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GLOBAL STABILITY OF TWO TUBERCULOSIS MODELS WITH TREATMENT AND SELF-CURE

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ABSTRACT. Two tuberculosis (TB) models with treatment and self-cure are investigated. It is assumed that the treated individuals may reenter either the latent compartment due to the remainder of Mycobacterium tuberculosis or the infectious compartment due to the treatment failure. On the other hand, infectious individuals with mild symptoms may reenter the latent compartment due to self-cure. After investigating a simple model with one latent compartment, a TB model with two latent compartments is studied to describe the slow and fast progression of the exposed individuals. The basic reproduction numbers of those two models are defined, and their epidemiological interpretation is given. Similar threshold dynamics is obtained for those two models: the disease dies out ultimately when the basic reproduction number is less than or equal to one; the unique endemic equilibrium is globally stable when the basic reproduction number is greater than one. The influence of treatment failure and self-cure on the basic reproduction number is also discussed.

1. Introduction. Tuberculosis (TB) is a bacterial disease caused by *Mycobacterium tuberculosis*, which is usually acquired through airborne infection from active TB cases. It is one of the most common infectious diseases and has been a leading cause of death in the world for centuries. About one-third of the world's population is infected with the TB bacillus [**1, 14**]. In comparison with other infective diseases, following primary infection, most of the individuals infected by TB (approximately 90 percent) stay in a latent stage, and only a small proportion of individuals develop the active TB. Therefore, introducing the latent compartment is necessary for modeling the transmission of TB.

Keywords and phrases. Tuberculosis, treatment, self-cure, equilibrium, global stability.

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There are various mathematical models on TB transmission. In [**4**], the treatment TB models with one-strain and two-strain are investigated. In [**9**], a two-strain TB model with age of infection is established, and the efficiency of the variable period of latency on disease dynamics is analyzed. In [**8**], the exogenous reinfection is incorporated in the transmission model of TB, and complex dynamics (backward bifurcation) is found under certain conditions. In [**13**], a TB model with case detection and two treatment stages is discussed, and the global dynamics of the model is obtained.

In [**4, 13**], it is assumed that the treated individual has a partial immunity, that is, the treated individual may be infected again. In this paper, we assume that the treated individuals are isolated, and they are not able to infect others and cannot be infected. After a period of treatment (usually 6–12 months) the treated one leaves the isolated environment. Since the tuberculosis bacillus may hide from the immune system in its host's fat cells, this pathogen is protected against even the most powerful antibiotics in these cells, in which it may remain dormant for years [**15, 16**]. Most treatment of infectious TB patients is incomplete. After being treated the TB symptoms of a patient may disappear, and there may still be a few tubercle bacillus in the body of the patient; then, these individuals may still be TB carriers and become latent, or may reenter the infectious compartment due to the failure of treatment [**2**].

In this paper, incomplete treatment and self-cure are incorporated in two models, which include one and two latent compartments, respectively. Self-cure means that infectious individuals revert to the latent compartment without being treated [**3**]. The basic TB model with treatment and self-cure is formulated and discussed in Section 2. Since TB has a long latent period between months and decades, and some latent TB cases may occur along with other diseases (such as in an HIV carrier) which can weaken a person's immunity and shorten the latent period of TB [**7, 17**], we divide the latent individuals into two compartments: slow and fast latent to describe the slow or fast progress of latent TB to active TB. A general TB model with treatment, self-cure and slow and fast progress is formulated and investigated in Section 3. The disease-free and endemic equilibria of those two models are studied and threshold dynamics is obtained on the basis of the basic reproduc-

tion number. At last, the influence of treatment failure and self-cure on the basic reproduction number is also discussed.

2. A basic TB model with treatment and self-cure. In this section, we introduce a basic TB model with treatment and self-cure. The total population is divided into four epidemiological compartments: the susceptible compartment (S), the latent compartment (L), the infectious compartment (I), and the treating compartment (T). The susceptible compartment consists of individuals who have not been infected but can become infected and enter the latent compartment. The latent individuals in L have been infected but are not infectious and may develop active TB and become infectious. The individual in I is infectious and is not treated. The individual in T is being treated. An individual may get infected through contacts with infectious individuals.

An individual first enters the latent compartment after being infected. The individual in the latent compartment may stay in the compartment for the rest of his/her life, or becomes active TB and infectious after a period. Persons with active TB can recover spontaneously, or be treated, or die.

It is assumed that the individuals in compartment T are in an isolated environment and cannot infect others. After leaving the treating compartment an individual may reenter compartment L due to treatment success or compartment I due to treatment failure. Some individuals in compartment I may reenter the latent compartment directly due to self-cure. The transfer among compartments is schematically depicted in Figure 1.

The transfer diagram leads to the following system of ordinary differential equations:

$$\begin{cases} dS/dt = \mu(A - S) - \beta IS, \\ dL/dt = \beta IS + (1-k)\delta T - (\mu + \varepsilon)L + q\gamma I, \\ dI/dt = \varepsilon L + k\delta T - (\mu + \gamma + \alpha_1)I, \\ dT/dt = (1-q)\gamma I - (\mu + \delta + \alpha_2)T, \end{cases} \tag{1}$$

where μ is the per capita natural death rate; μA the recruitment rate; β the transmission coefficient; ε the transfer rate at which an

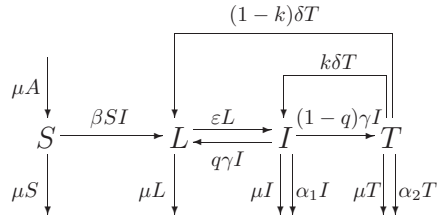

FIGURE 1. The transfer diagram for system (1).

individual leaves the latent compartment and becomes infectious; γ the rate at which an infective individual leaves the infectious compartment; q $(0 \le q < 1)$ the fraction of infectious individuals reentering the latent compartment through self-cure, and $1-q$ the fraction of infectious individuals transferred to the treatment compartment; α_1 and α_2 the per capita disease-induced death rate; δ the treatment rate; k $(0 \le k \le 1)$ the fraction of drug-resistant individuals in the treated compartment, which reflects treatment failure.

For simplicity, denote $b_1 = \mu+\varepsilon$, $b_2 = \mu+\gamma+\alpha_1$, and $b_3 = \mu+\delta+\alpha_2$. Then system (1) becomes

$$\begin{cases} dS/dt = \mu(A-S) - \beta IS, \\ dL/dt = \beta IS + (1-k)\delta T - b_1 L + q\gamma I, \\ dI/dt = \varepsilon L + k\delta T - b_2 I, \\ dT/dt = (1-q)\gamma I - b_3 T. \end{cases} \tag{2}$$

From system (1) or (2), it follows that

$$\begin{aligned} \frac{d(S+L+I+T)}{dt} &= \mu A - \mu(S+L+I+T) - \alpha_1 I - \alpha_2 T \\ &\le \mu A - \mu(S+L+I+T). \end{aligned}$$

Then $\limsup_{t\to\infty}(S+L+I+T) \le A$. This implies that the region

$$\Omega = \{(S,L,I,T) \in R_+^4 : S+L+I+T \le A\}$$

is a positively invariant set for system (1) or (2). In the rest of the paper, our dynamical analysis of system (2) is restricted in the positive invariant set Ω.

It is obvious that system (2) always has the disease-free equilibrium $E_0 = (A, 0, 0, 0)$. By using the method of next generation matrix formulated in [**5, 6**], we can easily obtain the basic reproduction number of system (2)

$$R_0 = \frac{\beta A \varepsilon b_3}{b_1 b_2 b_3 - k b_1 (1-q)\delta\gamma - \varepsilon q \gamma b_3 - (1-k)(1-q)\gamma\delta\varepsilon}. \tag{3}$$

The epidemiological interpretation of the basic reproduction number, R_0, is the expected number of secondary cases produced, in a completely susceptible population, by a typical infective individual. In order to understand the epidemiological meaning of R_0 better, we use the following notations

$$h_1 = \frac{\varepsilon}{b_1}, \qquad h_{21} = \frac{\gamma q}{b_2}, \quad h_{22} = \frac{\gamma(1-q)}{b_2},$$
$$h_{31} = \frac{(1-k)\delta}{b_3}, \quad h_{32} = \frac{k\delta}{b_3}, \quad h_2 = h_{21}h_1 + h_{22}h_{31}h_1 + h_{22}h_{32},$$

and rewrite $R_0 = \beta A \cdot 1/b_2 \cdot 1/(1-h_2) \cdot h_1$. The R_0 can be explained as follows: a fraction h_1 of latent individuals progress to compartment I; a fraction h_{21} of infectious individuals reenter compartment L due to self-cure; a fraction h_{22} of infectious individuals progress to compartment T due to treatment; a fraction h_{31} of individuals being treated reenter compartment L due to treatment success; a fraction h_{32} of individuals being treated reenter compartment I due to treatment failure. Hence, a fraction h_2 of infectious individuals pass through compartment I twice, and a fraction h_2^m of infectious individuals pass through compartment $m+1$ times. Since an infectious individual spends an average of $\tau = 1/b_2$ time units in compartment I when he enters I compartment, an infectious individual introduced into compartment I spends, on average, $\tau(1 + h_2 + h_2^2 + h_2^3 + \cdots) = 1/b_2 \cdot 1/(1-h_2)$ time units in compartment I over its expected lifetime. Therefore, $\beta A \cdot 1/b_2 \cdot 1/(1-h_2)$ is the number of susceptible individuals infected by an infectious individual introduced into a completely susceptible population over its expected lifetime. Notice that the fraction of new latent individuals from compartment L progressing to compartment I is h_1, and the epidemiological meaning of R_0 introduced in (3) is in agreement with the general understanding.

Direct calculation shows that, when $R_0 > 1$, besides the disease-free equilibrium $E_0(A, 0, 0, 0)$, system (2) also has a unique endemic equilibrium $E^*(S^*, L^*, I^*, T^*)$, where

$$\begin{aligned} S^* &= \frac{\mu A}{\mu + \beta I^*}, \\ L^* &= \frac{1}{\varepsilon}\left(b_2 - \frac{k\delta\gamma(1-q)}{b_3}\right) I^*, \\ I^* &= \frac{\mu}{\beta}(R_0 - 1), \\ T^* &= \frac{(1-q)\gamma}{b_3} I^*. \end{aligned}$$

For the global stability of system (2), we have the following results.

Theorem 1. *The disease-free equilibrium E_0 of (2) is globally stable on set Ω if $R_0 \leq 1$; the endemic equilibrium E^* of (2) is globally stable in the interior of the set Ω if $R_0 > 1$.*

Proof. Firstly, we prove global stability of the disease-free equilibrium E_0.

Define a function $V = \varepsilon b_3 L + b_1 b_3 I + \delta[(1-k)\varepsilon + b_1 k]T$. Then

$$\left.\frac{dV}{dt}\right|_{(2)} = \{\beta\varepsilon b_3 S - [b_1 b_2 b_3 - (1-q)\gamma\delta((1-k)\varepsilon + b_1 k) - q\varepsilon\gamma b_3]\} I.$$

Since $S \leq A$ for $(S, L, I, T) \in \Omega$, then

$$\begin{aligned} \left.\frac{dV}{dt}\right|_{(2)} &\leq \{\beta\varepsilon b_3 A - [b_1 b_2 b_3 - (1-q)\gamma\delta((1-k)\varepsilon + b_1 k) - q\varepsilon\gamma b_3]\} I \\ &= \beta\varepsilon b_3 A\left(1 - \frac{1}{R_0}\right) I \leq 0. \end{aligned}$$

It is obvious that $(dV/dt)|_{(2)} = 0$ if and only if $I = 0$ or $S = [b_1 b_2 b_3 - (1-q)\gamma\delta((1-k)\varepsilon + b_1 k) - q\varepsilon\gamma b_3]/(\beta\varepsilon b_3)$. Since $R_0 \leq 1$ implies that $[b_1 b_2 b_3 - (1-q)\gamma\delta((1-k)\varepsilon + b_1 k) - q\varepsilon\gamma b_3]/(\beta\varepsilon b_3) \geq A$, then the largest

invariant set of system (2) on the set $\{(S, L, I, T) \in \Omega : (dV/dt)|_{(2)} = 0\}$ is the singleton $\{E_0\}$. Therefore, it follows from the LaSalle invariance principle [**12**] that E_0 is globally stable if $R_0 \leq 1$.

Secondly, we prove the global stability of the endemic equilibrium E^*.

From system (2), S^*, L^*, I^* and T^* satisfy the following equations

$$\begin{cases} \mu = (\mu A/S) - \beta I, \\ b_1 = (\beta IS/L) + [(1-k)\delta T]/L + (q\gamma I/L), \\ b_2 = (\varepsilon L/I) + (k\delta T/I), \\ b_3 = [(1-q)\gamma I]/T, \end{cases}$$

then system (2) becomes

(4)
$$\begin{cases} dS/dt = S[\mu A((1/S) - (1/S^*)) - \beta(I - I^*)], \\ dL/dt = L[\beta((IS/L) - (I^*S^*/L^*)) + (1-k)\delta((T/L) - (T^*/L^*)) \\ +q\gamma((I/L) - (I^*/L^*))], \\ dI/dt = I[\varepsilon((L/I) - (L^*/I^*)) + k\delta((T/I) - (T^*/I^*))], \\ dT/dt = \gamma T(1-q)((I/T) - (I^*/T^*)). \end{cases}$$

Let $x = S/S^*$, $y = L/L^*$, $z = I/I^*$ and $u = T/T^*$. Then system (4) becomes

(5)
$$\begin{cases} dx/dt = x[(\mu A/S^*)((1/x) - 1) - \beta I^*(z-1)], \\ dy/dt = y[(\beta I^*S^*/L^*)((xz/y) - 1) + (1-k)\delta(T^*/L^*)((u/y) - 1) \\ +q\gamma(I^*/L^*)((z/y) - 1)], \\ dz/dt = z[\varepsilon(L^*/I^*)((y/z) - 1) + k\delta(T^*/I^*)((u/z) - 1)], \\ du/dt = [(\gamma I^*(1-q))/T^*]u((z/u) - 1). \end{cases}$$

In order to prove the global stability of equilibrium $\overline{E}(1,1,1,1)$ of system (5) (i.e., equilibrium $E^*(S^*, L^*, I^*, T^*)$ of system (4)), define the Lyapunov function

$$V = m_1(x - 1 - \ln x) + m_2(y - 1 - \ln y) + m_3(z - 1 - \ln z) + m_4(u - 1 - \ln u).$$

Then

(6)

$$\begin{aligned}
\left.\frac{dV}{dt}\right|_{(5)} &= m_1(x-1)\left[\frac{\mu A}{S^*}\left(\frac{1}{x}-1\right)-\beta I^*(z-1)\right]\\
&\quad + m_2(y-1)\left[\frac{\beta I^* S^*}{L^*}\left(\frac{xz}{y}-1\right)\right.\\
&\qquad\qquad \left. + (1-k)\delta\frac{T^*}{L^*}\left(\frac{u}{y}-1\right)+q\gamma\frac{I^*}{L^*}\left(\frac{z}{y}-1\right)\right]\\
&\quad + m_3(z-1)\left[\varepsilon\frac{L^*}{I^*}\left(\frac{y}{z}-1\right)+k\delta\frac{T^*}{I^*}\left(\frac{u}{z}-1\right)\right]\\
&\quad + m_4\gamma(1-q)\frac{I^*}{T_*}(u-1)\left(\frac{z}{u}-1\right)\\
&= m_1\frac{\mu A}{S^*}(x-1)\left(\frac{1}{x}-1\right)\\
&\quad + \beta I^*\left(\frac{m_2 S^*}{L^*}-m_1\right)xz + r_1 + m_1\beta I^* x + r_2 y\\
&\quad + r_3 z + r_4 u - m_2\frac{\beta S^* I^*}{L^*}\frac{xz}{y}\\
&\quad - m_2(1-k)\delta\frac{T^*}{L^*}\frac{u}{y} - m_2 q\gamma\frac{I^*}{L^*}\frac{z}{y}\\
&\quad - m_3\varepsilon\frac{L^*}{I^*}\frac{y}{z} - m_3 k\delta\frac{T^*}{I^*}\frac{u}{z} - m_4\gamma(1-q)\frac{I^*}{T^*}\frac{z}{u},
\end{aligned}$$

where

$$\begin{aligned}
r_1 &= -m_1\beta I^* + m_2\frac{\beta S^* I^*}{L^*} + m_2(1-k)\delta\frac{T^*}{L^*} + m_2 q\gamma\frac{I^*}{L^*}\\
&\quad + m_3\varepsilon\frac{L^*}{I^*} + m_3 k\delta\frac{T^*}{I^*} + m_4\gamma(1-q)\frac{I^*}{T^*}\\
r_2 &= -m_2\frac{\beta S^* I^*}{L^*} - m_2(1-k)\delta\frac{T^*}{L^*}\\
&\quad - m_2 q\gamma\frac{I^*}{L^*} + m_3\varepsilon\frac{L^*}{I^*},\\
r_3 &= m_1\beta I^* + m_2 q\gamma\frac{I^*}{L^*} - m_3\varepsilon\frac{L^*}{I^*}\\
&\quad - m_3 k\delta\frac{T^*}{I^*} + m_4\gamma(1-q)\frac{I^*}{T^*},
\end{aligned}$$

$$r_4 = m_2(1-k)\delta\frac{T^*}{L^*} + m_3 k\delta\frac{T^*}{I^*} - m_4\gamma(1-q)\frac{I^*}{T^*}.$$

In order to eliminate the terms xz, y, z and u, choose

$$m_1 = \varepsilon S^*, \quad m_2 = \varepsilon L^*, \quad m_3 = b_1 I^*, \quad m_4 = \frac{\delta[b_1 k + \varepsilon(1-k)]}{(1-q)\gamma I^*}T^{*2}.$$

Then

$$r_1 = b_1\varepsilon L^* + \varepsilon q\gamma I^* + 2\delta[b_1 k + \varepsilon(1-k)]T^*,$$
$$r_2 = -r_3 = -\varepsilon[\beta S^* I^* + (1-k)\delta T^* - b_1 L^* + q\gamma I^*] = 0,$$

since $(dL/dt)|_{(S^*,L^*,I^*,T^*)} = 0$ and $r_4 = 0$. Therefore,

$$\begin{aligned}\left.\frac{dV}{dt}\right|_{(5)} &= \varepsilon\mu A\left(2 - x - \frac{1}{x}\right) + r_1 \\ &\quad + \varepsilon\beta S^* I^* x - \beta\varepsilon S^* I^*\frac{xz}{y} - \varepsilon(1-k)\delta T^*\frac{u}{y} \\ &\quad - \varepsilon q\gamma I^*\frac{z}{y} - \varepsilon b_1 L^*\frac{y}{z} - b_1 k\delta T^*\frac{u}{z} \\ &\quad - \delta[b_1 k + \varepsilon(1-k)]T^*\frac{z}{u}.\end{aligned} \tag{7}$$

Since S^*, L^*, I^* and T^* satisfy $dS/dt = 0$ and $dL/dt = 0$, that is,

$$\mu A = \mu S^* + \beta S^* I^*,$$
$$b_1 L^* = \beta S^* I^* + (1-k)\delta T^* + q\gamma I^*,$$

then

$$\begin{aligned}\left.\frac{dV}{dt}\right|_{(5)} &= \varepsilon\mu S^*\left(2 - x - \frac{1}{x}\right) + b_1 k\delta T^*\left(2 - \frac{u}{z} - \frac{z}{u}\right) \\ &\quad + q\gamma I^*\varepsilon\left(2 - \frac{z}{y} - \frac{y}{z}\right) \\ &\quad + \varepsilon\beta I^* S^*\left(3 - \frac{1}{x} - \frac{xz}{y} - \frac{y}{z}\right) \\ &\quad + \varepsilon(1-k)\delta T^*\left(3 - \frac{z}{u} - \frac{u}{y} - \frac{y}{z}\right).\end{aligned}$$

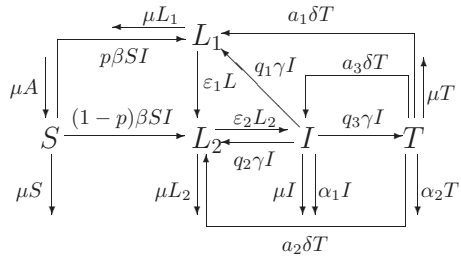

FIGURE 2. The transfer diagram for system (8).

The fact that the arithmetical mean is greater than, or equal to, the geometrical mean implies that

$$2 - x - 1/x \le 0 \quad \text{for } x > 0 \text{ and } 2 - x - 1/x = 0 \text{ if and only if } x = 1;$$

$$2 - u/z - z/u \le 0 \quad \text{for } u, z > 0 \text{ and}$$
$$2 - u/z - z/u = 0 \text{ if and only if } u = z;$$

$$2 - z/y - y/z \le 0 \quad \text{for } y, z > 0 \text{ and}$$
$$2 - z/y - y/z = 0 \text{ if and only if } y = z;$$

$$3 - 1/x - xz/y - y/z \le 0 \quad \text{for } x, y,\ z > 0 \text{ and}$$
$$3 - 1/x - xz/y - y/z = 0 \text{ if and only if } x = 1 \text{ and } y = z;$$

$$3 - z/u - u/y - y/z \le 0 \quad \text{for } y, z, u > 0 \text{ and}$$
$$3 - z/u - u/y - y/z = 0 \text{ if and only if } y = z = u.$$

Therefore, $(dV/dt)|_{(5)} \le 0$ for $x, y, z, u > 0$ and $(dV/dt)|_{(5)} = 0$ if and only if $x = 1$ and $y = z = u$. It is easy to see that the largest invariant set of system (5) on the set $\{(x, y, z, u) : x = 1, y = z = u, x, y, z, u > 0\}$ is the singleton $\overline{E}(1, 1, 1, 1)$. Thus, it follows from the LaSalle invariance principle [**12**] that the equilibrium $\overline{E}$ of system (5) is globally stable. That is, the endemic equilibrium E^* of system (2) is globally stable when it exists.

3. A general TB model with treatment, self-cure and slow and fast progress. Based on the assumptions in the previous section, in this section, we further divide the latent compartment

into two compartments: slow and fast latent compartments. We assume that, after being infected, a susceptible individual may enter either the slow latent compartment or the fast one, which depends upon the status of infected individuals, and that the individuals in the slow latent compartment must go through the fast one before entering the infectious one. Under these assumptions, the transfer among compartments is schematically depicted in the transfer diagram in Figure 2.

The transfer diagram leads to the following system of ordinary differential equations:

$$(8)\quad \begin{cases} dS/dt = \mu(A - S) - \beta IS, \\ dL_1/dt = p\beta IS + a_1\delta T - (\mu + \varepsilon_1)L_1 + q_1\gamma I, \\ dL_2/dt = (1-p)\beta IS + a_2\delta T + \varepsilon_1 L_1 - (\mu + \varepsilon_2)L_2 + q_2\gamma I, \\ dIdt = \varepsilon_2 L_2 + a_3\delta T - (\mu + \gamma + \alpha_1)I, \\ dTdt = q_3\gamma I - (\mu + \delta + \alpha_2)T. \end{cases}$$

Here, p $(0 \le p \le 1)$ is the fraction of susceptible individuals entering the slow latent compartment after being infected, $1 - p$ the fraction entering the fast one; ε_1 the transfer coefficient from the slow latent compartment to the fast one; a_1, a_2, and a_3 $(0 \le a_1, a_2, a_3 \le 1, a_1 + a_2 + a_3 = 1)$ the fractions of treated individuals reverting to the slow and fast latent compartments and infectious one, respectively, a_3 reflects the treatment failure; q_1, q_2 and q_3 $(0 \le q_1, q_2, q_3 \le 1, q_1 + q_2 + q_3 = 1)$ the fractions of infectious individuals reverting to the slow and fast latent compartments by self-cure and being treated, respectively. The meaning of other parameters is the same as those in system (1).

For simplicity, denote $b_1 = \mu + \varepsilon_1$, $b_2 = \mu + \varepsilon_2$, $b_3 = \mu + \gamma + \alpha_1$, and $b_4 = \mu + \delta + \alpha_2$. Then system (8) becomes

$$(9)\quad \begin{cases} dS/dt = \mu(A - S) - \beta IS, \\ dL_1/dt = p\beta IS + a_1\delta T - b_1 L_1 + q_1\gamma I, \\ dL_2/dt = (1-p)\beta IS + a_2\delta T + \varepsilon_1 L_1 - b_2 L_2 + q_2\gamma I, \\ dI/dt = \varepsilon_2 L_2 + a_3\delta T - b_3 I, \\ dT/dt = q_3\gamma I - b_4 T. \end{cases}$$

From system (8) or (9), it follows that

$$\frac{d(S + L_1 + L_2 + I + T)}{dt} = \mu A - \mu(S + L_1 + L_2 + I + T) - \alpha_1 I - \alpha_2 T.$$

Then $\limsup_{t\to\infty}(S + L_1 + L_2 + I + T) \le A$. This implies that the region

$$\Omega_1 = \{(S, L_1, L_2, I, T) \in R_+^5 : S + L_1 + L_2 + I + T \le A\}$$

is a positively invariant set for system (8) or (9). So we consider dynamics of system (9) in the set Ω_1 in the rest part of the paper.

It is obvious that system (9) always has the disease-free equilibrium $E_0 = (A, 0, 0, 0, 0)$. By using the method of next generation matrix formulated in [**5, 6**], we can obtain the basic reproduction number of system (9)

$$R_0 = \frac{\beta A\varepsilon_2 b_4[\varepsilon_1 p + (1-p)b_1]}{b_1b_2b_3b_4 - \delta\gamma q_3(b_1b_2a_3 + b_1\varepsilon_2 a_2 + \varepsilon_1\varepsilon_2 a_1) - b_1\varepsilon_2 q_2\gamma b_4 - \varepsilon_1\varepsilon_2 q_1\gamma b_4}.$$

Similar to Section 2, denote

$$h_1 = \frac{\varepsilon_1}{b_1}, \quad h_2 = \frac{\varepsilon_2}{b_2}, \quad h_{31} = \frac{q_1\gamma}{b_3}, \quad h_{32} = \frac{q_2\gamma}{b_3},$$
$$h_{33} = \frac{q_3\gamma}{b_3}, \quad h_{41} = \frac{a_1\delta}{b_4}, \quad h_{42} = \frac{a_2\delta}{b_4}, \quad h_{43} = \frac{a_3\delta}{b_4},$$

and $h = h_{31}h_1h_2 + h_{32}h_2 + h_{33}(h_{41}h_1h_2 + h_{42}h_2 + h_{43})$. Then R_0 can be rewritten as $R_0 = \beta A \cdot 1/b_3 \cdot 1/(1-h) \cdot [ph_1h_2 + (1-p)h_2]$. The terms in the expression of R_0 have the following explanation: a fraction h_1 of slow latent individuals progress to compartment L_2; a fraction h_2 of fast latent individuals progress to compartment I; the fractions h_{31} and h_{32} of infectious individuals reenter compartments L_1 and L_2 due to self-cure, respectively; a fraction h_{33} of infectious individuals progress to compartment T due to treatment; the fractions h_{41} and h_{42} of individuals being treated reenter compartments L_1 and L_2 due to treatment success, respectively; a fraction h_{43} of individuals being treated reenter compartment I due to treatment failure. A fraction h of infectious individuals pass through compartment I twice, and a fraction h^m of infectious individuals pass through compartment $m+1$ times. Since an infectious individual spends an average of $\tau = 1/b_3$ time units in compartment I when he enters compartment I, an infectious individual introduced into compartment I spends, on average, $\tau(1+h+h^2+h^3+\cdots) = 1/b_3 \cdot 1/(1-h)$ time units in compartment I over his

expected lifetime. The fractions p and $1-p$ of new latent individuals from compartment S progress to slow and fast compartments L_1 and L_2, respectively, and the fractions h_1h_2 and h_2 of individuals in compartments L_1 and L_2 progress to compartment I, respectively. Therefore, we can have the usual epidemiological interpretation of the basic reproductive number R_0.

Direct calculation shows that, when $R_0 > 1$, besides the disease-free equilibrium $E_0(A, 0, 0, 0, 0)$, system (9) also has a unique endemic equilibrium $E^*(S^*, L_1^*, L_2^*, I^*, T^*)$, where

$$S^* = \frac{\mu A}{\mu + \beta I^*}, \quad L_1^* = \frac{I^*}{b_1}\left(\frac{p\beta\mu A}{\mu + \beta I^*} + \frac{a_1\delta\gamma q_3}{b_4} + q_1\gamma\right),$$
$$L_2^* = \frac{I^*}{\varepsilon_2}\left(b_3 - \frac{a_3\delta\gamma q_3}{b_4}\right), \quad I^* = \frac{\mu}{\beta}(R_0 - 1), \quad T^* = \frac{\gamma q_3}{b_4} I^*.$$

For the global stability of system (9), we have the following results.

Theorem 2. *For system* (9)*, the disease-free equilibrium* E_0 *is globally stable on set* Ω_1 *if* $R_0 \leq 1$*; the endemic equilibrium* E^* *is globally stable in the interior of set* Ω_1 *if* $R_0 > 1$*.*

Proof. Firstly, we prove the global stability of the disease-free equilibrium E_0.

Let $V = b_4\varepsilon_1\varepsilon_2 L_1 + b_4\varepsilon_2 b_1 L_2 + b_1 b_2 b_4 I + \delta(b_1 b_2 a_3 + b_1\varepsilon_2 a_2 + \varepsilon_1\varepsilon_2 a_1)T$. Then direct calculation shows $dV/dt|_{(9)} = \{\beta\varepsilon_2 b_4[\varepsilon_1 p + (1-p)b_1]S - B\}I$, where $B = b_1 b_2 b_3 b_4 - \delta\gamma q_3(b_1 b_2 a_3 + b_1\varepsilon_2 a_2 + \varepsilon_1\varepsilon_2 a_1) - b_1\varepsilon_2 q_2\gamma b_4 - \varepsilon_1\varepsilon_2 q_1\gamma b_4$.

Then $dV/dt|_{(9)} \leq \{\beta\varepsilon_2 b_4[\varepsilon_1 p + (1-p)b_1]A - B\}I = \beta A\varepsilon_2 b_4[\varepsilon_1 p + (1-p)b_1](1 - 1/R_0)I \leq 0$, since $S \leq A$ for $(S, L_1, L_2, I, T) \in \Omega$.

It is obvious that $(dV/dt)|_{(9)} = 0$ if and only if $I = 0$ or $S = B/\{\beta\varepsilon_2 b_4[\varepsilon_1 p + (1-p)b_1]\}$. Since $R_0 \leq 1$ implies that $B/\{\beta\varepsilon_2 b_4[\varepsilon_1 p + (1-p)b_1]\} \geq A$, then the largest invariant set of system (9) on the set $\{(S, L_1, L_2, I, T) \in \Omega : (dV/dt)|_{(9)} = 0\}$ is the singleton $\{E_0\}$. Therefore, it follows from the LaSalle invariance principle [**12**] that E_0 is globally stable if $R_0 \leq 1$.

Secondly, we prove global stability of the endemic equilibrium E^*.

From system (9), S^*, L_1^*, L_2^*, I^* and T^* satisfy the following equations

$$(10)\quad \begin{cases} \mu = (\mu A/S) - \beta I, \\ b_1 = p\beta IS/L_1 + a_1\delta T/L_1 + q_1\gamma I/L_1, \\ b_2 = (1-p)\beta IS/L_2 + a_2\delta T/L_2 + \varepsilon_1 L_1/L_2 + q_2\gamma I/L_2, \\ b_3 = \varepsilon_2 L_2/I + a_3\delta T/I, \\ b_4 = q_3\gamma I/T. \end{cases}$$

Then system (9) becomes

$$(11)\quad \begin{cases} dS/dt = S[\mu A((1/S) - (1/S^*)) - \beta(I - I^*)], \\ dL_1/dt = L_1[p\beta((IS/L_1) - (I^*S^*/L_1^*)) \\ +a_1\delta((T/L_1) - (T^*/L_1^*)) + q_1\gamma((I/L_1) - (I^*/L_1^*))], \\ dL_2/dt = L_2[(1-p)\beta((IS/L_2) - (I^*S^*/L_2^*)) \\ +a_2\delta((T/L_2) - (T^*/L_2^*)) + \varepsilon_1((L_1/L_2) - (L_1^*/L_2^*)) \\ +q_2\gamma((I/L_2) - (I^*/L_2^*))], \\ dI/dt = I[\varepsilon_2((L_2/I) - (L_2^*/I^*)) + a_3\delta((T/I) - (T^*/I^*))], \\ dT/dt = q_3\gamma T((I/T) - (I^*/T^*)). \end{cases}$$

Let $x = S/S^*$, $y = L_1/L_1^*$, $z = L_2/L_2^*$, $u = I/I^*$, $v = T/T^*$; then system (11) becomes

$$(12)\quad \begin{cases} dx/dt = x[(\mu A/S^*)((1/x) - 1) - \beta I^*(u-1)], \\ dy/dt = y[(p\beta I^*S^*/L_1^*)((xu/y) - 1) + (a_1\delta T^*/L_1^*)((v/y) - 1) \\ +(q_1\gamma I^*/L_1^*)((u/y) - 1)], \\ dz/dt = z[((1-p)\beta I^*S^*)/L_2^*((xu/z) - 1) + (a_2\delta T^*)/L_2^*((v/z) - 1) \\ +(\varepsilon_1 L_1^*)/L_2^*((y/z) - 1) + (q_2\gamma I^*)/L_2^*((u/z) - 1)], \\ du/dt = u[(\varepsilon_2 L_2^*)/I^*((z/u) - 1) + (a_3\delta T^*)/I^*((v/u) - 1)], \\ dv/dt = (q_3\gamma I^*)/T^*v\mathbf{Z}((u/v) - 1). \end{cases}$$

In order to prove the global stability of equilibrium $\overline{E}(1,1,1,1,1)$ of system (12) (i.e., equilibrium $E^*(S^*, L_1^*, L_2^*, I^*, T^*)$ of system (9)), define the Lyapunov function

$$V = m_1(x - 1 - \ln x) + m_2(y - 1 - \ln y) + m_3(z - 1 - \ln z) + m_4(u - 1 - \ln u) + m_5(v - 1 - \ln v).$$

Then

(13)
$$\begin{aligned}
\left.\frac{dV}{dt}\right|_{(12)} &= m_1(x-1)\left[\frac{\mu A}{S^*}\left(\frac{1}{x}-1\right)-\beta I^*(u-1)\right]\\
&\quad + m_2(y-1)\left[\frac{p\beta I^*S^*}{L_1^*}\left(\frac{xu}{y}-1\right)+\frac{a_1\delta T^*}{L_1^*}\left(\frac{v}{y}-1\right)\right.\\
&\qquad\qquad \left. + \frac{q_1\gamma I^*}{L_1^*}\left(\frac{u}{y}-1\right)\right]\\
&\quad + m_3(z-1)\left[\frac{(1-p)\beta I^*S^*}{L_2^*}\left(\frac{xu}{z}-1\right)+\frac{a_2\delta T^*}{L_2^*}\left(\frac{v}{z}-1\right)\right.\\
&\qquad\qquad \left. + \frac{\varepsilon_1 L_1^*}{L_2^*}\left(\frac{y}{z}-1\right)+\frac{q_2\gamma I^*}{L_2^*}\left(\frac{u}{z}-1\right)\right]\\
&\quad + m_4(u-1)\left[\frac{\varepsilon_2 L_2^*}{I^*}\left(\frac{z}{u}-1\right)+\frac{a_3\delta T^*}{I^*}\left(\frac{v}{u}-1\right)\right]\\
&\quad + m_5\frac{q_3\gamma I^*}{T^*}(v-1)\left(\frac{u}{v}-1\right)\\
&= m_1\frac{\mu A}{S^*}(x-1)\left(\frac{1}{x}-1\right)\\
&\quad + \left[-m_1\beta I^* + m_2\frac{p\beta I^*S^*}{L_1^*}+\frac{m_3(1-p)\beta I^*S^*}{L_2^*}\right]xu\\
&\quad + r_1 + m_1\beta I^*x + r_2y + r_3z + r_4u + r_5v\\
&\quad - m_2\frac{p\beta I^*S^*}{L_1^*}\frac{xu}{y} - m_2\frac{a_1\delta T^*}{L_1^*}\frac{v}{y} - m_2\frac{q_1\gamma I^*}{L_1^*}\frac{u}{y}\\
&\quad - m_3\frac{(1-p)\beta I^*S^*}{L_2^*}\frac{xu}{z} - m_3\frac{a_2\delta T^*}{L_2^*}\frac{v}{z}\\
&\quad - m_3\frac{\varepsilon_1 L_1^*}{L_2^*}\frac{y}{z} - m_3\frac{q_2\gamma I^*}{L_2^*}\frac{u}{z} - m_4\frac{\varepsilon_2 L_2^*}{I^*}\frac{z}{u}\\
&\quad - m_4\frac{a_3\delta T^*}{I^*}\frac{v}{u} - m_5\frac{q_3\gamma I^*}{T^*}\frac{u}{v},
\end{aligned}$$

where

$$\begin{aligned}
r_1 &= -m_1\beta I^* + m_2p\beta\frac{S^*I^*}{L_1^*} + m_2a_1\delta\frac{T^*}{L_1^*} + m_2q_1\gamma\frac{I^*}{L_1^*}\\
&\quad + m_3(1-p)\beta\frac{I^*S^*}{L_2^*}
\end{aligned}$$

$$
\begin{aligned}
&+ m_3a_2\delta\frac{T^*}{L_2^*} + m_3\varepsilon_1\frac{L_1^*}{L_2^*} + m_3q_2\gamma\frac{I^*}{L_2^*} + m_4\varepsilon_2\frac{L_2^*}{I^*}\\
&+ m_4a_3\delta\frac{T^*}{I^*} + m_5q_3\gamma\frac{I^*}{T^*},\\
r_2 &= -m_2p\beta\frac{S^*I^*}{L_1^*} - m_2a_1\delta\frac{T^*}{L_1^*} - m_2q_1\gamma\frac{I^*}{L_1^*} + m_3\varepsilon_1\frac{L_1^*}{L_2^*},\\
r_3 &= -m_3(1-p)\beta\frac{S^*I^*}{L_2^*} - m_3a_2\delta\frac{T^*}{L_2^*} - m_3\varepsilon_1\frac{L_1^*}{L_2^*} - m_3q_2\gamma\frac{I^*}{L_2^*}\\
&+ m_4\frac{\varepsilon_2L_2^*}{I^*},\\
r_4 &= m_1\beta I^* + m_2q_1\gamma\frac{I^*}{L_1^*} + m_3q_2\gamma\frac{I^*}{L_2^*} - m_4\varepsilon_2\frac{L_2^*}{I^*} - m_4a_3\delta\frac{T^*}{I^*}\\
&+ m_5q_3\gamma\frac{I^*}{T^*},\\
r_5 &= m_2a_1\delta\frac{T^*}{L_1^*} + m_3a_2\delta\frac{T^*}{L_2^*} + m_4a_3\delta\frac{T^*}{I^*} - m_5q_3\gamma\frac{I^*}{T^*}.
\end{aligned}
$$

In order to eliminate the terms xu, y, z, u, and v, choose

$$
\begin{aligned}
&m_1 = [\varepsilon_1p + b_1(1-p)]S^*, \qquad m_2 = \varepsilon_1L_1^*, \qquad m_3 = b_1L_2^*,\\
&m_4 = \frac{b_1b_2}{\varepsilon_2}I^*, \qquad m_5 = \left(b_1a_2 + \varepsilon_1a_1 + \frac{b_1b_2a_3}{\varepsilon_2}\right)\frac{\delta T^{*2}}{q_3\gamma I^*},
\end{aligned}
$$

then

$$
\begin{aligned}
r_1 &= 2\left(b_1a_2 + \varepsilon_1a_1 + \frac{b_1b_2a_3}{\varepsilon_2}\right)\delta T^* + \varepsilon_1q_1\gamma I^*\\
&\quad + b_1\varepsilon_1L_1^* + b_1q_2\gamma I^* + b_1b_2L_2^*;\\
r_2 &= -\varepsilon_1\left(p\beta I^*S^* + a_1\delta T^* + q_1\gamma I^* - b_1L_1^*\right) = 0,
\end{aligned}
$$

since

$$
\begin{aligned}
\left.\frac{dL_1}{dt}\right|_{(S^*,L_1^*,L_2^*,I^*,T^*)} &= 0;\\
r_3 &= -b_1[(1-p)\beta I^*S^* + a_2\delta T^* + \varepsilon_1L_1^*\\
&\quad + q_2\gamma I^* - b_2L_2^*] = 0,
\end{aligned}
$$

since

$$\left.\frac{dL_2}{dt}\right|_{(S^*,L_1^*,L_2^*,I^*,T^*)} = 0;$$

$$\begin{aligned} r_4 &= [\varepsilon_1 p + b_1(1-p)]\,\beta I^* S^* + \varepsilon_1 q_1 \gamma I^* + b_1 q_2 \gamma I^* \\ &\quad - b_1 b_2 L_2^* + (b_1 a_2 + \varepsilon_1 a_1)\delta T^* = -(r_2 + r_3) = 0; \\ r_5 &= 0. \end{aligned}$$

Therefore,

$$\begin{aligned} \left.\frac{dV}{dt}\right|_{(12)} &= [\varepsilon_1 p + b_1(1-p)]\mu A(x-1)\left(\frac{1}{x} - 1\right) \\ &\quad + r_1 + [\varepsilon_1 p + b_1(1-p)]\beta I^* S^* x - \varepsilon_1 p \beta I^* S^* \frac{xu}{y} \\ &\quad - \varepsilon_1 a_1 \delta T^* \frac{v}{y} - \varepsilon_1 q_1 \gamma I^* \frac{u}{y} \\ &\quad - b_1(1-p)\beta I^* S^* \frac{xu}{z} - b_1 a_2 \delta T^* \frac{v}{z} - b_1 \varepsilon_1 L_1^* \frac{y}{z} \\ &\quad - b_1 q_2 \gamma I^* \frac{u}{z} - b_1 b_2 L_2^* \frac{z}{u} - \frac{b_1 b_2 a_3 \delta T^*}{\varepsilon_2} \frac{v}{u} \\ &\quad - \left(b_1 a_2 + \varepsilon_1 a_1 + \frac{b_1 b_2 a_3}{\varepsilon_2}\right) \delta T^* \frac{u}{v}. \end{aligned} \tag{14}$$

Since S^*, L_1^*, L_2^*, I^* and T^* satisfy $dS/dt = 0$, $dL_1/dt = 0$ and $dL_2/dt = 0$, that is,

$$\begin{aligned} \mu A &= \mu S^* + \beta S^* I^*, \\ b_1 L_1^* &= p\beta I^* S^* + a_1 \delta T^* + q_1 \gamma I^*, \\ b_2 L_2^* &= (1-p)\beta I^* S^* + a_2 \delta T^* + \varepsilon_1 L_1^* + q_2 \gamma I^*, \end{aligned}$$

then

$$\begin{aligned} \left.\frac{dV}{dt}\right|_{(12)} &= [\varepsilon_1 p + b_1(1-p)]\mu S^* \left(2 - x - \frac{1}{x}\right) \\ &\quad + \varepsilon_1 p \beta I^* S^* \left(4 - \frac{1}{x} - \frac{xu}{y} - \frac{y}{z} - \frac{z}{u}\right) \\ &\quad + b_1(1-p)\beta I^* S^* \left(3 - \frac{1}{x} - \frac{xu}{z} - \frac{z}{u}\right) \end{aligned}$$

$$
\begin{aligned}
&+\frac{b_1b_2a_3\delta T^*}{\varepsilon_2}\left(2-\frac{v}{u}-\frac{u}{v}\right)\\
&+\varepsilon_1a_1\delta T^*\left(4-\frac{v}{y}-\frac{y}{z}-\frac{z}{u}-\frac{u}{v}\right)\\
&+b_1a_2\delta T^*\left(3-\frac{v}{z}-\frac{z}{u}-\frac{u}{v}\right)\\
&+\varepsilon_1q_1\gamma I^*\left(3-\frac{u}{y}-\frac{y}{z}-\frac{z}{u}\right)+b_1q_2\gamma I^*\left(2-\frac{u}{z}-\frac{z}{u}\right).
\end{aligned}
$$

Similar to the proof of Theorem 1, $(dV/dt)|_{(12)} = 0$ holds if and only if $x = 1$ and $y = z = u = v$, and the largest invariant set of system (12) on the set $\{(x, y, z, u, v) : x = 1, y = z = u = v, x, y, z, u, v > 0\}$ is the singleton $\overline{E}(1, 1, 1, 1, 1)$. Thus, it follows from the LaSalle invariance principle [**12**] that the equilibrium $\overline{E}$ of system (12) is globally stable. That is, the endemic equilibrium E^* of system (9) is globally stable when it exists.

4. Discussion. Tuberculosis is a serious, re-emerging bacterial illness in many countries. Most people who have TB infection have no symptoms, never develop TB disease and cannot spread the infection to others. For some people with the TB disease, the body's immune system is able to fight the TB bacteria and stop them from multiplying, and they can get self-cured. In this paper, we formulated and studied two TB models with self-cure, treatment and fast and slow progress models. The basic model considers the simple case with one latent compartment. The general model describes fast and slow progress with two latent compartments. Basic reproduction numbers are defined by the spectrum method of the next generation matrix. By the method in [**10, 11**], threshold dynamics is established: the disease will die out if the basic reproductive number is less than, or equal to, one. The disease will persist and the numbers of infected individuals in the latent and infectious compartments tend to the positive constants, respectively, if the basic reproductive number is greater than one.

For the basic production number R_0 of model (1) (or (2)), direct calculation gives

$$
\frac{\partial R_0}{\partial k}=\frac{(1-q)\gamma\delta\mu R_0^2}{\beta Ab_3\varepsilon}>0, \qquad \frac{\partial R_0}{\partial q}=-\frac{\gamma R_0^2}{\beta A\varepsilon b_3}[k\mu\delta-\varepsilon(\mu+\alpha_2)].
$$

$\partial R_0/\partial k > 0$ implies that the basic production number R_0 increases with the fraction of treatment failure k increasing. On the other hand, $\partial R_0/\partial q < 0$ for $k > k^* := \varepsilon(\mu + \alpha_2)/(\mu\delta)$, and $\partial R_0/\partial q > 0$ for $k < k^*$. $k = k^*$ is a criterion to describe the influence of the self-cure fraction q on the basic reproduction number. When the self-cure fraction q increases, R_0 decreases for $k > k^*$ and increases for $k < k^*$. From the expression of the basic production number R_0 of model (8) (or (9)), we can find similar results about the effect of the fractions of treatment failure and self-cure on the basic reproduction number. In addition, for model (8) (or (9)), it is easy to see that R_0 decreases with increasing p, which is the fraction of susceptible individuals entering the slow latent compartment. The dynamics of those models and the influence of parameters on the basic reproductive number can help us to design and assess TB control measures.

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