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A Model for Tuberculosis with Exogenous Reinfection

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Following primary tuberculosis (TB) infection, only approximately 10% of individuals develop active T.B. 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 the possibility of a subcritical bifurcation at the critical value of the basic reproductive number $\mathscr{R}_0 = 1$, and hence the existence of multiple endemic equilibria for $\mathscr{R}_0 < 1$ and the exogenous reinfection rate larger than a threshold. Our results suggest that reducing $\mathscr{R}_0$ to be smaller than one may not be sufficient to eradicate the disease. An additional reduction in reinfection rate may be required. These results may also partially explain the recently observed resurgence of TB.

INTRODUCTION

Tuberculosis (TB) 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 different

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viruses, 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 (Waaler and Piot, 1962; Brogger, 1967; Waaler, 1967; ReVelle, 1967; ReVelle *et al.*, 1967; Waaler *et al.*, 1970; Azuma, 1975; Schulzer *et al.*, 1992; Schulzer *et al.*, 1994; Bermejo *et al.*, 1992; Blower *et al.*, 1995, 1996; Vinnicky and Fire, 1997; Castillo-Chavez and Feng, 1997, 1998a, 1998b).

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 we carry this bacterium the less likely we are to develop active TB unless our immune system becomes seriously compromised by other diseases. Consequently, age of infection and 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 not only look at TB infection as 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 pre-existing dormant infection) (Styblo, 1991; Smith and Moss, 1994). The exogenous theory says that exogenous reinfection plays an important role in disease progression and that, in fact, the inhalation of tubercle bacilli by persons who have had a primary tuberculosis infection for more than five years previously represents an increasing risk of development of active tuberculosis soon after 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). Exogenous infection was explicitly ignored by Blower *et al.* (1995) in their model of tuberculosis transmission because of their assumption that it occurs only 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 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, such as central Harlem in the USA (Hopewell, 1993), where HIV seroprevalence is high. Hence exogenous reinfections may play an important role in the observed increases of active-TB incidence in the inner cities of developed countries. Furthermore, recent Center for Disease Control (CDC) trace data on TB infection cases has proved that it is 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 data show that it may be quite possible to become infected while using crowded transportation—including public city transportation—for several hours a day. This hypothesis is supported by a nonresidential outbreak of tuberculosis that originated in a neighborhood bar (see 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%), 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. Tests on 12 culture isolates presented the same chromosomal-DNA restriction pattern. Dutt *et al.* (1995) reported an outbreak related to 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 in a survey. Hence, it is possible that individuals who have a latent infection are often exposed to exogenous infections through infectious friends and relatives, through the use of mass-transportation (Kolata, 1995), or by their presence in a closed environment where community members meet (Kline *et al.*, 1995; Dutt *et al.*, 1995). The role of exogenous reinfection in disease progression from latent to active TB for 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 exogenous reinfections into a "typical" epidemiological model for the transmission dynamics of TB. We explore the possibility that exogenous infections may play a fundamental role in the transmission dynamics and the epidemiology of TB at the population level. In fact, our mathematical analysis already shows that reinfection may—theoretically—increase the number of cases of active TB, may give rise to less predictable dynamics, and consequently may decrease the effectiveness of public health measures.

TB exhibits long and variable periods of latency. In our early work, 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, 1998b). However, we have yet to consider a model with reinfection and long and variable periods of latency. We suspect that the results of this article will hold in models with realistic distributed delay.

The purpose of this paper is to look at the effect of exogenous reinfections 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 $\mathcal{R}_0 < 1$ provided that the probability of reinfection p exceeds a threshold p_0. The implications of this result are varied. For example, a population 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 Hadeler and Castillo-Chavez, 1995).

This paper is organized as follows: Section 1 introduces a TB model incorporating exogenous reinfection. In Section 2 we compute the critical values of the basic reproductive number $\mathcal{R}_p < 1$ and reinfection probability level p_0 leading to multiple endemic equilibria wherever $\mathcal{R}_p < \mathcal{R}_0 < 1$ and $p > p_0$. Some stability results of equilibria of the model are also given in Section 2. Section 3 discusses the biological implications of our results as well as some of our current efforts and extensions including the incorporation of the effects of immigrants from countries where TB prevalence is high. An Appendix collects some of the mathematical details.

1. A 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 classes or subgroups: susceptibles (S), exposed (E, infected but not infectious), infectious (I), and effectively treated (T, still susceptible) individuals. N denotes the total population. We assume that an individual can be infected only through contacts with infectious individuals. The use of a distributed delay in the rate of removal from the infected class has not changed the qualitative dynamics of our basic TB model (see Castillo-Chavez and Feng, 1998b). Hence we assume constant per capita removal rates to focus exclusively on the role of exogenous reinfection. The model takes the following form:

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

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, $0 \leqslant \sigma \leqslant 1$; 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 $p\beta cE(I/N)$ models the exogenous reinfection

rates with p representing the level of reinfection. When $p=0$, system (1.1) reduces to our earlier TB model (Castillo-Chavez and Feng, 1997). A value of $p \in (0, 1)$ implies that reinfection is less likely than a new infection. In fact, a value of $p \in (0, 1)$ implies that a primary infection provides some degree of cross immunity to exogenous reinfections. A value of $p \in (1, \infty)$ implies that TB infection increases the likelihood of active TB. Here, we take the conservative view that $0 < p < 1$. A value of $p > 1$ may be reasonable for HIV-infected individuals.

The basic reproductive number for (1.1) is

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

This number is given by the product $\beta c/(\mu + r + d)$, that is, by the product of 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 $\mathscr{R}_0$ 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.

2. MULTIPLE ENDEMIC EQUILIBRIA AND THEIR STABILITY

It can be shown that for system (1.1) the first octant in the state space is positively invariant, that is, that solutions "live" in biological space where all the variables are non-negative. Adding equations in (1.1) gives

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

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

$$G = \left\{ (S, E, I, T) \mid S, E, I, T \geqslant 0,\ S + E + I + T \leqslant \frac{\Lambda}{\mu} \right\}.$$

In our analysis, we first 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 (see the discussion after Result 2). The N equation becomes $(d/dt)\, N = \Lambda - \mu N$ and $N(t) \to \Lambda/\mu$, as $t \to \infty$. 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 $(\Lambda/\mu, 0, 0, 0)$. Note that $\mathscr{R}_0$ does not depend on p. However, the number of endemic equilibria depends on the value of reinfection level p. The expression of $\mathscr{R}_0$ here is essentially the same as that computed for our TB model without a re-exposure term (see Castillo-Chavez and Feng, 1997). The model without re-exposure ($p = 0$) has been analyzed and its qualitative behavior changes only at the critical value $\mathscr{R}_0 = 1$. If $\mathscr{R}_0 < 1$, then the disease-free equilibrium is globally asymptotically stable (g.a.s.) while if $\mathscr{R}_0 > 1$, then there exists an unique endemic equilibrium which is locally asymptotically stable (l.a.s.) (see Castillo-Chavez and Feng, 1997). Here we show that as the value of p changes system (1.1) exhibits a subcritical bifurcation at $\mathscr{R}_0 = 1$. Hence, multiple endemic equilibria can occur for $\mathscr{R}_0 > 1$. In order to see this behavior we let

$$p_0 = \frac{(1 + Q)\, D_E}{1 - D_E}, \tag{2.1}$$

where

$$D_E = \frac{k}{\mu + k}, \qquad Q = \frac{k}{\mu + r}. \tag{2.2}$$

The existence of possible multiple endemic equilibria is given by the following result:

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

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

(c) If $\mathscr{R}_0 < 1$ and $p < p_0$, then (1.1) has no positive equilibrium. If $\mathscr{R}_0 < 1$ and $p = p_0$, then (1.1) has exactly one positive equilibrium.

Our result shows that for each fixed $p > p_0$, there is a branch of endemic equilibria bifurcating backwards from the disease-free equilibrium at $\mathscr{R}_0 = 1$. Hence System (1.1) has multiple endemic equilibria for $\mathscr{R}_0 < 1$. A bifurcation diagram is shown in Fig. 1 and the results of numerical studies are illustrated in Fig. 2. The proof of Result 1 is given in the Appendix.

Remark. The threshold value of the reinfection level is $p_0 = 0.3$ for the set of parameter values used in Fig. 2;

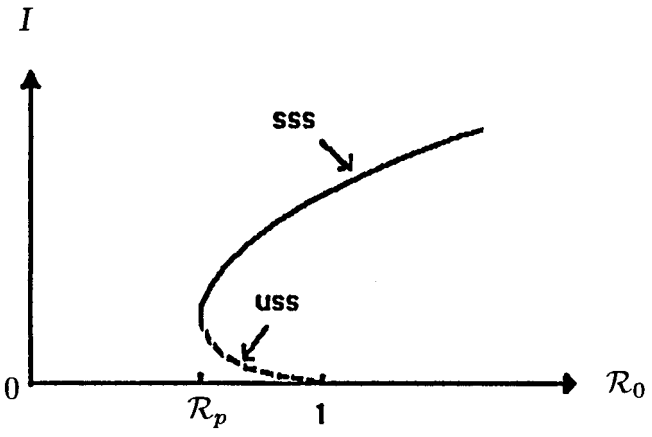

FIG. 1. A bifurcation diagram of endemic steady states. I denotes the number of infective individuals, *sss* stands for stable steady state, *uss* stands for the unstable steady state.

that is, a backward bifurcation is possible under cross-immunity.

An alternative way to look at the role of the reinfection level p and the relationship between p and $\mathcal{R}_0$ is to take $(p, \mathcal{R}_0)$ as a pair of bifurcation parameters. This approach may help to design disease control strategies that take exogenous reinfection into account (see Section 3). The following lemma leads to the $(p, \mathcal{R}_0)$ bifurcation diagram shown in Fig. 3.

LEMMA. *Let* $F(p) = \mathcal{R}_p$ *be the constant given in Result* 1. *Then* (a) $F(p) \geqslant D_E$ *for all* $p > p_0$; (b) $F(p) \to D_E$ *as* $p \to \infty$; *and* (c) $F(p_0) = 1$.

The lemma can be proved easily using (2.1), (2.2) and the definition of $\mathcal{R}_p$ given in (A.2). This lemma shows that multiple endemic equilibria exist if and only if the parameters are in the shaded area in Fig. 3. The conditions for stability of equilibria are given in the following result:

Result 2. Let $U^*_+ = (S^*_+, E^*_+, I^*_+, T^*_+)$ and $U^*_- = (S^*_-, E^*_-, I^*_-, T^*_-)$ be the two endemic equilibria with $I^*_+ > I^*_- > 0$. Then

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

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

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

Figure 2 illustrates the asymptotic behaviors of solutions for case (ii). The values for μ, d and k have been chosen from the parameter table in Blower *et al.* (1995), $r = 1/6$ months (time between becoming infectious and being treated), $p = 0.4$ (from Vinnicky and Fine, 1997, p could take values between 0 and 1), and $\sigma = 0.9$ represents a reduced infection rate among treated individuals due to temporary protection by antibiotics (Rossman and MacGregor, 1995). For these parameter values we have $p_0 = 0.3$, $\mathcal{R}_0 = 0.87$, and $\mathcal{R}_p = 0.84$. The graph shows the I component of three equilibria and the stability of each equilibrium: $I_0 = 0$ (stable); $I^*_- = 132$ (unstable); and $I^*_+ = 795$ (stable). Hence, if the proportion of exogenous reinfection is large ($p > p_0$), then a sudden rise of TB incidence is possible even when $\mathcal{R}_0 < 1$ (see Fig. 1). 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 shows this dependence. This result suggests that a sudden influx

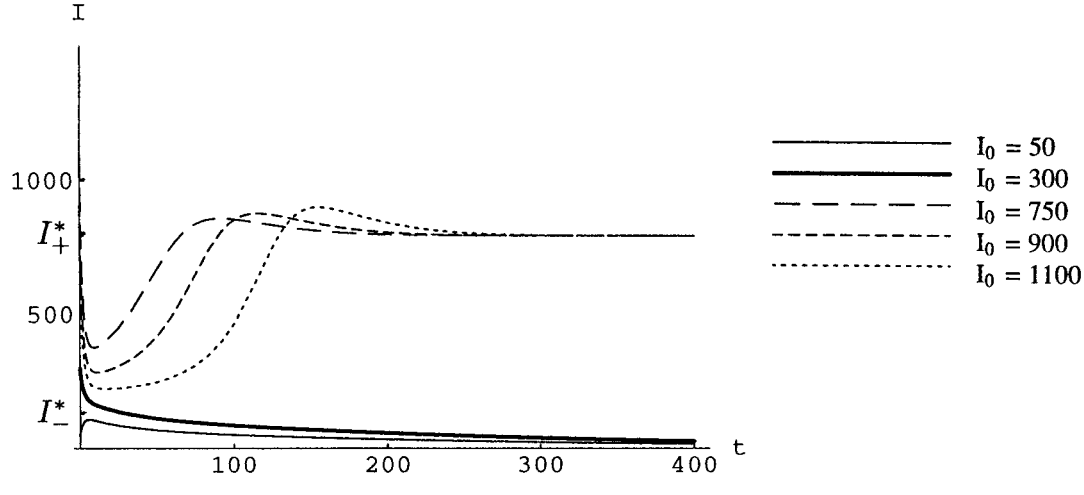

FIG. 2 A plot of infectives $I(t)$ vs time for $d > 0$, $\sigma < 1$, and $\mathcal{R}_0 < 1$. Parameter values are $\mu = 0.016$, $d = 0.1$, $p = 0.4$, $\sigma = 0.9$, $\Lambda = 417$ ($\Lambda/\mu = 25000$), $k = 0.005$, $r = 2$. For this set of parameter values, $p_0 = 0.3$, $\mathcal{R}_0 = 0.87$,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

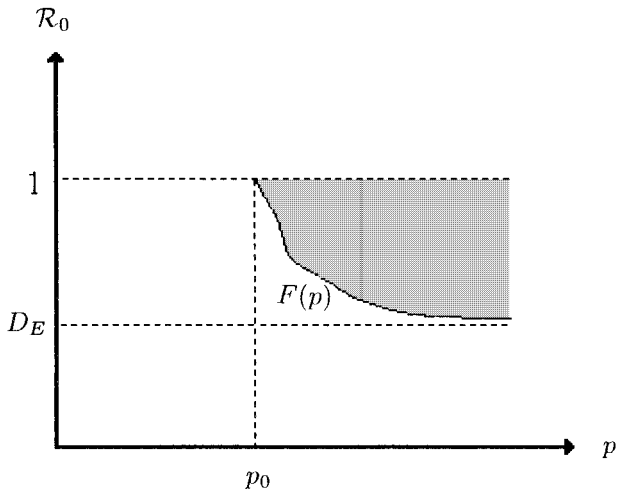

FIG. 3. A bifurcation diagram in the plane of parameters $(p, \mathcal{R}_0)$. Here $F(p) = \mathcal{R}_p$ (see (A.2)) and $D_E = k/(\mu + k)$ is the mean length that an individual spends in the latent class. In the shaded region $\{(p, \mathcal{R}_0): p > p_0, F(p) < \mathcal{R}_0 < 1\}$ there are two positive equilibria. For $(p, \mathcal{R}_0)$ outside the shaded region and $\mathcal{R}_0 < 1$ there is only the disease-free equilibrium. For all other parameter values, i.e., $\mathcal{R}_0 > 1$ and $p > 0$, there exists a unique endemic equilibrium.

of infectious individuals (immigrants, for example) may give rise to epidemic outbreaks that could stabilize at an endemic level which would have been unstable (or nonexistent) in the absence of exogenous reinfections (see Section 3). The proof of Result 2 is given in the Appendix.

3. DISCUSSION

The importance of exogenous reinfections is still highly debated. Stead (1967) has shown evidence which supports the conclusion that the reactivation from endogenous tuberculosis may be the main cause of chronical 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 contributions of the different ways of acquiring tuberculosis by relating the changes of annual risk of infection to 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 for total TB morbidity from pulmonary tuberculosis is described in Sutherland and Svandova (1971). Sutherland *et al.* (1982) estimated the risks of developing the disease following infection or reinfection using epidemiological information and data for the Netherlands (such as risk of tuberculosis infection and incidence of tuberculosis). 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 1951–1970 were (a) 5.06% annually (for 5 years) following primary infection; (b) 1.91% annually (for 5 years) following reinfection; (c) 0.0253% 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%, respectively. These researchers estimated that the degree of protection against pulmonary tuberculosis arising from a recent reinfection conferred by a distant primary infection was 63% for males and 81% for females. In this study progressive primary tuberculosis was dominant at the younger ages; exogenous and endogenous tuberculosis were dominant at older ages.

Ziegler *et al.* (1985), through their experimental airborne tuberculosis study using guinea pigs, provided no support for the hypothesis 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 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 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 that persons previously infected with *M. tuberculosis* will suffer 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 hypothesis most consistent 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. 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. Is our condition for the multiple endemic equilibria met with the epidemiological parameters reported in these studies? To answer this question requires knowledge of the unknown rate β or, equivalently, of the basic reproductive number $\mathscr{R}_0$. Our lack of knowledge of the exact value of β is not a critical drawback as, whatever its value may be, it must be such that $\mathscr{R}_0$ is in the neighborhood of 1. In fact, if we follow the results of Blower *et al.* then it must be large enough so that $\mathscr{R}_0 > 1$. Hence, choosing a value of β that makes $\mathscr{R}_0 < 1$ is indeed conservative step in the literature of theoretical TB models. Furthermore, it is clear that the range for the values of the reinfection level should be $0 < p < 1$ on a conservative approach. So the minimum reinfection levels ($p_0 = 0.3$) that lead to multiple endemic equilibria in our model are at least of the right order of magnitude, if not conservative.

The incorporation of exogenous reinfection into our model reveals qualitative dynamics unexpectedly different from those derived from models without reinfection. For example, from the expression of $\mathscr{R}_p$ (see (A-2)) we can draw a bifurcation diagram in the $(p, \mathscr{R}_0)$ plane (see Fig. 3). Results 1 and 2 show that there are multiple endemic equilibria for $(p, \mathscr{R}_0)$ in the shaded area, with U_+^* being stable, indicating that the disease will persist in the population even when $\mathscr{R}_0 < 1$. When $\mathscr{R}_0 < 1$ and $(p, \mathscr{R}_0)$ is outside the shaded area, only the disease-free equilibrium exists which is stable. Thus, in order to eradicate the disease, control strategies should either reduce $\mathscr{R}_0$ to a value below $\mathscr{R}_p$ (which is less than one) when p is known or, for given $\mathscr{R}_0$ with $D_E < \mathscr{R}_0 < 1$ and $(p, \mathscr{R}_0)$ in the shaded area, reduce p (by lowering the contact rate of exposed patients) to $(p, \mathscr{R}_0)$ outside the shaded area. Results I and 2 also show the possibility of fragile control measures which are just based on whether or not $\mathscr{R}_0$ is less or greater than one. Exogenous reinfections may in fact help re-establish TB to a new endemic level via the flux of infectious individuals into the system (via internal or external immigration).

If exogenous reinfections 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, combined with immigration and population growth, is constantly changing the contact structure of a population. Examples of this phenomenon 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 (United States), 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) 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, and on the type of measures that must be taken at various scales to develop public planning that are not limited to local environments or even national borders. For the United States in 1986, 22% of TB cases were diagnosed in persons of foreign birth (CDC 1987). For the period from 1986 to 1992, foreign-born persons composed 60% of the increase of TB cases in the Unites States (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 are 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 United States.

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% to nearly 40% (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% 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 for those who had immigrated 5 or more years previously was less than half that of new immigrants (Rieder *et al*., 1989). Also, the incidence of tuberculosis in cohorts of all immigrants decreased about 50% 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 six times higher than that among the residents of British Columbia (6% compared with 1%) (Wang *et al*., 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 among 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, household 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 source 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 United States.

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 United States) into a model for the transmission dynamics of TB allows for the possibility of nonstandard dynamics: endemic states can be permanently supported even when $R_0 < 1$. The

biological interpretation for this is that the effect of exogenous reinfection is to increase the number of individuals that are at risk of becoming infectious. Therefore a sudden influx of infectious immigrants individuals or the sudden relocation of individuals within a state or a country (open of a new factory, closing of an industrial zone, creation of new enterprise zones, etc.) may give rise to epidemic outbreaks that could stabilize at an endemic level that would have been unstable in the absence of exogenous reinfections. Waves of immigrants from countries with high TB incidence often hit inner cities. The number of individuals using public transportation—including airlines—not only has increased contact rates but also has changed the social contact structure that we live in (who mixes with whom). The intensity of interactions among individuals who live within the sphere of influence of political and/or economic borders also experience "nontypical" contact patterns (e.g., enterprise zones at the United States–Mexico border). TB control policies that ignore global issues seem doomed to failure.

APPENDIX

Proof of Result 1. (a) To find an endemic equilibrium (S^*, E^*, I^*, T^*) of (1.1) with $I^* > 0$ we let $x = I^*/N^*$. Then

$$I^* = \frac{\Lambda}{\mu} x,$$

$$S^* = \frac{\Lambda}{\mu + \beta c x},$$

$$E^* = \frac{\mu + r}{k + p\beta c x} \frac{\Lambda}{\mu} x,$$

$$T^* = \frac{r}{\mu + \beta c x} \frac{\Lambda}{\mu} x.$$

Using $S^* + E^* + I^* + T^* = N^* = \Lambda/\mu$ and the definition of $\mathcal{R}_0$ we get

$$Ax^2 + Bx + C = 0, \tag{A.1}$$

where

$$A = p\mathcal{R}_0,$$

$$B = (1 + p + Q)\, D_E - p\mathcal{R}_0,$$

$$C = D_E Q \left(\frac{1}{\mathcal{R}_0} - 1 \right),$$

and D_E, Q are given in (2.2). Since $\mathcal{R}_0 > 1$, we have $A > 0$ and $C > 0$. Hence (A.1) has exactly one positive solution, and hence (1.1) has exactly one endemic equilibrium.

(b) If $\mathcal{R}_0 < 1$ and $p > p_0$, then we can derive

$$\mathcal{R}_p = \frac{1}{p} \left(D_E(1 + p - Q) + 2\sqrt{D_E Q(p - pD_E - D_E)} \right) \tag{A.2}$$

such that $B^2 - 4AC > (=\text{ or } <)\, 0$ if $\mathcal{R}_0 > (=\text{ or } <)\, \mathcal{R}_p$. Using (2.1) it can be checked that $\mathcal{R}_p < 1$ for $p > p_0$. It follows that (1.1) has two (one or none) endemic equilibria if $\mathcal{R}_0 > (=\text{ or } <)\, \mathcal{R}_p$.

(c) If $\mathcal{R}_0 < 1$ and $p < p_0$, then $AC > 0$ and $B > 0$. Hence (A.1) has no positive solution and (1.1) has no endemic equilibrium.

This finishes the proof.

As mentioned in Section 2, the following analytical proof of Result 2 is for the case when $d = 0$, $\sigma = 1$. The question of stability for case when $d > 0$ and $\sigma < 1$ has only been explored via numerical simulations. These simulations support the same qualitative results (see Fig. 2).

Proof of Result 2. (i) Let $\mathcal{R}_0 < 1$. It is easy to check that the Jacobian of (1.1) at the disease-free equilibrium has all eigenvalues with negative real part if $\mathcal{R}_0 < 1$. The local asymptotic stability follows.

(ii) Let $p > p_0$ and $\mathcal{R}_p < \mathcal{R}_0 < 1$. Introduce a new variable $W = S + T$, and let $w = W/N$, $e = E/N$, $x = I/N$. Then the limiting system $(N = \Lambda/\mu)$ of (1.1) is equivalent to the following system:

$$\begin{aligned} \frac{d}{dt} w &= \mu - \beta c w x - \mu w + r x, \\ \frac{d}{dt} e &= \beta c w x - p\beta c e x - (\mu + k)\, e, \\ \frac{d}{dt} x &= p\beta c e x + k e - (\mu + r)\, x. \end{aligned} \tag{A.3}$$

Let $V_{\pm}^* = (w_{\pm}^*, e_{\pm}^*, x_{\pm}^*)$ be the endemic equilibria of (A.3). Then

$$w_{\pm}^* = \frac{\mu + r x_{\pm}^*}{\mu + \beta c x_{\pm}^*}, \qquad e^* = \frac{(\mu + r)\, x_{\pm}^*}{k + p\beta c x_{\pm}^*},$$

and x_+^* and x_-^* are positive solutions of (A.1) with $x_+^* > x_-^*$. The proof is simplified if we let $\beta' = \beta c$ and rewrite the equation (A.1) using β' (instead of $\mathcal{R}_0$) as

$$A_1 x^2 + B_1 x + C_1 = 0, \tag{A.4}$$

where

$$A_1 = p\beta',$$
$$B_1 = \mu + r + k + (\mu + r)\, p - p\beta',$$
$$C_1 = \frac{(\mu + r)(\mu + k)}{\beta'} - k.$$

The Jacobian of (A.3) at $V^*_\pm$ is

$$J_\pm = \begin{pmatrix} (-\beta' x^*_\pm + \mu) & 0 & \dfrac{\mu(w^*_\pm - 1)}{x^*_\pm} \\ \beta' x^*_\pm & -(p\beta' x^*_\pm + \mu + k) & \dfrac{(\mu + k)\, e^*_\pm}{x^*_\pm} \\ 0 & p\beta' x^*_\pm + k & -\dfrac{k e^*_\pm}{x^*_\pm} \end{pmatrix},$$

and the characteristic equation is

$$h_\pm(\lambda) = \lambda^3 + a_\pm \lambda^2 + b_\pm \lambda + c_\pm = 0, \qquad \text{(A.5)}$$

where

$$a_\pm = 2\mu + k + (1 + p)\, \beta' x^*_\pm + k \frac{e^*_\pm}{x^*_\pm},$$
$$b_\pm = (\beta' x^*_\pm + \mu)(\mu + k + p\beta' x^*_\pm) + (\mu k + k\beta' x^*_\pm - \mu p \beta' x) \frac{e^*_\pm}{x^*_\pm}, \qquad \text{(A.6)}$$
$$c_\pm = (\beta' x^*_\pm + \mu)\, \mu k \frac{e^*_\pm}{x^*_\pm} + \mu p \beta'^2 (x^*_\pm)^2 + \mu k \beta' x^*_\pm - \mu^2(\mu + r).$$

We observe that

$$c_- < 0, \qquad c_+ > 0. \qquad \text{(A.7)}$$

To establish the observation in (A.7), we let

$$\hat{c}_\pm = (\mu + r)(k - \mu p) + (k + p\beta' x^*_\pm)^2, \qquad \text{(A.8)}$$

and we note—after some algebra—that

$$c_\pm = \frac{\mu \beta' x^*_\pm}{k + p\beta' x^*_\pm}\, \hat{c}_\pm.$$

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

$$\delta = \frac{\sqrt{(\mu + r)(\mu p - k)} - k}{p\beta'}, \qquad \text{(A.9)}$$

then from (A.8) and (A.9) we can see that $\hat{c}_- < 0$ ($\hat{c}_+ > 0$) iff $x^*_- < \delta$ ($x^*_+ > \delta$). Let $f(x) = A_1 x^2 + B_1 x + C_1$, then $f(x^*_\pm) = 0$ (see (A.4)). Hence (A.7) holds iff $f(\delta) < 0$. Since $\beta' > \mu + r$ and $B_1 < 0$ for $p > p_0$ and $\mathscr{R}_0 > \mathscr{R}_p$ (see (2.1) and (A.2)), after some algebra we have

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

Therefore (A.7) holds. Notice from (A.5) and (A.7) that $h_-(0) = c_- < 0$ and $h_-(\lambda) \to \infty$ as $\lambda \to \infty$. It follows that $h_-(\lambda^*) = 0$ for some $\lambda^* > 0$. Therefore J_- has a positive eigenvalue, and V^*_- is unstable.

The Routh–Hurwitz criterion implies that all roots of $h_+(\lambda)$ have negative real parts if $a_+ > 0$, $c_+ > 0$, and $a_+ b_+ - c_+ > 0$. From (A.6) it is clear that $a_+ > 0$, and from (A.7) we have that $c_+ > 0$. Further algebra shows that

$$\begin{aligned} a_+ b_+ - c_+ &\geqslant a_+ (\beta' e^*_+ (k - \mu p) + \beta' x^*_+ (k + p\beta' x^*_+)) \\ &= \frac{a_+ \beta' x^*_+}{k + p\beta' x^*_+} \\ &\quad \times ((\mu + r)(k - \mu p) + (k + p\beta' x^*_+)^2) \\ &= \frac{a_+ \beta' x^*_+}{k + p\beta' x^*_+}\, c_+ \\ &> 0. \end{aligned}$$

It follows that V^*_+ is l.a.s.

(iii) Let $\mathscr{R}_0 > 1$. In this case the only endemic equilibrium is given by x^*_+. If $0 \leqslant p \leqslant k/\mu$ then it is easy to prove that $k > \mu p$ implies that $c_+ > 0$ and $a_+ b_+ - c_+ > 0$. If $p > k/\mu$ then the proof is the same as in (ii) for the stability of x^*_+.

This finishes the proof.

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