Drug Resistants Impact on Tuberculosis Transmission

SILVIA MARTORANO RAIMUNDO*
Universidade de São Paulo
Faculdade de Medicina
Rua Teodoro Sampaio 115, São Paulo, SP
BRASIL
silviamr@dim.fm.usp.br

EZIO VENTURINO
Università di Torino
Dipartimento di Matematica
via Carlo Alberto 10, 10123 Torino
ITALY
ezio.venturino@unito.it

Abstract: In epidemiology, measures for prophilaxis of infectious diseases are taken often using mathematical methods and statistical tools to evaluate possible future scenarios of the evolution of transmissible diseases. Here we present two models for TB transitions among different stages of the disease. We analyze them assuming to have a large basin of susceptible individuals available. The models account for immigration and demographic effects. A flow of infected members into the population is assumed. Part of it is made by a specified fraction is drug-sensitive latent individuals, while the other part consists of drug-resistant latent individuals. Our aim is the description and analysis of all the possible ways the infected individuals move. In particular, from the classes of latent to infectious, and possibly back upon successful treatment, or toward acute stages of the disease for drug resistant cases due to improper, incomplete or ineffective healing measures. Some conditions for the eradication of the disease are extracted from analytical considerations and simulation results and might be useful for epidemiological implementations.

Key–Words: Drug resistant, transmissible disease, tuberculosis.

1 Introduction

Tuberculosis (*TB)* is a bacterial disease that is caused by *Mycobacterium tuberculosis* (*MTB*). Although many people believe that *TB* is a scourge of the past, the disease is one of the most prevalent infections among humans and contributes considerably to illness and death around the world [29]. It is estimated that approximately one-third of the global population is infected with *MTB* and that seven to eight million new cases of tuberculosis occur each year [2, 3, 25]. Annual tuberculosis mortality is between two and three million people, making this disease the most common infectious cause of death in the world. According to the World Health Organization, more people died from *TB* in 1995 than in any other year in history. It has been estimated that, at current rates, up to one-half of a billion people will suffer from *TB* in the next 50 years.

Humans are the natural host for this pathogen, which is transmitted by respiratory route. Unlike most other infectious diseases, the course of *MTB* infection is unusual for bacterial pathogens, because it involves a delay between infection and disease that is extremely variable, ranging from a few weeks to a lifetime. Thus, *TB* is "typically" described as a slow disease. Following primary infection, only a small proportion of individuals develops the *TB* disease, most people remain in the latent stage of the disease. The infection can thus show no clinical symptoms for the lifetime of the host. Infected individuals develop active *TB* as a consequence of endogenous reactivation of latent bacilli or exogenous reinfection. However, the factors related to the disease progression are not still well described and a development of active *TB* raises the question whether that represents a reactivation of the initial infection (endogenous reactivation) or a new infection with *MTB* (exogenous reinfection, sometimes called super-infection or reinfection) [21, 27]. The relative importance of these two pathways to the development of active disease has significant implications for treatment and control strategies, most notably in deciding whether latently infected and treated individuals are at risk of reinfection [12].

The World Health Organization currently recommends, for all new cases of *TB,* standardized short-course chemotherapy based on a regimen of four first-line drugs taken for 6-8 months [18]. It is the mainstay of tuberculosis control worldwide. However, despite rapid progress in drug development, microbial infections in general are becoming increasingly difficult to treat as a result of the emergence of drug-resistant strains. Resistance to *TB* drug has been reported since the early days of the introduction of

*Work performed with the support of the WWS program of the University of Torino

chemotherapy. In spite of its global magnitude, the problem has not yet been adequately addressed. In the past decade it was revealed that some *MTB* strains are able to disseminate more quickly than others and, also, that multidrug-resistant tuberculosis (*MDR-TB)* may be one of the most important threats to *TB* control programs. The World Health Organization estimates that up to 50 million persons worldwide may be infected with drug-resistant strains of *TB*. Drug-resistant tuberculosis is produced by the selection of resistant strains in patients who fail to complete chemotherapy with the correct combination of drugs.

MDR-TB is a form of *TB* that is resistant to at least two drugs used for the treatment of *TB*, isoniazid and rifampicin. It is originally developed when a case of drug-susceptible *TB* is improperly or incompletely treated. Drug-resistant tuberculosis occurs when drug-resistant bacilli outgrow drug-susceptible bacilli. The drug-resistant organisms are produced by random mutations in the bacterial chromosomes. These mutations occur spontaneously in wild-type pansensitive strains even before the strains come in contact with an antituberculosis drug [8]. Studies have found that drug-resistance rates increase with a prolongued duration of the previous treatments [7]. Although persons previously treated for drug-sensitive tuberculosis can be reinfected with drug-resistant strains, as shown in [6, 11, 17, 24], in most instances drug resistance develops because of inadequate or erratic therapy. In the real world, the treatment of patients with active-*TB* requires a multiple drug regimen; treatment is highly effective (with a 95% cure rate) if the patient harbors drug-sensitive organisms and is compliant with the treatment regimen [4].

Our goal is to look at some of these features for *TB* pathogenesis. We propose a mathematical model to assess the transmission dynamics of both drug-sensitive and drug-resistant *TB* considering slow *TB*, i.e., cases that result from endogenous reactivation of drug-sensitive and drug-resistant latent infections.

The paper is organized as follows. In the next Section we present the model formulation, in Section 3 we analyze the basic model, its equilibria and their stability. Section 4 contains another version of the basic model, with newly infected recruited via a different mechanism. Conditions on the system parameters ensuring the endemicity of the disease are identified. Also, a conjecture involving the determinant of the Jacobian of the model matrix ensuring disease eradication is highlighted. Some numerical simulations and a final discussion of the results conclude the paper.

2 Model Formulation

In contrast to other models of similar nature, for other types of diseases [4, 5, 19, 20, 23, 26], our mathematical model monitors the temporal dynamics of latent individuals (infected but unable to infect others) and infectious individuals (active-*TB* infectious, i.e., infectious subjects which are also able to infect others). The reason for considering these simplified models is to ignore the infection mechanism and concentrate only on the transition mechanisms among classes of infected individuals. In order to accomplish this task, we assume that new infected individuals are introduced by exogenous terms into our system. Common to our whole discussion is the implicit assumption of an infinite pool of susceptibles, which are not explicitly modelled and thus do not appear in the recruitment terms for new latent individuals. This implicitly linearizes the equations in the system, since the relevant mechanism we model consists then in the transitions to and from different compartments of infection or disease. Under our assumptions, the infection cannot be eliminated from the population because of the constant inflow of newly infected individuals; in order to eradicate the disease it would be necessary to isolate the fraction of incoming latent individuals.

In particular, we will thus make two distinct assumptions. Firstly, that the newly infected, named latent individuals, are recruited via constant immigration rates (1). Secondly, that they are generated via rates that are proportional to the number of people that are already actively infected by the disease and can therefore spread it, i.e., the infectious individuals (10).

Since the model assesses the drug-resistant and drug-sensitive tuberculosis cases, two subclasses of latent and infectious individuals are required to build it. Hence, the total diseased population (N), is divided into four classes, namely, L_S, the drug-sensitive latent individuals; L_R, the drug-resistant latent individuals; TB_S, the drug-sensitive infectious *TB* individuals, and TB_R, the drug-resistant infectious *TB* individuals. Here, both active-*TB* and case-*TB* mean active *TB* infectious case, and the subscripts 'S' and 'R' stand for drug-sensitive and drug-resistant types.

The dynamic of drug-resistant *TB* is due to two independent but interacting processes: (i) endogenous reactivation of latent drug-resistant and, (ii) conversion of sensitive cases (wild-type pansensitive) to drug-resistant cases during the treatment (acquired resistance).

The progression rates from latent *TB* to active-*TB* are assumed to be proportional to the latent-*TB* cases, i.e., they are given by λL_S and λL_R, such that *TB* cases (TB_S or TB_R) arising as a result of en-

dogenous reactivation (slow progression) of the primary complex with the sensitive or resistant strain. Thus, we define p, $0 \leq p \leq 1$, as the proportion of drug-resistant latent *TB* individuals who develop drug-sensitive *TB*. Consequently $(1-p)$ is the proportion of drug-resistant latent *TB* individuals who develop drug-resistant *TB*.

Although we assume that all the drug-sensitive *TB* individuals (TB_S) are treated with a multiple drug regimen (isoniazid and rifampin), the treatment has opposing effects at the population-level: treatment cures drug-sensitive cases, but an acquired drug-resistance quickly emerges among patients who receive ineffective or inappropiate treatment regimes or which are noncompliant with a multiple drug treatment regimen.

In the model effective treatment of drug-sensitive *TB* individuals (TB_S) occurs at a rate ξ, where ξ^{-1} is the average period of treatment. Acquired drug resistance can arise directly, for whatever reason (with probability q), during the treatment of a drug-sensitive case. Consequently, q represents the probability that treatment failure occurs due to the development of drug resistance, $0 \leq q \leq 1$. Thus, the model includes the possibility that the treatment of a drug-sensitive case can result in one of three outcomes;

(a) treatment can cure the patients (cases are removed from the TB_S classes at a rate equal to $(1-q)\xi$, and enter the L_S classes),

(b) treatment failure can occur, and the patient acquires drug-resistant *TB* (cases are removed from the TB_S classes at a rate equal to $q\xi$, and enter the TB_R classes), or

(c) treatment failure can occur, yet the patient remains infected with drug-sensitive *TB* (treated cases remain in the TB_S classes).

Therefore, if $q = 0$ drug-sensitive cases are treated with effectiveness; if $q = 1$, the therapeutic methods of treatment are inefficient; and for $0 < q < 1$ drug-sensitive cases are only partially effectively treated.

It is also assumed that drug-resistant *TB* cases (TB_R) can be treated at rate σ, where σ^{-1} is the average period of treatment, but treatment efficacy is reduced. The relative treatment efficacy of drug-resistant cases (in comparasion with treatment of drug-sensitive cases) is specified by the parameter k (k_S for drug-sensitive, and k_R for drug-resistant cases). Thus, the model includes the possibility that treatment of a drug-resistant case can result in one of three outcomes:

(a) treatment can cure the patient, and a few cases can be removed from the TB_R classes at a rate equal to σk_S, and enter the L_S classes,

(b) treatment can cure the patient, and cases are removed from the TB_R classes at a rate equal to σk_R, and enter the L_R classes, or

(c) treatment failure occurs (treated cases remain in the TB_R classes).

Therefore, drug-resistant *TB* cases are untreatable (and/or untreated) if $k_S = k_R = 0$; drug-resistant cases are treated, with equal effectiveness if $k_S = k_R = 1$; and drug-resistant cases are only partially effectively treated if $0 < k_S < 1$ and $0 < k_R < 1$.

The model incorporates recruitment (π) and natural death (μ), as well as disease-related death (α), so that the total population size may vary in time. We define γ, as the proportion $0 \leq \gamma \leq 1$ of latent drug-resistant individuals who enter into the L_R class and $(1-\gamma)$ as the proportion of latent drug-sensitive individuals who enter into L_S class.

Based on the above assumptions and definitions we present next the analysis of the models.

3 Constant Immigration Model

First of all the transfer diagram of the basic model with constant immigration is shown in Figure 1. This model is governed by the following non-

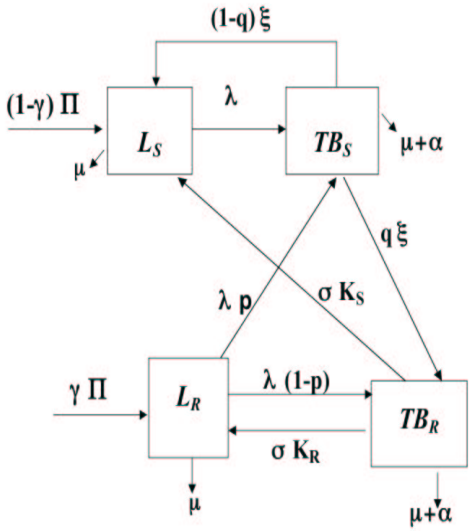

Figure 1: Model with constant immigration: transfer diagram

homogeneous linear system of differential equations:

$$\begin{cases} \frac{dL_S}{dt} &= (1-\gamma)\,\pi + (1-q)\xi TB_S \\ &\quad +\sigma k_S TB_R - (\mu+\lambda)\,L_S \\ \frac{dTB_S}{dt} &= \lambda L_S + p\lambda L_R - (\mu+\alpha+\xi)TB_S \\ \frac{dL_R}{dt} &= \gamma\pi + \sigma k_R TB_R - (\mu+\lambda)\,L_R \\ \frac{dTB_R}{dt} &= (1-p)\lambda L_R + q\xi TB_S - [\mu+\alpha \\ &\quad +\sigma\,(k_R+k_S)]\,TB_R, \end{cases} \tag{1}$$

where $N = L_S + L_R + TB_S + TB_R$ is the total population and the dynamics of the whole population is expressed by

$$\frac{dN}{dt} = \pi - \mu N - \alpha\,(TB_S + TB_R)\,. \tag{2}$$

Thus the total population is constant only if

$$\pi - \mu N - \alpha\,(TB_S + TB_R) = 0.$$

When there is no initial infection in the population, $TB_S \equiv TB_R \equiv 0$, equation (2) becomes

$$\frac{dN}{dt} = \pi - \mu N. \tag{3}$$

This equation has a single stable equilibrium $N^* = \frac{\pi}{\mu}$, for any initial value of N. Thus, in absence of the disease the total population will stabilize at the value N^* from any initial conditions and all individuals will be latent. In fact, by setting $\alpha = 0$, then equation (3) implies $N(t) \to \frac{\pi}{\mu}$, when $t \to \infty$. So, when $\alpha = 0$ and $\pi = \mu\,N$, we have

$$\frac{dN}{dt} = 0,$$

and the total population is a constant. However, if the disease has been previously established in a population the total population is given by

$$\frac{dN}{dt} = \pi - \mu N - \alpha\,(TB_S + TB_R) \le \pi - \mu N.$$

This equation has a single equilibrium $N^* = \frac{\pi}{\mu} - \frac{\alpha}{\mu}(TB_S^* + TB_R^*)$, for any initial value of N. Thus, once $N(t)$ is less than $\frac{\pi}{\mu}$, it remains so for all future times, and when $N(t)$ is greater than $\frac{\pi}{\mu}$, $N(t)$ declines until eventually $N(t) \le \frac{\pi}{\mu}$ for all sufficiently large t.

In the next section, the analysis of the model (1) is performed. We identify the steady state of the system (1) to analyse the dependence on the model parameters of the equilibrium and its stability.

3.1 Endemic equilibrium

To find the equilibrium point, let us set the derivatives of (1) to zero. This results in a unique non-trivial steady state $P^* = (L_S^*, TB_S^*, L_R^*, TB_R^*)$ with components given by

$$\begin{cases} L_R^* &= \frac{\gamma\pi}{\mu+\lambda} + \frac{\sigma k_R}{\mu+\lambda} TB_R^*, \\ TB_S^* &= -\frac{\lambda(1-p)\gamma\pi}{(\mu+\lambda)q\xi} + \frac{TB_R^*}{(\mu+\lambda)q\xi} E, \\ L_S^* &= \frac{TB_R^*}{(\mu+\lambda)q\xi\lambda} D \\ &\quad -\frac{\gamma\pi[(\mu+\alpha+\xi)(1-p)+pq\xi]}{(\mu+\lambda)q\xi}, \\ TB_R^* &= \frac{\lambda\pi}{A}\{(\mu+\lambda)q\xi \\ &\quad +\gamma(1\text{-}p)[\xi(1\text{-}q)\mu \\ &\quad +(\mu+\lambda)(\mu+\alpha)]\}, \end{cases} \tag{4}$$

where

$$\begin{aligned} E &= k_S\sigma(\mu+\lambda) + \sigma k_R(\mu+p\lambda) \\ &\quad +(\mu+\alpha)(\mu+\lambda), \end{aligned}$$

$$\begin{aligned} D &= \sigma k_R\{\mu(\mu+\alpha+\xi) \\ &\quad +\lambda p[\mu+\alpha+\xi\,(1-q)]\} \\ &\quad +(\mu+\alpha+\xi)(\mu+\lambda)[\mu+\alpha+k_S\sigma)], \\ A &= \sigma k_S(\mu+\lambda)[\mu(\mu+\alpha+\xi)+\lambda(\mu+\alpha)] \\ &\quad +\sigma k_R\{\mu\xi[\mu+\lambda p+\lambda(1-p)q] \\ &\quad +(\mu+\lambda)(\mu+\alpha)(\mu+\lambda p)\} \\ &\quad +(\mu+\alpha)(\mu+\lambda)[(\mu+\alpha+\xi)(\mu+\xi) \\ &\quad +\lambda(1-q)\xi] > 0. \end{aligned}$$

Clearly $L_R^* > 0$, $TB_R^* > 0$. Note that the vanishing of TB_R^* implies the infeasibility of P^*, since $TB_S^* < 0$ and $L_S^* < 0$. For feasibility we must impose also $TB_S^* > 0$, and $L_S^* > 0$. These give the lower bound

$$\begin{aligned} TB_R^* &> \max\{\tfrac{1}{E}[\lambda\,(1-p)\,\gamma\pi], \\ &\quad \tfrac{1}{D}[\gamma\pi\lambda\,[(\mu+\alpha+\xi)(1-p)+pq\xi]]\} \\ &\ge \tfrac{1}{D}[\gamma\pi\lambda\,[(\mu+\alpha+\xi)(1-p)+pq\xi]] \end{aligned}$$

3.2 Dynamical trajectories

We will now perform the stability analysis for the nonhomogeneous linear system (1). Letting $\mathbf{q} = ((1-\gamma)\pi, 0, \gamma\pi, 0)^T$, in matrix form it can be rewritten as

$$\dot{\mathbf{x}} \equiv \frac{d\mathbf{x}}{dt} = M\,\mathbf{x} + \mathbf{q}, \tag{5}$$

where $\mathbf{x}(t) \in R^4$, and $\mathbf{q} \in R^4$ is a constant vector, while M is a 4×4 constant matrix. In order to make a real phenomena compatible to its mathematical description we will study the behavior of trajectories in the neighborhood of the trivial solution of the system (1). Generally, the stability of some solutions of the system $\dot{\mathbf{x}} = A\mathbf{x} + \mathbf{q}$ is reconducted to the stability of a trivial solution, i.e., investigating the nature of the origin. This point is asymptotically stable when all roots λ_i of the characteristic equation are negative (if real) or have negative real parts (if complex).

The matrix M is given by

$$M = \begin{bmatrix} M_{11} & (1-q)\xi & 0 & \sigma k_S \\ \lambda & M_{22} & p\,\lambda & 0 \\ 0 & 0 & M_{33} & \sigma k_R \\ 0 & q\xi & (1-p)\,\lambda & M_{44} \end{bmatrix}, \quad (6)$$

with

$$\begin{aligned} M_{11} &= -(\mu+\lambda), \\ M_{22} &= -(\mu+\alpha+\xi) \equiv -A, \\ M_{33} &= -(\mu+\lambda), \\ M_{44} &= -[\mu+\alpha+\sigma(k_R+k_S)] \equiv -K. \end{aligned}$$

We can compute the characteristic equation by expanding $\det(M - \tau I) = 0$ along the first column and then explicitly evaluating the third order determinants appearing in this expansion. Upon suitable collection of terms as indicated below, we are led to the following equation

$$P_3(\theta) = P_1(\theta) + H(\theta) \quad (7)$$

where

$$\begin{aligned} P_3(\theta) &= [(\mu+\lambda)-\theta]\,[(\mu+\alpha+\xi)+\theta] \\ &\quad \times \{[\mu+\alpha+\sigma(k_R+k_S)]+\theta\}, \\ H(\theta) &= -\frac{\lambda^2(1-q)\xi\,\sigma k_R(1-p)}{[(\mu+\lambda)-\theta]}, \\ P_1(\theta) &= b_0 + b_1\theta, \end{aligned} \quad (8)$$

with

$$\begin{aligned} b_0 &= \lambda[\xi\sigma q(pk_R+k_S) + \sigma k_R(1-p)M_{22} \\ &\quad +\xi(1-q)M_{44}] > 0, \\ b_1 &= \lambda\sigma k_R(1-p) + \xi\lambda(1-q) > 0. \end{aligned}$$

Notice that the cubic polynomial has always two negative roots, $\theta_1 = -M_{22}$ and $\theta_2 = -M_{44}$ and a positive one $\theta_3 = \mu + \lambda$. The value at the origin is $P_3(0) = (\mu+\lambda)M_{22}M_{44} > 0$. Furthermore it tends to $-\infty$ as $t \to +\infty$. We must intersect it with the function given by the right hand side of (7), which is the sum of the straight line P_1 with positive slope and the hyperbola $H(\theta)$. The latter has the vertical asymptote located at $\theta = \theta_1$, it is positive for $\theta > \theta_1$ and tends to zero as $\theta \to +\infty$. Thus as $\theta \to +\infty$, the function $H + P_1$ is asymptotic to the straight line P_1. However, $H(0) + P_1(0)$ has no definite sign. Intersecting $H + P_1$ with P_3, there are four possible cases that can arise, depending on the signs of the two functions at $\theta = 0$. Given that one function has a zero at $\theta = \theta_1$ and the other one in the same location has a vertical asymptote, with

$$\lim_{\theta \to \theta_1^+} H(\theta) = -\infty,$$

we can conclude that the two functions interlace, giving an intersection for a positive value of θ if

$$H(0) + P_1(0) > P_3(0). \quad (9)$$

In such case then the interior equilibrium is unstable, since we would have a positive eigenvalue.

To further assess the system's equilibrium behavior in this 11-dimensional parameter space is rather difficult. Nevertheless, it would be interesting to determine whether the equilibrium can at all be destabilized.

In Figure 2 we show the simulations for a combination of realistic parameter values, given by $\gamma = 0.2$, $\pi = 0.0167$, $q = 0.05$, $\xi = 1.0$, $\sigma = 0.5$, $k_R = 0.35$, $k_S = 0.025$, $\mu = 0.0167$, $\lambda = 0.025$, $p = 0.05$, $\alpha = 0.001$. The solutions drop very fast, but a longer integration interval coupled with a semilogarithmic scale shows that as claimed above the disease remains endemic, since the trajectories approach the interior coexistence equilibrium at the values $L_S = .7582$, $TB_S = .0189$, $L_R = .01933$, $TB_R = .0270$, see Figures 3 and 4.

4 Model with Linear Immigration

We consider now a modification of the previous system (1). The rationale for this modification is again to bypass the infection process of the more complicated models and concentrate only on the transmission mechanisms among infected individuals. The previous model (1) has a constant immigration rate. Here, again ignoring the infection mechanism by contact among susceptibles and infectious individuals, we state that the newly infected individuals are generated proportionally to the sizes of the infectious ones (TB disease individuals), of their respective types. This assumption may be more realistic for mimicking the spreading of the disease via interactions among susceptibles and infectious individuals. In fact in com-

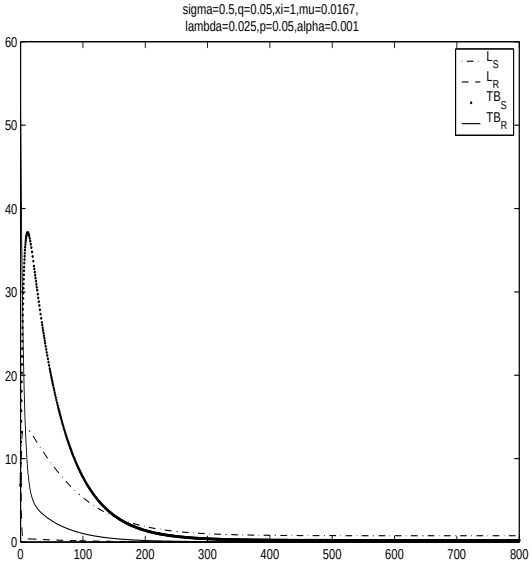

Figure 2: Model with constant immigration: solutions approach very fast the steady state solution

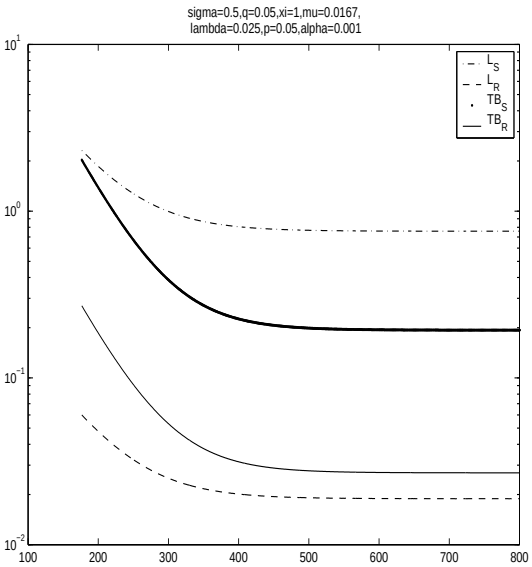

Figure 3: Model with constant immigration: semilogarithmic plot of interior coexistence equilibrium

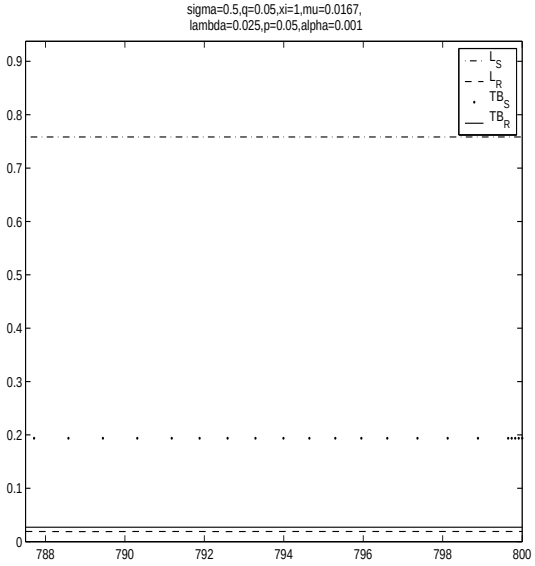

Figure 4: Model with constant immigration: blown up plot of interior coexistence equilibrium

mon mathematical epidemiology, the models are assumed to recruit new infected by either the mass action law, ie. via a bilinear term involving the sizes of each subpopulation of infected and susceptibles, leading to the so-called homogeneous mixing models, or via the standard incidence, i.e. the above bilinear product divided by the total population size. The latter is more apt to describe the disease spread by a few infectives in a large population, and leads to the proportionate mixing models. The bilinear product terms in both situations arise by counting the contacts that an infected can have with susceptibles, which lead to new cases of the disease, originated by the chosen infected individual. Multiplying the latter by the total number of contagious people, one obtains the rate at which the disease spreads, i.e. the rate at which new infected arise by contact among the two subpopulations. For a fairly recent review paper on these topics, and much more information on other more advanced models, the reader is referred to [14].

On the basis of the above considerations, in Figure 5 we represent the transfer diagram of the model with linear immigration. It is similar to the one of Figure 1, but for the immigration rates on the left.

If we consider thus the model with new infectives given by terms proportional to the size of infected, respectively TB_S and TB_R, namely with immigration rates given by $\Psi_S TB_S$ and $\Psi_R TB_R$, we obtain the

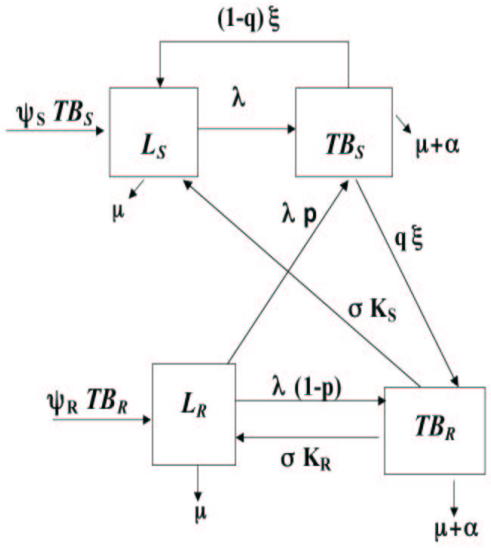

Figure 5: Model with linear immigration: transfer diagram

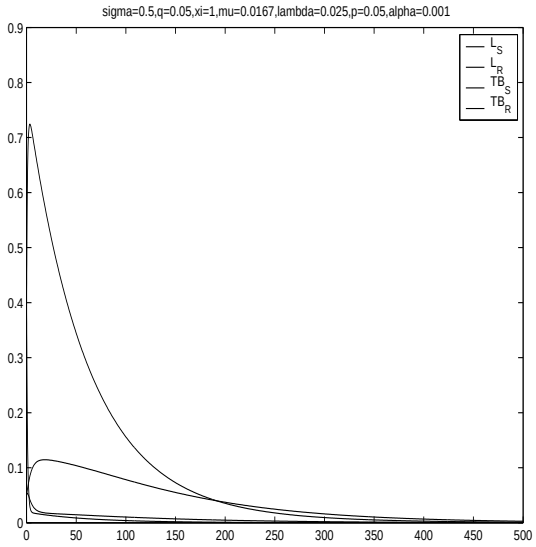

Figure 6: Model with linear immigration: trajectories decaying toward the origin when stable

following linear system

$$\begin{cases} \frac{dL_S}{dt} &= \Psi_S TB_S + (1-q)\xi TB_S \\ &\quad +\sigma k_S TB_R - (\mu+\lambda)\, L_S \\ \frac{dTB_S}{dt} &= \lambda L_S + p\lambda L_R - (\mu+\alpha+\xi) TB_S \\ \frac{dL_R}{dt} &= \Psi_R TB_R + \sigma k_R TB_R - (\mu+\lambda)\, L_R \\ \frac{dTB_R}{dt} &= (1-p)\lambda L_R + q\xi TB_S - [\mu+\alpha \\ &\quad +\sigma\,(k_R+k_S)]\, TB_R. \end{cases} \tag{10}$$

In contrast to (5), this system can thus be rewritten in matrix notation as

$$\frac{d\mathbf{x}}{dt} = \widetilde{M}\,\mathbf{x}, \tag{11}$$

where $\widetilde{M}$ coincides with M except for the following two entries

$$\widetilde{M}_{12} = M_{12} + \Psi_S = (1-q)\xi + \Psi_S,$$

$$\widetilde{M}_{34} = M_{34} + \Psi_R = \sigma k_R + \Psi_R.$$

Substituting al the possible combinations of vanishing and nonvanishing components, it is easily checked that all boundary solutions of (10), i.e. those equilibria with at least one zero component, are either impossible or infeasible, except for the origin. Since in seeking nontrivial equilibria of (10) we are led to the homogeneous system $\widetilde{M}\mathbf{x} = \mathbf{0}$ with nonsingular matrix, then only the trivial solution is found. Thus (10) does not allow interior coexistence solutions. Its only possible equilibrium point is thus given by the origin. However, this means that all the solutions of the system modeled via (10) vanish if such equilibrium is stable, and that depends on the eigenvalues of $\widetilde{M}$.

Thus the origin O being a stable equilibrium means that the infection disappears, an important result. The conditions under which this happens guarantee then the disease eradication. This is apparent also from the simulation results, compare Figure 6. The latter is obtained for the following parameter values: $\mu = 0.0167$, $\lambda = 0.025$, $\xi = 1$, $\sigma = 0.5$, $\alpha = 0.001$, $\gamma = 0.2$, $q = 0.05$, $k_S = 0.025$, $p = 0.05$, $k_R = 0.35$, $\psi_R = 0.09$, $\psi_S = 0.04$.

The characteristic equation of (10) is a quartic

$$\sum_{i=0}^{4} a_i \tau^i = 0,$$

where $a_0 = \det J(O) = \det \widetilde{M}$. On the other hand, by computing the determinant of the Jacobian, we find

$$\begin{aligned} a_0 &= [\mu(\mu+\alpha+\xi) + \lambda(\mu+\alpha+q\xi)] \\ &\quad \times[(\mu+\lambda)(\mu+\alpha) + \sigma k_R(\mu+p\lambda) + \\ &\quad (\mu+\lambda)\sigma k_S] \times \{1-R_S^*\}\{1-R_R^*\} \\ &\quad -(\mu+\lambda)q\xi\lambda\sigma(k_R+k_S), \end{aligned}$$

where

$$R_R^* = \frac{\Psi_R}{\Psi_R^C}$$

with

$$\begin{aligned} \Psi_R^C &= \frac{1}{\lambda(1-p)}[(\mu+\lambda)(\mu+\alpha) \\ &\quad +\sigma k_R(\mu+p\lambda) + (\mu+\lambda)\sigma k_S, \end{aligned}$$

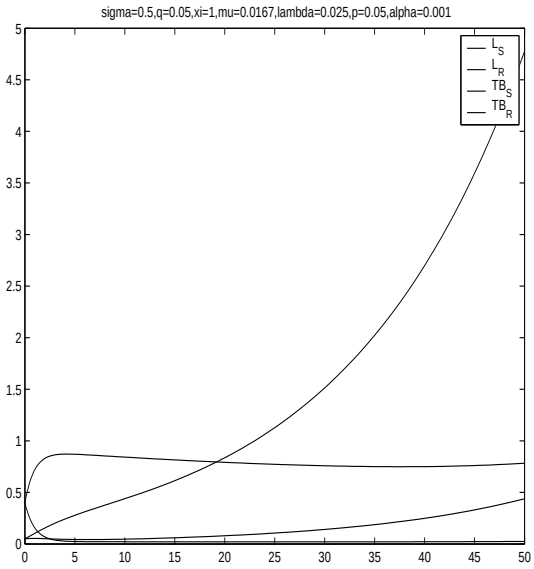

Figure 7: Model with linear immigration: trajectories growing unbounded when origin is unstable

and

$$R_S^* = \frac{\Psi_S}{\Psi_S^C}$$

with

$$\Psi_S^C = \frac{1}{\lambda}[\mu(\mu+\alpha+\xi)+\lambda(\mu+\alpha+q\xi)],$$

Thus a sufficient condition for instability amounts to $a_0 < 0$. However, notice that if $\Psi_S = \Psi_R = 0$ then $a_0 > 0$. We conjecture then that in such case since no new infected join the system, the disease dies away, since mortality will exhaust the compartments L_S, TB_S, L_R, TB_R. In such case then the origin, corresponding to disease disappearance, will become a stable equilibrium. On the other hand, if the origin is unstable, since no other equilibrium exists, the numerical simulations show that in this situation the system trajectories grow unbounded, see Figure 7, meaning that the disease spreads. The parameter values for the latter are the same as for Figure 6, but for the higher recruitment rates, namely $\psi_R = 0.9$, $\psi_S = 0.4$.

Note that in these simulations, the two curves corresponding to the drug-resistant cases, solid lines, grow more rapidly than the other ones. This indicates a tendence for which in the future more and more cases fo the disease that are not treatable with current means are to be expected. Although the latent resistant cases, asymptomatic as such, dominate the diseased ones, this scenario does not diminish its unwished implications, since the pool of infected individuals constitutes always a reservoir for the disease, and these people may always develop the full disease in their lifetimes.

5 Discussion

In classical deterministic epidemiological models for the transmission dynamics of an infectious disease there is a threshold behavior, with either a disease-free equilibrium or an endemic equilibrium approached by the solutions. However, as shown in the model (1), if there is a constant flow of infected into the population, it is not possible to have a disease-free equilibrium. There is always an endemic equilibrium approached by all solutions and the disease remain in the population at an endemic level.

We can reduce the prevalence of the disease by considering the immigration of infected individuals proportional to the number of people that are already infectious (TB diseased individuals) as shown in model (10). The prevalence of the disease can be reduced by decreasing the probability that treatment failure can occurs (increasing k_S and k_R).

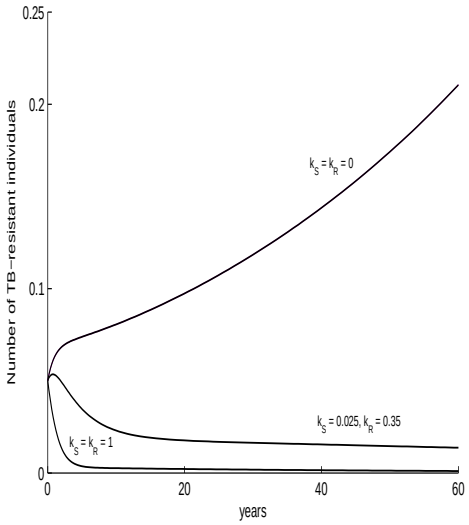

Figure 8: Model with linear immigration: evolution of the disease, drug-resistant population, TB_r. Top to bottom, the curves are for the parameter values $k_S = k_R = 0$, $k_S = k_R = 0$; $k_S = 0.025$, $k_R = 0.35$; $k_S = 1.0$, $k_R = 1.0$.

Figure 8 shows that even if all drug-resistant cases were treated ($k_S = 1$ and $k_R = 1$), the disease remains endemically in the population. To eradicate the disease from the population is necessary to decrease the probability that the treatment failure occurs during the treatment of a drug-sensitive case, i.e. we need to decrease q. Figure 9 describes the profile of the drug-resistant population, TB_r, with decreasing values of $q = 1,\ 0.5,\ 0$ from top to bottom.

Finally, in Figure 10 we show a further possible scenario worse that that of Figure 7 in which for the

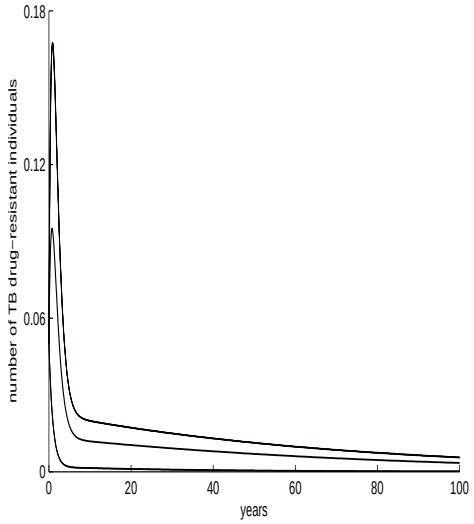

Figure 9: Model with linear immigration: drug-resistant population, TB_r. The curves correspond to $q = 1,\ 0.5,\ 0$ from top to bottom

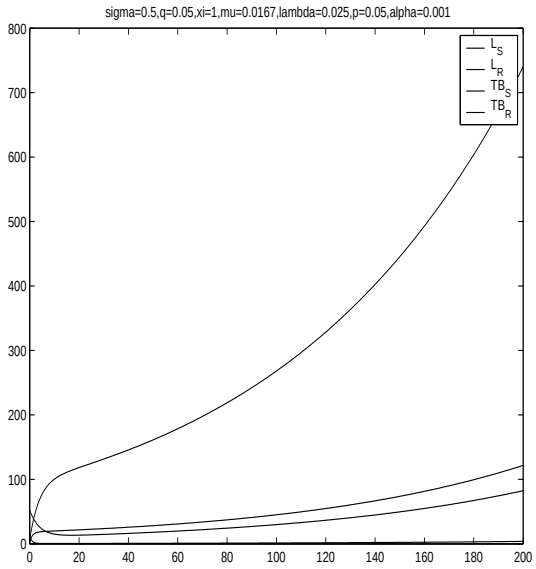

Figure 10: Model with linear immigration: scenario with disease cases much outnumbering the latent carriers

following parameter values, indicating higher recruitment rates, the disease cases would much outpass the number of latent carriers. It is obtained via the following parameter values, $\mu = 0.0167$, $\lambda = 0.025$, $\xi = 1$, $\sigma = 0.5$, $\alpha = 0.001$, $\gamma = 0.2$, $q = 0.05$, $k_S = 0.025$, $p = 0.05$, $k_R = 0.35$, $\psi_R = 0.29$ $\psi_S = 0.415$.

Common to both models presented here (1) and (10) is the assumption of ignoring the class of susceptible individuals. This is reasonable if we assume it to be a large basin, among which the "infected" can pick up their new recruits. We have concentrated instead on the way the infected move from the classes of latent to diseased, and possibly back upon successful treatment, or toward acute stages of the disease for drug resistant cases due to improper, incomplete or ineffective healing measures. Our conclusions give conditions for which the disease remain endemic, and a conjecture for disease eradication.

6 Conclusions

In epidemiology, measures for prophilaxis of infectious diseases are taken often using mathematical methods and statistical tools to evaluate possible future scenarios of the evolution of transmissible diseases. For instance, design of systems to monitor patients are presented and discussed in several situations, such as [1, 10, 15, 16, 22]. Also, evaluation of biological data for clinical purposes are investigated in [9]. The basic reproduction number discussed in [13] is an important quantity to assess the future evolution of infections spreading in a population, where individuals interact and by contact the disease is trasmitted from a generally asymptomatic carrier to a susceptible individual. This basic reproduction number is related to the incidence rate of the disease and allows to determine under which conditions the epidemics possibly vanishes. On this basis the World Health Organization in 1980 discontinued the vaccination against smallpox, since this century-long virulent disease could be assessed to be worldwide extinguished. In these considerations, the risk factors evaluation plays always an essential role also for other diseases which carry relevant costs for the community, [28].

The considerations presented in this paper are to be understood along the same lines, as theoretical tools to help in the fight against this disease, which has caused much damage in the past, and with the employment of modern medical treatments seemed to be eradicated, for which however in recent years a recrudescence has unfortunately been observed. An understanding of its causes may therefore help in future epidemiological policies.

References

[1] V. Alves, J. Machado, A. Abelha, J. Neves, Agent Based Decision Support Systems in Medicine Wseas Transactions on Biology and Biomedicine, 2, 204-213, 2005.

[2] Bleed, D., Watt, C. and Dye, C. World Health Report 2001: Global Tuberculosis Control, tech.

rep., World Health Organization, WHO /CDS /TB /2001.287, 2001. (http://www.who.int/ gtb/ publications/ globrep01/ index.html).

[3] Bloom, B. ed., *Tuberculosis: Pathogenesis, Protection and Control*. Washington D.C.: ASM Press, 1994.

[4] Blower, S.M., Gerberding, J.L., (1998), Understanding, predicting and controlling the emergence of drug-resistant tuberculosis: a theoretical framework. J. Mol. Med, 76:624-636and the amplification dynamics of drug resistance. Nature medicine 10 (10):1111-1116.

[5] Castillo-Chavez, C., and Song, B. (2004) Dynamical models of tuberculosis and their applications. Math. Biosc. and Engineering, 1(2), 361-404.

[6] CDC, (1985), Drug resistant tuberculosis among the homeless Boston, MMWR, 34: 429-431.

[7] Costello H.D., Caras G.J., Snider D.E. Jr., (1980), Drug resistance among previously treated tuberculosis patients, a brief report. Am. Rev. Respir. Dis., 121: 313-316.

[8] David H.L., (1970), Probability distribution of drug-resistant mutants in unselected populations of Mycobacteria tuberculosis, Applied Microbiology 20: 810-814.

[9] M. Doepp, G. Edelmann, Frequency Distribution Analysis of Biological Data: Clinical Evaluation Wseas Transactions on Biology and Biomedicine, 1, 215-223, 2004.

[10] M. Doepp, G. Edelmann, Chaos in Human Being: An Aid for Medical Decision Making Wseas Transactions on Biology and Biomedicine, 1, 403-409, 2004.

[11] Espinal, M.A., (2003), The global situation of MDR-TB, Tuberculosis, 83: 44-51.

[12] Fine, P., and Small, P. (1999), Exogenous Reinfection in Tuberculosis, The New England Journal of Medicine, 341,1226-1227.

[13] J. Guardiola, A. Vecchio, The Basic Reproduction Number for Infections Dynamics Models and the Global Stability of Stationary Points, Wseas Transactions on Biology and Biomedicine, 2, 337, 2005.

[14] H.W. Hethcote, The mathematics of infectious diseases, SIAM Review 42 (2000) 599-653.

[15] C.-L. Hsu, S.-Y. Yang, D.-L. Lee, L. Y. Deng, Practical design of intelligent reminder system of having medicine for chronic patients, Wseas Transactions on Biology and Biomedicine, 4, 122-129, 2007.

[16] P.-H. Huang, Medical healthy information system-based on IPv6 platform, Wseas Transactions on Biology and Biomedicine, 3, 615-627, 2006.

[17] Nardell E, McInnes B., Thomas B., Weidhaas S., (1986), Exogenous reinfection with tuberculosis in a shelter for the homeless. N. Engl. J. Med., 315: 1570-1575.

[18] Pio, A., Chaulet, P., (1998), Tuberculosis handbook (World FHealth Organization, Geneva)

[19] Raimundo, S.M., Yang, H.M; Bassanezi, R.C. and Ferreira, M.A.C., (2002), The Attraction Basins and the Assessment of the Transmission Coefficients for HIV and M. tuberculosis Infections among Women Inmates. J. Biol. Syst. 10 (1), 61- 83.

[20] Raimundo, S.M.; Yang, H.M.; Engel, A.B. and Bassanezi, R.C., (2003), An approach to estimating the Transmission Coefficients for AIDS and for Tuberculosis. Systems Analysis Modelling Simulation 43 (4), 423-442.

[21] Romeyn, J., (1970), Exogenous reinfection in tuberculosis, American Rewiew of Respiratory Diseases, 101(6), 923-927.

[22] B.-Y. Shih, W.-I. Lee, Y.-S. Chung, A.-W. Chen, The development of a mobile emergency healthcare information system in Taiwan, Wseas Transactions on Biology and Biomedicine, 4, 54-58, 2007.

[23] Singer, B. H., and Kirschiner, D. (2004) Influence of backward bifurcation on interpretation of R_0 in a model of epidemic tuberculosis with reinfection. Math. Biosc. and Engineering, 1(1),81-93.

[24] Small P.M., Shafer R.W., Hopewell P.C., et al., (1993),) Exogenous reinfection with multidrug-resistant Mycobacterium tuberculosis in patients with advanced HIV infection, N. Engl. J. Med., 328 (16): 1137-1144.

[25] Snider, D. Jr., Raviglione, M., and Kochi, A., (1994), *Global Burden of Tuberculosis*, pp.3-11. In Bloom [2].

[26] Song, B., Castillo-Chavez, C., and Aparicio, J. P. (2002) Tuberculosis models with fast and slow dynamics: the role of close and casual conatcts. Math. Biosc. 180, 187-205.

[27] Stead, W. (1967), Phatogenesis of a first episode of chronic pulmonary tuberculosis in man: Recrudescence of residuals of the primary infection or exogenous reinfection?, American Review of Respiratory Diseases, 95, 729-745.

[28] L. S. Waldbeser, M. Abudiab, S. Ommani, Risk Factors Assessment and Mathematical Modeling of Neisseria Meningitidis Carriage in a University Student Population, Wseas Transactions on Biology and Biomedicine, 3, 421-428, 2006.

[29] WHO (2006) Global tuberculosis control: surveillance, planning, financing, p.77. World Health Organization, Geneva, Switzerland.