On the role of variable latent periods in mathematical models for TB[1]

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Abstract. We study a system of ordinary differential equations and a system of integral equations to look at the effects of long and variable periods of latency on the dynamics of TB. We 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.

Introduction

Many mathematical models have been developed to study 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 1985, Schenzle 1984, Hethcote and Van Ark 1987, Castillo-Chavez et al. 1988, Feng 1994, Feng and Thieme 1995). These infectious diseases have several features in common; for example, they cause recurrent epidemic outbreaks, and transmission rates depend strongly on age-dependent contact rates. The etiological agents of these communicable diseases are viruses from different families but all are capable of generating similar epidemiological responses (symptoms) at the level of the individual. Common responses include relatively short latent periods, followed by also relatively short infectious periods and permanent immunity after recovery. It is not completely clear when individuals become infectious (that is, capable of transmitting the disease) as some may become infectious while symptomless. The situation of tuberculosis (TB) is different than the situation observed in "childhood" diseases.

One of the differences between TB and childhood diseases is that a relatively small proportion of those infected go on to develop clinical disease (Smith and Moss 1994). Data from a variety of sources suggest that the life-time 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). As people age, immunity may wane, and the risk of developing active TB as a consequence of either exogenous reinfection (i.e., acquiring a new infection from another infectious individual) or endogenous reactivation of latent bacilli (i.e., reactivation of a preexisting dormant infection) may increase (Styblo 1991, Smith and Moss 1994). 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 tuberculosis 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. 1974); 2) for adults in the 15-34 age range, the reported risk of progression is between 0.0008-0.0009, 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 of the infection-age, one of the important questions in epidemiology will be what is the impact of long and variable latent period on the transmission dynamics of TB.

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 integral equations). Some global stability results of the ODEs are given in Section 2. The model of 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 [39] 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; 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 and 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

$$p(s) \geq 0, \dot{p}(s) \leq 0, p(0) = 1,$$

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:

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

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 found in 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 $\mathcal{R}_0$ of (1.1) has been derived in Castillo-Chavez and Feng (1997a) as

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

It has also been proved in Castillo-Chavez and Feng (1997a) that
(1) If $\mathcal{R}_0 \leq 1$, then the disease-free equilibrium of (1.1) is globally stable.
(2) If $\mathcal{R}_0 > 1$, 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 $\mathcal{R}_0 > 1$ 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, $r_1 > 1$ (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 $\mathcal{R}_0 > 1$ and $r_1 + \mu > d$.

Our main approach is to exclude the existence of 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 " $\cdot = \frac{d}{dt}$". 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) as

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

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

$$\tilde{\Omega} = \{(N, V, I) \in R^3_+ : \frac{\Lambda}{\mu} \geq N \geq V \geq I\}.$$

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*

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

Proof: Since $\mathcal{R}_0 > 1$, 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

$$I(t)\geq\varepsilon,\quad \forall t\geq t_0.$$

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 $\mathcal{R}_0 > 1$). Now if $I(t)\geq\varepsilon$ for all $t\geq t_0$, 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 $I/N\leq 1$ and

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

It follows that

$$g(t)\geq g(t_0)e^{-\sigma\int_{t_0}^{t}\frac{I(s)}{N(s)}ds}.\tag{2.3}$$

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

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

Hence

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

From (2.3) we get

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

Now, if we let

$$\Omega = \{(N,V,I) \in R^3_+,\ N \geq V \geq I,\ \sigma + r_1 - r_2 - d \geq \sigma\frac{V}{N}\},$$

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 $\Phi(t) = (N(t), V(t), I(t))$ 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 by

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

then a straightforward computation shows that

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

is a non-positive matrix. Hence the lemma follows from the strong Poincare-Bendixson Theorem (Theorem 4.1, Smith (1995)).

The following Lemma can be found in 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 stable.*

Proof: Let $u = (x, y, z)^T$, then (2.4) can be written as

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

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

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

Also from the equations in (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

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

Let

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

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

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

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

(2) If $Q(t) = \frac{V(t)}{I(t)}|y(t)|$, then

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

(3) If $V(t) = \frac{N(t)}{I(t)}|z(t)|$, then

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

If we let

$$\begin{aligned} h_1(t) &= -\mu + \frac{\dot{V}(t)}{V(t)}, \\ h_2(t) &= \frac{\dot{N}(t)}{N(t)} - \frac{\dot{I}(t)}{I(t)} - 2\mu - d - k - r_1 - r_2, \end{aligned}$$

then we have

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

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

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

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

$$e^{\int_0^\omega h(t)dt} < e^{-\gamma\omega}.$$

Consequently we have

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

It 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 Lemma 2.1 – 2.3 and Theorem 2.2 we can prove Theorem 2.1 in the same way as in Li and Muldowney (1995).

3. Analysis of the system (1.2)

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

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

and notice that

$$\begin{aligned} &\int_s^t e^{-(\mu+r_1)(\tau-s)} [-\dot{p}(\tau-s) e^{-(\mu+r_2+d)(t-\tau)}] d\tau \\ &= -e^{-(\mu+r_2+d)(t-s)} \int_0^{t-s} \dot{p}(u) e^{(r_2+d-r_1)u} du \\ &=: a(t-s). \end{aligned} \tag{3.1}$$

Therefore we can rewrite the I equation in (1.2) as

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

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

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

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

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

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

$$\mathcal{R}_0 = \sigma D_I = \big(\frac{\sigma}{\mu + d + r_2}\big)\big(\frac{k}{\mu + k + r_1}\big).$$

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

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

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

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

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

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

The proof of Theorem 3.1:

Let $\mathcal{R}_0 < 1$. 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

$$\dot{I} = -(\mu+r_2+d)I - \int_0^t B(s)\dot{p}(t-s)e^{-(\mu+r_1)(t-s)}ds - (\mu+r_2+d)I_0e^{-(\mu+r_2+d)t}. \tag{3.7}$$

Then

$$\begin{aligned}\dot{N} =& \Lambda - \mu N - dI - (\mu+r_2+d)I_0e^{-(\mu+r_2+d)t} \\ \leq& \Lambda - \mu N.\end{aligned} \tag{3.8}$$

It follows that

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

Hence

$$N^\infty \leq \frac{\Lambda}{\mu}.$$

Therefore $B(t) = \sigma S(t)\frac{I(t)}{N(t)}$ is uniformly bounded on $[0,\infty)$. Let $\mathcal{R}_0 < 1$, we claim $I^\infty = 0$. Suppose on 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

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

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

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

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

$$I(t_{n+1}) = I_0e^{-(\mu+r_2+d)t_{n+1}} + \int_0^{t_n} a(t_{n+1}-s)B(s)ds + \int_{t_n}^{t_{n+1}} a(t_{n+1}-s)B(s)ds. \tag{3.11}$$

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

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

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

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

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

$$\begin{aligned}\int_{t_n}^{t_{n+1}} a(t_{n+1}-s)B(s)ds &\leq \sigma\tilde{I}(t_n)\int_{t_n}^{\infty} a(\tau)d\tau \\ &\leq \mathcal{R}_0\tilde{I}(t_n).\end{aligned} \tag{3.13}$$

(3.11)–(3.13) yield that

$$I^{\infty} \leq \mathcal{R}_0 I^{\infty}.$$

Thus we have $\mathcal{R}_0 \geq 1$ 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 $I^{\infty} = 0$ 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

$$\begin{aligned}S(t) &= \frac{\Lambda}{\mu}(1-e^{-\mu t}) + S(0)e^{-\mu t} + \int_0^t e^{-\mu(t-s)}\Big(r_1E(s) + r_2I(s) - B(s)\Big)ds \\ &\to \frac{\Lambda}{\mu} \quad \text{as } t \to \infty.\end{aligned} \tag{3.16}$$

From (3.14)–(3.16) we have

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

This finishes the proof.

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

Theorem 3.2. *If $\mathcal{R}_0 > 1$, 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*

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

We first prove the following lemma.

Lemma 3.2. *If $\mathcal{R}_0 > 1$, 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

$$I(t) = I_0 e^{-(\mu+r_2+d)t} + \int_0^t a(t-s)B(s)ds. \tag{3.17}$$

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

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

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 noticing 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

$$I(t) \geq I(t_n), \quad t \in (s_n, t_n). \tag{3.19}$$

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

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

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

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

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

$$1 \geq \sigma D_I = \mathcal{R}_0.$$

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

The proof of Theorem 3.2:

Noticing that $-\dot{p}(t) \geq 0$ and

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

using Lemma 3.1 and the E equation (3.6) we have

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

or

$$E^{\infty} \leq \frac{\sigma}{\mu+r_1}\left(1+(\mu+r_1)D_E\right)I^{\infty}. \tag{3.22}$$

Similarly by the I equation (3.7) and Lemma 3.1 we have

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

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

$$(\frac{E+I}{N})^{\infty} \geq 1 - \frac{1}{\mathcal{R}_0}. \tag{3.24}$$

On the other hand, from (3.22) we can get

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

Let

$$\eta = \frac{(1-\frac{1}{\mathcal{R}_0})\frac{\Lambda}{\mu+d}}{1+\frac{\sigma}{\mu+r_1}(1+(\mu+r_1)D_E)},$$

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

$$I^{\infty} \geq \eta.$$

This finishes the proof.

According to Miller (1971), an endemic equilibrium of the 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 $B^* = \sigma S^* \frac{I^*}{N^*}$. Then

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

Similarly we can get

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

Then using (3.27) and $B^* = \sigma S^* \frac{I^*}{N^*}$ we get

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

Using (3.28), (3.29) and $S^* + E^* + I^* = N^*$ we get

$$\begin{aligned} \frac{I^*}{N^*} &= \big(1 - \frac{1}{\mathcal{R}_0}\big) \frac{D_I}{D_I + D_E}, \\ \frac{E^*}{N^*} &= (1 - \frac{1}{\mathcal{R}_0}) \frac{D_E}{D_I + D_E}. \end{aligned} \tag{3.30}$$

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 get

$$N^* = \frac{\Lambda \mathcal{R}_0}{\mu + (\mathcal{R}_0 - 1)\frac{1 - r_1 D_E - r_2 D_I}{D_I + D_E}}. \tag{3.32}$$

Note that

$$r_1 D_E + r_2 D_I < r_1 D_E + (\mu + r_2 + d) D_I = r_1 D_E + 1 - (\mu + r_1) D_E = 1 - \mu D_E \leq 1,$$

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

$$\begin{aligned} S^* &= \frac{1}{\mathcal{R}_0} N^*, \\ E^* &= \big(1 - \frac{1}{\mathcal{R}_0}\big) \frac{D_E}{D_I + D_E} N^*, \\ I^* &= \big(1 - \frac{1}{\mathcal{R}_0}\big) \frac{D_I}{D_I + D_E} N^*, \end{aligned}$$

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

Theorem 3.3. *If $\mathcal{R}_0 > 1$, 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 $\hat{S} = S - S^*$, $\hat{E} = E - E^*$, $\hat{I} = I - I^*$. First we rewrite the S equation in (3.26) as

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

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

$$S^* = \frac{\Lambda}{\mu}(1 - e^{-\mu t}) + S^* e^{-\mu t} + \int_0^t \Big(r_1 E^* + r_2 I^* - B^*\Big)e^{-\mu(t-s)}ds \tag{3.35}$$

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

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

where

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

Similarly from the second and the 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 equations (3.36)–(3.38) are in the form (3.33) with

$$F(t) = \begin{pmatrix} \hat{S}(0)e^{-\mu t} \\ \int_{-\infty}^0 p(t-s)e^{-(\mu+r_1)(t-s)}[\hat{B}(s) - B^*]ds \\ \int_{-\infty}^0 a(t-s)[\hat{B}(s) - B^*]ds \end{pmatrix},$$

$$A(\tau) = \begin{pmatrix} 0 & -e^{-\mu\tau} & e^{-\mu\tau} \\ 0 & p(\tau)e^{-(\mu+r_1)\tau} & 0 \\ 0 & a(\tau) & 0 \end{pmatrix}, \tag{3.39}$$

$$G(X) = \begin{pmatrix} \hat{S} \\ \hat{B} - B^* \\ r_1\hat{E} + r_2\hat{I} \end{pmatrix},$$

$$X = \begin{pmatrix} \hat{S} \\ \hat{E} \\ \hat{I} \end{pmatrix}.$$

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

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

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 $\mathcal{R}_0 > 1$. The condition (i) is satisfied.

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

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

where

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

Then

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

$$= \det \begin{pmatrix} 1+\frac{m_3}{\mu+\lambda} & -\frac{m_2+r_1}{\mu+\lambda} & \frac{m_1-r_2}{\mu+\lambda} \\ -m_3P(\lambda) & 1+m_2P(\lambda) & -m_1P(\lambda) \\ -m_3Q(\lambda) & m_2Q(\lambda) & 1-m_1Q(\lambda) \end{pmatrix},$$

where

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

After canceling terms we get

$$\begin{aligned} H(\lambda) = 1 &+ \frac{m_3}{\mu+\lambda} + \frac{m_2}{\mu+r_1+\lambda} \\ &- \left(m_1 + \frac{r_2m_3}{\mu+\lambda}\right)\int_0^\infty a(\tau)e^{-\lambda\tau}d\tau \\ &+ \frac{m_2}{\mu+r_1+\lambda}\int_0^\infty \dot{p}(\tau)e^{-(\mu+r_1+\lambda)\tau}d\tau. \end{aligned} \tag{3.41}$$

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

$$\begin{aligned} |H(\lambda)| \geq & |1+\frac{m_3}{\mu+\lambda}+\frac{m_2}{\mu+r_1+\lambda}| \\ & -|\left(m_1+m_2+\frac{r_2m_3}{\mu+\lambda}+\frac{m_2(r_2+d-r_1)}{\mu+r_1+\lambda}\right)\int_0^\infty a(\tau)e^{-\lambda\tau}d\tau|. \end{aligned} \tag{3.43}$$

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

$$\begin{aligned} & x = \frac{S^*}{N^*} = \frac{1}{\mathcal{R}_0}, \\ & \sigma D_I = \mathcal{R}_0, \\ & (m_1+m_2)D_I = \sigma x(x+y+z)D_I = 1, \\ & \max\{r_2D_I, (r_2+d-r_1)D_I\} < (r_2+d+\mu)D_I = 1-(\mu+r_1)D_E < 1. \end{aligned} \tag{3.44}$$

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

$$\begin{aligned} |H(\lambda)| \geq & |1+\frac{m_3}{\mu+\lambda}+\frac{m_2}{\mu+r_1+\lambda}| \\ & -|(m_1+m_2)D_I+\frac{m_3}{\mu+\lambda}r_2D_I+\frac{m_2}{\mu+r_1+\lambda}(r_2+d-r_1)D_I| \\ > & 0, \end{aligned}$$

whenever $\Re\lambda \geq 0$.

Furthermore, clearly for any $\epsilon_0 > 0$, there is a $\delta_0 > 0$ such that $\{\sup|F(t)| : 0 \leq t < \infty\} \leq \epsilon_0$ and $F(t) \to 0$ as $t \to \infty$, for any $|\hat{S}(\tau)| \leq \delta_0, |\hat{E}(\tau)| \leq \delta_0, |\hat{I}(\tau)| \leq \delta_0$, and $-\infty \leq \tau \leq 0$.

This finishes the proof.

4. Discussion

In this paper we have proved the global stability of the endemic equilibrium of an ODEs model of TB that we previously developed (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 not 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 tuberculosis quickly after primary infection while a second group is formed of those who will develop disease slowly through endogenous reactivation. Since there is only one group of susceptible 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 in this article show that this artificial division plays no role in the qualitative dynamics. The fixed fraction model (referred to in 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 a relevant factor, but it cannot *just* be assumed *a priori* that a fixed proportion of individuals in a particular age bracket develop active TB. Contact rates — conducive 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 exclusively 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 towards 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 different dynamics than 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 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. 1997c). The incorporation of exogenous reinfection into the basic TB model (1.1) allows for the possibility of a subcritical bifurcation. Thus, a "backwards" bifurcation of an endemic equilibrium may occur at the critical value of the reproductive number $\mathcal{R}_0 = 1$ and hence, our system can have multiple endemic equilibria for $\mathcal{R}_0 < 1$. 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 prevalence of TB is high on TB dynamics, reactivition of latent TB among HIV-infected, as well as their effects on the disease control programs.

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