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A TWO-STRAIN TUBERCULOSIS MODEL WITH AGE OF INFECTION*

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Abstract. Long periods of latency and the emergence of antibiotic resistance due to incomplete treatment are very important features of tuberculosis (TB) dynamics. Previous studies of two-strain TB have been performed by ODE models. In this article, we formulate a two-strain TB model with an arbitrarily distributed delay in the latent stage of individuals infected with the drug-sensitive strain and look at the effects of variable periods of latency on the disease dynamics.

Key words. stability, distributed delays, tuberculosis, mathematical models

AMS subject classifications. 35L60, 45D05, 65M06, 92D25, 92D30

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1. Introduction.

It is reported that eight million people develop active tuberculosis (TB) every year, each of which can infect between 10 and 15 people in one year just by breathing [12], [20]. In the United States, the estimated total number of TB infections lies between 10–15 million persons [14]. TB incidence (new cases per year) and outbreaks of multidrug-resistant TB in the United States have also increased over the past few years, and drug resistance has become a serious hindrance to global TB control. The new TB control strategy, directly observed treatment short-course (DOTS), produces an 85 percent cure rate for drug-sensitive TB, but its effectiveness depends on several elements.

A first critical element is that the health care system needs to achieve a complete cure of TB patients. Incomplete treatment of patients with infectious TB may lead to relapse or to the development of antibiotic-resistant TB. Therefore, a challenge in mathematical biology has been to study possible mechanisms for the survival and spread of naturally resistant strains of TB, as well as for the generation of antibiotic-resistant strains of TB.

A second key feature associated with the regular strain of TB is that the bacillus has evolved to form a sort of symbiotic relationship with its human host. Only a relatively small proportion of those who are infected with the sensitive strain eventually develops disease symptoms (active TB). Most individuals seem to mount effective immune responses to initial infections, that is, responses that limit proliferation of the bacilli. This immune response may lead to long-lasting but partial immunity (see [13]). Consequently, the age of infection (the time lapsed since infection) is an important factor in disease progression.

Previous work on TB modeling has tried to incorporate these two features into the models (see [2], [6], [7], [8]). Actually, one-strain and two-strain TB models have been developed mainly using ODEs (see [1], [2], [3], [4]). The results in the second of

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these articles lead to the important conclusion that nonantibiotic-induced coexistence is possible but rare for *naturally* resistant strains, while coexistence is almost the rule for strains that result from the lack of compliance with antibiotic treatment by TB-infected individuals.

Also, the effect of long incubation periods has been investigated in a single-strain model with arbitrarily distributed delays in the latent stage (see [7]). It is shown there that a distributed delay alone in the one-strain TB model does not change the qualitative dynamics of the disease.

In this article, we consider a two-strain TB model with arbitrarily distributed delays in the latent class of individuals with drug-sensitive TB. We shall use the adjectives *active*, *infectious*, and *infective* as synonyms, while *latent* will mean infected but not infectious. The latency period for the drug-resistant TB is neglected since individuals infected with resistant TB usually die shortly after being diagnosed. One central question to be addressed using this model is whether the introduction of host heterogeneity in latency will change the basic conclusion of earlier studies of ODE models. This formulation makes it possible to study the model in general cases instead of using a quasi-steady-state assumption as done for the previous ODE model. It also allows us to introduce control mechanisms for the disease, a problem which will be studied in a subsequent paper [8].

We consider two scenarios based on the treatment failure rate q of the individuals infected with drug-sensitive TB. The first case, $q = 0$, corresponds to the situation where all treated individuals finish their treatment, and new cases of drug-resistant TB are produced only through contacts with individuals with drug-resistant TB. Hence we have a competition model between the regular strain and naturally resistant strains. The analysis for $q = 0$ does not intend to imply that primary resistance actually occurs without acquired resistance. We rather have in mind a population that at the beginning of the study has some individuals with primary resistance. This situation is a sort of limiting case for the case in which $q > 0$, and it constitutes a starting point for our analysis of the case in which $q > 0$. The latter case takes into account the possible appearance of resistant strains due to deficient compliance with treatment schedules; i.e., a proportion q of treated individuals with drug-sensitive TB will develop resistance due to incomplete treatment. Conditions on the endemicity of either one or both strains are derived in terms of the basic reproductive numbers $\mathcal{R}_1$ and $\mathcal{R}_2$ of the regular and resistant strains. We find that the incorporation of distributed delays does not change the qualitative behaviors dramatically. More specifically, we show that coexistence is impossible for *naturally* resistant strains, while coexistence is very likely (if $\mathcal{R}_1 > \mathcal{R}_2$) for strains that result from the lack of compliance with antibiotic treatment.

This paper is organized as follows: section 2 introduces a two-strain TB model with arbitrarily distributed delays in the latent class (infecteds with drug-sensitive TB). In section 3, we study its steady-states under the two distinct assumptions described above: (1) we are dealing only with two competing strains; and (2) the second strain is the result of antibiotic resistance. The basic reproductive numbers associated with each strain are computed and related to the existence of the steady-states. The roles of these reproductive numbers on the dynamics and stability properties of this model are studied in section 4. Section 5 is devoted to the discussion of numerical simulations that support or complete our analytic results. Section 6 discusses the results and some of our current efforts and extensions including the control strategies for TB epidemics.

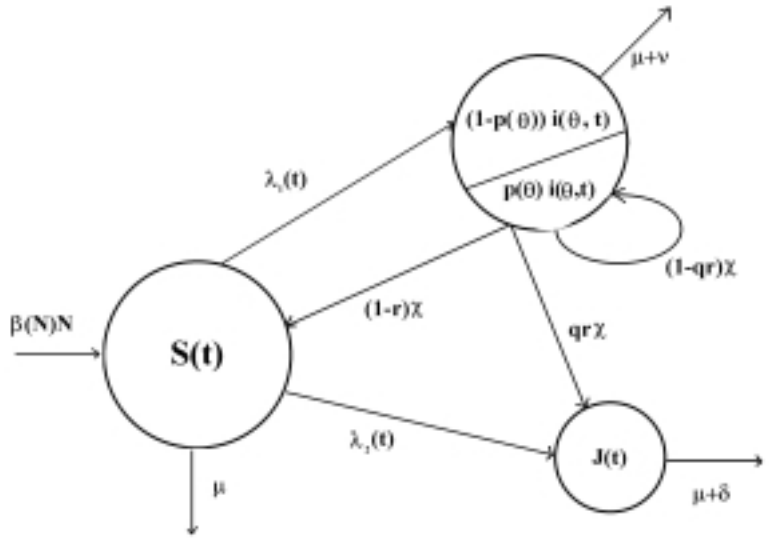


FIG. 1.

2. The model formulation. In this section, we introduce a two-strain TB model with arbitrarily distributed delays in the latent stage of drug-sensitive TB. The host population is divided into three epidemiological classes or subgroups: susceptibles, infected with drug-sensitive TB, and infected with drug-resistant TB. Infecteds with drug-sensitive TB are further subdivided into *latents* (infected but not infectious) and *actives* (infected and infectious). Let us introduce the following notation:

$$\begin{aligned} S(t) &= \text{number of susceptibles at time } t, \\ i(\theta,t) &= \text{infection-age density of infected individuals with the drug-sensitive strain at time } t, \\ J(t) &= \text{number of infected individuals with a drug-resistant strain at time } t. \end{aligned} \tag{2.1}$$

Here the variable θ denotes the *age of the infection with drug-sensitive TB*, i.e. the time that has lapsed since the individual became infected. We note that this class of infected individuals includes both latent and infectious individuals. In fact, as already pointed out in the introduction, the majority of infected individuals remains latent, while, as experimentally observed, only a small proportion of them develop and exhibit the disease, becoming infective.

To account for this, we introduce the function $p(\theta)$ $(0 \le p(\theta) \le 1)$ as the *proportion of sensitive-strain-infected individuals that are active at infection-age* θ. This function is assumed constant in time and is based on experimental data (see section 5). Thus

$$\begin{aligned} p(\theta)i(\theta,t) &= \text{age density of infectious individuals,} \\ (1-p(\theta))i(\theta,t) &= \text{age density of latent individuals.} \end{aligned} \tag{2.2}$$

The dynamics of the model is described in Figure 1, where the demographic

process is also indicated. In fact, we assume that the population involved is a closed population undergoing a per capita mortality rate μ and a density dependent growth rate with the per capita birth rate

$$\beta = \beta(N), \quad \beta'(N) < 0. \tag{2.3}$$

In (2.3), N denotes the total number of individuals, which actually changes with time, namely,

$$N(t) = S(t) + J(t) + I(t), \tag{2.4}$$

where we have set

$$I(t) = \int_0^\infty i(\theta, t)d\theta. \tag{2.5}$$

Concerning the mechanism of infection, we give the following constitutive form to the *force of infection* relative to the sensitive strain:

$$\lambda_1(t) = \frac{\rho_1}{N(t)} \int_0^\infty p(\theta)i(\theta, t)d\theta, \tag{2.6}$$

with $\rho_1 = Ck > 0$, where k is the *infectivity per contact* (probability of transmission of disease per contact) and C is the *contact rate* per individual per unit of time.

The same function $p(\theta)$ is used to give a shape to the removal rate $\gamma(\theta)$, i.e., the rate at which sensitive-strain-infected individuals leave the i class due to treatment. In fact, we assume

$$\gamma(\theta) = \big[(1 - r + qr)\chi + \nu\big]p(\theta), \tag{2.7}$$

where χ denotes the *treatment rate*, that is, the fraction of infectious people detected and treated per unit of time (for individuals with drug-sensitive TB), and ν is the disease-induced mortality rate. The factor $(1 - r + qr)$ in (2.7) introduces the effect of incomplete treatment: in fact, we assume that a fraction r of the treated individuals with sensitive TB does not recover due to incomplete treatment and that the remaining fraction $1 - r$ is actually cured and becomes susceptible again. Moreover, we assume that, among the individuals who do not finish their treatment, a fraction q of them will develop drug-resistant TB, and the remaining fraction will remain infectious. Therefore, $\gamma(\theta)$ is the sum of the three terms

$$\begin{aligned}
&(1 - r)\chi p(\theta) &&= \text{recovery rate of the treated individuals,}\\
&qr\chi p(\theta) &&= \text{rate of developing drug-resistant TB,}\\
&\nu p(\theta) &&= \text{disease-induced mortality rate of individuals}\\
&&&\quad \text{infected with the drug-sensitive strain.}
\end{aligned} \tag{2.8}$$

Concerning the resistant class, J, we do not consider its age-structure nor latency period since these individuals die quickly after acquiring drug-resistant TB. Thus we assume the following constitutive form for the force of infection:

$$\lambda_2(t) = \rho_2 \frac{J(t)}{N(t)}. \tag{2.9}$$

Additionally, we introduce an additional mortality rate δ, for the individuals of the drug-resistant class, with the condition

$$\beta(0) > \mu + \delta + \nu, \tag{2.10}$$

which is necessary in order to have a sustained population; i.e., when the population size is small, the birth rate needs to exceed the total death rate.

Based on Figure 1, we formulate the following system:

$$\begin{aligned}
&\frac{d}{dt}S(t) = \beta(N)N(t) - (\mu + \lambda_1(t) + \lambda_2(t))\, S(t) \\
&\qquad\qquad + (1-r)\chi \int_0^\infty p(\theta) i(\theta,t) d\theta, \\
&\frac{\partial}{\partial t} i(\theta,t) + \frac{\partial}{\partial \theta} i(\theta,t) + \mu\ i(\theta,t) + \gamma(\theta) i(\theta,t) = 0, \\
&\frac{d}{dt}J(t) = \lambda_2(t)S(t) - (\mu+\delta)J(t) + qr\chi \int_0^\infty p(\theta) i(\theta,t) d\theta, \\
&i(0,t) = \lambda_1(t) S(t), \\
&S(0) = S_0 > 0, \quad i(\theta,0) = i_0(\theta) \geq 0, \quad J(0) = J_0 > 0,
\end{aligned} \tag{2.11}$$

where the initial density $i_0(\theta)$ is assumed to be integrable and compactly supported in $[0,\infty)$. (These are technical assumptions that are also biologically natural.)

We note that, by standard methods, it is possible to prove existence and uniqueness of solutions to the system (2.11) (see [11], [19]). Moreover, it is easy to show that all the variables remain nonnegative and bounded for $t > 0$ for nonnegative initial data.

The following notation will be used often in the paper:

$$\begin{aligned}
&K_0(\theta) = e^{-\mu\theta - \int_0^\theta \gamma(s)ds}, \qquad A = \frac{1}{(1-r+qr)\chi + \nu}, \\
&K_1(\theta) = \rho_1 p(\theta) K_0(\theta) = -\rho_1 A \left(\frac{d}{d\theta} K_0(\theta) + \mu K_0(\theta) \right), \\
&K_2(\theta) = qr\chi p(\theta) K_0(\theta) = -qr\chi A \left(\frac{d}{d\theta} K_0(\theta) + \mu K_0(\theta) \right), \\
&K_3(\theta) = \nu p(\theta) K_0(\theta) = -\nu A \left(\frac{d}{d\theta} K_0(\theta) + \mu K_0(\theta) \right), \\
&\mathcal{K}_i = \int_0^\infty K_i(\theta) d\theta, \quad i = 0,1,2,3.
\end{aligned} \tag{2.12}$$

Note that $\mathcal{K}_0$ and $\mathcal{K}_1$ are positive, while $\mathcal{K}_2$ (respectively, $\mathcal{K}_3$) is positive for $q > 0$ (respectively, $\nu > 0$) and vanishes at $q = 0$ (respectively, $\nu = 0$). Also, the following

relationships are useful for simplifying future calculations:

$$\mathcal{K}_0 = \frac{1}{\mu}\left(1 - \frac{\mathcal{K}_1}{\rho_1 A}\right), \quad \mathcal{K}_2 = \frac{qr\chi}{\rho_1}\mathcal{K}_1, \quad \mathcal{K}_3 = \frac{\nu}{\rho_1}\mathcal{K}_1. \tag{2.13}$$

For convenience, we introduce the new variable

$$v(t) = i(0,t) = \lambda_1(t)S(t).$$

Integrating the second equation in (2.11) along the characteristic lines $t - \theta =$ constant, we get the following formula:

$$i(\theta,t) = \begin{cases} i_0(\theta - t)\dfrac{K_0(\theta)}{K_0(\theta - t)} & \text{for } \theta \geq t, \\ \\ v(t-\theta)K_0(\theta) & \text{for } \theta < t. \end{cases} \tag{2.14}$$

This can be used to replace the i and J equations in (2.11) by differential-integral equations for v and J:

$$\begin{aligned} v(t) &= \frac{S(t)}{N(t)}\int_0^t K_1(\theta)v(t-\theta)d\theta + F_1(t), \\ \frac{d}{dt}J(t) &= \rho_2 S(t)\frac{J(t)}{N(t)} - mJ(t) + \int_0^t K_2(\theta)v(t-\theta)d\theta + F_2(t), \end{aligned} \tag{2.15}$$

where $m = \mu + \delta$ is the removal rate from the J class due to death, and

$$F_1(t) = \frac{S(t)}{N(t)}\int_t^\infty i_0(\theta - t)\frac{K_1(\theta)}{K_0(\theta - t)}d\theta,$$

$$F_2(t) = \int_t^\infty i_0(\theta - t)\frac{K_2(\theta)}{K_0(\theta - t)}d\theta.$$

We note that

$$\lim_{t\to\infty} F_i(t) = 0 \quad (i = 1, 2).$$

Moreover, using $\lim_{\theta\to\infty} i(\theta,t) = 0$ and integrating the second equation in (2.11) (see (2.5)) give

$$\frac{d}{dt}I(t) = \lambda_1(t)S(t) - \mu I(t) - \int_0^\infty \gamma(\theta)i(\theta,t)d\theta,$$

and, using (2.4), we have

$$\frac{d}{dt}N(t) = \beta(N)N - \mu N(t) - \delta J(t) - \int_0^t K_3(\theta)v(t-\theta)d\theta - F_3(t), \tag{2.16}$$

where

$$F_3(t) = \int_t^\infty i_0(\theta - t)\frac{K_3(\theta)}{K_0(\theta - t)}d\theta.$$

Notice that

$$S(t) = N(t) - J(t) - \int_0^t v(t-\theta)K_0(\theta)d\theta - F_4(t),$$

where

$$F_4(t) = \int_t^\infty i_0(\theta - t)\frac{K_0(\theta)}{K_0(\theta - t)}d\theta.$$

We note that, just as for $i = 1, 2$,

$$\lim_{t\to\infty} F_i(t) = 0 \quad (i = 3, 4).$$

This allows us to replace the first equation in (2.11) by (2.16) for N and to study a system of differential and integral equations in the variables $v(t) = i(0, t)$, $J(t)$, and $N(t)$, which we find easier to analyze.

$$\begin{aligned}
v(t) &= \frac{N(t) - J(t) - \displaystyle\int_0^t K_0(\theta)v(t-\theta)d\theta}{N(t)} \int_0^t K_1(\theta)v(t-\theta)d\theta + \tilde{F}_1(t),\\
\frac{d}{dt}J(t) &= \rho_2\left(N(t) - J(t) - \int_0^t K_0(\theta)v(t-\theta)d\theta\right)\frac{J(t)}{N(t)}\\
&\qquad -mJ(t) + \int_0^t K_2(\theta)v(t-\theta)d\theta + \tilde{F}_2(t),\\
\frac{d}{dt}N(t) &= \beta(N)N - \mu N(t) - \delta J(t) - \int_0^t K_3(\theta)v(t-\theta)d\theta - F_3(t),
\end{aligned} \tag{2.17}$$

where

$$\tilde{F}_1(t) = F_1(t) - \frac{F_4(t)}{N(t)} \int_0^t K_1(\theta)\, v(t-\theta)\, d\theta,$$

$$\tilde{F}_2(t) = F_2(t) - \rho_2 \frac{F_4(t)}{N(t)}\, J(t)$$

are linear combinations of the functions $F_i(t)$, $i = 1, 2, 3, 4$, with bounded coefficients; thus they also approach 0 as $t \to \infty$.

The system (2.17) is the main tool for the stability analysis that we will perform in the following sections.

3. Steady-states and disease extinction. According to [15], any equilibrium of the system (2.17), if it exists, must be a constant solution of the limiting system

associated with (2.17), which is given by the following set of equations:

$$
\begin{aligned}
v(t) &= \frac{(N(t) - J(t) - K_0 * v)}{N(t)} (K_1 * v), \\
\frac{d}{dt}J(t) &= \rho_2 (N(t) - J(t) - K_0 * v) \frac{J(t)}{N(t)} - mJ(t) + K_2 * v, \\
\frac{d}{dt}N(t) &= \beta(N)N(t) - \mu N(t) - \delta J(t) - K_3 * v,
\end{aligned}
\tag{3.1}
$$

where

$$K_i * v = \int_0^\infty K_i(\theta)v(t-\theta)d\theta, \quad i = 0, 1, 2, 3.$$

Thus we look for solutions (v^*, J^*, N^*) of the system

$$
\begin{aligned}
v^* &= \frac{(N^* - J^* - \mathcal{K}_0 v^*)}{N^*} \mathcal{K}_1 v^*, \\
\rho_2 (N^* - J^* - \mathcal{K}_0 v^*) \frac{J^*}{N^*} &- mJ^* + \mathcal{K}_2 v^* = 0, \\
\beta(N^*)N^* - \mu N^* - \delta J^* &- \mathcal{K}_3 v^* = 0.
\end{aligned}
\tag{3.2}
$$

Any solution of this system corresponds to the following steady-state for the distribution of infecteds:

$$i^*(\theta) = v^* K_0(\theta).$$

The system (3.2) always has the disease-free equilibrium

$$E_0 = (0, 0, \beta^{-1}(\mu)),$$

while existence of nontrivial equilibria will depend on the values of the two parameters

$$\mathcal{R}_1 = \mathcal{K}_1 = \rho_1 \int_0^\infty p(\theta) e^{-\mu\theta - \int_0^\theta \gamma(s)ds} d\theta$$

and

$$\mathcal{R}_2 = \frac{\rho_2}{\mu + \delta} = \frac{\rho_2}{m}$$

that are the basic reproductive numbers for the sensitive and resistant strains, respectively. We can interpret $\mathcal{R}_1$ (respectively, $\mathcal{R}_2$) as the average number of secondary infectious cases produced by an infected individual with the drug-sensitive bacillus (respectively, by infected individual with the drug-resistant bacillus) during his or her entire *effective* infectious period in a purely susceptible population.

Solving system (3.2), we see that, besides E_0, the following equilibria are feasible, under some conditions on $\mathcal{R}_1$ and $\mathcal{R}_2$. Namely, we have the following:

(1) *If* $\mathcal{R}_1 > 1$ *and* $q = 0$*, then the following equilibrium exists*:

$$E_1 = (v_1^*, 0, N_1^*),$$

where

$$N_1^* = \beta^{-1}\left(\mu + \frac{\mathcal{K}_3}{\mathcal{K}_0}\left(1 - \frac{1}{\mathcal{R}_1}\right)\right), \quad v_1^* = \left(1 - \frac{1}{\mathcal{R}_1}\right)\frac{N_1^*}{\mathcal{K}_0}.$$

(2) *If* $\mathcal{R}_2 > 1$*, then the following equilibrium exists*:

$$E_2 = (0, J_2^*, N_2^*),$$

where

$$N_2^* = \beta^{-1}\left(\mu + \delta\left(1 - \frac{1}{\mathcal{R}_2}\right)\right), \quad J_2^* = \left(1 - \frac{1}{\mathcal{R}_2}\right)N_2^*.$$

(3) *If* $\mathcal{R}_1 > 1$*,* $q > 0$*, and* $\mathcal{R}_2 < \mathcal{R}_1$*, then the following equilibrium exists*:

$$E_* = (v_*, J_*, N_*),$$

where

$$N_* = \beta^{-1}\left(\mu + \delta\xi\mathcal{K}_2 + \mathcal{K}_3\xi(\mu+\delta)\left(1 - \frac{\mathcal{R}_2}{\mathcal{R}_1}\right)\right), \qquad J_* = \xi\mathcal{K}_2 N_*,$$

$$v_* = \xi(\mu+\delta)\left(1 - \frac{\mathcal{R}_2}{\mathcal{R}_1}\right)N_*, \qquad \textit{with} \qquad \xi = \frac{\left(1 - \frac{1}{\mathcal{R}_1}\right)}{\mathcal{K}_2 + \mathcal{K}_0(\mu+\delta)\left(1 - \frac{\mathcal{R}_2}{\mathcal{R}_1}\right)}.$$

Note that, in case (3), we have the relations $\xi\mathcal{K}_2 \le 1 - \frac{1}{\mathcal{R}_1} \le 1$ and, similarly, $\mathcal{K}_3\xi(\mu+\delta)(1-\frac{\mathcal{R}_2}{\mathcal{R}_1}) \le \nu\mathcal{K}_0\xi(\mu+\delta)(1-\frac{\mathcal{R}_2}{\mathcal{R}_1}) \le \nu(1-\frac{1}{\mathcal{R}_1}) \le \nu$, whence $\beta(0) > \mu+\delta+\nu > \mu+\delta\xi\mathcal{K}_2+\mathcal{K}_3\xi(\mu+\delta)(1-\frac{\mathcal{R}_2}{\mathcal{R}_1})$, and thus $N_* > 0$. Also, note that no other equilibrium exists, unless $q = 0$ and $\mathcal{R}_1 = \mathcal{R}_2 > 1$, when there exists a continuum of equilibria: for each $\sigma > 1$, choose any $\varepsilon \in (0, \frac{\mathcal{R}_1-1}{\sigma\mathcal{R}_1})$, $\zeta = \frac{1}{\mathcal{K}_0}(\frac{\mathcal{R}_1-1}{\mathcal{R}_1} - \varepsilon)$, $N^* = \beta^{-1}(\mu + \varepsilon\delta + \zeta\mathcal{K}_3)$, $v^* = \zeta N^*$, and $J^* = \varepsilon N^*$; then $E^* = (v^*, J^*, N^*)$ is an equilibrium of (3.1). This is a pathological case that we disregard. In Figure 2, we show the bifurcation diagram of the equilibria.

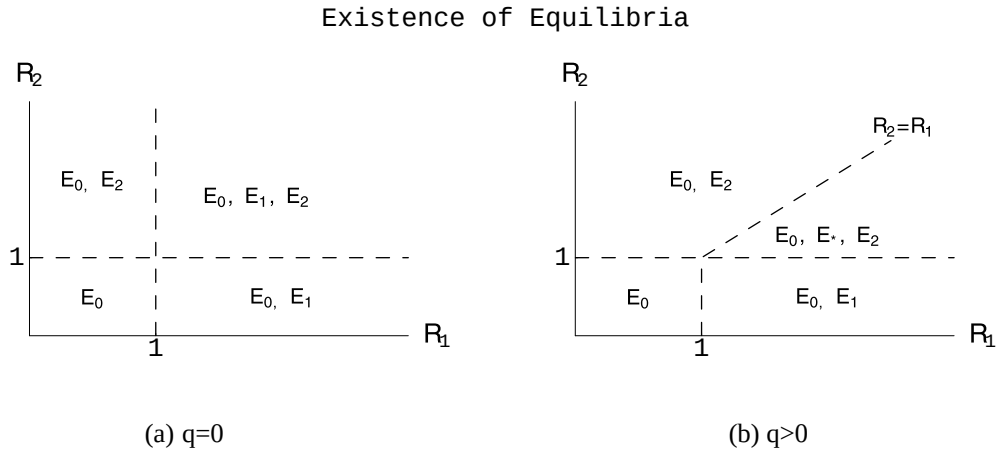
The stability properties of the nontrivial equilibria are discussed in the next section. Here we consider only the case when

$$\mathcal{R}_1 < 1 \quad \text{and} \quad \mathcal{R}_2 < 1. \tag{3.3}$$

In this case, only the disease-free equilibrium E_0 exists, and the disease goes to extinction. In fact, we have the following theorem.

THEOREM 1. *For any positive solution of the system* (2.17)*,* $(v(t), J(t), N(t))$*, if condition* (3.3) *holds, then the disease-free equilibrium* $E_0 = (0, 0, \beta^{-1}(\mu))$ *is a global attractor, i.e.,*

$$\lim_{t\to\infty}(v(t), J(t), N(t)) \to (0, 0, \beta^{-1}(\mu)).$$



(a) q=0 (b) q>0

FIG. 2.

To prove Theorem 1, we need the following two lemmas, which use the following notation: *for any bounded real-valued function f on $[0,\infty)$, let*

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

LEMMA 1. *Let $f : [0,\infty) \to \mathbf{R}$ be bounded, and let $K \in L^1(0,\infty)$. Then*

$$\limsup_{t\to\infty} \left| \int_0^t K(\theta) f(t-\theta) d\theta \right| \le |f|^\infty \, \|K\|_{L^1(0,\infty)}.$$

Proof. For any given $\varepsilon > 0$, choose $A_\varepsilon \in (0,\infty)$ such that

$$|f|^\infty \int_{A_\varepsilon}^\infty |K(\theta)| d\theta < \varepsilon.$$

Then, a fortiori,

$$\left| \int_{A_\varepsilon}^t K(\theta) f(t-\theta) d\theta \right| < \varepsilon \quad \text{for all} \quad t > A_\varepsilon.$$

Now let $t_0 > A_\varepsilon$ be such that

$$|f(t-\theta)| < |f|^\infty + \varepsilon \quad \text{for all} \quad t \ge t_0 \quad \text{and} \quad \theta \le A_\varepsilon.$$

Then we have, for $t \ge t_0$,

$$\begin{aligned} \left| \int_0^t K(\theta) f(t-\theta) d\theta \right| &\le \int_0^{A_\varepsilon} |K(\theta) f(t-\theta)| d\theta + \left| \int_{A_\varepsilon}^t K(\theta) f(t-\theta) d\theta \right| \\ &\le (|f|^\infty + \varepsilon) \, \|K\|_{L^1(0,\infty)} + \varepsilon, \end{aligned}$$

and, since ε is arbitrary, the thesis follows.

LEMMA 2 (see [18]). *Let $f : [0,\infty) \to \mathbf{R}$ be bounded and twice differentiable with bounded second derivative. Let $t_n \to \infty$ and $f(t_n)$ converge to f^∞ or f_∞ for $n \to \infty$. Then*

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

To prove Theorem 1, let $\mathcal{R}_1 < 1$ and $\mathcal{R}_2 < 1$. For convenience, we use the equivalent v and J equations in (2.15). Note that $v(t)$ is nonnegative and bounded and also that $\frac{S(t)}{N(t)} < 1$. Moreover, we have $F_1(t) \to 0$ as $t \to \infty$ so that, using the v equation in (2.15) and Lemma 1, we have

$$v^\infty \le \mathcal{R}_1 v^\infty.$$

Since $\mathcal{R}_1 < 1$, we conclude that $v^\infty = 0$. Thus

$$v(t) \to 0 \quad \text{as} \quad t \to \infty.$$

Next we choose a sequence $t_n \to \infty$ such that $J(t_n) \to J^\infty$ and $J'(t_n) \to 0$. Since $v(t) \to 0$ as $t \to \infty$, using the J equation in (2.15) and Lemma 2, we have

$$0 \le \rho_2 J^\infty - m J^\infty.$$

Since $\rho_2 < m$, we see that $J^\infty = 0$.

Finally, from the third equation in (3.1) and the relations $0 \le J(t) \le N(t)$ and $\int_0^\infty K_3(\theta) i(t,\theta)\, d\theta \le \nu I(t) \le \nu N(t)$, we have

$$\frac{d}{dt} N(t) \ge (\beta(N) - \mu - \delta - \nu) N(t).$$

Since $\beta(0) > m$, it is easy to see that dN/dt is positive when N becomes small. Thus $N(t)$ is bounded away from zero for all $t > 0$ if $N(0) > 0$, i.e., $N_\infty > 0$. We use Lemma 1 again to choose sequences $t_n \to \infty$, $s_n \to \infty$ for $n \to \infty$, such that $N(t_n) \to N^\infty$, $N(s_n) \to N_\infty$, $N'(t_n) \to 0$, and $N'(s_n) \to 0$. It also follows from the N equation, noticing that $J(t), v(t), F_3(t) \to 0$ as $t \to \infty$, that

$$0 = \big(\beta(N^\infty) - \mu\big) N^\infty = \big(\beta(N_\infty) - \mu\big) N_\infty.$$

Since $N^\infty \ge N_\infty > 0$, the above equations yield

$$\beta(N^\infty) = \beta(N_\infty) = \mu.$$

The monotonicity of $\beta(N)$ yields $N^\infty = N_\infty = \beta^{-1}(\mu)$, which finishes the proof of Theorem 1.

4. Stability analysis. In this section, we are concerned with the cases in which condition (3.3) is not fulfilled and new equilibria exist other than E_0. Actually, a first consequence of this situation is that E_0 is unstable. Specifically, we have the following theorem.

THEOREM 2. *If*

$$\mathcal{R}_1 > 1 \quad \textit{and/or} \quad \mathcal{R}_2 > 1, \tag{4.1}$$

then the disease-free equilibrium E_0 is unstable.

Proof. Taking the linearization of system (3.1) at the point E_0, we get the characteristic equation

$$(1-\hat{K}_1(\lambda))\,(\lambda-\rho_2+m)\left(\lambda-\beta'(\beta^{-1}(\mu))\beta^{-1}(\mu)\right)=0,$$

where $\hat{f}(\lambda)$ denotes the Laplace transform of $f(\theta)$, i.e.,

$$\hat{f}(\lambda)=\int_0^\infty e^{-\lambda\theta}f(\theta)d\theta.$$

We see that, if (4.1) holds, then at least one solution of this equation has a positive real part: if $\hat{K}_1(0)=\mathcal{R}_1>1$, then there is a positive real root of the factor $(1-\hat{K}_1(\lambda))$, while $\rho_2-m>0$ if and only if $\mathcal{R}_2>1$.

Our next step is to consider the case in which $q=0$ that corresponds to the possible existence of the two nontrivial equilibria E_1 and E_2, while there is no coexistence equilibrium E_* (see section 3). In this case, we have the following theorem.

THEOREM 3. *Let $q=0$. Then the following hold.*

(a) *If $\mathcal{R}_1>1$, the boundary equilibrium E_1 is unstable for $\mathcal{R}_2>\mathcal{R}_1$ and stable for $\mathcal{R}_2<\mathcal{R}_1$ and $\nu=0$.*

(b) *If $\mathcal{R}_2>1$, the boundary equilibrium E_2 is stable for $\mathcal{R}_2>\mathcal{R}_1$ and unstable for $\mathcal{R}_2<\mathcal{R}_1$.*

Proof. Let $\mathcal{R}_1>1$; then the equilibrium E_1 exists, and the linearization of (3.1) at this point gives the following characteristic equation:

$$\det\begin{pmatrix} 1-\dfrac{\hat{K}_1(\lambda)}{\mathcal{R}_1}+\dfrac{\mathcal{R}_1-1}{\mathcal{K}_0}\hat{K}_0(\lambda) & -\dfrac{\mathcal{R}_1-1}{\mathcal{K}_0} & \dfrac{(\mathcal{R}_1-1)^2}{\mathcal{R}_1\mathcal{K}_0} \\ 0 & \lambda-\dfrac{\rho_2}{\mathcal{R}_1}+m & 0 \\ \hat{K}_3(\lambda) & \delta & \lambda-\beta'(N_1^*)N_1^* \end{pmatrix}=0.$$

The roots of this equation are $\rho_2/\mathcal{R}_1-m$ and others given by the following equation:

$$\left(1-\frac{\hat{K}_1(\lambda)}{\mathcal{R}_1}+\frac{\mathcal{R}_1-1}{\mathcal{K}_0}\hat{K}_0(\lambda)\right)\left(\lambda-\beta'(N_1^*)N_1^*\right)-\frac{(\mathcal{R}_1-1)^2}{\mathcal{R}_1\mathcal{K}_0}\hat{K}_3(\lambda)=0. \tag{4.2}$$

Since $\rho_2/\mathcal{R}_1-m$ is positive if and only if $\mathcal{R}_2>\mathcal{R}_1$, the first statement in part (a) is proved.

Using (2.12), (4.2) can be rewritten for $\lambda\neq\beta'(N_1^*)N_1^*$ in the following form:

$$\frac{\hat{\mathcal{K}}_1(\lambda)}{\mathcal{R}_1} = \frac{\lambda+\mu+\frac{\mathcal{R}_1-1}{\mathcal{K}_0}}{\lambda+\mu+\frac{\mathcal{R}_1(\mathcal{R}_1-1)}{\rho_1 A\mathcal{K}_0}+\frac{\nu}{\rho_1\mathcal{K}_0}(\mathcal{R}_1-1)^2\frac{\lambda+\mu}{\lambda-\beta'(N_1^*)N_1^*}}. \tag{4.3}$$

We would like to show that (4.3) has no solution λ with nonnegative real part. In fact, we are able to do this only for the case in which $\nu=0$. In order to prove the second statement in part (a), we now assume that $\nu=0$. Then (4.2) has the root $\beta'(N_1^*)N_1^*<0$ and also the roots of the simplified (4.3):

$$\frac{\hat{K}_1(\lambda)}{\mathcal{R}_1}=\frac{\lambda+\mu+\frac{\mathcal{R}_1-1}{\mathcal{K}_0}}{\lambda+\mu+\left(\frac{\mathcal{R}_1}{\rho_1 A}\right)\left(\frac{\mathcal{R}_1-1}{\mathcal{K}_0}\right)}. \tag{4.4}$$

Note that the denominator in the right-hand side is not zero for any λ with $\Re\lambda \geq 0$. Also note that, by (2.13),

$$\frac{\mathcal{R}_1}{\rho_1 A} = \frac{\mathcal{K}_1}{\rho_1 A} = 1 - \mu\mathcal{K}_0 < 1. \tag{4.5}$$

Then, for any λ with $\Re\lambda \geq 0$, from $\mathcal{R}_1 > 1$ and (4.5) we know that the modulus of the fraction on the right-hand side of (4.4) is greater than one, while the modulus of $\hat{K}_1(\lambda)/\mathcal{R}_1$ is always less than one. We conclude that (4.4) does not have roots with nonnegative real parts. Therefore, all roots of (4.2) have negative real parts if and only if $\mathcal{R}_2 < \mathcal{R}_1$, and part (a) is proved.

To prove part (b), we assume that $\mathcal{R}_2 > 1$ and linearize (3.1) at the equilibrium E_2, obtaining the characteristic equation

$$\det \begin{pmatrix} 1 - \dfrac{\hat{K}_1(\lambda)}{\mathcal{R}_2} & 0 & 0 \\ \rho_2 x\hat{K}_0(\lambda) - \hat{K}_2(\lambda) & \lambda + \rho_2 x & -\rho_2 x^2 \\ \hat{\mathcal{K}}_3(\lambda) & \delta & \lambda - \beta'(N_2^*)N_2^* - \delta x \end{pmatrix} = 0, \tag{4.6}$$

where

$$x = \left(1 - \frac{1}{\mathcal{R}_2}\right) > 0$$

since $\mathcal{R}_2 > 1$. The roots of (4.6) are given by the two equations

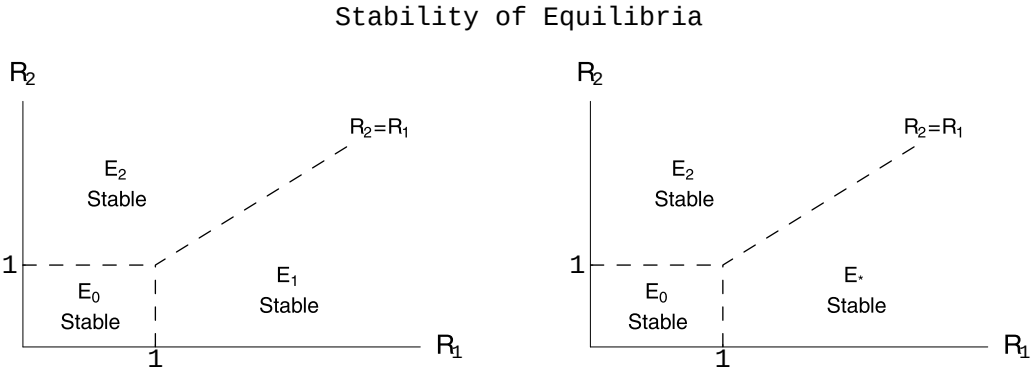
$$\frac{\hat{K}_1(\lambda)}{\mathcal{R}_2} = 1 \quad \text{or} \quad \lambda^2 + \alpha_1\lambda + \alpha_2 = 0, \tag{4.7}$$

where $\alpha_1 = (\rho_2 - \delta)x - \beta'(N_2^*)N_2^* > 0$ and $\alpha_2 = -\rho_2 x\beta'(N_2^*)N_2^* > 0$ since $x > 0$, $\rho_2 > \delta$, and $\beta'(N_2^*) < 0$. These two inequalities imply that the second equation in (4.7) has two roots with negative real part. Concerning the first equation in (4.7), we have that, since $\hat{K}_1(0) = \mathcal{R}_1$ and $K_1(t) \geq 0$, the dominant real root is negative if $\mathcal{R}_1 < \mathcal{R}_2$ and positive if $\mathcal{R}_1 > \mathcal{R}_2$. It follows that E_2 is stable if $\mathcal{R}_2 > \mathcal{R}_1$ and unstable if $\mathcal{R}_2 < \mathcal{R}_1$, which finishes the proof of part (b).

Figure 3(a) is a bifurcation diagram for the case $q = 0$ that describes the situation relative to Theorems 1 and 2. The stable equilibria are indicated for the different values of the parameters $\mathcal{R}_1$ and $\mathcal{R}_2$. The other existing equilibria, listed in Figure 2(a), are not indicated and are all unstable. We note that in 3(a) the stability of E_1 has only been proved for $\nu = 0$.

We next consider the case $q > 0$ and discuss how the situation changes with q ($q \in (0, 1]$) and ν. In this case (3.1) cannot have the boundary equilibrium E_1.

It is clear that J_2^* (and hence E_2) does not depend on q or ν, whereas $v_* = v_*(q, \nu)$, $J_* = J_*(q, \nu)$, and $N_* = N_*(q, \nu)$ are indeed functions of q and ν. Moreover, $\mathcal{R}_1$ depends only on $\tau = qr\chi + \nu$, $\mathcal{R}_1 = \mathcal{R}_1(\tau)$ is a strictly decreasing function of τ, and $\mathcal{R}_1(\tau) \to 0$ as $\tau \to \infty$. Since $\mathcal{R}_2$ is independent of τ, we see that, if $\mathcal{R}_1(0) > \mathcal{R}_2 > 1$, there exists a unique $\tau_c > 0$ such that $\mathcal{R}_1(\tau_c) = \mathcal{R}_2$. Hence E_* exists if and only if



(a) q=0 (b) q>0

FIG. 3.

$0 < \tau < \tau_c$. We also have, for any $\nu \geq 0$,

$$\lim_{q\to 0^+} v_*(q,\nu) = \left(1 - \frac{1}{\mathcal{R}_1(\nu)}\right)\frac{\beta^{-1}(\mu)}{\mathcal{K}_0} = v_1^*,$$

$$\lim_{q\to 0^+} J_*(q,\nu) = 0,$$

$$\lim_{q\to 0^+} N_*(q,\nu) = \beta^{-1}\left(\mu + \frac{\mathcal{K}_3}{\mathcal{K}_0}\left(1 - \frac{1}{\mathcal{R}_1(\nu)}\right)\right) = N_1^*;$$

that is,

$$\lim_{q\to 0^+} E_*(q,\nu) \to E_1 = E_1(\nu).$$

Moreover, if $q_c = \dfrac{\tau_c - \nu}{r\chi} > 0$, then

$$\lim_{q\to q_c^-} v_*(q,\nu) = 0,$$

$$\lim_{q\to q_c^-} J_*(q,\nu) = \left(1 - \frac{1}{\mathcal{R}_1(\tau_c)}\right) N_2^* = \left(1 - \frac{1}{\mathcal{R}_2}\right) N_2^* = J_2^*,$$

$$\lim_{q\to q_c^-} N_*(q,\nu) = \beta^{-1}\left(\mu + \delta\left(1 - \frac{1}{\mathcal{R}_2}\right)\right) = N_2^*;$$

that is,

$$\lim_{q\to q_c^-} E_*(q,\nu) \to E_2.$$

Then we have the following analytic result for the system (3.1).

THEOREM 4. *Assume that $q > 0$. Then the following hold.*

(a) *If $\mathcal{R}_2 > 1$, the boundary equilibrium E_2 is stable if $\mathcal{R}_2 > \mathcal{R}_1(\tau)$ and unstable if $\mathcal{R}_2 < \mathcal{R}_1(\tau)$.*
(b) *If $\mathcal{R}_1(0) > \mathcal{R}_2 > 1$, the interior equilibrium E_* is stable if either τ is small or τ is close to τ_c.*

Proof. The proof of part (a) is identical to that of part (b) in Theorem 3. In fact, the linearization at E_2 produces the same characteristic equation.

Concerning E_*, we have the equation

$$\det \begin{pmatrix} 1 - \dfrac{\hat{K}_1(\lambda)}{\mathcal{R}_1} + x_* \mathcal{R}_1 \hat{K}_0(\lambda) & x_* \mathcal{R}_1 & x_*(1 - \mathcal{R}_1) \\ \rho_2 y_* \hat{K}_0(\lambda) - \hat{K}_2(\lambda) & \lambda - D_* & \rho_2 y_* \left(\dfrac{1}{\mathcal{R}_1} - 1 \right) \\ \hat{\mathcal{K}}_3(\lambda) & \delta & \lambda - B_* \end{pmatrix} = 0, \tag{4.8}$$

where

$$x_* = \frac{v_*}{N_*} = \xi m \left(1 - \frac{\mathcal{R}_2}{\mathcal{R}_1} \right), \qquad y_* = \frac{J_*}{N_*} = \xi \mathcal{K}_2,$$

$$B_* = \beta'(N_*) N_* + \delta \xi \mathcal{K}_2 + \mathcal{K}_3 \xi (\mu + \delta) \left(1 - \frac{\mathcal{R}_2}{\mathcal{R}_1} \right), \qquad D_* = \frac{\rho_2}{\mathcal{R}_1} - m - \rho_2 y_*.$$

Next we bring up the following identities (see (2.12)):

$$\hat{K}_0(\lambda) = \frac{1 - \frac{\hat{K}_1(\lambda)}{\rho_1 A}}{\lambda + \mu}, \qquad \hat{K}_2(\lambda) = qr\chi \frac{\hat{K}_1(\lambda)}{\rho_1}, \qquad \hat{K}_3(\lambda) = \nu \frac{\hat{K}_1(\lambda)}{\rho_1}.$$

Then, after some simplification, (4.8) can be written as

$$0 = m_1(\lambda) \left(1 - \frac{\hat{K}_1(\lambda)}{\mathcal{R}_1} \right) + m_2(\lambda) \left(1 - \frac{\hat{K}_1(\lambda)}{\rho_1 A} \right) + m_3(\lambda) \frac{\hat{K}_1(\lambda)}{\rho_1},$$

where

$$m_1(\lambda) = (\lambda + \mu) \left((\lambda - B_*)(\lambda - D_*) + \delta \rho_2 y_* \left(1 - \frac{1}{\mathcal{R}_1} \right) \right),$$

$$m_2(\lambda) = x_* \mathcal{R}_1 (\lambda - B_*) \left(\lambda + m - \frac{\rho_2}{\mathcal{R}_1} \right),$$

$$m_3(\lambda) = x_* (\lambda + \mu) \left[qr\chi \mathcal{R}_1 \left(\lambda - B_* + \delta \left(1 - \frac{1}{\mathcal{R}_1} \right) \right) + \nu (\mathcal{R}_1 - 1) \left(\lambda + m - \frac{\rho_2}{\mathcal{R}_1} \right) \right].$$

We now define

$$H(\lambda, q) = m_1(\lambda) + m_2(\lambda) - \frac{\hat{K}_1(\lambda)}{\mathcal{R}_1} \left(m_1(\lambda) + \frac{\mathcal{R}_1}{\rho_1 A} m_2(\lambda) - \frac{\mathcal{R}_1}{\rho_1} m_3(\lambda) \right),$$

and we need to solve

$$H(\lambda, q) = 0. \tag{4.9}$$

We note that, since $\tau = 0$ is equivalent to $q = \nu = 0$,

$$\lim_{\tau \to 0^+} H(\lambda, q, \nu) = H(\lambda, 0, 0)$$

$$= \left[(\lambda + \psi_1) - \frac{\hat{K}_1(\lambda)}{\mathcal{R}_1}(\lambda + \psi_2)\right]\left(\lambda - \beta'(N_1^*)N_1^*\right)\left(\lambda + \mu - \frac{\rho_2}{\mathcal{R}_1}\right),$$

with

$$\psi_1 = \mu + \left(1 - \frac{1}{\mathcal{R}_1}\right)\frac{\mathcal{R}_1}{\mathcal{K}_0} > 0 \quad \text{and} \quad \psi_2 = \mu + \left(1 - \frac{1}{\mathcal{R}_1}\right)\frac{\mathcal{R}_1^2}{A\mathcal{K}_0} > 0,$$

where $\mathcal{R}_1$, A, and $\mathcal{K}_0$ are all computed at $q = \nu = 0$.

Since the equation $H(\lambda, 0, 0) = 0$ has the real roots $\beta'(N_1^*)N_1^*$ and $\frac{\rho_2}{\mathcal{R}_1} - \mu$ but does not have the root $\lambda = -\psi_2$, its remaining roots are the solutions of the following equation:

$$\frac{\hat{K}_1(\lambda)}{\mathcal{R}_1} = \frac{\lambda + \psi_1}{\lambda + \psi_2}.$$

Now, since $\mathcal{R}_1/A < 1$ (see (4.5)), we have $\psi_2 < \psi_1$, and it is easy to show that

$$\Re\, \frac{\lambda + \psi_1}{\lambda + \psi_2} > 1$$

for all λ with $\Re\, \lambda > 0$. On the other hand, $\Re\, \hat{K}_1(\lambda)/\mathcal{R}_1 < 1$ if $\Re\, \lambda > 0$. Hence (4.9) has no roots with positive real part for τ sufficiently small because of the continuous dependence on parameters. This is the first half of part (b).

Concerning the values of τ close to τ_c, we let $\tau_c = q_0 r\chi + \nu_0$ ($q_0 > 0$) and note that

$$\lim_{\tau \to \tau_c^-} H(\lambda, q, \nu) = H(\lambda, q_0, \nu_0) = \left(1 - \frac{\hat{K}_1(\lambda)}{\mathcal{R}_1}\right)(\lambda + \mu)(\lambda^2 + \alpha_1\lambda + \alpha_2),$$

where α_1 and α_2 are the same as in (4.7). Thus the equation $H(\lambda, q_0, \nu_0) = 0$ has three roots with negative real part from its cubic polynomial factor and a fourth root $\lambda = 0$ from its first (transcendental) factor. In order to understand the stability of E_* for τ near τ_c, it suffices to determine the direction in which this root moves when τ decreases from the value τ_c. The following conditions ensure that this root moves to the left in the complex plane:

$$H_q(0, q_0, \nu_0)H_\lambda(0, q_0, \nu_0) < 0, \qquad H_\nu(0, q_0, \nu_0)H_\lambda(0, q_0, \nu_0) < 0. \tag{4.10}$$

Now note that we have (since the polynomials $m_2(\lambda)$ and $m_3(\lambda)$ are identically zero when $\tau = \tau_c$ because of the factor x_*, as $\mathcal{R}_1(\tau_c) = \mathcal{R}_2$)

$$H_\lambda(0, q_0, \nu_0) = \mu\beta'(N_2^*)N_2^*\frac{\hat{K}_1'(0)}{\mathcal{R}_2}\rho_2\left(1 - \frac{1}{\mathcal{R}_2}\right) > 0,$$

$$H_q(0,q_0,\nu_0) = -\frac{\mu m}{\rho_1 \mathcal{K}_2} q_0 r\chi\beta'(N_2^*)N_2^*\big(\mathcal{R}_2-1\big)\frac{d}{dq}\mathcal{R}_1\bigg|_{\tau=\tau_c} < 0,$$

and

$$H_\nu(0,q_0,\nu_0) = -\frac{\mu m}{\rho_1 \mathcal{K}_2} q_0 r\chi\beta'(N_2^*)N_2^*\big(\mathcal{R}_2-1\big)\frac{d}{d\nu}\mathcal{R}_1\bigg|_{\tau=\tau_c} < 0.$$

Thus conditions (4.10) are fulfilled, and E_* is stable as soon as τ is close enough to τ_c. This finishes the proof of part (b).

In the previous theorem, we proved that, when τ is positive and small enough, the interior equilibrium E_* inherits the stability properties of E_1 from which it bifurcates. On the other hand, when τ is close enough to τ_c, then E_* is stable and bifurcates from E_2, which is neutral when $\tau = \tau_c$. Figure 3(b) gives a bifurcation diagram for this case.

5. Numerical exploration. In this section, we provide some numerical simulations that support and extend the results of Theorem 3 for arbitrary q, $0 \le q \le q_c$, when $\nu = 0.14$.

We consider an explicit discretization of problem (2.11), based on backward Euler finite differences for the ODEs, a linearized finite difference method of characteristics for the PDE, and Simpson's rule for the quadratures.

Let T be the final time of simulation, and let h be the discretization step. Define $M_1 = \frac{\sup\{\theta : i_0(\theta) > 0\}}{h}$ and $M_2 = \frac{T}{h}$. It will be assumed, without loss of generality, that M_1 and M_2 are positive integers. We shall use the symbols i_j^n, N^n, J^n, I^n, λ^n to denote, respectively, the approximations of $i(jh,nh)$, $N(nh)$, $J(nh)$, $I(nh)$, $\lambda_1(nh)$ for $j,n \ge 0$.

Our numerical method, defined for $1 \le n \le M_2$, $0 \le j \le M_1 + n$, is given by

$$\begin{cases} \frac{i_j^n - i_{j-1}^{n-1}}{h} + [\mu + \gamma(jh)]\, i_j^n = 0, \\ i_0^n = \lambda^{n-1}\left(N^{n-1} - I^{n-1} - J^{n-1}\right), \\ \frac{N^n - N^{n-1}}{h} = b\left(1 - \frac{N^{n-1}}{L}\right)N^n - \mu N^n - \delta J^{n-1} - \nu A^{n-1}, \\ I^n = \frac{h}{3}\sum_{j=0}^{\frac{M_1+n-2}{2}}(i_j^n + 4i_{j+1}^n + i_{j+2}^n), \\ A^n = \frac{h}{3}\sum_{j=0}^{\frac{M_1+n-2}{2}}\left[p(jh)i_j^n + 4p(jh+h)i_{j+1}^n + p(jh+2h)i_{j+2}^n\right], \\ \lambda^n = \frac{h}{3}\frac{\rho_1}{N^n}\sum_{j=0}^{\frac{M_1+n-2}{2}}\left[p(jh)i_j^n + 4p(jh+h)i_{j+1}^n + p(jh+2h)i_{j+2}^n\right], \\ \frac{J^n - J^{n-1}}{h} = \rho_2\frac{J^{n-1}}{N^n}(N^n - I^n - J^n) - (\mu+\delta)J^n + qr\chi A^n. \end{cases}$$

We explore the behavior of the solution for a fairly realistic set of values of some of the parameters, while others are given values that allow us to examine numerically the stability of the coexistence equilibrium E_*. We selected them as follows:

$$\mu = 0.014, \quad \chi = 2, \quad r = 0.5, \quad \rho_1 = 7, \quad \rho_2 = 7, \quad \nu = 0.14, \quad \delta = 1.8.$$

Except for r (which is nondimensional), these parameters are in units of $\frac{1}{\text{yr}}$. The reciprocal of μ gives a median life of 70 years for uninfected individuals, while the

reciprocal of χ gives a median sojourn time in the class of individuals with active drug-sensitive TB of 182 days (the actual treatment lasts for six months (see [5])), and that of ν gives a median survival time for untreated active TB of 7 years (see [16]); ρ_1 is the parameter effective contact rate (ECR) of [16], with a distribution taken from [17] with mode 7.0 and maximum value 13. Lacking a better estimate, we use for ρ_2 the same value as for ρ_1 and for δ, which is a value over 10 times larger than that of ν—and one which gives a mean sojourn time of 200 days in the drug-resistant infectious class (until death from drug-resistant TB occurs). For the birth function β, we choose the logistic form

$$\beta(N) = b\left(1 - \frac{N}{L}\right),$$

where $b = 2$ and $L = 6 \cdot 10^6$. Furthermore, following the literature (see [17]), we take the function $p(\theta)$ as piecewise constant in the specific form

$$p(\theta) = \begin{cases} 0.06, & \theta \in [0,1), \\ 0.084, & \theta \in [1,2), \\ 0.093, & \theta \in [2,3), \\ 0.097, & \theta \in [3,4), \\ 0.098, & \theta \in [4,5), \\ 0.099, & \theta \in [5,6), \\ 0.1, & \theta \in [6,\infty), \end{cases} \tag{5.1}$$

where θ is measured in *years*.

When q is very small, the positive equilibrium E_* is very close to the boundary equilibrium $E_1 = (578091; 0; 5926271)$ with a prevalence of drug-sensitive TB of 81.6 percent ($\frac{I_1^*}{N_1^*} \times 100$), where I_1^* is obtained from v_1^* using (2.5) and (2.14). On the other hand, when q is very close to q_c, the positive equilibrium E_* is very close to the boundary equilibrium $E_2 = (0; 1450133; 1957371)$ with a prevalence of drug-resistant TB of 74.1 percent ($\frac{J_2^*}{N_2^*} \times 100$) (see the discussion preceding Theorem 4).

We show in Figures 4–7 the results from simulations for four different values of q, from very close to 0 to very close to $q_c \approx 0.51897012$.

In all cases, the simulations show that the dynamics stabilizes at E_*, which matches the theoretical results for τ near the boundary of the interval $[0, \tau_c]$ and suggests that the same stability result holds away from the boundary of this interval.

We also see that, as q increases from 0 to q_c, the prevalence of drug-resistant TB, $\frac{J_*}{N_*} \times 100$, increases from 0 to 74.1 percent, while the prevalence of drug-sensitive TB, $\frac{I_*}{N_*} \times 100$, decreases from 81.6 percent to 0.

6. Discussion. In this paper, we constructed and analyzed a two-strain model for drug-sensitive TB and drug-resistant TB with the purpose of examining the effects of variable periods of latency on the transmission dynamics of TB at the population level. This model combines a two-strain ODE model and a one-strain TB model with

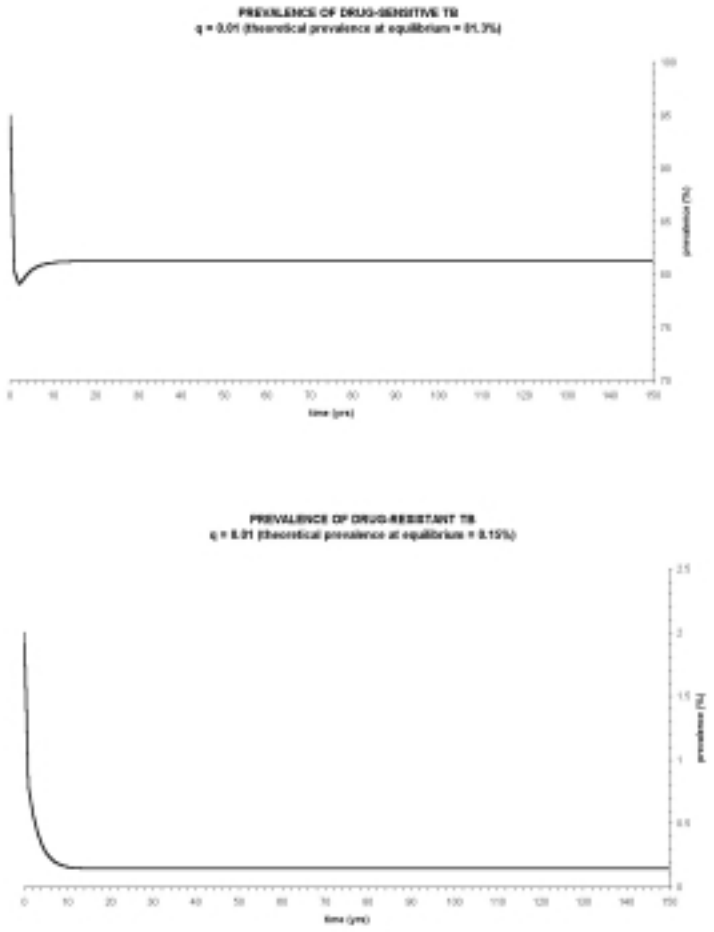


FIG. 4.

distributed delays that were previously developed [2], [7]. This paper is intended to determine whether the conclusions from either the two-strain ODE model or the one-strain distributed-delay model are changed when both multiple strains and distributed delays are considered.

It is shown in [2] that, in a homogeneously mixing population, coexistence of naturally resistant strains (the case of $q = 0$) is limited. However, antibiotic resistance (the case of $q > 0$) enhances coexistence. This, as pointed out in their paper, reminds us of the challenges facing public health officials. That is, drug-resistant TB will remain a serious threat to our communities as long as many members of our society do not have regular access to medical care. A natural criticism of the two-strain ODE model is that it did not take into account long and variable periods of latency—an important feature of TB. The one-strain TB model in [7] is the first step in this direction. Their results show that the qualitative behavior of the model with distributed

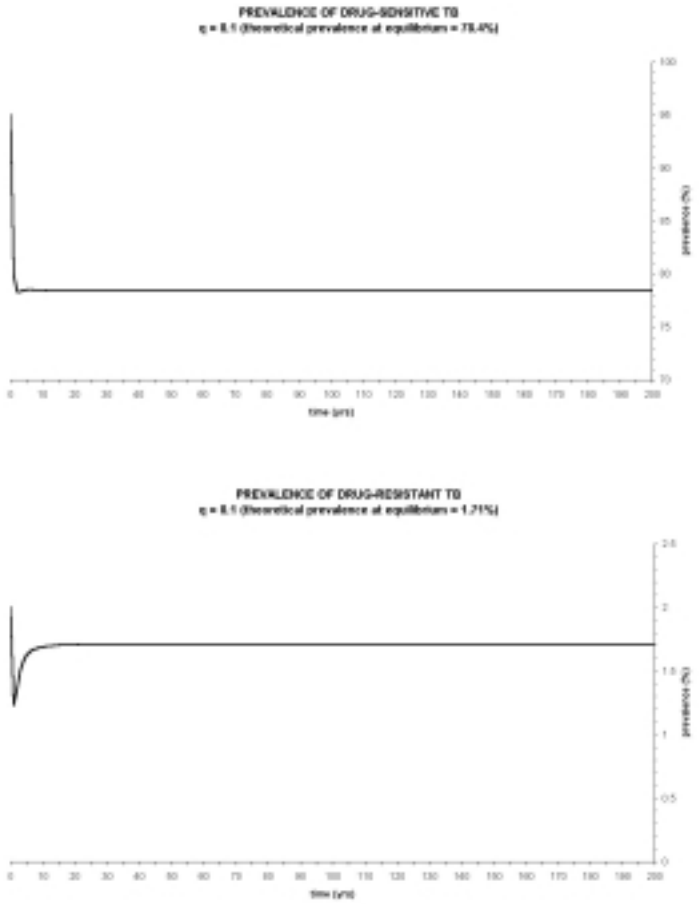


FIG. 5.

delays is not very different from those given by the corresponding ODE model.

The results of the two-strain model in this article lead to the same conclusion. That is, the variable periods of latency do not lead to complex dynamics. We considered again two cases, $q = 0$ and $q > 0$, as was done for the ODE model. We derived conditions for the existence and stability of all possible steady-states. These conditions are expressed in terms of the basic reproductive numbers for the two strains. These computations help us understand the role that key epidemiological parameters play in the maintenance of TB, especially the role of the parameters associated with an arbitrary distribution that models long and variable periods of latency. The fact that better interpretations of model results may be obtained when using arbitrary stage distributions (instead of an exponentially distributed stage duration) has been worked out recently (see [9], [10]). However, the introduction of an arbitrarily distributed delay into the model makes the analytical analysis more difficult. In this

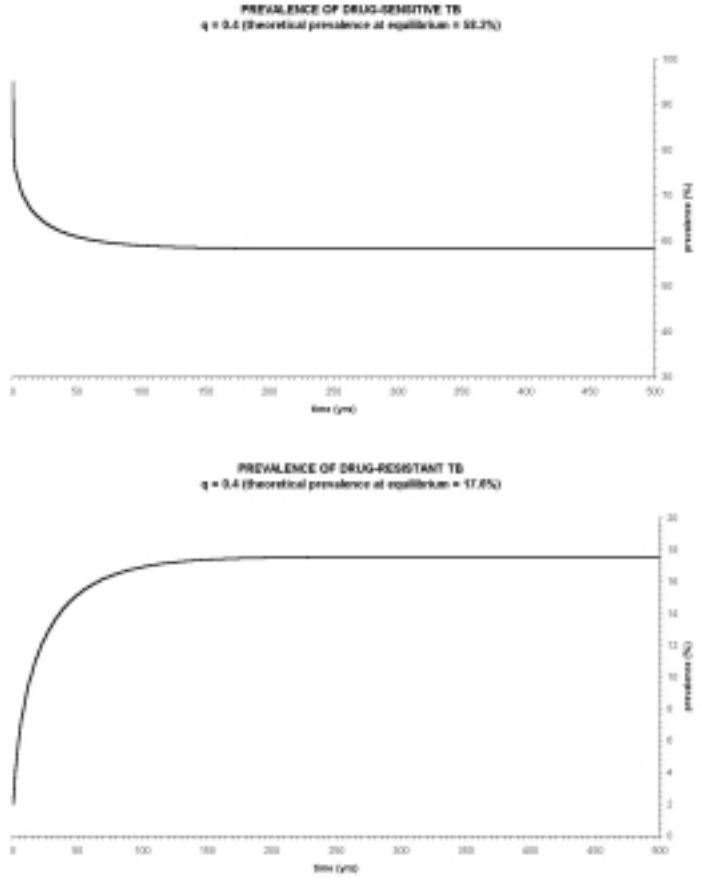


FIG. 6.

paper, we have combined both analytical and numerical studies to obtain the stability result of the interior equilibrium.

While the introduction of variable latency periods does not produce very different qualitative dynamics, factors such as exogenous reinfection and heterogeneous contact rates can indeed generate radically different dynamics from those given by the class of models discussed in [2]. Exogenous reinfection is capable of sustaining TB even when the basic reproductive number is below one (see [6]). Immigration effects on TB incidence rates have been found in several developed countries. The influence of immigrants from high-prevalence countries on the notifications in a low-prevalence country can be observed in recent data from Switzerland. Undetected active disease in immigrants is a significant source of infection among uninfected immigrants, as well as for children of immigrant parents born in the new country. We are particularly interested in looking at the impact of immigration of infected individuals from coun-

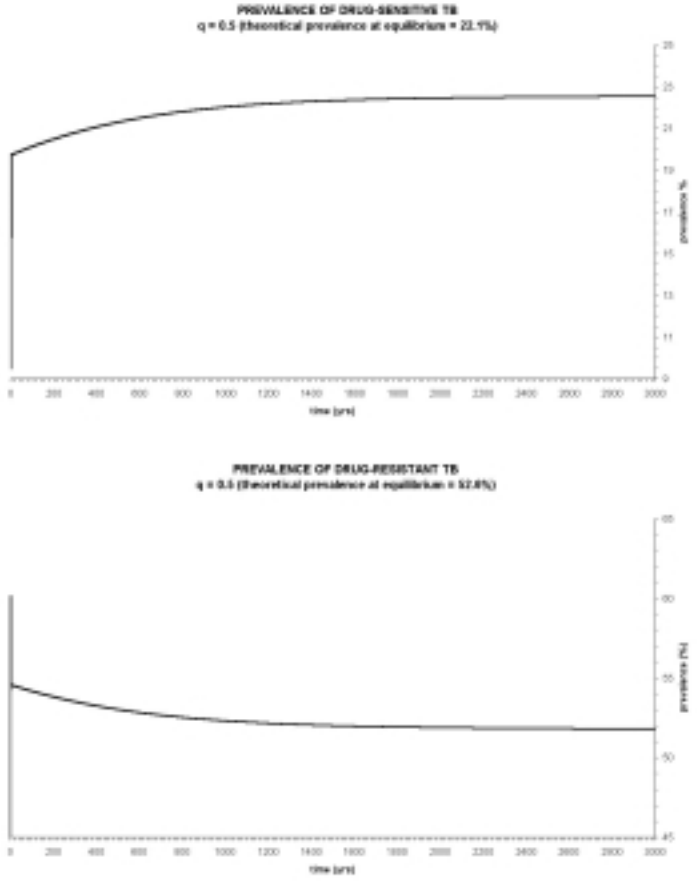


FIG. 7.

tries where prevalence of TB is high on TB dynamics as well as their effects on the disease control programs (see [8]).

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