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Research Article

Analysis of a TB model with treatment interruptions

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Abstract

In this article, a TB transmission model with treatment interruptions is established. The control reproduction numbers which completely determine the long behaviors of the TB model are explicitly given. By applying the comparison principle and constructing proper Lyapunov functions, the global asymptotic stability of equilibria is analyzed. The numerical simulations show that the treatment of active TB cases has always a positive effect on controlling the TB epidemic; while treatment interruptions may have a negative, positive or no effect on combating the TB epidemic.

Keywords: TB transmission model, treatment interruptions, the control reproduction number, Lyapunov function, globally asymptotically stable.
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1. Introduction

Tuberculosis (TB) is a very common and an infectious airborne disease caused by infection with the bacillus *Mycobacterium tuberculosis* (*M. tuberculosis*), which is preventable and curable. About one-third of the world's population has been infected with the *M. tuberculosis* [1]. Furthermore, an estimated 9.0 million people developed TB and 1.5 million died from the disease (including 360 thousand deaths among HIV-positive people) in 2013. Although the rate of new TB cases and TB incidence rates are falling worldwide and the TB mortality rate has been reduced, the absolute number of incident cases of TB is increasing because of population growth. Therefore, TB remains a major global health problem.

Although the treatment success rate of all new TB cases was high at 87% in 2011, there were about 3 million people who developed TB and were missed by national notification systems. In fact, treatment interruptions of TB cases often occur during the intensive phase and the continuation phase because of a

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wide range of reasons [4]. It may be recognized that treatment interruptions and the missed TB cases are the key factors to cause more drug-resistant TB cases and the high TB mortality [4, 7, 12]. Treatment interruptions of TB cases may lead to more infects as well.

Once susceptible individuals are infected, they enter a latent period which varies from person to person. Most of them carry the bacillus *M. tuberculosis* for decades and do not progress TB cases, but some may fast progress TB cases during one or two years after infection and some may slowly progress TB cases after they carry the bacillus *M. tuberculosis* for decades. In [14], Ziv *et.al.* first introduced two latent periods into their TB model. In [3, 6, 7, 8], latent period has been considered in the TB mathematical models. Therefore, the latency of TB can not be ignored in analyzing the TB models because of long-term latency and variance. In the present paper, We focus on the factors of treatment interruptions and the latency.

The rest of the paper is organized as follows. In Section 2, the mathematical TB model is developed. The stabilities of equilibria of the TB model are analyzed in Section 3. Section 4 illustrates the effects of treatment of TB cases and treatment interruptions on the development of TB epidemic are. Finally, a brief conclusion is given.

2. The mathematical model

In this section, the TB model with treatment interruptions is formulated. The whole population is divided into six compartments according to their epidemiological status. The compartments are susceptible individuals ($S(t)$), the early latent individuals ($E_1(t)$), the later latent individuals ($E_2(t)$), the TB cases who have regular treatment ($I(t)$), the TB cases who have interrupted treatment ($D(t)$) and the removed people ($R(t)$), respectively, where t is the time variable. Notice that once the treatment of TB cases stops, there is no more treatment. Fig. 1 shows the transmission diagram and the mathematical model is described by the following system of ordinary differential equations.

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - \beta SI - \sigma SD - \mu S, & \frac{dE_1}{dt} &= \beta SI + \sigma SD + (1-q)\eta D - (\mu + k)E_1,\\
\frac{dE_2}{dt} &= (1-p)kE_1 + q\eta D - (\mu + \omega)E_2, & \frac{dI}{dt} &= pkE_1 + \omega E_2 - (\mu + d_1 + \gamma + r)I,\\
\frac{dD}{dt} &= \gamma I - (\mu + d_2 + \eta)D, & \frac{dR}{dt} &= rI - \mu R.
\end{aligned} \tag{2.1}$$

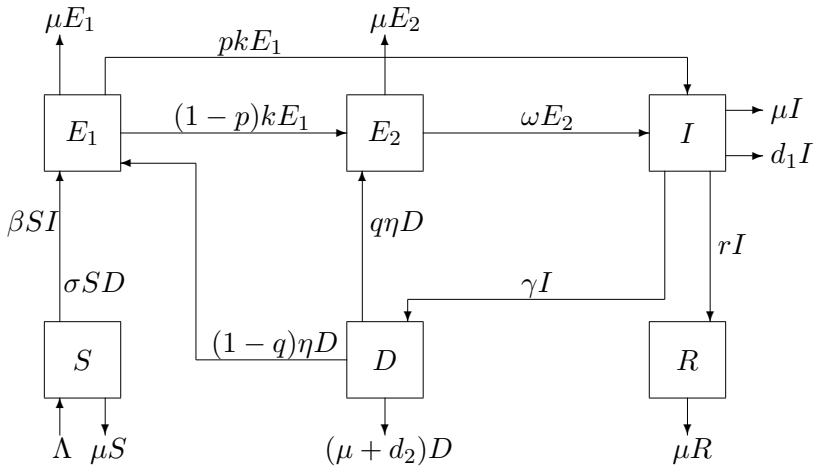

Figure 1: The transfer diagram of the transmission TB model.

In the Model (2.1), Λ stands for the recruitment rate. μ is the per-capital natural death rate. $d_i, i = 1, 2$ is the disease induced death rate in classes I and D, respectively. β and σ are the transmission coefficients from class I and class D to class S , respectively. Let p $(0\leq p\leq 1)$ as the fraction of the early latent persons who progress TB fast. k is the reactivation rate of the early latent persons. ω is the reactivation rate of the later long-term latent persons. η is the self-cured rate of the persons in class D because of their immune system being strengthened. q $(0\leq q\leq 1)$ is the fraction of the self-cured persons in class D who enters class E_2. r is the regular treatment rate of the TB cases in the class I. γ is the rate of treatment interruptions in the class I. It is assumed that all the parameters are positive because of the biological consideration.

Since R does not appear in the first five equations of the System (2.1), it is necessary to discuss the following equivalent system instead of the System (2.1):

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - \beta SI - \sigma SD - \mu S,\\
\frac{dE_1}{dt} &= \beta SI + \sigma SD + (1-q)\eta D - (\mu + k)E_1,\\
\frac{dE_2}{dt} &= (1-p)kE_1 + q\eta D - (\mu + \omega)E_2,\\
\frac{dI}{dt} &= pkE_1 + \omega E_2 - (\mu + d_1 + r + \gamma)I,\\
\frac{dD}{dt} &= \gamma I - (\mu + d_2 + \eta)D.
\end{aligned} \tag{2.2}$$

It then follows from [10, Theorem 5.2.1] that for any initial value in $\mathbb{R}^5_+$, the System (2.2) has a unique local nonnegative solution through the initial value.

In this present paper, $N(t)$ denotes the number of the total population in time t. That is,

$$N = S + E_1 + E_2 + I + D + R.$$

Adding the equations in the Model (2.1) gives

$$\frac{dN}{dt} = \Lambda - \mu N - d_1 I - d_2 D \leq \Lambda - \mu N. \tag{2.3}$$

It is quite clear that if $N > \Lambda/\mu$, $dN/dt < 0$. Therefore, all the solutions of the System (2.2) with nonnegative initial values in the space $\mathbb{R}^5_+$ are bounded and exist in the interval $[0, +\infty)$. Moreover, it is easily shown that the set

$$\Omega = \{(S, E_1, E_2, I, D) \in \mathbb{R}^5_+ | S \leq N \leq \Lambda/\mu\}$$

is positively invariant and attracts all nonnegative solution of the Model (2.2). Therefore, without loss of generality, it is only necessary to consider the solutions of the Model (2.2) with initial values in Ω.

To simplify the presentation, we let

$$\begin{aligned}
&A_1 = \frac{\omega}{\mu + \omega}, \qquad A_2 = \frac{q\eta}{\mu + d_2 + \eta}, \qquad A_3 = \frac{(1-q)\eta}{\mu + d_2 + \eta},\\
&A_4 = \frac{\gamma}{\mu + d_1 + \gamma + r}, \qquad A_5 = \frac{pk}{\mu + k}, \qquad A_6 = \frac{(1-p)k}{\mu + k},\\
&A_7 = (\mu + d_1 + \gamma + r) - \frac{\omega q \eta \gamma}{(\mu + \omega)(\mu + d_2 + \eta)}.
\end{aligned} \tag{2.4}$$

Clearly the System (2.2) possesses the disease-free equilibrium $P_0(\frac{\Lambda}{\mu}, 0, 0, 0, 0)$ for all the parameters. The control reproduction number can be calculated by using the next generation matrix method [13]. The matrices F and V for the new infection terms and the remaining transfer terms are given by

$$F = \begin{pmatrix} 0 & 0 & \beta\frac{\Lambda}{\mu} & \sigma\frac{\Lambda}{\mu} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

and

$$V = \begin{pmatrix} \mu+k & 0 & 0 & -(1-q)\eta \\ -(1-p)k & \mu+\omega & 0 & -q\eta \\ -pk & -\omega & \mu+d_1+\gamma+r & 0 \\ 0 & 0 & -\gamma & \mu+d_2+\eta \end{pmatrix},$$

respectively. Therefore, the control reproduction number R_{ti} [13] can be computed as follows

$$\begin{aligned} R_{ti} = \rho(FV^{-1}) =& \frac{\beta\frac{\Lambda}{\mu}(A_5 + A_1A_6)}{(\mu+d_1+\gamma+r) - A_1A_2\gamma - A_3A_5\gamma - A_1A_3A_6\gamma} \\ &+ \frac{\sigma\frac{\Lambda}{\mu}(A_4A_5 + A_1A_4A_6)}{(\mu+d_2+\eta) - A_1A_4q\eta - A_4A_5(1-q)\eta - A_1A_4A_6(1-q)\eta}, \end{aligned} \tag{2.5}$$

where $\rho(M)$ is the spectral radius of matrix M. [13, Theorem 2] implies the following results.

Theorem 2.1. *If the control reproduction number $R_{ti} < 1$, the disease-free equilibrium P_0 is locally asymptotically stable; while the control reproduction number $R_{ti} > 1$, the disease-free equilibrium P_0 is unstable.*

Lemma 2.2. *Let $M = F - V$ and $s(M_1)$ be the maximum real part of all the eigenvalues of the matrix M_1. Then $s(M_1) < 0$ if and only if $\mathcal{R}_{ti} < 1$ and $s(M_1) > 0$ if and only if $\mathcal{R}_{ti} > 1$.*

We are now in the position to give the existence of the endemic equilibrium.

Theorem 2.3. *If the control reproduction number $R_{ti} > 1$, the TB transmission Model* (2.2) *exists exactly one endemic equilibrium $P_*(S^*, E_1^*, E_2^*, I^*, D^*)$, where*

$$\begin{aligned} &S^* = \frac{\Lambda}{\mu R_{ti}}, \qquad I^* = \frac{\mu(R_{ti}-1)}{\beta + \frac{\sigma\gamma}{\mu+d_2+\eta}}, \qquad D^* = \frac{\gamma}{\mu+d_2+\eta}I^*, \\ &E_1^* = \frac{A_7}{pk + A_1(1-p)k}I^*, \quad E_2^* = \frac{(1-p)k}{\mu+\omega}E_1^* + \frac{A_2\gamma}{\mu+\omega}I^*. \end{aligned} \tag{2.6}$$

Proof. It is worth to note that $R_{ti} > 1$. Letting the right hand sides of the equations in the System (2.2) to zero, we get

$$\begin{aligned} &\Lambda = \beta S^*I^* + \sigma S^*D^* + \mu S^*, \\ &\beta S^*I^* + \sigma S^*D^* + (1-q)\eta D^* = (\mu+k)E_1^*, \\ &(1-p)kE_1^* + q\eta D^* = (\mu+\omega)E_2^*, \\ &pkE_1^* + \omega E_2^* = (\mu+d_1+r+\gamma)I^*, \\ &\gamma I^* = (\mu+d_2+\eta)D^*. \end{aligned} \tag{2.7}$$

The fifth formula of the Equation (2.7) implies

$$D^* = \frac{\gamma}{\mu+d_2+\eta}I^*. \tag{2.8}$$

Substituting (2.8) into the third formula of the Equation (2.7) leads to

$$E_2^* = \frac{(1-p)k}{\mu+\omega}E_1^* + \frac{A_2\gamma}{\mu+\omega}I^*. \tag{2.9}$$

Equations (2.9) and the fourth formula of the Equation (2.7) yields

$$E_1^* = \frac{A_7}{pk + A_1(1-p)k}I^*. \tag{2.10}$$

By substituting Equations (2.8) and (2.10) into the second formula of the Equation (2.7), we obtain

$$S^* = \frac{\Lambda}{\mu R_{ti}}. \tag{2.11}$$

By using the Equations (2.8) , (2.11) and the first formula of the Equation (2.7), we have

$$I^* = \frac{\mu(R_{ti}-1)}{\beta + \frac{\sigma\gamma}{\mu+d_2+\eta}},$$

which ends the proof. □

3. The stability analysis

In this section, the stabilities of the equilibria are discussed by applying the comparison principle and constructing the so-called Lyapunov functions [5, 8, 9, 10]. The following theorem states the global stability of the disease-free equilibrium.

Theorem 3.1. *If the control reproduction number $R_{ti} < 1$, the disease-free equilibrium P_0 is globally asymptotically stable.*

Proof. To obtain the global stability of the disease-free equilibrium, it is sufficient to prove the global attractivity of P_0 if $R_{ti} < 1$. Because of the first equation of the System (2.2), we have

$$\frac{dS}{dt} \leq \Lambda - \mu S.$$

It follows that for any ε, we have $S(t) < \Lambda/\mu + \varepsilon$ for sufficiently large t. Therefore, when t is sufficiently large, we obtain

$$\begin{aligned}
\frac{dE_1}{dt} &< \beta(\frac{\Lambda}{\mu}+\varepsilon)I + \sigma(\frac{\Lambda}{\mu}+\varepsilon)D + (1-q)\eta D - (\mu+k)E_1,\\
\frac{dE_2}{dt} &\leq (1-p)kE_1 + q\eta D - (\mu+\omega)E_2,\\
\frac{dI}{dt} &\leq pkE_1 + \omega E_2 - (\mu+d_1+r+\gamma)I,\\
\frac{dD}{dt} &\leq \gamma I - (\mu+d_2+\eta)D.
\end{aligned} \tag{3.1}$$

It suffices to prove the solutions of the following auxiliary system

$$\begin{aligned}
\frac{d\hat{E}_1}{dt} &= \beta(\frac{\Lambda}{\mu}+\varepsilon)\hat{I} + \sigma(\frac{\Lambda}{\mu}+\varepsilon)\hat{D} + (1-q)\eta\hat{D} - (\mu+k)\hat{E}_1,\\
\frac{d\hat{E}_2}{dt} &= (1-p)k\hat{E}_1 + q\eta\hat{D} - (\mu+\omega)\hat{E}_2,\\
\frac{d\hat{I}}{dt} &= pk\hat{E}_1 + \omega\hat{E}_2 - (\mu+d_1+r+\gamma)\hat{I},\\
\frac{d\hat{D}}{dt} &= \gamma\hat{I} - (\mu+d_2+\eta)\hat{D},
\end{aligned} \tag{3.2}$$

approach zero as t tends to infinity. Let M_2 be the following matrix

$$M_2 = \begin{pmatrix} 0 & 0 & \beta & \sigma \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}.$$

Because of $R_{ti} < 1$, Lemma 2.2 implies $s(M_1) < 0$. By the continuity of $s(M_1 + \varepsilon M_2)$ in ε, we can choose ε small enough so that $s(M_1 + \varepsilon M_2) < 0$. Consequently, all the solutions of the System (3.2) tend to zero as t goes to infinity. By the comparison principle of cooperative systems [10, Theorem B.1], we have $(E_1(t), E_2(t), I(t), D(t)) \to 0$ as $t \to \infty$. By the theory of asymptotically autonomous systems [11, Theorem 1.2], it then follows that $\lim_{t\to\infty} S(t) = \Lambda/\mu$. This completes the proof. □

Theorem 3.2. *If the control reproduction number $R_{ti} > 1$, the endemic equilibrium P_* of the Model (2.2) is globally asymptotically stable.*

Proof. At the endemic equilibrium P_*, all the parameters and the components S^*, E_1^*, E_2^*, I^* and D^* of the endemic equilibrium P_* satisfy the following equations:

$$\begin{aligned}
\Lambda &= \beta S^* I^* + \sigma S^* D^* + \mu S^*, \\
\mu + k &= \frac{\beta S^* I^*}{E_1^*} + \frac{\sigma S^* D^*}{E_1^*} + \frac{(1-q)\eta D^*}{E_1^*}, \\
\mu + \omega &= \frac{(1-p)kE_1^*}{E_2^*} + \frac{q\eta D^*}{E_2^*} \\
\mu + d_1 + \gamma + r &= \frac{pkE_1^*}{I^*} + \frac{\omega E_2^*}{I^*}, \\
\mu + d_2 + \eta &= \frac{\gamma I^*}{D^*}.
\end{aligned} \tag{3.3}$$

Let the Lyapunov function as follows:

$$U = S - S^* \ln S + E_1 - E_1^* \ln E_1 + C_1(E_2 - E_2^* \ln E_2) + C_2(I - I^* \ln I) + C_3(D - D^* \ln D), \tag{3.4}$$

where

$$C_1 = A_1 C_2, \qquad C_2 = \frac{\beta S^* I^* + \sigma S^* D^* + (1-q)\eta D^*}{[pk + \frac{\omega}{\mu+\omega}(1-p)k]E_1^*}, \qquad C_3 = \frac{\sigma S^* D^* + (1-q)\eta D^* + C_1 q\eta D^*}{\gamma I^*}. \tag{3.5}$$

Differentiating U along the solutions of the System (2.2) with respect to time t gives

$$\left.\frac{dU}{dt}\right|_{(2.2)} = (1 - \frac{S^*}{S})\frac{dS}{dt} + (1 - \frac{E_1^*}{E_1})\frac{dE_1}{dt} + C_1(1 - \frac{E_2^*}{E_2})\frac{dE_2}{dt} + C_2(1 - \frac{I^*}{I})\frac{dI}{dt} + C_3(1 - \frac{D^*}{D})\frac{dD}{dt}. \tag{3.6}$$

Substituting the System (2.2) into Equation (3.6) yields:

$$\begin{aligned}
\left.\frac{dU}{dt}\right|_{(2.2)} =& (1 - \frac{S^*}{S})[\Lambda - \beta SI - \sigma SD - \mu S] + (1 - \frac{E_1^*}{E_1})[\beta SI + \sigma SD + (1-q)\eta D - (\mu + k)E_1] \\
&+ C_1(1 - \frac{E_2^*}{E_2})[(1-p)kE_1 + q\eta D - (\mu + \omega)E_2] + C_2(1 - \frac{I^*}{I})[pkE_1 + \omega E_2 - (\mu + d_1 + r + \gamma)I] \\
&+ C_3(1 - \frac{D^*}{D})[\gamma I - (\mu + d_2 + \eta)D].
\end{aligned}$$

Using the Equation (3.3), we have

$$\begin{aligned}
\left.\frac{dU}{dt}\right|_{(2.2)} =& (1 - \frac{S^*}{S})[\beta S^* I^* + \sigma S^* D^* + \mu S^* - \beta SI - \sigma SD - \mu S] \\
&+ (1 - \frac{E_1^*}{E_1})[\beta SI + \sigma SD + (1-q)\eta D - (\frac{\beta S^* I^*}{E_1^*} + \frac{\sigma S^* D^*}{E_1^*} + \frac{(1-q)\eta D^*}{E_1^*})E_1] \\
&+ C_1(1 - \frac{E_2^*}{E_2})[(1-p)kE_1 + q\eta D - \frac{(1-p)kE_1^*}{E_2^*}E_2 - \frac{q\eta D^*}{E_2^*}E_2] \\
&+ C_2(1 - \frac{I^*}{I})[pkE_1 + \omega E_2 - \frac{pkE_1^*}{I^*}I - \frac{\omega E_2^*}{I^*}I] + C_3(1 - \frac{D^*}{D})[\gamma I - \frac{\gamma I^*}{D^*}D].
\end{aligned}$$

The above Equation can be rearranged as:

$$\begin{aligned}\left.\frac{dU}{dt}\right|_{(2.2)} =& -\mu\frac{(S^*-S)^2}{S}+\beta S^*I^*(1-\frac{S^*}{S})(1-\frac{SI}{S^*I^*})+\sigma S^*D^*(1-\frac{S^*}{S})(1-\frac{SD}{S^*D^*})\\ &+\beta S^*I^*(1-\frac{E_1^*}{E_1})(\frac{SI}{S^*I^*}-\frac{E_1}{E_1^*})+\sigma S^*D^*(1-\frac{E_1^*}{E_1})(\frac{SD}{S^*D^*}-\frac{E_1}{E_1^*})\\ &+(1-q)\eta D^*(1-\frac{E_1^*}{E_1})(\frac{D}{D^*}-\frac{E_1}{E_1^*})+C_1(1-p)kE_1^*(1-\frac{E_2^*}{E_2})(\frac{E_1}{E_1^*}-\frac{E_2}{E_2^*})\\ &+C_1q\eta D^*(1-\frac{E_2^*}{E_2})(\frac{D}{D^*}-\frac{E_2}{E_2^*})+C_2pkE_1^*(1-\frac{I^*}{I})(\frac{E_1}{E_1^*}-\frac{I}{I^*})\\ &+C_2\omega E_2^*(1-\frac{I^*}{I})(\frac{E_2}{E_2^*}-\frac{I}{I^*})+C_3\gamma I^*(1-\frac{D^*}{D})(\frac{I}{I^*}-\frac{D}{D^*}).\end{aligned}$$

Let $x=\frac{S}{S^*}$, $y=\frac{E_1}{E_1^*}$, $z=\frac{E_2}{E_2^*}$, $u=\frac{I}{I^*}$ and $v=\frac{D}{D^*}$. Then, we get:

$$\begin{aligned}\left.\frac{dU}{dt}\right|_{(2.2)} =& -\mu\frac{(S^*-S)^2}{S}+\beta S^*I^*(1-\frac{1}{x})(1-xu)+\sigma S^*D^*(1-\frac{1}{x})(1-xv)\\ &+\beta S^*I^*(1-\frac{1}{y})(xu-y)+\sigma S^*D^*(1-\frac{1}{y})(xv-y)+(1-q)\eta D^*(1-\frac{1}{y})(v-y)\\ &+C_1(1-p)kE_1^*(1-\frac{1}{z})(y-z)+C_1q\eta D^*(1-\frac{1}{z})(v-z)+C_2pkE_1^*(1-\frac{1}{u})(y-u)\\ &+C_2\omega E_2^*(1-\frac{1}{u})(z-u)+C_3\gamma I^*(1-\frac{1}{v})(u-v).\end{aligned}$$

In other words, we obtain

$$\begin{aligned}\left.\frac{dU}{dt}\right|_{(2.2)} =& -\mu\frac{(S^*-S)^2}{S}+\beta S^*I^*(1-xu-\frac{1}{x}+u)+\sigma S^*D^*(1-xv-\frac{1}{x}+v)\\ &+\beta S^*I^*(xu-y-\frac{xu}{y}+1)+\sigma S^*D^*(xv-y-\frac{xv}{y}+1)+(1-q)\eta D^*(v-y-\frac{v}{y}+1)\\ &+C_1(1-p)kE_1^*(y-z-\frac{y}{z}+1)+C_1q\eta D^*(v-z-\frac{v}{z}+1)+C_2pkE_1^*(y-u-\frac{y}{u}+1)\\ &+C_2\omega E_2^*(z-u-\frac{z}{u}+1)+C_3\gamma I^*(u-v-\frac{u}{v}+1).\end{aligned}$$

Applying expressions in (3.5) yields:

$$\begin{aligned}\left.\frac{dU}{dt}\right|_{(2.2)} =& -\mu\frac{(S^*-S)^2}{S}+E_1^*[\frac{2\beta S^*I^*}{E_1^*}+\frac{2\sigma S^*D^*}{E_1^*}+\frac{(1-q)\eta D^*}{E_1^*}\\ &+C_1(1-p)k+\frac{C_1q\eta D^*}{E_1^*}+C_2pk+\frac{C_2\omega E_2^*}{E_1^*}+\frac{C_3\gamma I^*}{E_1^*}]\\ &-E_1^*[\frac{\beta S^*I^*}{E_1^*}(\frac{1}{x}+\frac{xu}{y})+\frac{\sigma S^*D^*}{E_1^*}(\frac{1}{x}+\frac{xv}{y})+\frac{(1-q)\eta D^*}{E_1^*}\frac{v}{y}\\ &+C_1(1-p)k\frac{y}{z}+\frac{C_1q\eta D^*}{E_1^*}\frac{v}{z}+C_2pk\frac{y}{u}+\frac{C_2\omega E_2^*}{E_1^*}\frac{z}{u}+\frac{C_3\gamma I^*}{E_1^*}\frac{u}{v}].\end{aligned}\tag{3.7}$$

Applying Equations (2.6) and (3.5), it is easy to see that

$$\frac{\beta S^*I^*}{E_1^*}=\beta S^*\frac{pk+A_1(1-p)k}{A_7}=\frac{\beta S^*pk}{A_7}+\frac{\beta S^*(1-p)kA_1}{A_7},$$

$$\begin{aligned}
\frac{\sigma S^* D^*}{E_1^*} &= \frac{\sigma S^* pk\gamma}{(\mu+d_2+\eta)A_7} + \frac{\sigma S^*(1-p)kA_1\gamma}{(\mu+d_2+\eta)A_7},\\
\frac{(1-q)\eta D^*}{E_1^*} &= \frac{(1-q)\eta pk\gamma}{(\mu+d_2+\eta)A_7} + \frac{(1-q)\eta(1-p)kA_1\gamma}{(\mu+d_2+\eta)A_7},\\
C_1(1-p)k &= A_1C_2(1-p)k = A_1(1-p)k(\frac{\beta S^*}{A_7} + \frac{\sigma S^*\gamma}{(\mu+d_2+\eta)A_7} + \frac{(1-q)\eta\gamma}{(\mu+d_2+\eta)A_7})\\
&= \frac{\beta S^*(1-p)kA_1}{A_7} + \frac{\sigma S^*(1-p)kA_1\gamma}{(\mu+d_2+\eta)A_7} + \frac{(1-q)\eta(1-p)kA_1\gamma}{(\mu+d_2+\eta)A_7},\\
C_2pk &= \frac{\beta S^* pk}{A_7} + \frac{\sigma S^* pk\gamma}{(\mu+d_2+\eta)A_7} + \frac{(1-q)\eta pk\gamma}{(\mu+d_2+\eta)A_7},\\
\frac{C_2\omega E_2^*}{E_1^*} &= C_2\omega[\frac{(1-p)k}{\mu+\omega} + \frac{q\eta\gamma(pk+A_1(1-p)k)}{(\mu+\omega)(\mu+d_2+\eta)A_7}]\\
&= (1-p)kA_1(\frac{\beta S^*}{A_7} + \frac{\sigma S^*\gamma}{(\mu+d_2+\eta)A_7} + \frac{(1-q)\eta\gamma}{(\mu+d_2+\eta)A_7}) + C_2A_1\frac{q\eta\gamma(pk+A_1(1-p)k)}{(\mu+d_2+\eta)A_7}\\
&= \frac{\beta S^*(1-p)kA_1}{A_7} + \frac{\sigma S^*(1-p)kA_1\gamma}{(\mu+d_2+\eta)A_7} + \frac{(1-q)\eta(1-p)kA_1\gamma}{(\mu+d_2+\eta)A_7} + \frac{C_1q\eta D^*}{E_1^*},\\
\frac{C_3\gamma I^*}{E_1^*} &= \frac{\sigma S^* pk\gamma}{(\mu+d_2+\eta)A_7} + \frac{\sigma S^*(1-p)kA_1\gamma}{(\mu+d_2+\eta)A_7} + \frac{(1-q)\eta pk\gamma}{(\mu+d_2+\eta)A_7} + \frac{(1-q)\eta(1-p)kA_1\gamma}{(\mu+d_2+\eta)A_7} + \frac{C_1q\eta D^*}{E_1^*}.
\end{aligned}$$

By using the above equations, the Equation (3.7) can be rewritten as follows:

$$\begin{aligned}
\left.\frac{dU}{dt}\right|_{(2.2)} =& -\mu\frac{(S^*-S)^2}{S} + E_1^*[\frac{3\beta S^* pk}{A_7} + \frac{4\beta S^*(1-p)kA_1}{A_7} + \frac{4\sigma S^* pk\gamma}{(\mu+d_2+\eta)A_7}\\
&+ \frac{5\sigma S^*(1-p)kA_1\gamma}{(\mu+d_2+\eta)A_7} + \frac{3(1-q)\eta pk\gamma}{(\mu+d_2+\eta)A_7} + \frac{4(1-q)\eta(1-p)kA_1\gamma}{(\mu+d_2+\eta)A_7} + \frac{3C_1q\eta D^*}{E_1^*}]\\
&- E_1^*[\frac{\beta S^* pk}{A_7}(\frac{1}{x} + \frac{xu}{y} + \frac{y}{u}) + \frac{\beta S^*(1-p)kA_1}{A_7}(\frac{1}{x} + \frac{xu}{y} + \frac{y}{z} + \frac{z}{u})\\
&+ \frac{\sigma S^* pk\gamma}{(\mu+d_2+\eta)A_7}(\frac{1}{x} + \frac{xv}{y} + \frac{y}{u} + \frac{u}{v}) + \frac{(1-q)\eta pk\gamma}{(\mu+d_2+\eta)A_7}(\frac{v}{y} + \frac{y}{u} + \frac{u}{v})\\
&+ \frac{\sigma S^*(1-p)kA_1\gamma}{(\mu+d_2+\eta)A_7}(\frac{1}{x} + \frac{xv}{y} + \frac{y}{z} + \frac{z}{u} + \frac{u}{v})\\
&+ \frac{(1-q)\eta(1-p)kA_1\gamma}{(\mu+d_2+\eta)A_7}(\frac{v}{y} + \frac{y}{z} + \frac{z}{u} + \frac{u}{v}) + \frac{C_1q\eta D^*}{E_1^*}(\frac{v}{z} + \frac{z}{u} + \frac{u}{v})].
\end{aligned}$$

By the inequality of the arithmetic mean-geometric mean, we get

$$\left.\frac{dU}{dt}\right|_{(2.2)} \leq -\mu\frac{(S^*-S)^2}{S} \leq 0,$$

with equality if and only if $x = 1$ and $y = z = u = v$.

Combining those inequalities, we have that $(dU(t))/dt|_{(2.2)} \leq 0$ with equality only if $S = S^*$, $E_1 = E_1^*$, $E_2 = E_2^*$, $I = I^*$ and $D = D^*$. Therefore, an application of the LaSalle's invariance principle [11]yields that the endemic equilibrium $\{P_*\}$ is globally asymptotically stable in Ω. □

From Theorems 3.1 and 3.2, we can see that R_{ti} is indeed a sharp threshold parameter to determine whether or not the TB epidemic in the population. Furthermore, Fig. 2 demonstrates the theoretical analysis that the disease-free equilibrium P_0 is globally asymptotically stable when $R_{ti} = 0.9659 < 1$. Numerical simulation illustrates there exists a global asymptotical stable endemic equilibrium P_* when $R_{ti} = 1.0308 > 1$ (see, Fig 3), where year is used as the unit of time.

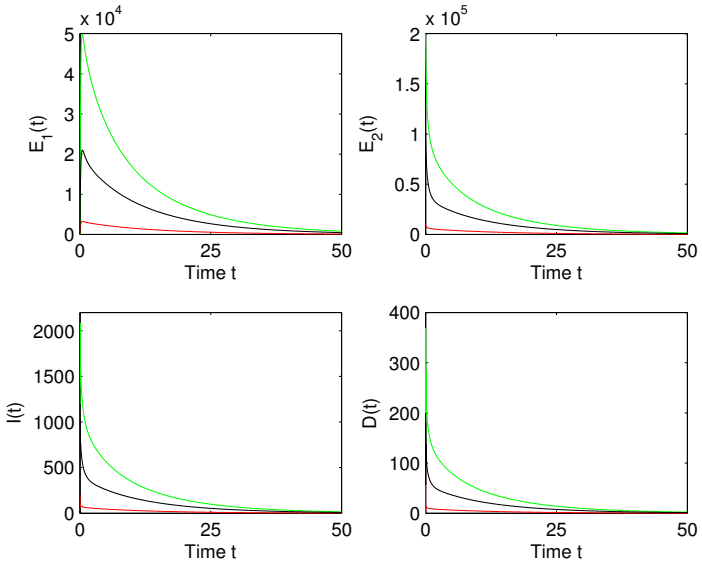

Figure 2: The global asymptotic stability of the disease-free equilibrium P_0 when $R_{ti} = 0.9659$. We chose $\beta = 0.00000039$. Other parameter values are in Table 1.

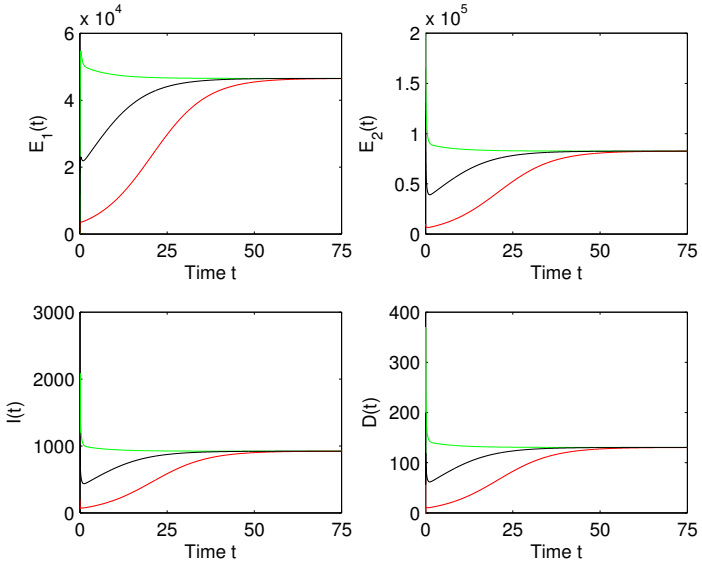

Figure 3: The global asymptotic stability of the endemic equilibrium P_* when $R_{ti} = 1.0308$. We chose $\beta = 0.00000042$. Other parameter values are in Table 1.

4. Effects of treatment and treatment interruptions

The first line anti-tuberculosis drugs are taken daily for the first two months of intensive phase and Rifampicin and Isoniazid are taken daily for the later four months of continuation phase in order to treat TB cases. However, the treatment interruptions frequently occur during the period of treatment due to a great many reasons [4], which may be one of the main factors to cause drug-resistant TB cases. We now discuss the effects of treatment of TB cases and treatment interruptions and study the effects on the development of TB. It is assumed that if the treatment rate of TB cases $r = 0$, the rate of treatment interruptions γ must be zero because the treatment interruptions occurs during the period of treatment of

TB cases.

If there are no treatment of TB cases and in fact there is no treatment interruptions either, we have $r = 0$ and $\gamma = 0$. The System (2.2) becomes

$$\begin{aligned} \frac{dS}{dt} &= \Lambda - \beta SI - \mu S, \\ \frac{dE_1}{dt} &= \beta SI - (\mu + k)E_1, \\ \frac{dE_2}{dt} &= (1-p)kE_1 - (\mu + \omega)E_2, \\ \frac{dI}{dt} &= pkE_1 + \omega E_2 - (\mu + d_1)I. \end{aligned} \tag{4.1}$$

Hence, the basic reproduction number of the System (4.1) is given by

$$\lim_{(r,\gamma)\to(0,0)} R_{ti} = \frac{\beta\frac{\Lambda}{\mu}(A_5 + A_1A_6)}{(\mu + d_1)} =: R_0. \tag{4.2}$$

If there are no treatment interruptions in during the period of treatment of TB cases, in other words, $\gamma = 0$, then the system (2.2) becomes

$$\begin{aligned} \frac{dS}{dt} &= \Lambda - \beta SI - \mu S, \\ \frac{dE_1}{dt} &= \beta SI - (\mu + k)E_1, \\ \frac{dE_2}{dt} &= (1-p)kE_1 - (\mu + \omega)E_2, \\ \frac{dI}{dt} &= pkE_1 + \omega E_2 - (\mu + d_1 + r)I, \end{aligned} \tag{4.3}$$

which implies that

$$\lim_{\gamma\to 0} R_{ti} = \frac{\beta\frac{\Lambda}{\mu}(A_5 + A_1A_6)}{(\mu + d_1 + r)} =: R_t, \tag{4.4}$$

where R_t is the treatment induced reproduction number for the model (4.3). The treatment induced reproduction number can be written as

$$R_t = HR_0,$$

where

$$H = \frac{\mu + d_1}{\mu + d_1 + r}.$$

It is clear that $R_t < R_0$ and $H < 1$ if the treatment rate of TB cases r is greater than zero. Differentiating partially R_t with respect to r we obtain

$$\frac{\partial R_t}{\partial r} = \frac{-R_t}{\mu + d_1 + r} < 0.$$

In fact, treatment of TB cases slows down the TB epidemic if there are no treatment interruptions during the period of treatment of TB cases.

For the sake of simplicity, let

$$\Delta_1 = \frac{\beta}{\sigma}[(\mu + d_2 + \eta) - A_1q\eta - (A_5 + A_1A_6)(1-q)\eta] - (\mu + d_1 + r). \tag{4.5}$$

The simple calculation implies that

(i) when $\Delta_1 > 0$, $R_{ti} < R_t$ and $\frac{\partial R_{ti}}{\partial \gamma} < 0$;

(ii) when $\Delta_1 < 0$, $R_{ti} > R_t$ and $\frac{\partial R_{ti}}{\partial \gamma} > 0$;

(iii) and when $\Delta_1 = 0$, $R_{ti} = R_t$ and $\frac{\partial R_{ti}}{\partial \gamma} = 0$.

From the biological and epidemiological point of view, treatment interruptions may reduce or accelerate the develop of the epidemic or may have no effect on the development of the epidemic.

From (4.5), we pay attention to the following scenarios.

Case 1: $\Delta_1 > 0$**.**

In this case, both treatment of TB cases and treatment interruptions slow the development of epidemic. Furthermore, we have $R_{ti} < R_t < R_0$. If $R_0 < 1$, TB can not develop into epidemic and treatment of TB cases is not necessary either, but treatment of TB cases and treatment interruptions may accelerate the extinction of TB.

If $R_t < 1 < R_0$, it is sufficient to determine the condition for slowing the development of TB. Letting $R_t = 1$ and solving the critical treatment rate of TB cases denoted by r_1^c if there is no treatment interruption, we get

$$r_1^c = (\mu + d_1)(R_0 - 1). \tag{4.6}$$

When $r > r_1^c$, TB will be eradicated due to treatment only. If $r < r_1^c$, there is a reduction of the TB epidemic but it is not enough to eradicate the TB epidemic.

If $R_{ti} < 1 < R_t$, we need to determine the condition for slowing the development of TB. If follows from letting $R_{ti} = 1$ that

$$\gamma_1^c = \frac{[\beta\frac{\Lambda}{\mu}(A_5 + A_1A_6) - (\mu + d_1 + r)](\mu + d_2 + \eta)}{(\mu + d_2 + \eta) - A_1q\eta - (A_5 + A_1A_6)[(1-q)\eta + \sigma\frac{\Lambda}{\mu}]}, \tag{4.7}$$

where γ_1^c denotes the critical rate of treatment interruptions. When $\gamma > \gamma_1^c$, TB will be controlled and die out from the population eventually. On the contrary, if $\gamma < \gamma_1^c$, treatment interruptions slow down the development of TB but not control the TB epidemic.

If $R_{ti} > 1$, then the treatment of TB cases and treatment interruptions can not control the epidemic and other intervention strategies should be introduced.

Case 2: $\Delta_1 < 0$**.**

In this case, treatment interruptions have a negative effect on the development of TB because of $\frac{\partial R_{ti}}{\partial \gamma} > 0$. Reducing the rate of treatment interruptions helps to control TB. To simplify the presentation, set

$$\Delta_2 = \frac{\beta}{\sigma}[(\frac{r}{\gamma} + 1)(\mu + d_2 + \eta) - A_1q\eta - (A_5 + A_1A_6)(1-q)\eta] - (\mu + d_1). \tag{4.8}$$

The direct algebraic calculation yields

(I) when $\Delta_2 > 0$, $R_{ti} < R_0$;

(II) when $\Delta_2 < 0$, $R_{ti} > R_0$;

(III) and when $\Delta_2 = 0$, $R_{ti} = R_0$.

Cases (II) and (III) illustrate that treatment of TB cases is not enough to compensate for the treatment interruptions. Therefore, according to the practical situation, we just need to consider case (I) rather than cases (II) and (III). If $\Delta_2 > 0$, we get $R_t < R_{ti} < R_0$. If $R_0 < 1$, TB will be eradicated from the population and treatment of TB cases is not necessary.

If $R_{ti} < 1 < R_0$, it is need to take measures to prevent the spread of TB, for instance, treatment of TB cases. We have to determine the necessary conditions for slowing the TB epidemic. If TB cases are treated and there are treatment interruptions, setting $R_{ti} = 1$, we obtain the critical values of treatment rate of TB cases and the rate of treatment interruptions denoted by r_2^c and γ_2^c, respectively. Moreover, r_2^c and γ_2^c are satisfied

$$\begin{aligned} &\frac{\sigma\frac{\Lambda}{\mu}(A_5 + A_1A_6)}{(\mu + d_1 + \gamma_2^c + r_2^c) - (A_1A_2 + A_3A_5 + A_1A_3A_6)\gamma_2^c}\frac{\gamma_2^c}{\mu + d_2 + \eta} \\ &+ \frac{\beta\frac{\Lambda}{\mu}(A_5 + A_1A_6)}{(\mu + d_1 + \gamma_2^c + r_2^c) - (A_1A_2 + A_3A_5 + A_1A_3A_6)\gamma_2^c} = 1. \end{aligned} \tag{4.9}$$

When one of the conditions

(c1) $r > r_2^c$ and $\gamma = \gamma_2^c$;

(c2) $r = r_2^c$ and $\gamma < \gamma_2^c$;

(c3) $r > r_2^c$ and $\gamma < \gamma_2^c$;

is fulfilled, TB will not develop epidemic and die out from the population. If there just exists treatment of TB cases but no treatment interruptions, letting $R_t = 1$ provides the critical value for treatment rate of TB cases r_3^c. As the matter of fact, r_3^c is exactly the same as r_1^c. When $r > r_3^c$, TB will be controlled and does not develop the epidemic; otherwise treatment of TB cases results in the reduction of TB epidemic but not enough to control it.

If $R_t < 1 < R_{ti}$, the critical value of rate of treatment interruptions γ_3^c can be obtained by letting $R_{ti} = 1$. It is clear that γ_3^c is the same as γ_1^c. When $\gamma < \gamma_3^c$, TB will be eradicated from the population. If $\gamma > \gamma_3^c$, decreasing the rate of treatment interruptions will reduce the development of TB but not enough to control it.

If $R_t > 1$, treatment of TB cases will cut down the spread of TB but more steps should be taken to control TB.

Case 3: $\Delta_1 = 0$**.**

In this case, treatment interruptions have no effect on the development of TB due to $\frac{\partial R_{ti}}{\partial \gamma} = 0$ or $R_{ti} = R_t$. If $R_0 < 1$, TB will eventually disappear from the population and treatment of TB cases is not necessary. On the contrary, if $R_0 > 1$, we determine the critical condition of treatment rate. Let $R_t = 1$ and the critical treatment rate denoted by r_4^c which is the same as r_1^c. When $r > r_4^c$, TB will be eradicated through treatment of TB cases. But if $r < r_4^c$, treatment of TB cases results in the reduction of the TB epidemic but not enough to eradicate it.

We are now doing numerical simulations of the models (2.2), (4.1) and (4.3). The parameter values used for the numerical simulations are listed in Table 1. Most of the parameter values are from [2] and others are estimated from the relatively reasonable point of view. For the simulation result in Fig. 4, the initial conditions are assumed that $S(0) = 6,300,000$, $E_1(0) = 250,000$, $E_2(0) = 280,000$, $I(0) = 5,000$ and $D(0) = 1,000$.

Fig. 4 is a graphical representation demonstrating the trends of all classes except for class D where there is no treatment and when treatment of TB cases is used. β is chosen as 0.00000039. It is easy to calculate that $\Delta_1 = 0.2283 > 0$, $R_0 = 1.2967$, $R_t = 0.9921$ and $R_{ti} = 0.9659$, which implies that $R_{ti} < R_t < 1 < R_0$. In the absence of treatment, the number of susceptible people decreases as they are infected by TB cases.

However, it stops falling and soon reaches a point where it remains constant as shown in the first panel of Fig. 4. In the presence of treatment of TB cases, the number of susceptible people increases gradually and reaches a point where it keeps constant as shown in the first panel of Fig. 4. In the later three panels of Fig. 4, in the absence of treatment, the numbers of three classes increase rapidly as susceptible people are infected and then reach their maximums where they keep constants. In the present of treatment, the numbers of all classes gradually diminish and ultimately reach the stable state zero.

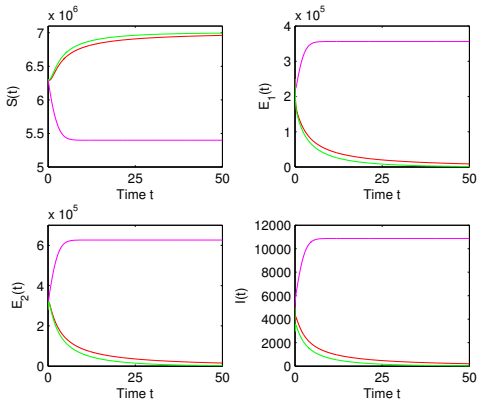

Figure 4: Simulation results showing the effect of treatment of TB cases and treatment interruptions on all compartments except for class D. β is fixed as 0.00000039. Other parameter values are seen in Table 1. The pink line, the red line and the green line correspond to no treatment, treatment of TB cases but no treatment interruptions, treatment of TB cases and treatment interruptions, respectively.

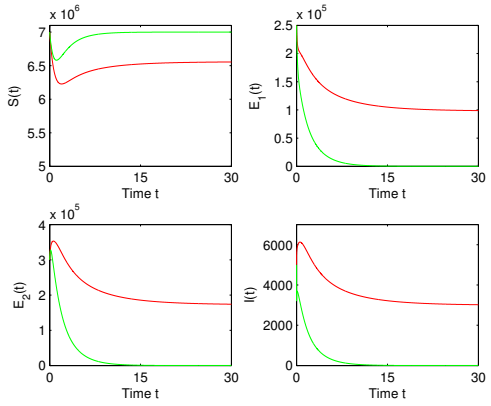

Figure 5: Simulation results showing the effect of treatment of TB cases and treatment interruptions on all classes except for class D. β is chosen as 0.000000321. Other parameter values are seen in Table 1. The red line and the green line correspond to no treatment of TB cases and treatment of TB cases and treatment interruptions, respectively.

Fig. 5 is also a graphical representation showing the trends of all classes except for class D where there is no intervention and when treatment of TB cases and treatment interruptions are applied. β is fixed as 0.000000321. Simple calculation gives $\Delta_1 = -0.0003543 < 0$, $\Delta_2 = 1.6684 > 0$, $R_0 = 1.0673$, $R_t = 0.81659$ and $R_{ti} = 0.81663$. Therefor, $R_t < R_{ti} < 1 < R_0$. The numbers of all classes corresponding to $R_t = 0.81659$ are not drawn because they are very similar to that of the case when $R_{ti} = 0.81663$. The numbers of susceptible population decrease rapidly to low levels as susceptible population are infected by TB cases and then increase to points where they remain constants whether or not there is treatment of TB cases in the first panel of Fig. 5. In the later three panels of Fig. 5, all classes fall off gradually and are reduced to their

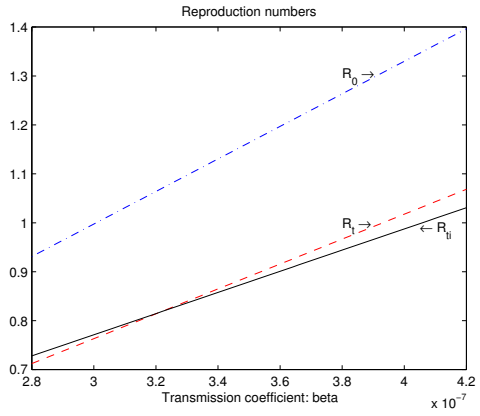

Figure 6: Trends of the reproduction numbers R_0, R_t and R_{ti}. β varies from 2.8×10^{-7} to 4.2×10^{-7}. Other parameter values are seen in Table 1.

Table 1: Model parameters and their interpretations

Definition	Symbol	Estimate
Recruitment rate	Λ	100,000
Natural death rate	μ	1/70
TB induced death rate in classes I	d_1	0.8
TB induced death rate in classes D	d_2	1.2
Transmission coefficient from class I to S	β	Variable
Transmission coefficient from class D to S	σ	4×10^{-7}
Reactivation rate of the early latent persons	k	0.05
Reactivation rate of the later long-term latent persons	ω	0.012
Self-cured rate of the persons in class D	η	0.2
Regular treatment rate of the TB cases in class I	k	0.05
Rate of treatment interruptions	γ	0.2
Fraction of the early latent persons who progress TB fast	p	0.075
Fraction of the self-cured persons in class D who enter class E_2	q	0.8

stable states in the absence of treatment. However, in the present of treatment of TB cases and treatment interruptions, the numbers of all classes diminish to zero quickly.

Fig. 6 shows the trends of all reproduction numbers as transmission coefficient β varies under the given parameter values. Comparing the results in Fig. 6 and Fig. 4, it is concluded that only treatment of TB cases is the best approach to control TB epidemic when β is smaller. However, if β is bigger, the holistic approach of treatment of TB cases and treatment interruptions may be the most effective way of defeating the TB epidemic and the treatment interruptions have positive effect on the spread of TB.

5. Conclusion

A mathematical TB model with treatment interruptions and two latent periods has been formulated. The threshold parameter R_{ti} is defined which is completely determined the global stabilities of the equilibria. It is found that the disease-free equilibrium is globally asymptotically stable and TB will die out in the population if the control reproduction number R_{ti} is below one and the unique endemic equilibrium is globally asymptotically stable and TB will persist in the population if the control reproduction number R_{ti} is greater than one. By comparing reproduction numbers R_t and R_{ti} with the treatment rate of TB cases r and the rate of treatment interruptions γ, it is worth noting that treatment of TB cases always slows down the development of the TB epidemic and helps to control TB spread. However, if the transmission

coefficient β is larger, the control reproduction number R_{ti} decreases as γ increases; while if the transmission coefficient β is smaller, the control reproduction number R_{ti} increases as the rate of treatment interruptions γ increases.

L. Liu and Y. Wang in [7] also have discussed the TB transmission model with treatment interruptions and two latent periods. But all the people are divided into seven groups. Furthermore, the numerical results show that if the disease induced death rate of class D is lower, the control reproduction number R_{ti} increases as the rate of treatment interruptions increases and treatment interruptions can not help control TB epidemic; while if the disease induced death rate of class D is higher, the control reproduction number R_{ti} decreases as the rate of treatment interruptions increases and treatment interruptions may be able to slow down the TB epidemic.

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