ISSN: 2394-7772

International Journal of

Biomathematics and Systems Biology

Official Journal of Biomathematical Society of India

Volume 1, No. 2, Year 2015

Modelling the impact of treatment on tuberculosis transmission dynamics

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Received on 18 Nov 2015
Accepted on 16 Dec 2015

Abstract. *Effective tuberculosis (TB) control depends on the case findings to discover infectious cases, investigation of contacts of those with TB and appropriate treatment. However, treatment depends critically on detection, adherence and successful completion. Unfortunately, due to a number of personal, psychosocial, economic, medical and health service factors, a significant number of TB patients become irregular and default from treatment. We formulate a mathematical model of TB treatment and investigate the stability of the disease-free and endemic equilibria. We also performed numerical simulations to investigate the effects of adherence and detection. If the reproduction numbers of both the drug-sensitive and drug-resistant strains are less than one,*

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then the disease can be controlled. If the reproduction numbers for either strain are larger than unity, but close to it, then one or both strains will persist. Numerical simulations also showed that detection and adherence are the factors under our control that will have the greatest effect on reducing the disease burden. Early detection and strong adherence are critical factors in applying treatment and can overcome the effects of drug resistance.

Key words: TB, treatment, detection, adherence, defaulter, reproductive number

1 Introduction

Tuberculosis (TB) is a global health concern. It is a major cause of illness and death worldwide, especially in low- and middle-income countries, where it is fuelled by coinfection with human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), by population increases where TB is most prevalent and by increased poverty [3, 9]. TB is the most common infection for the estimated 5.5 million South Africans living with HIV/AIDS (in a national population of 48 million). The co-infection rate of HIV is estimated at 73% in all TB cases. The estimated incidence of TB in South Africa is 692 per 100,000 people [9], a rate the World Health Organization (WHO) classifies as a serious epidemic. Even though the Directly Observed Treatment Short-course (DOTS) program has been active since 1995, TB remains a major health problem in South Africa and especially in the Eastern Cape [31]. The cure rate of 65% remains well below the 85% rate recommended by the WHO [9]. At 41%, the Eastern Cape's cure rate lags even further behind the national average [29].

Adhering to a treatment schedule and successfully completing it are crucial to the control of TB [34]. Poor adherence to self-administration of treatment of a chronic disease is a common behavioral problem [24, 32] that particularly affects TB [13, 14, 15, 24, 32]. Health-seeking behaviour and non-adherence to therapy has been cited as major barrier to the control of TB [7, 8, 10, 11, 16, 17, 19, 20, 23, 26, 27, 28, 30]. Non-adherence is a complex, dynamic phenomenon with a wide range of interacting factors affecting treatment [23]. It poses a significant threat to both the individual patient and public health, and it is associated with higher transmission rates, morbidity and costs of TB control programs [9, 23]. Furthermore, it leads to persistence and resurgence of TB and is regarded as a major cause of relapse and drug resistance [9, 17]. The WHO defines a defaulter as a patient who does not complete the stipulated course of treatment [34]. Other terms used synonymously include absentees, discontinuation, non-compliance and non-adherence.

In a number of national programmes, as many as 48% of newly detected TB patients have been considered defaulters [32, 24]. As long as defaulters continue to live in their place of residence and have yet to complete the full course of TB treatment, they remain potential sources of infection, and the patients may suffer from irreversible complications such as developing multidrug-resistant TB. Reasons for defaulting may be due to a number of personal, psychosocial, economic, medical and health-service factors.

We use a deterministic model to investigate the effect of early therapy for non-symptomatic TB carriers on controlling the dynamics of TB in a community where there is non-adherence. A defaulter is defined as a patient who has not undergone TB treatment for two consecutive months and has discontinued the treatment.

2 Model Formulation

Treatment initially provides temporary immunity, which is lost slowly or quickly depending on the degree of adherence of the patient. Based on epidemiological status, the population is divided into eleven classes according to individual's disease status: susceptible (S), undetected non-symptomatic (latent) carriers with drug-sensitive TB (E), undetected non-symptomatic carriers with drug-resistant TB (E_r), detected non-symptomatic (latent) carriers with drug-sensitive TB (E_d) [T_d for those under treatment], detected non-symptomatic carriers with drug-resistant TB (E_{dr}) [T_{dr} for those under treatment], symptomatic carriers with drug-sensitive TB (I) [T_I for those under treatment] and symptomatic carriers with drug-resistant TB (I_r) [T_r for those under treatment].

For the dynamics of the drug density R (per square kilometer), we assume that the demand increases proportionally to the demand, characterised by a factor α. The removal rate of the drug supply due to consumption is d_g. The total population (N) at time t is given by $N = S+E+E_d+T_d+I+T_I+E_r+E_{dr}+T_{dr}+I_r+T_r$. For $t \neq t_k$, the model takes the form:

$$S' = \Lambda + \phi I + \sigma_d T_d + \sigma T + \sigma_{dr} T_{dr} + \sigma_r T_r - (\lambda + \lambda_r + \mu) S \tag{2.1}$$

$$E' = p\lambda S - (\gamma + k + \mu + \delta\lambda + \delta_r \lambda_r) E \tag{2.2}$$

$$E'_d = \gamma E + f_1 \mu_r T_d - \big((z_1 r_1 + k(1-z_1) r_1) f(R) + \mu\big) E_d \tag{2.3}$$

$$T'_d = z_1 r_1 f(R) E_d - (\mu + \mu_r + \sigma_d) T_d \tag{2.4}$$

$$I' = (1-p)\lambda S + (\delta\lambda + k) E + k(1-z_1) r_1 f(R) E_d + f_2 \mu_r T - \Big(z_2 r_2 f(R) + \phi + \mu + d\Big) I \tag{2.5}$$

$$T' = z_2 r_2 f(R) I - (\mu + \mu_r + \sigma) T \tag{2.6}$$

$$E'_r = q\lambda_r S + e\delta_r \lambda_r E - (\gamma_r + k_r + \mu + \delta\lambda + \delta_r \lambda_r) E_r \tag{2.7}$$

$$E'_{dr} = \gamma_r E_r + (1-f_1)\mu_r T_d + \mu_r T_{dr} - \big((z_3 r_3 + k_r(1-z_3) r_3) f(R) + \mu\big) E_{dr} \tag{2.8}$$

$$T'_{dr} = z_3 r_3 f(R) E_{dr} - (\mu + \mu_r + \sigma_{dr}) T_{dr} \tag{2.9}$$

$$I'_r = (1-q)\lambda_r S + (1-f_2)\mu_r T + (\delta\lambda + \delta_r \lambda_r + k_r) E_r + k_r(1-z_3) r_3 f(R) E_{dr} + \mu_r T_r + (1-e)\delta_r \lambda_r E - (z_4 r_4 f(R) + \mu + d_r) I_r \tag{2.10}$$

$$T'_r = z_4 r_4 f(R) I_r - (\mu + \mu_r + \sigma_r) T_r \tag{2.11}$$

$$R' = \alpha(E_d + T_d + I + T + E_r + E_{dr} + T_{dr} + I_r + T_r) - d_g R. \tag{2.12}$$

The force of infection terms are $\lambda = \frac{\beta I}{N}$ and $\lambda_r = \frac{\beta I_r}{N}$. Drug availability is described by the function $f(R) = \frac{R}{N-S-E-E_r}$ (per person portion). Natural mortality occurs in all classes at a constant rate μ. I and I_r have additional disease-mortality rates d and d_r. Note that z_i ($i = 1,2,3,4$), are constants between 0 and 1 representing the fraction of treated individuals, while f_1 and f_2 are the fraction of those who stop treatment without developing drug resistance.

For $t = t_k$, the impulsive condition is

$$\Delta R = R^i \text{ with } \Delta R = R(t_k^+) - R(t_k^-),$$

where R^i represents the medication supply at time t_k. The model is illustrated in Figure 1, and parameter definitions are given in Table 1.

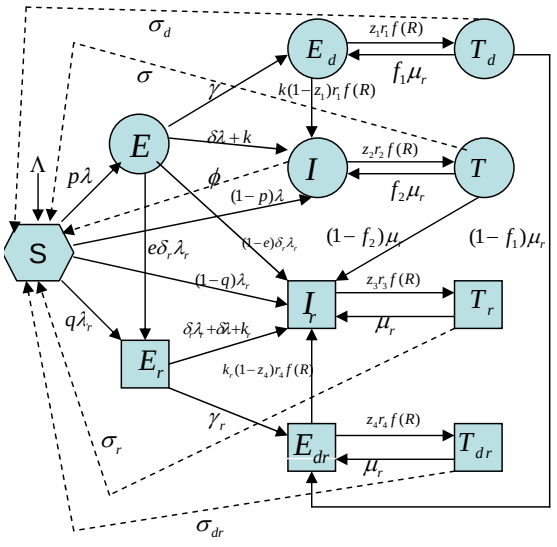

Fig. 1 The model. People are either susceptible or infected. Infected are classified depending on the appearance of symptoms, detection of disease, treatment and drug resistance.

Remark 1. Note that the model has no singularity. Indeed, if $S \to N$, then $E_d + T_d + I + T + E_{dr} + T_{dr} + I_r + T_r \to 0$. Therefore $R \to 0$. As a result, $Kf(R) \to 0$ for $K = E_d, T_d, I, T, E_{dr}, T_{dr}, I_r, T_r$.

Table 1 Parameter definitions

Variable	Definition
$S(t)$	Susceptible population at time t
$E(t)$	Undetected non-symptomatic (latent) carriers with drug-sensitive TB at time t
$E_r(t)$	Undetected non-symptomatic carriers with drug-resistant TB at time t
$E_d(t)$	Detected non-symptomatic (latent) carriers with drug-sensitive TB at time t
$E_{dr}(t)$	Detected non-symptomatic carriers with drug-resistant TB at time t
$I(t)$	Symptomatic carriers with drug-sensitive TB at time t
$I_r(t)$	Symptomatic carriers with drug-resistant TB at time t
$T_d(t)$	Treated latent detected carrier with drug-sensitive TB at time t
$T_{dr}(t)$	Treated latent detected with carrier drug-resistant TB at time t
$T(t)$	Treated symptomatic carrier with drug-sensitive TB at time t
$T_r(t)$	Treated symptomatic carrier with drug-resistant TB at time t
Λ	Recruitment rate
β_d	Transmission rate for drug-sensitive individuals
β_r	Transmission rate for drug-resistant individuals
μ	Natural mortality rate
μ_r	Rate of stopping treatment
d	Disease-induced mortality rate for drug-sensitive individuals
d_r	Disease-induced mortality rate for drug-resistant individuals
k	Natural rate of progression to active TB from latent drug-sensitive individuals
k_r	Natural rate of progression to active TB from latent drug-resistant individuals
δ	Relative susceptibility of latent drug-sensitive TB
δ_r	Relative susceptibility of latent drug-resistant TB
p	Proportion of newly infected susceptible individuals with latent TB
q	Proportion of newly infected susceptible individuals with latent drug-resistant TB
z_1	Proportion of non-symptomatic carriers who receive treatment
z_2	Proportion of active infected individuals who receive treatment
z_3	Proportion of active drug-resistant infected individuals who receive treatment
z_4	Proportion of non-symptomatic drug resistant carriers who receive treatment
f_1	Proportion of detected individuals who do not develop resistance when stopping treatment
f_2	Proportion of non-detected individuals who do not develop resistance when stopping treatment
ϕ	Natural recovery rate
r_1	Treatment rate for latent drug-sensitive individuals
r_2	Treatment rate for actively infected drug-sensitive individuals
r_3	Treatment rate for actively infected drug-resistant individuals
r_4	Treatment rate for latent drug-resistant individuals
γ	Rate of detection for individuals with latent drug-sensitive TB
γ_r	Rate of detection for individuals with latent drug-resistant TB
e	Proportion of latent drug-sensitive individuals infected by active drug-resistant TB
α	The demand for drugs
σ_d	Rate of recovery due to drug for latent drug-sensitive individuals
σ	Rate of recovery due to drug for active drug-sensitive individuals
σ_{dr}	Rate of recovery due to drug for active drug-resistant individuals
σ_r	Rate of recovery due to drug for latent drug-resistant individuals
d_g	Drug-consumption rate

We start with the following proposition.

Proposition 1. If $f_1 = f_2 = 1$, $\beta_r = 0$ and $E(0)+E_d(0)+I(0) \leq \frac{\beta\Lambda}{\mu}$, then $E(t)+E_d(t)+I(t) \leq \frac{\beta\Lambda}{\mu}$ for all $t \geq 0$.

Proof. Define $y(t) \equiv E(t)+E_d(t)+I(t)$. Then y satisfies

$$\begin{aligned} y'(t) &\leq \lambda S(t) - \mu y(t) \\ &\leq \frac{\beta\Lambda}{\mu} - \mu y(t), \end{aligned}$$

which implies that

$$y(t) \leq \frac{\beta\Lambda}{\mu} + C\exp(-\mu t).$$

Here C is a nonpositive constant, because $y(0) \leq \frac{\beta\Lambda}{\mu}$, and the result follows. □

In this section, we have proved that if the disease starts less than the quantity $\frac{\beta\Lambda}{\mu}$, then it remains so for all time.

3 The absence of treatment

In the absence of treatment, we have

$$S' = \Lambda - (\lambda + \lambda_r + \mu)S \tag{3.1}$$

$$E' = p\lambda S - (\gamma + k + \mu + \delta\lambda + \delta_r\lambda_r)E \tag{3.2}$$

$$E'_d = \gamma E - \mu E_d \tag{3.3}$$

$$I' = (1-p)\lambda S + (\delta\lambda + k)E - (\phi + \mu + d)I \tag{3.4}$$

$$E'_r = q\lambda_r S + e\delta_r\lambda_r E - (\gamma_r + k_r + \mu + \delta\lambda + \delta_r\lambda_r)E_r \tag{3.5}$$

$$E'_{dr} = \gamma_r E_r - \mu E_{dr} \tag{3.6}$$

$$I'_r = (1-q)\lambda_r S + (\delta\lambda + \delta_r\lambda_r + k_r)E_r + (1-e)\delta_r\lambda_r E - (\mu + d_r)I_r. \tag{3.7}$$

System (3.1)–(3.7) has a disease-free equilibrium (DFE) given by

$$\mathcal{E}^0 = (S^0, E^0, E^0_d, I^0, E^0_r, E^0_{dr}, I^0_r) = \left(\frac{\Lambda}{\mu}, 0, 0, 0, 0, 0, 0\right).$$

The linear stability of $\mathcal{E}^0$ is obtained using the next-generation matrix [18, 33] for system (3.1)–(3.7). Using the notation in [33], the non-negative matrix F for the new infection terms and the non-singular matrix V for the remaining transfer terms (at the disease-free equilibrium) are given by

$$F = \begin{bmatrix} F_{11} & F_{12} \\ F_{21} & F_{22} \end{bmatrix} \quad V = \begin{bmatrix} V_{11} & V_{12} \\ V_{21} & V_{22} \end{bmatrix},$$

with

$$F_{11} = \begin{bmatrix} 0 & 0 & p\beta \\ 0 & 0 & 0 \\ 0 & 0 & (1-p)\beta \end{bmatrix} \quad F_{22} = \begin{bmatrix} 0 & 0 & q\beta \\ 0 & 0 & 0 \\ 0 & 0 & (1-q)\beta \end{bmatrix},$$

$$F_{21} = F_{12} = V_{12} = V_{21} = O_{3\times 3} \quad \text{(zero matrix)}.$$

$$V_{11} = \begin{bmatrix} K_1 & 0 & 0 \\ -\gamma & \mu & 0 \\ -k & 0 & K_3 \end{bmatrix} \quad V_{22} = \begin{bmatrix} K_2 & 0 & 0 \\ -\gamma_r & \mu & 0 \\ -k_r & 0 & K_4 \end{bmatrix},$$

where $K_1 = k+\gamma+\mu$, $K_2 = k_r+\gamma_r+\mu$, $K_3 = \mu+d$, $K_4 = \mu+d_r$.

It follows that the stability of system (3.1)–(3.7) is determined by

$$\begin{aligned} R_A &= \rho(FV^{-1}) \\ &= \max\left\{\rho(F_{11}V_{11}^{-1}), \rho(F_{22}V_{22}^{-1})\right\} \\ &= \max\left\{R_d, R_r\right\}, \end{aligned}$$

where

$$R_d = \frac{p\beta k}{K_1 K_3} + \frac{(1-p)\beta}{K_3} \tag{3.8}$$

$$R_r = \frac{q\beta k_r}{K_2 K_4} + \frac{(1-q)\beta}{K_4} \tag{3.9}$$

are the reproduction numbers for the drug-sensitive and the drug-resistance strains respectively. Note that the reproduction numbers given here are threshold quantities and not necessarily the average number of secondary infections [21]. The p and q terms in (3.8) and (3.9) represent the new cases resulting from slow progression while $1-p$ and $1-q$ represent those resulting from fast progression.

Using Theorem 2 in [33], the following result is established.

Lemma 1. The disease-free equilibrium $\mathcal{E}^0$ of system (3.1)–(3.7) is locally asymptotically stable (LAS) if $R_A < 1$ and unstable if $R_A > 1$.

Remark 2. Note that $\frac{\partial R_d}{\partial \gamma} < 0$ and $\frac{\partial R_r}{\partial \gamma_r} < 0$, which means that R_A is decreasing in γ and γ_r. See Figure 2. As a result, the greater the detection, the more we can control the disease.

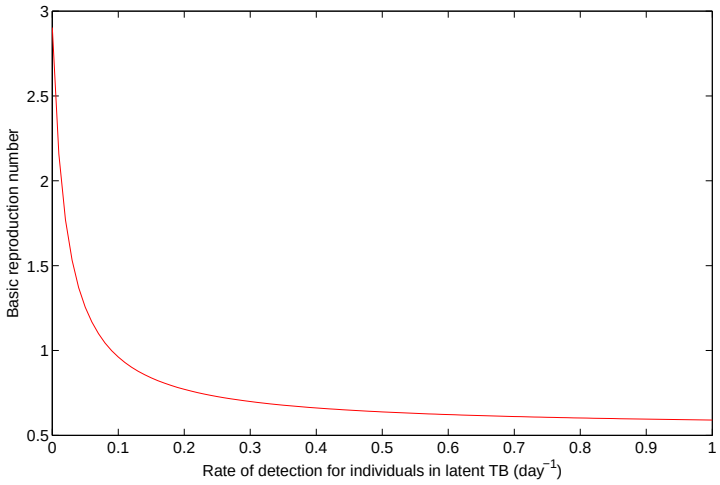

Fig. 2 The basic reproduction R_d as a function of the detection rate γ.

If parameters for drug-sensitive and drug-resistant individuals are identical (i.e., $q = p$, $\gamma_r = \gamma$, $r_2 = r_3$, $k_r = k$, and $d_r = d$), then $R_A = R_d$. Note that if $p \to 1$, then $R_d = \frac{\beta k}{(\gamma+k+\mu)(\mu+d)}$, which agrees with the result given in [12].

In this section, we have found the basic reproduction number, and we have proved that the DFE is locally stable when its value is less than unity and unstable otherwise.

4 Limiting cases

Depending on the detection rate we have the following two cases:

1. Low detection of latent TB:
   Suppose $\gamma, \gamma_r \to 0$. Then $R_A \to R_{A0}$, where
   $$R_{A0} = \max\left\{R_{d0}, R_{r0}\right\},$$
   with
   $$R_{d0} = \frac{p\beta k}{(k+\mu)K_3} + \frac{(1-p)\beta}{K_3}$$
   $$R_{r0} = \frac{q\beta k_r}{(k_r+\mu)K_4} + \frac{(1-q)\beta}{K_4}.$$
2. High detection of latent TB:
   Suppose $\gamma, \gamma_r \to \infty$. Then $R_A \to R_{A\infty}$, where
   $$R_{A\infty} = \max\left\{R_{d\infty}, R_{r\infty}\right\},$$
   with
   $$R_{d\infty} = \frac{(1-p)\beta}{K_3}$$
   $$R_{r\infty} = \frac{(1-q)\beta}{K_4}.$$

These are the reproduction numbers for sensitive or resistant strains at a demographic steady state resulting from fast progression.

Remark 3. Note that
$$R_{d0} - R_d = \frac{p\beta k}{K_3}\frac{\gamma}{(k+\mu)(k+\mu+\gamma)},$$
with a maximum difference of $\frac{p\beta k}{(k+\mu)K_3}$ when $\gamma \to \infty$. Also
$$R_{r0} - R_r = \frac{q\beta k_r}{K_4}\frac{\gamma_r}{(k_r+\mu)(k_r+\mu+\gamma_r)},$$
with a maximum difference of $\frac{q\beta k_r}{(k_r+\mu)K_4}$ when $\gamma_r \to \infty$.

In this section, we have found some limiting values for the basic reproduction number depending on the detection rates, and we found the maximum reduction value in both R_d and R_r due to detection rates.

5 Drug-sensitive submodel

The following change of variables is required. Let $x_1 = S$, $x_2 = E$, $x_3 = E_d$ and $x_4 = I$. Then $N_d = x_1 + x_2 + x_3 + x_4$. Using vector notation $\mathbf{x_d} = (x_1, x_2, x_3, x_4)^T$, the drug-sensitive submodel of the system (2.1)–(2.11) (assuming no treatment and neglecting natural recovery (i.e., $\phi = 0$)) can be written in the form $\frac{d\mathbf{x}_d}{dt} = F_d(\mathbf{x_d})$, with $F_d = (f_1, f_2, f_3, f_4)^T$. That is,

$$x_1' = f_1 = \Lambda - (\lambda+\mu)x_1 \tag{5.1}$$
$$x_2' = f_2 = p\lambda x_1 - (\gamma+k+\mu+\delta\lambda)x_2 \tag{5.2}$$
$$x_3' = f_3 = \gamma x_2 + f_1\mu_r x_4 - \mu x_3 \tag{5.3}$$
$$x_4' = f_4 = (1-p)\lambda x_1 + (\delta\lambda+k)x_2 - (\mu+d)x_4, \tag{5.4}$$

with $\lambda = \frac{\beta x_4}{x_1+x_2+x_3+x_4}$.

5.1 Stability for the drug-sensitive submodel

Note that the basic reproductive number of model system (5.1)–(5.4) is $R_d = \rho(F_{11}V_{11}^{-1})$, which proves the following.

Lemma 2. The disease-free equilibrium $\mathcal{E}_d^0 = (\frac{\Lambda}{\mu}, 0, 0, 0)$ of system (5.1)–(5.4) is LAS if $R_d < 1$ and unstable if $R_d > 1$.

The equilibrium values of (DS1)–(DS4) satisfy

$$x_1^* = \frac{\Lambda}{\mu + \lambda^*} \tag{5.5}$$

$$x_2^* = \frac{p\lambda^*\Lambda}{(\lambda^* + \mu)(\gamma + k + \mu + \delta\lambda^*)} \tag{5.6}$$

$$x_3^* = \frac{\gamma p\lambda^*\Lambda}{(\lambda^* + \mu)(\gamma + k + \mu + \delta\lambda^*)} \tag{5.7}$$

$$x_4^* = \frac{(1-p)\lambda^*\Lambda(\gamma + k + \mu + \delta\lambda^*) + p\lambda^*\Lambda(\delta\lambda^* + k)}{(\mu + d)(\lambda^* + \mu)(\gamma + k + \mu + \delta\lambda^*)} \tag{5.8}$$

with

$$\lambda^* = \frac{\beta x_4^*}{N_d^*}.$$

Solving (5.8) and (5.1) for λ^*, we have

$$\lambda^* g(\lambda^*) = 0,$$

where

$$g(\lambda^*) = \delta N_d^*(\mu + d)(\lambda^*)^2 + \Big((\delta(\mu+1) + \mu + k)N_d^*(\mu + d) - p\delta\beta\Lambda\Big)\lambda^* + \mu(\delta + k + \mu)N_d^*(\mu + d) - \beta\Lambda\big((1-p)(\gamma + k + \mu) + pk\big).$$

Note the following:

- g is continuous.
- $\lim_{\lambda^* \to \infty} g(\lambda^*) = \infty$.
- $g(0) < 0$ iff $R_d > \frac{\mu N_d^*}{\Lambda}$.

From the Intermediate Value Theorem, there exists $\lambda_e^* > 0$ such that $g(\lambda_e^*) = 0$, which means that the endemic equilibrium (EE) for the drug-sensitive model $\mathcal{E}_d^*$ exists. Moreover, since $\frac{\mu N_d^*}{\Lambda} \leq 1$, then the EE $\mathcal{E}_d^*$ may exist even for $R_d < 1$.

One can get an explicit formula for $\lambda^* > 0$, by solving $g(\lambda^*) = 0$ with $N_x^* = x_1^* + x_2^* + x_3^* + x_4^*$ and $x_1^*, x_2^*, x_3^*, x_4^*$ as in (5.5)–(5.8). We have

$$\lambda_e^* = \frac{-b \pm \sqrt{b^2 - 4ac}}{4a},$$

with

$$\begin{aligned} a &= \delta \\ b &= (\mu + d)(\delta + p + \gamma p) + (1-p)(\gamma + \mu) + k - \delta \\ c &= (\gamma + k + \mu)\big(\mu + d - (1-p)\big) - pk \end{aligned}$$

for the DFE.

We now study the stability of the EE, $\mathcal{E}_d^*$. We utilize Theorem 4 in [6]. The method entails evaluating the Jacobian of system (5.1)–(5.4) at the DFE, $\mathcal{E}_d^0$. This gives

$$J(\mathcal{E}_d^0) = \begin{bmatrix} -\mu & 0 & 0 & -\beta \\ 0 & -K_1 & 0 & p\beta \\ 0 & \gamma & -\mu & 0 \\ 0 & k & 0 & (1-p)\beta - (\mu + d) \end{bmatrix}.$$

For $R_d = 1$, solving for $\beta (= \beta_d^*)$, we have $\beta_d^* = \frac{K_1 K_3}{(1-p)K_1 + pk}$. Thus the linearized system of the transformed equation (5.1)–(5.4) with $\beta = \beta_d^*$ chosen as the bifurcation parameter has a simple zero eigenvalue. Hence it can be shown that the Jacobian of (5.1)–(5.4) at $\beta = \beta_d^*$ has right eigenvector (associated with the zero eigenvalue) given by $\mathbf{u} = (u_1, u_2, u_3, u_4)^T$, where

$$
\begin{aligned}
u_1 &= \frac{-\beta_d^*}{\mu} u_4 \\
u_2 &= \frac{p\beta_d^*}{K_1} u_4 \\
u_3 &= \frac{\gamma p \beta_d^*}{\mu K_1} u_4 \\
u_4 &= u_4 > 0.
\end{aligned}
$$

The Jacobian $J(\mathcal{E}_d^0)$ has a left eigenvector (associated with the zero eigenvalue) given by $\mathbf{u} = (v_1, v_2, v_3, v_4)^T$, where

$$
\begin{aligned}
v_1 &= 0 \\
v_2 &= \frac{k}{K_1} v_4 \\
v_3 &= 0 \\
v_4 &= v_4 > 0.
\end{aligned}
$$

$$
a = -v_2 \left[2\left(\frac{p\beta\mu}{\Lambda} + \frac{\delta\beta\mu}{\Lambda} \right) u_2 u_4 + 2\frac{p\beta\mu}{\Lambda} u_3 u_4 + 2\frac{p\beta\mu}{\Lambda} u_4^2 \right] - v_4 \left[2\left(\frac{(1-p)\beta\mu}{\Lambda} + \frac{\delta\beta\mu}{\Lambda} \right) u_2 u_4 + 2\frac{(1-p)\beta\mu}{\Lambda} u_3 u_4 + 2\frac{(1-p)\beta\mu}{\Lambda} u_4^2 \right] \tag{5.9}
$$

$$
b = pv_2 u_4 + (1-p) v_4 u_4. \tag{5.10}
$$

Note that $a < 0$ (equation (5.9)).

Lemma 3. If $R_d > 1$ but close to one, then the endemic equilibrium $\mathcal{E}_d^*$ of the system (5.1)–(5.4) is locally asymptotically stable.

Proof. We utilize Theorem 4 in [6]. It is clear that $b > 0$ and $a < 0$ (equation (5.9) and equation (5.10) respectively). This implies (iv) in Theorem 4 [6] is applicable. This means that when β changes from $\beta < \beta_d^*$ to $\beta > \beta_d^*$, $\mathcal{E}_d^0$ changes from stable to unstable and $\mathcal{E}_d^*$ (changes from negative to positive) is locally asymptotically stable.

□

In this section, we have found the EE for the drug-sensitive submodel and determined the stability for both the DFE and the EE, depending on the basic reproduction number.

6 Drug-resistance submodel

This model has reproduction number R_r. The following change of variables are required. Let $y_1 = S$, $y_2 = E$, $y_3 = E_d$ and $y_4 = I$ so that $N_r = y_1 + y_2 + y_3 + y_4$. Using vector notation $\mathbf{y_r} = (y_1, y_2, y_3, y_4)^T$, the drug-resistance submodel of the system (2.1)–(2.11) can be written in the form $\frac{d\mathbf{y}_r}{dt} = G(\mathbf{y_r})$, with $G = (g_1, g_2, g_3, g_4)^T$. That is,

$$
y_1' = g_1 = \Lambda - (\lambda_r + \mu) y_1 \tag{6.1}
$$

$$
y_2' = g_2 = q\lambda_r y_1 - (\gamma_r + k_r + \mu + \delta_r \lambda_r) y_2 \tag{6.2}
$$

$$
y_3' = g_3 = \gamma_r y_2 - \mu y_3 \tag{6.3}
$$

$$
y_4' = g_4 = (1-q)\lambda_r y_1 + (\delta_r \lambda_r + k_r) y_2 - (\mu + d_r) y_4, \tag{6.4}
$$

with $\lambda = \frac{\beta y_4}{y_1 + y_2 + y_3 + y_4}$.

6.1 Stability of the drug-resistance submodel

The reproductive number of model system (6.1)–(6.4) is $R_r = \rho(F_{22} V_{22}^{-1})$, which proves the following.

Lemma 4. The disease-free equilibrium $\mathcal{E}_0^r = \left(\frac{\Lambda}{\mu}, 0, 0, 0 \right)$ of system (6.1)–(6.4) is LAS if $R_r < 1$ and unstable if $R_r > 1$.

Similar to Subsection 5.1, $\mathcal{E}_r^*$ exists iff $R_r > \frac{\mu N_r^*}{\Lambda}$. The method entails evaluating the Jacobian of the system (6.1)–(6.4) at $\mathcal{E}_r^0$. This gives

$$J(\mathcal{E}_r^0) = \begin{bmatrix} -\mu & 0 & 0 & -\beta \\ 0 & -K_2 & 0 & q\beta \\ 0 & \gamma_r & -\mu & 0 \\ 0 & k_r & 0 & (1-q)\beta - (\mu + d_r) \end{bmatrix}.$$

For $R_r = 1$, solving for $\beta = \beta_r^*$, we have $\beta_r^* = \frac{K_2 K_4}{((1-q)K_2 + qk_r)}$. Thus the linearized system of the transformed equation (6.1)–(6.4) with $\beta = \beta_r^*$ chosen as the bifurcation parameter has a simple zero eigenvalue. Hence it can be shown that the Jacobian of (6.1)–(6.4) at $\beta = \beta_r^*$ has right and left eigenvectors (associated with the zero eigenvalue) given by $\mathbf{v} = (v_1, v_2, v_3, v_4)^T$, where

$$\begin{aligned} v_1 &= 0 \\ v_2 &= \tfrac{k_r}{K_2} v_4 \\ v_3 &= 0 \\ v_4 &= v_4 > 0, \end{aligned}$$

with

$$a = -v_2 \left[2\left(\frac{q\beta\mu}{\Lambda} + \frac{\delta_r \beta\mu}{\Lambda} \right) u_2 u_4 + 2\frac{q\beta\mu}{\Lambda} u_3 u_4 + 2\frac{q\beta\mu}{\Lambda} u_4^2 \right] - v_4 \left[2\left(\frac{(1-q)\beta\mu}{\Lambda} + \frac{\delta_r \beta\mu}{\Lambda} \right) u_2 u_4 + 2\frac{(1-q)\beta\mu}{\Lambda} u_3 u_4 + 2\frac{(1-q)\beta\mu}{\Lambda} u_4^2 \right] \tag{6.5}$$

$$b = q v_2 w_4 + (1-q) v_4 w_4. \tag{6.6}$$

Note that $a < 0$ (equation (6.5).

Lemma 5. If $R_r > 1$ but close to one, then the endemic equilibrium $\mathcal{E}_r^*$ of the system (6.1)–(6.4) is locally asymptotically stable.

Proof. We utilize Theorem 4 in [6]. It is clear that $b > 0$ and $a < 0$ (equations (6.5) and (6.6)). This implies that (iv) in Theorem 4 [6] is applicable. This means that when β changes from $\beta < \beta_r^*$ to $\beta > \beta_r^*$, $\mathcal{E}_r^0$ changes from stable to unstable and $\mathcal{E}_r^*$ changes from negative to positive and LAS.

□

In this section, we have found the EE for the drug-resistance submodel and determined the stability for both the DFE and the EE, depending on the basic reproduction number.

Summary

For the stability of the full model, we have the following cases (see Figure 3)

1. If $R_d < 1$ and $R_r < 1$, then $R_A < 1$ and $\mathcal{E}_0$ is LAS.
2. If $R_d > 1$ but close to one and $R_r < 1$, then $R_A > 1$ and the drug-sensitive strain persists.
3. If $R_d < 1$ and $R_r > 1$ but close to one, then $R_A > 1$ and the drug-resistance strain persists.
4. If $R_d > 1$ and $R_r > 1$ but both are close to one, then $R_A > 1$ and both the drug-sensitive and the drug-resistance strains persist.
5. If $R_i > \frac{\mu N_i^*}{\Lambda}$ for $i = d, r$, then both $\mathcal{E}_d^*$ and $\mathcal{E}_r^*$ exist.

7 Analysis of the full model

Assume that $z_1 = z_4 = 1$ (all latently detected individuals are receiving treatment). The DFE is

$$\mathcal{E}^0 = (S^0, E^0, E_d^0, T_d^0, I^0, T_0, E_r^0, E_{dr}^0, T_{dr}^0, I_r^0, T_r^0) = \left(\frac{\Lambda}{\mu}, 0,0,0,0,0,0,0,0,0,0 \right)$$

and the components of the next-generation matrix are

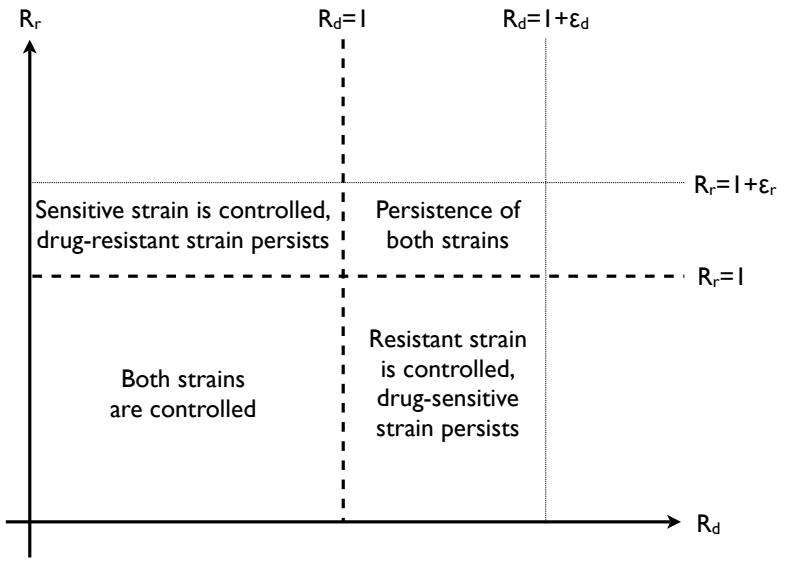

Fig. 3 The possible regions in which EE equilibrium stability changes. Note that $\varepsilon_d, \varepsilon_r > 0$ but may not be large.

$$F_{11} = \begin{bmatrix} 0 & 0 & 0 & p\beta & 0 \\ 0 & 0 & f_1\mu_r & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & (1-p)\beta & f_2\mu_r \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix} \quad F_{21} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & (1-f_1)\mu_r & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & (1-f_2)\mu_r \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

$$F_{12} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix} \quad F_{22} = \begin{bmatrix} 0 & 0 & 0 & q\beta & 0 \\ 0 & 0 & \mu_r & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & (1-q)\beta & \mu_r \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

$$V_{11} = \begin{bmatrix} L_1 & 0 & 0 & 0 & 0 \\ -\gamma & L_2 & 0 & 0 & 0 \\ 0 & -z_2 r_2 & L_3 & 0 & 0 \\ -k & 0 & 0 & L_4 & 0 \\ 0 & 0 & 0 & -r_1 & L_5 \end{bmatrix} \quad V_{12} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

$$V_{21} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix} \quad V_{22} = \begin{bmatrix} L_6 & 0 & 0 & 0 & 0 \\ -\gamma_r & L_7 & 0 & 0 & 0 \\ 0 & -z_3 r_3 & L_8 & 0 & 0 \\ -k_r & 0 & 0 & L_9 & 0 \\ 0 & 0 & 0 & -r_4 & L_{10} \end{bmatrix}$$

$$\begin{aligned} R_T &= \rho(FV^{-1}) \\ &= \max\left\{R_{dt}, R_{rt}\right\}, \end{aligned}$$

where

$$R_{dt} = \max\left\{R_{d1}, R_{d2}\right\}$$
$$R_{rt} = \max\left\{R_{r1}, R_{r2}\right\}.$$

Here

$$R_{d1} = \frac{r_1\alpha f_1\mu_r}{d_g L_2 L_3} \qquad R_{d2} = \frac{1}{2}\left[R_D + \sqrt{R_D^2 + \frac{4f_2\mu_r}{L_4}\left(\frac{kp\beta}{L_1L_4} + \frac{(1-p)\beta z_2 r_2}{L_4 L_5}\right)}\right]$$
$$R_{r1} = \frac{r_4\mu_r}{L_7 L_8} \qquad R_{r2} = \frac{1}{2}\left[R_R + \sqrt{R_R^2 + \frac{4\mu_r}{L_9}\left(\frac{k_r q\beta}{L_6L_9} + \frac{(1-q)\beta z_3 r_3}{L_9 L_{10}}\right)}\right]$$
$$R_D = \frac{kp\beta}{L_1L_4} + \frac{(1-p)\beta}{L_4} \qquad R_R = \frac{k_r q\beta}{L_6L_9} + \frac{(1-q)\beta}{L_9}$$

and

$$L_1 = k+\gamma+\mu \quad (=K_1)$$
$$L_2 = r_1+\mu$$
$$L_3 = \mu+\mu_r+\sigma_d$$
$$L_4 = \phi+\mu+d+z_2r_2 \quad (=K_3+z_2r_2)$$
$$L_5 = \mu+\mu_r+\sigma$$
$$L_6 = \gamma_r+k_r+\mu \quad (=K_2)$$
$$L_7 = \mu$$
$$L_8 = \mu+\mu_r+\sigma_{dr}$$
$$L_9 = \mu+d+z_3r_3 \quad (=K_4+z_3r_3)$$
$$L_{10} = \mu+\mu_r+\sigma_r.$$

Note that $H(K) = f(R)K$ (for $K = E_d, E_{dr}, I, I_r$) is differentiated using the product and chain rules, with $R = R(K)$. Then L'Hôpital's rule is used to evaluate the derivative at $\mathcal{E}^0$. We thus have the following.

Lemma 6. The disease-free equilibrium $\mathcal{E}^0$ of system (2.1)–(2.11), with f constant and $z_1 = z_4 = 1$, is LAS if $R_T < 1$ and unstable if $R_T > 1$.

Here R_T is the reproduction number when both detection and treatment programs are in place.

8 Numerical simulations

The data used for the simulations are given in Table 2, in addition to the initial condition $(S, E_d, T_d, I, T, E_r, E_{dr}, T_{dr}, I_r, T_r, R) = (24000, 0, 0, 0, 1000, 0, 0, 0, 0, 0, 0, 0, 0)$. We start by investigating the sensitivity analysis of R_d (the basic reproduction number for the drug-sensitive-without-treatment submodel) to parameters.

8.1 Sensitivity analysis

Due to the degree of uncertainty in the parameter values, we investigated the dependence of R_d on parameter variation for the drug-sensitive model. We use Latin Hypercube sampling and partial rank correlation coefficients (PRCCs) to identify which parameters R_d is most sensitive to [4]. Latin Hypercube Sampling is a statistical sampling method that evaluates the sensitivity of an outcome variable to all input variables. PRCCs measure the relative degree of sensitivity to each parameter, regardless of whether the parameter has a positive or negative influence on the outcome variable. Figure 4 plots PRCCs for each input parameter. This demonstrates that R_d is most sensitive to variations in transmissibility (β), the proportion of individuals newly infected with latent TB (p) and the disease mortality rate (d).

Thus the disease is reliably controlled only for sufficiently small transmissibility and a high proportion of individuals newly infected with latent TB. It should be noted that variations in β and p will change R_d from values greater than one to small values, resulting in significant dependence of R_d on these parameters. See Figure 5.

Table 2 Parameter ranges

Variable	Sample value	Unit	Range considered	Reference
Λ	400	individual $\times$ yr^{-1}	300–500	Assumed
μ	0.0167	yr^{-1}	0.009–0.02	[25]
μ_r	variable	yr^{-1}	–	Assumed
d	0.15	yr^{-1}	0.1–0.2	[5]
d_r	0.2	yr^{-1}	0.02–0.2	Assumed
β_d	1.8	yr^{-1}	0.1–1.8	Estimated
β_r	1.6	yr^{-1}	0.1–1.5	Assumed
k	0.005	yr^{-1}	0.004–0.006	[1]
k_r	0.01	yr^{-1}	0.004–0.007	Assumed
δ	0.7		0.5–0.9	[1]
δ_r	0.7		0.5–0.9	[1]
p	0.95		0.65–0.95	[1]
q	0.95		0.65–0.95	[1]
z_1	$0.7z_2$		0–0.5	Assumed
z_2	variable		0–0.75	Assumed
z_3	$0.7z_2$		0–0.5	Assumed
z_4	z_2		0–0.98	Assumed
f_1	0.9		0.1–0.9	Assumed
f_2	0.7		0.1–0.9	Assumed
ϕ	0.09	yr^{-1}		[22]
r_1	$(1/7) \times 365$	yr^{-1}	0.5–0.8	Assumed
r_2	$(1/2)r_1$	yr^{-1}	0.4–0.7	Assumed
r_3	$(1/3)r_1$	yr^{-1}	0.1–0.3	Assumed
r_4	$(1/2)r_1$	yr^{-1}		Assumed
γ	0.2	–	0.1–0.5	Assumed
γ_r	0.9	–	0.1–0.95	Assumed
e	0.7		0.65–0.95	Assumed
α	0.5475	yr^{-1}		Assumed
σ_d	2	yr^{-1}		Assumed
σ	2	yr^{-1}		Assumed
σ_{dr}	$0.25 \times \sigma_d$	yr^{-1}		Assumed
σ_r	$0.1 \times \sigma_d$	yr^{-1}		Assumed
d_g	2.6927	yr^{-1}		Assumed
R^i	1/12	yr^{-1}		Assumed

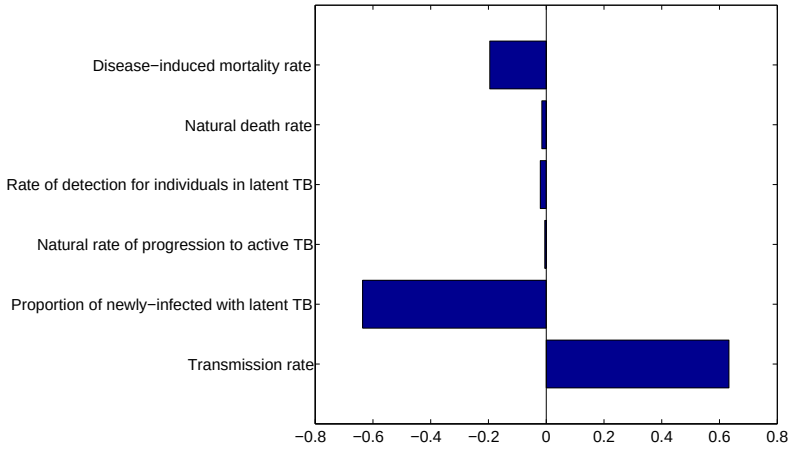

Fig. 4 Partial rank correlation coefficients indicate that the proportion of individuals newly infected with latent TB has the greatest effect on R_0 followed by the transmission rate. Parameters with PRCCs > 0 will increase R_d when they are increased, while parameters with PRCCs < 0 will decrease R_d when they are increased.

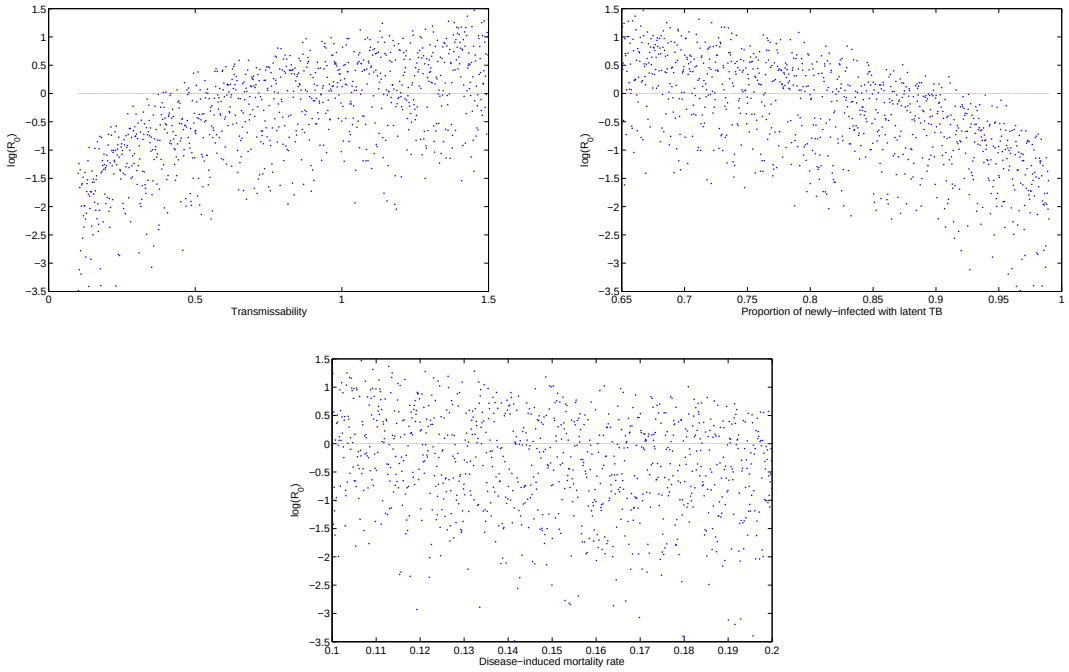

Fig. 5 Monte Carlo simulations for 1000 runs drawn from parameter ranges using Latin Hypercube Sampling for the three parameters with the greatest effect on R_d as indicated in Figure 4. If p is close to one or β small, then the disease can be controlled.

8.2 The impact of adherence

We considered adherence as a way of controlling the disease. We used μ_r as a proxy for adherence: high rates of μ_r are associated with low adherence, while low values are associated with high adherence.

We examined the effect of adherence by comparing the infected classes in the model (2.1)–(2.11) for different adherence rates ($\mu_r = 12, 6, 0$) after 10 years. From Figure 6, it is clear that high adherence rates reduce the percentage of infected in all classes. We added the time-series solution on the left of Figure 7 (from top to bottom, $\mu_r = 12, 6, 0$) to support our conclusion. On the right of Figure 7, we have the drug density, from which we see that non-adherence implies more consumption of drugs.

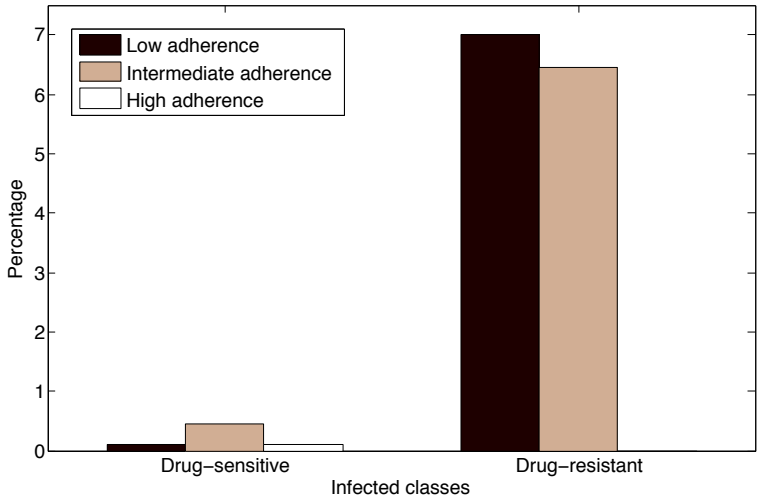

Fig. 6 Comparison between percentage of infected in different classes (after 10 years), different adherence rates are adopted ($\mu_r = 12, 6, 0$, representing stopping medication after a very short time, after an intermediate time and 100% adherence respectively). Here $(\gamma, \gamma_r) = (0.2, 0.9)$.

8.3 The impact of detection

We considered testing as another method of controlling the disease. We examined the effect of detection by comparing the infected classes in model (2.1)–(2.11) for different detection rates $(\gamma, \gamma_r) = (0.1, 0.1), (0.5, 0.5), (1, 1)$ after 10 years. Here $\mu_r = 2$. The result is given in Figure 8, in which it is clear that high detection rates reduce the percentage of infection in all classes. We added the time-series solution Figure 9 (top right, top left and bottom correspond to $(\gamma, \gamma_r) = (0.1, 0.1), (0.5, 0.5), (1, 1)$ respectively) to support our conclusion.

9 Discussion

We used a mathematical model to explore the population-level impact of treatment on TB transmission dynamics. The disease-free equilibrium is shown to be locally asymptotically stable when the reproduction number is less than one and unstable if the basic reproduction number is greater than one for the full model and when the model is considered with no treatment. Centre manifold theory is employed to show that if the endemic equilibrium exists, then it is locally asymptotically stable when the reproduction number is slightly greater than one and does not exist when the basic reproduction number is less than one. Moreover, some explicit values are given for the EE depending on some limiting values for detection rates. In the case of high detection and high adherence, the EE does not exist.

A sensitivity analysis of the basic reproduction number shows that it is most sensitive to transmissibility, high proportion of individuals newly infected with latent TB and adherence to treatment. Note that transmissibility and a high proportion of individuals newly infected with latent TB have more effect, but we have little control over them. Mathematical analysis and numerical simulations

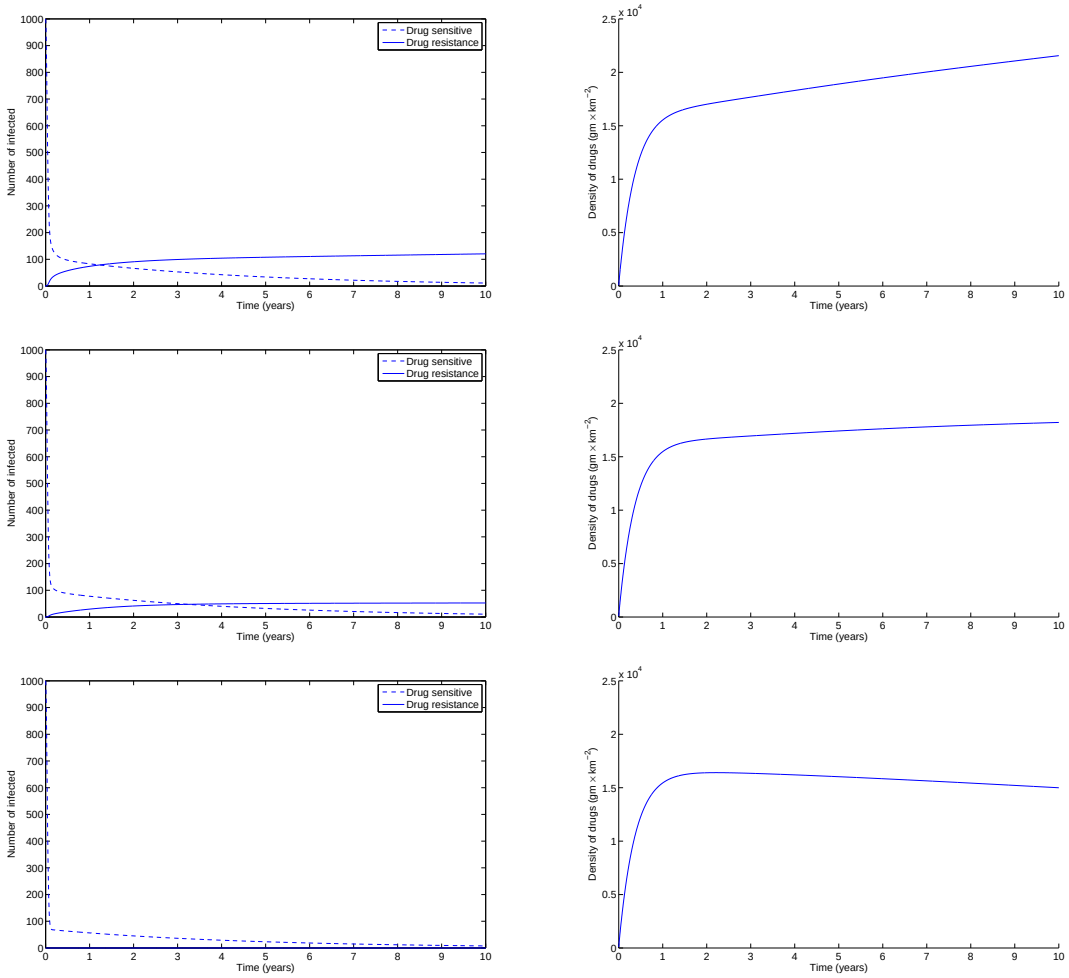

Fig. 7 Comparison between the continuous drug-sensitive and drug-resistance infected functions (from top to bottom, $\mu_r = 12, 6, 0$). On the right, we have the density of drug when different adherence rates are adopted. Here $(\gamma, \gamma_r) = (0.2, 0.9)$.

show that high detection rates and high adherence to treatment decrease the prevalence of both drug sensitive and drug resistant strains of TB.

Surprisingly, we observed a counterintuitive effect of drug availability. Figure 7 showed that more drugs were used as adherence fell. This is explained by the fact that low adherence results in a high demand but low consumption of drugs, increasing their overall availability.

Our model has some limitations, which should be acknowledged. We focused on treating individuals and ignoring other ways like isolation and education. Also, a lot of parameters are assumed, limiting the usefulness of our numerical simulations (although we have partially overcome that with Latin Hypercube Sampling). We ignored multi-drug resistance.

In summary, treatment has the potential to have an enormous impact on the TB epidemic. Early detection is critical, but adherence to treatment regimens is also crucial. This is especially true if we are to overcome the effects of drug resistance.

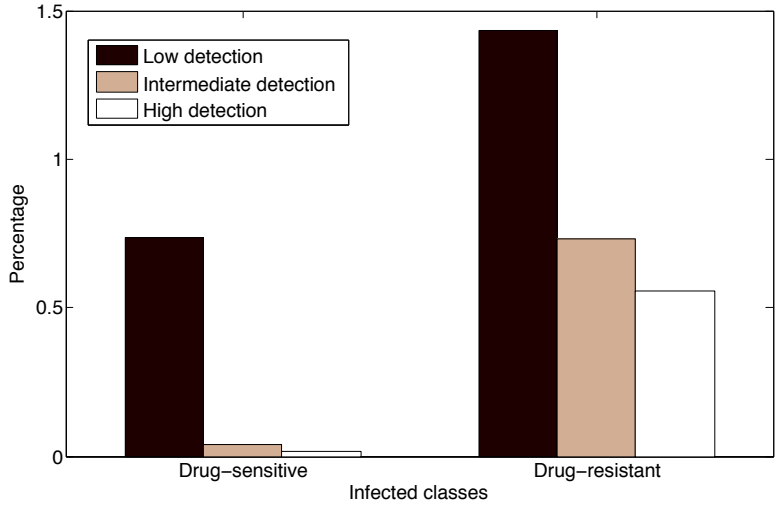

Fig. 8 Comparison between percentage of infected in different classes (after 10 years) when different detection rates are adopted. Here $(\gamma, \gamma_r) = (0.1, 0.1)$, $(0.5, 0.5)$, $(1, 1)$ and $\mu_r = 2$.

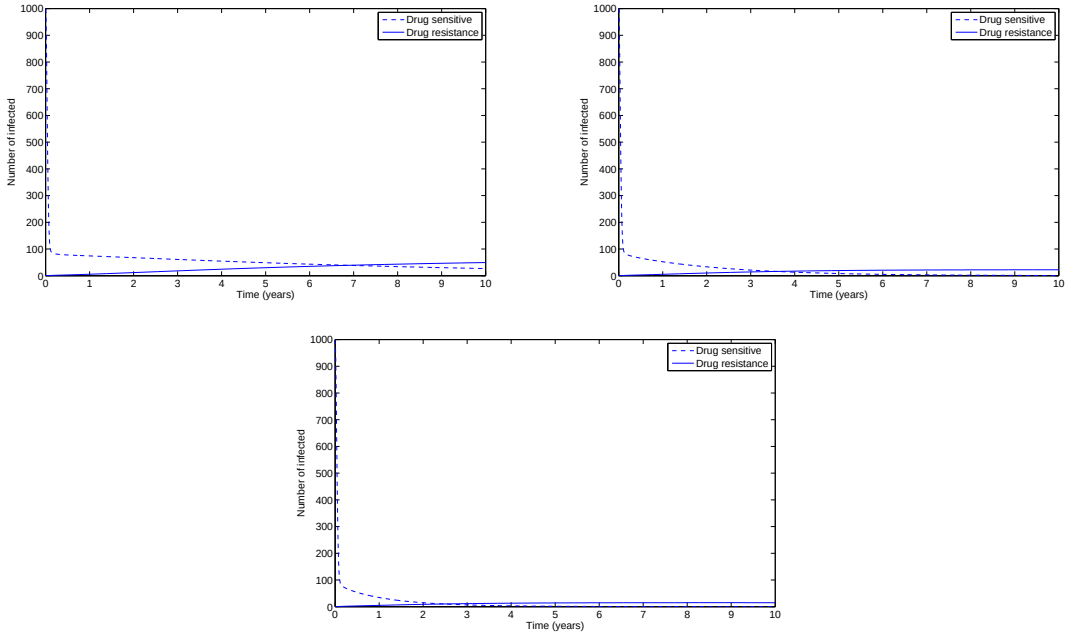

Fig. 9 Comparison between the continuous (continuous function of time) drug-sensitive and drug-resistance infected functions when different adherence rates are adopted (top left, top right and bottom correspond to $(\gamma, \gamma_r) = (0.1, 0.1)$, $(0.5, 0.5)$, $(1, 1)$). Here $\mu_r = 2$.

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