MATHEMATICAL MODELS FOR THE DISEASE DYNAMICS OF TUBERCULOSIS

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Four mathematical models for the study of the disease transmission dynamics of tuberculosis (TB) are presented. We also discuss issues related to optimal vaccination strategies for TB. A two-strain TB model is formulated to determine possible mechanisms for the survival and spread of naturally resistant strains of TB as well as antibiotic-generated resistant strains of TB. Analysis of this model shows that non-antibiotic co-existence is possible but rare for naturally resistant strains while co-existence is almost the rule for strains that result from the lack of compliance with antibiotic treatment by TB infected individuals. A distributed delay model is used to look at the effects of long and variable periods of latency on the dynamics of TB. We use a third model to show that exogenous reinfection has a drastic effect on the qualitative dynamics of TB. Finally an age-structured model is used to determine optimal vaccination strategies for TB. We only outline our results in this short article.

1. Introduction. Tuberculosis is a bacterial disease with an astimated one third of the world human population as its reservoir. The disease is most commonly transmitted from a person suffering from infectious (active) tuberculosis to susceptible (and possibly latently infected) persons by infected droplets created when the person with active TB coughs or sneezes. Among generally healthy persons, infection with TB is highly likely to be asymptomatic. Data from a variety of sources suggest that the life time risk of developing clinically active TB after being infected is approximately 10% (Hopewell 1994). Individuals who have a latent TB infection are not clinically ill nor capable of transmitting TB (Miller 1993). At greater ages, the immunity of persons who have been previously infected may wane, and they may be then at 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., re-activation of a pre-existing dormant infection) (Styblo 1991, Smith 1994).

Latent and active TB can be treated with antibiotics. However, its treatment has side effects (sometimes quite serious) and takes a long time. Carriers of the tubercle bacillus who have not developed TB disease can be treated with a single drug *INH*; unfortunately, it must be taken religiously for 6-9 months. Treatment for those with active TB requires the simultaneous use of three drugs for a period of at least 12 months. Lack of compliance with these drug treatments (a very serious problem) not only may lead to a relapse but to the development of antibiotic resitant TB – one of the most serious public health problems facing society today.

In the United States, the estimated total number of TB infections lies between 10-15 million persons (Miller 1993). However, dramatic increases in the incidence of TB (new cases per year) have occurred within the United States over the past few years. From 1985 to 1991, the number of reported cases of TB has increased 18% with 26,283 cases reported in 1991 (Kent 1993). Outbreaks of drug resistant TB in the United States have begun to alarm doctors and public health officials. Over 80% of the patients in these outbreaks have died, often within weeks of being diagnosed as having tuberculosis. These problems are compounded by economics, as the cost of treating a patient with MDR-TB can exceed $250,000: nearly 100 times the cost of treating most other TB cases (Press release WHO /89 Nov. 1994). The emergence of the HIV epidemic has dramatically increased the risk of developing clinical TB in infected persons and it has contributed to the observed dramatic increase of TB rates globally.

A TB vaccine called BCG (*Bacillus of Calmette and Guérin*) has been available for many decades but its effectiveness in preventing TB is controversial (Salyers 1994). Results of field trials of the vaccine have differed widely, some indicating protection rates as high as 70% to 80% while others showing as a completely ineffective vaccine for the prevention of TB.

Many mathematical models have been developed to study communicable diseases such as measles, influenza, rubella, and chicken pox (see Hethcote 1976, Dietz 1979, Hethcote, Stech, and van den Driescsche 1981, Anderson 1982, Anderson and May 1982, 1991, Dietz and Schenzle 1985, Dietz 1985, Anderson and May 1983, Schenzle 1984, Hethcote and Van Ark 1987, Castillo-Chavez et al. 1988, 1989, 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 capable of generating similar epidemiological responses at the level of the individual (symptoms). 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 TB despite its fundamental role in the development of bacteriology and modern epidemiology is paradoxically different. The study of the spread of TB using statistical and mathematical models has not received enough attention. In fact we have observed only an extremely limited use of mathematical models in the study of the transmission dynamics of TB in human populations.

In this paper we formulate a series of mathematical models to study the dynamics of TB. We use a system of ODE's to study the role that lack of drug treatment compliance by TB patients plays on the maintenance of antibiotic resistant strain. A distributed delay model is used to study the effect of the long and variable latency periods in the progression of TB on the disease dynamics. We also use a simple system of ODE's to assess the role of "reinfection" in the development of active TB. We construct an age-structured TB model to explore possible optimal vaccination strategies for TB. In the following section we present a series of models for the transmission of TB and some results. Section 3 is devoted to the conduction of numerical simulations that support or complete some of our analytical results. Section 4 collects our thoughts and conclusions.

2. TB models. We basically divide the host population into the following epidemiological classes or subgroups: Susceptible (S), Latent (L, infected but not infectious), Infectious (I), and (effectively) Treated (T) individuals. N is used to denote the total population. We assume that an individual may be infected only through contacts with infectious individuals. We also assume that treated individuals can become infected again.

2.1. A two-strain TB model. Consider two trains of TB: the regular TB (strain 1) and the resistant TB (strain 2). Let L_1 and L_2 denote latent with strain 1 and strain 2, respectively. I and J stand for infectious with strain 1 and 2. Using Fig. 1 we can write the following system of ordinary differential equations:

$$
\begin{aligned}
&\frac{d}{dt}S = \Lambda - \beta cS\frac{I}{N} - \beta^* cS\frac{J}{N} - \mu S \\
&\frac{d}{dt}L_1 = \beta cS\frac{I}{N} - (\mu + k)L_1 - r_1 L_1 + pr_2 I + \beta' cT\frac{I}{N} - \beta^* cL_1\frac{J}{N} \\
&\frac{d}{dt}I = kL_1 - (\mu + d)I - r_2 I \\
&\frac{d}{dt}T = r_1 L_1 + (1 - p - q)r_2 I - \beta' cT\frac{I}{N} - \beta^* cT\frac{J}{N} - \mu T \\
&\frac{d}{dt}L_2 = qr_2 I - (\mu + k')L_2 + \beta^* c(S + L_1 + T)\frac{J}{N} \\
&\frac{d}{dt}J = k'L_2 - (\mu + d')J \\
&N = S + L_1 + I + T + L_2 + J.
\end{aligned}
\tag{1}
$$

Λ is the recruitment rate; β and β' are the average proportions of susceptible and treated individuals infected by one infectious individual per contact per unit of time, respectively; β^* is the average proportion of individuals infected by one resistant-TB infectious individual per contact per unit of time; c is the per-capita contact rate; μ denotes the per-capita natural death rate; k and k' are the rates at which individuals leave the latent classes L_1 and L_2, respectively, by becoming infectious; d and d' stand for the per-capita disease induced death rates by strains 1 and 2; and r_1 and r_2 are the per-capita treatment rates for (regular TB) latent and infectious individuals, respectively; $p+q$ is the total proportion of those treated infectious individuals who did not complete their treatment. The proportion p modifies the rate that departs from the latent class; qr_2I gives the rate at which individuals develop resistant-TB because they did not complete the treatment of active TB. We assumed that the treatment rate for resistant TB individuals is very small and can be neglected.

The basic reproductive numbers for the two strains (natural and resistant) are given by

$$\mathcal{R}_1 = \left(\frac{\beta c + pr_2}{\mu + d + r_2}\right)\left(\frac{k}{\mu + k + r_1}\right)$$

and

$$\mathcal{R}_2 = \left(\frac{\beta^* c}{\mu + d'}\right)\left(\frac{k'}{\mu + k'}\right),$$

respectively. We can interpret $\mathcal{R}_1$ and $\mathcal{R}_2$ as the average numbers of secondary infectious cases produced by an ordinary TB strain and one resistant-TB infectious individual during his or her *effective* infectious period, respectively.

If we let

$$\mathcal{R}_0 = \max\{\mathcal{R}_1, \mathcal{R}_2\},$$

then $\mathcal{R}_0 = 1$ gives a threshold condition in the sense that the disease will die out if $\mathcal{R}_0 < 1$ while the disease may become endemic if $\mathcal{R}_0 > 1$.

Next we consider the case when the infection probability per contact for the treated class is the same as that of the susceptible class, i.e., $\beta' = \beta$. There are four possible equilibrium points: the disease free equilibrium E_0; two boundary equilibria

E_1 (when only the first strain is present); E_2 (when only the second strain is present); and the interior equilibrium E^* (when both strains present).

To conduct an analytical analysis of asymptotical behaviors of the equilibria we assume that there is no disease-induced death rate, i.e., $d = d' = 0$. For $d > 0$ and $d' > 0$ our numerical simulations support similar results (see Section 3). Hence we have that

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

and, consequently, $N(t) \to \Lambda/\mu$ as $t \to \infty$. Without loss of generality (see Thieme 1992, 1994) we assume that our population has reached its limiting value, i.e.,

$$N \equiv \Lambda/\mu \equiv S + T + L_1 + I + L_2 + J.$$

Introducing the fractions

$$x_1 = \frac{L_1}{N}, \qquad x_2 = \frac{I}{N}, \qquad y_1 = \frac{L_2}{N}, \qquad y_2 = \frac{J}{N},$$

and using $\beta' = \beta$, we can eliminate the equations for S and T and replace $S + T$ by $N - L_1 - I - L_2 - J$ to obtain from (1) the equivalent limiting system (Thieme 1993)

$$\begin{aligned}
\frac{d}{dt}x_1 &= \beta c(1 - x_1 - x_2 - y_1 - y_2)x_2 - (\mu + k + r_1)x_1 + pr_2x_2 - \beta^* c x_1 y_2 \\
\frac{d}{dt}x_2 &= kx_1 - (\mu + r_2)x_2 \\
\frac{d}{dt}y_1 &= qr_2x_2 - (\mu + k')y_1 + \beta^* c(1 - x_2 - y_1 - y_2)y_2 \\
\frac{d}{dt}y_2 &= k'y_1 - \mu y_2.
\end{aligned} \tag{2}$$

With this notation, we are able to setablish the following result:

Result 1 *Assume that $q = 0, d = d' = 0$. Then*

(a). The disease-free equilibrium E_0 of System (2) is g.a.s. if $\mathcal{R}_0 < 1$, i.e., if $\mathcal{R}_1 < 1$ and $\mathcal{R}_2 < 1$.

(b). If $\mathcal{R}_1 > 1$, then there exists a threshold curve given by the function $f(\mathcal{R}_1)$ such that the boundary equilibrium E_1 of (2) is l.a.s. if $\mathcal{R}_2 < f(\mathcal{R}_1)$ and unstable if $\mathcal{R}_2 > f(\mathcal{R}_1)$. Moreover, $f(\mathcal{R}_1) > 1$ for all $\mathcal{R}_1 > 1$ and $f(1) = 1$.

(c). If $\mathcal{R}_2 > 1$, then there exists a second threshold curve given by the function $g(\mathcal{R}_1)$ such that the boundary equilibrium E_2 of (2) is l.a.s. if $\mathcal{R}_1 < 1$ or if $\mathcal{R}_1 > 1$ and $\mathcal{R}_2 > g(\mathcal{R}_1)$. E_2 is unstable if $\mathcal{R}_1 > 1$ and $\mathcal{R}_2 < g(\mathcal{R}_1)$. Moreover $g(\mathcal{R}_1) > f(\mathcal{R}_1) > 1$ for all $\mathcal{R}_1 > 1$ and $g(1) = 1$.

(d). The equilibrium E^* of (2) exists if $\mathcal{R}_1 > 1$ and $f(\mathcal{R}_1) < \mathcal{R}_2 < g(\mathcal{R}_1)$. At the quasi-steady state $\frac{d}{dt}x_2 = \frac{d}{dt}y_2 = 0$, i.e., when $x_2 = \frac{k}{\mu+d+r_2}x_1$ and $y_2 = \frac{k'}{\mu+d'}y_1$, the corresponding positive equilibrium is l.a.s. when it exists.

The assumption $q = 0$ in Result 1 implies that we are considering the case where the resistant strain is not the result of antibiotic resistance. Result 1 states that $\mathcal{R}_1$ and $\mathcal{R}_2$ as parameters determine the existence the existences as well as the stabilities of all possible equilibria of (2) using the auxillary conditions $\mathcal{R}_0 = 1$, $\mathcal{R}_2 = f(\mathcal{R}_1)$, and $\mathcal{R}_2 = g(\mathcal{R}_1)$. Fig. 2.a gives a bifurcation diagram for the case $q = 0$. Our numerical simulations suggest that

E^* is l.a.s. not only at the quasi-steady state (when the conditions in (d) are satisfied) but in general, and that non-trivial equilibriun points are g.a.s. whenever they are l.a.s..

We now consider the case $q > 0$, i.e., the rate at which individuals develop resistant-TB because they did not complete the treatment of active TB is positive. In this case System (2) has only three equilibrium points E_0, E_2, and E^*. We have established the following result:

Result 2 *Assume that* $q > 0, d = d' = 0$. *Then*

(i). The disease-free equilibrium E_0 *of (2) is g.a.s. if* $\mathcal{R}_0 < 1$, *i.e., if* $\mathcal{R}_1 < 1$ *and* $\mathcal{R}_2 < 1$.

(ii). If $\mathcal{R}_2 > 1$, *then the boundary equilibrium* E_2 *of (2) is l.a.s. if* $\mathcal{R}_1 < 1$ *or if* $\mathcal{R}_1 > 1$ *and* $\mathcal{R}_2 > g(\mathcal{R}_1)$. *(g is the function given in Result 1 (c)).* E_2 *is unstable if* $\mathcal{R}_1 > 1$ *and* $\mathcal{R}_2 < g(\mathcal{R}_1)$.

(iii). The equilibrium E^* *of (2) exists iff* $\mathcal{R}_1 > 1$ *and* $\mathcal{R}_2 < g(\mathcal{R}_1)$. *(In this case* E_2 *is unstable). When it exists,* E^* *is l.a.s. at the quasi-steady state* $\frac{d}{dt}x_2 = \frac{d}{dt}y_2 = 0$, *i.e., when* $x_2 = \frac{k}{\mu+d+r_2}x_1$ *and* $y_2 = \frac{k'}{\mu+d'}y_1$.

Notice that the region for existence of the stable interior equilibrium E^* has changed from $\{(\mathcal{R}_1, \mathcal{R}_2) \mid \mathcal{R}_1 > 1, f(\mathcal{R}_1) < \mathcal{R}_2 < g(\mathcal{R}_1)\}$ for the case $q = 0$ to $\{(\mathcal{R}_1, \mathcal{R}_2) \mid \mathcal{R}_1 > 1, \mathcal{R}_2 < g(\mathcal{R}_1)\}$ for the case $q > 0$. Fig. 2.b gives a bifurcation diagram for the case $q > 0$. For the case when $d > 0, d' > 0$ our numerical simulations and bifurcation diagram also support similar results (see Fig. 5).

Analysis of our model shows that non-antibiotic co-existence (for parameters corresponding to $(\mathcal{R}_1, \mathcal{R}_2)$ in the region between the two curves f and g, see Fig. 2.a) is possible but rare for naturally resistant strains. However, for strains that result from the lack of compliance with antibiotic treatment by TB infected individuals co-existence (for parameters corresponding to $(\mathcal{R}_1, \mathcal{R}_2)$ in the region below the curve g, see Fig. 1.b) is almost the rule.

2.2. A distributed delay model for TB. A feature of tuberculosis disease is that the infectious agent has evolved a "friendly" relationship with the human host as only a relatively small proportion of those who are infected go on to develop clinical disease. This is a result of probably two forces the reduction in virulence of natural strains as well as the evolution of a more resistant host population. Most seem 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 origional infection. The risk of disease is highest shortly after receipt of infection and declines thereafter. Relevant information on the development of clinical TB in tuberculin converters in general population can be found in the British Medical Research

Council's TB vaccines trial (MRC 1972) in which there were totally 243 cases among the participants who were initially tuberculin-negative developed the disease within 8 years. Observations from this study indicate that 54% had developed the disease within a year. 29% developed during the next 3 years, and 17% during the last 4 years. This typical feature of TB, long and variable periods of latency, was not considered in our previous model as our emphasis was on the study of resistant TB. The purpose of the following distributed delay model is to look at the effects of variable periods of latency (rather than exponentially distributed) on the dynamics of TB.

Let $p(s)$ be a function representing the proportion of those individuals that become exposed at time t and that, if alive, are still infected (but not infectious) at time $t+s$; that is, they survive as infected but not infectious. 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 L is given by

$$\int_0^t \beta c\big[S(s) + \sigma T(s)\big] \frac{I(s)}{N(s)} p(t-s) e^{-\mu(t-s)} ds.$$

Noticing that $-\dot{p}(\tau)$ is the rate of removal of individuals from L class into I class τ units of time after exposed, the number of individuals who become infectious from time 0 to t and are still alive and in I class is

$$\int_0^t \int_0^\tau \beta c\big[S(s) + \sigma T(s)\big] \frac{I(s)}{N(s)} e^{-\mu(\tau-s)} [-\dot{p}(\tau - s) e^{-(\mu+r+d)(t-\tau)}] ds d\tau.$$

Then we have the following model:

$$\begin{aligned}
\frac{d}{dt}S &= \Lambda - \beta c S \frac{I}{N} - \mu S \\
L(t) &= L_0(t) + \int_0^t \beta c\big[S(s) + \sigma T(s)\big] \frac{I(s)}{N(s)} p(t-s) e^{-\mu(t-s)} ds \\
I(t) &= \int_0^t \int_0^\tau \beta c\big[S(s) + \sigma T(s)\big] \frac{I(s)}{N(s)} e^{-\mu(\tau-s)} [-\dot{p}(\tau - s) e^{-(\mu+r+d)(t-\tau)}] ds d\tau \\
&\quad + I_0 e^{-(\mu+r+d)t} + I_0(t) \\
\frac{d}{dt}T &= rI - \sigma\beta c T \frac{I}{N} - \mu T \\
N &= S + L + I + T.
\end{aligned} \tag{3}$$

Λ is the constant recruitment rate; β and $\sigma\beta$ denote the probability that susceptible and treated individuals will be 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; d is the per-capita disease-induced death rate; r is the per-capita treatment rate. $L_0(t)$ denotes those individuals that were in L class at time $t = 0$ and are still in the latent class; $I_0(t)$ denotes those initially in class L who have moved into class I and are still alive at time t; and $I_0 e^{-(\mu+r+d)t}$ with $I_0 = I(0)$ represents those who are infectious at time 0 and are still alive and in the I class. $L_0(t)$ and $I_0(t)$ are assumed to have compact support.

If we change the order of integrations as the following, the I equation in (3) becomes a Volterra integral equation if we change the order of integrations as the following :

$$\int_0^t \int_s^t \beta c\big[S(s) + \sigma T(s)\big] \frac{I(s)}{N(s)} e^{-\mu(\tau-s)} [-\dot{p}(\tau - s) e^{-(\mu+r+d)(t-\tau)}] d\tau ds.$$

We note that

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

Therefore we can rewrite the I equation in (3) as

$$I(t) = \int_0^t a(t-s)\beta c\big[S(s) + \sigma T(s)\big] \frac{I(s)}{N(s)} ds + I_0 e^{-(\mu+r+d)t} + I_0(t). \tag{4}$$

Results on well-posedness found in Miller (1971) guarantee the existence and uniqueness of solutions for System (3) as well as their continuous dependence on parameters. The positivity of solutions can be proved similarly to Castillo-Chavez et al (1989).

In the following we assume that the probability that a treated individual becomes infected is the same as that of a susceptible individual, i.e., we let $\sigma = 1$. Letting

$$W = S + T, \quad B = \beta c W \frac{I}{N},$$

System (3) with the I equation replaced by (4) becomes

$$\begin{aligned} &\frac{d}{dt} W = \Lambda - B - \mu W, \\ &L(t) = L_0(t) + \int_0^t B(s) p(t-s) e^{-\mu(t-s)} ds, \\ &I(t) = I_0 e^{-(\mu+r+d)t} + I_0(t) + \int_0^t a(t-s) B(s) ds, \\ &B(t) = \beta c W(t) \frac{I(t)}{N(t)}. \end{aligned} \tag{5}$$

The basic reproductive number in this case is given by

$$\mathcal{R}_0 = \beta c \int_0^\infty a(\tau)d\tau =: \beta c D_I,$$

where

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

Let

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

then D_L is the death justed mean length of the latent period. The relation between D_I and D_L is given by

$$D_I = \frac{1}{\mu + r + d}(1 - \mu D_L).$$

System (5) with $L_0(t) = I_0(t) = I_0 = 0$ always has the disease-free equilibrium

$$(W_0, L_0, I_0) = (\frac{\Lambda}{\mu}, 0, 0),$$

and has no other constant solution. Since $L_0(t)$ and $I_0(t)$ are zero for large t, and $e^{-(\mu+r+d)t} \to 0$ as $t \to \infty$, it could be expected that $(\Lambda/\mu, 0, 0,)$ is an asymptotic equilibrium of (5) as $t \to \infty$. The following results (proofs ommitted) describe our asymptotical results on this model.

Result 3 *If $\mathcal{R}_0 \leq 1$, then the disease-free equilibrium $(\frac{\Lambda}{\mu}, 0, 0)$ of the system (5) is a global attractor, i.e., $\lim_{t\to\infty}(W(t), L(t), I(t)) \to (\frac{\Lambda}{\mu}, 0, 0)$ for any positive solutions of (5).*

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

Result 4 *If $\mathcal{R}_0 > 1$, then the disease-free equilibrium of System (5) is unstable. Furthermore, there exists a constant $\eta > 0$, such that any solution $(W(t), L(t), I(t))$ of (5) with $I(0) > 0$ satisfies*

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

According to Miller (1971), an endemic equilibrium of the system (5), if exists, must satisfy the limiting system associated with (5), which is given by the following set of

equations:

$$
\begin{aligned}
\frac{d}{dt}W &= \Lambda - B - \mu W + rI \\
L(t) &= \int_{-\infty}^{t} B(s)p(t-s)e^{-\mu(t-s)}ds \\
I(t) &= \int_{-\infty}^{t} a(t-s)B(s)ds \\
B(t) &= \beta c W(t)\frac{I(t)}{N(t)}.
\end{aligned}
\tag{6}
$$

Sysatem (6) has a constant solution (W^*, L^*, I^*) with $I^* > 0$ (an endemic equilibrium) given by

$$
\begin{aligned}
W^* &= \frac{1}{\mathcal{R}_0}N^*, \\
L^* &= \left(1 - \frac{1}{\mathcal{R}_0}\right)\frac{D_L}{D_I + D_L}N^*, \\
I^* &= \left(1 - \frac{1}{\mathcal{R}_0}\right)\frac{D_I}{D_I + D_L}N^*,
\end{aligned}
$$

where

$$
N^* = \frac{\Lambda \mathcal{R}_0}{\mu + (\mathcal{R}_0 - 1)\frac{1 - rD_I}{D_I + D_L}}.
$$

We have the following result about the endemic equilibrium of (6).

Result 5 *If $\mathcal{R}_0 > 1$, then the limiting system (6) has a unique endemic equilibrium which is locally asymptotically stable.*

Our results show that the qualitative dynamics of TB predicted by this model are not very different from that given by models with an exponentially distributed latency period. The disease either dies out or remains endemic. Nevertheless the computation of the basic reproductive number allows us to understand the role of different parameters in maintenance or eradication of TB.

2.3. A TB model with exogenous reinfection. We note that a person infected with TB may develop active TB in a variety of ways. One possibility is that such a person may become TB active as a consequence of exogenous reinfection (i.e., acquiring a new infection from another infectious individual; Smith 1993). Our results from the following model suggest that exogenous reinfection has a drastic effect on the qualitative dynamics of TB. More explicitly, the incorporation of exogenous reinfection into our basic 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 equilibia for $\mathcal{R}_0 < 1$

becomes a possibility. This type of behavior has been observed in recent epidemiological models in the context of sexually-transmitted diseases (see Hadeler and Castillo-Chavez 1995).

Since using a distributed delay in the removal rate from the infected class will not change the qualitative dynamics and will make the mathematics complicated, then we assume an exponential removal rate. The model with exogenous reinfection takes the following form:

$$
\begin{aligned}
\frac{d}{dt}S &= \Lambda - \beta c S\frac{I}{N} - \mu S \\
\frac{d}{dt}L &= \beta c S\frac{I}{N} - p\beta c L\frac{I}{N} - (\mu+k)L + \sigma\beta c T\frac{I}{N} \\
\frac{d}{dt}I &= p\beta c L\frac{I}{N} + kL - (\mu+r+d)I \\
\frac{d}{dt}T &= rI - \sigma\beta c T\frac{I}{N} - \mu T \\
N &= S+L+I+T.
\end{aligned} \tag{7}
$$

The term $p\beta cL\frac{I}{N}$ reflects the exogenous reinfection rate. In the case where $p = 0$, the system (7) reduces to a model which produces similar results to that given by standard SEIR models, i.e., the disease-free equilibrium is a global attractor when $\mathcal{R}_0 < 1$ while the unique endemic equilibrium exists and is l.a.s. when $\mathcal{R}_0 > 1$. We assume in the following that $p > 0$.

The basic reproductive number for (7) is given by

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

Note that $\mathcal{R}_0$ does not depend on the parameter p (we assume that $\mathcal{R}_0$ is defined in such a way that the dominant eigenvalue of the Jacobian matrix at the disease-free equilibrium is greater than zero if and only if $\mathcal{R}_0 > 1$). In fact the expression of $\mathcal{R}_0$ here is the same as that for the case $p = 0$. Let

$$p_0 = \frac{k}{\mu}\left(1+\frac{k}{\mu+r}\right),$$

then we have the following result (proof ommitted).

Result 6. *(a). If $\mathcal{R}_0 > 1$, then System (7) has exactly one positive equilibrium.*

(b). If $p > p_0$, then there exists a $\mathcal{R}_p < 1$ such that System (7) has exactly two positive equilibrium points $E^*_\pm$ ($E^*_- < E^*_+$) if and only if $\mathcal{R}_p < \mathcal{R}_0 < 1$.

(c). If $\mathcal{R}_0 < \mathcal{R}_p$, then the system (7) has only the disease-free equilibrium.

Moreover, the disease-free equilibrium is l.a.s. in the case (c), E_+^* is l.a.s. and E_-^* is unstable in the case (b), and the disease-free equilibrium is unstable while the endemic equilibrium is l.a.s. in the case (a).

Result 6 indicates 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 the system (7) has multiple equilibria for $\mathcal{R}_0 < 1$. The bifurcation diagram is shown in Fig. 6.

2.4. An age-structrued TB model. Because TB is a communicable disease primarily spread by the airborne route, the risk of an uninfected person becoming infected is strongly associate with the probability of coming in contact with an infectious individual and the duration of that contact (Reichman 1993). There are evidences showing that TB case rates are highly age-dependent. It is clear that mixing plays a key role in TB transmission. To look at the effects of age-dependent contact rates on TB dynamics and to look for optimal ages for vaccination, we formulate an age-structured model which we study in two cases: 1) in the absence of a vaccine and 2) with an age-dependent vaccination rate. Let $s(t,a), l(t,a), i(t,a)$ and $j(t,a)$ be density functions in the respective classes. Assume that all newborns are susceptible, that the mixing is proportional, and that the disease-induced death rate can be neglected. Then in the absence of vaccination the dynamics of the classes are governed by the following initial boundary value problem:

$$
\begin{aligned}
&(\frac{\partial}{\partial t}+\frac{\partial}{\partial a})s(t,a) = -c(a)B(t)s(t,a) - \mu s(t,a),\\
&(\frac{\partial}{\partial t}+\frac{\partial}{\partial a})l(t,a) = c(a)B(t)s(t,a) - (k+\mu)l(t,a) + \sigma c(a)B(t)j(t,a),\\
&(\frac{\partial}{\partial t}+\frac{\partial}{\partial a})i(t,a) = kl(t,a) - (r+\mu)i(t,a),\\
&(\frac{\partial}{\partial t}+\frac{\partial}{\partial a})j(t,a) = ri(t,a) - \sigma c(a)B(t)j(t,a) - \mu j(t,a),\\
&\qquad B(t) = \int_0^\infty \frac{i(t,a')}{n(t,a')}\beta p(t,a,a')da',\\
&\qquad p(t,a,a') = \frac{c(a')n(t,a')}{\int_0^\infty c(u)n(t,u)du},\\
&\qquad s(t,0) = \Lambda,\ \ l(t,0) = i(t,0) = j(t,0) = 0,\\
&\qquad s(0,a) = s_0(a),\ \ l(0,a) = l_0(a),\ \ i(0,a) = i_0(a),\ \ j(0,a) = j_0(a),\\
&\qquad\qquad n(t,a) = s(t,a) + l(t,a) + i(t,a) + j(t,a),
\end{aligned}
\tag{8}
$$

where Λ is the recruitment rate; β is the probability that a susceptible individual becomes infected by one infectious individual per contact per unit of time; $c(a)$ is the age-specific per-capita contact rate; μ, k and r are as before; $p(t,a,\alpha)$ gives the probability that a contact takes place between a susceptible of age a and an infectious individual of age α at time t given that a contact has taken place.

We use the method of "next generation operator" developed by Diekmann *et al* (1990) (also see Heesterbeek (1992)) to calculate the basic reproductive number $\mathcal{R}_0$ for (8). Following Diekmann (1992) we let $S(a)$ denote the density function describing the *steady demographic state* in the absence of the disease, and define $A(\tau, a, \alpha)$ to be the expected infectivity of an individual which was infected τ units of time ago while at age α towards an uninfected individual of age a at the steady demographic state. The function $A(\tau, a, \alpha)$ combines information on the probability (per unit of time) that contacts between certain ages take place and the probability that, given a contact, the disease agent is actually transmitted. Then under the special assumption of *proportionate-mixing* $A(\tau, a, \alpha)$ can be written in the form $A(\tau, a, \alpha) = f(a)g(\tau, \alpha)$.

Lemma 7. (*Diekmann*) *Under assumptions above,* $\mathcal{R}_0$ *is given by the formula*

$$\mathcal{R}_0 = \int_0^\infty \int_0^\infty g(\tau, \alpha) S(\alpha) f(\alpha) d\tau d\alpha.$$

Now we use the Lemma 7 to calculate $\mathcal{R}_0$ for System (8). Consider a demographic steady state $(s(a), 0, 0, 0)$ of System (8) with every one susceptible and ignore the fact that $S(a)$ decreases due to the infection process (see Diekmann (1992)). Then $s(a) = n(a) = \Lambda e^{-\mu a}$. Since we are assuming proportionate mixing we have that

$$p(a) = \frac{c(a)n(a)}{\int_0^\infty c(u)n(u)du}.$$

Let $\gamma(\tau, \alpha)$ be the probability that an individual of age $\alpha+\tau$ who was infected τ time units ago is in class i. Let $u \in (0, \tau)$, then the probability that an individual of age $\alpha + \tau$ who was infected τ time units ago is in class l at time u after infection (probability of remaining in l class times probability of still alive at age $\alpha + u$ given alive at age α) is given by

$$e^{-ku} \frac{e^{-\mu(\alpha+u)}}{e^{-\mu\alpha}} = e^{-(\mu+k)u}.$$

The density function for entering class i is therefore

$$ke^{-(\mu+k)u}. \tag{9}$$

In order to be in the class i with infection age τ one should

i) have entered i at some time $u \in (0, \tau)$
ii) have remained in i in the interval (u, τ).

The probability that ii) holds is

$$e^{-(\mu+r)(\tau-u)}. \tag{10}$$

Then from (9) and (10) we have

$$\gamma(\tau,\alpha) = \int_0^\tau k e^{-(\mu+k)u} e^{-(r+\mu)(\tau-u)} du$$
$$= \frac{k}{r-k}(e^{-k\tau} - e^{-r\tau})e^{-\mu\tau}.$$

It is easy to check that $\gamma(\tau,\alpha) > 0$ for all $r > 0, k > 0$. By the definition of $A(\tau,a,\alpha)$ we have

$$A(\tau,a,\alpha) = \beta(a)c(a)p(\alpha+\tau)\frac{\gamma(\tau,\alpha)}{n(\alpha+\tau)}$$
$$= \beta(a)c(a)p(\alpha+\tau)\frac{k}{r-k}(e^{-k\tau} - e^{-r\tau})e^{\mu\alpha}\frac{1}{\Lambda}$$
$$=: f(a)g(\tau,\alpha),$$

where

$$f(a) = \beta(a)c(a),$$
$$g(\tau,\alpha) = p(\alpha+\tau)\frac{k}{r-k}(e^{-k\tau} - e^{-r\tau})e^{\mu\alpha}\frac{1}{\Lambda}$$

Noticing that $s(\alpha) = \Lambda e^{-\mu\alpha}$ we get by Lemma 7 that

$$\mathcal{R}_0 = \int_0^\infty \int_0^\infty \beta c(\alpha)p(\alpha+\tau)\frac{k}{r-k}(e^{-k\tau} - e^{-r\tau})d\tau d\alpha. \tag{11}$$

We can now state the following result (proof ommitted)

Result 8: *(a) The disease-free equilibrium of System (8) is stable if $\mathcal{R}_0 < 1$ and unstable if $\mathcal{R}_0 > 1$. (b) When $\mathcal{R}_0 > 1$, there exists an endemic steady state age distribution.*

The formula (11) for $\mathcal{R}_0$ can be used to formulate optimaization problems related to vaccination strategies for TB as stated in the following.

We assume next that susceptibles in the same age-structured population are vaccinated at an age-dependent vaccination rate $\psi(a)$ (similar results can be obtained in the case where susceptible can not be recognized and thus every one will be vaccinated (see Hadeler)). We also assume that vaccination lasts. Let $\mathcal{R}(\psi)$ be the basic reproduction number in the presence of the vaccination strategy ψ. Note that for the calculation of $\mathcal{R}(\psi)$ we only need to consider the equation for s since the population is assumed to be at demographic equilibrium consisting of pure susceptible. The equation for s in (8) now has the following form:

$$(\frac{\partial}{\partial t} + \frac{\partial}{\partial a})s(t,a) = -c(a)B(t)s(t,a) - \mu s(t,a) - \psi(a)s(t,a).$$

Let $s_\psi(a)$ denote the density function describing the steady demographic state in the absence of disease, and let

$$\mathcal{F}_v(a) = e^{-\Phi(a)}, \quad \Phi(a) = \int_0^a \psi(u)du.$$

Then

$$s_\psi(a) = \Lambda e^{-\mu a}\mathcal{F}_v(a).$$

Similarly to the derivation of the the formula for $\mathcal{R}_0$, we obtain the following expression for $\mathcal{R}(\psi)$:

$$\mathcal{R}(\psi) = \int_0^\infty \int_0^\infty \beta c(\alpha)p(\alpha+\tau)\frac{k}{r-k}(e^{-k\tau} - e^{-r\tau})\mathcal{F}_v(\alpha)d\tau d\alpha.$$

Since $\psi(a) \geq 0$, we have

$$\mathcal{R}(\psi) \leq \mathcal{R}_0, \quad \mathcal{R}(0) = \mathcal{R}_0,$$

and the representation

$$\mathcal{R}(\psi) = \mathcal{R}_0 + F(\psi),$$

where

$$F(\psi) = \int_0^\infty \int_0^\infty \beta c(\alpha)p(\alpha+\tau)\frac{k}{r-k}(e^{-k\tau} - e^{-r\tau})(1-\mathcal{F}_v(\alpha))d\tau d\alpha.$$

Remark: *The quantity $F(\psi)$ is the reduction in the reproductive number that can be achieved by applying the vaccination strategy ψ.*

In the case when $\mathcal{R}_0 > 1$, one would like to choose a vaccination strategy ψ which makes $F(\psi)$ large, and thus possibly reduces $\mathcal{R}(\psi)$ to values below 1 and leads to the elimination of the disease. In Dietz and Schenzle (1985) a simpler formula is derived which can be used to compute $\phi(a)$ to reduce $\mathcal{R}(\phi)$ below 1 in cases where infectious periods are short. Because of the long and variable periods of infectiousness in the case of TB, we will consider the equivalent problems to those proposed in Hadeler (1993) for HIV.

In practice the application of vaccination strategies is limited by costs. We assume that the expenses of one vaccination at age a are given by a positive number $\kappa(a)$, and that the total cost depends linearly on the number of vaccinations (see Hadeler). Note that vaccination here means a transition from the susceptible state to the vaccinated state. Applications of vaccine which do not lead to a vaccination are incorporated into the cost function κ. Let $C(\psi)$ be the total cost of the vaccination strategy ψ, then

$$C(\psi) = \int_0^\infty \kappa(a)\psi(a)s_\psi(a)da,$$

where $s_\psi(a)$ is given by (11). Now we can define the following optimization problems.

(I) Find a vaccination strategy $\psi(a)$ that minimizes $C(\psi)$ constrained by $\mathcal{R}(\psi) \leq \mathcal{R}_*$.

(II) Find a vaccination strategy $\psi(a)$ that minimizes $\mathcal{R}(\psi)$ constrained by $C(\psi) \leq \kappa_*$.

Notice that

$$C(\psi) = \int \Lambda\kappa(a)e^{-\mu a}\psi(a)e^{-\int_0^a \psi(s)ds}da.$$

To make both $C(\psi)$ and $F(\psi)$ linear functionals we apply the following transformation

$$\phi(a) = -\frac{d}{da}e^{\int_0^a \psi(s)ds} = \psi(a)e^{-\int_0^a \psi(s)ds}.$$

Denote $\bar{F}(\phi) = F(\psi), \bar{C}(\phi) = C(\psi)$. Then noticing that

$$1 - \mathcal{F}(\psi) = 1 - e^{-\int_0^a \psi(s)ds} = \int_0^a \phi(s)ds,$$

and also noticing that (by exchanging the order of integrations)

$$\begin{aligned}\bar{F}(\phi) &= \int_0^\infty \int_0^\infty \beta c(\alpha)p(\alpha+\tau)\frac{k}{r-k}(e^{-k\tau} - e^{-r\tau}) \int_0^\alpha \phi(s)ds d\tau d\alpha \\ &= \int_0^\infty \left\{ \int_a^\infty \int_0^\infty \beta c(\alpha)p(\alpha+\tau)\frac{k}{r-k}(e^{-k\tau} - e^{-r\tau}) d\tau d\alpha \right\} \phi(a)da,\end{aligned}$$

we arrive at

$$\begin{aligned}\bar{F}(\phi) &= \int_0^\infty K(a)\phi(a)da, \\ \bar{C}(\phi) &= \int_0^\infty B(a)\phi(a)da,\end{aligned}$$

where

$$\begin{aligned}K(a) &= \int_a^\infty \int_0^\infty \beta c(\alpha)p(\alpha+\tau)\frac{k}{r-k}(e^{-k\tau} - e^{-r\tau}) d\tau d\alpha, \\ B(a) &= \Lambda\kappa(a)e^{-\mu a}.\end{aligned}$$

Let

$$Q(\phi) = \int_0^\infty \phi(a)da,$$

it is easy to see that $Q(\phi) \leq 1$. Let $\rho = \mathcal{R}_0 - \mathcal{R}_*$, then the problem (I) can be written as:

$$\begin{aligned}\text{Minimize} \quad & \bar{C}(\phi) \quad \text{subject to} \\ & f(\phi) \leq 0, \\ & \phi \geq 0,\end{aligned}$$

where

$$f(\phi) = \begin{pmatrix} f_1(\phi) \\ f_2(\phi) \end{pmatrix} = \begin{pmatrix} \rho - \bar{F}(\phi) \\ \bar{C}(\phi) - 1 \end{pmatrix}, \tag{12}$$

and $f(\phi) \leq 0$ is equivalent to $f_i(\phi) \leq 0$ $(i = 1, 2)$.

Analysis of the optimization problem (12) leads us to the following result (pfoof ommitted).

Result 9: *In a generic situation the optimal vaccination strategy in problem (I) is either a one-age strategy with vaccination at exactly one age A, or it is a two-age strategy where part of the population is vaccinated at an age A_1 and all remaining susceptible are vaccinated at a later age A_2.*

For the explanation of the word "generic" see Hadeler. A similar conclusion for problem (II) can be obtained, i.e., the optimal vaccination strategy is either a one-age strategy or a two-age strategy.

Remark *Formulas can be derived to calculate the corresponding total costs and to find the optimal ages for these two vaccination strategies.*

3. Numerical simulations. In this section we study the system (1) and (2) numerically to confirm our analytical results as well as to provide evidences that our results are likely to hold in more general situations. First we "extend" the result of Result 1 (d) numerically. Our simulations support the stability of the interior equilibrium E_3 for the system (2) not only at the quasi-steady state but in general (see Fig. 3). Fig. 3 presents some phase portraits for the system (2) which show that (for parameters in certain region (see Fig. 2)) the corresponding l.a.s. equilibrium (E_1, E_2 and E^*) attracts all solutions with positive initial data. Similar simulations have been carried out when $q > 0$ to support the same conclusion (see Result 2) that the interior equilibrium E^* is asymptotically stable whenever it exists not only at the quasi-steady state but in general, and that the non-trivial equilibrium points switch stability as the parameters change as specified in the bifurcation diagram (see Fig. 2.b and Fig. 4). We also "extend" the results of Result 2 numerically to the case when $d > 0$ and $d' > 0$. This is done by establishing a functional relationship between β and β' and by showing numerically that this function plays a role similar to that of the function g in Result 2 (see Fig. 5).

For the construction of Fig. 3 we have selected for illustration purposes the following parameter values: $\mu = 0.0143$ ($1/\mu = 70$ years), $\beta = 13, c = 1, k = 1, q = 0, p = 0.5, r_1 = 1, r_2 = 2, k' = 1, \Lambda = 35, d = d' = 0$. This choice of parameter values gives $\mathcal{R}_1 = 3.45$. By calculating the formulas for $f(\mathcal{R}_1)$ and $g(\mathcal{R}_1)$ we get

$$(\mathcal{R}_1, \mathcal{R}_2) \in III \quad \text{iff} \quad 1.34 < \mathcal{R}_2 < 4.13,$$
$$(\mathcal{R}_1, \mathcal{R}_2) \in II \quad \text{iff} \quad \mathcal{R}_2 > 4.13,$$
$$(\mathcal{R}_1, \mathcal{R}_2) \in IV \quad \text{iff} \quad \mathcal{R}_2 < 1.34.$$

The value of $\mathcal{R}_2$ for Fig. 3.a is chosen to be 2. Our simulations show that E^* attracts all solutions with positive initial data. Values of $\mathcal{R}_2$ for Fig. 3.b and Fig. 3.c are 4.5 and 1.2, and our simulations support the global stabilities of E_1 and E_2, respectively.

Fig. 4 is for the case when $q > 0$, and $d = d' = 0$. The parameter values used in Fig. 4 are $k = 0.5, k' = 1, \mu = 0.0143, q = 0.01, p = 0.4, r_1 = 2, r_2 = 1, d = 0, d' = 0, \Lambda = 500$.

β is chosen to be 13 as it corresponds to $\mathcal{R}_1 = 2.627$ and $\mathcal{R}_2 = g(\mathcal{R}_1) = 2.7364$. This last selection implies that E_2 is l.a.s. if $\mathcal{R}_2 > 2.7364$ and it also implies that E^* exists and is l.a.s. if $\mathcal{R}_2 < 2.7364$. In Fig. 4, the values for $\mathcal{R}_2$ are chosen to be (a) $\mathcal{R}_2 = 0.9$, (b) $\mathcal{R}_2 = 1.5$, (c) $\mathcal{R}_2 = 2$, and (d) $\mathcal{R}_2 = 3$.

Our analytic results for the stabilities of equilibrira E_2 and E^* (see Result 2) hold only for $d = 0$ and $d' = 0$. Since the death rate d' from resistant-TB may be high, one would like to know if similar results hold when $d > 0$ and $d' > 0$. Our numerical simulations suggest that this is the case (see Fig. 5). The parameter values used in Fig. 5 are the same as those used in Fig. 4 except that $d = 0.1$ and $d' = 0.5$. By choosing $\beta = 13$ (corresponding to $\mathcal{R}_1 = 2.39$) and by calculating $\mathcal{R}_2 = g(\mathcal{R}_1) = 2.139$ we conclude that E_2 is l.a.s. if $\mathcal{R}_2 > 2.139$ and E^* exists and is l.a.s. if $\mathcal{R}_2 > 2.139$. In Fig. 5 the values for $\mathcal{R}_2$ are chosen to be (a) $\mathcal{R}_2 = 0.9$, (b) $\mathcal{R}_2 = 1.5$, (c) $\mathcal{R}_2 = 2$, and (d) $\mathcal{R}_2 = 3$.

4. Conclusion. In this paper we introduced a series of models to study the dynamics of TB. We discuss a two-strain model for TB and resistant TB with the purpose of determining the role that lack of drug treatment compliance by TB patient plays on the maintenance of antibiotic resistant strain (for details see Castillo-Chavez and Feng, 1995). To make the role of antibiotic resistance transparent, we first studied a special version of our two-strain model with two competing strains of TB: the typical strain plus a resistant strain that was not the result of antibiotic resistance. In the last situation, We found that co-existence is possible but rare while later we noticed that co-existence is almost certain when the second strain is the result of antibiotic resistance.

To study the effects of long and variable periods of latency on the dynamics of TB we constructed a TB model with distributed delay (see Castillo-Chavez and Feng, 1996a). We found that the qualitative dynamics of TB predicted by this model is not very different from that given by a corresponding model with an exponentially distributed latency period. Qualitative behaviors change only at a critical value $\mathcal{R}_0 = 1$, i.e., if $\mathcal{R}_0 < 1$ then an unique equilibrium (the disease-free equilibrium) exists and is g.a.s., while if $\mathcal{R}_0 > 1$ then the disease-free equilibrium is unstable and there exists an unique endemic equilibrium which is l.a.s..

Relatively drastic changes of qualitative behaviors of the disease dynamics occur when the effect of exogenous reinfection is incorporated into the model (see Castillo-Chavez and Feng, 1996b). Our results suggest that the introduction of exogenous reinfection into the basic TB model allows for the possibility of a subcritical bifurcation of endemic equilibrium points at the critical value of the basic reproductive number $\mathcal{R}_0 = 1$, and hence the existence of multiple endemic equilibria for $\mathcal{R}_0 < 1$.

We also constructed an age-structured TB model to look at optimal vaccination strategy problems (see Castillo-Chavez and Feng, 1996c). Under the assumption of proportion-

ate mixing we calculated the basic reproductive number which were used to study cost related optimization problems. We found that the optimal vaccination strategies have the form of one-age strategies or of two-age strategies.

It has been suggested that the emergence of the HIV epidemic has dramatically increased the risk of developing clinical TB in infected persons, substantially increasing TB rates globally (Miller (1993)). The evidence though seems weak. Immigration from countries with higher TB prevalence to the United States has always contributed to the dramatic increases in the incidence of TB within USA particularly over the past few decades. Here we have introduced a few models to illustrate how we can address a —— of questions that are important in our understanding of TB dynamics.

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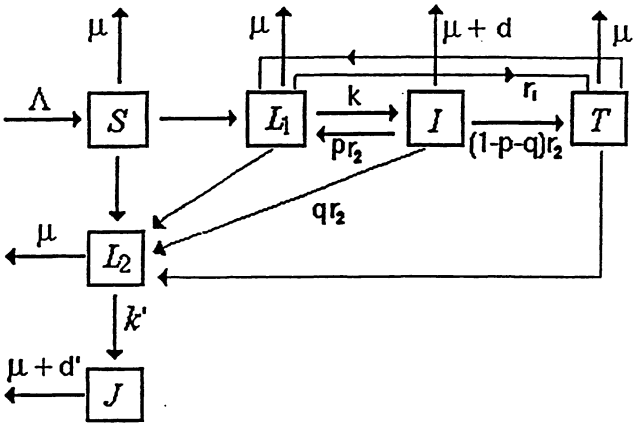

Fig.1. A diagram for two-strains TB transmission.

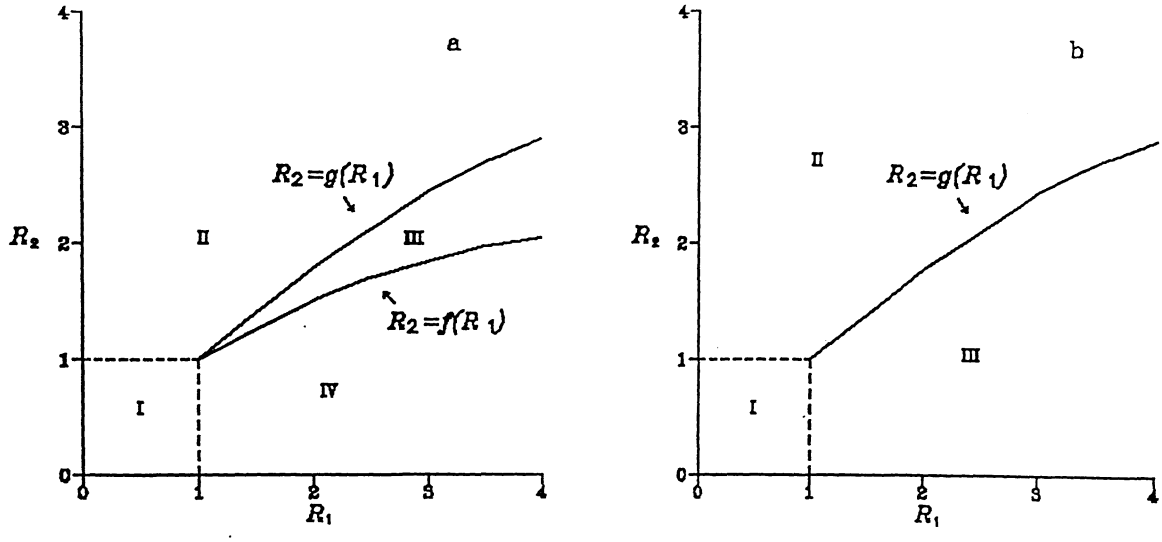

Fig.2.a. A bifurcation diagram for the system (2.5) in the case $q = 0$. There are four regions I, II, III, and IV in the parameter space $(\mathcal{R}_1, \mathcal{R}_2)$. In the region I E_1 is a global atractor and other equilibria are unstable when they exist. In regions II and IV E_3 does not exist and E_2 and E_4 are l.a.s., respectively. In the region III E_3 exists and is l.a.s..

Fig.2.b. A bifurcation diagram for the system (2.5) in the case $q > 0$. There are three regions I, II and III in the parameter space $(\mathcal{R}_1, \mathcal{R}_2)$ (E_4 does not exist.), and they correspond to stabilities of E_1, E_2, and E_3, respectively.

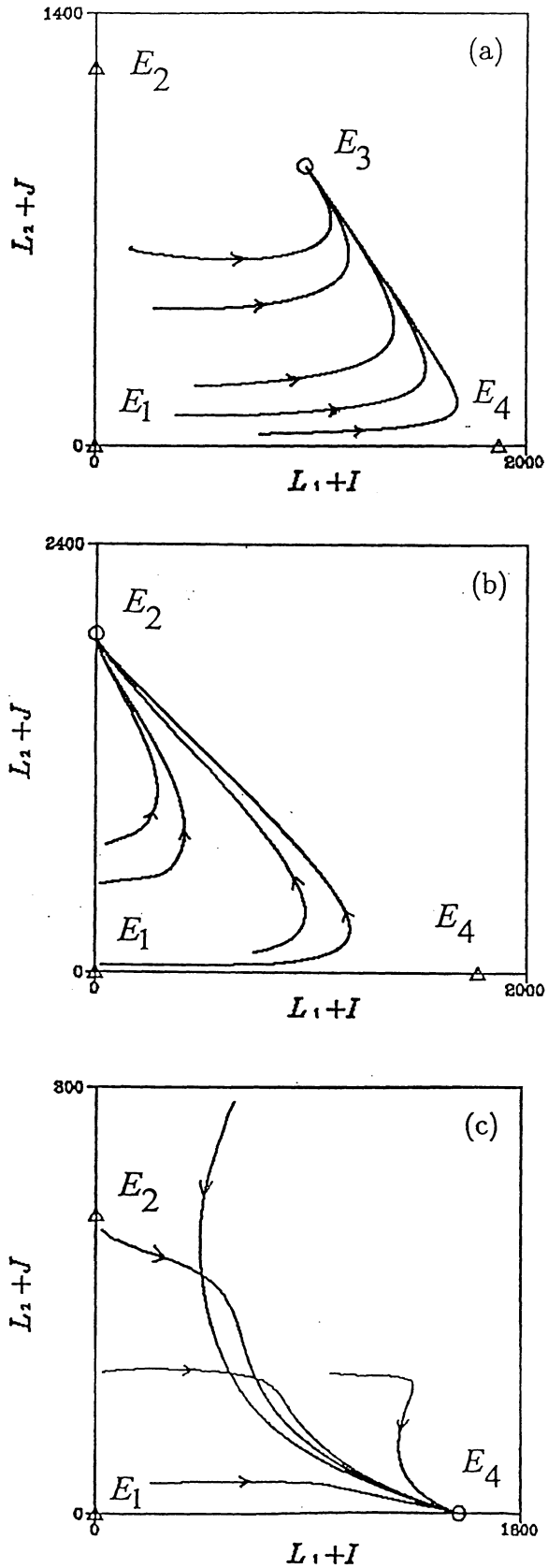

Fig.3. Phase portraits of solutions to (2.5) . Parameter values for all three graphs are chosen to be: $\mu = 0.0143, \beta = 13, c = 1, k = 1, q = 0, p = 0.5, r_1 = 1, r_2 = 2, k' = 1, \Lambda = 35, d = d' = 0$. This choice of parameters give a fixed value $\mathcal{R}_1 = 3.45$. In (a) $\mathcal{R}_2 = 2$ and hence $(\mathcal{R}_1, \mathcal{R}_2)$ $\in$III. In (b) $\mathcal{R}_2 = 4.5$ and hence $(\mathcal{R}_1, \mathcal{R}_2)$ $\in$II. In (c) $\mathcal{R}_2 = 1.2$ and $(\mathcal{R}_1, \mathcal{R}_2)$ $\in$IV. Circle "$\bigcirc$" indicates a stable equilibrium and triangle "$\triangle$" indicates an unstable equilibrium. (Graphs are given by Phsplan).

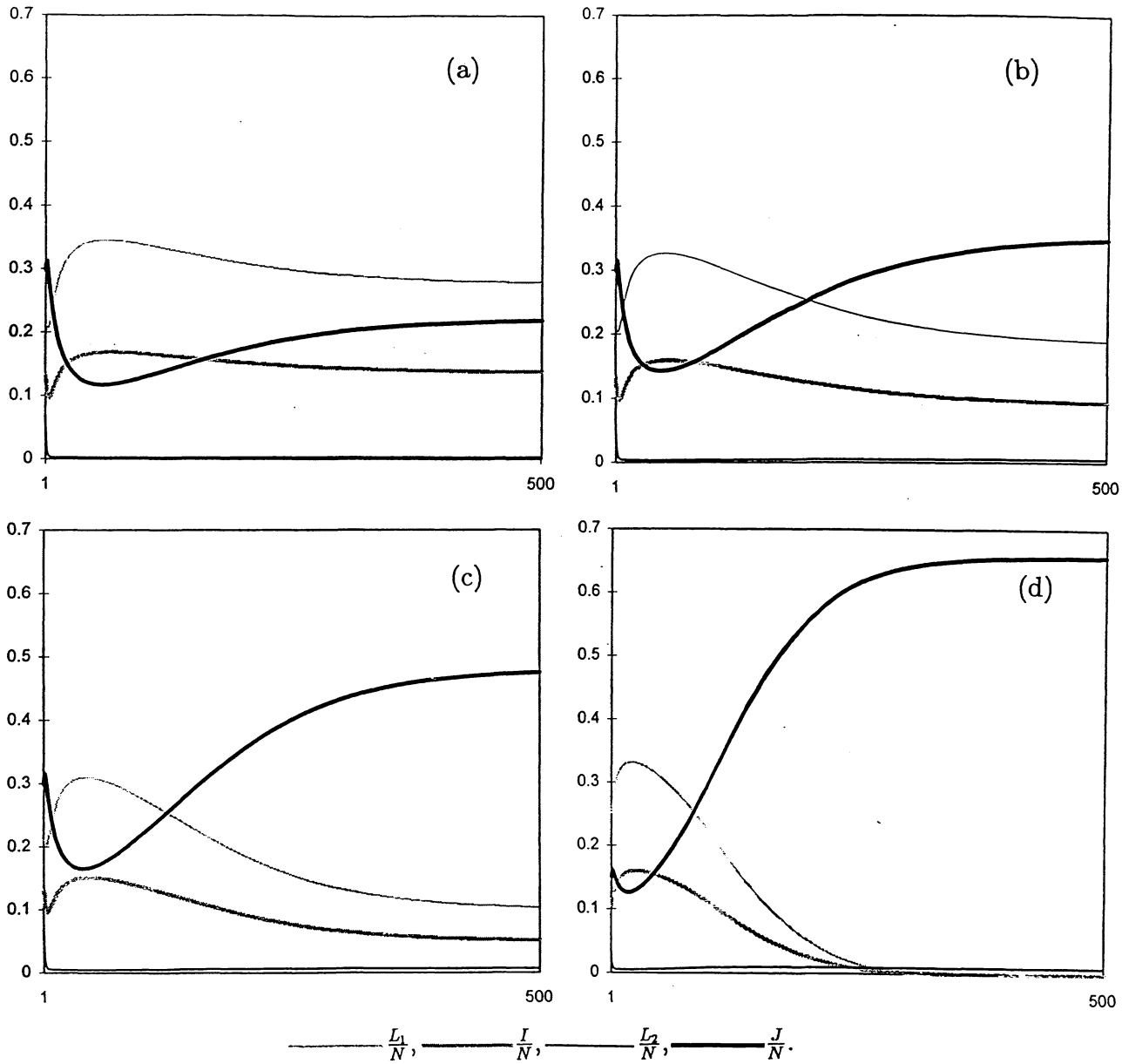

Fig.4. Plots of fractions of infected and infectious population versus time in the case $q > 0, d = d' = 0$. Parameters for all graphs are chosen to be: $\mu = 0.143, \beta = 13, c = 1, k = 0.5, q = 0.01, p = 0.4, r_1 = 2, r_2 = 1, k' = 1, \Lambda = 500, d = d' = 0$.

In (a) $\mathcal{R}_2 = 0.9$ and hence $(\mathcal{R}_1, \mathcal{R}_2) \in III$. In (b) $\mathcal{R}_2 = 1.5$ and $(\mathcal{R}_1, \mathcal{R}_2) \in III$. In (c) $\mathcal{R}_2 = 2$ and $(\mathcal{R}_1, \mathcal{R}_2) \in III$. In (d) $\mathcal{R}_2 = 3$ and $(\mathcal{R}_1, \mathcal{R}_2) \in IV$.

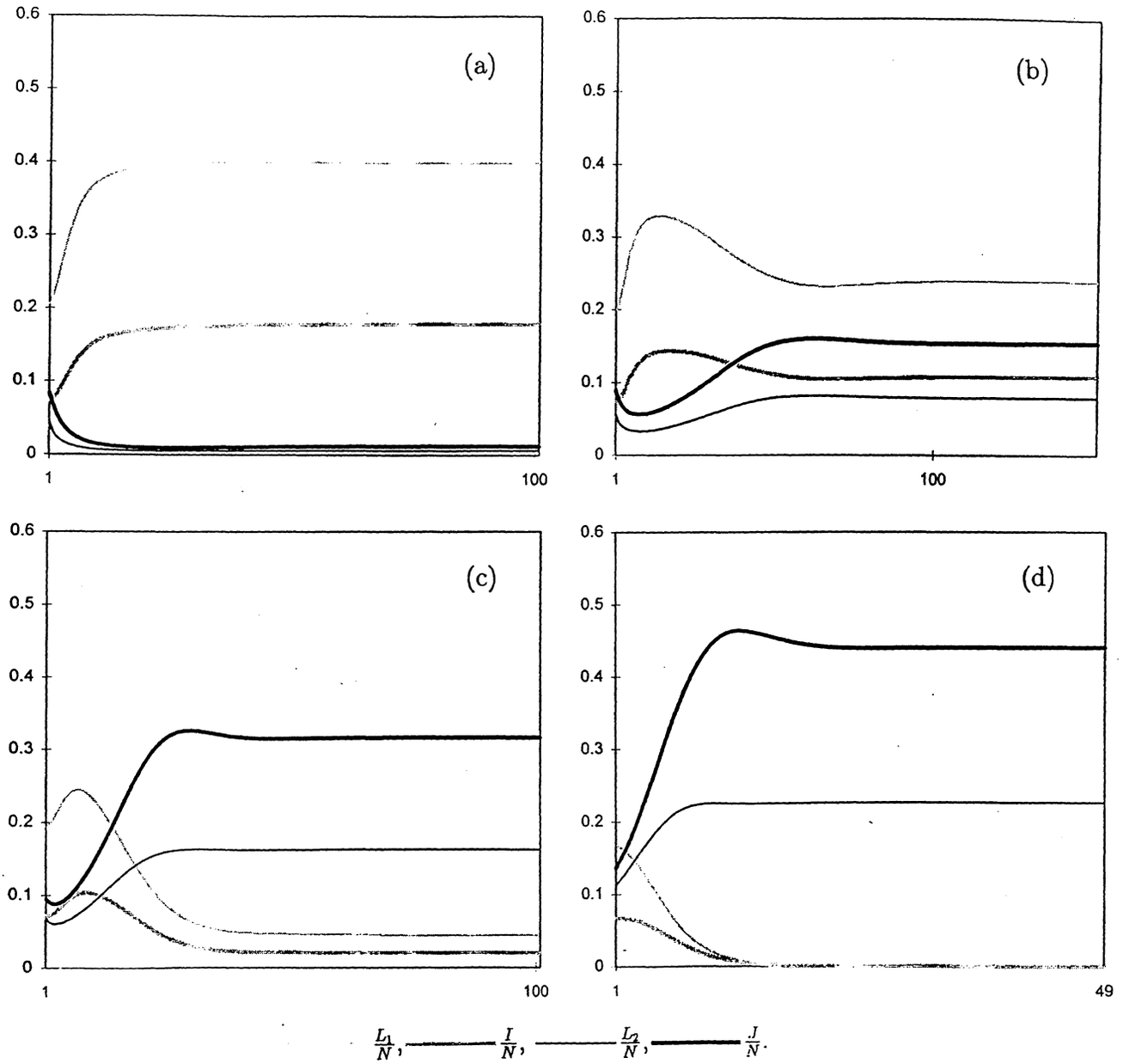

Fig.5. Plots of fractions of infected and infectious population versus time in the case $q > 0, d > 0, d' > 0$. Parameters for all graphs are chosen to be: $\mu = 0.143, \beta = 13, c = 1, k = 0.5, q = 0.01, p = 0.4, r_1 = 2, r_2 = 1, k' = 1, \Lambda = 500, d = 0.1, d' = 0.5$.

In (a) $\mathcal{R}_2 = 0.9$ and hence $(\mathcal{R}_1, \mathcal{R}_2) \in III$. In (b) $\mathcal{R}_2 = 1.5$ and $(\mathcal{R}_1, \mathcal{R}_2) \in III$. In (c) $\mathcal{R}_2 = 2$ and $(\mathcal{R}_1, \mathcal{R}_2) \in III$. In (d) $\mathcal{R}_2 = 3$ and $(\mathcal{R}_1, \mathcal{R}_2) \in IV$.