$ against b and x with upper limit values for the parameters.

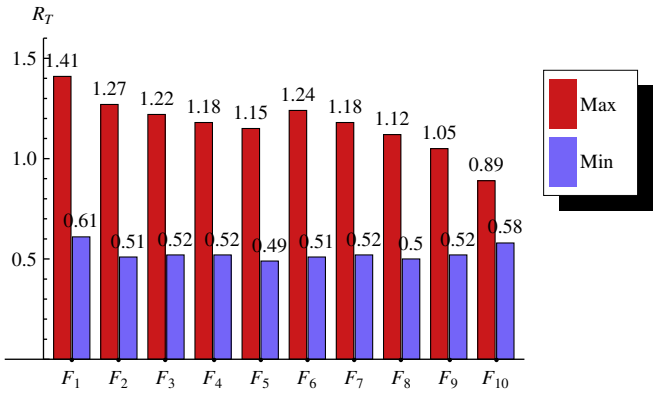

Fig. 21. Bar chart for $\mathcal{R}_T$ using upper limit values of parameters for different f_{ij}.

In the 'good' case scenario of $b = 1$ and $x = 0$, the values of Q_5 and Q_6 are relatively small, indicated by the minimum values in Figs. 13 and 14, respectively. Here, Q_5 was contributing more values to $\mathcal{R}_T$ than Q_6.

Figs. 15 and 16 shows the values of B_1 and B_2, respectively, for the 'worse' case scenario ($b = 5, x = 1$), which gives the maximum values, and the 'good' case scenario ($b = 1, x = 0$), which gives the minimum values. Clearly, the 'worse' and 'good' case scenarios, for all sets of values in the F_i's, had nearly equal values, regardless of the set of values for the f_{ij}'s.

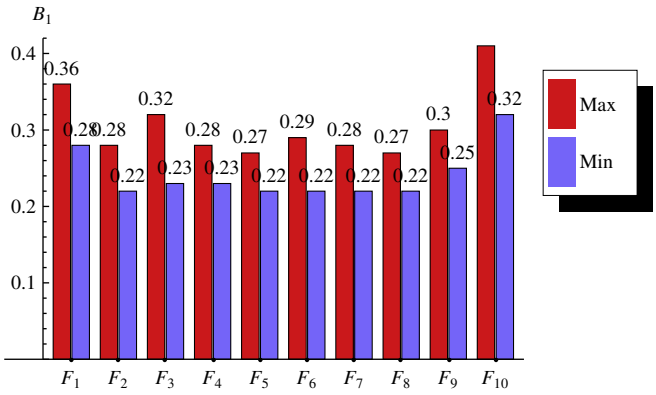

Fig. 22. Bar chart for B_1 using upper limit values of parameters for different f_{ij}.

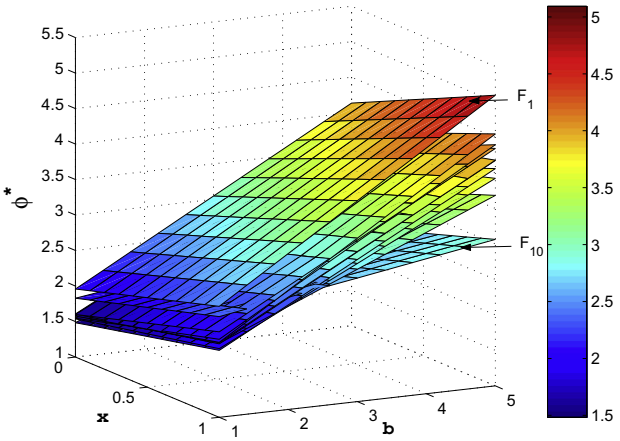

Fig. 23. Plot of ϕ^* against b and x with upper limit values for the parameters. In this case, $n = 0.25$ and $r = 3.24$.

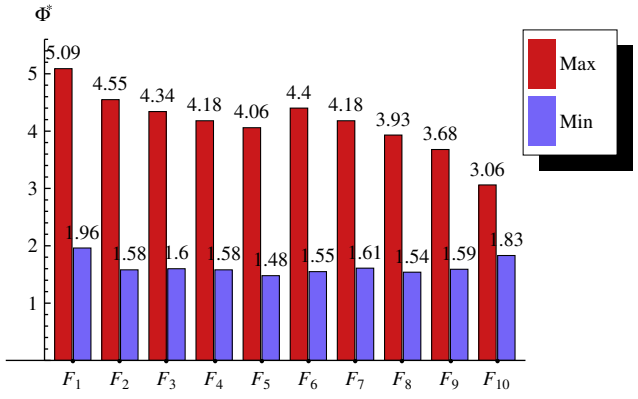

Fig. 24. Bar chart for ϕ^* using upper limit values of parameters for different f_{ij}.

Since the values of B_1 and B_2 are relatively small, with $0.15 \leqslant B_1 \leqslant 0.26$ when $0 < x < 1$ and $0 < b < 5$, and $0.22 \leqslant B_2 \leqslant 0.37$ when $0 < x < 1$ and $0 < b < 5$, it then implies that the relative contributions of Q_1, Q_2, Q_5 and Q_6, with their respective characteristics are significant, for the 'worse' case scenarios but relatively small for the 'good' case scenarios for sets of values of the f_{ij}'s other than the set of values in F_{10}.

In Fig. 17, we have the critical values of the common joint treatment and self cure rates, for $b \in [1, 5]$ and $0 < x < 1$, required to have the effective reproduction number $\mathcal{R}_T < 1$. Again, we are using the lower limits of the parameter values. The

value of ϕ^* increases with b but not too sensitive to x as has been the case for all other variables considered until now. We can see that the set of the f_{ij}'s in F_{10} gave better results as a smaller value for ϕ would be required for driving down the epidemic. Fig. 18 shows that the critical values for ϕ^* were between 0.17 and 0.33 for the F_{10} values. For the 'worse' case scenario of $b = 5, x = 1$, we see that $0.33 \leqslant \phi^* \leqslant 0.62$ but for the 'good' case scenario of $b = 1, x = 0$, we observe that $0.11 \leqslant \phi^* \leqslant 0.19$ for all sets of values from F_1 to F_{10}. With the F_{10} values, $\phi^* = 0.33$ will be the minimum value of ϕ required to make $\mathcal{R}_T < 1$; in this case, the epidemic may not be serious enough and a small treatment and self cure rates will help reduce the burden of TB in the population.

Case 2: Using the upper limit values in the intervals of the parameters in Table 2

In this case, we examined changes in the values of $\mathcal{R}_T, \mathcal{R}_0, B_1$ and ϕ^*. Of course this is without prejudice to other variables that were considered in Case I above.

When we carried out the following simulations using the upper limit values of some of the parameters, we observed marked and significant differences in the behaviors of the reproduction numbers, B_1 and ϕ^*.

Figs. 19 and 20 shows the plot of $\mathcal{R}_T$ and $\mathcal{R}_0$, as functions of x and b, respectively. Of course, both reproduction numbers are more sensitive to b than to x. Although $\mathcal{R}_T$ had better results than $\mathcal{R}_0$ obviously due to the effect of intervention on the former, the values of $\mathcal{R}_0$ in Fig. 20 are significantly larger compared to the corresponding values in Fig. 2. However, the values of $\mathcal{R}_T$ are close to the corresponding values of $\mathcal{R}_T$ in Fig. 1. It seems that $\mathcal{R}_T$ is not sensitive to the changes in the values of the parameters in Table 2 as we move from the lower limit to the upper limit values, unlike what we observe for the values of $\mathcal{R}_0$.

Fig. 21 shows that the values of $\mathcal{R}_T$ for both the 'worse'case scenarios and the good'case situations were slightly higher than for the values of $\mathcal{R}_T$ in Fig. 4. Fig. 22 shows that the effect of B_1 on the value of the effective reproduction number $\mathcal{R}_T$, is not too different from the results earlier discussed for B_1 while considering its effect using the lower limit values, as seen in Fig. 15.

Figs. 23 presents the critical values of the common joint treatment and self cure rates, ϕ^*, required to make $\mathcal{R}_T < 1$, with $\phi*$ more sensitive to b than to x. Fig. 24 presents the the worse case scenarios (maximum values) when $b = 5, x = 1$ and the good case scenario (minimum values) when $b = 1, x = 0$. We notice a huge jump in the values of ϕ^* compared to when we were considering its value using the lower limit parameter values. Observe that, for the worse case scenario, $1.83 \leqslant \phi^* \leqslant 5.09$ while for the good case situation, we have $1.48 \leqslant \phi^* \leqslant 1.96$, for the different set of values for the f_{ij}'s as seen in F_1 to F_{10}.

In all it seems the F_{10} cases are better in all situation just considered, whether it is the lower limit analysis or the upper limit analysis.

8. Concluding remarks

In this work, we have presented a novel and realistic mathematical model that incorporate genetic heterogeneity into tuberculosis epidemiology. The model accommodates heterogeneous susceptibility and disease progression related to genotype of certain locus and allows interventions that include effective treatment of infectious cases as well as implicit incidences of self-cure (which minimizes the number of infectious cases over time). The effective reproduction number for this model, $\mathcal{R}_T$, has been derived and the relative contributions from different infected groups were discussed. Due to lack of data, rough estimates, based on the conditions imposed, were provided for distributing fractions of infecteds, f_{ij}, to a reasonable degree.

Among the two free parameters, x and b, it was seen that the effective reproduction number, $\mathcal{R}_T$, was more sensitive to a factor of the transmission rate, b than to the reduction factor x. In fact, the other reproduction numbers considered, $\mathcal{R}_0$ and $\mathcal{R}_{0S}$, were also more sensitive to b than to x. This indicates that efforts should be geared towards obtaining proper estimates for b, or equivalently, β.

From the simulations carried out, it is seen that if a large fraction of susceptible individuals that have no or partial resistance to TB gets infected and 'move' into the class of normal progressors (as seen from F_{10} in Table 3), then even in the worse case scenario of having a huge transmission rate, the disease can still be managed with effective and comprehensive treatment and little incidences of self cure. It seems, however, that this feat is possible if a much smaller fraction of these infected susceptibles move into the class of rapid progressors. Therefore we are suggesting that medical research should focus on developing new treatment drugs that could help in reducing the transmission rates rather than the progression rates. This is because, for smaller values of b, effective control of the disease is possible, irrespective of the f_{ij} values, it seems.

So having a large pool of normal progressors allows for better control with effective treatment. Hence attention should shift to 'protecting' susceptible individuals who have no or partial protection to tuberculosis from becoming infected and becoming rapid progressors. Focus should also be on obtaining or estimating the transmission rate that results in the generation of normal progressors as an effective management of this group can assist us in controlling the disease.

A proper TB epidemiological survey can be conducted to obtain more accurate information on the f_{ij} as this has been seen to be very significant in the overall dynamics of the disease and provides an idea of the disease burden on the population. Even slight changes in this parameter significantly changed the behavior of the system.

It is hoped that this work would motivate clinical researchers to collect relevant data (e.g. x, β, f_{ij}, y, z) as well as the key parameter b for further and better understanding of the effect of genetic heterogeneity on the dynamics of tuberculosis under various control strategies that may go beyond effective treatment, say isolation of infectious cases and vaccination.

Possible extensions can be made to our model. We could examine the effect of vaccination on the heterogeneity as well as take into account effect of incomplete treatment, drug resistance, treatment of latent cases and immigration and emigration of infected individuals.

Appendix A

The Endemic equilibrium, (if it exists), for the model in (17),
$\xi_1 = (S_1^e, S_2^e, S_3^e, E_1^e, E_2^e, E_3^e, I_1^e, I_2^e, T_1^e, T_2^e, R^e)$ written in terms of the force of infection $\lambda^e = \frac{\beta(b_1 I_1^e + I_2^e)}{N^e}$, at equilibrium, is given by

$$\begin{aligned}
S_1^e &= \frac{h_1\Lambda}{\lambda^e+\mu}\\
S_2^e &= \frac{h_2\Lambda}{x\lambda^e+\mu}\\
S_3^e &= \frac{h_3\Lambda}{\mu}\\
E_1^e &= H_8\left[f_{11}H_2 + f_{21}H_3 + g_{11}H_4\frac{G_1}{G_2} + g_{21}H_5\frac{G_3}{G_4}\right]\\
E_2^e &= H_9\left[f_{12}H_2 + f_{22}H_3 + g_{12}H_4\frac{G_1}{G_2} + g_{22}H_5\frac{G_3}{G_4}\right]\\
E_3^e &= H_{10}\left[f_{13}H_2 + f_{23}H_3 + g_{13}H_4\frac{G_1}{G_2} + g_{23}H_5\frac{G_3}{G_4}\right]\\
I_1^e &= \frac{D_1((1-D_6)(1-D_2)-D_5D_3)+D_3(D_4(1-D_2)+D_1D_5)}{(1-D_2)((1-D_6)(1-D_2)-D_5D_3)} \equiv \frac{G_1}{G_2}\\
I_2^e &= \frac{D_4(1-D_2)+D_1D_5)}{(1-D_6)(1-D_2)-D_5D_3)} \equiv \frac{G_3}{G_4}\\
T_1^e &= \frac{m_1r_1G_1}{(\mu+z\lambda)G_2}\\
T_2^e &= \frac{m_2r_2G_3}{(\mu+zy\lambda)G_4}\\
R^e &= \frac{1}{\mu}\left[\frac{a_{66}G_1}{G_2} + \frac{a_{77}G_3}{G_4}\right]
\end{aligned} \tag{54}$$

where $D_1 = H_1(f_{11}H_2 + f_{21}H_3), D_2 = g_{11}H_1H_4, D_3 = g_{21}H_1H_5,\quad D_4 = H_6(f_{12}H_2 + f_{22}H_3) + H_7(f_{13}H_2 + f_{23}H_3), D_5 + H_4(g_{12}H_6 + g_{13}H_7), D_6 = H_5(g_{22}H_6 + g_{23}H_7)$ with $H_1 = \lambda\ \frac{p_1}{a_{44}+\frac{\epsilon\lambda+k_1}{a_{44}}\frac{\lambda(1-p_1)}{\epsilon\lambda+a_{11}}}$, $H_2 = \frac{h_1\Lambda}{\mu+\lambda}$, $H_3 = \frac{xh_2\Lambda}{x\lambda+\mu}$, $H_4 = \frac{zm_1r_1}{\mu+z\lambda}$, $H_5 = \frac{zym_2r_2}{\mu+zy\lambda}, H_6 = \frac{\lambda p_2}{a_{55}} + \frac{\epsilon x_3\lambda+k_2}{a_{55}}\frac{\lambda(1-p_2)}{\epsilon x_3}$ $\lambda + a_{22}, H_7 = \frac{\lambda k_3}{a_{33}a_{55}}$, $H_8 = \frac{\lambda(1-p_1)}{\epsilon\lambda+a_{11}}$, $H_9 = \frac{\lambda(1-p_2)}{\epsilon x_3\lambda+a_{22}}$ and $H_{10} = \frac{\lambda}{a_{33}}$.

The complexity of this equlibria can be seen from the fact that, for example

$$G_3 = \frac{Z_5\lambda^{e5} + Z_4\lambda^4 + Z_3\lambda^3 + Z_2\lambda^2 + Z_1\lambda}{C_5\lambda^5 + C_4\lambda^4 + C_3\lambda^3 + C_2\lambda^2 + C_1\lambda + C_0} \tag{55}$$

and

$$G_4 = \frac{X_4\lambda^4 + X_3\lambda^3 + X_2\lambda^2 + X_1\lambda + X_0}{Y_4\lambda^4 + Y_3\lambda^3 + Y_2\lambda^2 + Y_1\lambda + Y_0} \tag{56}$$

where the coefficients in the polynomials above are all in terms of the parameters in the model (17); some of the coefficients are so complex to be written down and their magnitude (positive or negative) are not easily discernable. However the above clearly shows the possibility of multiple endemic equilibria for certain values of the parameters.

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