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On the Role of Variable Latent Periods in Mathematical Models for Tuberculosis

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The qualitative behaviors of a system of ordinary differential equations and a system of differential-integral equations, which model the dynamics of disease transmission for tuberculosis (TB), have been studied. It has been shown that the dynamics of both models are governed by a reproductive number. All solutions converge to the origin (the disease-free equilibrium) when this reproductive number is less than or equal to the critical value one. The disease-free equilibrium is unstable and there exists a unique positive (endemic) equilibrium if the reproductive number exceeds one. Moreover, the positive equilibrium is stable. Our results show that the qualitative behaviors predicted by the model with arbitrarily distributed latent stage are similar to those given by the TB model with an exponentially distributed period of latency.

KEY WORDS: Global stability; distributed delay; tuberculosis; mathematical models.

0. INTRODUCTION

Differential equations and differential-integral equations have been developed as mathematical models to study the dynamics of disease transmission for many communicable diseases such as measles, influenza, rubella, and chicken pox (see Hethcote, 1976, Dietz, 1979; Hethcote *et al*., 1981; Anderson, 1982; Anderson and May, 1982, 1991; Dietz and Schenzle, 1985; Dietz,

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1985; Schenzle, 1984; Hethcote and Van Ark, 1987; Castillo-Chavez *et al.*, 1988; Feng, 1994; Feng and Thieme, 1995). The main interest in studying these models is to understand the long-time behavior of the dynamics of disease transmission–whether the disease will die out eventually or will persist. A clear answer to this question is practically important to the design of strategies of the disease control.

The purpose of this paper is to study differential equations and differential-integral equations that describe the dynamics of disease transmission for tuberculosis (TB). One of the important features of TB is that a relatively small proportion of those infected go on to develop clinical disease (Smith and Moss, 1994). Most people are assumed to mount an effective immune response to the initial infection that limits proliferation of the bacilli and may lead to long-lasting partial immunity both to further infection and to reactivation of latent bacilli remaining from the original infection. Data from a variety of sources suggest that the lifetime risk of developing clinically evident TB after being infected is approximately 10%, with a 90% likelihood of the infection remaining latent (Hopewell, 1994). Individuals who have latent infection are not clinically ill or capable of transmitting TB (Miller, 1993). The ability of the organism to survive in a latent state and then reactivate many years after the original infection indicates that the tubercle bacillus has enjoyed a long period of coevolution with the human host, a period that has enabled the bacillus to survive in small population groups for long periods of time.

The annual risk of developing TB in individuals previously infected with *M. tuberculosis* who have survived the initial and higher risk period that follows infection changes with the age of the individual. The following annual risks have been estimated: (1) for children, aged 1–6, the risk of progression is estimated to be around 0.001648, while for those in the 7–12 age range, the risk is about 0.000770 (Comstook *et al.*, 1984); (2) for adults in the 15–34 age range, the reported risk of progression is between 0.0008 and 0.0009, while for adults who are over 55 years of age, the risk is reported to be around 0.0010 (Comstock and Edwards, 1975). Since the development of active TB after infection is highly dependent on the infection age, one of the important questions in epidemiology will be, What is the impact of a long and variable latent period on the transmission dynamics of TB.

Almost all existing mathematical models for TB assume that the duration of the latent stage is exponentially distributed and hence the models can be reduced into a system of ordinary differential equations. In this article we first give a complete analysis for an ODE model introduced early by Castillo-Chavez and Feng (1997a). We show that there is a global stability switch from the disease-free equilibrium to the positive endemic

equilibrium when the basic reproductive number passes through the critical value 1. We then develop a model for TB with an arbitrarily distributed latent period, a system of differential equations coupled with an integral equation. Our investigation shows that the second model shares a dynamical property similar to the ODE model in the following sense: the dynamics of disease transmission is governed by a reproductive number $\mathscr{R}_0$. If $\mathscr{R}_0 \leqslant 1$, then all solutions converge to the disease-free equilibrium. If $\mathscr{R}_0 > 1$, then the disease-free equilibrium is unstable and there exists a unique positive equilibrium which is locally stable.

This paper is organized as follows: Section 1 introduces two models of TB—one with an exponentially distributed latency period (ODEs) and the other one with an arbitrarily distributed latent stage (a system of differential-integral equations). Global stability results of the ODEs are given in Section 2. The model of differential-integral equations is studied in Section 3. We compute the basic reproductive number and study its role in the dynamics and stability properties of this model. Section 4 details some of our current efforts and extensions including the incorporation of immigration and the effects of HIV.

1. THE MODELS

We divide the host population into the following epidemiological classes or subgroups: susceptibles (S), exposed (E; infected but not infectious), and infected (I; assumed infectious) individuals. N denotes the total population. Our previous paper (Castillo-Chavez and Feng, 1997a) introduced a simple model for the transmission of TB:

$$\begin{aligned} \frac{d}{dt} S &= \Lambda - \beta c S \frac{I}{N} - \mu S + r_1 E + r_2 I \\ \frac{d}{dt} E &= \beta c S \frac{I}{N} - (\mu + k + r_1) E \\ \frac{d}{dt} I &= kE - (\mu + d + r_2) I \\ N &= S + E + I \end{aligned} \tag{1.1}$$

Λ is the constant recruitment rate, c is the per-capita contact rate, β is the average number of susceptible individuals infected by one infectious individual per contact per unit of time, μ is the per-capita natural death rate, k is the rate at which an individual leaves the latent class by becoming infectious, d is the per-capita disease-induced death rate, and r_1 and r_2 are

the per-capita treatment rates of latent and infectious individuals, respectively. We assumed that an individual can be infected only by contacting infectious individuals. In the following we let $\sigma = \beta c$.

We modify the above model by assuming a variable removal rate (instead of an exponentially distributed latency period) from the E class to the I class. Let $p(s)$ be a function representing the proportion of those individuals exposed at time t who, if alive, are still infected (but not infectious) at time $t+s$. Then $-\dot{p}(\tau)$ is the rate of removal of individuals from E class into I class τ units of time after exposed. Assume that

$$p(s) \geqslant 0, \qquad \dot{p}(s) \leqslant 0, \qquad p(0) = 1$$

and

$$\int_0^\infty p(s)\, ds < \infty$$

Then the number of individuals who have been exposed from time 0 to t and are still in class E is given by

$$\int_0^t \sigma S(s) \frac{I(s)}{N(s)}\, p(t-s)\, e^{-(\mu + r_1)(t-s)}\, ds$$

Thus the number of individuals who become infectious from time 0 to t and are still alive and in class I is

$$\int_0^t \int_0^\tau \sigma S(s) \frac{I(s)}{N(s)}\, e^{-(\mu + r_1)(\tau - s)} [-\dot{p}(\tau - s)\, e^{-(\mu + r_2 + d)(t-\tau)}]\, ds\, d\tau$$

Then we have the following model:

$$\begin{aligned}
\frac{d}{dt} S &= \Lambda - \sigma S \frac{I}{N} - \mu S + r_1 E + r_2 I \\
E(t) &= E_0(t) + \int_0^t \sigma S(s) \frac{I(s)}{N(s)}\, p(t-s)\, e^{-(\mu + r_1)(t-s)}\, ds \\
I(t) &= \int_0^t \int_0^\tau \sigma S(s) \frac{I(s)}{N(s)}\, e^{-(\mu + r_1)(\tau - s)} [-\dot{p}(\tau - s)\, e^{-(\mu + r_2 + d)(d-\tau)}]\, ds\, d\tau \\
&\quad + I_0 e^{-(\mu + r_2 + d)t} + I_0(t) \\
N &= S + E + I
\end{aligned} \tag{1.2}$$

where $E_0(t)$ denotes those individuals in E class at time $t=0$ and still in the latent class, $I_0(t)$ denotes those initially in class E who have moved into class I and are still alive at time t, and $I_0 e^{-(\mu+r_2+d)t}$ with $I_0 = I(0)$ represents those who are infectious at time 0 and are still alive and in the I class. $E_0(t)$ and $I_0(t)$ are assumed to have compact support (that is, they vanish for large enough t).

Results on well-posedness given by Miller (1971) guarantee the existence and uniqueness of solutions as well as their continuous dependence on parameters for system (1.2) as a system of nonlinear integral equations.

The positivity of solutions can be proved similarly to Castillo-Chavez *et al.* (1989).

2. GLOBAL STABILITY OF THE ENDEMIC EQUILIBRIUM OF (1.1)

The reproductive number $\mathscr{R}_0$ of (1.1) has been derived by Castillo-Chavez and Feng (1997a) as

$$\mathscr{R}_0 = \frac{\sigma k}{(\mu+d+r_2)(\mu+k+r_1)}$$

and they have proved the following.

(1) If $\mathscr{R}_0 \leqslant 1$, then the disease-free equilibrium of (1.1) is globally stable.

(2) If $\mathscr{R}_0 > 1$, then system (1.1) has unique positive endemic equilibrium. Furthermore, the endemic equilibrium is locally asymptotically stable.

In this section we show the following global result.

Theorem 2.1. *If $\mathscr{R}_0 > 1$ and $r_1 + \mu > d$, then the endemic equilibrium of (1.1) is globally asymptotically stable.*

Recall that r_1 is the treatment rate of latent individuals and d is the disease-induced death rate. Since the treatment period is about 6–9 months, $r_1 > 1\ (\text{year})^{-1}$, which should be greater than the value of d in the case of TB. Therefore the condition $r_1 + \mu > d$ is easily satisfied. Through the rest of this section we assume that $\mathscr{R}_0 > 1$ and $r_1 + \mu > d$.

On our main approach is to exclude the existence of a periodic solution and then, by applying the strong Poincare–Bendixson theorem, to conclude the global stability of the endemic equilibrium.

From (1.1) we can get an equation for the total population N:

$$\dot{N} = \Lambda - \mu N - dI$$

Here "$\cdot = d/dt$." System (1.1) is equivalent to the following system:

$$\begin{aligned} \dot{N} &= \Lambda - \mu N - dI \\ \dot{E} &= \sigma(N - E - I)\frac{I}{N} - (\mu + k + r_1)E \\ \dot{I} &= kE - (\mu + d + r_2)I \end{aligned} \tag{2.1}$$

Let $V = E + I$ and rewrite system (2.1)

$$\begin{aligned} \dot{N} &= \Lambda - \mu N - dI \\ \dot{V} &= \sigma(N - V)\frac{I}{N} - (\mu + r_1)V + (r_1 - r_2 - d)I \\ \dot{I} &= kV - (k + \mu + d + r_2)I \end{aligned} \tag{2.2}$$

It is clear that any nonnegative solution of (2.2) will eventually enter the set

$$\tilde{\Omega} = \left\{ (N, V, I) \in R_+^3 : \frac{\Lambda}{\mu} \geqslant N \geqslant V \geqslant I \right\}$$

So we will consider only the solutions of (2.2) in $\tilde{\Omega}$.

Lemma 2.1. *Let $(N(t), V(t), I(t))$ be any nonnegative solution of system (2.2). Then*

$$\liminf_{t \to \infty} \left(\sigma \frac{N(t) - V(t)}{N(t)} + r_1 - r_2 - d \right) \geqslant 0$$

Proof. Since $\mathscr{R}_0 > 1$, the disease-free equilibrium is unstable, and then it is easy to prove that either $I(t) \equiv 0$ or $\exists t_0 > 0$ and $\varepsilon > 0$ such that

$$I(t) \geqslant \varepsilon, \qquad \forall t \geqslant t_0$$

If $I(t) \equiv 0$, then $\dot{V}(t) = -(\mu + r_1)V(t)$ implies $\lim_{t \to \infty} V(t) = 0$. It, therefore, follows that

$$\liminf_{t \to \infty} \left(\sigma \frac{N(t) - V(t)}{N(t)} + r_1 - r_2 - d \right) = \sigma + r_1 - r_2 - d > 0$$

for $\sigma > r_2 + d$ (from the assumption $\mathscr{R}_0 > 1$). Now if $I(t) \geqslant \varepsilon$ for all $t \geqslant t_0$, let

$$g(t) = \sigma \frac{N(t) - V(t)}{N(t)} + r_1 - r_2 - d = \sigma + r_1 - r_2 - d - \sigma \frac{V(t)}{N(t)}$$

then we have

$$\begin{aligned} \dot{g}(t) &= -\sigma \frac{V(t)}{N(t)} \left(\frac{\dot{V}(t)}{V(t)} - \frac{\dot{N}(t)}{N(t)} \right) \\ &= -\sigma \frac{I(t)}{N(t)} g(t) + \sigma \left(r_1 + \frac{\Lambda}{N(t)} - \frac{dI(t)}{N(t)} \right) \\ &> -\sigma \frac{I(t)}{N(t)} g(t) \end{aligned}$$

Here we have used the fact that $I/N \leqslant 1$ and

$$r_1 + \frac{\Lambda}{N(t)} - \frac{dI(t)}{N(t)} \geqslant r_1 + \frac{\Lambda}{\Lambda/\mu} - d = r_1 + \mu - d > 0$$

It follows that

$$g(t) \geqslant g(t_0)\, e^{-\sigma \int_{t_0}^{t} (I(s)/N(s))\, ds} \tag{2.3}$$

Note that $I(s)/N(s) \geqslant \varepsilon\mu/\Lambda$ for $s \geqslant t_0$ and that

$$e^{-(\sigma\mu\varepsilon/\Lambda)(t - t_0)} \to 0, \qquad t \to \infty$$

Hence

$$g(t_0)\, e^{-\sigma \int_{t_0}^{t} (I(s)/N(s))\, ds} \to 0, \qquad t \to \infty$$

From (2.3) we get

$$\liminf_{t \to \infty} g(t) \geqslant 0$$

Now if we let

$$\Omega = \left\{ (N, V, I) \in R_+^3,\ N \geqslant V \geqslant I,\ \sigma + r_1 - r_2 - d \geqslant \sigma \frac{V}{N} \right\}$$

then any nonnegative solution of system (2.2) will eventually enter Ω. Moreover, it should not be difficult to check that Ω is convex.

Let $\Omega(t) = (N(t), V(t), I(t))$ be a nonnegative solution of (2.2).

Lemma 2.2. *If $\Phi(t)$ does not converge to the endemic equilibrium, then the ω limit set of $\Phi(t)$ contains a periodic solution of (2.2).*

Proof. Let system (2.2) be denoted

$$\dot{X} = f(X), \qquad X = (N, V, I)^T \in \Omega \tag{2.4}$$

then a straightforward computation shows that

$$E^{-1} \frac{\partial f(X)}{\partial X} E, \qquad E = \begin{pmatrix} -1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & -1 \end{pmatrix}$$

is a nonpositive matrix. Hence the lemma follows from the strong Poincare–Bendixson theorem (Smith, 1995, Theorem 4.1).

The following lemma is given by Muldowney (1990).

Lemma 2.3. *Suppose $X(t)$ is a periodic solution of (2.4). Then the periodic solution $X(t)$ is asymptotically stable if the linear system*

$$\dot{u} = \frac{\partial f(X(t))^{[2]}}{\partial X} u \tag{2.5}$$

is asymptotically stable, where for a 3×3 matrix $A = [a_{ij}]$, $A^{[2]}$ is defined as

$$A^{[2]} = \begin{pmatrix} a_{11} + a_{22} & a_{23} & -a_{13} \\ a_{32} & a_{11} + a_{33} & -a_{12} \\ -a_{31} & a_{21} & a_{22} + a_{33} \end{pmatrix}$$

Theorem 2.2. *Any periodic solution of (2.2) in Ω, if it exists, is asymptotically stable.*

Proof. Let f denote the right-hand side nonlinearity of Eq. (2.2). Suppose that $X(t) = (N(t), V(t), I(t))$ is a periodic solution of (2.2) in Ω. Then a direct computation yields that

$$\frac{\partial f(X(t))}{\partial X} = \begin{pmatrix} -\mu & 0 & -d \\ \dfrac{\sigma V(t)\, I(t)}{N^2(t)} & -\dfrac{\sigma I(t)}{N(t)} - \mu - r_1 & \sigma - \dfrac{\sigma V(t)}{N(t)} + r_1 - r_2 - d \\ 0 & k & -(k + \mu + d + r_2) \end{pmatrix}$$

Let $u=(x, y, z)^T$; then (2.5) can be written

$$\begin{aligned}
\dot{x} &= -\left(2\mu + r_1 + \frac{\sigma I(t)}{N(t)}\right) x + \left(r_1 - r_2 - d + \frac{\sigma(N(t) - V(t))}{N(t)}\right) y + dz \\
\dot{y} &= kx - (2\mu + d + k + r_2)\, y \\
\dot{z} &= \frac{\sigma V(t)\, I(t)}{N^2(t)}\, y - \left(2\mu + d + k + r_1 + r_2 + \frac{\sigma I(t)}{N(t)}\right) z
\end{aligned} \tag{2.6}$$

Note that $\mathscr{R}_0 > 1$ implies that

$$\sigma > d \tag{2.7}$$

Also from Eqs. (2.2) we have the following equalities:

$$\left(r_1 - r_2 - d + \frac{\sigma(N(t) - V(t))}{N(t)}\right) \frac{I(t)}{V(t)} = \frac{\dot{V}(t)}{V(t)} + \mu + r_1 \tag{2.8}$$

$$\frac{kV(t)}{I(t)} = \frac{\dot{I}(t)}{I(t)} + \mu + d + k + r_2 \tag{2.9}$$

If we let

$$D_+ f(t) = \limsup_{h \to 0^+} \frac{f(t+h) - f(t)}{h}$$

then

$$\begin{aligned}
D_+ |x(t)| &\leqslant -\left(2\mu + r_1 + \frac{\sigma I(t)}{N(t)}\right) |x(t)| \\
&\quad + \left(r_1 - r_2 - d + \frac{\sigma(N(t) - V(t))}{N(t)}\right) |y(t)| + d\, |z(t)| \\
D_+ |y(t)| &\leqslant k\, |x(t)| - (2\mu + d + k + r_2)\, |y(t)| \\
D_+ |z(t)| &\leqslant \frac{\sigma V(t)\, I(t)}{N^2(t)}\, |y(t)| - \left(2\mu + d + k + r_1 + r_2 + \frac{\sigma I(t)}{N(t)}\right) |z(t)|
\end{aligned} \tag{2.10}$$

Let

$$Q(t) = \max\left\{|x(t)|, \frac{V(t)}{I(t)}\, |y(t)|, \frac{N(t)}{I(t)}\, |z(t)|\right\}$$

then using (2.6)–(2.10) we obtain the following inequalities.

(1) If $Q(t) = x(t)$, then

$$\begin{aligned} D_+ |x(t)| &\leqslant \Bigg(-2\mu - r_1 - (\sigma - d)\frac{I(t)}{N(t)} \\ &\qquad + \left(r_1 - r_2 - d + \frac{\sigma(N(t) - V(t))}{N(t)} \right) \frac{I(t)}{N(t)} \Bigg) |x(t)| \\ &= \left(-2\mu - r_1 - (\sigma - d)\frac{I(t)}{N(t)} + \frac{\dot{V}(t)}{V(t)} + \mu + r_1 \right) |x(t)| \\ &= \left(-\mu + \frac{\dot{V}(t)}{V(t)} \right) Q(t) \end{aligned}$$

(2) If $Q(t) = (V(t)/I(t))\,|y(t)|$, then

$$\begin{aligned} & D_+ \left(\frac{V(t)}{I(t)} |y(t)| \right) \\ &= \left(\frac{\dot{V}(t)}{V(t)} - \frac{\dot{I}(t)}{I(t)} \right) \frac{V(t)}{I(t)} |y(t)| + \frac{V(t)}{I(t)} D_+ |y(t)| \\ &\leqslant \left(\frac{\dot{V}(t)}{V(t)} - \frac{\dot{I}(t)}{I(t)} \right) \frac{V(t)}{I(t)} |y(t)| + k \frac{V(t)}{I(t)} |x(t)| - (2\mu + d + k + r_2) \frac{V(t)}{I(t)} |y(t)| \\ &\leqslant \left(\frac{\dot{V}(t)}{V(t)} - \mu \right) \frac{V(t)}{I(t)} |y(t)| \\ &= \left(\frac{\dot{V}(t)}{V(t)} - \mu \right) Q(t) \end{aligned}$$

(3) If $V(t) = (N(t)/I(t))\,|z(t)|$, then

$$\begin{aligned} & D_+ \left(\frac{N(t)}{I(t)} |z(t)| \right) \\ &= \left(\frac{\dot{N}(t)}{N(t)} - \frac{\dot{I}(t)}{I(t)} \right) \frac{I(t)}{N(t)} |z(t)| + \frac{N(t)}{I(t)} D_+ |z(t)| \\ &\leqslant \left(\frac{\dot{N}(t)}{N(t)} - \frac{\dot{I}(t)}{I(t)} + \frac{\sigma I(t)}{N(t)} \right) - \left(2\mu + d + k + r_1 + r_2 + \frac{\sigma I(t)}{N(t)} \right) \frac{N(t)}{I(t)} |z(t)| \\ &\leqslant \left(\frac{\dot{N}(t)}{N(t)} - \frac{\dot{I}(t)}{I(t)} - 2\mu - d - k - r_1 - r_2 \right) Q(t) \end{aligned}$$

If we let

$$h_1(t) = -\mu + \frac{\dot{V}(t)}{V(t)}$$

$$h_2(t) = \frac{\dot{N}(t)}{N(t)} - \frac{\dot{I}(t)}{I(t)} - 2\mu - d - k - r_1 - r_2$$

then we have

$$\dot{Q}(t) \leqslant h(t)\, Q(t)$$

where $h(t) = \max\{h_1(t), h_2(t)\}$. Now let $(N(t), V(t), I(t))$ have period $T > 0$. Since

$$\int_0^T \frac{\dot{N}(t)}{N(t)}\, dt = \int_0^T \frac{\dot{I}(t)}{I(t)}\, dt = \int_0^T \frac{\dot{V}(t)}{V(t)}\, dt = 0$$

it becomes clear from the expression of $h_i(t)$, $i = 1, 2$ that there is a constant $\gamma > 0$ such that

$$e^{\int_0^T h(t)\, dt} < e^{-\gamma T}$$

Consequently we have

$$\lim_{t \to \infty} Q(t) = 0$$

which shows that

$$\lim_{t \to \infty} x(t) = \lim_{t \to \infty} y(t) = \lim_{t \to \infty} z(t) = 0$$

The result follows from Lemma 2.3.

Using Lemmas 2.1–2.3 and Theorem 2.2 we can prove Theorem 2.1 by using the same argument given by Li and Muldowney (1995). We provide an outline of the proof as follows.

Proof of Theorem 2.1. Let Σ be the basin of the attraction of the positive endemic equilibrium $X^* = (N^*, V^*, I^*) \in \Omega$. To show that X^* is globally asymptotically stable, it suffices to prove that $(\Omega \backslash \{(\Lambda/\mu, 0, 0)\}) \subseteq \Sigma$. Note that the equilibrium X^* is locally asymptotically stable; it follows that Σ is an open set in R^3. If $(\Omega \backslash (\{(\Lambda/\mu, 0, 0)\}) \not\subseteq \Sigma$, then it is clear that there is an $X_0 \in (\Omega \backslash \{(\Lambda/\mu), 0, 0)\}) \cap \partial\Sigma$. Let $\Phi(t, X_0)$ be the solution of (2.2) with $\Phi(0, X_0) = X_0$. Then $\Phi(t, X_0) \in \Omega$ for all $t \geqslant 0$ and $\Phi(t, X_0)$ does not converge to the equilibria X^* and $((\Lambda/\mu), 0, 0)$ [note that the

equilibrium $((\Lambda/\mu), 0, 0)$ has an unstable manifold pointing to inside Ω]. Since X^* and $((\Lambda/\mu), 0, 0)$ are the only equilibria in Ω, from Lemma 2.2 it follows that the ω limit set of $\Phi(t, X_0)$ contains a periodic solution $X(t)$ of (2.2) in Ω. Moreover, Theorem 2.2 implies that $X(t)$ is asymptotically stable. It follows that $\Phi(t, X_0)$ converges to the orbit $\Gamma = \{X(t) : 0 \leqslant t \leqslant T\}$ as $t \to \infty$, where T is the period of $X(t)$. Since $X(t)$ is asymptotically stable and $X_0 \in \partial\Sigma$, we can pick a point $X_1 \in \Sigma$ sufficiently close to X_0 so that the solution $\Phi(t, X_1)$ of (2.2) through X_1 converges to Γ as $t \to \infty$. This contradicts the definition of Σ.

3. ANALYSIS OF SYSTEM (1.2)

The I equation in (1.2) is a Volterra integral equation if we change the order of integrations as follows

$$\int_0^t \int_s^t \sigma S(s) \frac{I(s)}{N(s)} e^{-(\mu+r_1)(\tau-s)}[-\dot{p}(\tau-s)\, e^{-(\mu+r_2+d)(t-\tau)}]\, d\tau\, ds$$

and note that

$$\int_s^t e^{-(\mu+r_1)(\tau-s)}[-\dot{p}(\tau-s)\, e^{-(\mu+r_2+d)(t-\tau)}]\, d\tau$$

$$= -e^{-(\mu+r_2+d)(t-s)} \int_0^{t-s} \dot{p}(u)\, e^{(r_2+d-r_1)u}\, du =: a(t-s) \tag{3.1}$$

Therefore we can rewrite the I equation in (1.2)

$$I(t) = \int_0^t a(t-s)\, \sigma S(s) \frac{I(s)}{N(s)}\, ds + I_0 e^{-(\mu+r_2+d)t} + I_0(t) \tag{3.2}$$

Let

$$B(t) = \sigma S(t) \frac{I(t)}{N(t)}$$

Then system (1.2) with the I equation replaced by (3.2) becomes

$$\begin{aligned} \dot{S} &= \Lambda - B - \mu S + r_1 E + r_2 I \\ E(t) &= E_0(t) + \int_0^t B(s)\, p(t-s)\, e^{-(\mu+r_1)(t-s)}\, ds \\ I(t) &= I_0 e^{-(\mu+r_2+d)t} + I_0(t) + \int_0^t a(t-s)\, B(s)\, ds \end{aligned} \tag{3.3}$$

The basic reproductive number in this case is given by

$$\mathscr{R}_0 = \sigma \int_0^\infty a(\tau)\, d\tau =: \sigma D_I \tag{3.4}$$

where

$$D_I = \int_0^\infty a(\tau)\, d\tau$$

and $a(u)$ is given by (3.1). Let

$$D_E = \int_0^\infty p(s)\, e^{-(\mu + r_1)s}\, ds$$

then D_E is the death-adjusted mean length of the latent period. The relation between D_I and D_E is given by

$$D_I = \frac{1}{\mu + r_2 + d}\,(1 - (\mu + r_1)\, D_E) \tag{3.5}$$

Remark. In the case of an exponentially distributed latent period with a mean length $1/k$, we have $p(t) = e^{-kt}$, and formulae (3.4) and (3.5) give

$$\mathscr{R}_0 = \sigma D_I = \left(\frac{\sigma}{\mu + d + r_2}\right)\left(\frac{k}{\mu + k + r_1}\right)$$

System (3.3) with $E_0(t) = I_0(t) = I_0 = 0$ always has the disease-free equilibrium

$$(S_0, E_0, I_0) = \left(\frac{\Lambda}{\mu}, 0, 0\right)$$

and has no other constant solution. Since $E_0(t)$ and $I_0(t)$ are zero for large t, and $e^{-(\mu + r_2 + d)t} \to 0$ as $t \to \infty$, it could be expected that $(\Lambda/\mu, 0, 0)$ is an asymptotic equilibrium of (2.1) as $t \to \infty$. This is shown by the following theorem.

Theorem 3.1. *If $\mathscr{R}_0 \leqslant 1$, then the disease-free equilibrium $(\Lambda/\mu, 0, 0)$ of system (3.3) is a global attractor, i.e., $\lim_{t \to \infty}(S(t), E(t), I(t)) \to (\Lambda/\mu, 0, 0)$ for any positive solutions of system (3.3).*

We need the following lemma to prove Theorem 3.1.

For a bounded real-valued function f on $[0, \infty)$ we define

$$f_\infty = \liminf_{t \to \infty} f(t), \qquad f^\infty = \limsup_{t \to \infty} f(t)$$

Lemma 3.1 (Thieme, 1993). *Let $f: [0, \infty) \to R$ be bounded and twice differentiable with a bounded second derivative. Let $t_n \to \infty$ and $f(t_n)$ converge to f^∞ or f_∞ for $n \to \infty$. Then*

$$f'(t_n) \to 0, \qquad n \to \infty$$

Proof of Theorem 3.1. Let $\mathscr{R}_0 < 1$. Differentiating the E and I equations in (3.3) and using the fact that $E_0(t)$, $I_0(t)$ have compact supports, we get (for large t)

$$\dot{E} = B(t) + \int_0^t B(s)\, \dot{p}(t-s)\, e^{-(\mu + r_1)(t-s)}\, ds - (\mu + r_1)\, E \tag{3.6}$$

and

$$\begin{aligned} \dot{I} = & -(\mu + r_2 + d)\, I - \int_0^t B(s)\, \dot{p}(t-s)\, e^{-(\mu + r_1)(t-s)}\, ds \\ & -(\mu + r_2 + d)\, I_0 e^{-(\mu + r_2 + d)\, t} \end{aligned} \tag{3.7}$$

Then

$$\dot{N} = \Lambda - \mu N - dI - (\mu + r_2 + d)\, I_0 e^{-(\mu + r_2 + d)\, t} \leqslant \Lambda - \mu N \tag{3.8}$$

It follows that

$$N(t) \leqslant N(0)\, e^{-\mu t} + \frac{\Lambda}{\mu}\,(1 - e^{-\mu t})$$

Hence

$$N^\infty \leqslant \frac{\Lambda}{\mu}$$

Therefore $B(t) = \sigma S(t)(I(t)/N(t))$ is uniformly bounded on $[0, \infty)$. Let $\mathscr{R}_0 < 1$; we claim that $I^\infty = 0$. Suppose, on the contrary, that $I^\infty > 0$. Then there is a sequence $t_n \to \infty$ as $n \to \infty$ such that $I(t_n) \to I^\infty$ as $n \to \infty$. Without loss of generality we can suppose that

$$t_{n+1} - t_n \to \infty \qquad \text{as} \quad n \to \infty \tag{3.9}$$

for otherwise we can choose a subsequence having the property (3.9). Moreover, by definition we have

$$I^{\infty} = \lim_{t \to \infty} \tilde{I}(t) \qquad \text{with} \quad \tilde{I}(t) = \sup_{s \geqslant t} \{I(s)\} \tag{3.10}$$

It follows from the equation for $I(t)$ in (3.3) that

$$I(t_{n+1}) = I_0 e^{-(\mu + r_2 + d)\, t_{n+1}} + \int_0^{t_n} a(t_{n+1} - s)\, B(s)\, ds + \int_{t_n}^{t_{n+1}} a(t_{n+1} - s)\, B(s)\, ds \tag{3.11}$$

Since $B(s)$ is bounded on $[0, \infty)$ there is an $M > 0$ such that

$$B(s) \leqslant M \qquad \text{for all} \quad s \in [0, \infty)$$

Hence the convergence of $\int_0^a a(\tau)\, d\tau$ and (3.9) imply that

$$\begin{aligned} \int_0^{t_n} a(t_{n+1} - s)\, B(s)\, ds &\leqslant M \int_{t_{n+1} - t_n}^{t_{n+1}} a(\tau)\, d\tau \\ &\leqslant M \int_{t_{n+1} - t_n}^{\infty} a(\tau)\, d\tau \to 0 \qquad \text{as} \quad n \to \infty \end{aligned} \tag{3.12}$$

Furthermore, using (3.4) and (3.10) we have

$$\int_{t_n}^{t_{n+1}} a(t_{n+1} - s)\, B(s)\, ds \leqslant \sigma \tilde{I}(t_n) \int_{t_n}^{\infty} a(\tau)\, d\tau \leqslant \mathscr{R}_0 \tilde{I}(t_n) \tag{3.13}$$

and (3.11)–(3.13) yield that

$$I^{\infty} \leqslant \mathscr{R}_0 I^{\infty}$$

Thus we have $\mathscr{R}_0 \geqslant 1$, which is a contradiction. Hence

$$\lim_{t \to \infty} I(t) = 0 \tag{3.14}$$

Now with the use of the E equation in (3.3) and the fact that $I^{\infty} = 0$, one easily deduces that

$$E^{\infty} = 0 \tag{3.15}$$

Finally, $\lim_{t\to\infty} I(t)=0$ implies that $B(t)\to 0$ as $t\to\infty$. Hence the first equation in (3.3) gives that

$$S(t)=\frac{\Lambda}{\mu}(1-e^{-\mu t})+S(0)\,e^{-\mu t}+\int_0^t e^{-\mu(t-s)}(r_1E(s)+r_2I(s)-B(s))\,ds$$

$$\to\frac{\Lambda}{\mu}\qquad\text{as}\quad t\to\infty \tag{3.16}$$

From (3.14)–(3.16) we have

$$\lim_{t\to\infty}(S(t),E(t),I(t))=\left(\frac{\Lambda}{\mu},0,0\right)$$

This finishes the proof.

The following result shows that when $\mathscr{R}_0>1$, the disease will persist in the population.

Theorem 3.2. *If $\mathscr{R}_0>1$, then the disease-free equilibrium of system (3.3) is unstable. Furthermore, there exists a constant $\eta>0$, such that any solution $(S(t),E(t),I(t))$ of (3.3) with $I(0)>0$ satisfies*

$$\limsup_{t\to\infty} I(t)\geqslant\eta$$

We first prove the following lemma.

Lemma 3.2. *If $\mathscr{R}_0>1$, then any solution $(S(t),E(t),I(t))$ of (3.3) with $I(0)>0$ satisfies*

$$\limsup_{t\to\infty} I(t)>0$$

Proof. Since $I_0(t)$ has compact support, we can replace the I equation in (3.3) by

$$I(t)=I_0e^{-(\mu+r_2+d)t}+\int_0^t a(t-s)\,B(s)\,ds \tag{3.17}$$

Suppose that the conclusion of the lemma is not true. Then $I^\infty=0$, or $\lim_{t\to\infty} I(t)=0$. This also implies that (see the proof of Theorem 1)

$\lim_{t\to\infty} E(t)=0$. It follows that $\lim_{t\to\infty} S(t)/N(t)=1$. Hence there is a sequence $\{k_n\}>0$ such that $k_n\to\infty$ as $n\to\infty$, and

$$\frac{S(t)}{N(t)}>1-\frac{1}{n} \qquad \text{for all} \quad t\geqslant k_n \tag{3.18}$$

Note, by (3.7), that $\dot{I}(t)\to 0$ as $t\to\infty$. Whenever $I(t)$ gets close to 0 for large t it will stay close to 0 for a long time. Also, noting that $I(0)>0$ and $I^\infty=0$, we can find sequences s_n, t_n such that $t_n-s_n\to\infty$, $s_n\to\infty$, and

$$I(t)\geqslant I(t_n), \qquad t\in(s_n, t_n) \tag{3.19}$$

Then by (3.17)–(3.19), after choosing a subsequence, we get

$$\begin{aligned} I(t_n) &= I_0 e^{-(\mu+r_2+d)\,t_n}+\int_0^{t_n} a(t_n-s)\,\sigma S(s)\,\frac{I(s)}{N(s)}\,ds \\ &> \sigma\left(1-\frac{1}{n}\right) I(t_n)\int_{s_n}^{t_n} a(t_n-s)\,ds \end{aligned} \tag{3.20}$$

Note that $I(t_n)>0$ for all n and

$$\int_{s_n}^{t_n} a(t_n-s)\,ds=\int_0^{t_n-s_n} a(\tau)\,d\tau\to D_I, \qquad n\to\infty \tag{3.21}$$

Then by (3.20) and (3.21), dividing both sides of (3.20) by $I(t_n)$ and taking $n\to\infty$, we get

$$1\geqslant \sigma D_I=\mathscr{R}_0$$

But $\mathscr{R}_0>1$, a contradiction.

Proof of Theorem 3.2. Note that $-\dot{p}(t)\geqslant 0$ and

$$\begin{aligned} 0 &\leqslant \int_0^{t_n} -\dot{p}(t_n-s)\,e^{-(\mu+r_1)(t_n-s)}\,ds \\ &= \int_0^{t_n} -\dot{p}(\tau)\,e^{-(\mu+r_1)\,\tau}\,d\tau \\ &\to \int_0^{\infty} -\dot{p}(\tau)\,e^{-(\mu+r_1)\,\tau}\,d\tau \\ &= 1-(\mu+r_1)\,D_E, \qquad t\to\infty \end{aligned}$$

From Lemma 3.1 and the E Eq. (3.6),

$$\begin{aligned} 0 &\leqslant \sigma \left(S \frac{I}{N} \right)^{\infty} - \sigma \left(S \frac{I}{N} \right)_{\infty} (1 - (\mu + r_1) D_E) - (\mu + r_1) E^{\infty} \\ &\leqslant \sigma \left(S \frac{I}{N} \right)^{\infty} (1 + (\mu + r_1) D_E) - (\mu + r_1) E^{\infty} \\ &\leqslant \sigma I^{\infty} (1 + (\mu + r_1) D_E) - (\mu + r_1) E^{\infty} \end{aligned}$$

or

$$E^{\infty} \leqslant \frac{\sigma}{\mu + r_1} (1 + (\mu + r_1) D_E) I^{\infty} \tag{3.22}$$

Similarly from the I Eq. (3.7) and Lemma 3.1,

$$\begin{aligned} 0 &\geqslant \sigma \left(\frac{S}{N} \right)_{\infty} I^{\infty} (1 - (\mu + r_1) D_E) - (\mu + r_2 + d) I^{\infty} \\ &\geqslant \sigma \left[1 - \left(\frac{E + I}{N} \right)^{\infty} \right] (1 - (\mu + r_1) D_E) I^{\infty} - (\mu + r_2 + d) I^{\infty} \end{aligned} \tag{3.23}$$

Since $I^{\infty} > 0$ (see Lemma 3.2), (3.23) yields [see also (3.4) and (3.5)] that

$$\left(\frac{E + I}{N} \right)^{\infty} \geqslant 1 - \frac{1}{\mathscr{R}_0} \tag{3.24}$$

On the other hand, (3.22) yields

$$\left(\frac{E + I}{N} \right)^{\infty} \leqslant \left(1 + \frac{\sigma}{\mu + r_1} (1 + (\mu + r_1) D_E) \right) \frac{I^{\infty}}{N_{\infty}} \tag{3.25}$$

Let

$$\eta = \left[\left(1 - \frac{1}{\mathscr{R}_0} \right) \frac{\Lambda}{\mu + d} \right] \Big/ \left[1 + \frac{\sigma}{\mu + r_1} (1 + (\mu + r_1) D_E) \right]$$

then $\eta > 0$ since $\mathscr{R}_0 > 1$. By (3.24), (3.25), and $N_{\infty} \geqslant \Lambda/(\mu + d)$, we get

$$I^{\infty} \geqslant \eta$$

This finishes the proof.

According to Miller (1971), an endemic equilibrium of system (3.3), if it exists, must satisfy the limiting system associated with (3.3), which is given by the following set of equations:

$$\begin{aligned} \dot{S} &= \Lambda - B - \mu S + r_1 E + r_2 I \\ E(t) &= \int_{-\infty}^{t} B(s)\, p(t-s)\, e^{-(\mu + r_1)(t-s)}\, ds \\ I(t) &= \int_{-\infty}^{t} a(t-s)\, B(s)\, ds \\ B(t) &= \sigma S(t)\, \frac{I(t)}{N(t)} \end{aligned} \tag{3.26}$$

Let (S^*, E^*, I^*) be a constant solution of (3.26) with $I^* > 0$, and let $B^* = \sigma S^*(I^*/N^*)$. Then

$$\begin{aligned} I^* &= B^* \left(\int_{-\infty}^{0} a(t-s)\, ds + \int_{0}^{t} a(t-s)\, ds \right) \\ &= B^* \left(\int_{t}^{\infty} a(\tau)\, d\tau + \int_{0}^{t} a(\tau)\, d\tau \right) \\ &= B^* D_I \end{aligned} \tag{3.27}$$

and

$$E^* = B^* D_E \tag{3.28}$$

Thus, from (3.27),

$$\frac{S^*}{N^*} = \frac{1}{\sigma D_I} = \frac{1}{\mathscr{R}_0} \tag{3.29}$$

Note that $S^* + E^* + I^* = N^*$. Then (3.28) and (3.29) yield

$$\begin{aligned} \frac{I^*}{N^*} &= \left(1 - \frac{1}{\mathscr{R}_0}\right) \frac{D_I}{D_I + D_E} \\ \frac{E^*}{N^*} &= \left(1 - \frac{1}{\mathscr{R}_0}\right) \frac{D_E}{D_I + D_E} \end{aligned} \tag{3.30}$$

Also note that

$$\Lambda = B^* + \mu S^* - r_1 E^* - r_2 I^* \tag{3.31}$$

Dividing both sides of (3.31) by N^* and using (3.28)–(3.30) we obtain

$$N^* = \Lambda \mathscr{R}_0 \Big/ \left[\mu + (\mathscr{R}_0 - 1) \frac{1 - r_1 D_E - r_2 D_I}{D_I + D_E} \right] \tag{3.32}$$

Note that

$$\begin{aligned} r_1 D_E + r_2 D_I &< r_1 D_E + (\mu + r_2 + d)\, D_I \\ &= r_1 D_E + 1 - (\mu + r_1)\, D_E = 1 - \mu D_E \leqslant 1 \end{aligned}$$

hence $N^* > 0$ if $\mathscr{R}_0 > 1$. It is easy to see from (3.30) that only when $\mathscr{R}_0 > 1$ does the unique endemic equilibrium exist, and it is given by

$$S^* = \frac{1}{\mathscr{R}_0} N^*$$

$$E^* = \left(1 - \frac{1}{\mathscr{R}_0}\right) \frac{D_E}{D_I + D_E} N^*$$

$$I^* = \left(1 - \frac{1}{\mathscr{R}_0}\right) \frac{D_I}{D_I + D_E} N^*$$

where N^* is given by (3.32). The stability of the endemic equilibrium is given in the following result.

Theorem 3.3. *If $\mathscr{R}_0 > 1$, then the limiting system (3.26) has a unique endemic equilibrium which is locally asymptotically stable.*

Proof. The proof of this result reduces to the study of the local stability of the trivial equilibrium ($X = 0$) for a Volterra integral equation of the type

$$X(t) = F(t) + \int_0^t A(t-s)\, G(X(s))\, ds \tag{3.33}$$

Let $\hat{S} = S - S^*$, $\hat{E} = E - E^*$, and $\hat{I} = I - I^*$. First we rewrite the S equation in (3.26)

$$S(t) = \frac{\Lambda}{\mu}(1 - e^{-\mu t}) + S(0)\, e^{-\mu t} + \int_0^t (r_1 E(s) + r_2 I(s) - B(s))\, e^{-\mu(t-s)}\, ds \tag{3.34}$$

Since (S^*, E^*, I^*) is an equilibrium of (3.26), it follows that

$$S^* = \frac{\Lambda}{\mu}(1 - e^{-\mu t}) + S^* e^{-\mu t} + \int_0^t (R_1 E^* + r_2 I^* - B^*)\, e^{-\mu(t-s)}\, ds \tag{3.35}$$

with $B^* = \sigma S^*(I^*/N^*)$. By subtracting (3.35) from (3.34) we obtain

$$\hat{S}(t) = \hat{S}(0)\, e^{-\mu t} + \int_0^t (r_1 \hat{E}(s) + r_2 \hat{I}(s) - (\hat{B}(s) - B^*))\, e^{-\mu(t-s)}\, ds \tag{3.36}$$

where

$$\hat{B}(t) = \sigma(\hat{S}(t) + S^*)\, \frac{\hat{I}(t) + I^*}{\hat{N}(t) + N^*}$$

Similarly from the second and third equations in (3.26) we have

$$\begin{aligned} \hat{E}(t) = &\int_{-\infty}^0 p(t-s)\, e^{-(\mu + r_1)(t-s)} (\hat{B}(s) - B^*)\, ds \\ &+ \int_0^t p(t-s)\, e^{-(\mu + r_1)(t-s)} (\hat{B}(s) - B^*)\, ds \end{aligned} \tag{3.37}$$

$$\hat{I}(t) = \int_{-\infty}^0 a(t-s)(\hat{B}(s) - B^*)\, ds + \int_0^t a(t-s)(\hat{B}(s) - B^*)\, ds \tag{3.38}$$

Thus Eqs. (3.36)–(3.38) are in the form (3.33) with

$$\begin{aligned} F(t) &= \begin{pmatrix} \hat{S}(0)\, e^{-\mu t} \\ \displaystyle\int_{-\infty}^0 p(t-s)\, e^{-(\mu + r_1)(t-s)} [\hat{B}(s) - B^*]\, ds \\ \displaystyle\int_{-\infty}^0 a(t-s)[\hat{B}(s) - B^*]\, ds \end{pmatrix} \\ A(\tau) &= \begin{pmatrix} 0 & -e^{-\mu\tau} & e^{-\mu\tau} \\ 0 & p(\tau)\, e^{-(\mu + r_1)\tau} & 0 \\ 0 & a(\tau) & 0 \end{pmatrix} \\ G(X) &= \begin{pmatrix} \hat{S} \\ \hat{B} - B^* \\ r_1 \hat{E} + r_2 \hat{I} \end{pmatrix} \\ X &= \begin{pmatrix} \hat{S} \\ \hat{E} \\ \hat{I} \end{pmatrix} \end{aligned} \tag{3.39}$$

It remains to show that the conditions specified in Miller's theorem are satisfied. To simplify expressions, let

$$x = \frac{S^*}{N^*}, \qquad y = \frac{E^*}{N^*}, \qquad z = \frac{I^*}{N^*}$$

Note that

$$DG(0) = \begin{pmatrix} 1 & 0 & 0 \\ \sigma z(y+z) & -\sigma xz & \sigma x(x+y) \\ 0 & r_1 & r_2 \end{pmatrix} \tag{3.40}$$

Then $\det DG(0) = -r_2 \sigma xz \neq 0$ since $x > 0$, $z > 0$ when $\mathscr{R}_0 > 1$. Condition (i) is satisfied.

Next we check condition (ii). Note that by (3.39) and (3.40),

$$A(\tau)\, DG(0) = \begin{pmatrix} -e^{-\mu\tau} m_3 & e^{-\mu\tau}(m_2 + r_1) & e^{-\mu\tau}(r_2 - m_1) \\ p(\tau)\, e^{-(\mu + r_1)\tau} m_3 & -p(\tau)\, e^{-(\mu + r_1)\tau} m_2 & p(\tau)\, e^{-(\mu + r_1)\tau} m_1 \\ a(\tau)\, m_3 & -a(\tau)\, m_2 & a(\tau)\, m_1 \end{pmatrix}$$

where

$$m_1 = \sigma x(x+y), \qquad m_2 = \sigma xz, \qquad m_3 = \sigma z(y+z)$$

Then

$$H(\lambda) = \det\left(I_n - \int_0^\infty e^{-\lambda\tau} A(\tau)\, DG(0)\, d\tau \right)$$

$$= \det \begin{pmatrix} 1 + \dfrac{m_3}{\mu + \lambda} & -\dfrac{m_2 + r_1}{\mu + \lambda} & \dfrac{m_1 - r_2}{\mu + \lambda} \\ -m_3 P(\lambda) & 1 + m_2 P(\lambda) & -m_1 P(\lambda) \\ -m_3 Q(\lambda) & m_2 Q(\lambda) & 1 - m_1 Q(\lambda) \end{pmatrix}$$

where

$$P(\lambda) = \int_0^\infty p(\tau)\, e^{-(\mu + r_1 + \lambda)\tau}\, d\tau, \qquad Q(\lambda) = \int_0^\infty a(\tau)\, e^{-\lambda\tau}\, d\tau$$

After canceling terms we get

$$H(\lambda) = 1 + \frac{m_3}{\mu+\lambda} + \frac{m_2}{\mu+r_1+\lambda} - \left(m_1 + \frac{r_2 m_3}{\mu+\lambda}\right) \int_0^\infty a(\tau)\, e^{-\lambda\tau}\, d\tau$$
$$+ \frac{m_2}{\mu+r_1+\lambda} \int_0^\infty \dot{p}(\tau)\, e^{-(\mu+r_1+\lambda)\,\tau}\, d\tau \tag{3.41}$$

It is easier to estimate $|H(\lambda)|$ if we express $\int_0^\infty \dot{p}(\tau)\, e^{-(\mu+r_1+\lambda)\,\tau}\, d\tau$ in terms of $\int_0^\infty a(\tau)\, e^{-\lambda\tau}\, d\tau$. Using the definition of $a(t)$ [see (3.1)] we have

$$\int_0^\infty \dot{p}(\tau)\, e^{-(\mu+r_1+\lambda)\,\tau}\, d\tau = -(\mu+r_2+d+\lambda) \int_0^\infty a(\tau)\, e^{-\lambda\tau}\, d\tau \tag{3.42}$$

Then (3.41) and (3.42) yield

$$|H(\lambda)| \geqslant \left|1 + \frac{m_3}{\mu+\lambda} + \frac{m_2}{\mu+r_1+\lambda}\right|$$
$$- \left|\left(m_1 + m_2 + \frac{r_2 m_3}{\mu+\lambda} + \frac{m_2(r_2+d-r_1)}{\mu+r_1+\lambda}\right) \int_0^\infty a(\tau)\, e^{-\lambda\tau}\, d\tau\right| \tag{3.43}$$

Note that $\int_0^\infty |a(\tau)\, e^{-\lambda\tau}|\, d\tau \leqslant D_I$, for any λ with $\Re\lambda \geqslant 0$. Also note that

$$\begin{gathered} x = \frac{S^*}{N^*} = \frac{1}{\mathscr{R}_0} \\ \sigma D_I = \mathscr{R}_0 \\ (m_1+m_2)\, D_I = \sigma x (x+y+z)\, D_I = 1 \\ \max\{r_2 D_I,\, (r_2+d-r_1)\, D_I\} < (r_2+d+\mu)\, D_I = 1 - (\mu+r_1)\, D_E < 1 \end{gathered} \tag{3.44}$$

Then by (3.42)–(3.44) we can show that

$$|H(\lambda)| \geqslant \left|1 + \frac{m_3}{\mu+\lambda} + \frac{m_2}{\mu+r_1+\lambda}\right|$$
$$- \left|(m_1+m_2)\, D_I + \frac{m_3}{\mu+\lambda}\, r_2 D_I + \frac{m_2}{\mu+r_1+\lambda}\, (r_2+d-r_1)\, D_I\right|$$
$$> 0$$

whenever $\Re\lambda \geqslant 0$.

Furthermore, clearly for any $\varepsilon_0 > 0$, there is a $\delta_0 > 0$ such that $\{\sup |F(t)|: 0 \leqslant t < \infty\} \leqslant \varepsilon_0$ and $F(t) \to 0$ as $t \to \infty$, for any $|\hat{S}(\tau)| \leqslant \delta_0$, $|\hat{E}(\tau)| \leqslant \delta_0$, $|\hat{I}(\tau)| \leqslant \delta_0$, and $-\infty \leqslant \tau \leqslant 0$.

This finishes the proof.

The global stability of the endemic equilibrium is expected if certain conditions are satisfied. However, we have not been able to prove this at this moment. The main difficulty arises from the fact that (1.2) is infinite dimensional. Some stability results have been established for epidemiological models with different structures than (1.2). For example, Stech and Williams (1981) show a nice global stability result for the endemic equilibrium in a model with an arbitrarily distributed immunity period; their result was recently extended by Thieme and van den Driessche (2000) to diseases that cause fatalities. To the best of our knowledge there is no efficient approach so far to handle the global structure of a system like (1.2) except for some monotone systems. This will be our further research effort.

4. DISCUSSION

In this paper we have prove the global stability of the endemic equilibrium of an ODE model of Tb that we developed previously (see Castillo-Chavez and Feng, 1997a). We have also constructed a TB model with a distributed delay to study the effect of variable periods of latency on the transmission dynamics of Tb at the population level. These long and variable periods of latency were no considered in our previous paper, as our emphasis there was on the study of resistant TB. The purpose of this paper is to look at the effects of variable (rather than exponentially distributed) periods of latency on the dynamics of TB.

Li and Muldowney (1995) have shown the global stability of the endemic equilibrium for the *SEIR* model. Our basic TB model (1.1) in this article is different from their model. We considered an "*SEIS*" type, with individuals moving back to the S class from both the E and the I classes due to treatments, and we proved a similar global stability result for such a model. We also found that the addition of an arbitrarily distributed latency period to the basic TB model does not alter the qualitative dynamics of TB. The disease either dies out or remains endemic regardless of the shape of the incubation/latent period distribution. Blower *et al.* (1995) have developed a differential equation model with "two" latent groups: one group involves those who will develop TB quickly after primary infection, while the second group is formed of those who will develop the disease slowly through endogenous reactivation. Since there is

only one group of susceptibles in their model, the "two-group" effect is achieved by assuming that some fixed proportion of those who become infected (per unit of time) follows the fast route, while the remaining proportion follows the slow route. The results of the model is this article show that this artificial division plays no role in the qualitative dynamics. The fixed fraction model (referred to by Blower *et al.*, 1995) actually depends on factors that are not part of Blower *et al.*'s model and/or the model in this article (e.g., the age of the infected person). Age is relevant factor, but it cannot *just* be assume a priori that a fixed proportion of individuals in a particular age bracket develops active TB. Contact rates—conductive to TB transmission—are very likely to be age-dependent and the mixing between age classes is nonlinear. Therefore, to study the dynamics of "fast" versus "slow" TB, one must really use an age-structured model. The analysis of age-structured models, while complex, is not impossible (see Castillo-Chavez and Feng, 1998). Blower *et al.* (1995) compute $\mathcal{R}_0$ but study the dynamics of their model exclusivity through simulations which turn out to be "typical." Our analytical results have confirmed their limited simulations not only for the "slow/fast" TB model but also for models where individuals progress toward active TB at "all" possible rates. The fact that long and variable periods of "latency" do not lead to complex dynamics has been worked out before. For example, Castillo-Chavez *et al.* (1989) established that long and variable periods of infection for the transmission dynamics of HIV/AIDS have the same qualitative behavior as the dynamics of models with unrealistic exponentially distributed latent/infectious periods. However, factors such as exogenous infection and heterogeneous contact rates can indeed generate radically dynamics different from those given by the class of models discussed in this article. Exogenous reinfection is capable of sustaining TB even when the basic reproductive number $\mathcal{R}_0 < 1$ (see Castillo-Chavez and Feng, 1997b). Computation of the reproductive number in this article helps us understand the role that key epidemiological parameters play in the maintenance of TB—including the role of the parameters associated with an arbitrary distribution that models long and variable periods of latency.

To summarize our perspective, a person infected with TB may develop active TB in a variety of ways. One possibility is that a person may develop active TB as a result of an endogenous infection—the subject of this article. In this case, there is no impact on the qualitative dynamics of the transmission dynamics of TB. A second possibility is that such a person may develop active TB as a consequence of exogenous reinfection [i.e., acquiring a new infection from another infectious individual (Smith and Moss, 1994)]. Our results show that exogenous reinfection can have a drastic effect on the qualitative dynamics of TB (see Castillo-Chavez *et al.*, 2000).

The incorporation of exogenous reinfection into the basic TB model (1.1) allows for the possibility of a subcritical bifurcation. Thus, a "backward" bifurcation of an endemic equilibrium may occur at the critical value of the reproductive number $\mathscr{R}_0 = 1$, and hence, our system can have multiple endemic equilibria for $\mathscr{R}_0 < 1$. This type of behavior has been observed in recent epidemiological models in the context of sexually transmitted diseases (see Hadeler and Castillo-Chavez, 1995).

Immigration effects on TB incidence rates have been found in several developed countries. The influence of immigrants from high-prevalence countries on the notifications in a low-prevalence country can be observed in recent data from Switzerland. Undetected active disease in immigrants is a significant sources of infection among uninfected immigrants, as well as for children of immigrant parents born in the new country. HIV also plays an important role in TB transmission. We are particularly interested in looking at the impact of immigration of infected individuals from countries where the prevalence of TB is high on TB dynamics and reactivation of latent TB among the HIV-infected, as well as their effects on disease control programs.

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