

A Model for TB with Exogenous Reinfection*

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Abstract

Following a primary tuberculosis (TB) infection, only approximately 10% of individuals develop active TB. Most people are assumed to mount an effective immune response to the initial infection that limits proliferation of the bacilli and leads to long-lasting partial immunity both to further infection and to reactivation of latent bacilli remaining from the original infection. Infected individuals may develop active TB as a consequence of exogenous reinfection, i.e., acquiring a new infection from another infectious individual. Our results in this paper suggest that exogenous reinfection has a drastic effect on the qualitative dynamics of TB. The incorporation of exogenous reinfection into our TB model allows for the possibility of a subcritical bifurcation at the critical value of the basic reproductive number $\mathcal{R}_0 = 1$, and hence the existence of multiple endemic equilibria for $\mathcal{R}_0 < 1$. These results may partially explain the recently observed resurgence of TB.

Introduction

Tuberculosis is a bacterial disease caused by *Mycobacterium tuberculosis* with at least one third of the world human population as its reservoir (Bloom 1994, Miller 1993). TB is usually acquired through airborne infection from someone who has active TB (smear-positive TB). Mathematical models have been developed to study communicable diseases such as measles, influenza, rubeola, and chicken pox (see Hethcote 1976, Dietz 1979, Hethcote et al 1981, Anderson 1982, Anderson and May 1982, 1991, Dietz and Schenzle 1985, Schenzle 1984, Hethcote and Van Ark 1987, Castillo-Chavez et al. 1988, 1989, Feng 1994, Feng and Thieme 1995). These infectious diseases cause recurrent epidemic outbreaks, and their associated transmission rates depend strongly on age-specific contact rates. The etiological agents of these communicable diseases are viruses from different families, but all are capable of generating similar symptoms at the level of the individual. Common responses include short latent periods, followed by relatively short infectious periods, and permanent immunity after recovery. In contrast, the study of the spread of TB using statistical and mathematical models has not received enough attention. In fact, there has been only an extremely limited use of mathematical models in the study of the transmission dynamics of TB in human populations (Waalder and Piot 1962, Brogger 1967, Waalder 1967, ReVelle 1967, ReVelle et al. 1967, Waalder et al. 1970, Azuma, 1975, Schulzer et al. 1987; Schulzer et al. 1994, Bermejo et al. 1992, Blower et al. 1995, Castillo-Chavez and Feng 1996, 1997a,b).

One of the differences between TB and other infectious diseases is that following primary infection, only a small proportion (approximately 10%) of individuals develop the progressive disease (active TB). Most people are assumed to mount an effective immune response to the initial infection that limits proliferation of the bacilli and leads to long-lasting partial immunity both to further infection and to the reactivation of latent bacilli remaining from the original infection (Smith and Moss 1994). Individuals who have a latent infection are not clinically ill or capable of transmitting TB (Miller 1993). Exposed individuals may remain in this latent stage for long and variable periods of time (in fact, many die without ever developing active TB). Apparently, the longer that we carry this bacteria the less likely that we are to develop active TB unless our immune system becomes seriously compromised by other diseases. Consequently, age of infection as well as chronological age are important factors in disease progression. However, progression towards active TB may accelerate with re-exposure to TB bacilli through repeated contacts with individuals with active TB. Hence, we must look at TB infection as not only the progression from primary infection but also include the possibility of 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) (Styblo 1991, Smith and Moss 1994). The exogenous theory says that exogenous reinfection plays

an important role in the development of the disease and that the inhalation of tubercle bacilli by persons who had a primary tuberculosis infection more than five years previously represents a definite risk of development of the disease soon after this reinfection.

Exogenous reinfection was reported in immunocompetent (Raleigh and Wichelhausen, 1973, Raleigh et al. 1975, Bates et al. 1976) and immunosuppressed people (Nardell et al. 1986, Small et al. 1993). Its relative importance when compared with the role of primary infection and endogenous reactivation was illustrated using epidemiological modeling (Sutherland, 1976; Sutherland et al. 1982). Nevertheless, exogenous infection was explicitly ignored by Blower et al. (1995) in their model of tuberculosis transmission because of their belief that it only occurs in heavily exposed and/or immunocompromised individuals. Ignoring exogenous reinfection may or may not be appropriate in developed countries. However, high incidence rates (greater than 100 per 100,000) in developing countries, particularly in Africa—where HIV seroprevalence is also high—(Snider et al. 1994) make it difficult to ignore exogenous reinfections in theoretical studies and models. TB incidence rates are also high (over 160 per 100,000) in inner cities of developed countries, like Central Harlem in the USA (Hopewell, 1993), where HIV seroprevalence is also high. Hence exogenous infections may play an important role in the observed increases of active-TB incidence in the inner cities of developed countries. Furthermore, recent Center for Diseases Control (CDC) trace data on TB infection cases has proved that it is indeed possible to contract TB while traveling by airplane (Kolata, 1995). These data show that TB infections may not be *only* the result of extensive and repeated exposure to TB-active individuals. In fact, the airline cases show that it may be quite possible to become infected while using crowded transportation—including public city transportation—for several hours a day. Also recently a nonresidential outbreak of tuberculosis that originated in a neighborhood bar was reported (Kline et al. 1995). A homeless patient with highly infectious pulmonary tuberculosis was a regular patron in a neighborhood bar during a long symptomatic interval before diagnosis. The index patient infected 41 of 97 contacts (42 percent), resulting in 14 cases of active tuberculosis and 27 cases of infection but no disease (indicated by positive tuberculin skin tests). There were also two secondary cases. Twelve culture isolates had been tested and had presented the same chromosomal-DNA restriction pattern. Dutt et al. (1995) reported an outbreak related with a 48 year-old man (index case) in a church, where 184 of 200 members of the church congregation were positive to a PPD tuberculin test survey. The TB bacilli is variable and it is possible that individuals who have a latent infection are often exposed to exogenous infections through infectious friends and relatives or even through the use of mass-transportation (Kolata 1995) or any closed environment where community members could meet (Kline et al. 1995, Dutt et al. 1995). The role of exogenous reinfection on disease progression from latent to active TB by individuals who face high contact rates (e.g. those using crowded public

transportation for several hours a day) needs to be assessed. Here, we incorporate this view into a “typical” epidemiological model for the transmission dynamics of TB. We explore the possibility that exogenous infections may play a fundamental role on the transmission dynamics and the epidemiology of TB at the population level. Our mathematical analysis shows that reinfection may—theoretically—increase the number of cases of active TB, may indeed give rise to less predictable dynamics, and may decrease the effectiveness of public health measures.

TB exhibits long and variable periods of latency. We concluded that the addition of a distributed delay to model the long and variable periods of latency did not alter the qualitative dynamics of our TB model (see Castillo-Chavez and Feng 1997b). However, we have not considered the possibility of reinfection in combination with long and variable periods of latency.

The purpose of this paper is to look at the effect that exogenous reinfections have on the transmission dynamics of TB in the simplest possible scenario. The incorporation of exogenous reinfection into our basic TB model shows surprising results including the possibility of a subcritical bifurcation, that is, a “backwards” bifurcation. This bifurcation implies that our system can sustain multiple endemic equilibria when $\mathcal{R}_0 < 1$. The implications of this result are varied. For example, a population which may be experiencing a sustained decline in the number of cases of active TB may by the introduction of enough new cases (due to the sudden influx of infectious individuals) force epidemic outbreaks that could stabilize at an endemic state (even though the epidemiological parameters have not changed). In other words, where the system “ends” (at an endemic or at the infection-free state) depends, due to exogenous reinfection, on the initial conditions of the system and not just on the parameters. This type of behavior has been observed in recent epidemiological models in the context of sexually-transmitted diseases which are often driven by core subpopulations (see Haderler and Castillo-Chavez 1995).

This paper is organized as follows: Section 1 introduces a TB model incorporating exogenous reinfection. We compute the critical value of the basic reproductive number $\mathcal{R}_0^c < 1$ leading to as multiple endemic equilibria wherever $\mathcal{R}_0^c < \mathcal{R}_0 < 1$. In Section 2 we study the stability of all possible equilibria. Section 3 discusses some of our current efforts and extensions including the incorporation of the effects of age-dependent contact rates and vaccination for TB.

1. A TB model with exogenous reinfection

As mentioned earlier, only a small proportion of individuals develop progressive TB disease following primary infection. Most people remain latent and are at risk of developing active TB as a consequence of either exogenous reinfection or endogenous reinfection of latent bacilli. In this section we formulate a TB model that incorporates exogenous

reinfection. The host population is divided into the following epidemiological class or subgroups: susceptibles (S), exposed (E , infected but not infectious), infectious (I), and effectively treated (T) individuals. N denotes the total population. We assume that an individual may be infected only through contacts with infectious individuals. The use of a distributed delay in the removal rate from the infected class has not change the qualitative dynamics of our basic TB model (see Castillo-Chavez and Feng, 1997b). Hence we assume constant per capita removal rates to focus exclusively on the role of exogenous reinfection. The model takes the following form:

$$\begin{aligned}
\frac{d}{dt}S &= \Lambda - \beta cS \frac{I}{N} - \mu S \\
\frac{d}{dt}E &= \beta cS \frac{I}{N} - p\beta cE \frac{I}{N} - (\mu + k)E + \sigma\beta cT \frac{I}{N} \\
\frac{d}{dt}I &= p\beta cE \frac{I}{N} + kE - (\mu + r + d)I \\
\frac{d}{dt}T &= rI - \sigma\beta cT \frac{I}{N} - \mu T \\
N &= S + E + I + T.
\end{aligned} \tag{1.1}$$

Λ is the constant recruitment rate; β and $\sigma\beta$ are the average numbers of susceptible and treated individuals infected by one infectious individual per contact per unit of time, $0 \leq \sigma \leq 1$; c is the per-capita contact rate; 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 is the per-capita treatment rate. We assumed that an individual can be infected only by contacting infectious individuals. The term $p\beta cE \frac{I}{N}$ models the exogenous reinfection rates. When $p = 0$, System (1.1) reduces to our earlier TB model (Castillo-Chavez and Feng, 1997a).

The basic reproductive number for (1.1) is

$$\mathcal{R}_0 = \left(\frac{\beta c}{\mu + r + d} \right) \left(\frac{k}{\mu + k} \right).$$

This number is given by the product $\beta c/(\mu + r + d)$, the average number of susceptibles infected by one infectious individual during his or her effective infectious period, and $k/(\mu + k)$, the fraction of the population which survives the latent period. Therefore \mathcal{R}_0 gives the number of secondary infectious cases produced by an infectious individual during his or her effective infectious period in a population of susceptible individuals.

Note that \mathcal{R}_0 does not depend on the parameter p . The expression of \mathcal{R}_0 here is essentially the same to that computed for our TB model without a re-exposure term (see Castillo-Chavez and Feng 1997a). The model without re-exposure ($p = 0$) has been analyzed and its qualitative behavior changes only at the critical value $\mathcal{R}_0 = 1$. If $\mathcal{R}_0 < 1$,

then the disease-free equilibrium is globally asymptotically stable (g.a.s.) while if $\mathcal{R}_0 > 1$, then there exists an unique endemic equilibrium which is locally asymptotically stable (l.a.s.) (see Castillo-Chavez and Feng, 1997a). Here we show that by changing the value of p , System (1.1) exhibits a subcritical bifurcation from the endemic equilibrium at $\mathcal{R}_0 = 1$. Hence, multiple endemic equilibria can occur for $\mathcal{R}_0 < 1$. The following basic computations are needed before we can establish this result.

It can be shown that for System (1.1) the first octant in the state space is positively invariant. Adding equations in (1.1) gives

$$\frac{d}{dt}N = \Lambda - \mu N - dI.$$

Note that $\frac{d}{dt}N(t) < 0$ for $N > \Lambda/\mu$. Hence, without loss of generality, we can consider only solutions of (1.1) in the following positively invariant subset of \mathbf{R}^4 :

$$G = \{ (S, L, I, T) \mid S, E, I, T \geq 0, S + E + I + T \leq \frac{\Lambda}{\mu} \}.$$

First we assume that $d = 0$ and $\sigma = 1$, a limiting assumption. The potential validity of our results for the case $d > 0$ and $\sigma < 1$ is supported by numerical simulations to get some preliminary results (see Figure 2). The $\frac{d}{dt}N$ equation becomes $\frac{d}{dt}N = \Lambda - \mu N$. Hence $N(t) \rightarrow \Lambda/\mu$, as $t \rightarrow \infty$ and, therefore, we may assume without loss of generality that the population size has reached its limiting value Λ/μ (see Thieme 1992, 1993, 1994; Castillo-Chavez and Thieme, 1995).

System (1.1) always has the disease-free equilibrium $(\frac{\Lambda}{\mu}, 0, 0, 0)$. To find an endemic equilibrium of the system (1.1), we let (S^*, E^*, I^*, T^*) be a positive steady state of (1.1), and let $x = I^*/N^*$. Then

$$\begin{aligned} I^* &= \frac{\Lambda}{\mu}x, \\ S^* &= \frac{\Lambda}{\mu + \beta cx}, \\ E^* &= \frac{\mu + r}{k + p\beta cx} \frac{\Lambda}{\mu}x, \\ T^* &= \frac{r}{\mu + \beta cx} \frac{\Lambda}{\mu}x. \end{aligned} \tag{1.2}$$

Using $S^* + E^* + I^* + T^* = N^* = \Lambda/\mu$ we get

$$\frac{\mu + r}{k + p\beta cx} + 1 + \frac{r}{\mu + \beta cx} - \frac{\beta c}{\mu + \beta cx} = 0. \tag{1.3}$$

To simplify expressions we introduce the following notation:

$$\begin{aligned}
D_E &= \frac{k}{\mu + k}, \\
Q &= \frac{k}{\mu + r}, \\
p_0 &= \frac{(1 + Q)D_E}{1 - D_E}, \\
\tilde{R} &= \frac{D_E(1 + p + Q)}{p}.
\end{aligned} \tag{1.4}$$

Note that D_E is the fraction of the population which survives the latent period. Then using the definition of \mathcal{R}_0 we can rewrite (1.3) as the following quadratic equation:

$$Ax^2 + Bx + C = 0, \tag{1.5}$$

where

$$\begin{aligned}
A &= p\mathcal{R}_0, \\
B &= (1 + p + Q)D_E - p\mathcal{R}_0, \\
C &= D_EQ\left(\frac{1}{\mathcal{R}_0} - 1\right).
\end{aligned} \tag{1.6}$$

Lemma 1. *Let $\mathcal{R}_0 < 1, p > p_0$. Then there exists a $\mathcal{R}_p < 1$ such that (1.5) has exactly two distinct positive roots if and only if $\mathcal{R}_p < \mathcal{R}_0 < 1$; only one positive root if $\mathcal{R}_0 = \mathcal{R}_p$; and no positive root if $\mathcal{R}_p > \mathcal{R}_0$.*

Proof: Let $\mathcal{R}_0 < 1, p > p_0$. Using the definition of p_0 we can easily check that $\tilde{R} < 1$, as well as

$$B < 0 \text{ iff } \mathcal{R}_0 > \tilde{R}. \tag{1.7}$$

If we denote the determinant of (1.5) by Δ , then Δ can be given as the following quadratic function of \mathcal{R}_0

$$\begin{aligned}
\Delta(\mathcal{R}_0) &= B^2 - 4AC \\
&= p^2\mathcal{R}_0^2 - 2pD_E(1 + p - Q)\mathcal{R}_0 + D_E^2(1 + p + Q)^2 - 4pD_EQ.
\end{aligned} \tag{1.8}$$

Thus, the equation $\Delta(\mathcal{R}_0) = 0$ has two roots:

$$\mathcal{R}_0^\pm = \frac{1}{p} \left(D_E(1 + p - Q) \pm 2\sqrt{D_EQ(p - pD_E - D_E)} \right). \tag{1.9}$$

Since $1 - D_E > 0$ and $p > p_0$ then

$$p - pD_E - D_E > p_0(1 - D_E) - D_E = D_EQ > 0.$$

Therefore \mathcal{R}_0^\pm are both real. Since $A > 0$, we have that

$$\Delta(\mathcal{R}_0) > 0, \quad \text{iff } \mathcal{R}_0 > \mathcal{R}_0^+ \quad \text{or } \mathcal{R}_0 < \mathcal{R}_0^-, \quad (1.10)$$

and $1 > \mathcal{R}_0^+$ since $\Delta(1) > 0$. By observing that $\Delta(\tilde{R}) < 0$ and using the inequality (1.10) we show that

$$\mathcal{R}_0^- < \tilde{R} < \mathcal{R}_0^+. \quad (1.11)$$

Let $\mathcal{R}_p = \mathcal{R}_0^+$. It follows from (1.7), (1.10), and (1.11) that $B < 0$ and $B^2 - 4AC > 0$ if and only if

$$\mathcal{R}_p < \mathcal{R}_0 < 1,$$

a condition under which Equation (1.5) has two distinct positive real roots. If we let $\mathcal{R}_0 = \mathcal{R}_p = \mathcal{R}_0^+$ then $B < 0$, $\Delta(\mathcal{R}_0) = 0$ and Equation (1.5) has exactly one positive root. If $\mathcal{R}_0 < \mathcal{R}_p$, then $\Delta(\mathcal{R}_0) < 1$ and Equation (1.5) has no real root.

Lemma 2. *The equation (1.5) has exactly one positive root if $\mathcal{R}_0 > 1$, and no positive root if $\mathcal{R}_0 < 1, p < p_0$.*

Proof: Let $\mathcal{R}_0 > 1$. Since $\tilde{R} < 1$, we have

$$B < (1 + p + Q)D_E - p = p(\tilde{R} - 1) < 0.$$

Since $A > 0$ and $C < 0$, then $B^2 - 4AC > B^2$ and Equation (1.5) has exactly one positive root.

Let $\mathcal{R}_0 < 1, p < p_0$. Then $AC > 0, B^2 - 4AC < B^2$ and

$$\begin{aligned} B &> (1 + p + Q)D_E - p = (1 + Q)D_E - p(1 - D_E) \\ &> (1 + Q)D_E - p_0(1 - D_E) \\ &= 0. \end{aligned}$$

It follows that (1.5) has no positive root.

Result 1. (a). *If $\mathcal{R}_0 > 1$, then the system (1.1) has exactly one positive equilibrium.*

(b). *If $p > p_0$, then there exists a $\mathcal{R}_p < 1$ such that the system (1.1) has exactly two positive equilibria if and only if $\mathcal{R}_p < \mathcal{R}_0 < 1$; only one positive root if $\mathcal{R}_0 = \mathcal{R}_p$; and no positive equilibrium if $\mathcal{R}_p > \mathcal{R}_0$.*

(c). *If $\mathcal{R}_0 < \mathcal{R}_p$, then the system (1.1) has only the disease-free equilibrium.*

Proof: From (1.2) we know that (S^*, E^*, I^*, T^*) is feasible if and only if x is a positive root of (1.5). The proof of Result 1 follows immediately from Lemma 1 and Lemma 2.

Result 1 shows that for each fixed $p > p_0$ there is a branch of endemic equilibria bifurcating backwards from the disease-free equilibrium at $\mathcal{R}_0 = 1$, and hence System (1.1) has multiple endemic equilibria for $\mathcal{R}_0 < 1$. The bifurcation diagram is shown in Figure 1. Our numerical studies support the same results for the case when $d > 0$ and $\sigma < 1$ (see Figure 2).

Remark 1: $p_0 = 0.3$ for the set of parameter values used in Figure 2.

An alternative way to look at the role of the parameter p and the relation between p and \mathcal{R}_0 is to take (p, \mathcal{R}_0) as a pair of bifurcation parameters. The following Lemma shows how to draw the bifurcation diagram shown in Figure 3.

Lemma 3. *Let $F(p) = \mathcal{R}_p$ be the constant given in Result 1. Then*

- (a) $F(p) \geq D_E$ for all $p > p_0$.
- (b) $F(p) \rightarrow D_E$ as $p \rightarrow \infty$.
- (c) $F(p_0) = 1$.

Proof: (a) Let $p > p_0$. Since $F(p) = \mathcal{R}_p = \mathcal{R}_0^+$ where \mathcal{R}_0^+ is given by (1.9), and since $p - pD_E - D_E > D_EQ$, we have

$$\begin{aligned} F(p) &\geq \frac{1}{p}(D_E(1 + p - Q) + 2D_EQ) \\ &= \frac{1}{p}(D_E + pD_E + D_EQ) \\ &> D_E. \end{aligned}$$

Part (b) is trivial.

(c). Using the definition of p_0 we have

$$F(p_0) = \frac{1}{p_0} \frac{D_E}{1 - D_E} (1 + Q) = \frac{p_0}{p_0} = 1.$$

Remark 2: From the analysis about the positive steady-states of System (1.1) we can see that Equation (1.5) always has two real roots x_{\pm} whenever $\mathcal{R}_0 > F(p)$. However, x_- is positive only if $p > p_0$ and $F(p) < \mathcal{R}_0 < 1$ while x_+ is positive for all $\mathcal{R}_0 > F(p)$.

2. Stability of equilibria

We only study the case $d = 0, \sigma = 1$ analytically. The question of stability for case when $d > 0$ and $\sigma < 1$ has been only been explored via numerical simulations. These simulations support the same qualitative results (see Figure 2). Let $W = S + T$, and let

$w = W/N, e = E/N, x = I/N$. Then the limiting system ($N = \Lambda/\mu$) of (1.1) in the case $d = 0, \sigma = 1$ is equivalent to the following system:

$$\begin{aligned}\frac{d}{dt}w &= \mu - \beta cw x - \mu w + r x \\ \frac{d}{dt}e &= \beta cw x - p\beta c e x - (\mu + k)e \\ \frac{d}{dt}x &= p\beta c e x + k e - (\mu + r)x.\end{aligned}\tag{2.1}$$

Let

$$E_{\pm}^* = (w_{\pm}^*, e_{\pm}^*, x_{\pm}^*)$$

be endemic equilibria of System (2.1) corresponding to positive solutions x_{\pm} of (1.5). Then

$$w_{\pm}^* = \frac{\mu + r x_{\pm}^*}{\mu + \beta c x_{\pm}^*}, \quad e_{\pm}^* = \frac{(\mu + r)x_{\pm}^*}{k + p\beta c x_{\pm}^*},\tag{2.2}$$

and x_{\pm}^* are positive solutions of (1.5).

We can now state the following result:

Result 2. (i). If $\mathcal{R}_0 < 1$, then the disease-free equilibrium of System (2.1) is l.a.s..

(ii). If $p > p_0$ and $\mathcal{R}_0^+ < \mathcal{R}_0 < 1$, then E_+^* is l.a.s., and E_-^* is unstable.

(iii). If $\mathcal{R}_0 > 1$, then the disease-free equilibrium is unstable and the unique endemic equilibrium of (2.1) is l.a.s..

In conclusion, if the proportion of exogenous reinfection is large ($p > p_0$), then a sudden rise of TB incidence is possible even when $\mathcal{R}_0 < 1$. When \mathcal{R}_0 increases passing the critical value \mathcal{R}_0^+ , the disease dynamics changes from no endemic steady state to the existence of a stable positive endemic steady state E_+^* (see Figure 1).

Proof. (i). Let $\mathcal{R}_0 < 1$. The characteristic equation of the Jacobian of (2.1) at the disease-free equilibrium is

$$(\lambda + \mu)(\lambda^2 + (2\mu + k + r)\lambda + k\beta c(\frac{1}{\mathcal{R}_0} - 1)) = 0.$$

Three roots of this characteristic equation have negative real parts for $\mathcal{R}_0 < 1$. The local asymptotic stability of the disease-free equilibrium follows.

(ii). Let $p > p_0, \mathcal{R}_0^+ < \mathcal{R}_0 < 1$. The proof is simplified if we let $\beta' = \beta c$ and rewrite the equation for x_{\pm} (see (1.5)). Using $\beta' = \beta c$ instead of \mathcal{R}_0 we arrive at the following equivalent expression:

$$\begin{aligned}f(x) &= p\beta' x^2 + (\mu + r + k + (\mu + r)p - p\beta')x + \frac{(\mu + r)(\mu + k)}{\beta'} - k = 0 \\ &=: A_1 x^2 + B_1 x + C_1.\end{aligned}\tag{2.3}$$

Furthermore, because $p > p_0$ and $\mathcal{R}_0 > \mathcal{R}_0^+ > \tilde{R}$ then

$$\beta' > \mu + r, \quad \text{and} \quad B_1 < 0. \quad (2.4)$$

The Jacobian of (2.1) at E_{\pm}^* is

$$J_{\pm} = \begin{pmatrix} -(\beta' x_{\pm}^* + \mu) & 0 & \frac{\mu(w_{\pm}^* - 1)}{x_{\pm}^*} \\ \beta' x_{\pm}^* & -(p\beta' x_{\pm}^* + \mu + k) & \frac{(\mu + k)e_{\pm}^*}{x_{\pm}^*} \\ 0 & p\beta' x_{\pm}^* + k & -\frac{ke_{\pm}^*}{x_{\pm}^*} \end{pmatrix}.$$

The characteristic equations of J_{\pm} are given by the cubic equations

$$h_{\pm}(\lambda) = \lambda^3 + a_{\pm}\lambda^2 + b_{\pm}\lambda + c_{\pm} = 0, \quad (2.5)$$

where

$$\begin{aligned} a_{\pm} &= 2\mu + k + (1 + p)\beta' x_{\pm}^* + k \frac{e_{\pm}^*}{x_{\pm}^*}, \\ b_{\pm} &= (\beta' x_{\pm}^* + \mu)(\mu + k + p\beta' x_{\pm}^*) + (\mu k + k\beta' x_{\pm}^* - \mu p\beta' x_{\pm}^*) \frac{e_{\pm}^*}{x_{\pm}^*}, \\ c_{\pm} &= (\beta' x_{\pm}^* + \mu)\mu k \frac{e_{\pm}^*}{x_{\pm}^*} + \mu p\beta'^2 (x_{\pm}^*)^2 + \mu k\beta' x_{\pm}^* - \mu^2(\mu + r). \end{aligned} \quad (2.6)$$

We observe that

$$c_- < 0, \quad c_+ > 0. \quad (2.7)$$

To establish the observation in Equation (2.7), we note that

$$\hat{c}_{\pm} = (\mu + r)(k - \mu p) + (k + p\beta' x_{\pm}^*)^2, \quad (2.8)$$

and, we observe—after some algebra—that

$$c_{\pm} = \frac{\mu\beta' x_{\pm}^*}{k + p\beta' x_{\pm}^*} \hat{c}_{\pm}. \quad (2.9)$$

Hence, clearly $c_- < 0$ ($c_+ > 0$) iff $\hat{c}_- < 0$ ($\hat{c}_+ > 0$). We also note that $p > p_0$ implies that $k < \mu p$ and, if we let

$$\delta = \frac{\sqrt{(\mu + r)(\mu p - k)} - k}{p\beta'}, \quad (2.10)$$

then from (2.8) and (2.10) we can see that $\hat{c}_{\pm} > 0$ iff $x_{\pm}^* > \delta$. Hence (2.7) holds if and only if $f(\delta) < 0$ (see (2.3)). Since $B_1 < 0$ and $\beta' > r$ (see (2.4)), after some algebra we have

$$\begin{aligned} f(\delta) &= p\beta'\delta^2 + (\mu + r + k + (\mu + r)p - p\beta')\delta + \frac{(\mu + r)(\mu + k)}{\beta'} - k \\ &= \frac{\sqrt{(\mu + r)(\mu p - k)}}{p\beta'} \left[-(\sqrt{\mu + r} - \sqrt{\mu p - k})^2 + 2B_1 - 4k - p(\beta' - r) \right] \\ &< 0. \end{aligned}$$

Therefore (2.7) holds. Notice from (2.5) and (2.7) that $h_-(0) = c_- < 0$ and $h_-(\lambda) \rightarrow \infty$ as $\lambda \rightarrow \infty$. It follows that $h_-(\lambda^*) = 0$ for some $\lambda^* > 0$. Therefore J_- has a positive eigenvalue, and E_-^* is unstable.

The Routh-Hurwitz criteria implies that all roots of $h_+(\lambda)$ have negative real parts if $a_+ > 0, c_+ > 0$, and $a_+b_+ - c_+ > 0$. From (2.6) it is easy to see that $a_+ > 0$, and from (2.7) we have that $c_+ > 0$. Further algebra shows that

$$\begin{aligned} a_+b_+ - c_+ &\geq a_+(\beta'e_+(k - \mu p) + \beta'x_+(k + p\beta'x_+)) \\ &= \frac{a_+\beta'x_+}{k + p\beta'x_+}((\mu + r)(k - \mu p) + (k + p\beta'x_+)^2) \\ &= \frac{a_+\beta'x_+}{k + p\beta'x_+}c_+ \\ &> 0. \end{aligned}$$

It follows that E_+^* is l.a.s..

(iii). Let $\mathcal{R}_0 > 1$. If $p > k/\mu$ then the proof is the same as in (ii) for the stability of x_+^* . If $0 \leq p \leq k/\mu$ then it is easy to prove that $k > \mu p$ implies that $c_+ > 0$ and hence that $a_+b_+ - c_+ > 0$.

This finishes the proof.

The existence of multiple endemic equilibria for $\mathcal{R}_0 < 1$ indicates that the asymptotical behavior of solutions to (1.1) is dependent of initial conditions. Figure 2 illustrates the dependence.

3. Discussion

The possibility that persons previously infected with *M. tuberculosis* will suffer an exogenous reinfection has been debated for a long time (Lurie, 1964; Stead, 1967; Romeyn, 1970; Raleigh and Wichelhausen, 1973; Raleigh et al. 1975; Sutherland, 1976; Nardell et al. 1986; Styblo, 1991; Small et al. 1993). Exogenous reinfection has been reported in immunocompetent people. Raleigh et al. (1975) found that in a group of 26 patients, 9 patients contained different phage type organisms than were isolated previously. In addition, Bates et al. (1976) found similar results in 3 out of 87 patients. There are several explanations for these data including laboratory error, the possibility of a simultaneous primary infection with organisms of two phage types, and exogenous reinfection. The latter is believed to be the most consistent hypothesis with the droplet-nuclei theory of transmission (Nardell et al. 1986).

Exogenous reinfection has also been reported in immunosuppressed people. Nardell et al. (1986) investigated an outbreak in a large shelter for the homeless in Boston (USA). They found evidence for exogenous reinfection in 4 of 22 cases. These cases were among

patients who had experienced a previously documented tuberculosis infection or a case of active tuberculosis disease and presented poor general health and malnutrition. Small et al. (1993) found that 4 of 17 HIV-infected patients were exogenously reinfected with multidrug-resistant tuberculosis. Their results were confirmed by analysis of restriction-fragment-length polymorphism.

Stead (1967) has shown evidence which supports that the reactivation from endogenous tuberculosis may be the main cause of chronic tuberculosis in the USA. However, Romeyn (1970) using the same epidemiological data has also shown the importance of reinfection when high exposure was likely. Using modeling, Sutherland (1976) estimated the contribution of endogenous and exogenous reinfection to the total disease load in a population in the Netherlands. Sutherland used data from a series of annual surveys of skin tests with tuberculin among new recruits to the military service. For each survey, he estimated the cumulative risk of infection up to their current age using the proportion of tuberculin positive reaction, and taking into account successive cohorts, estimated the annual risk of infection and its changes over time. Sutherland was able to estimate the relative contribution of the different ways of acquiring tuberculosis by relating the changes of annual risk of infection with changes in the occurrence of cases of clinical disease at different times. The relative importance of progressive primary TB, endogenous TB reactivation, and exogenous TB reinfection to total TB morbidity from pulmonary tuberculosis is shown in Figure 4 (Sutherland and Svandova, 1972, cited in Styblo, 1994; here modified from Styblo's). Sutherland et al. (1982) using the Netherlands' epidemiological information and data, such as risk of tuberculosis infection and incidence of tuberculosis, estimated the risks of developing the disease following infection or reinfection. These researchers postulated that: (a) those with a recent primary infection had a characteristic risk of developing progressive primary tuberculosis; (b) those with a distant (i.e. not recent) primary infection and a recent reinfection had a characteristic risk of developing exogenous tuberculosis; and (c) those with a distant primary infection but no recent reinfection had a characteristic risk of developing endogenous tuberculosis. By using their information on the risk of tuberculosis infection, they estimated the size of the population in each of these infection classes for different age-groups and calendar years in the Netherlands. To estimate the three risks of developing tuberculosis, they related these population figures with the information on tuberculosis incidence in the same age group and calendar year by using multiple regression analysis. Their estimation of the reinfection rates for Netherlands males aged 15-69 years during the period 1951-70 were: (a) 5.06 per cent annually (for 5 years) following primary infection; (b) 1.91 per cent annually (for 5 years) following reinfection; (c) 0.0253 per cent annually, after the first 5 years following primary infection, in the absence of reinfection. The analogous figures for females in the same age classes were 5.85, 1.10 and 0.0020 per cent respectively. These researchers estimated that the degree of protection conferred by a

distant primary infection, against pulmonary tuberculosis arising from a recent reinfection, was 63 per cent for males and 81 per cent for females. In this study progressive primary tuberculosis was dominant at the younger ages, exogenous and endogenous tuberculosis at older ages.

Ziegler et al. (1985), through their experimental airborne tuberculosis study using guinea pigs, provided no support for the hypothesis that suggests that a second or third exposure to the tubercle bacilli leads to an adverse effect on host response to the first infecting strain or to the reinfecting strain. These researchers found that the principal effect of the first infection was to protect against a subsequent infection. But McMurray et al. (1989) suggested that malnutrition may be a predisposing host factor in the development of exogenous-reinfection with tuberculosis. By experimenting with guinea pigs these researchers found that malnutrition interferes with the protection afforded by a primary infection (they also noted that this interference does not result in additional disease severity in reinfected individuals over that observed in singly infected subjects.) This last study lends some supports to the hypothesis that exogenous reinfection may play an important role in the spread of tuberculosis epidemics, particularly in developing countries or inner cities where malnutrition and/or immunocompromised individuals are more common. The TB bacilli is variable and it is possible that individuals who have a latent infection are often exposed to exogenous infections through infectious friends and relatives or even through the use of mass-transportation (see Kolata, 1995).

The possibility of acquiring a TB-infection during a short period of time (less than 8 hours) in a public place, has now been corroborated (see Kolata 1995). If exogenous infections provide an alternative mechanism that accelerates the progression to active TB then our results are troublesome. As urban centers grow, individuals spend longer periods of time in close contact with large populations of individuals in situations where the ventilation is poor (subways, buses, and airplanes). The extensive use of public transportation changes combined with immigration and population growth is constantly changing the contact structure of a population. Examples of this phenomena can be seen directly from the observed changes over the last two decades in urban centers such as Mexico City (Mexico), Rio de Janeiro (Brazil), New York City (USA), and Buenos Aires (Argentina). Fast changing urban environments provide alternative evolutionary paths that may have already changed the epidemiology of TB at the population level. We (Capurro, Castillo-Chavez, and Velasco-Hernández, ms in preparation) have begun to look at models that take into account the heterogeneity in contact structures due to changes in the way we move and travel: household versus public transportation transmission.

It was believed that TB was just a disease of the poor. Obviously, social factors are central to what is commonly referred as the social spread of disease. However, the dramatic changes that we have experienced in social dynamics due to shifts in movement

patterns at local, national, and global scales will continue to have a dramatic impact on the way diseases are spread, on the emergence of new diseases, as well as on the type of measures that must be taken at various scales to develop public planning policies that are not limited to local environments or even national borders. For USA in 1986, 22 percent of TB cases were diagnosed in persons of foreign birth (CDC, 1987). For the period from 1986 to 1992, foreign-born persons comprised 60 percent of the increase of TB cases in the U.S. (Cantwell, et al. 1994). Such foreign-born persons with TB may be responsible for many TB cases in their U.S.-born counterparts within racial or ethnic groups. The foreign regions which have contributed the highest percentage of immigrants and the highest number of TB cases to the United States were: Mexico, the Philippines, Indochina (Vietnam, Laos, Kampuchea), South Korea, Haiti, and the People's Republic of China (CDC, 1990). The change in case numbers within some minority populations, could be partially explained by the proportion of foreign-born persons in the minority group (Braden, et al. 1996). In general, they came from countries with a high prevalence of TB cases, and that fact could explain the much higher rate of TB cases among foreign-born persons in the USA. For example, of Asian/Pacific Islanders who developed TB in 1992, over 90 percent were foreign-born; the rate of foreign birth among Hispanics with TB was approximately 50 percent (Onorato, et al. 1994).

In Canada, similar trends have been observed. Although in the early 1970's the notification rate of active tuberculosis among foreign-born persons living in Canada corresponded closely to the rate among their countrymen who had not emigrated (Enarson, et al. 1980), the rate has changed in recent years. For example, between 1965 and 1985, the proportion of all notified cases of tuberculosis among persons who had immigrated to Canada rose from 20 percent to nearly 40 percent (Enarson, et al. 1990). Such increase could be explained by changes in the country of the immigrants' origin. Before 1965, most immigrants to Canada came from Europe or the U.S., but by 1985 a large proportion of immigrants came from Asia, where the incidence of tuberculosis is considerably higher than in Europe or USA (Enarson and Murray, 1996).

Immigration effects on TB incidence rates also have been found in other developed countries. In Auckland (New Zealand) , between 1992 and 1993, 63 percent of new cases were found among foreign-born from Asia and Pacific Islands (Calder and Priest, 1996). Similar patterns were also found in Australia (McIntyre, et al. 1987; Alperstein, et al. 1994). For Western Europe, it has been shown that the prevalence of tuberculosis among immigrants from high-prevalence countries could explain much of the resurgence of the disease (Raviglione, et al. 1993). The influence of immigrants from high-prevalence countries on the notifications in a low-prevalence country can be observed in recent data from Switzerland.

The risk of developing disease for immigrants may be very high within the first few

years of entry to a new country. During 1992 in the U.S., the risk of developing TB for Asian immigrants arriving within the previous year ranged from 117 to 360 per 100,000 individuals. However, the rate was less than half that of new immigrants, for those who had immigrated 5 or more years previously (Rieder, et al. 1989). Also, the incidence of tuberculosis in cohorts of all immigrants decreased about 50 percent by the fifth year following arrival to Canada and Europe (Orr and Hershfield, 1993). A study of immigrants from five Asian countries to British Columbia from 1982 to 1985, showed that the prevalence of previous tuberculosis among the recent immigrants was 6 times higher than the residents of British Columbia (6 compared with 1 percent) (Wang, 1991).

Enarson and Murray (1996) have pointed out that many immigrants are poor and hence are obligated to settle in low-income areas, particularly inner cities, where housing is densely crowded. Crowded housing, poverty, stress and problems in accessing health care, all may contribute to high rates of TB transmission within immigrants (Beaujot, et al. 1988; Perez-Stable, et al. 1986; Joint Tuberculosis Committee 1978; McNicol 1983, Powell, et al. 1981; Enarson, et al. 1979; Orr and Hershfield 1993). If they have a reactivation of tuberculosis in these circumstances, households members will be at risk for heavy exposure. Enarson and Murray (1996) suggested it could be worse due to the presence of illegal immigrants, who are moving in increasing numbers from high-prevalence areas to industrialized countries. These individuals are afraid to seek medical attention, including care for infectious tuberculosis because identification is often perceived to result in deportation. Therefore, the period of transmission of tuberculosis bacilli to household and other contacts may be longer with more people risking infection. 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 (Ashley, et al. 1974; Mortensen, et al. 1989). For example, Perez-Stable, et al. 1985 found in a study of American-born children of Latino immigrant parents that the tuberculin conversion rate was 15-30 times higher than that of the general population within the U.S.

In this article, we have looked at the effect of exogenous reinfections on the dynamics of TB. The incorporation of this epidemiological effect (supported in Europe and not considered important in the USA) into a model for the transmission dynamics of TB allows for the possibility of nonstandard dynamics: endemic states can be permanently support even when $R_0 < 1$. Therefore a sudden influx of infectious immigrants individuals may give rise to epidemic outbreaks that could stabilize at an endemic level that would have been unstable in the absence of exogenous infections. Immigrants waves from countries with high TB incidence often hit inner cities. Public transportation—including airlines—has not only increased contact rates but has also changed the social contact structure that we live in (who mixes with whom). The intensity of the interactions among individuals that live within the sphere of influence of political and/or economic borders also experience

‘nontypical’ contact patterns. TB control policies that ignore global issues seem doomed to failure.

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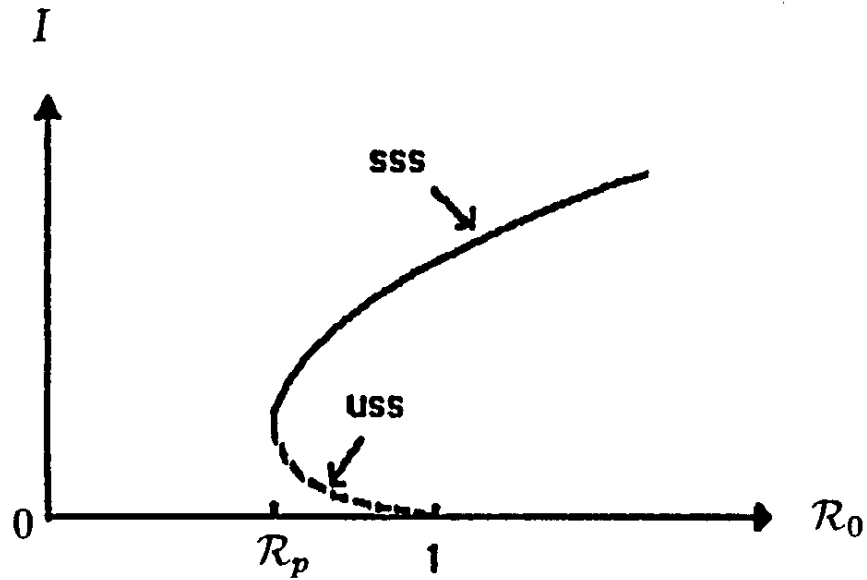


Fig. 1. A bifurcation diagram of endemic steady states. I denotes the number of infective individuals, *sss* stands for stable steady state, *uss* stands for the unstable steady state.

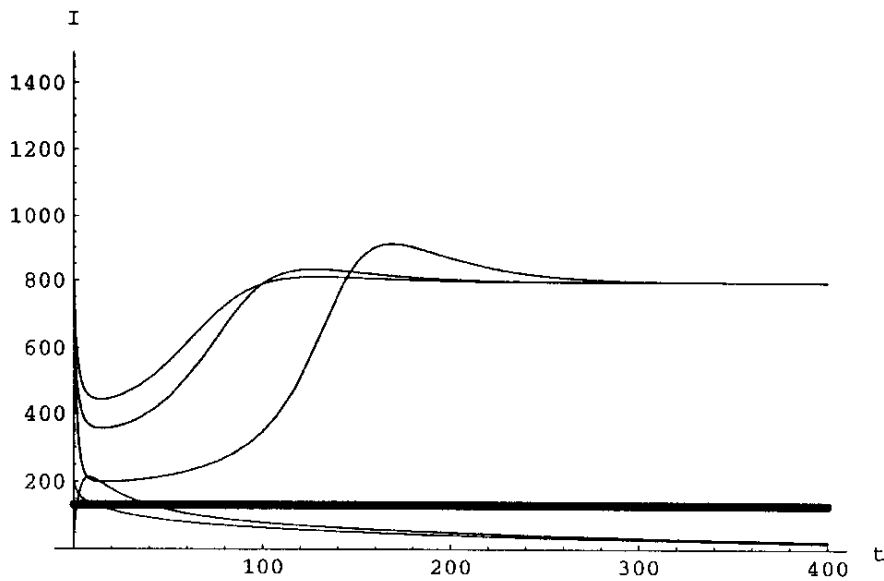


Fig. 2. A plot of infectives $I(t)$ vs. time for $d > 0, \sigma < 1$ and $\mathcal{R}_0 < 1$. Parameter values are: $\mu = 0.016, d = 0.1, p = 0.4, \sigma = 0.9, \Lambda = 417$ ($\Lambda/\mu = 25000$), $k = 0.005, r = 2$. For this set of parameter values, $p_0 = 0.3, \mathcal{R}_0 = 0.87$, and $\mathcal{R}_p = 0.84$. It shows that there are three equilibria with corresponding I components: $I_0 = 0$ (stable), $I_-^* = 132$ (unstable), and $I_+^* = 795$ (stable).

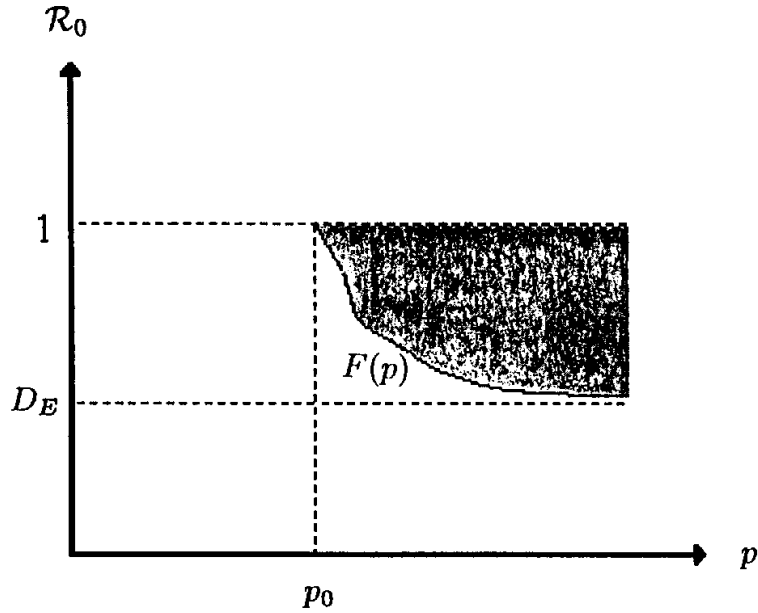


Fig. 3. A bifurcation diagram in the plane of parameters (p, \mathcal{R}_0) . Here $D_E = k/(\mu+k)$ is the mean length that an individual spends in the latent class. In the region $\{(p, \mathcal{R}_0) : D_E < \mathcal{R}_0 < 1, p > f(\mathcal{R}_0)\}$, there are two positive equilibria. In the region $\{(p, \mathcal{R}_0) : 0 < \mathcal{R}_0 < 1, p < f(\mathcal{R}_0)\}$, there is only the disease-free equilibrium. For almost all other parameter values, i.e., $\mathcal{R}_0 > 1, p > 0$, there exists unique endemic equilibrium.

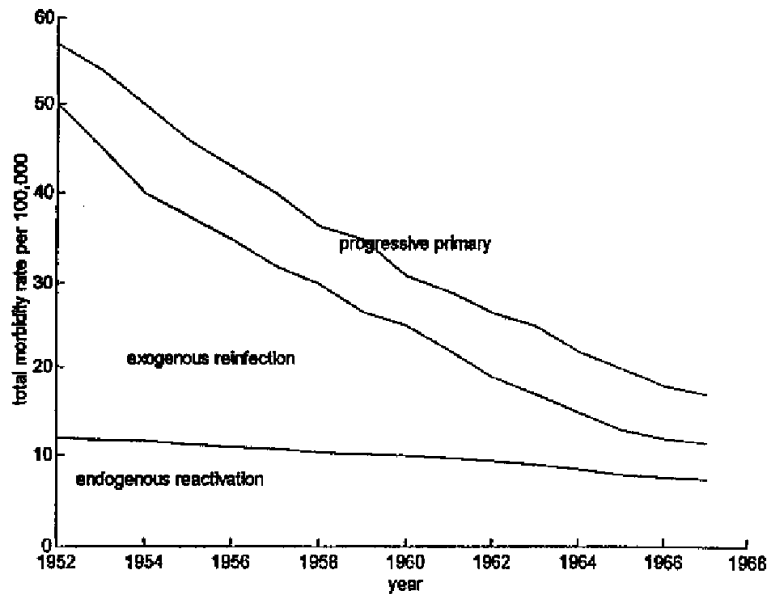


Fig. 4. Relative importance of progressive primary TB, endogenous reactivation TB, exogenous reinfection TB to total morbidity from pulmonary tuberculosis data from the Netherlands for individuals with ages between 45 to 49, 1952-1967 (Sutherland and Svandova, 1972, cited in Styblo, 1994; here modified from Styblo's).