ROCKY MOUNTAIN
JOURNAL OF MATHEMATICS
Volume 38, Number 5, 2008

GLOBAL DYNAMICS IN A TB MODEL INCORPORATING CASE DETECTION AND TWO TREATMENT STAGES

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ABSTRACT. Case detection of an infectious individual and differentiation of infectiveness of a treated patient during two different stages of treatment are recognized as among key factors for the successful control and management of tuberculosis (TB) transmission. In this paper, a dynamic compartmental model is developed that incorporates these factors, and proofs are provided to show that the model's global dynamics are completely characterized by the control reproduction number, and in particular the disease eradication condition in terms of the case detection fraction is obtained, along with some numerical simulations.

1. Introduction. Tuberculosis (TB) caused by infection with the bacterium M. tuberculosis is an ancient and chronic infectious disease. It is estimated that one-third of the world's population has been infected with M. tuberculosis, resulting in nearly 3 million deaths each year [**2, 3, 18**]. Furthermore, there are more than 6.5 million new cases of tuberculosis each year [**20**].

Many mathematical models have been proposed and analyzed to examine TB transmission dynamics, and to suggest and evaluate control strategies [**4, 5, 6, 8, 12**]. In particular, issues such as vaccination, drug-resistance, the reinfection and relapse of cured individuals have been addressed in different models [**7, 10, 17**]. Of particular concern in this paper is the impact of case detection on an effective treatment program. This is motivated by the observation that, in China, a fraction of case detection of smear-positive pulmonary tuberculosis was only 41.4

Keywords and phrases. TB model, case detection, relapse, treatment, M. tuberculosis.

This study was supported by the National Natural Science Foundation of China (10531030), by the Natural Sciences and Engineering Research Council of Canada, by the Canada Research Chairs Program, by Mathematics for Information Technology and Complex Systems, and by the Canada-China Thematic Program on Disease Modeling sponsored by International Development and Research Center.

Received by the editors on September 6, 2007, and in revised form on January 24, 2008.

DOI:10.1216/RMJ-2008-38-5-1541

percent in 2000 [**16**]. Since smear-positive pulmonary tuberculosis can survive for a long period, improving the low fraction of case detection is obviously important, but which level of case detection fraction is needed for disease control remains to be a challenging task.

Treatment strategies for the M. tuberculosis infection depend upon disease status, and treatment of an active disease usually follows a six-month course (directly observed treatment, short-course) [**1, 9**]. A treatment is usually divided into two stages: the first two months and subsequent four months. If treatment compliance is maintained and the Mycobacterium strain is drug-sensitive, 85 percent of patients convert from sputum positive to sputum negative, becoming noninfectious, within the first two months [**1**]. Nearly 95 percent of patients convert to sputum negative by completion of a treatment [**1, 12**].

Motivated by the above considerations and inspired by studies such as [**1, 7, 12, 16**], we here formulate a TB model incorporating case detection and two treatment stages (Section 2). We then, in Section 3 provide a detailed proof based on the construction of nontrivial Lyapunov functions and the use of LaSalle's invariance principle to show that the global dynamics of such a model can be fully characterized by the control reproduction number R_0. Such a number can be calculated using the next generation matrix method [**19**], $R_0 < 1$ implies disease eradication and $R_0 > 1$ leads to the global asymptotic stability of an endemic equilibrium. The dependence of this endemic equilibrium and the control reproduction number on the case detection fraction are determined, both numerically (Section 4) and analytically (Sections 2 and 3). Annual new cases of infectious TB and annual new infections of TB in the short time are also given by simulation under the condition of different case detection rates of infectious cases (Section 4).

2. The TB model with two treatment stages and the undetected case. To formulate our TB transmission model focusing on case detection and staged treatment, we divide the host population into seven classes, based on their epidemiological status. In particular, the treatment period of an infected individual, if treated, consists of two stages: the first two months since the treatment is initiated when the individual is infectious, and the subsequent four months when the individual is no longer infectious. The compartments are susceptible (S), early latent (E_1) (early latent class with high risk of developing

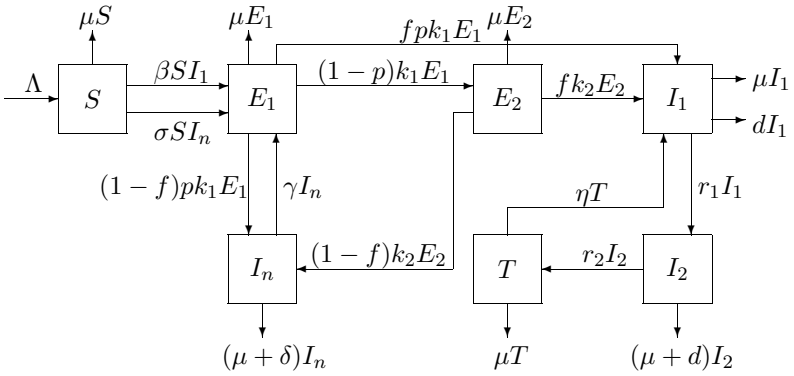

FIGURE 1. The schematic diagram of TB transmission with two treatment stages and undetected cases.

infectious TB), later latent (E_2) (later latent class with low risk of developing infectious TB), infectious and treated (I_1) (those who are treated and infectious) and treated but not infectious (I_2) (those who are treated but are no longer infectious), infectious and untreated (I_n) (those who are infectious, but are not detected and thus not treated), and effectively treated (T). The transmission diagram is given in Figure 1, and the model is a system of ordinary differential equations.

$$
\begin{aligned}
\frac{dS(t)}{dt} &= \Lambda - \beta SI_1 - \sigma SI_n - \mu S \\
\frac{dE_1(t)}{dt} &= \beta SI_1 + \sigma SI_n + \gamma I_n - (\mu + k_1)E_1 \\
\frac{dE_2(t)}{dt} &= (1-p)k_1E_1 - (\mu + k_2)E_2 \\
\frac{dI_1(t)}{dt} &= fpk_1E_1 + fk_2E_2 + \eta T - (\mu + d + r_1)I_1 \\
\frac{dI_n(t)}{dt} &= (1-f)pk_1E_1 + (1-f)k_2E_2 - (\mu + \delta + \gamma)I_n \\
\frac{dI_2(t)}{dt} &= r_1I_1 - (\mu + d + r_2)I_2 \\
\frac{dT(t)}{dt} &= r_2I_2 - (\mu + \eta)T.
\end{aligned} \tag{1}
$$

In the model, Λ is the recruitment rate, μ is the per-capita natural death rate, d is the disease induced death rate in classes I_1 and I_2, and δ is the disease induced death rate (per capita) of class I_n. Because individuals in the I_n class are not treated, $\delta > d$.

The fast and slow progressions are incorporated into the model via introduction of the fraction p: infected individuals initially enter class E_1 and then can have either fast progression to infectious TB (at a rate pk_1) or slow progression to class E_2 (at a rate $(1-p)k_1$), with $1/k_1$ denoting the mean length that an individual stays in the E_1 class. During the later long-term latency, individuals have a relatively lower risk of reactivation to infectious TB, at a rate k_2. β and σ are the transmission coefficients from class I_1 and class I_n to the S class, respectively. The bilinear transmission rate is used here. r_1 and r_2 denote the transfer rates from class I_1 to I_2, and from class I_2 to T, respectively. The treated individuals may relapse and move into class I_1 at the rate η. Also, we assume untreated individuals may recover and move back to class E_1 at the constant rate γ. A fraction f of infectious individuals is detected and the remaining fraction $1-f$ is not detected. Detected individuals are treated, while undetected cases are not treated–they will either die (naturally or from the disease) or recover.

The TB transmission model becomes more complicated than those considered in the literature, due to the introduction of the undetected class.

Let $N(t)$ denote the size of the total population at time t. That is,

$$N(t) = S(t) + E_1(t) + E_2(t) + I_1(t) + I_n(t) + I_2(t) + T(t).$$

By adding the equations in model (1), we get

$$\frac{dN(t)}{dt} = \Lambda - \mu N(t) - d(I_1(t) + I_2(t)) - \delta I_n(t). \tag{2}$$

Since $d/dtN(t) < 0$ if $N(t) > \Lambda/\mu$, we can easily show that the set

$$\Omega = \{(S, E_1, E_2, I_1, I_n, I_2, T) \in \mathbf{R}_7^+ \mid S \leq N \leq \Lambda/\mu\}$$

is positively invariant and attracts all nonnegative solutions of model (1). Therefore, without loss of generality, we will only consider solutions of model (1) with initial values in Ω.

To simplify the presentation, we let

$$
\begin{aligned}
A_1 &= p + \frac{k_2}{\mu + k_2}(1-p), \\
A_2 &= \mu + k_1 - \frac{(1-f)A_1\gamma}{\mu+\delta+\gamma}k_1, \\
A_3 &= \mu + d + r_1 - \frac{\eta r_2}{(\mu+\eta)(\mu+d+r_2)}r_1.
\end{aligned} \tag{3}
$$

Clearly, there always exists a disease-free equilibrium $P_0 = (\Lambda/\mu, 0, 0, 0, 0, 0, 0)$. Using the next generation matrix method [**19**], we can calculate the control reproduction number for model (1) as

$$R_0 = \beta\frac{\Lambda}{\mu}\frac{fk_1A_1}{A_2A_3} + \sigma\frac{\Lambda}{\mu}\frac{(1-f)k_1A_1}{A_2(\mu+\delta+\gamma)}.$$

The control reproduction number R_0 gives the average number of secondary cases generated by one infectious case in the population with the treatment program in place as described above.

3. Equilibria, stabilities and global dynamics. Model (1) has the disease-free equilibrium P_0 for all possible values of the parameters. Simple algebraic calculation also shows that if $R_0 > 1$, model (1) has exactly one endemic equilibrium $P^* = (S^*, E_1^*, E_2^*, I_1^*, I_n^*, I_2^*, T^*)$, where

$$
\begin{aligned}
&S^* = \frac{\Lambda}{\mu R_0}, \qquad E_1^* = \frac{\Lambda(R_0-1)}{A_2R_0}, \qquad E_2^* = \frac{(1-p)k_1}{\mu+k_2}E_1^*, \\
&I_1^* = \frac{fk_1A_1}{A_3}E_1^*, \quad I_n^* = \frac{(1-f)k_1A_1}{\mu+\delta+\gamma}E_1^*, \quad I_2^* = \frac{r_1}{\mu+d+r_2}I_1^*,
\end{aligned} \tag{4}
$$

$$T^* = \frac{r_1r_2}{(\mu+\eta)(\mu+d+r_2)}I_1^*.$$

Theorem 3.1. *If $R_0 < 1$, the disease-free equilibrium P_0 of model* (1) *is globally asymptotically stable and, if $R_0 > 1$, the disease-free equilibrium P_0 of model* (1) *is unstable.*

Proof. Define the nonnegative function in the invariant domain Ω as

$$V_1(t) = E_1(t) + B_1E_2(t) + B_2I_1(t) + B_3I_n(t) + B_4I_2(t) + B_5T(t), \tag{5}$$

where

$$B_1 = B_2\frac{fk_2}{\mu+k_2} + B_3\frac{(1-f)k_2}{\mu+k_2},\ B_2 = \frac{A_2}{fk_1A_1}\left[1-\sigma\frac{\Lambda}{\mu}\frac{(1-f)k_1A_1}{A_2(\mu+\delta+\gamma)}\right], \tag{6}$$

$$B_3 = \frac{\sigma(\Lambda/\mu)+\gamma}{\mu+\delta+\gamma}, \qquad B_4 = \frac{r_1r_2}{(\mu+\eta)(\mu+d+r_2)}B_2,$$

$$B_5 = \frac{\eta}{\mu+\eta}B_2.$$

The fact that $R_0 < 1$ implies that

$$\sigma\frac{\Lambda}{\mu}\frac{(1-f)k_1A_1}{A_2(\mu+\delta+\gamma)} < 1,$$

and B_1, B_2, B_3, B_4 and $B_5 > 0$. Differentiating $V_1(t)$ with respect to time t along the solutions of model (1) yields

$$\begin{aligned}\left.\frac{dV_1(t)}{dt}\right|_{(1)} &= \frac{dE_1(t)}{dt} + B_1\frac{dE_2(t)}{dt} + B_2\frac{dI_1(t)}{dt}\\ &\quad + B_3\frac{dI_n(t)}{dt} + B_4\frac{dI_2(t)}{dt} + B_5\frac{dT(t)}{dt}\\ &= E_1[-(\mu+k_1) + B_1(1-p)k_1 + B_2fpk_1 + B_3(1-f)pk_1]\\ &\quad + E_2[-B_1(\mu+k_2) + B_2fk_2 + B_3(1-f)k_2]\\ &\quad + I_1[\beta S - B_2(\mu+d+r_1) + B_4r_1]\\ &\quad + I_n[\sigma S + \gamma - B_3(\mu+\delta+\gamma)] + T[B_2\eta - B_5(\mu+\eta)]\\ &\quad + I_2[-B_4(\mu+d+r_2) + B_5r_2].\end{aligned}$$

In the positive invariant domain Ω, $S \le \Lambda/\mu$, and we have

$$\begin{aligned}\left.\frac{dV_1(t)}{dt}\right|_{(1)} &\le E_1[-(\mu+k_1) + B_1(1-p)k_1 + B_2fpk_1 + B_3(1-f)pk_1]\\ &\quad + E_2[-B_1(\mu+k_2) + B_2fk_2 + B_3(1-f)k_2]\\ &\quad + I_1\left[\beta\frac{\Lambda}{\mu} - B_2(\mu+d+r_1) + B_4r_1\right]\\ &\quad + I_n\left[\sigma\frac{\Lambda}{\mu} + \gamma - B_3(\mu+\delta+\gamma)\right] + T[B_2\eta - B_5(\mu+\eta)]\\ &\quad + I_2[-B_4(\mu+d+r_2) + B_5r_2].\end{aligned}$$

Using equation (6), direct algebraic calculation yields

$$\left.\frac{dV_1(t)}{dt}\right|_{(1)} \leq I_1 \frac{A_2 A_3}{f k_1 A_1}(R_0 - 1),$$

with equality only at P_0. For $R_0<1$, this shows $(dV_1(t))/dt|_{(1)} \leq 0$ with equality only if $I_1 = 0$. By LaSalle's invariance principle [**14**], the limit set of each solution of model (1) is contained in the largest invariant set $I_1 = 0$, which is the singleton $\{P_0\}$. This completes the proof of the first part of Theorem 3.1.

The instability of P_0 when $R_0 > 1$ is immediately derived from Theorem 2 of [**19**]. □

We now establish the stability of the endemic equilibrium.

Theorem 3.2. *When $R_0 > 1$, the unique endemic equilibrium P^* is globally asymptotically stable.*

Proof. When $R_0 > 1$, the unique endemic equilibrium P^* is given in (4). The endemic components S^*, E_1^*, E_2^*, I_1^*, I_n^*, I_2^*, T^* and parameters satisfy the following equations:

$$\Lambda = \beta S^* I_1^* + \sigma S^* I_n^* + \mu S^*, \quad \mu + k_1 = \beta \frac{S^* I_1^*}{E_1^*} + \sigma \frac{S^* I_n^*}{E_1^*} + \gamma \frac{I_n^*}{E_1^*},$$

$$\mu + k_2 = (1-p)k_1 \frac{E_1^*}{E_2^*}, \quad \mu + d + r_1 = fpk_1 \frac{E_1^*}{I_1^*} + fk_2 \frac{E_2^*}{I_1^*} + \eta \frac{T^*}{I_1^*}, \tag{7}$$

$$\mu + \delta + \gamma = (1-f)pk_1 \frac{E_1^*}{I_n^*} + (1-f)k_2 \frac{E_2^*}{I_n^*}, \quad \mu + d + r_2 = r_1 \frac{I_1^*}{I_2^*},$$

$$\mu + \eta = r_2 \frac{I_2^*}{T^*}.$$

We now construct a Lyapunov function and use the method in [**13, 15**] to prove the stability of the endemic equilibrium. Let

$$\begin{aligned} V_2(t) = &\left(S(t) - S^* - S^* \ln \frac{S(t)}{S^*}\right) + \left(E_1(t) - E_1^* - E_1^* \ln \frac{E_1(t)}{E_1^*}\right) \\ &+ C_1\left(E_2(t) - E_2^* - E_2^* \ln \frac{E_2(t)}{E_2^*}\right) + C_2\left(I_1(t) - I_1^* - I_1^* \ln \frac{I_1(t)}{I_1^*}\right) \\ &+ C_3\left(I_n(t) - I_n^* - I_n^* \ln \frac{I_n(t)}{I_n^*}\right) + C_4\left(I_2(t) - I_2^* - I_2^* \ln \frac{I_2(t)}{I_2^*}\right) \\ &+ C_5\left(T(t) - T^* - T^* \ln \frac{T(t)}{T^*}\right), \end{aligned}$$

where

$$\begin{aligned} &C_2 = \frac{\beta S^*}{A_3}, \quad C_3 = \frac{\sigma S^* + \gamma}{\mu + \delta + \gamma}, \quad C_4 = C_2 \frac{\eta T^*}{r_1 I_1^*}, \\ &C_1 = C_2 \frac{f k_2}{\mu + k_2} + C_3 \frac{(1-f)k_2}{\mu + k_2}, \quad C_5 = C_2 \frac{\eta T^*}{r_2 I_2^*}. \end{aligned} \tag{8}$$

Differentiating $V_2(t)$ along the trajectories of model (1) gives

$$\begin{aligned} \left.\frac{dV_2(t)}{dt}\right|_{(1)} = &\left(1 - \frac{S^*}{S}\right)[\Lambda - \beta S I_1 - \sigma S I_n - \mu S] \\ &+ \left(1 - \frac{E_1^*}{E_1}\right)[\beta S I_1 + \sigma S I_n + \gamma I_n - (\mu + k_1) E_1] \\ &+ C_1\left(1 - \frac{E_2^*}{E_2}\right)[(1-p)k_1 E_1 - (\mu + k_2) E_2] \\ &+ C_2\left(1 - \frac{I_1^*}{I_1}\right)[f p k_1 E_1 + f k_2 E_2 + \eta T - (\mu + d + r_1) I_1] \\ &+ C_3\left(1 - \frac{I_n^*}{I_n}\right)[(1-f) p k_1 E_1 \\ &\qquad + (1-f) k_2 E_2 - (\mu + \delta + \gamma) I_n] \\ &+ C_4\left(1 - \frac{I_2^*}{I_2}\right)[r_1 I_1 - (\mu + d + r_2) I_2] \\ &+ C_5\left(1 - \frac{T^*}{T}\right)[r_2 I_2 - (\mu + \eta) T]. \end{aligned}$$

Substituting expressions of (7) into the above equation leads to

$$\begin{aligned}
\left.\frac{dV_2(t)}{dt}\right|_{(1)} &= -\mu\frac{(S-S^*)^2}{S} + \beta S^* I_1^*\left(1-\frac{S^*}{S}\right)\left(1-\frac{SI_1}{S^*I_1^*}\right)\\
&\quad + \sigma S^* I_n^*\left(1-\frac{S^*}{S}\right)\left(1-\frac{SI_n}{S^*I_n^*}\right)\\
&\quad + \beta S^* I_1^*\left(1-\frac{E_1^*}{E_1}\right)\left(\frac{SI_1}{S^*I_1^*}-\frac{E_1}{E_1^*}\right)\\
&\quad + \sigma S^* I_n^*\left(1-\frac{E_1^*}{E_1}\right)\left(\frac{SI_n}{S^*I_n^*}-\frac{E_1}{E_1^*}\right)\\
&\quad + \gamma I_n^*\left(1-\frac{E_1^*}{E_1}\right)\left(\frac{I_n}{I_n^*}-\frac{E_1}{E_1^*}\right)\\
&\quad + C_1(1-p)k_1E_1^*\left(1-\frac{E_2^*}{E_2}\right)\left(\frac{E_1}{E_1^*}-\frac{E_2}{E_2^*}\right)\\
&\quad + C_2fpk_1E_1^*\left(1-\frac{I_1^*}{I_1}\right)\left(\frac{E_1}{E_1^*}-\frac{I_1}{I_1^*}\right)\\
&\quad + C_2fk_2E_2^*\left(1-\frac{I_1^*}{I_1}\right)\left(\frac{E_2}{E_2^*}-\frac{I_1}{I_1^*}\right)\\
&\quad + C_2\eta T^*\left(1-\frac{I_1^*}{I_1}\right)\left(\frac{T}{T^*}-\frac{I_1}{I_1^*}\right)\\
&\quad + C_3(1-f)pk_1E_1^*\left(1-\frac{I_n^*}{I_n}\right)\left(\frac{E_1}{E_1^*}-\frac{I_n}{I_n^*}\right)\\
&\quad + C_3(1-f)k_2E_2^*\left(1-\frac{I_n^*}{I_n}\right)\left(\frac{E_2}{E_2^*}-\frac{I_n}{I_n^*}\right)\\
&\quad + C_4r_1I_1^*\left(1-\frac{I_2^*}{I_2}\right)\left(\frac{I_1}{I_1^*}-\frac{I_2}{I_2^*}\right)\\
&\quad + C_5r_2I_2^*\left(1-\frac{T^*}{T}\right)\left(\frac{I_2}{I_2^*}-\frac{T}{T^*}\right)\\
&= -\mu\frac{(S-S^*)^2}{S} + E_1^*h(x,y,z,u,v,w,q),
\end{aligned}$$

where

$$(x,y,z,u,v,w,q) = \left(\frac{S}{S^*},\frac{E_1}{E_1^*},\frac{E_2}{E_2^*},\frac{I_1}{I_1^*},\frac{I_n}{I_n^*},\frac{I_2}{I_2^*},\frac{T}{T^*}\right),$$

and

$$
\begin{aligned}
&h(x,y,z,u,v,w,q)\\
&\quad= \frac{2\beta S^*I_1^*}{E_1^*}+\frac{2\sigma S^*I_n^*}{E_1^*}+\frac{\gamma I_n^*}{E_1^*}+C_1(1-p)k_1+C_2fpk_1\\
&\qquad+C_2\eta\frac{T^*}{E_1^*}+C_2fk_2\frac{E_2^*}{E_1^*}+C_3(1-f)pk_1\\
&\qquad+C_3(1-f)k_2\frac{E_2^*}{E_1^*}+C_4r_1\frac{I_1^*}{E_1^*}+C_5r_2\frac{I_2^*}{E_1^*}\\
&\qquad+y\left[-(\mu+k_1)+C_1(1-p)k_1+C_2fpk_1+C_3(1-f)pk_1\right]\\
&\qquad+z\left[-C_1(1-p)k_1+C_2fk_2\frac{E_2^*}{E_1^*}+C_3(1-f)k_2\frac{E_2^*}{E_1^*}\right]\\
&\qquad+u\left[\frac{\beta S^*I_1^*}{E_1^*}-C_2fpk_1-C_2fk_2\frac{E_2^*}{E_1^*}-C_2\eta\frac{T^*}{E_1^*}+C_4r_1\frac{I_1^*}{E_1^*}\right]\\
&\qquad+v\left[\frac{\sigma S^*I_n^*}{E_1^*}+\frac{\gamma I_n^*}{E_1^*}-C_3(1-f)pk_1-C_3(1-f)k_2\frac{E_2^*}{E_1^*}\right]\\
&\qquad+w\left[-C_4r_1\frac{I_1^*}{E_1^*}+C_5r_2\frac{I_2^*}{E_1^*}\right]+q\left[-C_5r_2\frac{I_2^*}{E_1^*}+C_2\eta\frac{T^*}{E_1^*}\right]\\
&\qquad-\left[\frac{\beta S^*I_1^*}{E_1^*}\frac{1}{x}+\frac{\sigma S^*I_n^*}{E_1^*}\frac{1}{x}+\frac{\beta S^*I_1^*}{E_1^*}\frac{xu}{y}+\frac{\sigma S^*I_n^*}{E_1^*}\frac{xv}{y}\right.\\
&\qquad\quad+\frac{\gamma I_n^*}{E_1^*}\frac{v}{y}+C_1(1-p)k_1\frac{y}{z}+C_2fpk_1\frac{y}{u}\\
&\qquad\quad+C_2fk_2\frac{E_2^*}{E_1^*}\frac{z}{u}+C_2\eta\frac{T^*}{E_1^*}\frac{q}{u}+C_3(1-f)pk_1\frac{y}{v}\\
&\qquad\quad\left.+C_3(1-f)k_2\frac{E_2^*}{E_1^*}\frac{z}{v}+C_4r_1\frac{I_1^*}{E_1^*}\frac{u}{w}+C_5r_2\frac{I_2^*}{E_1^*}\frac{w}{q}\right].
\end{aligned}
\tag{9}
$$

The fact that $(\mu+k_1)E_1^*=\beta S^*I_1^*+\sigma S^*I_n^*+\gamma I_n^*$ is applied in the coefficient of y of the above equation.

Using expressions in (4) and (8), we know that the coefficients of y,z,u,v,w and q reduce to zero. Applying equations (3), (4) and (8), it is easy to see that

$$
\begin{aligned}
C_1(1-p)k_1 &= C_2(1-p)k_1\frac{fk_2}{\mu+k_2} + C_3(1-p)k_1\frac{(1-f)k_2}{\mu+k_2}\\
&= \frac{\beta S^* fk_2(1-p)k_1}{A_3(\mu+k_2)} + \frac{\sigma S^*(1-f)k_2(1-p)k_1}{(\mu+\delta+\gamma)(\mu+k_2)}\\
&\quad + \frac{\gamma(1-f)k_2(1-p)k_1}{(\mu+\delta+\gamma)(\mu+k_2)},\\
C_2fpk_1 &= \frac{\beta S^* fpk_1}{A_3}, \qquad C_2fk_2\frac{E_2^*}{E_1^*} = \frac{\beta S^* fk_2(1-p)k_1}{A_3(\mu+k_2)},\\
C_3(1-f)pk_1 &= \frac{\sigma S^*(1-f)pk_1}{\mu+\delta+\gamma} + \frac{\gamma(1-f)pk_1}{\mu+\delta+\gamma},\\
C_3(1-f)k_2\frac{E_2^*}{E_1^*} &= C_3(1-f)k_2\frac{(1-p)k_1}{\mu+k_2}\\
&= \frac{\sigma S^*(1-f)k_1k_2(1-p)}{(\mu+\delta+\gamma)(\mu+k_2)} + \frac{(1-f)k_1k_2(1-p)\gamma}{(\mu+\delta+\gamma)(\mu+k_2)},\\
\frac{\beta S^* I_1^*}{E_1^*} &= \beta S^*\frac{fk_1A_1}{A_3} = \frac{\beta S^* fk_1p}{A_3} + \frac{\beta S^* fk_1k_2(1-p)}{A_3(\mu+k_2)},\\
\frac{\sigma S^* I_n^*}{E_1^*} &= \sigma S^*\frac{(1-f)k_1A_1}{\mu+\delta+\gamma} = \frac{\sigma S^*(1-f)k_1p}{\mu+\delta+\gamma}\\
&\quad + \frac{\sigma S^*(1-f)k_1k_2(1-p)}{(\mu+\delta+\gamma)(\mu+k_2)},\\
\frac{\gamma I_n^*}{E_1^*} &= \gamma\frac{(1-f)k_1A_1}{\mu+\delta+\gamma} = \frac{(1-f)k_1p\gamma}{\mu+\delta+\gamma}\\
&\quad + \frac{(1-f)k_1k_2(1-p)\gamma}{(\mu+\delta+\gamma)(\mu+k_2)}.
\end{aligned}
\tag{10}
$$

Applying equations (8) and (10), equation (9) can be rewritten as follows:

$$
\begin{aligned}
&h(x,y,z,u,v,w,q)\\
&= \Bigg(4\frac{\beta S^* fk_1(1-p)k_2}{A_3(\mu+k_2)} + 2\frac{(1-f)k_1\gamma p}{\mu+\delta+\gamma}\\
&\quad + 3\frac{(1-f)k_1\gamma(1-p)k_2}{(\mu+\delta+\gamma)(\mu+k_2)} + 3C_2\eta\frac{T^*}{E_1^*} + 3\frac{\beta S^* fk_1p}{A_3}
\end{aligned}
$$

$$
\begin{aligned}
&+ 3\frac{\sigma S^*(1-f)k_1p}{\mu+\delta+\gamma} + 4\frac{\sigma S^*(1-f)k_1(1-p)k_2}{(\mu+\delta+\gamma)(\mu+k_2)}\Big)\\
&- \frac{\beta S^* f k_1(1-p)k_2}{A_3(\mu+k_2)}\Big(\frac{y}{z}+\frac{z}{u}+\frac{1}{x}+\frac{xu}{y}\Big) - \frac{(1-f)k_1\gamma p}{\mu+\delta+\gamma}\Big(\frac{v}{y}+\frac{y}{v}\Big)\\
&- \frac{(1-f)k_1\gamma(1-p)k_2}{(\mu+\delta+\gamma)(\mu+k_2)}\Big(\frac{y}{z}+\frac{z}{v}+\frac{v}{y}\Big) - C_2\eta\frac{T^*}{E_1^*}\Big(\frac{q}{u}+\frac{u}{w}+\frac{w}{q}\Big)\\
&- \frac{\beta S^* f k_1 p}{A_3}\Big(\frac{y}{u}+\frac{1}{x}+\frac{xu}{y}\Big) - \frac{\sigma S^*(1-f)k_1p}{\mu+\delta+\gamma}\Big(\frac{y}{v}+\frac{1}{x}+\frac{xv}{y}\Big)\\
&- \frac{\sigma S^*(1-f)k_1(1-p)k_2}{(\mu+\delta+\gamma)(\mu+k_2)}\Big(\frac{y}{z}+\frac{z}{v}+\frac{1}{x}+\frac{xv}{y}\Big).
\end{aligned}
$$

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

$$
\begin{aligned}
h(x,y,z,u,v,w,q) \le &\Big(4\frac{\beta S^* f k_1(1-p)k_2}{A_3(\mu+k_2)} + 2\frac{(1-f)k_1\gamma p}{\mu+\delta+\gamma}\\
&+ 3\frac{(1-f)k_1\gamma(1-p)k_2}{(\mu+\delta+\gamma)(\mu+k_2)} + 3C_2\eta\frac{T^*}{E_1^*} + 3\frac{\beta S^* f k_1 p}{A_3}\\
&+ 3\frac{\sigma S^*(1-f)k_1p}{\mu+\delta+\gamma} + 4\frac{\sigma S^*(1-f)k_1(1-p)k_2}{(\mu+\delta+\gamma)(\mu+k_2)}\Big)\\
&- 4\frac{\beta S^* f k_1(1-p)k_2}{A_3(\mu+k_2)} - 2\frac{(1-f)k_1\gamma p}{\mu+\delta+\gamma}\\
&- 3\frac{(1-f)k_1\gamma(1-p)k_2}{(\mu+\delta+\gamma)(\mu+k_2)} - 3C_2\eta\frac{T^*}{E_1^*} - 3\frac{\beta S^* f k_1 p}{A_3}\\
&- 3\frac{\sigma S^*(1-f)k_1p}{\mu+\delta+\gamma} - 4\frac{\sigma S^*(1-f)k_1(1-p)k_2}{(\mu+\delta+\gamma)(\mu+k_2)}\\
= &\ 0,
\end{aligned}
$$

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

Combining those inequalities, we have that $(dV_2(t))/dt|_{(1)} \le 0$ with equality only if $S = S^*$, $E_1 = E_1^*$, $E_2 = E_2^*$, $I_1 = I_1^*$, $I_n = I_n^*$, $I_2 = I_2^*$ and $T = T^*$. Therefore, an application of the LaSalle's invariance principle [**14**] yields that the endemic equilibrium $\{P^*\}$ is globally asymptotically stable in Ω. □

From Theorems 3.1 and 3.2, we see that the global dynamics of model (1) are fully determined by the threshold parameter R_0: if $R_0 < 1$, the

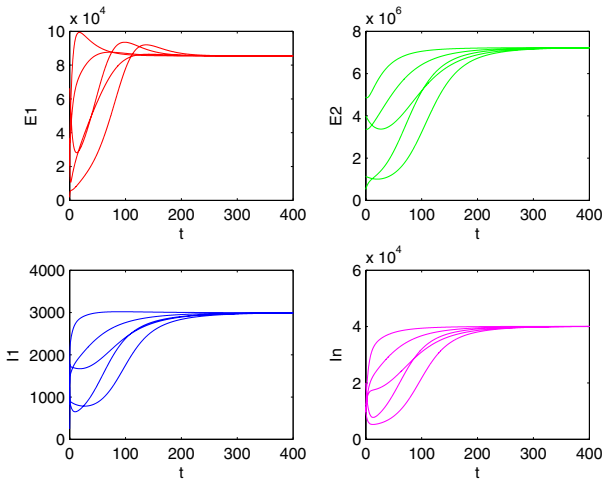

FIGURE 2. The global asymptotic stability of the endemic equilibrium P^*, with $f = 0.414$ [**16**], and hence $R_0 = 3.4743$.

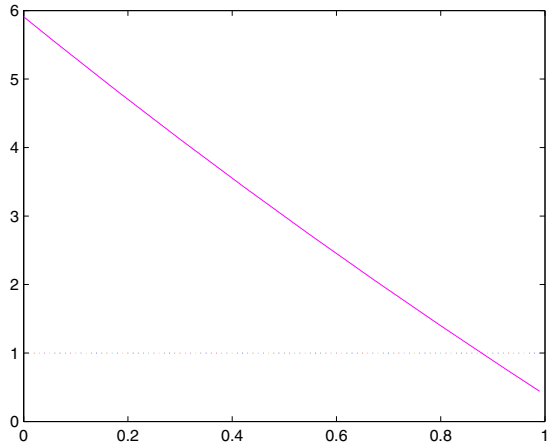

FIGURE 3. The relationship between R_0 and f, when other parameter values are set as described in the text. Note that f needs to be larger than 0.828 to ensure $R_0 < 1$.

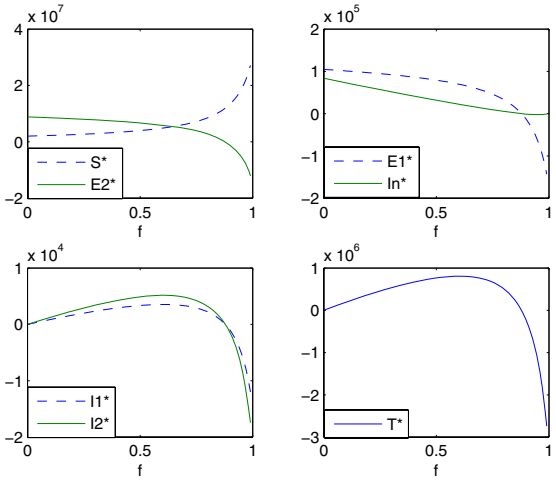

FIGURE 4. The relationship between the components of the endemic equilibrium P^* and f. Note the sharp decrease after $f > 0.828$.

disease-free equilibrium is globally asymptotically stable, and thus the disease always dies out; if $R_0 > 1$, the unique endemic equilibrium is globally asymptotically stable and the disease persists at the unique endemic equilibrium.

4. Numerical simulation results. We now carry out some numerical simulations, where we assume the average life expectancy of uninfected individuals is 70 years and hence $\mu = 1/70$ [**5**] (Figures 2, 3 and 4). We also assume $\Lambda = 170,460$ (Figures 2–4) so that the population size is 11,932,200 in the absence of TB. We also follow the work [**5**] and assume that $p = 0.05$ for the probability of progressing to active TB by fast progression; $k_2 = 0.00256$ so that 5 percent develop the TB disease over 20 years during the long-term latent stage; $d = 0.06$ and $\delta = 0.15$. Furthermore, in the work [**7**], the relapse rate of cured individuals (per year) η is 0.001 and the corresponding γ is 0.2. One infectious individual infects seven susceptible individuals each year [**5**], so $\beta = 1/1704600$ (Figures 2–4). Since the class I_n is not treated, it will infect more individuals in their infectious period, yielding $\sigma > \beta$. We will assume each untreated and infectious individual infects 10 susceptible persons, so that $\sigma = 1/(7 \times 170460)$ (Figures 2–4). We set

$k_1 = 1.5$ [**21**]. Moreover, $r_1 = 3.6$ corresponds to the assumption that 60 percent of class I_1 converts from sputum positive to sputum negative within the first two months of treatment, and $r_2 = 2.4$ corresponds to the assumption that 80 percent of class I_2 transfers to class T within the subsequent four months of treatment.

Figure 2 demonstrates the global asymptotic stability of the unique endemic equilibrium P^* when $R_0 > 1$; here only the curves of E_1, E_2, I_1 and I_n as functions of t are plotted. From the simulation results, we see that E_1, E_2, I_1 and I_n all converge to respective values at the endemic equilibrium, despite the fact that they start from different initial values.

Figures 3 and 4 illustrate the impact of f on R_0 and the components of the endemic equilibrium P^*. It is evident that much improvement of case detection from the reported $f = 0.414$ [**16**] is required to control TB transmission. More specifically, doubling the current case detection rate will be needed to ensure R_0 falls below 1 when we see a sharp decrease of the endemic equilibrium value.

Figures 5, 6 and 7 give trends of the annual new infections and cases of infectious TB, which are two important indices used to evaluate and control TB. We first need to give two definitions. Here we define annual new infections as the number of individuals infected by all infectious cases in one year. We calculate it by using the formula

$$P(t) := \beta S(t) I_1(t) + \sigma S(t) I_n(t). \tag{11}$$

Annual new cases of infectious TB are defined as the number of new infectious cases detected in one year. We use the formula

$$C(t) := f p k_1 E_1(t) + f k_2 E_2(t) + \eta T(t). \tag{12}$$

From recent data, we know that the birthrate of the population was 0.01403 in China in 2000 [**11**], and the total number of population was 1,214,980,875 in China in 2000 [**16**]. Thus, Λ is 17,046,201, and μ is 0.01403. We suppose that one detected infectious individual infects seven persons and one undetected infectious individual infects ten persons in one year. So, β is $7/1214980875$ and σ is $10/1214980875$. Other parameters except for f have the same values as those in Figures 2, 3 and 4. In [**16**], 44.5 percent of the population has been infected

by M. tuberculosis, and there are 4.51 million active cases and 1.5 million infectious cases. The case detection rate of infectious cases is 0.414. So, $S(0) = 674,314,386$, $I_1(0) = 621,000$, $I_n(0) = 879,000$ and $I_2(0) = 3,010,000$, when we let 2000 be the initial time. We assume that 92 percent of infections is latent TB. Infections will stay in the latent class for an average of 20 years and cost 1 year to develop fast infectious TB. Thus, $E_1(0) = 39$, 793,054, $E_2(0) = 457,620,116$ and $T(0) = 38,743,319$.

From Figure 5, we know that annual new infections of TB will decrease if case detection rate of infectious cases increases. The more detected infectious cases, the more treated infectious cases and fewer infectious cases infect others. The increase of $P(t)$ will last for several years, and then it will decrease slowly if f has no big increase.

Figure 6 indicates that $C(t)$ has some change in the first several years and no big difference in subsequent years. The larger f is, the more the infectious cases will be detected, and the larger $C(t)$ from the viewpoint of short duration. If 44.5 percent of the population is infected by the infectious cases, some latent persons will develop infectious cases every year even though the case detection rate of infectious cases is very large in upcoming decades.

Figure 7 illustrates the long-term behavior of $C(t)$ over time. The larger the fraction of the case detection rate of infectious cases, the less the annual new infections (Figure 5), and then there will be fewer detected infectious cases of TB (Figure 7). Because the latency of TB is a long time, the decline of the number of annual new infections of TB cannot immediately indicate the decrease of annual new cases of infectious TB, which has a time delay between them. It is greatly effective to increase the fraction of the case detection rate of infectious cases to control and eradicate TB from the viewpoint of long periods of time.

5. Conclusion. We have developed a compartmental model to describe TB transmission by incorporating fast and slow progression, case detection and different stages of treatment. In our model, the class of treated individuals is divided into two compartments depending on whether they are still infectious or not: treated patients can infect

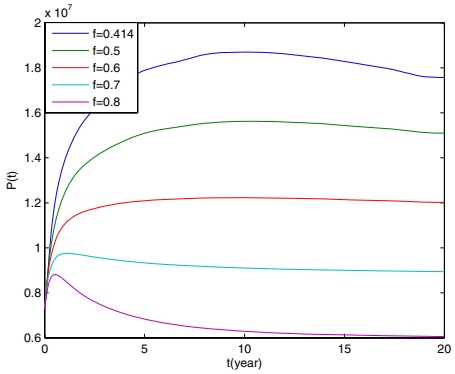

FIGURE 5. Annual new infections of TB with ongoing time.

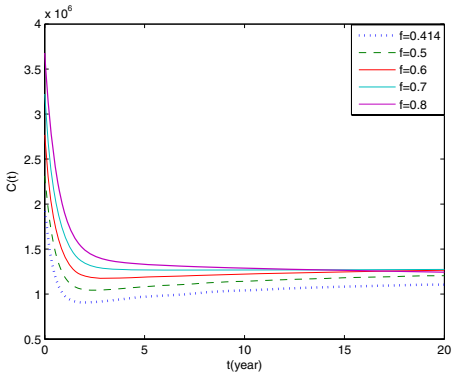

FIGURE 6. The rate of annual new cases of infectious TB under the condition of different case detection rates of the infectious cases.

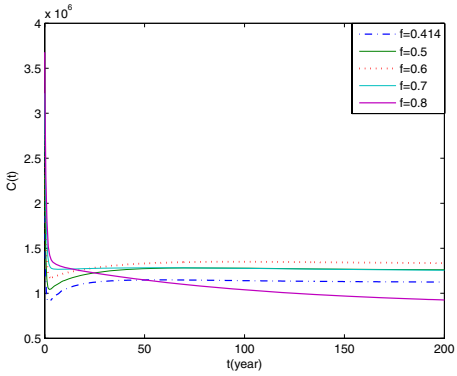

FIGURE 7. Long-term behavior of the rate of annual new cases of infectious TB.

others in the first two months of their treatment, but if they become sputum negative (normally after the first two months of treatment) they enter into the next compartment I_2 when they are no longer infectious.

These additional biological realities make our model more complicated than those previously proposed and investigated in the literature. Nevertheless, we are able to calculate the control reproduction number R_0 using the next generation matrix method, and to show that this number is the threshold for the global dynamics of the model: the global stabilities of the disease-free equilibrium (when $R_0 < 1$) and the endemic equilibrium (if $R_0 > 1$) are obtained based on the construction of Lyapunov functions and using LaSalle's invariance principle. Our simulations also show that the fraction of case detection is critical for effective TB control–doubling the current case detection rate reported from China which is required for a possible TB eradication.

Acknowledgments. We are grateful to the referees of the journal for their good suggestions and thoughtful comments that have improved the presentation of the manuscript.

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