Applied Mathematical Modelling 36 (2012) 4173–4185

Contents lists available at SciVerse ScienceDirect

Applied Mathematical Modelling

journal homepage: www.elsevier.com/locate/apm

Assessing the effects of poverty in tuberculosis transmission dynamics

C.P. Bhunu [a,*], S. Mushayabasa [b], R.J. Smith? [c]

[a] University of Zimbabwe, Department of Mathematics, P.O. Box MP 167, Harare, Zimbabwe
[b] Modelling Biomedical Systems Research Group, Department of Applied Mathematics, National University of Science and Technology, P.O. Box AC939, Ascot, Bulawayo, Zimbabwe
[c] Department of Mathematics and Faculty of Medicine, The University of Ottawa, 585 King Edward Ave., Ottawa, ON, Canada K1N 6N5

ARTICLE INFO

Article history:
Received 25 March 2011
Received in revised form 11 October 2011
Accepted 14 November 2011
Available online 25 November 2011

Keywords:
Tuberculosis
Rich
Poverty
Reproduction number
Latin Hypercube Sampling
Partial rank correlation coefficients

ABSTRACT

Tuberculosis (TB) transmission is enhanced by poor living conditions. In this study, a deterministic model was developed to assess the impact of socioeconomic conditions on TB transmission, taking into account heterogeneous mixing patterns. The epidemic thresholds known as the reproduction numbers, as well as equilibria for the model, are determined and stabilities analysed. Results from the study suggest that TB transmission is more common in poverty-stricken communities than in rich communities, supporting the argument that TB is a disease of the poor. The outcome is significantly dependent on the probability of latency, so that if the number of fast TB cases could be reduced, the epidemic would significantly improve. Interestingly, our results illustrate that heterogeneous mixing of the rich and poor will make the epidemic worse, but homogenous mixing will slightly improve the outcome. Further, even when all other factors are equal, the poor contact rate will have more impact than the rich contact rate. It follows that the rich community can help themselves by helping those less fortunate.

1. Introduction

Tuberculosis (TB) is the most prevalent airborne infectious cause of death, killing around three million people, principally young adults in the world's poorest nations each year [1]. TB cases have been made worse by the HIV/AIDS pandemic and emergence of MTB (multi-drug resistant TB) [2]. Infection by HIV greatly increases the likelihood that a person infected with MTB will develop active TB [2], since it impairs the immune system.

Despite the availability of therapy that is highly effective in terms of years of human lives saved, and highly cost effective, TB continues to flourish [3]. The distribution of TB in both developed and developing nations is grossly uneven and points to poverty as a causal factor [1,4]. The World Bank defines absolute poverty as living on one United States dollar or less per person per day. The World Bank also recognises that poverty encompasses vulnerability to shocks, and lack of opportunities and capabilities [5]. Poverty-stricken people lack food security, income stability, and access to water, sanitation and health care [6,7]. Extreme poverty is concentrated among certain subgroups of the population and may be associated with other social and political crises. The devastating effects of TB, particularly in patients with HIV/AIDS, led the World Health Organization (WHO) to declare a global emergency for TB in April 1993 [8], and the ministers' conference in Amsterdam in 2000 to designate 24 March of each year as 'World TB Day' [9]. The global emergency of TB at a time when cheap and effective anti-TB drugs are available has been described as a paradox that should now be addressed through societal and political means [2].

* Corresponding author.
E-mail addresses: cpbhunu@gmail.com, cp-b@hotmail.co.uk (C.P. Bhunu).

0307-904X/$ - see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.apm.2011.11.046

Globally, 80% of avoidable mortality has been attributed to communicable diseases in low-income countries [7]. The world's poorest nations therefore carry an inequitable burden of avoidable mortality [7]. TB thrives in conditions of hardship and can worsen poverty. While TB is not exclusively a disease of the poor, the association between poverty and TB is well established and widespread [2,10–13,6]. Once a person succumbs to TB and HIV/AIDS, they easily become poor, since they are not able to become economically productive [2,14]. TB control and poverty reduction cannot be achieved solely by seeking improvements of target indicators on averages across populations; instead, specific needs of vulnerable communities must be addressed.

In some poverty-stricken settings, individuals known to have TB are stigmatised, leading to denial, and preventing timely diagnosis and effective treatment. This can be addressed by tackling stigma through knowledge dissemination and behavioural change with the support of former TB patients and others [7]. Implementation of the Directly Observed Treatment Strategy (DOTS) in TB control is difficult in areas with high concentrations of poor and vulnerable people such as city slums and geographically remote places due to lack of health service personnel, poor remuneration for the health staff and lack of staff motivation in these settings. Nutritional status also plays an important role, as malnourished people tend to have their immune systems compromised [15,16]. Overcrowding increases contact rates and thus the chances of being infected with TB [17,11].

A number of studies have been carried out to examine the link between poverty and TB [11,17–21]. Beggs et al. [17] and Delfino and Simmons [21] used statistical analysis in their assessment of poverty in relation to TB. Our work differs from these studies in that we use deterministic models to assess the impact of poverty in the transmission dynamics of tuberculosis. Most studies [19,17,11] analysed the link between overcrowding and TB, and found that overcrowding enhances TB transmission; in this study, in addition to overcrowding, we consider other aspects of poverty, such as poor nutrition and reduced treatment uptake.

This paper is organised as follows. Section 2 presents the model framework and analysis. In Section 3, numerical simulations are presented and the last section concludes the paper.

2. Model description

The model subdivides the population based on poverty. Although thresholds of absolute poverty are set at those earning less than US $1 a day, here we divide the population in two, according to health status and living conditions. Poverty-stricken individuals are here defined as those who exist in overcrowded living situations, suffer from poor health, are less likely to receive treatment and who have an increased risk of death from TB. It should be noted that this line is clearly not absolute and may be difficult to find explicitly, but that it nevertheless exists. However, by keeping the threshold fluid, our model applies to a broad range of definitions of poverty, rather than an arbitrary cutoff based simply on earning ability. Individuals living in poverty fall into the following population classes: susceptibles S_p, exposed E_p, infectives I_p and the recovered R_p. Similarly, individuals not living in poverty consists of the following classes: susceptibles S_r, exposed E_r, infectives I_r and the recovered R_r. There is interaction between individuals in these two distinct classes (rich and poverty-stricken), making TB transmission across different socioeconomic classes possible. The total sub-population sizes for the rich and poor are given by

$$N_r(t) = S_r(t) + E_r(t) + I_r(t) + R_r(t) \quad \text{and} \quad N_p(t) = S_p(t) + E_p(t) + I_p(t) + R_p(t), \tag{1}$$

respectively. Individuals in different human subgroups suffer from natural death at a constant rate μ, which is proportional to the number in each class. We assume that interaction is heterogeneous. The group j members make c_j ($j = r,p$) contacts per unit time and a fraction of the contacts made by a member of group j with a member of group i is p_{ji} ($i = r,p$). Then $p_{rr} + p_{rp} = p_{pp} + p_{pr} = 1$. The total number of contacts made in unit time by members of group 'p' (poor people) with members of group 'r' (rich people) is $c_p p_{pr} N_p$ and this must be equal to the total number of contacts made by members of group 'r' with members of group 'p'; we have a balance relation:

$$\frac{p_{pr}c_p}{N_r} = \frac{p_{rp}c_r}{N_p}. \tag{2}$$

The forces of TB infection for the poor and the rich are given by λ_p and λ_r, with

$$\lambda_p = \frac{p_{pp}c_p\beta_p I_p}{N_p} + \frac{p_{pr}c_p\beta_r I_r}{N_r} \quad \text{and} \quad \lambda_r = \frac{p_{rr}c_r\beta_r I_r}{N_r} + \frac{p_{rp}c_r\beta_p I_p}{N_p}, \tag{3}$$

respectively.

In Eq. (3), β_i ($i = r,p$) is the probability of one individual being infected by one infectious individual from the r or p class, while c_j ($j = r,p$) is the per capita effective contact rate. It is worth mentioning that $c_p = b_1 c_r$, with $b_1 \geqslant 1$. The term b_1 is an accelerating term showing that poor people live in overcrowded conditions. Individuals are recruited into the rich and poor susceptible populations at rates $(1-\rho)\Lambda$ and $\rho\Lambda$, respectively. Rich and poor susceptibles are infected with MTB at rates λ_r and λ_p, respectively. Rich susceptibles infected with MTB enter the latent stage at a rate $f\lambda_r$ and develop fast TB at a rate $(1-f)\lambda_r$. Rich latently infected individuals progress to active TB as a result of endogenous reactivation of the latent bacilli and exogenous reinfection at rates k_r and $\psi_r\lambda_r$, with $\psi_r \in (0,1)$, since primary infection confers some degree of immunity.

Rich TB infectives are treated at rate r_r and treated individuals move into the recovered class. Rich TB infectives have an additional disease-induced death rate d_r. Rich individuals recovered from TB are infected with MTB at rate $\delta_r\lambda_r$ to enter rich latently infected and TB infective classes at rates $f\delta_r\lambda_r$ and $(1-f)\delta_r\lambda_r$, respectively, with $\delta_r \in (0,1)$, since primary infection confers some degree of immunity. Poor susceptibles infected with MTB enter the latently infected class at a rate $f\lambda_p$ and develop fast TB at a rate $(1-f)\lambda_p$. Poor latently infected individuals progress from latency to active TB as a result of endogenous reactivation and exogenous reinfection at rates k_p and $\psi_p\lambda_p$, respectively, where $k_p = b_2k_r$, with $b_2 \geqslant 1$ and $\psi_p \in (0,1)$, since primary infection confers some degree of immunity. The term b_2 is an acceleration parameter showing that latently infected poor individuals have an increased rate of progressing to active TB due to the effects of malnutrition on the immune system. Poor TB patients are treated at rate r_p, where $r_p = \frac{1}{b_3}r_r$, with $b_3 \geqslant 1$. The term $\frac{1}{b_3}$ represents decreased treatment uptake. Due to impediments, such as having money for transport to and from the hospital, and negative attitude of health professionals towards individuals in this socioeconomic class, there is a reduced compliance of TB treatment in poor people. Due to reduced socioeconomic status, poor TB infectives have an additional TB-induced death rate d_p, where $d_p = b_4d_r$, with $b_4 \geqslant 1$. This is because most poor individuals do not have easy access to life-saving drugs and thus experience higher disease-induced death than their corresponding rich individuals. Poor individuals recovered from TB are infected with MTB at rate $\delta_p\lambda_p$ and move into the latently infected and infective classes at rates $f\delta_p\lambda_p$ and $(1-f)\delta_p\lambda_p$, respectively; $\delta_p \leqslant 1$, since primary infection confers some degree of immunity. The model flow diagram is given in Fig. 1.

We assume any transfer from rich to poor status or vice versa is negligible. Based on the aforementioned, the following system of differential equations describe the dynamics of TB in different social settings:

$$
\begin{aligned}
S_r'(t) &= (1-\rho)\Lambda - \lambda_r S_r - \mu S_r,\\
E_r'(t) &= f\lambda_r(S_r + \delta_r R_r) - (\mu + k_r)E_r - \psi_r\lambda_r E_r,\\
I_r'(t) &= (1-f)\lambda_r(S_r + \delta_r R_r) + k_r E_r + \psi_r\lambda_r E_r - (\mu + d_r + r_r)I_r,\\
R_r'(t) &= r_r I_r - \mu R_r - \delta_r\lambda_r R_r,\\
S_p'(t) &= \rho\Lambda - \lambda_p S_p - \mu S_p,\\
E_p'(t) &= f\lambda_p(S_p + \delta_p R_p) - (\mu + k_p)E_p - \psi_p\lambda_p E_p,\\
I_p'(t) &= (1-f)\lambda_p(S_p + \delta_p R_p) + k_p E_p + \psi_p\lambda_p E_p - (\mu + d_p + r_p)I_p,\\
R_p'(t) &= r_p I_p - \mu R_p - \delta_p\lambda_p R_p.
\end{aligned}
\tag{4}
$$

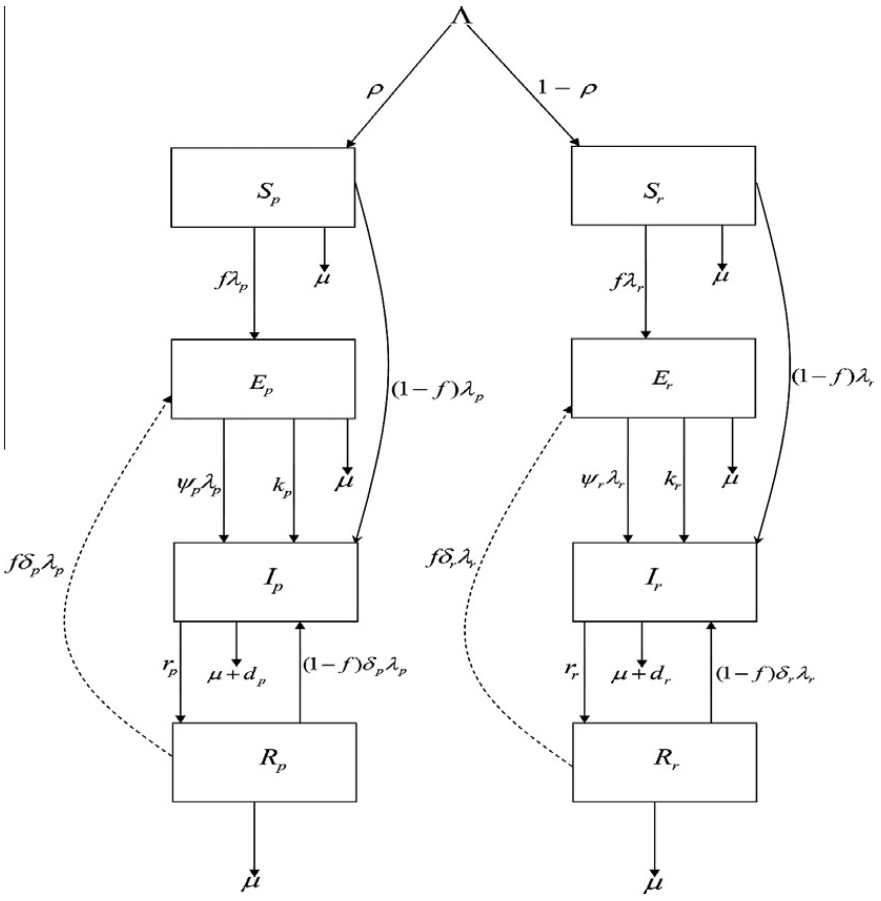

Fig. 1. Structure of the model.

2.1. Basic properties of solutions

In this section, we study some basic results of solutions of model system (4) which will be useful in the proofs of stability and persistence results. Let $\mathbb{R}^n_+$ denote the set $x = (x_1, x_2, \ldots, x_n)$ with $x_j > 0$ for $j = 1, 2, \ldots, n$. We will use the following results in Appendix A of [22].

Lemma 1. *Let $F : \mathbb{R}^n_+ \to \mathbb{R}^n, F(x) = (F_1(x), F_2(x), \ldots, F_n(x)), x = (x_1, x_2, \ldots, x_n)$ be continuous and have partial derivatives $\frac{\partial F_j}{\partial x_k}$ which exist and are continuous in $\mathbb{R}^n_+$ for $j, k = 1, 2, \ldots, n$. Then F is locally Lipschitz continuous in $\mathbb{R}^n_+$.*

Theorem 1. *Let $F : \mathbb{R}^n_+ \to \mathbb{R}^n$ be locally Lipschitz continuous and for each $j = 1, 2, \ldots, n$ satisfy $F_j(x) \geqslant 0$ whenever $x \in \mathbb{R}^n_+, x_j = 0$. Then, for every $x_0 \in \mathbb{R}^n_+$, there exists a unique solution of $x' = F(x), x(0) = x_0$ with values in $\mathbb{R}^n_+$ which is defined in some interval $(0, b]$ with $b \in (0, \infty]$. If $b < \infty$, then $\sup \sum_{j=1}^n x_j(t) = \infty$.*

Theorem 2. *For all $S_r^0, E_r^0, I_r^0, R_r^0, S_p^0, E_p^0, I_p^0, R_p^0 > 0$, there exists S_r, E_r, I_r, R_r, S_p, E_p, I_p, R_p: $(0, \infty) \to (0, \infty)$ which solve model system (4) with initial conditions $S_r = S_r^0, E_r = E_r^0, I_r = I_r^0, R_r = R_r^0, S_p = S_p^0, E_p = E_p^0, I_p = I_p^0$ and $R_p = R_p^0$.*

Proof. Applying Theorem 1, we define

$$F_1(x) = S_r'(t) \quad F_2(x) = E_r'(t) \quad F_3(x) = I_r'(t) \quad F_4(x) = R_r'(t) \quad F_5(x) = S_p'(t) \quad F_6(x) = E_p'(t) \quad F_7(x) = I_p'(t) \quad F_8(x) = R_p'(t),$$

where $x = (S_r, E_r, I_r, R_r, S_p, E_p, I_p, R_p)$.

By the properties of continuity over operations, we have continuity of F_i for all $i = 1, 2, \ldots, 8$. Furthermore,

$$\begin{aligned}
\frac{\partial F_1}{\partial x_1} &= -\mu - \frac{p_{rp} c_r \beta_p I_p}{N_p} - \frac{p_{rr} c_r \beta_r I_r (E_r + I_r + R_r)}{N_r^2}, \\
\frac{\partial F_1}{\partial x_2} &= \frac{p_{rr} c_r \beta_r I_r S_r}{N_r^2}, \\
\frac{\partial F_1}{\partial x_3} &= -\frac{p_{rr} c_r \beta_r S_r (S_r + E_r + R_r)}{N_r^2}, \\
\frac{\partial F_1}{\partial x_4} &= \frac{p_{rr} c_r \beta_r I_r S_r}{N_r^2}, \\
\frac{\partial F_1}{\partial x_5} &= \frac{p_{rp} c_r \beta_p I_p S_r}{N_p^2}, \\
\frac{\partial F_1}{\partial x_6} &= \frac{p_{rp} c_r \beta_p I_p S_r}{N_p^2}, \\
\frac{\partial F_1}{\partial x_7} &= -\frac{p_{rp} c_r \beta_p S_r (S_p + E_p + R_p)}{N_p^2}, \\
\frac{\partial F_1}{\partial x_8} &= \frac{p_{rp} c_r \beta_p I_p S_r}{N_p^2},
\end{aligned} \tag{5}$$

and these partial derivatives exist and are continuous. By Lemma 1, F is locally Lipschitz continuous. Let $x_1 = S_r = 0$, with $x_2 = E_r > 0$, $x_3 = I_r > 0$, $x_4 = R_r > 0$, $x_5 = S_p > 0$, $x_6 = E_p > 0$, $x_7 = I_p > 0$ and $x_8 = R_p > 0$. Then

$$F_1(x) = (1 - \rho)\Lambda > 0.$$

Now let $x_2 = E_r = 0$, with $x_1 = S_r > 0$, $x_3 = I_r > 0$, $x_4 = R_r > 0$, $x_5 = S_p > 0$, $x_6 = E_p > 0$, $x_7 = I_p > 0$ and $x_8 = R_p > 0$. Then

$$F_2(x) = f\left(\frac{p_{rr} c_r \beta_r I_r}{N_r} + \frac{p_{rp} c_r \beta_p I_p}{N_p}\right)(S_r + \delta_r R_r) > 0.$$

This is further done up to the case when $x_8 = R_p = 0$, with $x_1 = S_r > 0$, $x_2 = E_r > 0$, $x_3 = I_r > 0$, $x_4 = R_r > 0$, $x_5 = S_p > 0$, $x_6 = E_p > 0$ and $x_7 = I_p > 0$. Then

$$F_8(x) = r_p I_p > 0.$$

By Theorem 1, for every $x_0 = \left(S_r^0, E_r^0, I_r^0, R_r^0, S_p^0, E_p^0, I_p^0, R_p^0\right) \in \mathbb{R}^8_+$, there exists a unique solution of $x' = F(x), x(0) = x_0$ with values in $\mathbb{R}^8_+$ which is defined in some interval $(0, b]$ with $b \in (0, \infty]$. If $b < \infty$, then

$$\sup_{0 \leqslant t \leqslant b} [N_r(t) + N_p(t)] = \infty.$$

Thus, $N' = \Lambda - \mu N - d_r I_r - d_p I_p \leqslant \Lambda - \mu N$, $N = N_r + N_p$. Using [23],

$$0 \leqslant N \leqslant \frac{\Lambda}{\mu} + N(0)e^{-\mu t},$$

where $N(0)$ represents the value of Eq. (1) evaluated at the initial conditions of the respective variables. As $t \to \infty$,

$$0 \leqslant N \leqslant \frac{\Lambda}{\mu},$$

so $N(t)$ is bounded, a contradiction to Theorem 1. As a result, $b = \infty$, implying that solutions of model system (4) are positive and are defined on $(0, \infty)$. □

For the boundedness of solutions, the following Theorem is established.

Theorem 3. *All solutions of model system (4) are bounded.*

Proof. Using model system (4), we have $N' = \Lambda - \mu N - d_r I_r - d_p I_p \leqslant \Lambda - \mu N$. Assume $N(t) \leqslant M$ for all $t \geqslant 0$, where $M = \frac{\Lambda}{\mu} + 1$. Suppose the assumption is not true. Then there exists a $t_1 > 0$ such that

$$N(t_1) = \frac{\Lambda}{\mu} + 1, \quad N(t) < \frac{\Lambda}{\mu} + 1, \quad t < t_1, \quad N'(t_1) \geqslant 0.$$

However,

$$N'(t_1) \leqslant \Lambda - \mu N(t_1) = -\mu < 0,$$

which is a contradiction. This means $N(t) \leqslant M$ for all $t \geqslant 0$. □

Therefore, all feasible solutions of system (4) enter the region

$$\Omega = \left\{ (S_r, E_r, I_r, R_r, S_p, E_p, I_p, R_p) \in \mathbb{R}^8_+ : N \leqslant \frac{\Lambda}{\mu} \right\}.$$

Thus, Ω is positively invariant and it is sufficient to consider solutions in Ω. Existence, uniqueness and continuation results for system (4) hold in this region and all solutions of system (4) starting in Ω remain in Ω for all $t \geqslant 0$. All parameters and state variables for model system (4) are assumed to be non-negative (for biological relevance) for all $t \geqslant 0$ since it monitors human population.

2.2. Disease-free equilibrium and stability analysis

The disease-free equilibrium of model system (4), $\mathcal{E}^0$, is given by

$$\mathcal{E}^0 = \left(S_r^0, E_r^0, I_r^0, R_r^0, S_p^0, E_p^0, I_p^0, R_p^0\right) = \left(\frac{(1-\rho)\Lambda}{\mu}, 0, 0, 0, \frac{\rho\Lambda}{\mu}, 0, 0, 0\right).$$

Following van den Driessche [24], the reproduction number for model system (4) is given as

$$\mathcal{R}_{r_p} = \frac{G_1 + G_2}{2}$$

where

$$G_1 = \frac{p_{pp} c_p \beta_p \theta_p}{h_3 h_4} + \frac{p_{rr} c_r \beta_r \theta_r}{h_1 h_2},$$

$$G_2 = \sqrt{\frac{4 c_r c_p p_{rp} p_{pr} \beta_p \beta_r \theta_p \theta_r}{h_1 h_2 h_3 h_4} + \left(\frac{p_{pp} c_p \beta_p \theta_p}{h_3 h_4} - \frac{p_{rr} c_r \beta_r \theta_r}{h_1 h_2}\right)^2}$$

with

$$h_1 = \mu + k_r \quad h_2 = \mu + d_r + r_r \quad \theta_r = \mu(1-f) + k_r,$$
$$h_3 = \mu + k_p \quad h_4 = \mu + d_p + r_p \quad \theta_p = \mu(1-f) + k_p.$$

The utility of the basic reproductive number has been questioned, but we use it here as a threshold with the understanding that there may be further complexities in its application [25].

The next theorem follows from [24] Theorem 2.

Theorem 4. *The disease-free equilibrium $\mathcal{E}^0$ is locally asymptotically stable for $\mathcal{R}_{r_p} < 1$ and unstable otherwise.*

2.2.1. Analysis of the reproduction number $\mathcal{R}_{r_p}$

In the case that like mixes with like, $p_{rr} = p_{pp} = 1$, $p_{rp} = p_{pr} = 0$, then $\mathcal{R}_{r_p} = \max\{R_r, R_p\}$, where

$$\mathcal{R}_p = \frac{\beta_p c_p \theta_p}{h_3 h_4} \quad \text{and} \quad \mathcal{R}_r = \frac{\beta_r c_r \theta_r}{h_1 h_2}. \tag{6}$$

These are the treatment-induced reproduction numbers for TB transmission when poor people mix only among themselves ($\mathcal{R}_p$) or treatment-induced reproduction numbers for TB transmission when rich people mix only among themselves ($\mathcal{R}_r$). This allows us to compare the various components of the two reproduction numbers $\mathcal{R}_p$ and $\mathcal{R}_r$ for different scenarios such as overcrowding, poor nutrition, increased endogeneous reactivation and reduced treatment uptake.

In Table 1, the various attributes of poverty are singly assessed: Case 1 suggests that poor people living in overcrowded homes are at a comparative disadvantage when it comes to TB infection, as overcrowding increases contact rates, making poor people more prone to TB infections than their rich counterparts. Case 2 describes the effect of exogeneous reactivation by capturing the increased probability of TB transmission among the poor than among the rich. Poor nutrition tends to compromise one's immunity, also contributing to an increase in endogeneous reactivation of the latent bacilli as noted in Case 2. Case 3 captures the effects of reduced treatment uptake among the poor. Results from Table 1 suggest that poor people are at an increased disadvantage when it comes to infection with TB and are driving the epidemic. Case 4 describes the effect of lower socioeconomic class, while Case 5 deals with the direct effect of poor nutrition. All the signifiers of poverty serve to exasperate the risk of transmission between the poor versus the rich.

Similar results are also obtained by using the Wells–Riley equation [26] which shows an increase in active new TB cases I_i^N ($i = r,p$) with time for steady-state quanta levels in a room space assuming the same initial susceptible population sizes for poor and rich people:

$$I_i^N = S\left\{1 - \exp\left[-\left(\frac{(I_r + I_p)p_m q t}{A_i V_i}\right)\right]\right\},$$

where I_i^N is the number of new TB cases in class i; p_m is the average pulmonary ventilation or the breathing rate of susceptibles per hour (m^3/hr); q is the quanta production rate per infector ($quanta/hr$); V_i ($i = r,p$) is the room volume (m^3); A_i ($i = p,r$) is the ventilation rate in air changes per hour (AC/hr) and t is the total exposure time (seconds). These terms account for the fact that poor people live in small overcrowded rooms and ventilation is bad. Thus, for the poor, $\frac{(I_r+I_p)p_m q t}{A_p V_p}$ is greater than $\frac{(I_r+I_p)p_m q t}{A_r V_r}$, since $A_p < A_r$ (ventilation rate for the poor is bad) and $V_p < V_r$ (poor people live in smaller rooms). Thus, if we start off with the same initial susceptible poor and rich populations, then

$$I_p^N = S\left\{1 - \exp\left[-\left(\frac{(I_r + I_p)p_m q t}{A_p V_p}\right)\right]\right\} > I_r^N = S\left\{1 - \exp\left(-\left(\frac{(I_r + I_p)p_m q t}{A_r V_r}\right)\right]\right\},$$

meaning that there are more new TB cases among the poor than among the rich.

2.3. Endemic equilibria

Model system (4) has three endemic equilibria: rich-only endemic equilibrium, poverty-only endemic equilibrium and a coexistence equilibrium. It is worth mentioning that if there are no poor (or no rich) people, model system (4) becomes an ordinary TB model, so the rich-only and poor-only endemic equilibrium states are simple TB equilibrium states whose analysis has been carried out in depth by a number of researchers [27]. For that reason, we do not discuss them here.

The coexistence equilibrium occurs when the disease exists in the entire community regardless of the socioeconomic status of individuals. This endemic equilibrium is denoted by

$$\mathcal{E}^{**} = \left(S_r^{**}, E_r^{**}, I_r^{**}, R_r^{**}, S_p^{**}, E_p^{**}, I_p^{**}, R_p^{**}\right),$$

where all states are positive. The permanence of the disease destabilises the disease-free equilibrium $\mathcal{E}^0$, since the coexistence equilibrium $\mathcal{E}^{**}$ exists for $\mathcal{R}_{r_p} > 1$.

Table 1
Effects of overcrowding, increased endogenous reactivation, reduced socioeconomic status, reduced treatment uptake and poor nutrition on TB dynamics. In each case, all parameters are equalized between rich and poor, except those under the heading "conditions".

Case	Description	Conditions	$\mathcal{R}_p - \mathcal{R}_r$
1	Overcrowding	$c_p = b_1 c_r$, $b_1 > 1$	$\frac{(b_1-1)c_r\beta_r\theta_r}{h_3 h_4} > 0$
2	Increased endogenous reactivation	$k_p = b_2 k_r$, $b_2 > 1$	$\frac{c_r\beta_r f\mu k_r(b_2-1)}{h_3 h_4 h_2} > 0$
3	Reduced treatment uptake	$r_r = b_3 r_p$, $b_3 \geqslant 1$	$\frac{(b_3-1)\beta_r c_r\theta_r}{h_1 h_2 h_4} > 0$
4	Reduced socioeconomic status	$d_p = b_4 d_r$, $b_4 \geqslant 1$	$\frac{(b_4-1)c_r\beta_r\theta_r d_r}{h_3 h_2 h_4} > 0$
5	Poor nutrition	$\beta_p = b_5\beta_r$, $b_5 > 1$	$\frac{(b_5-1)c_r\beta_r\theta_r}{h_3 h_4} > 0$

Lemma 2 [28]. *Let $x \mapsto F(t)$ be a differentiable function with finite limit as $t \to \infty$. If $\dot{F}$ is uniformly continuous, then $\dot{F} \to 0$ as $t \to \infty$.*

Theorem 5. *System (4) is uniformly persistent on Ω.*

Proof. Uniform persistence of system (4) implies that there exists a constant $\zeta > 0$ such that any solution of (4) which starts in

$$\left(S_r^0, E_r^0, I_r^0, R_r^0, S_p^0, E_p^0, I_p^0, R_p^0\right) \in \Omega^\circ,$$

satisfies

$$\begin{aligned}
&\liminf_{t\to\infty} S_r(t) \geqslant \zeta \quad \liminf_{t\to\infty} E_r(t) \geqslant \zeta \quad \liminf_{t\to\infty} I_r(t) \geqslant \zeta \quad \liminf_{t\to\infty} R_r(t) \geqslant \zeta \\
&\liminf_{t\to\infty} S_p(t) \geqslant \zeta \quad \liminf_{t\to\infty} E_p(t) \geqslant \zeta \quad \liminf_{t\to\infty} I_p(t) \geqslant \zeta \quad \liminf_{t\to\infty} R_p(t) \geqslant \zeta.
\end{aligned}$$

Using the Lyapunov functional [29],

$$\begin{aligned}
V(S_r, E_r, I_r, R_r, S_p, E_p, I_p, R_p) = {} & C_1\left(S_r - S_r^{**} \ln S_r\right) + C_2\left(E_r - E_r^{**} \ln E_r\right) + C_3\left(I_r - I_r^{**} \ln I_r\right) + C_4\left(R_r - R_r^{**} \ln R_r\right) \\
& + C_5\left(S_p - S_p^{**} \ln S_p\right) + C_6\left(E_p - E_p^{**} \ln E_p\right) + C_7\left(I_p - I_p^{**} \ln I_p\right) + C_8\left(R_p - R_p^{**} \ln R_p\right),
\end{aligned}$$

the time derivative of $V(S_r, E_r, I_r, R_r, S_p, E_p, I_p, R_p)$ along the solution path is given by

$$\begin{aligned}
V' = {} & C_1\left(S_r' - S_r^{**}\frac{S_r'}{S_r}\right) + C_2\left(E_r' - E_r^{**}\frac{E_r'}{E_r}\right) + C_3\left(I_r' - I_r^{**}\frac{I_r'}{I_r}\right) + C_4\left(R_r' - R_r^{**}\frac{R_r'}{R_r}\right) + C_5\left(S_p' - S_p^{**}\frac{S_p'}{S_p}\right) + C_6\left(E_p' - E_p^{**}\frac{E_p'}{E_p}\right) \\
& + C_7\left(I_p' - I_p^{**}\frac{I_p'}{I_p}\right) + C_8\left(R_p' - R_p^{**}\frac{R_p'}{R_p}\right) \\
= {} & \left(S_r - S_r^{**}\right)\frac{S_r'}{S_r} + C_2\left(E_r - E_r^{**}\right)\frac{E_r'}{E_r} + C_3\left(I_r - I_r^{**}\right)\frac{I_r'}{I_r} + C_4\left(R_r - R_r^{**}\right)\frac{R_r'}{R_r} + C_5\left(S_p - S_p^{**}\right)\frac{S_p'}{S_p} + C_6\left(E_p - E_p^{**}\right)\frac{E_p'}{E_p} \\
& + C_7\left(I_p - I_p^{**}\right)\frac{I_p'}{I_p} + C_8\left(R_p - R_p^{**}\right)\frac{R_p'}{R_p} \\
\leqslant {} & -C_1\left(S_r - S_r^{**}\right)(\lambda_r + \mu) - C_2\left(E_r - E_r^{**}\right)(\mu + k_r + \psi_r\lambda_r) - C_3\left(I_r - I_r^{**}\right)(\mu + d_r + r_r) - C_4\left(R_r - R_r^{**}\right)(\mu + \delta_r\lambda_r) \\
& - C_5\left(S_p - S_p^{**}\right)(\mu + \lambda_p) - C_6\left(E_p - E_p^{**}\right)(\mu + k_p + \psi_p\lambda_p) - C_7\left(I_p - I_p^{**}\right)(\mu + d_p + r_p) - C_8\left(R_p - R_p^{**}\right)(\mu + \delta_p\lambda_p) \\
\leqslant {} & \eta\left[\left(S_r - S_r^{**}\right) + \left(E_r - E_r^{**}\right) + \left(I_r - I_r^{**}\right) + \left(R_r - R_r^{**}\right) + \left(S_p - S_p^{**}\right) + \left(E_p - E_p^{**}\right) + \left(I_p - I_p^{**}\right) + \left(R_p - R_p^{**}\right)\right], \qquad (7)
\end{aligned}$$

where

$$\begin{aligned}
\eta = \min\{ & -C_1(\lambda_r + \mu), -C_2(\mu + k_r + \psi_r\lambda_r), -C_3(\mu + d_r + r_r), -C_4(\mu + \delta_r\lambda_r), -C_5(\mu + \lambda_p), -C_6(\mu + k_p + \psi_p\lambda_p), \\
& -C_7(\mu + d_p + r_p), -C_8(\mu + \delta_p\lambda_p)\}.
\end{aligned}$$

Thus, $V(S_r, E_r, I_r, R_r, S_p, E_p, I_p, R_p) > 0$ and $V'(S_r, E_r, I_r, R_r, S_p, E_p, I_p, R_p) = 0$ only at $\mathcal{E}^{**}$. Hence, $V(S_r, E_r, I_r, R_r, S_p, E_p, I_p, R_p)$ is a Lyapunov function since all the variables $S_r(t), E_r(t), I_r(t), R_r(t), S_p(t), E_p(t), I_p(t), R_p(t) \in L^1$ are continuous and bounded with derivatives in L^∞ (indeed, $\frac{d}{dt}\left(S_r - S_r^{**}\right)$ is also uniformly bounded). We have

$$\left(S_r - S_r^{**}\right) + \left(E_r - E_r^{**}\right) + \left(I_r - I_r^{**}\right) + \left(R_r - R_r^{**}\right) + \left(S_p - S_p^{**}\right) + \left(E_p - E_p^{**}\right) + \left(I_p - I_p^{**}\right) + \left(R_p - R_p^{**}\right) \to 0 \text{ as } t \to \infty,$$

a result adapted from Lemma 2.

Hence, $V'(S_r, E_r, I_r, R_r, S_p, E_p, I_p, R_p) = 0$ with equality only at $\mathcal{E}^{**}$. The only invariant subset in Ω_1, the interior of

$$\Omega_1 = \left\{(S_r, E_r, I_r, R_r, S_p, E_p, I_p, R_p) : S_r = S_r^{**}, E_r = E_r^{**}, I_r = I_r^{**}, R_r = R_r^{**}, S_p = S_p^{**}, E_p = E_p^{**}, I_p = I_p^{**}, R_p = R_p^{**}\right\} \subset \Omega$$

is the singleton $\{\mathcal{E}^{**}\} = \left\{\left(S_r^{**}, E_r^{**}, I_r^{**}, R_r^{**}, S_p^{**}, E_p^{**}, I_p^{**}, R_p^{**}\right)\right\}$. Therefore, from the Lyapunov-Lasalle properties [30], system (4) is uniformly persistent. The above result can be ascertained from the fact that V' is positive in the neighbourhood of an unstable disease-free equilibrium $\mathcal{E}^0$ with $\mathcal{R}_{r_p} > 1$, because all solutions starting in that vicinity remain away from $\mathcal{E}^0$, except those starting on the semi-axes OS_r and OS_p (O being the origin). The only biologically meaningful compact invariant subset on the boundary of Ω is $\left\{S_r^0, 0, 0, 0, S_p^0, 0, 0, 0\right\}$ and, by a result of [31], system (4) is uniformly persistent. □

Table 2
Model parameters and their interpretations.

Definition	Symbol	Units	Point estimate	Range	Source
Recruitment rate	Λ	People/Year	$8.7 \cdot 10^4$	–	CSOZ
Natural mortality rate	μ	1/Year	0.02	0.015–0.02	CSOZ
Contact rates	c_r, c_p	–	3	1–10	Assumed
TB induced death rate	d_r	1/Year	0.3	0.1–0.5	a^*
Transmission probabilities	β_r, β_p	–	0.35	0.3–0.5	a^*
Homogeneous mixing	p_{pp}, p_{rr}	–	0.3	0–1	Assumed
Heterogeneous mixing	p_{rp}, p_{pr}	–	0.3	0–1	Assumed
Endogenous reactivation rates	k_r, k_p	1/Year	0.00013	10^{-4} to 3×10^{-4}	a^*
Treatment rate for rich	r_r	1/Year	0.88	0.7–1	c^*
Treatment rate for poor	r_r	1/Year	0.88	0.3–1	c^*
Protective factor for exposed	ψ_r, ψ_p	–	0.7	–	d^*
Protective factor for recovered	δ_r, δ_p	–	0.9	–	d^*
Probability of being recruited poor	ρ	–	0.5	–	Assumed
Latency probability	f	–	0.99	0–1	d^*
Overcrowding factor	b_1	–	Variable	$(\geqslant 1)$	Assumed
Increased activation factor	b_2	–	Variable	$(\geqslant 1)$	Assumed
Reduced treatment factor	b_3	–	Variable	$(\geqslant 1)$	Assumed
Reduced socioeconomic status factor	b_4	–	Variable	$(\geqslant 1)$	Assumed
Reduced nutritional status factor	b_5	–	Variable	$(\geqslant 1)$	Assumed

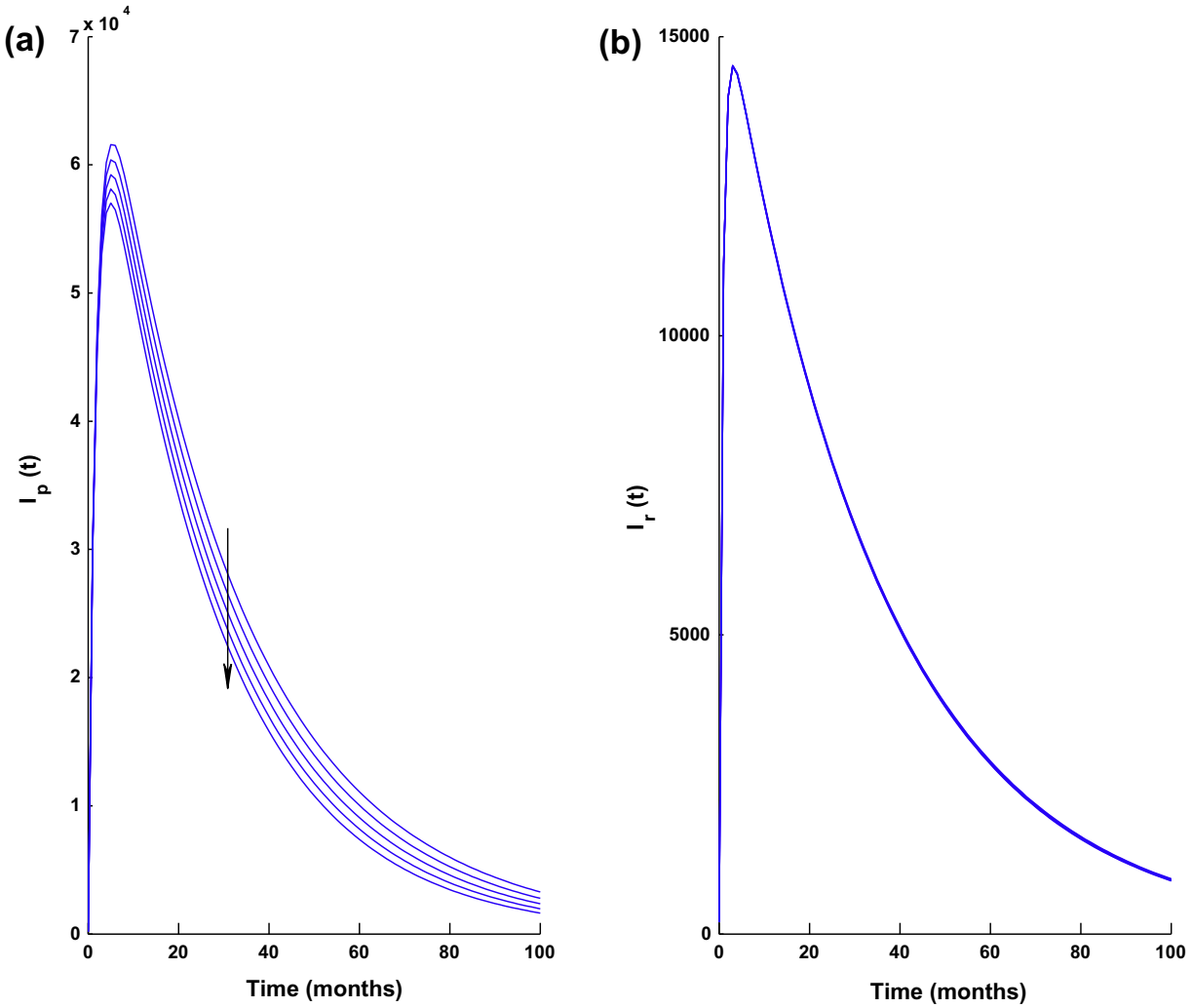

Fig. 2. Simulations of model system (4) showing effects of overcrowding in the transmission dynamics of TB in heterogenous settings obtained by considering simulations of the active TB cases starting from $b_1 = 1$ with a step size of 0.05 and other parameter values as in Table 2. The direction of the arrow shows the direction of decrease in the levels of overcrowding.

3. Numerical simulations

The fourth-order Runge–Kutta numerical scheme coded in C++ and parameter values in Table 2 were used in carrying out the numerical simulations. For effective comparison of the effects of poverty on TB transmission we assume the same initial population size for the rich and poverty-stricken populations in the corresponding classes.

In Table 2, CSOZ means Central Statistics Office of Zimbabwe, a^* denotes parameter values and ranges from [32,33], c^* denotes parameter values from [34] and d^* denotes parameter values from [35]. Due to lack of data to calibrate the model and for parameter estimation, other parameter values are assumed within realistic ranges for illustrative purpose. Note that the data reflects the population of Zimbabwe and that "Range" refers to values used in our sensitivity analysis (Section 3.1).

We now show the general dynamics of TB in the different socioeconomic settings.

Fig. 2 is a graphical representation showing the number of active TB cases as the term signifying levels of crowdedness is varied. Even in the presence of treatment, there are more active TB cases among the poor than the rich. A decrease in overcrowding levels results in a decrease of active TB cases among the poor (Fig. 2(a)). This tends to suggest improving the housing conditions for the poor people will result in a decrease of TB cases. However, even when the poor are living in the same housing conditions as the rich ($b_1 = 1$), there are more active TB cases among the poor. This suggests that a reduction in overcrowding is necessary but not sufficient to eliminate TB in poor overcrowded communities.

In Fig. 3, the possible effects of nutritional status on TB are illustrated. With increasing nutritional status for the poor people, there is a corresponding marked decrease of TB cases in approximately the first 60 months as noted for different nutritional levels in the presence of treatment. However, from 60 months onwards, TB cases are the same for people in different levels of nutritional status (the poor and the rich). This suggests that the long-term disease dynamics of TB in the presence of treatment are not highly dependent on nutritional status and accompanying immune compromisation. Results from Figs. 2 and 3 suggest that overcrowding plays a more important role in the transmission dynamics of TB than poor nutrition.

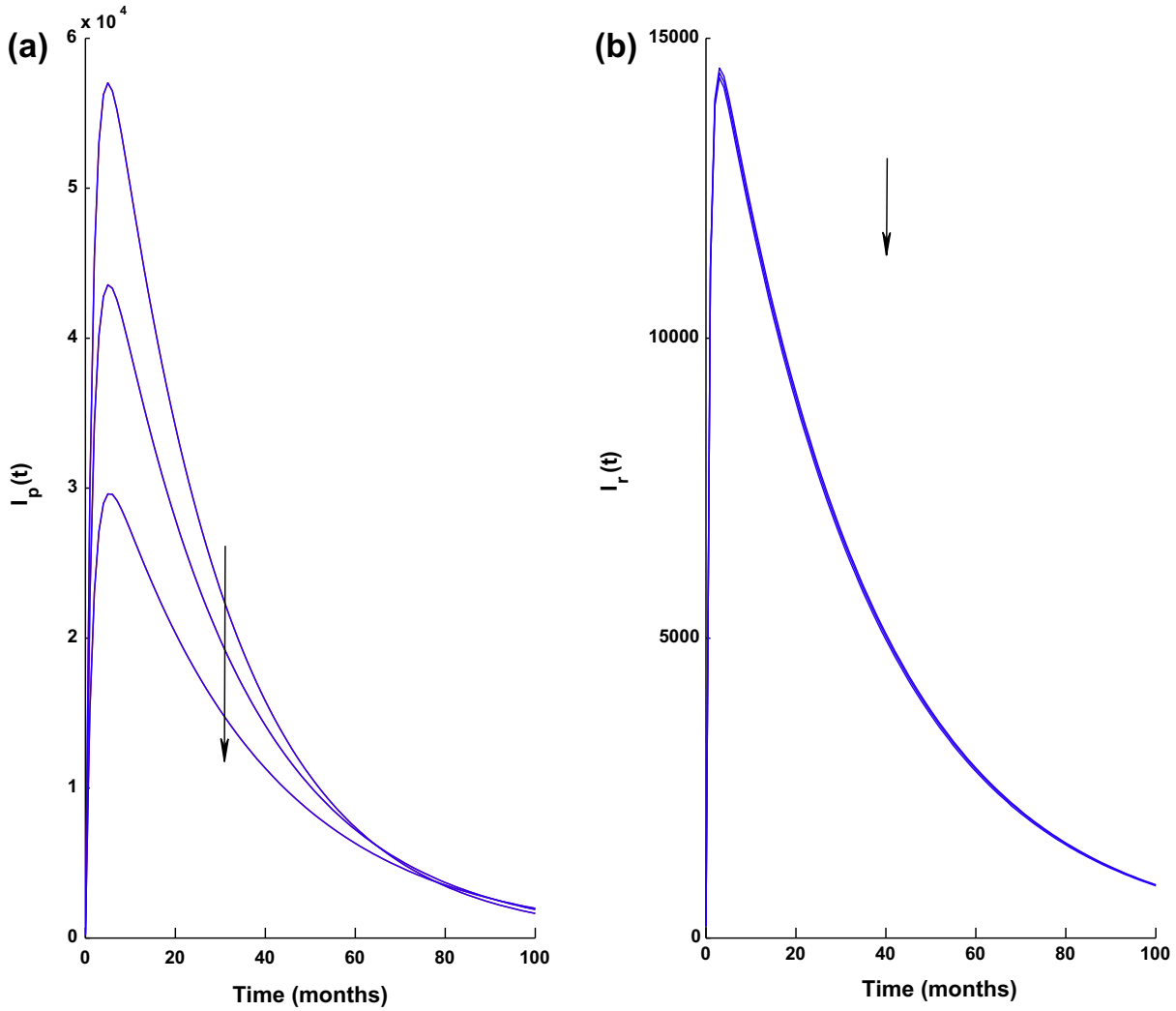

Fig. 3. Simulations of model system (4) showing effects of nutritional status and state of the immune system in the transmission dynamics of TB in heterogenous settings obtained by considering simulations of the active TB cases starting from $b_5 = 1$ with a step size of 0.5 and other parameter values as in Table 2. The direction of the arrow shows the direction of increase in the improvement of a poor individual's nutritional status.

Fig. 4 shows the effect that different levels of treatment uptake have on TB dynamics. Improvement in treatment uptake is accompanied by a reduction in active TB cases among the poor. However, it is worth mentioning that there are different reasons that account for differential levels of treatment uptake, ranging from food availability to the distance poor people have to travel access medication. Taking anti-TB drugs while hungry makes someone weak; thus, food unavailability compromises uptake of TB drugs for those who are sick. Furthermore, the further the distance poor people are from the TB treatment centre, the higher the chances of them missing and/or stopping treatment. Results from Figs. 2–4 suggest that TB treatment should not be considered solely as a biomedical problem, as effective TB elimination requires strategies that target social and economic factors as well.

Fig. 5 depicts the effects of poverty on TB transmission dynamics. It suggests that overcrowding promotes the transmission of TB more than either exogeneous reactivation or reduced treatment uptake as it results in a big increase of the reproduction number $\mathcal{R}_p$. However, comparing the effect of exogeneous reactivation and reduced TB treatment uptake suggests that exogeneous reactivation worsens TB more than reduced treatment uptake, as shown by an increase of the reproduction number $\mathcal{R}_p$ (which is closely related to disease transmission). Thus, as long as TB control is taken as a medical condition, it may be bound to failure as overcrowding and exogeneous reactivation aid TB transmission by increasing the chances of one getting infected and progressing to active TB. Consequently, improving the living standards will in turn reduce the poverty-induced reproduction number $\mathcal{R}_p$, meaning it will have a positive impact on TB control.

3.1. Sensitivity analysis

In order to investigate the effects of variations in $\mathcal{R}_{r_p}$ to its constituent parameters, we used Latin Hypercube Sampling and Partial Rank Correlation Coefficients (PRCCs) with 1000 simulations per run. Latin Hypercube Sampling is a statistical

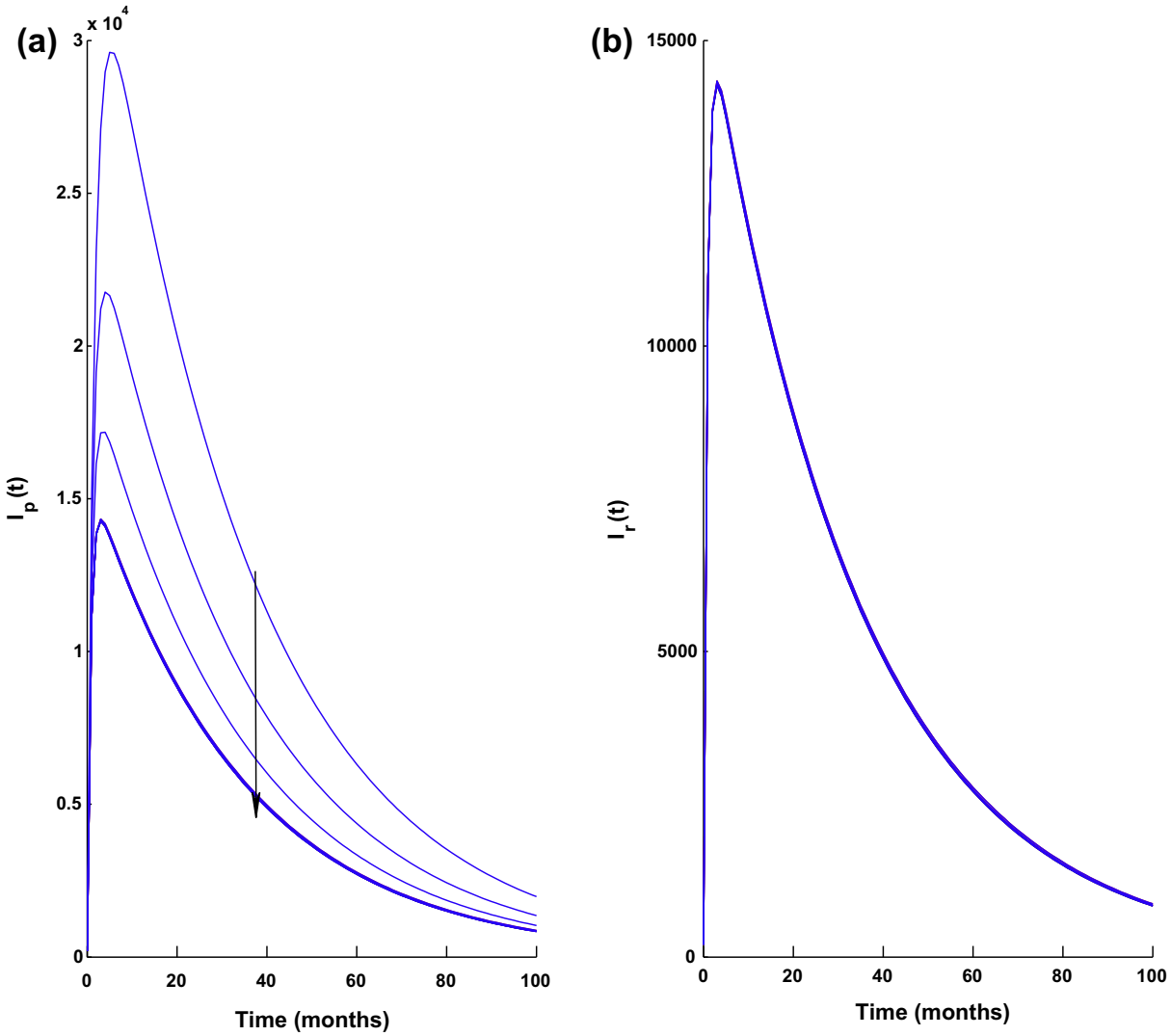

Fig. 4. Simulations of model system (4) showing effects of reduced treatment uptake in the transmission dynamics of TB in heterogenous settings obtained by considering simulations of active TB cases starting from $b_3 = 1$ with a step size of 0.25 and other parameter values as in Table 2. The direction of the arrow shows the direction of increase in the improvement of a poor individual's nutritional status.

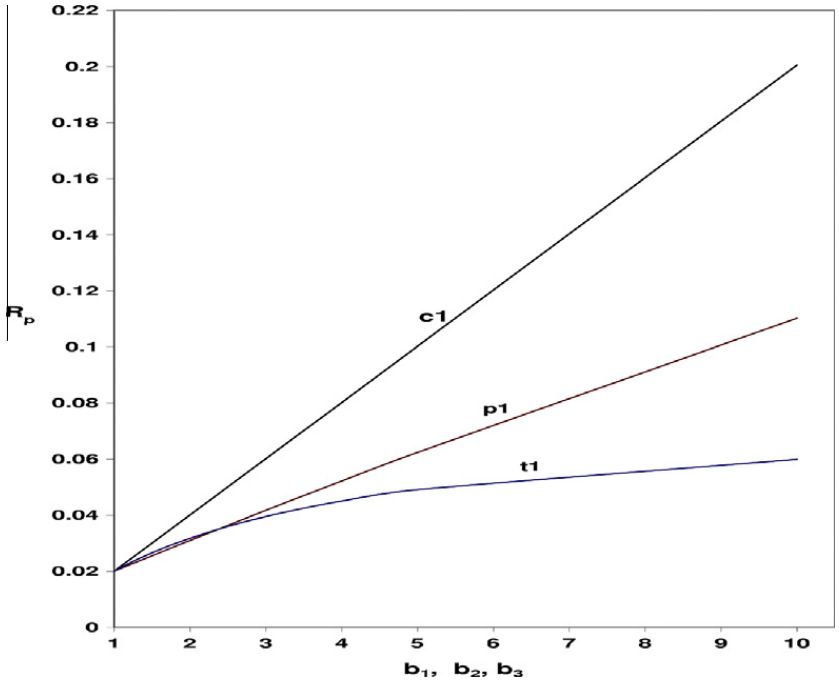

Fig. 5. Effects of overcrowding, exogeneous reactivation and reduced treatment uptake. Here $c1$, $p1$ and $t1$ denote effect of varying b_1, b_2 and b_3, respectively, noting that $c_p = b_1 c_r$, $k_p = b_2 k_r$ and $r_p = \frac{1}{b_3} r_r$. Parameter values are as in Table 2.

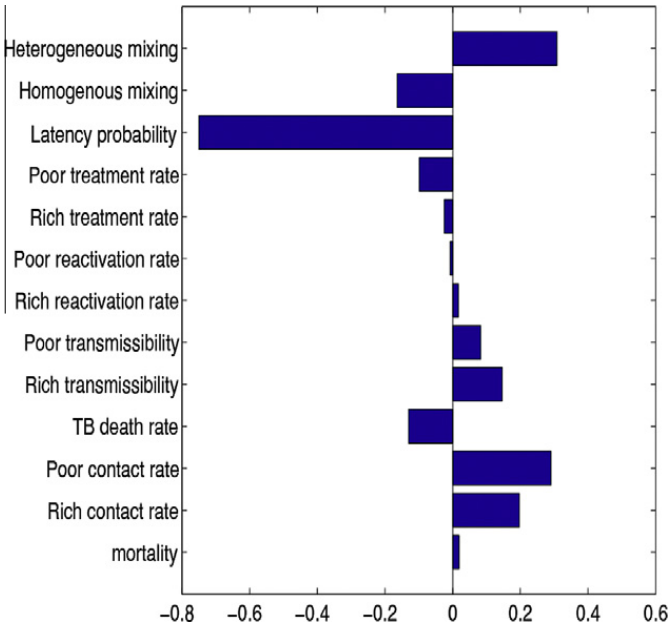

Fig. 6. Partial rank correlation coefficients showing the effect of parameter variations on $\mathcal{R}_{r_p}$ using ranges in the table. Parameters with positive PRCCs will increase $\mathcal{R}_{r_p}$ when they are increased, whereas parameters with negative PRCCs will decrease $\mathcal{R}_{r_p}$ when they are increased. Note that we assumed $b_i = 1$ for all i.

sampling method that allows for an efficient analysis of parameter variations across simultaneous uncertainty ranges in each parameter [36]. PRCCs illustrate the degree of the effect that each parameter has on the outcome.

Fig. 6 illustrates the PRCCs using $\mathcal{R}_{r_p}$ as an output variable. The parameter with the greatest effect on the outcome is the latency probability. Interestingly, heterogeneous mixing increases $\mathcal{R}_{r_p}$, whereas homogenous mixing decreases it. Furthermore, the poor contact rate has a greater effect on the outcome than the rich contact rate, suggesting that poverty has a strong effect on the disease.

Fig. 7 illustrates the effect that varying three sample parameters will have on $\mathcal{R}_{r_p}$. If the latency probability is sufficiently high, then $\mathcal{R}_{r_p} < 1$ and the disease can be controlled. However, if the latency probability is low, then $\mathcal{R}_{r_p} > 1$ and the disease will persist. If the latency probability is low, then many individuals will develop fast TB and will relapse after recovery.

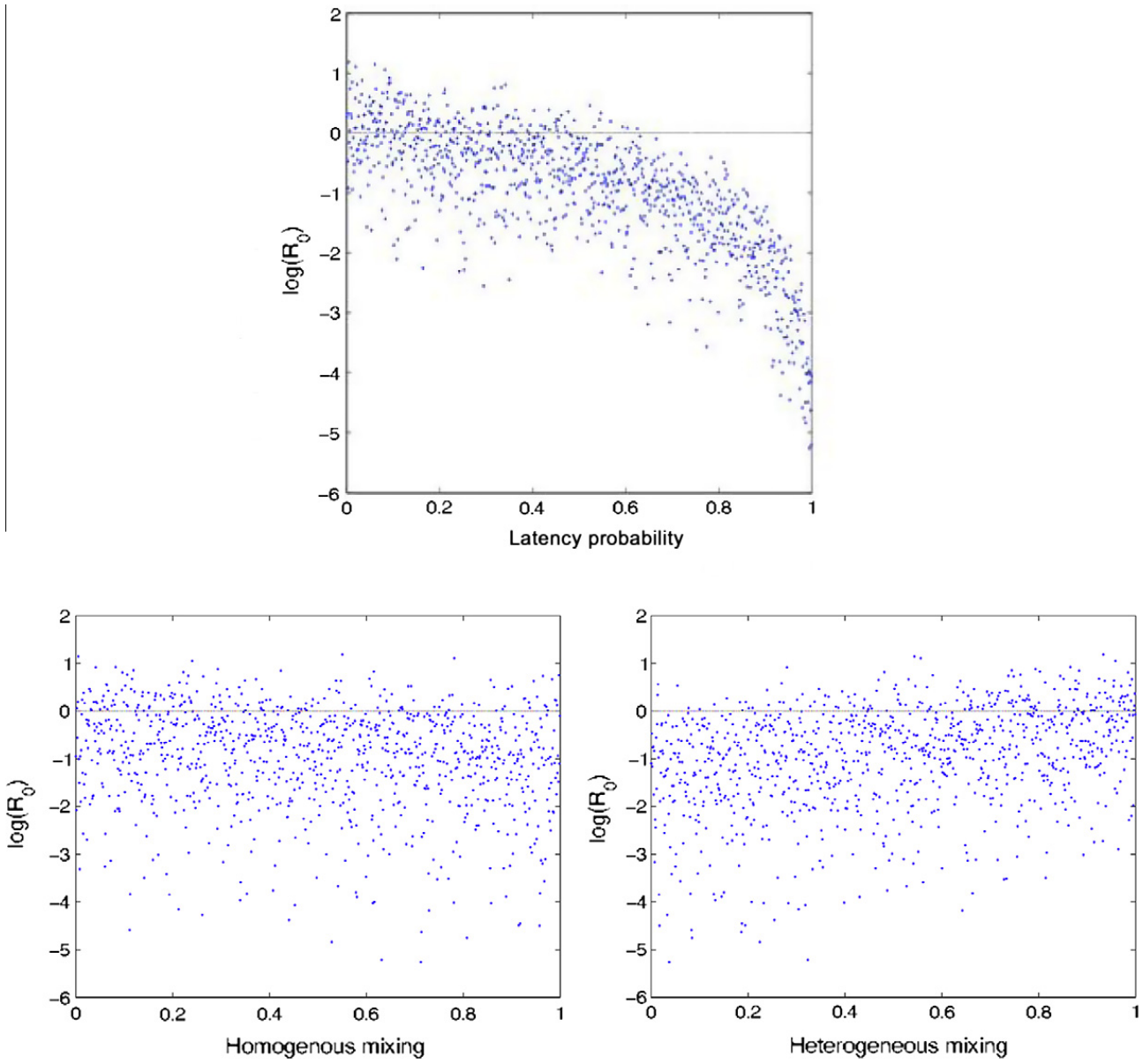

Fig. 7. Monte Carlo simulations of 1000 sample values for three illustrative parameters (latency probability, homogenous mixing and heterogeneous mixing) chosen via Latin Hypercube Sampling.

4. Discussion

Poverty is a an important driver of the TB epidemic. We computed and compared the reproduction numbers for the poverty–stricken and rich communities. Results from the analysis of reproduction numbers suggest that overcrowding, poor nutrition, reduced treatment uptake and lower socioeconomic status worsen TB; that is, TB transmission rates are higher in poor communities than in the rich ones. Even for identical parameter ranges among rich and poor contact rates, a sensitivity analysis shows that the poor contact rate has a greater effect on the outcome than the rich contact rate; in practice, the poor contact rate may be very much higher, as poverty-stricken individuals live in overcrowded conditions and may therefore come into contact with a great many other individuals. This agrees with previous studies [37] that poverty enhances TB transmission.

Interestingly, homogenous mixing (poor mixing wth poor or rich mixing with rich) has a slight beneficial effect on the epidemic. Conversely, heterogeneous mixing (poor mixing with rich) has a detrimental effect on the epidemic. This is likely because an epidemic that may be prevalent in the poor community can be made worse if it has more opportunities to enter the rich community; indeed, this is one of the higher drivers of the epidemic. We illustrate these results with caution: the take-home message here is not that mixing with poverty-stricken individuals should be avoided, but rather that the rich community can help themselves by helping those less fortunate.

Results from this theoretical study suggest that improving the living standards of poverty-stricken individuals will in turn have a positive impact on TB control, as overcrowding, poor nutrition, reduced socioeconomic status and reduced treatment uptake are shown to increase the poverty-induced reproduction number.

There are a number of limitations to our study, which should be acknowledged. We assumed that "rich" versus "poor" is a state assigned at birth, with no possibility of transfer later in life. While true to some degree in large parts of the world, this is obviously not always the case. We also assumed that the latency probability was the same for disease-naïve individuals as for disease-experienced individuals. Finally, we did not impose a threshold for a strict cutoff between rich and poor, but rather assigned these categories fluidly, in order to reflect the relative nature of wealth.

The largest driver of the epidemic is the latency probability. If this factor is itself affected by poverty (perhaps due to a mutated strain among poor communities) then it remains possible that poverty may cause a much more dangerous form of TB to evolve. This potential scenario only underscores the importance of global TB management among both the rich and the poor. Without investments from the rich community in the welfare of the poor, TB remains a scourge to all.

Acknowledgements

The authors are grateful to an anonymous referee and the handling editor for their valuable comments and suggestions. This work was made possible through the Schlumberger fellowship (Clare Hall College, University of Cambridge) received by C.P. Bhunu. Robert J. Smith? is supported by an NSERC Discovery Grant, an Early Researcher Award and funding from MITACS. For citation purposes, note that the question mark in Smith? is part of his name.

References

[1] WHO, TB: a global emergency, Lepr. Rev. 66 (1995) 270–271. WHO, July 1994.
[2] J. Grange, A. Zumla, Paradox of the global emergency of tuberculosis, Lancet 353 (1999) 996.
[3] C.J. Murray, K. Styblo, A. Rouillon, Tuberculosis in developing countries: burden, intervention and cost, Bull. Int. Union Tuberc. Lung Dis. 65 (1) (1990) 6–24.
[4] [4] N. Bhatti, M.R. Law, J.K. Morris, R. Halliday, J. Moore-Gillon, Increasing incidence of tuberculosis in England and Wales: a study of the likely causes, BMJ 310 (1995).
[5] World Bank, Operational Policy on Poverty Reduction, World Bank, Washington DC, 2004.
[6] WHO, Stop TB partnership. Stop TB: fight poverty, in: Satellite Symposium on TB and Poverty, WHO, Geneva, 2002.
[7] WHO, Addressing Poverty in TB Control: Options for National TB Control Programmes, WHO/HTM/TB/2005.352, World Health Organization, Geneva, 2005.
[8] WHO, Tuberculosis: a global emergency, World Health Forum 14 (1993) 438.
[9] T. Sheldon, Twenty countries pledge to wipe out TB, Br. Med. J. 320 (2000) 893.
[10] S. Accorsi, M. Fabiani, M. Lukwiya, M. Ravera, A. Constanzi, L. Ojom, et al, Impact of insecurity, the AIDS pandemic, and poverty on population health: disease patterns and trends in Northern Uganda, Am. J. Trop. Med. Hyg. 64 (2001) 214–221.
[11] F. Elender, G. Bentham, I. Langford, Tuberculosis mortality in England and Wales during 1982–1992: its association with poverty, ethnicity and AIDS, Soc. Sci. Med. 46 (1998) 673–681.
[12] J. Grange, A. Story, A. Zumla, Tuberculosis in disadvantaged groups, Curr. Opin. Pulm. Med. 7 (2001) 160–164.
[13] J. Watts, Targets now set by G8 countries to reduce diseases of poverty, Lancet 356 (2000) 408.
[14] J. Killewo, Poverty, TB and HIV infection: a vicious cycle, J. Health Popul. Nutr. 20 (4) (2002) 281–284.
[15] D.C. Macallan, Malnutrition in tuberculosis, Diagn. Microbiol. Infect. Dis. 34 (2) (1999) 153–157.
[16] M. Van Lettow, J.J. Kumwenda, A.D. Harries, et al, Malnutrition and the severity of lung disease in adults with pulmonary tuberculosis in Malawi, Int. J. Tuberc. Lung Dis. 8 (2) (2004) 211–217.
[17] C.B. Beggs, C.J. Noakes, P.A. Sleigh, L.A. Fletcher, K. Siddiqi, The transmission dynamics of tuberculosis in confined spaces: an analytical review of alternative epidemiology models, Int. J. Tuberc. Lung Dis. 7 (11) (2003) 1015–1026.
[18] R.G. Barr, A.V. Diez-Roux, C.A. Knirsch, A. Pablos-Mendez, Neighbourhood poverty and resurgence of tuberculosis in New York city, 1984–1992, Am. J. Public Health 91 (2001) 1487–1493.
[19] M. Baker, D. Das, K. Venugopal, P. Howden-Chapman, Tuberculosis associated with household crowding in a developed country, J. Epidemiol. Commun. Health 62 (2008) 715–721.
[20] F.M. Cantwell, T.M. McKenna, E. McCray, I.M. Onorato, Tuberculosis and race/ethnicity in the United States: impact of socio economic class, Am. J. Resp. Crit. Care Med. 157 (4) (1998) 1016–1020.
[21] D. Delfino, P.J. Simmons, Dynamics of tuberculosis and economic growth, Environ. Dev. Econ. 10 (2005) 719–743.
[22] H.R. Thieme, Mathematics in Population Biology, Princeton University Press, Princeton, 2003.
[23] G. Birkhoff, G.C. Rota, Ordinary differential equations, Ginn (1982).
[24] P. van den Driessche, J. Watmough, Reproduction numbers and sub-threshold endemic equilibria for the compartmental models of disease transmission, Math. Biosci. 180 (2002) 29–48.
[25] J. Li, D. Blakeley, R.J. Smith?, The failure of R_0, Comput. Math. Methods Med., 2011. Article ID: 527610.
[26] C.J. Noakes, C.B. Beggs, P.A. Sleigh, K.G. Kerr, Modelling the transmission of airborne infections in enclosed spaces, Epidemiol. Infect. (2006) 1–10, doi:10.1017/S0950268806005875.
[27] C.P. Bhunu, S. Mushayabasa, et al, Assessing the effects of smoking on the transmission dynamics of Tuberculosis, Bull. Math. Biol. 73 (6) (2011) 1333–1357.
[28] I. Barbalat, Systèmes d'équations différentielles d'oscillations non linéaires, Revue Roumaine de Mathématiques Pures Appliquées 4 (1959) 267–270.
[29] A. Korobeineikov, P.K. Maini, A Lyapunov functional and global properties for SIR and SEIR epidemiological models with nonlinear incidence, Math. Biosci. Eng. 1 (1) (2004) 57–60.
[30] J.P. LaSalle, The stability of dynamical systems, CBMS-NSF Regional Conference Series in Applied Mathematics, vol. 25, SIAM, Philadelphia, 1976.
[31] J. Hofbauer, J.W.H. So, Uniform persistence and repellors for maps, Proc. Am. Math. Soc. 107 (1989) 1137–1142.
[32] C. Dye, S. Schele, P. Dolin, V. Pathania, M. Raviglione, Global burden of tuberculosis estimated incidence, prevalence and mortality by country, JAMA 282 (1999) 677–686.
[33] C. Dye, B.G. William, Criteria for the control of drug resistant tuberculosis, Proc. Natl. Acad. Sci. USA 97 (2000) 8180–8185.
[34] B. Qing-Song, D. Yu-Hua, L. Ci-Yong, Treatment outcome of new pulmonary tuberculosis in Guangzhou, China 1993–2002: a register-based cohort study, BMC Public Health 7 (2007) 344.
[35] C.P. Bhunu, Z. Mukandavire, W. Garira, M. Zimba, Tuberculosis transmission model with chemoprophylaxis and treatment, Bull. Math. Biol. 70 (2008) 1163–1191.
[36] S.M. Blower, H. Dowlatabadi, Sensitivity and uncertainty analysis of complex models of disease transmission: an HIV model, as an example, Int. Stat. Rev. 2 (1994) 229–243.
[37] S. Jackson, A.C. Sleigh, G.J. Wang, X.L. Liu, Poverty and the economic effects of TB in rural China, Int. J. Tuberc. Lung Dis. 10 (10) (2006) 1104–1110.