Chapter 7
Models for Tuberculosis

In this chapter we describe several models for tuberculosis (TB). The disease is endemic in many areas of the world. The models in this chapter will be extensions of the standard SIR or SEIR type of endemic models presented in Chap. 3. Depending on the typical characteristics of a specific disease, various modifications of the standard models will be considered.

According to the recent WHO report [25], there were 8.6 million new TB cases in 2012 and 1.3 million TB deaths. TB remains a major global health problem and is the leading cause of death by an infectious disease, after the human immunodeficiency virus (HIV). It is reported that about three million people who developed TB in 2012 were missed by national notification systems. Key actions needed to detect people with the illness and ensure that they get the right treatment and care include: expanded services (including rapid tests) throughout health systems bolstered by the support of nongovernmental organizations, community workers, and volunteers to diagnose and report cases.

A typical epidemiological feature associated with TB is its long period of latency. As pointed out by G.W. Comstock, "tuberculosis is an infectious disease with an incubation period from weeks to a lifetime." Figure 7.1 illustrates that TB has a long and variable period of latency. Treating a patient with an active TB is more difficult and requires a much longer time to complete the treatment than treating a latent TB infection (LTBI). This makes it important to identify and treat latent people before they develop the disease. One of the approaches to achieve this is through screening. However, such screening programs require resources. An optimal control problem can be formulated using mathematical models for TB.

Figure 7.2 shows the data from observation in adolescents who had developed clinical tuberculosis following primary infection [24]. It suggests that among the 10% of latent individuals who eventually develop active TB, around 60% will do so during the first year post-infection. The rest will develop active TB in either 2 years (20%), 5 years (15%), 20 years (5%), or even longer.

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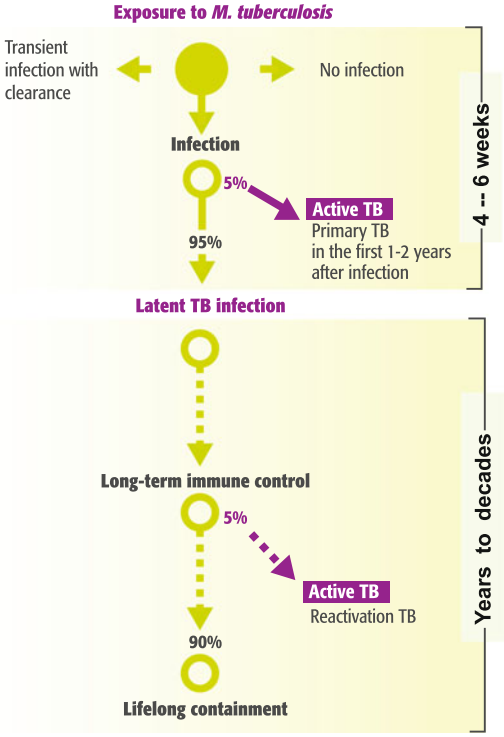

Fig. 7.1 A diagram showing the progression from latent to active TB during the period of infection (adopted from www.biomerieux-Řediagnos6cs.com). It shows that only about 10% of latently infected will develop active TB and 5% of those will stay in the latent stage for long time

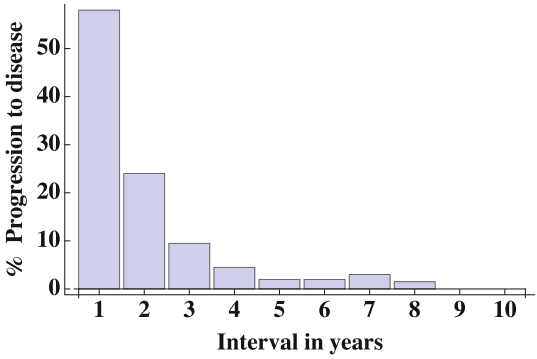

Fig. 7.2 An example of distribution of progression from latent to active TB [24]

The good news is that latent and active TB can be treated with antibiotics. The bad news is that 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 months [6]. Treatment for those with active TB requires the simultaneous use of three drugs for a period of about 9 months. Lack of compliance with these drug treatments (a very serious problem) may lead to not only a relapse but also to the development of multidrug-resistant TB (MDR-TB)—one of the most serious

public health problems facing society today. According to the WHO report [25], globally in 2012, approximately 450,000 people developed MDR-TB and there were approximately 170,000 deaths from MDR-TB. An individual can become infected with the resistant strain of TB in two ways, one is the so-called primary resistance which is obtained by direct transmission from someone with resistant TB, and the other is the acquired resistance which is developed from the sensitive TB due to incomplete or inappropriate treatment. This also creates a challenge for designing treatment policy, and should be incorporated in the modeling of optimal control for TB.

In this chapter we present several TB models that can be used to study the above mentioned problems. We begin with a relatively simple TB model with a single strain, and then extend it to include both drug-sensitive and drug-resistant strains. The two-strain model will be further extended to include two control measures representing "case-finding" (i.e., identifying people with LTBI) and "case-holding" (i.e., making sure the treatment of active TB infections is complete) and study the optimal control strategies.

7.1 A One-Strain Model with Treatment

Because there is no permanent immunity and an individual after treatment for TB can still become infected with possibly reduced susceptibility, we divide the population into four epidemiological classes: susceptible (S), latently infected (L), infectious (I), and treated (T). Assume that latent and infectious individuals are treated at rates r_1 and r_2, respectively, and latent individuals develop active TB at rate κ. The model reads

$$\begin{aligned} S' &= \mu N - cS\frac{I}{N} - \mu S + r_1 L + r_2 I, \\ L' &= cS\frac{I}{N} + c^* T\frac{I}{N} - (\kappa + r_1 + \mu)L, \\ I' &= \kappa L - (r_2 + \mu)I, \\ T' &= r_1 L + r_2 I - c^* T\frac{I}{N} - \mu T, \end{aligned} \tag{7.1}$$

where $N = S + L + I + T$ is the total population, which will remain constant for all time due to the balanced birth and natural death rate μ. The parameters c and c^* denote the average numbers of susceptible and treated individuals, respectively, infected by one infective individual per unit of time. If the treated individuals have a reduced susceptibility to infection, then $c^* < c$.

The dynamics of system (7.1) is standard in the sense that the disease will either go extinct or persist depending on whether the reproduction number

$$\mathscr{R}_0 = \frac{c\kappa}{(\kappa + r_1 + \mu)(r_2 + \mu)} \tag{7.2}$$

is less or greater than 1. It is clear from (7.2) that $\mathscr{R}_0$ is a decreasing function of treatment rates r_1 and r_2. The effect of treatment on the disease prevalence can be examined by considering the fraction of infectives I/N at the endemic equilibrium in the case $\mathscr{R}_0 > 1$. In the simpler case when $c = c^*$, the equilibrium value of I/N is given by

$$\frac{I^*}{N^*} = \frac{\kappa}{\kappa + r_2 + \mu}\left(1 - \frac{1}{\mathscr{R}_0}\right), \tag{7.3}$$

which is a decreasing function of r_1 and r_2 as well. This shows that in the absence of the resistant strain, treatment is beneficial in reducing the disease burden. This is not the case when a resistant strain is considered, as shown in the two-strain model presented next.

7.2 A Two-Strain TB Model

As mentioned earlier, treatment of active TB may take as long as 12 months, and lack of compliance with these treatments may lead to the development of antibiotic resistant TB. The one-strain model (7.1) can be extended to include both drug-sensitive (DS) and drug-resistant (DR) strains of TB, with possible development of resistance due to treatment failure. A transition diagram between the epidemiological classes is shown in Fig. 7.3. The latent and infectious individuals with sensitive TB are denoted by L_1 and I_1, respectively. Two additional classes are included for the resistant strain, i.e., the latent and infectious classes with resistant strain denoted by L_2 and I_2, respectively. The sensitive and resistant strains will be referred to as strain 1 and 2, respectively. Because it is very hard to cure a patient with resistant TB, we ignore the treatment of the resistant strain. Furthermore, assume that I_2 individuals can infect S, L_1, and T individuals. The λ functions represent the forces of infection, which are given by

$$\lambda_i(t) = c_i \frac{I_i}{N}, \quad \lambda_1^*(t) = c_1^* \frac{I_1}{N}, \quad i = 1, 2,$$

where c_1 and c_1^* have the meaning as c and c^* in the one-strain model (7.1); c_2 is similar to c_1 but for the resistant strain; r_i $(i = 1, 2)$ and μ are the same as in (7.1); κ_i denotes the progression rate from latent to infectious stage of strain i.

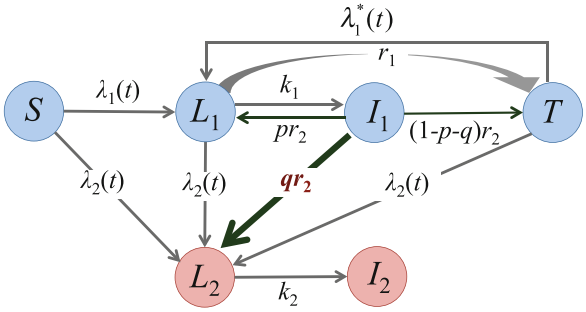

Fig. 7.3 A diagram for the two-strain TB model showing transitions between the epidemiological classes. The thicker arrow and the rate qr_2 represent the development of resistant TB due to the failure of treatment for infections with the sensitive strain. The birth and death rates are omitted

The additional parameters are related to treatment failure and the development of resistant TB. For example, $p+q$ denotes the proportion of those treated infectious individuals who did not complete their treatment, where the proportion p modifies the rate that departs from the sensitive TB latent class; qr_2I_1 gives the rate at which individuals develop resistant TB because they did not complete the treatment of active TB. Therefore, $p \geq 0, q \geq 0$ and $p+q \leq 1$. From the disease transmission diagram (see Fig. 7.3) we can write the following system of ordinary differential equations:

$$\begin{aligned}
S' &= \mu N - c_1 S\frac{I_1}{N} - c_2 S\frac{I_2}{N} - \mu S,\\
L_1' &= c_1 S\frac{I_1}{N} - (\mu+\kappa_1)L_1 - r_1 L_1 + pr_2 I_1 + c_1^* T\frac{I_1}{N} - c_2 L_1\frac{I_2}{N},\\
I_1' &= \kappa_1 L_1 - \mu I_1 - r_2 I_1,\\
L_2' &= qr_2 I_1 - (\mu+\kappa_2)L_2 + c_2(S+L_1+T)\frac{I_2}{N},\\
I_2 &= \kappa_2 L_2 - \mu I_2,\\
T' &= r_1 L_1 + (1-p-q)r_2 I_1 - c_1^* T\frac{I_1}{N} - c_2 T\frac{I_2}{N} - \mu T,
\end{aligned} \tag{7.4}$$

where $N = S + L_1 + I_1 + T + L_2 + I_2$ is the total population, which remains constant.

The detailed analysis of the model (7.4) is presented in [4]. System (7.4) has up to four possible equilibria denoted by E_0 (infection-free), E_1 (only the sensitive strain is present), E_2 (only the resistant strain is present), and E^* (coexistence of both strains). The existence of these equilibria depends on the reproduction numbers for the sensitive and resistant strains, which are given by

$$\mathscr{R}_S = \left(\frac{c_1 + pr_2}{\mu + r_2}\right)\left(\frac{\kappa_1}{\mu + \kappa_1 + r_1}\right) \tag{7.5}$$

and

$$\mathscr{R}_R = \left(\frac{c_2}{\mu}\right)\left(\frac{\kappa_2}{\mu+\kappa_2}\right), \tag{7.6}$$

respectively.

The dynamics of system (7.4) are dramatically different for the cases $q = 0$ and $q > 0$ (development of resistant TB due to treatment failure), particularly in terms of the number of equilibria and their stability, as well as the likelihood for coexistence of both strains. In addition to the reproduction numbers, there are two functions, $\mathscr{R}_R = f(\mathscr{R}_S)$ and $\mathscr{R}_R = g(\mathscr{R}_S)$, which divide the parameter region in the $(\mathscr{R}_S, \mathscr{R}_R)$ plane into sub-regions for the stability of equilibria:

$$\begin{aligned} f(\mathscr{R}_S) &= \frac{1}{1+\frac{1-\mathscr{R}_S}{(\mathscr{R}_S-AB)(1+1/B)}} \\ g(\mathscr{R}_S) &= \frac{1}{C}\left(AB+C-1 \pm \sqrt{(AB+C-1)^2+4(\mathscr{R}_S-AB)C}\right), \end{aligned} \tag{7.7}$$

for $\mathscr{R}_S \geq 1$ where

$$A = \frac{pr_2}{\mu+\kappa_1+r_1}, \quad B = \frac{\kappa_1}{\mu+d_1+r_2}, \quad C = \frac{\mu}{\mu+\kappa_1+r_1}.$$

The properties of f and g include

$$f(1) = g(1) = 1, \quad f(\mathscr{R}_S) < g(\mathscr{R}_S) \quad \text{for } \mathscr{R}_S > 1$$

(see Fig. 7.4). The two curves of f and g and the lines $\mathscr{R}_i = 1$ $(i = S, R)$ divide the first quadrant of the $(\mathscr{R}_S, \mathscr{R}_R)$ plane into either four regions in the case $q = 0$ (see Fig. 7.4a) or three regions in the case $q > 0$ (see Fig. 7.4b). The stability results for system (7.4) in the case of $q = 0$ and $q > 0$ are summarized in Theorems 7.1 and 7.2, respectively.

Theorem 7.1 *Assume $q = 0$. Let Regions I–IV be as in Fig. 7.4a.*

(a) The disease-free equilibrium E_0 is g.a.s. if $(\mathscr{R}_S, \mathscr{R}_R)$ is in Region I.
(b) For $\mathscr{R}_S > 1$, the boundary equilibrium E_1 is locally asymptotically stable if $(\mathscr{R}_S, \mathscr{R}_R)$ is in Region II and unstable in Regions III and IV.
(c) For $\mathscr{R}_R > 1$, the boundary equilibrium E_2 is locally asymptotically stable if $(\mathscr{R}_S, \mathscr{R}_R)$ is in Region IV and unstable if in Regions II and III.
(d) The coexistence equilibrium E^* exists and is locally asymptotically stable if $(\mathscr{R}_S, \mathscr{R}_R)$ is in Region III.

When $q > 0$, the equilibrium E_1 (sensitive strain only) is never stable, and the coexistence region *III* is much larger than that in the case of $q = 0$, as stated in the following theorem and illustrated in Fig. 7.4b.

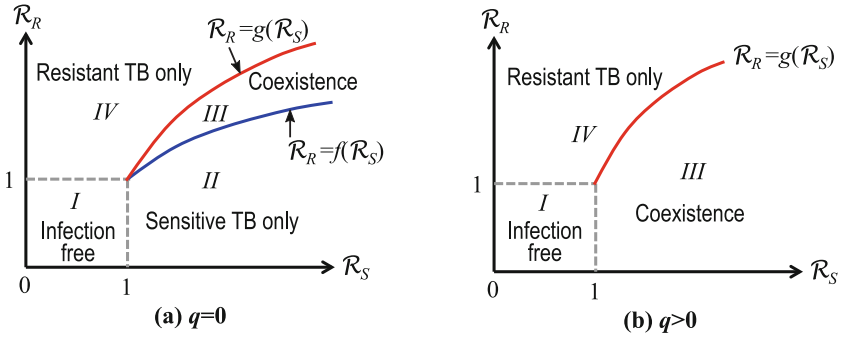

Fig. 7.4 (**a**) A bifurcation diagram for the system in the case $q = 0$. There are four Regions I, II, III, and IV in the parameter space $(\mathcal{R}_S, \mathcal{R}_R)$. In Region I, E_0 is a global attractor and other equilibria are unstable when they exist. In Regions II and IV, E^* does not exist, while E_1 and E_2 are locally asymptotically stable, respectively. In Region III, E^* exists and is locally asymptotically stable . (**b**) A bifurcation diagram for the system in the case $q > 0$. There are three Regions I, III, and IV in the parameter space $(\mathcal{R}_S, \mathcal{R}_R)$ (E_1 does not exist), in which E_0, E_2, and E^* are stable, respectively

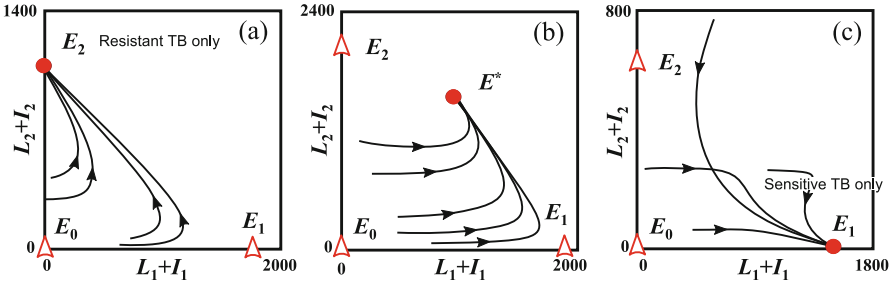

Fig. 7.5 Phase portraits of solutions to (7.4) in the case of $q = 0$. The choice of parameter values gives a fixed value $\mathcal{R}_S = 3.45$. In (**a**) $\mathcal{R}_R = 2$ and $(\mathcal{R}_S, \mathcal{R}_R) \in$ IV. In (**b**) $\mathcal{R}_R = 2.4$ and $(\mathcal{R}_S, \mathcal{R}_R) \in$ III. In (**c**) $\mathcal{R}_R = 1.2$ and $(\mathcal{R}_S, \mathcal{R}_R) \in$ II. A circle indicates a stable equilibrium, and a triangle indicates an unstable equilibrium

Theorem 7.2 *Assume that $q > 0$. Let Regions I–III be as in Fig. 7.4b.*

(a) The disease-free equilibrium E_1 is g.a.s. if $\mathcal{R}_S < 1$ and $\mathcal{R}_R < 1$ (Region I).
(b) For $\mathcal{R}_R > 1$, the boundary equilibrium E_2 is locally asymptotically stable if $\mathcal{R}_S < 1$ or if $\mathcal{R}_S > 1$ and $\mathcal{R}_R > g(\mathcal{R}_S)$ (Region IV). E_2 is unstable if $\mathcal{R}_S > 1$ and $\mathcal{R}_R < g(\mathcal{R}_S)$ (Region III).
(c) The equilibrium E_3 exists and is locally asymptotically stable iff $\mathcal{R}_S > 1$ and $\mathcal{R}_R < g(\mathcal{R}_S)$ (Region III).

Figure 7.5 shows some simulation results of the model in the case of $q = 0$, illustrating the disease outcomes for $(\mathcal{R}_S, \mathcal{R}_R)$ in different regions as shown in Fig. 7.4a. In this figure, the parameter values used are $\mu = 0.143, c_1 = 13, \kappa_1 = 1, q = 0, p = 0.5, r_1 = 1, r_2 = 2, \kappa_2 = 1$. For this set of values, $\mathcal{R}_S = 3.45$.

Figure 7.5a–c corresponds to different values of $\mathscr{R}_R$ (or equivalently c_2), for which $(\mathscr{R}_S, \mathscr{R}_R)$ is in Regions IV, III, and II, respectively.

These results demonstrate that lack of drug treatment compliance by TB patients may have an important implication for the maintenance of antibiotic resistant strains. 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 ($q = 0$). In this last situation, we found that coexistence is possible but rare while later we noticed that coexistence is almost certain when the second strain is the result of antibiotic resistance. In our two-strain model there is a superinfection-like term $c_2 L_1 I_2/N$. Is this necessary to obtain the coexistence result because it is well known that superinfection can cause coexistence (see [16, 18])? The answer is no. In fact, it can be shown that in the absence of the superinfection-like term coexistence is still almost the rule when the second strain is the result of antibiotic resistance (see Fig. 7.4).

7.3 Optimal Treatment Strategies

Analysis of the two-strain model in Sect. 7.2 demonstrated that treatment may facilitate the spread of resistant TB and increase the level of TB prevalence. Thus, the effort levels devoted to treating latent and infectious TB individuals may lead to different outcomes.

Let $u_1(t)$ and $u_2(t)$ denote the time-dependent control efforts, which represent the fractions of individuals in L_1 and I_1 classes receiving prophylaxis and drug treatment, respectively, at time t. The state system with controls $u_1(t)$ and $u_2(t)$ reads:

$$\begin{aligned}
S' &= \mu N - c_1 S\frac{I_1}{N} - c_2 S\frac{I_2}{N} - \mu S,\\
L_1' &= c_1 S\frac{I_1}{N} - (\mu+\kappa_1)L_1 - u_1(t) r_1 L_1\\
&\quad +(1-u_2(t))pr_2 I_1 + c_1^* T\frac{I_1}{N} - c_2 L_1\frac{I_2}{N},\\
I_1' &= \kappa_1 L_1 - \mu I_1 - r_2 I_1,\\
L_2' &= (1-u_2(t))qr_2 I_1 - (\mu+\kappa_2)L_2 + c_2(S+L_1+T)\frac{I_2}{N},\\
I_2 &= \kappa_2 L_2 - \mu I_2,\\
T' &= u_1(t) r_1 L_1 + \big[1-\big(1-u_2(t)\big)(p+q)\big]r_2 I_1 - c_1^* T\frac{I_1}{N} - c_2 T\frac{I_2}{N} - \mu T,
\end{aligned} \tag{7.8}$$

with initial values $S(0), L_1(0), I_1(0), L_2(0), I_2(0), T(0)$.

The control functions, $u_1(t)$ and $u_2(t)$, are bounded, *Lebesgue* integrable functions. The "case-finding" control, $u_1(t)$, represents the fraction of typical TB latent individuals that is identified and will be put under treatment (to reduce the number of individuals that may be infectious). The coefficient, $1-u_2(t)$, represents the effort that prevents the failure of the treatment in the typical TB infectious individuals (to reduce the number of individuals developing resistant TB). When the "case-holding" control $u_2(t)$ is near 1, there is low treatment failure and high implementation costs.

Our objective function to be minimized is

$$J(u_1,u_2)=\int_0^{t_f}\left[L_2(t)+I_2(t)+\frac{B_1}{2}u_1^2(t)+\frac{B_2}{2}u_2^2(t)\right]dt, \tag{7.9}$$

where we want to minimize the latent and infectious groups with resistant-strain TB while also keeping the cost of the treatments low. We assume that the costs of the treatments are nonlinear and take quadratic form here. The coefficients, B_1 and B_2, are balancing cost factors due to size and importance of the three parts of the objective functional. We seek to find an optimal control pair, u_1^* and u_2^*, such that

$$J(u_1^*,u_2^*)=\min_{\Omega} J(u_1,u_2), \tag{7.10}$$

where $\Omega=\{(u_1,u_2)\in L^1(0,t_f)\mid a_i\le u_i\le b_i, i=1,2\}$ and a_i and b_i, $i=1,2$, are fixed positive constants.

The necessary conditions that an optimal pair must satisfy come from Pontryagin's maximum principle [19]. This principle converts (7.8)–(7.10) into a problem of minimizing pointwise a Hamiltonian, H, with respect to u_1 and u_2:

$$H=L_2+I_2+\frac{B_1}{2}u_1^2+\frac{B_2}{2}u_2^2+\sum_{i=1}^{6}\lambda_i g_i, \tag{7.11}$$

where g_i is the right-hand side of the differential equation of the ith state variable. By applying Pontryagin's maximum principle [19] and the existence result for the optimal control pairs from [13], we know that there exists an optimal control pair u_1^*, u_2^* and corresponding solution, S^*, L_1^*, I_1^*, L_2^*, I_2^*, and T^*, that minimizes $J(u_1,u_2)$ over Ω. Furthermore, there exist adjoint functions, $\lambda_1(t),\ldots,\lambda_6(t)$, such that

$$\lambda_1'=\lambda_1(c_1\frac{I_1^*}{N}+c_1^*\frac{I_2^*}{N}+\mu)+\lambda_2(-c_1\frac{I_1^*}{N})+\lambda_4(-c_1^*\frac{I_2^*}{N}),$$

$$\lambda_2'=\lambda_2(\mu+\kappa_1+u_1(t)r_1+c_1^*\frac{I_2^*}{N})+\lambda_3(-\kappa_1)+\lambda_4(-c_1^*\frac{I_2^*}{N})+\lambda_6(-u_1^*(t)r_1),$$

$$\lambda_3'=\lambda_1(c_1\frac{S^*}{N})+\lambda_2(-c_1\frac{S^*}{N}-(1-u_2^*(t))pr_2-c_2\frac{T^*}{N})+\lambda_3(\mu+r_2)$$

$$+\lambda_4(-(1-u_2^*(t))qr_2)+\lambda_6(-(1-(1-u_2^*(t))(p+q))r_2+c_2\frac{T^*}{N}),$$

$$\lambda_4' = -1+\lambda_4(\mu+\kappa_2)+\lambda_5(-\kappa_2),$$

$$\lambda_5' = -1+\lambda_1(c_1^*\frac{S^*}{N})+\lambda_2(c_1^*\frac{L_1^*}{N})-\lambda_4(\beta^*\frac{S^*+L_1^*+T^*}{N})+\lambda_5\mu+\lambda_6(c_1^*\frac{T^*}{N}),$$

$$\lambda_6' = \lambda_2(-c_2\frac{I_1^*}{N})+\lambda_4(-c_1^*\frac{I_2^*}{N})+\lambda_6(c_2\frac{I_1^*}{N}+c_1^*\frac{I_2^*}{N}+\mu), \tag{7.12}$$

with transversality conditions

$$\lambda_i(t_f)=0, \quad i=1,\ldots,6 \tag{7.13}$$

and $N = S^* + L_1^* + I_1^* + L_2^* + I_2^* + T^*$. Moreover, the characterization holds:

$$\begin{aligned} u_1^*(t) &= \min\left(\max(a_1, \tfrac{1}{B_1}(\lambda_2-\lambda_6)r_1L_1^*), b_1\right)\\ u_2^*(t) &= \min\left(\max(a_2, \tfrac{1}{B_2}(\lambda_2 p+\lambda_4 q-\lambda_6(p+q)r_2I_1^*)), b_2\right). \end{aligned} \tag{7.14}$$

Due to the a priori boundedness of the state and adjoint functions and the resulting Lipschitz structure of the ODEs, we obtain the uniqueness of the optimal control for small t_f. The uniqueness of the optimal control follows from the uniqueness of the optimality system, which consists of (7.8) and (7.12)–(7.14). There is a restriction on the time interval in order to guarantee the uniqueness of the optimality system. This smallness restriction on the length on the time interval is due to the opposite time orientations of (7.8), (7.12), and (7.13); the state problem has initial values and the adjoint problem has final values. This restriction is very common in control problems (see [12, 15]).

The optimal treatment is obtained by solving the optimality system, consisting of the state and adjoint equations. An iterative method is used for solving the optimality system. We start to solve the state equations with a guess for the controls over the simulated time using a forward fourth-order Runge–Kutta scheme. Because of the transversality conditions (7.13), the adjoint equations are solved by a backward fourth-order Runge–Kutta scheme using the current iteration solution of the state equations. Then, the controls are updated by using a convex combination of the previous controls and the value from the characterizations (7.14). This process is repeated and iteration is stopped if the values of unknowns at the previous iteration are very close to the ones at the present iteration.

For the figures presented here, we assume that the weight factor B_2 associated with control u_2 is greater than or equal to B_1 which is associated with control u_1. This assumption is based on the following facts: The cost associated with u_1 will include the cost of screening and treatment programs, and the cost associated with u_2 will include the cost of holding the patients in the hospital or sending people to watch the patients to finish their treatment. Treating an infectious TB individual takes longer (by several months) than treating a latent TB individual. In these three

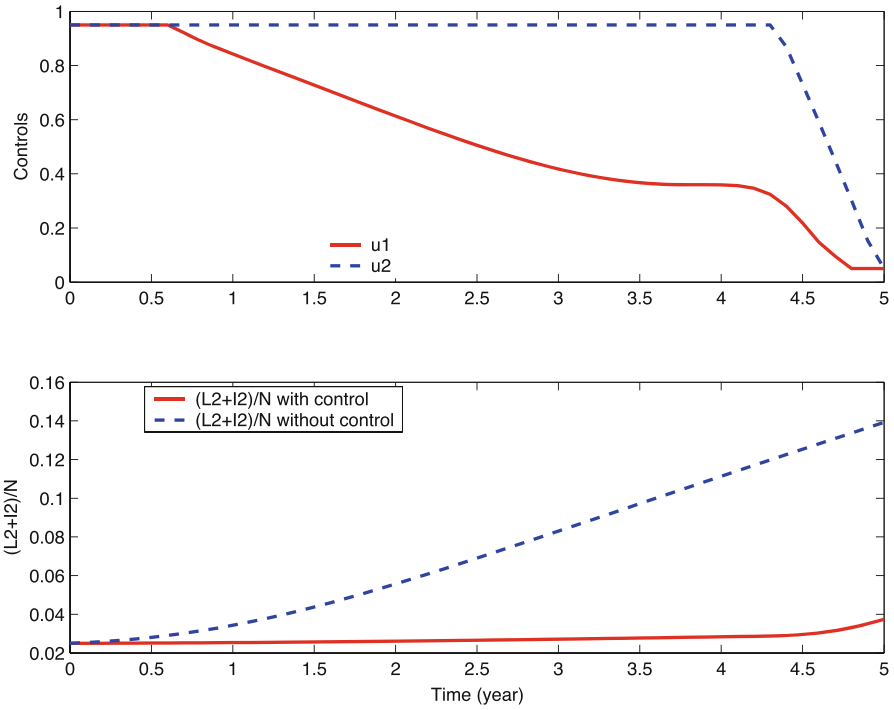

Fig. 7.6 The optimal control strategy for the case of $B_1 = 50$ and $B_2 = 500$

figures, the set of the weight factors, $B_1 = 50$ and $B_2 = 500$, is chosen to illustrate the optimal treatment strategy. Other epidemiological and numerical parameters are presented in [14].

In the top frame of Fig. 7.6, the controls, u_1 (solid curve) and u_2 (dashdot curve), are plotted as a function of time. In the bottom frame, the fractions of individuals infected with resistant TB, $(L_2 + I_2)/N$, with control (solid curve) and without control (dashed curve) are plotted. Parameters $N = 30{,}000$ and $\beta^* = 0.029$ are chosen. Results for other parameters are presented in [14]. To minimize the total number of the latent and infectious individuals with resistant TB, $L_2 + I_2$, the optimal control u_2 is at the upper bound during almost 4.3 years and then u_2 is decreasing to the lower bound, while the steadily decreasing value for u_1 is applied over the most of the simulated time, 5 years. The total number of individuals $L_2 + I_2$ infected with resistant TB at the final time $t_f = 5$ (years) is 1123 in the case with control and 4176 without control, and the total number of cases of resistant TB prevented at the end of the control program is 3053 $(= 4176 - 1123)$.

In Fig. 7.7, the controls, u_1 and u_2, are plotted as a function of time for $N = 6000$, 12,000, and 30,000 in the top and bottom frame, respectively. Other parameters except the total number of individuals and $c_1^* = 0.029$ are fixed for

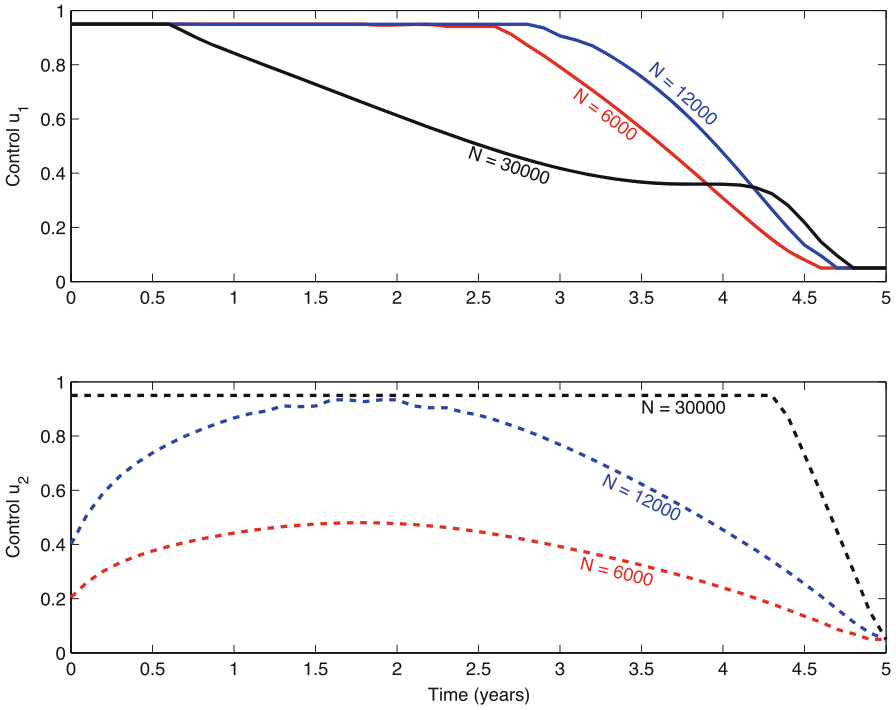

Fig. 7.7 The controls, μ_1 and μ_2, are plotted as a function of time for $N = 6000$, 12,000, and 30,000 in the top and bottom frame, respectively

these three cases. These results show that more effort should be devoted to "case-finding" control u_1 if the population size is small, but "case-holding" control u_2 will play a more significant role if the population size is big. Note that, in general, with B_1 fixed, as B_2 increases, the amount of u_2 decreases. A similar result holds if B_2 is fixed and B_1 increases.

In conclusion, our optimal control results show how a cost-effective combination of treatment efforts (case holding and case finding) may depend on the population size, cost of implementing treatments controls, and the parameters of the model. We have identified optimal control strategies for several scenarios. Control programs that follow these strategies can effectively reduce the number of latent and infectious resistant-strain TB cases.

7.4 Modeling of the Long and Variable Latency of TB

As indicated in Figs. 7.1 and 7.2, the latent period of TB can range from a couple of years to lifetime. One of the approaches to incorporate this feature is to divide latent individuals into two classes based on the rates of progression to the disease stage,

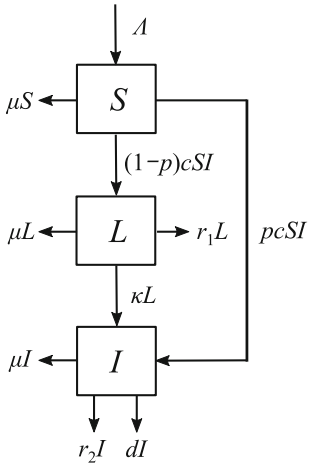

Fig. 7.8 A transition diagram of TB with fast and slow progressions [3]

with one class having a faster progression than the other. For example, based on the transition diagram shown in Fig. 7.8, Blower et al. considered the following model in [3]:

$$\begin{aligned} S' &= \Lambda - cSI - \mu S, \\ L' &= (1-p)cSI - (\kappa + r_1 + \mu)L, \\ I' &= pcSI + \kappa L - (r_2 + \mu + d)I, \\ C' &= r_1 L - \mu C, \\ T' &= r_2 I - \mu T, \end{aligned} \tag{7.15}$$

which includes five epidemiological classes: susceptible (S), latently infected (L), infectious (I), effectively chemoprophylaxed (C), and effectively treated (T). The model assumes that a fraction p of the newly infected individuals will become infectious within 1 year (fast progression, $p \approx 0.05$), while the remaining $1 - p$ fraction of newly infected individuals will enter the latent stage first and develop active TB at a rate κ (slow progression, approximately 1/20 (years)). The model suggests that for fast progression, an infected individual enters the infectious class I immediately. The parameters r_1 and r_2 denote the rates of prophylaxis and treatment, respectively. The per-capita natural and disease mortalities are μ and d, respectively.

The control reproduction number of the model (7.15) is

$$\mathscr{R}_C = \mathscr{R}_C^{\text{fast}} + \mathscr{R}_C^{\text{slow}}, \tag{7.16}$$

where

$$\mathscr{R}_C^{\text{fast}} = \left(\frac{cp\Lambda}{\mu}\right)\left(\frac{1}{r_2 + \mu + d}\right)$$

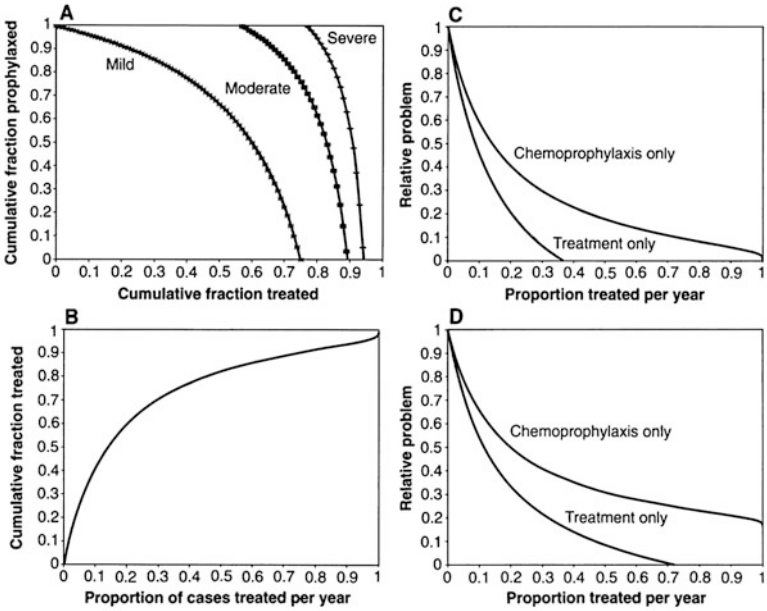

Fig. 7.9 Plots of the curve $\mathscr{R}_C = 1$ for severity levels of mild, moderate, and severe, which correspond to the basic reproduction number $\mathscr{R}_0$ values of 4, 9, and 17, respectively [3]

and

$$\mathscr{R}_C^{\text{slow}} = \Big(\frac{c(1-p)\Lambda}{\mu}\Big)\Big(\frac{\kappa}{r_1+\kappa+\mu}\Big)\Big(\frac{1}{r_2+\mu+d}\Big)$$

represent the reproduction numbers associated with the fast and slow paths, respectively. The formula (7.16) can be used to evaluate the possibility to eradicate tuberculosis either by treatment alone or by a combination of treatment and chemoprophylaxis, as demonstrated in Fig. 7.9 (adopted from [3]).

To investigate the role of treatment failure for drug-sensitive (DS) cases in the prevalence of drug-resistant (DR) TB, Blower et al. [3] extended the one-strain TB model (7.15) to include a drug-resistant strain as follows:

$$\begin{aligned}
S' &= \Lambda - \Big(c_S I_S + c_R I_R\Big)S - \mu S,\\
L_S' &= (1-p)c_S I_S S - (r_1+\kappa+\mu)L_S,\\
I_S' &= pc_S I_S S + \kappa L_S - (r_2+\mu+d)I_S,\\
C_S' &= r_1 L_S - \mu C_S,\\
T_S' &= r_2(1-q)I_S - \mu T_S,\\
L_R' &= (1-p)c_R I_R S - (\kappa+\mu)L_R,\\
I_R' &= pc_R I_R S + qr_2 I_S + \kappa L_R - (r_2\delta+\mu+d)I_R,\\
T_R' &= \delta r_2 T_R - \mu T_R,
\end{aligned} \tag{7.17}$$

where the epidemiological classes associated with the DS and DR tuberculosis are indicated by the subscripts S and R, respectively. The parameter q represents the fraction of treatment failure for DS tuberculosis that leads to the development of DR tuberculosis, and the parameter δ denotes the relative effectiveness of treatment for a resistant case.

Blower et al. [3] showed that the model (7.17) can help gain insights into the impact of treatment failure (q) on the development of DR tuberculosis.

Another approach to incorporate the long and variable latency is to consider an arbitrarily distributed latency, in which case the model consists of a system of integro-differential equations. Examples can be found in [10, 11]. It is shown in [10] that the model with a distributed latency has the same dynamical behavior as the ODE model, although it can provide a more detailed description for the reproduction number as it involves a more realistic distribution of the latent period. The model considered in [11] includes both DS and DR strains with infection age-dependent progression (e.g., the progression distribution shown in Fig. 7.2).

7.5 Backward Bifurcation in a TB Model with Reinfection

As mentioned earlier, the latent period of TB can be as long as many years and even lifetime. Re-exposure to TB bacilli through repeated contacts with individuals with active TB may accelerate the progression of LTBI towards active TB, and exogenous reinfection (i.e., acquiring a new infection from another infected individual) may occur. To investigate the impact of exogenous reinfection in the spread and control of TB, we can extend the one-strain model (7.1) by incorporating the exogenous reinfection. It is demonstrated in [9] that exogenous reinfection may play a fundamental role in the transmission dynamics and the epidemiology of TB at the population level. Particularly, the model is capable of exhibiting a backward bifurcation, i.e., a stable endemic equilibrium can exist even when the reproduction number is less than 1. Although some studies (e.g., see [23]) find that, for parameter values in a certain range, the onset of the backward bifurcation is unlikely to occur, other scenarios are possible in which the conditions for backward bifurcation can be satisfied. In either case, it is helpful to know that exogenous reinfection may play an important role in TB dynamics, which can be critical for the design of control programs for TB.

An extension of the one-strain model (7.1) when reinfection is included takes the form:

$$\begin{aligned} S' &= \mu N - cS\frac{I}{N} - \mu S, \\ L' &= cS\frac{I}{N} + c^*T\frac{I}{N} - pcL\frac{I}{N} - (\kappa+\mu)L, \\ I' &= pcL\frac{I}{N} + \kappa L - (r+\mu)I, \\ T' &= rI - c^*T\frac{I}{N} - \mu T. \end{aligned} \tag{7.18}$$

The model (7.18) ignores the treatment of latent individuals and only infectious individuals may receive treatment at the rate r. The parameter p is a factor reflecting the difference between primary infections (infection from susceptibles) and exogenous reinfections (infection from latent individuals). A value of $p \in (0, 1)$ implies that a primary infection provides some degree of cross-immunity to exogenous reinfections. Other parameters have the same meaning as in (7.1).

The reproduction number for (7.18) is

$$\mathscr{R}_0 = \frac{c\kappa}{(\kappa + \mu)(r + \mu)}. \tag{7.19}$$

The usual result that the disease-free equilibrium is locally asymptotically stable when $\mathscr{R}_0 < 1$ still holds. However, the usual result that there is no endemic equilibrium when $\mathscr{R}_0 < 1$ no longer holds. To show that an endemic equilibrium may exist when $\mathscr{R}_0 < 1$, consider the simpler case when $c^* = c$. Let $U^* = (S^*, L^*, I^*, T^*)$ denote an endemic equilibrium, i.e., $I^* > 0$. Let $x = I^*/N$, then

$$\frac{S^*}{N} = \frac{\mu}{\mu + cx^*}, \quad \frac{L^*}{N} = \frac{(\mu + r)x^*}{\kappa + pcx^*}, \quad \frac{T^*}{N} = \frac{rx}{\mu + cx},$$

and x^* is a solution of the quadratic equation

$$Ax^2 + Bx + C = 0, \tag{7.20}$$

where

$$A = p\mathscr{R}_0, \quad B = (1 + p + Q)D_E - p\mathscr{R}_0, \quad C = D_E Q\Big(\frac{1}{\mathscr{R}_0} - 1\Big),$$

and $D_E = \kappa/(\mu+\kappa)$ and $Q = \kappa/(\mu+r)$. Note that $D_E < 1$ denotes the probability that a latent individual survives and becomes infective. Let

$$\mathscr{R}_p = \frac{1}{p}\Big(D_E(1 + p - Q) + s\sqrt{D_E Q(p - pD_E - D_E)}\Big) \tag{7.21}$$

and

$$p_0 = \frac{(1 + Q)D_E}{1 - D_E}. \tag{7.22}$$

Then $\mathscr{R}_p < 1$ if $p > p_0$, and $B^2 - 4AC > (=, <)\, 0$ if $\mathscr{R}_0 > (=, <)\, \mathscr{R}_p$, in which case Eq. (7.20) has two (one, none) positive solutions $x_\pm$ (see [9] for more detailed proofs). This establishes the following result:

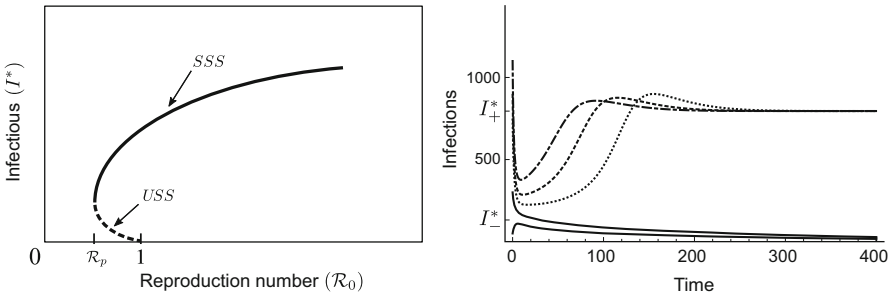

Fig. 7.10 The left plot is a depiction of the backward bifurcation for the model with reinfection (7.18). The I^* component of an equilibria is plotted as a function of $\mathcal{R}_0$. The curve demonstrates that there are two positive steady states for $\mathcal{R}_p < \mathcal{R}_0 < 1$. The solid part of the curve corresponds to the stable steady state (SSS) and the dashed part corresponds to the unstable steady state (USS). The right figure shows the numerical solutions of system (7.18) for parameter values in the region where the backward bifurcation occurs ($\mathcal{R}_p < \mathcal{R}_0 < 1$ and $p > p_0$). The number of infectious individuals $I(t)$ is plotted. It illustrates that, depending on the initial conditions, the solution will converge to either the infection-free equilibrium (the solid curves) or the stable positive equilibrium (dashed curves)

Theorem 7.3 *Let $\mathcal{R}_0$, $\mathcal{R}_p$, and p_0 be as defined in* (7.19), (7.21), *and* (7.22).

(a) If $\mathcal{R}_0 > 1$, then system (7.18) *has exactly one endemic equilibrium and it is locally asymptotically stable*

(b) If $\mathcal{R}_0 < 1$, then the disease-free equilibrium is locally asymptotically stable Moreover,

(i) for each $p > p_0$ there exists a positive constant $\mathcal{R}_p < 1$ such that system (7.18) *has exactly two (one, none) positive equilibria when $\mathcal{R}_0 > (=, <)\ \mathcal{R}_p$. In the case of two positive equilibria, the one with large (smaller) I^* component is stable (unstable), as depicted in Fig. 7.10 (left).*

(ii) for $p = (<) p_0$, system (7.18) *has exactly one (no) positive equilibrium.*

Numerical simulations of the model (7.18) confirm the backward bifurcation. Figure 7.10 (right) shows the I component of the solutions with different initial values in the case $p > p_0$ and $\mathcal{R}_p < \mathcal{R}_0 < 1$. We observe that solutions with initial I values near 0 converge to the disease-free steady state (see the solid curves), whereas other solutions converge to the endemic steady state with a larger I value (see the dashed curves).

7.6 Other TB Models with More Complexities

The models considered above assume homogeneity in several aspects including mixing and age structure of the population. In many cases, the problems under investigation require the consideration of some of the heterogeneities. For example,

in [1] TB models involving non-homogeneous mixing that incorporates "household" contacts and age-dependent mixing are considered to assess the possible causes for the observed historical decline of tuberculosis notifications. In [5], an age-structured TB model is used to study optimal age-dependent vaccination strategies $\psi(a)$, where a denotes the chronological age of an individual. One of the optimal control problems is to minimize the reproduction number corresponding to $\psi(a)$, $\mathscr{R}_\psi$, under the constraint on the cost $C(\psi) < C^*$, where C^* is a fixed constant. Results suggest that the optimal vaccination strategy is either a one-age strategy (vaccinate every one at a single age A determined by the parameter and parameter functions in the model) or two-age strategy (vaccinate the population at two fixed ages A_1 and A_2 determined by model parameters).

Models with multiple resistant strains have been used to answer various questions associated with the establishment and spread of drug-resistant TB. Blower and Chou [2] use a model with three strains of resistant TB to study how to effectively control MDR-TB in "hot zones" (i.e., areas that have $> 5\%$ prevalence of MDR-TB). The findings of the model suggest that the levels of MDR are driven by case-finding rates, cure rates, and amplification probabilities (the probability that a case will develop further resistance during treatment). In [7], heterogeneity in the relative fitness of MDR strains is incorporated in a TB model. The model includes two resistant strains (one is more fit than the other), as well as a drug-sensitive strain, and is used to study the impact of initial fitness estimates on the emergence of MDR-TB. The model results show that "even when the average relative fitness of MDR strains is low and a well-functioning control program is in place, a small sub-population of a relatively fit MDR strain may eventually outcompete both the drug-sensitive strains and the less fit MDR strains."

A two-strain TB model with reinfection is considered in [21] to study the role of reinfection in the transmission dynamics of drug-resistant TB and the coexistence of sensitive and resistant strains of TB. In [17] multiple sub-populations are considered with one sub-population being genetically susceptible to TB. Different strategies involving treatment of latent TB infections and active TB disease are examined and in different populations are examined. Results from the model analysis suggest that the presence of a genetically susceptible sub-population dramatically alters effects of treatment. To study the impact of treatment failure and its influence in the criteria for the control of drug-resistant TB, a model with multiple stages of treatment failure with different probabilities of leading to resistant TB is considered in [8]. Model results indicate that case detection and treatment can be a critical factor in the control of MDR-TB.

To explore the influence of HIV on TB prevalence, models including the interaction between TB and HIV can be used, in which case the model analysis can be very challenging due to the possible coinfections of TB and HIV. For example, a model incorporating both TB and HIV with multiple stages of HIV is studied in [20]. The model results suggest that "an HIV epidemic can significantly increase the

frequency and severity of tuberculosis outbreaks, but that this amplification effect of HIV on tuberculosis outbreaks is very sensitive to the tuberculosis treatment rate." Another model that includes both TB and HIV is studied in [22]. The model results suggest that the accelerated progression from LTBI to active TB in individuals co-infected with HIV can have a significant influence in TB prevalence.

7.7 Project: Some Calculations for the Two-Strain Model

Exercise 1 Derive the formulas of the reproduction numbers $\mathscr{R}_S$ and $\mathscr{R}_R$ given in (7.5) and (7.6), respectively, for the two-strain TB model (7.4) by considering the stability of the disease-free equilibrium

$$E_0 = \left(S^{(0)}, L_1^{(0)}, I_1^{(0)}, L_2^{(0)}, I_2^{(0)}, T^{(0)}\right) = (N, 0, 0, 0, 0, 0).$$

The Jacobian a E_0 is

$$J(E_0) = \begin{bmatrix} -\mu & 0 & -c_1 & 0 & -c_2 & 0 \\ 0 & -(\mu+\kappa_1+r_1) & c_1+pr_2 & 0 & 0 & 0 \\ 0 & \kappa_1 & -(\mu+r_2) & 0 & 0 & 0 \\ 0 & 0 & qr_2 & -(\mu+\kappa_2) & c_2 & 0 \\ 0 & 0 & 0 & \kappa_2 & -\mu & 0 \\ 0 & r_1 & (p+q)r_2 & 0 & 0 & -\mu \end{bmatrix}.$$

Clearly, $J(E_0)$ has the negative eigenvalues μ with multiplicity 2, and other eigenvalues are given by the eigenvalues of J_1 and J_2, where

$$J_1 = \begin{bmatrix} -(\mu+\kappa_1+r_1) & c_1+pr_2 \\ \kappa_1 & -(\mu+r_2) \end{bmatrix}, \quad J_2 = \begin{bmatrix} -(\mu+\kappa_2) & c_2 \\ \kappa_2 & -\mu \end{bmatrix}.$$

Show that J_1 has negative eigenvalues if and only if $\mathscr{R}_S < 1$ and J_2 has negative eigenvalues if and only if $\mathscr{R}_R < 1$.

Exercise 2 Consider the two-strain TB model (7.4) and conduct numerical simulations of the system for parameter values specified below. Given the parameter values $\mu = 0.0143$ (or $1/\mu = 70$), $c_1 = 13$, $\kappa_1 = \kappa_2 = 1$, $r_1 = 1$, $r_2 = 2$, $q = 0$, $p = 0.5$. Choose the values of c_2 such that

(a) E_1 is stable;
(b) E_2 is stable;
(c) E^* is stable.

Exercise 3 Similar to Exercise 2 but for the case when $q > 0$. Given the same values for other parameters as in Exercise 2, and choose the values of c_2 such that

(a) E_2 is stable;
(b) E^* is stable.

7.8 Project: Refinements of the One-Strain Model

The model (7.1) is a one-strain model for TB, which assumes that infected people stay in the latent stage L before entering the infective stage I. The model (7.15) includes fast and slow progression (represented by p and $1-p$, respectively), which assumes that with fractions $1-p$ and p infected individuals will enter the latent L and infectious I stages, respectively. In both models, the stage duration is assumed to be exponentially distributed with parameter k. That is, the probability that an infected individual has not become infective s units of time after infection is e^{-ks}. This assumption may not be appropriate for TB due to the long and variable latency, as shown in Figs. 7.1 and 7.2. To examine whether or not a model with a more realistic assumption on the distribution of latent period, we can consider a model in which the exponential survival function e^{-ks} is replaced by a general distribution $p(s)$, as described below.

Let $p(s)$ be a function representing the proportion of those individuals latent at time t and who, if alive, are still infected (but not infectious) at time $t+s$. Then $-\dot{p}(\tau)$ is the rate of removal of individuals from E class into I class τ units of time after becoming latent. Assume that

$$p(s) \geq 0, \quad \dot{p}(s) \leq 0, \quad p(0) = 1, \quad \int_0^\infty p(s)ds < \infty.$$

Let $S(t)$, $E(t)$, $I(t)$, and $T(t)$ denote the number of individuals in the susceptible, latent, infectious, and treated classes, respectively. Consider the following model with $p(s)$ being the arbitrary distribution of the latent stage:

$$\begin{aligned}
S' &= \Lambda - cS\tfrac{I}{N} - \mu S,\\
E(t) &= E_0(t) + \int_0^t \left[cS(s) + c^*T(s)\right]\frac{I(s)}{N(s)}p(t-s)e^{-(\mu+r_1)(t-s)}ds,\\
I(t) &= \int_0^t \int_0^\tau \left[cS(s) + c^*T(s)\right]\frac{I(s)}{N(s)}e^{-(\mu+r_1)(\tau-s)}\\
&\qquad \times[-\dot{p}(\tau-s)e^{-(\mu+r_2)(t-\tau)}]ds\,d\tau + I_0e^{-(\mu+r_2)t} + I_0(t),\\
T' &= r_1E + r_2I - c^*T\tfrac{I}{N} - \mu T,\\
N &= S + E + I,
\end{aligned} \tag{7.23}$$

where $E_0(t)$ denotes those individuals in E class at time $t = 0$ and still in the latent class, $I_0(t)$ denotes those initially in class E who have moved into class I and are still alive at time t, and $I_0 e^{-(\mu+r_2)t}$ with $I_0 = I(0)$ represents those who are infective at time 0 and are still alive and in I class. $E_0(t)$ and $I_0(t)$ are assumed to have compact support (that is, they vanish for large enough t). All other parameters have the same meanings as in model (7.1).

Question 1 Derive the formula below for the reproduction number $\mathscr{R}_0$

$$\mathscr{R}_0 = c \int_0^\infty a(\tau) d\tau, \tag{7.24}$$

where $a(u)$ is defined by

$$a(t-s) = \int_s^t e^{-(\mu+r_1)(\tau-s)}[-\dot{p}(\tau-s)e^{-(\mu+r_2)(t-\tau)}]d\tau.$$

Provide biological interpretations for the $a(u)$ and the factors in the expression of $a(u)$.

Question 2 Show that the disease will die out if $\mathscr{R}_0 < 1$ and persist if $\mathscr{R}_0 > 1$.

Question 3 Find all biologically feasible steady-state solutions of the model (7.23). Determine the condition for the existence of a coexistence steady state (i.e., $I > 0$ and $J > 0$).

Question 4 For each steady state, identify the conditions under which the steady state is locally asymptotically stable.

Question 5 Does the model with a more realistic distribution for the latent stage provide new qualitative behavior of the disease dynamics in comparison with the ODE model (7.1)? Identify the additional insights that the model (7.23) can provide.

7.9 Project: Refinements of the Two-Strain Model

Model (7.4) is a two-strain model for TB with drug-sensitive and drug-resistant strains. In this model, the latent stages for both strain are assumed to be exponentially distributed with parameters κ_1 and κ_2. The long and variable latency for the sensitive strain make this assumption unrealistic (the latent period for the resistant strain is much shorter). The model below is an alternative two-strain model with distributed delay in latency, in which $p(\theta)$ is used to describe the progression from latent stage to infectious stage and θ is the age of infection (time since becoming infected):

$$\begin{aligned}
\frac{dS}{dt} &= \mu N - (\mu + \lambda_1(t) + \lambda_2(t))\, S + (1-r)\chi \int_0^\infty p(\theta) i(\theta, t) d\theta, \\
&\frac{\partial i}{\partial t} + \frac{\partial i}{\partial \theta} + \mu\, i(\theta, t) + (1 - r + qr)\chi p(\theta) i(\theta, t) = 0, \qquad (7.25) \\
\frac{dJ}{dt} &= \lambda_2(t) S - \mu J + qr\chi \int_0^\infty p(\theta) i(\theta, t) d\theta, \\
i(0, t) &= \lambda_1(t) S(t), \quad S(0) = S_0 > 0, \quad i(\theta, 0) = i_0(\theta) \geq 0, \quad J(0) = J_0 > 0.
\end{aligned}$$

$S(t)$ is the number of susceptibles at time t; $i(\theta, t)$ denotes the density of infection age θ individuals with the drug-sensitive strain at time t; $J(t)$ is the number of infected individuals with a drug-resistant strain at time t; and $N = S + I + J$, where

$$I(t) = \int_0^\infty i(\theta, t) d\theta$$

is the total number of individuals infected with the sensitive strain. The function $p(\theta)$ $(0 \leq p(\theta) \leq 1)$ is assumed constant in time and is based on experimental data (e.g., the distribution in Fig. 7.2). Note that $p(\theta) i(\theta, t)$ represents the age density of infectious individuals. The transmission rates of sensitive and resistant strains are

$$\lambda_1(t) = \frac{c_1}{N(t)} \int_0^\infty p(\theta) i(\theta, t) d\theta \quad \text{and} \quad \lambda_2(t) = c_2 \frac{J(t)}{N(t)}, \qquad (7.26)$$

respectively, with c_1 and c_2 being the per-capita transmission rates of the sensitive and resistant strains. The rate at which sensitive-strain-infected individuals leave the i class due to treatment is $(1 - r + qr)\chi p(\theta)$, where χ denotes the treatment rate for individuals with drug-sensitive TB. The factor $(1 - r + qr)$ introduces the effect of incomplete treatment: a fraction r of the treated individuals with sensitive TB do not recover due to incomplete treatment, and the remaining fraction $1 - r$ is actually cured and becomes susceptible again. Moreover, 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 latent. The per-capita birth and natural death rates are assumed to be the same and equal to μ. In this model, for simplicity, treated individuals are assumed to have the same susceptibility.

Question 1 Let $v(t) = i(0, t) = \lambda_1(t) S(t)$. Show that system (7.25) is equivalent to the following system, which is easier to analyze:

$$
\begin{aligned}
v(t) &= \frac{N(t) - J(t) - \int_0^t K_0(\theta)v(t-\theta)d\theta}{N(t)} \int_0^t K_1(\theta)v(t-\theta)d\theta + \tilde{F}_1(t),\\
\frac{dJ}{dt} &= \beta_2 \left(N(t) - J(t) - \int_0^t K_0(\theta)v(t-\theta)d\theta \right) \frac{J(t)}{N(t)}\\
&\quad -mJ(t) + \int_0^t K_2(\theta)v(t-\theta)d\theta + \tilde{F}_2(t),\\
\frac{dN}{dt} &= b(N)N(t) - \mu N(t) - \delta J(t),
\end{aligned}
\tag{7.27}
$$

where $\tilde{F}_i(t)$ involve parameters and initial condition with $\lim_{t\to\infty} \tilde{F}_i(t) = 0$, $i = 1, 2$, and

$$
\begin{aligned}
K_0(\theta) &= e^{-\mu\theta - \int_0^\theta (1-r+qr)\chi p(s)ds},\\
K_1(\theta) &= \beta_1 p(\theta)K_0(\theta) = -\frac{\beta_1}{\chi(1-r+qr)} \left(\frac{d}{d\theta}K_0(\theta) + \mu K_0(\theta) \right),\\
K_2(\theta) &= qr\chi p(\theta)K_0(\theta) = -\frac{qr}{(1-r+qr)} \left(\frac{d}{d\theta}K_0(\theta) + \mu K_0(\theta) \right).
\end{aligned}
\tag{7.28}
$$

Question 2 Let $\mathscr{R}_1$ and $\mathscr{R}_2$ denote the reproduction numbers for the sensitive and resistant strains. Derive a formula for $\mathscr{R}_1$ and $\mathscr{R}_2$.

Question 3 Explore how the existence and stability of steady states of the model (7.25) depend on $\mathscr{R}_1$ and $\mathscr{R}_2$.

Question 4 Does the model with a more realistic distribution for the latent stage for the sensitive strain provide new qualitative behavior of the disease dynamics in comparison with the ODEs model (7.4)? Identify the additional insights that the model (7.25) may provide.

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