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GLOBAL STABILITY IN A MATHEMATICAL MODEL OF TUBERCULOSIS

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ABSTRACT. Mathematical analysis is carried out for a mathematical model of Tuberculosis (TB) that incorporates both latent and clinical stages. Our analysis establishes that the global dynamics of the model are completely determined by a basic reproduction number R_0. If $R_0 \leq 1$, the TB always dies out. If $R_0 > 1$, the TB becomes endemic, and a unique endemic equilibrium is globally asymptotically stable in the interior of the feasible region.

1 Introduction Tuberculosis (TB) is an ancient disease caused by the infection of bacterium *Mycobacterium tuberculosis*. Once thought under control using antibiotic therapies, TB made a dramatic come back in the late nineteen eighties and early nineteen nineties, largely due to the emergence of antibiotic resistant stains and to co-infection with HIV. Currently, the global per capita incidence rate of TB is growing at approximately 1.1% per year, and the number of cases at 2.4% per year. According to the 2004 WHO report "Global Tuberculosis Control" [**1**], there were 8.8 million new cases of TB worldwide in 2002, with close to 2 million TB-related deaths, more than any other infectious diseases. TB remains as one of the most serious health problems facing the world today.

Mathematical models have been used to improve our understanding of the basic transmission dynamics of TB and to evaluate the effectiveness of various control and prevention strategies [**2**–**11**]. The TB bacteria can spread in the air from a person with active TB disease to others when they are in close contact. When first infected with TB bacteria, a person typically goes through a latent, asymptomatic and non-infectious period during which the body's immune system fights the TB bacteria. There are two distinct stages of the latent TB infection. During the first two years, the risk of developing active disease is much higher, whereas

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during the later stage, the progression to active disease is much slower. Using a compartmental approach, the total host population can be partitioned into four compartments: susceptible individuals (X), early latent (E) and late latent (L) individuals, and individuals with active TB disease (T). Only individuals in compartment T are infectious, and new infections result from contacts between a susceptible and an infectious individual, with an incidence rate $\beta X(t)T(t)$. Here $X(t)$, $E(t)$, $L(t)$ and $T(t)$ denote the density of populations in the four corresponding compartments at time t. Once infected, individuals progress through the early latent stage with an average rate ω. A fraction p, $0 < p \leq 1$, of these individuals progress directly to the active TB stage, and the remaining $1 - p$ fraction progresses to the late latent stage. Once there, the rate of progression to active disease is at a lower rate ν. The input of the susceptibles is assumed to be a constant π, and removal rates for the four compartments are μ_X, μ_E, μ_L and μ_T, respectively. Here removal may include natural death, death due to TB, and removal from treatment. The dynamical transfer among the four compartments is depicted in the following transfer diagram. Here all parameters are assumed to be positive.

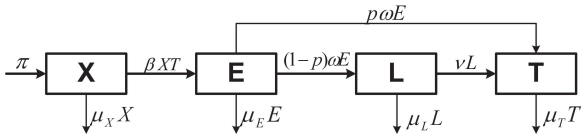

FIGURE 1: The transfer diagram for model (1).

Based on our assumptions and the transfer diagram, the model can be described by four ordinary differential equations as follow:

$$
\begin{aligned}
X' &= \pi - \beta XT - \mu_X X, \\
E' &= \beta XT - (\mu_E + \omega)E, \\
L' &= (1-p)\omega E - (\mu_L + \nu)L, \\
T' &= p\omega E + \nu L - \mu_T T.
\end{aligned} \tag{1}
$$

A similar model was first proposed by Ziv, *et al.* [**11**] to discuss effectiveness of treating TB patients at the early latent stage, where

treatment rates were singled out from removal rates μ_E, μ_L and μ_T. A basic reproduction number R_0 is derived in [**11**],

$$R_0 = \frac{\beta\pi\omega(\nu + p\mu_L)}{\mu_X(\mu_E + \omega)(\mu_L + \nu)\mu_T}, \tag{2}$$

based on which quantitative analysis was carried out. The parameter R_0 measures the average number of infections caused by one infectious individual throughout the infectious period, when introduced into an entirely susceptible population. It is expected that if $R_0 < 1$, then no TB epidemic can develop in the population, and if $R_0 > 1$, a TB epidemic can develop and become endemic in the population. In the present paper, we give a rigorous mathematical analysis of model (1), and prove that the global dynamics of the model is completely determined by the parameter R_0 in (2). More specifically, we prove that if $R_0 \leq 1$, then the disease-free equilibrium $P_0 = (\pi/\mu_X, 0, 0, 0)$ is globally stable in the feasible region; if $R_0 > 1$, P_0 is unstable, and a unique endemic equilibrium $P^* = (X^*, E^*, L^*, T^*)$ with $X^*, E^*, L^*, T^* > 0$ exists and is asymptotically stable. Furthermore, all solutions in the interior of the feasible region converge to P^*. In particular, our results establish that the expression of R_0 in (2) as derived in [**11**] represents the true basic reproduction number.

In the next section, we discuss the feasible region of the model and its equilibria. The global dynamics when $R_0 \leq 1$ are established in Section 3, and the global results when $R_0 > 1$ is given in Section 4.

2 Feasible region and equilibria of the system It can be verified that if a solution to (1) starts in the nonnegative cone $\mathbb{R}^4_+$ of $\mathbb{R}^4$, it remains in $\mathbb{R}^4_+$. Furthermore, from (1) we have

$$X' \leq \pi - \mu_X X$$

and thus $\limsup_{t\to\infty} X(t) \leq \pi/\mu_X$ along each solution to (1). Let $N(t) = X(t) + E(t) + L(t) + T(t)$. Then using (1) we have

$$N' = \pi - \mu_X X - \mu_E E - \mu_L L - \mu_T T \leq \pi - \overline{\mu} N,$$

where $\overline{\mu} = \min\{\mu_X, \mu_E, \mu_L, \mu_T\}$. This implies that $\limsup_{t\to\infty} N(t) \leq \pi/\overline{\mu}$. Therefore the model can be studied in the feasible region

$$\Gamma = \left\{(X, E, L, T) \in \mathbb{R}^4_+ \,:\, 0 \leq X \leq \frac{\pi}{\mu_X},\ 0 \leq X+E+L+T \leq \frac{\pi}{\overline{\mu}}\right\}. \tag{3}$$

The closed set Γ is positively invariant with respect to (1). We denote by $\operatorname{Int}\Gamma$ the interior of Γ in $\mathbb{R}^4_+$.

An equilibrium (X, E, L, T) of (1) satisfies the following equations

$$\pi = \beta XT + \mu_X X, \tag{4}$$

$$\beta XT = (\mu_E + \omega)E, \tag{5}$$

$$(1-p)\omega E = (\mu_L + \nu)L, \tag{6}$$

$$p\omega E + \nu L = \mu_T T. \tag{7}$$

Simplifying these equations we obtain

$$\left[\beta X - \frac{(\mu_E+\omega)(\mu_L+\nu)\mu_T}{\omega(\nu+p\mu_L)}\right] T = 0.$$

Therefore,

$$\text{either} \quad T = 0 \quad \text{or} \quad X = \frac{(\mu_E+\omega)(\mu_L+\nu)\mu_T}{\beta\omega(\nu+p\mu_L)}.$$

Correspondingly, system (1) has two possible equilibria: the disease-free equilibrium $P_0 = (\pi/\mu_X, 0, 0, 0)$ and the endemic equilibrium $P^* = (X^*, E^*, L^*, T^*)$ where

$$X^* = \frac{(\mu_E+\omega)(\mu_L+\nu)\mu_T}{\beta\omega(\nu+p\mu_L)}\,. \tag{8}$$

In [11], the basic reproduction number is defined as

$$R_0 = \frac{\beta\pi\omega(\nu+p\mu_L)}{\mu_X(\mu_E+\omega)(\mu_L+\nu)\mu_T}\,, \tag{9}$$

which describes the average number of infections produced when one infectious individual is introduced into a population at the disease-free equilibrium, namely, R_0 satisfies

$$R_0\, X^* = \frac{\pi}{\mu_X}\,.$$

Using R_0 we have the following expressions for the coordinates of P^*:

$$\begin{aligned} X^* &= \frac{\pi}{\mu_X R_0}, & E^* &= \frac{\pi}{(\mu_E+\omega)}\left(1-\frac{1}{R_0}\right), \\ L^* &= \frac{(1-p)\mu_X\mu_T}{\beta(\nu+p\mu_L)}(R_0-1), & T^* &= \frac{\mu_X}{\beta}(R_0-1). \end{aligned} \tag{10}$$

It follows from (10) that P^* exists only when $R_0 > 1$. The following result is immediate.

Proposition 1. *System* (1) *has two possible equilibria. When* $R_0 \leq 1$, *the disease-free* $P_0 = (\pi/\mu_X, 0, 0, 0)$ *is the only equilibrium in* Γ; *when* $R_0 > 1$, *both* P_0 *and the unique endemic equilibrium* $P^* = (X^*, E^*, L^*, T^*)$ *exist in* $\overline{\Gamma}$, *where* X^*, E^*, L^*, T^* *are given in* (10).

For epidemic models of this type, it is generally expected that the global dynamics are determined by the basic reproduction number R_0: if $R_0 \leq 1$, then all solutions converge to the disease-free equilibrium P_0, and the TB dies out from the population irrespective of the initial incidence; while if $R_0 > 1$, all solutions with positive initial conditions will be persistent and converge to the unique endemic equilibrium P^*, and any initial TB epidemics will become endemic in the population. In the next two sections, we rigorously establish this threshold behaviour.

3 Stability of the disease-free equilibrium P_0. In this section, we show that the disease-free equilibrium P_0 is globally asymptotically stable with respect to $\overline{\Gamma}$ if $R_0 \leq 1$, and P_0 is unstable if $R_0 > 1$.

Theorem 2. *If* $R_0 \leq 1$, *then the disease-free equilibrium* P_0 *is locally asymptotically stable and all solutions in* $\overline{\Gamma}$ *converge to* P_0. *If* $R_0 > 1$, *then* P_0 *is unstable.*

Proof. Consider a Lyapunov function

$$L = \omega(\nu + p\mu_L)E + \nu(\mu_E + \omega)L + (\mu_E + \omega)(\mu_L + \nu)T.$$

Direct calculation leads to

$$\begin{aligned} L' &= \omega(\nu + p\mu_L)E' + \nu(\mu_E + \omega)L' + (\mu_E + \omega)(\mu_L + \nu)T' \\ &= \beta\omega(\nu + p\mu_L)XT - (\mu_E + \omega)(\mu_L + \nu)\mu_T T \\ &= \beta\omega(\nu + p\mu_L)T\left(X - \frac{\pi}{\mu_X R_0}\right). \end{aligned}$$

Therefore $L' \leq 0$ in $\overline{\Gamma}$ if $R_0 \leq 1$. Furthermore

$$L' = 0 \iff T = 0 \quad \text{or} \quad R_0 = 1 \quad \text{and} \quad X = \frac{\pi}{\mu_X R_0}\,.$$

Therefore, the largest compact invariant set in $G = \{(X, E, L, T) \in \overline{\Gamma} : L' = 0\}$, when $R_0 \leq 1$, is the singleton $\{P_0\}$. LaSalle's Invariance Principle ([**12,** Chapter 2, Theorem 6.4]) implies that all solutions in $\overline{\Gamma}$

converges to P_0. This global convergence also implies that P_0 is locally stable, since otherwise P_0 will have a homoclinic orbit that has to belong entirely in the set $G \subset \overline{\Gamma}$ where $L' = 0$, and thus contradicting the fact that the largest compact invariant set in G is the singleton $\{P_0\}$.

If $R_0 > 1$, then $L' > 0$ for X sufficiently close to π/μ_X except when $E = L = T = 0$. Solutions in $\overline{\Gamma}$ starting sufficiently close to P_0 leave a neighborhood of P_0 except those on the invariant X-axis, on which (1) reduces to $X' = \pi - \mu_X X$ and thus $X(t) \to \pi/\mu_X$, as $t \to \infty$. This establishes the theorem. □

By Theorem 2, the infection-free equilibrium point P_0 is unstable when $R_0 > 1$. Moreover, the local dynamics near P_0 imply that system (1) is uniformly persistent if $R_0 > 1$. Namely, there exists constant $c > 0$, such that

$$\liminf_{t\to\infty} X(t) > c, \qquad \liminf_{t\to\infty} E(t) > c,$$
$$\liminf_{t\to\infty} L(t) > c, \qquad \liminf_{t\to\infty} T(t) > c,$$

provided $(X(0), E(0), L(0), T(0)) \in \operatorname{Int} \mathbb{R}^4_+$, the positive cone of $\mathbb{R}^4$. Here constant c is independent of initial data in $\mathbb{R}^4_+$. We thus have the following corollary, whose proof is similar to that of Proposition 3.3 of [**13**].

Corollary 3. *System* (1) *is uniformly persistent if and only if* $R_0 > 1$.

Theorem 2 completely determines the global dynamics of (1) in Γ when $R_0 \leq 1$. It establishes the basic reproduction number R_0 in (9) as a sharp threshold parameter. Namely, if $R_0 \leq 1$, all solutions in the feasible region converge to the disease-free equilibrium P_0, and the TB will die out from the population irrespective of the initial conditions. If $R_0 > 1$, P_0 is unstable and the system is uniformly persistent, and a TB epidemic will always become endemic.

4 Stability of the endemic equilibrium P^* when $R_0 > 1$ We have shown in the previous section that system (1) is uniformly persistent if and only if $R_0 > 1$. In this section, we further establish that all solutions in the interior of the feasible region Γ converge to the unique endemic equilibrium P^* if $R_0 > 1$. Therefore, the TB will persist at the endemic equilibrium level. The proof is accomplished by constructing a global Lyapunov function. Lyapunov functions of similar type have been used in the literature, see [**14**–**16**].

Theorem 4. *Assume $R_0 > 1$. Then the endemic equilibrium $P^* = (X^*, E^*, L^*, T^*)$ is asymptotically stable. Furthermore, all solutions in* $\operatorname{Int}\Gamma$ *converge to P^*.*

Proof. Set $x = (X, E, L, T) \in \Gamma \subset \mathbb{R}^4_+$. Consider a Lyapunov function

$$V = V(x) = \left(X - X^* - X^* \ln \frac{X}{X^*}\right) + \left(E - E^* - E^* \ln \frac{E}{E^*}\right) + A\left(L - L^* - L^* \ln \frac{L}{L^*}\right) + B\left(T - T^* - T^* \ln \frac{T}{T^*}\right),$$

where $x^* = P^* = (X^*, E^*, L^*, T^*)$ is the endemic equilibrium and

$$A = \frac{\beta\nu X^*}{(\mu_L + \nu)\mu_T}, \qquad B = \frac{\beta X^*}{\mu_T}. \tag{11}$$

We note that $V(x) \geq 0$, for $x \in \operatorname{Int}\Gamma$, the interior of Γ, and $V(x) = 0 \iff x = x^*$. So function V is positive definite with respect to the endemic equilibrium $x^* = P^*$. Computing the derivative of V along the solutions of system (1), we obtain

$$\frac{dV}{dt} = \left(1 - \frac{X^*}{X}\right)X' + \left(1 - \frac{E^*}{E}\right)E' + A\left(1 - \frac{L^*}{L}\right)L' + B\left(1 - \frac{T^*}{T}\right)T'. \tag{12}$$

Using (1) and $\pi = \mu_X X^* + \beta X^* T^*$ from (4), we have

$$\begin{aligned}\left(1 - \frac{X^*}{X}\right)X' &= \pi - \beta XT - \mu_X X - \pi\frac{X^*}{X} + \beta X^* T + \mu_X X^* \\ &= 2\mu_X X^* + \beta X^* T^* - \beta XT - \mu_X X \\ &\qquad - \mu_X \frac{X^{*2}}{X} - \frac{\beta X^{*2} T^*}{X} + \beta X^* T \\ &= \beta X^* T^* + \mu_X X^* \left(2 - \frac{X}{X^*} - \frac{X^*}{X}\right) \\ &\qquad - \beta XT - \frac{\beta X^{*2} T^*}{X} + \beta X^* T.\end{aligned} \tag{13}$$

Similarly,

$$\begin{aligned}
\left(1-\frac{E^*}{E}\right)E' &= \beta XT-(\mu_E+\omega)E-\frac{\beta XTE^*}{E}+(\mu_E+\omega)E^*,\\
A\left(1-\frac{L^*}{L}\right)L' &= A(1-p)\omega E-A(\mu_L+\nu)L\\
&\quad -\frac{A(1-p)\omega EL^*}{L}+A(\mu_L+\nu)L^*,\\
B\left(1-\frac{T^*}{T}\right)T' &= Bp\omega E+B\nu L-B\mu_T T\\
&\quad -\frac{Bp\,\omega ET^*}{T}-\frac{B\nu LT^*}{T}+B\mu_T T^*.
\end{aligned} \tag{14}$$

Notice that

$$\begin{aligned}
A(1-p)\omega+Bp\omega &= (1-p)\omega\frac{\beta\nu X^*}{(\mu_L+\nu)\mu_T}+p\omega\frac{\beta X^*}{\mu_T}\\
&= \frac{\beta\omega X^*}{(\mu_L+\nu)\mu_T}\left[(1-p)\nu+p(\mu_L+\nu)\right]\\
&= \frac{\beta\omega(\nu+p\mu_L)X^*}{(\mu_L+\nu)\mu_T}=(\mu_E+\omega),
\end{aligned} \tag{15}$$

and from (11)

$$A(\mu_L+\nu)=B\nu,\qquad \beta X^*=B\mu_T. \tag{16}$$

Using (13)–(16) we can simplify (12) as

$$\begin{aligned}
\frac{dV}{dt} &= \beta X^*T^*+\mu_X X^*\left(2-\frac{X}{X^*}-\frac{X^*}{X}\right)-\frac{\beta {X^*}^2T^*}{X}\\
&\quad -\frac{\beta XTE^*}{E}-\frac{A(1-p)\omega EL^*}{L}-\frac{Bp\omega ET^*}{T}-\frac{B\nu LT^*}{T}\\
&\quad +(\mu_E+\omega)E^*+A(\mu_L+\nu)L^*+B\mu_T T^*.
\end{aligned} \tag{17}$$

From (5) and (11) we have

$$(\mu_E+\omega)E^*=\beta X^*T^*,\qquad B\mu_T T^*=\beta X^*T^*. \tag{18}$$

From (6), (8), (16) and (18), we obtain

$$A(\mu_L+\nu)L^* = \frac{\beta\nu X^*L^*}{\mu_T} = \frac{\beta\nu X^*}{\mu_T}\cdot\frac{(1-p)\omega E^*}{\mu_L+\nu} = \frac{\beta\omega X^*}{(\mu_E+\omega)(\mu_L+\nu)\mu_T}(1-p)\nu\beta X^*T^* = \frac{(1-p)\nu}{\nu+p\mu_L}\beta X^*T^*. \tag{19}$$

Substituting (18) and (19) into (17), we get

$$\frac{dV}{dt} = \left[3+\frac{(1-p)\nu}{\nu+p\mu_L}\right]\beta X^*T^* + \mu_X X^*\left(2-\frac{X}{X^*}-\frac{X^*}{X}\right) - \frac{\beta X^{*2}T^*}{X} - \frac{\beta XTE^*}{E} - \frac{A(1-p)\omega EL^*}{L} - \frac{pB\omega ET^*}{T} - \frac{B\nu LT^*}{T}. \tag{20}$$

Define

$$q = \frac{(1-p)\nu}{\nu+p\mu_L}, \qquad r = \frac{p(\mu_L+\nu)}{\nu+p\mu_L}. \tag{21}$$

Then $q+r=1$, $q>0$, $r>0$, and

$$3+\frac{(1-p)\nu}{(\nu+p\mu_L)} = 3+q = 4q+3r.$$

We can rewrite (20) as

$$\begin{aligned}\frac{dV}{dt} &= \mu_X X^*\left(2-\frac{X}{X^*}-\frac{X^*}{X}\right) + (4q+3r)\,\beta X^*T^* - \frac{\beta X^{*2}T^*}{X} - \frac{\beta XTE^*}{E} - \frac{A(1-p)\omega EL^*}{L} - \frac{pB\omega ET^*}{T} - \frac{B\nu LT^*}{T} \\ &= \mu_X X^*\left(2-\frac{X}{X^*}-\frac{X^*}{X}\right) + \left(3r\beta X^*T^* - \frac{r\beta X^{*2}T^*}{X}\right.\end{aligned} \tag{22}$$

$$
\begin{aligned}
&- \frac{r\beta XTE^*}{E} - \frac{pB\omega ET^*}{T}\Big) \\
&+ \Big(4q\beta X^*T^* - \frac{q\beta {X^*}^2T^*}{X} - \frac{q\beta XTE^*}{E} \\
&- \frac{A(1-p)\omega EL^*}{L} - \frac{B\nu LT^*}{T}\Big) \\
&\doteq I_1 + I_2 + I_3.
\end{aligned}
$$

Applying the inequality

$$
\frac{a_1 + a_2 + \cdots + a_n}{n} \ \geq \ \sqrt[n]{a_1 \cdot a_2 \cdots a_n}, \quad \text{for} \quad a_i \geq 0, \quad i = 1, \cdots, n,
$$

we obtain

$$
I_1 = \mu_X X^* \left(2 - \frac{X}{X^*} - \frac{X^*}{X}\right) \leq 0. \tag{23}
$$

Moreover,

$$
\begin{aligned}
I_2 &= 3r\beta X^*T^* - \frac{r\beta {X^*}^2T^*}{X} - \frac{r\beta XTE^*}{E} - \frac{pB\omega ET^*}{T} \\
&\leq 3r\beta X^*T^* - 3\sqrt[3]{r\beta {X^*}^2T^* \cdot r\beta E^* \cdot pB\omega T^*} \\
&= 3r\beta X^*T^* - 3\sqrt[3]{r^2\beta^2 {X^*}^2 {T^*}^2 \frac{\beta X^*T^*}{(\mu_E + \omega)} \frac{p\beta X^*}{\mu_T}\omega} \\
&= 3r\beta X^*T^* - 3\beta X^*T^* \sqrt[3]{pr^2 \frac{\beta\omega X^*}{(\mu_E + \omega)\mu_T}} \\
&= 3r\beta X^*T^* - 3\beta X^*T^* \sqrt[3]{r^2 \frac{p(\mu_L + \nu)}{(\nu + p\mu_L)}} = 0,
\end{aligned} \tag{24}
$$

by (18), (11), the expression of X^* in (8), and the definition of r in (21). Similarly

$$
\begin{aligned}
I_3 = 4q\beta X^*T^* &- \frac{q\beta {X^*}^2T^*}{X} - \frac{q\beta XTE^*}{E} \\
&- \frac{A(1-p)\omega EL^*}{L} - \frac{B\nu LT^*}{T}
\end{aligned} \tag{25}
$$

$$
\begin{aligned}
&\leq 4q\beta X^*T^* - 4\big(q\beta X^{*2}T^* \cdot q\beta E^* \cdot A(1-p)\omega L^* \cdot B\nu T^*\big)^{1/4} \\
&= 4q\beta X^*T^* - 4\bigg(q^2\beta^2 X^{*2}T^{*2} \cdot \frac{\beta X^*T^*}{(\mu_E+\omega)} \cdot (1-p)\omega \\
&\qquad \times \frac{(1-p)\nu}{(\mu_L+\nu)(\nu+p\mu_L)}\beta X^*T^* \cdot \frac{\beta X^*}{\mu_T}\nu\bigg)^{1/4} \\
&= 4q\beta X^*T^* - 4\beta X^*T^*\bigg(q^2 \cdot (1-p)^2\nu^2 \\
&\qquad \times \frac{\beta\omega X^*}{(\mu_E+\omega)(\mu_L+\nu)(\nu+p\mu_L)\mu_T}\bigg)^{1/4} \\
&= 4q\beta X^*T^* - 4\beta X^*T^* \sqrt[4]{q^2\frac{(1-p)^2\nu^2}{(\nu+p\mu_L)^2}} = 0,
\end{aligned}
$$

by (18), (19), (8) and (21). Using (23)–(25) we obtain

$$
\frac{dV}{dt} = I_1 + I_2 + I_3 \leq 0, \quad x \in \operatorname{Int}\Gamma. \tag{26}
$$

Furthermore, $dV/dt = 0$ if and only if equalities hold in (23)–(25), and if and only if $x = x^*$. Therefore dV/dt is negative definite in $\operatorname{Int}\Gamma$ with respect to the endemic equilibrium $x^* = P^*$. This implies that the basin of attraction of P^* contains the interior of Γ. The positive definiteness of $V(x)$ with respect to P^* implies that P^* is also locally stable. This completes the proof. □

5 Summary In this paper, mathematical analysis is carried out for a model of latent TB. Global dynamics of the model is shown to be completely determined by a basic reproduction number R_0, first derived in [**11**]. More specifically, we proved that if $R_0 \leq 1$, then the disease-free equilibrium P_0 is asymptotically stable and all solutions in the feasible region converge to P_0. If $R_0 > 1$, then P_0 becomes unstable, and a unique endemic equilibrium P^* exists and is asymptotically stable. In this case, all of the solutions in the interior of the feasible region converge to P^*. The proofs of global convergence use the method of Lyapunov functions. Our results provide a mathematical basis and justification for the expression of R_0 in [**11**].

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