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Global analysis of a dynamical model for transmission of tuberculosis with a general contact rate

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ABSTRACT

This paper deals with the global analysis of a dynamical model for the spread of tuberculosis with a general contact rate. The model exhibits the traditional threshold behavior. We prove that when the basic reproduction ratio is less than unity, then the disease-free equilibrium is globally asymptotically stable and when the basic reproduction ratio is great than unity, a unique endemic equilibrium exists and is globally asymptotically stable under certain conditions. The stability of equilibria is derived through the use of Lyapunov stability theory and LaSalle's invariant set theorem. Numerical simulations are provided to illustrate the theoretical results.

1. Introduction

Tuberculosis (TB), one of the most wide spread infectious diseases, is the leading cause of death due to a single infectious agent among adults in the world. According to the World Health Organization, one third of the world's population is infected with Mycobacterium tuberculosis (M. tuberculosis), leading to between two and three millions death each year. Although between 90% and 95% of infections occur in developing countries [1], emergence of HIV as well as multi-drug-resistant (MDR) strains of M. tuberculosis will dramatically change the dynamics of infection world-wide [2]. Other factors may contribute to the TB epidemic including elimination of TB control programs, drug use, poverty, and immigration [3,4]. Humans are the natural reservoir for M. tuberculosis, which is spread from person to person via airborne droplets [5]. M. tuberculosis may need only a low infectious dose to establish infection [6]. Factors that affect transmission of M. tuberculosis include the number, viability, and virulence of organisms within sputum droplet nuclei, and most importantly, time spent in close contact with an infectious person [5–8]. Socio-economic status, family size, crowding, malnutrition, and limited access to health care or effective treatment also influence transmission [9,10]. Consistent estimates of M. tuberculosis transmission rates do not exist; however, it is known that transmission is rather inefficient for most strains [11]. Infection with M. tuberculosis is

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dependent on nonlinear contact processes that are determined by population size and density, as well as other factors. Demographic characteristics of a population, therefore, play a significant role in the development and progression of a TB epidemic.

Mathematical models can provide a useful tool to analyze the spread and control of infectious diseases [14,15]. Mathematical models for tuberculosis are especially useful tools in assessing the epidemiological consequences of medical or behavioral interventions (which may cause many direct and indirect effects) because they contain explicit mechanisms that link individuals with a population-level outcome such as incidence or prevalence. Different mathematical models for tuberculosis have been formulated and studied (see e.g. [16–26] and references therein). The simplest models include classes of susceptible, exposed and infective individuals, and hence are known as SEI models. However, global stability properties of a nonlinear system are generally a difficult problem. The global stability of SIR or SIRS models, in relation with the basic reproduction ratio, is known since eighties. Since the stability of these systems can be reduced to the study of a two-dimensional system, the Poincaré–Bendixson criterion is used to establish the global stability. Global stability for SEIRS and SEIS has long been conjectured. If the global stability of the disease-free equilibrium was known when the basic reproduction number is less than one, on the other hand the global stability for the endemic equilibrium, when the basic reproduction number is great than one, was an open problem. This was solved in 1995 by Li and Muldowney [28] using the Poincaré–Bendixson properties of competitive systems in dimensions three combined with sophisticated use of compound matrices.

This study extends previous works by formulating, and rigorously analyzing, a deterministic model for tuberculosis transmission dynamics with a general contact rate that incorporate constant recruitment, slow and fast progression, effective chemoprophylaxis (given to latently infected individuals) and therapeutic treatments (given to infectious). To the best of author knowledge, the global analysis of tuberculosis models with general contact rate is not well discussed in the literature. We completely analyze the stability behavior of the model. We compute the basic reproduction ratio $\mathscr{R}_0$, and prove the global asymptotic stability of the disease-free equilibrium (DFE) when $\mathscr{R}_0 \leqslant 1$, and that when $\mathscr{R}_0 > 1$ a unique endemic equilibrium exists and is globally asymptotically stable on the non-negative orthant minus the DFE under certain conditions. The global dynamics of the model is resolved through the use of Lyapunov functions which are the same from as those used recently in Refs. [30–37] to determine the global dynamics of SEIR, SEIS, and SIR models. It should be pointed out that this kind of Lyapunov function has long history of applications to Lotka–Volterra models and was originally discovered by Volterra himself, although he did not use the vocabulary and the theory of Lyapunov functions.

The paper is organized in the following manner. In the next section, we present our motivations. A brief introduction to the epidemiology of TB is provided in Section 3. We formulate a transmission model with a general contact rate to study the dynamics of TB in as simple a setting as possible in Section 4. We use the well-known TB model [20], which, in our opinion, captures the essentials of Mycobacterium tuberculosis transmission. Numerical simulation are presented to illustrate analytical results. Finally, Section 5 contains the conclusion.

2. Motivation

In most of the models discussed in the literature, the question of contact rate has not been a central one. Nevertheless, the mode of transmission is crucially important for two reasons. First, it determines the probable response of the disease to control. Second, the objective in many models of disease in animals is to predict what will happen when a pathogen is introduced into a system in which it does not currently exist. For example, standard mass action is considered, for human disease, more accurate than mass action (see e.g., [27] and references therein). Indeed the incidence of a disease which is the number of new cases per unit time plays an important role in the study of mathematical epidemiology. In [41], Thieme and Castillo-Chavez argued that the general form of a population size dependent incidence should be written as $\beta C(N)SI/N$, where S and I are respectively, the numbers of susceptible and infective at time t, β is the probability per unit time of transmitting the infection between two individuals taking part in a contact and, $C(N)$ is the "unknown" probability for an individual to take part in a contact and N is the size of the total population. Thus, $C(N)$ is usually called the contact rate, and $\beta C(N)$, which is the average number of adequate contacts of an individual per unit time, is said to be the adequate contact rate. An adequate contact is a contact which is sufficient for transmission of the infection from an infective to a susceptible. Our model considers a general contact rate which encompass the contact rates discussed above. However, in most of the epidemiological literature, the adequate contact rate frequently takes two forms. One is linearly proportional to the total population size N or βN, so that the corresponding incidence is the bilinear form $\beta NSI/N = \beta SI$, the other is a constant λ and the corresponding incidence $\lambda SI/N$ is called standard form. When the total population size N is not too large, since the number of contacts made by an individual per unit time should increase as the total population size N increases, the linear adequate contacts rate βN would be suitable. But, when the total population size is quite large, since the number of contacts made by an infective per unit time should be limited, or should grow less rapidly as the total population size N increases, the linear adequate contact rate βN is not suitable and the constant adequate contact rate λ may be more realistic. Hence, the two adequate contact rates mentioned above are actually two extreme cases for the total population size N being very small and very large, respectively. More generally, it may be reasonable to assume that the adequate contact rate is a function $C(N)$ of the total population size N. Some reasonable demands on $C(N)$ are that it should be a non-decreasing function of N and that $C(N)/N$ should be a non-increasing function of N. Furthermore, $C(N)$ should behave linearly in N, for small N, and it should be independent of N, for large N. On the other hand, a problem that has been around for a long time in mathematical epidemiology is

to give a mechanistic description of the saturation in the number of new contacts of infective per unit time made by an individual. Frequently, a Holling-type argument borrowed from the predator–prey systems, is thought to be a solution to the problem. However, as Heesterbeek and Metz explained in Ref. [29], on closer examination the application of the usual Holling argument to epidemic models cannot be justified. Of course, many other function forms can, and have been, suggested that have these properties, but a mechanistically derived form was lacking. Using a mechanistic argument, Heesterbeek and Metz [29] derived the expression for the saturating contact rate of individuals contacts in a population that mixes randomly, that is

$$C(N) = \frac{bN}{1 + bN + \sqrt{1 + 2bN}}.$$

Furthermore, $C(N)$ is non-decreasing and $C(N)/N$ is non-increasing.

In this paper, we assume that the contact rate $\beta(N)$ is a non-negative C^2 function of the total population $N \geqslant 0$. For clarity, we state that the symbol $'$ is used henceforth to refer to differentiation with respect to N. It is natural to assume that the transmission coefficient $\beta(N)$ satisfy the following conditions:

$$\beta(N) > 0, \quad \beta'(N) \leqslant 0, \quad (N\beta(N))' \geqslant 0 \quad \text{and} \quad \beta(N) \leqslant \beta(N^*), \tag{1}$$

where N^* is the endemic equilibrium point of the total population.

Remark 1. It is easy to see that $\beta(N) = \frac{C}{N}$ corresponds to the standard incidence rate, that $\beta(N) = \beta$ corresponds to the mass action incidence rate, and that $\beta(N) = \beta C(N)$ corresponds to the saturating contact rate, where

$$C(N) = \frac{bN}{1 + bN + \sqrt{1 + 2bN}}.$$

3. Epidemiology of tuberculosis

TB was assumed to be on its way 'out' in developed countries until the number of TB cases began to increase in the late 1980s. The causes behind recent observed increases of active TB cases are the source of many studies (see e.g., [5–12] and references therein). TB is an airborne transmitted disease. Mycobacterium tuberculosis droplets are released in the air by coughing or sneezing infectious individuals [13]. Tubercle bacillus carried by such droplets lives in the air for a short period time (about two hours) and, therefore, it is believed that occasional contacts with TB-active persons (infectious) rarely lead to transmission (but see [14] and references therein) and that most secondary cases are the result of prolonged and sustained close contacts with a primary case. The case of a teacher librarian with active TB who infected the children in her classroom but not the children who visited the library [15] supports the incorporation of differences between casual and close contacts. Latently infected individuals (inactive TB) become infectious (active TB) after a variable (typically long) latency period. Latent periods range from months to decades. Most infected individuals never progress towards the active TB state. On the other hand, average infectious periods are relatively short (few months but see [3]) and becoming shorter in developing nations due to the availability of treatment. There is a strong evidence [15] that TB transmission occurs mostly in groups of close associates of infectious individuals and that such a risk is limited to the life of the e.a. cluster (a couple of months) to which they belong. These beliefs, views and facts are incorporated into as simple framework as possible in the next section. In other words, a pedagogical model is used to explore the role of casual and close contacts on TB dynamics. However, due to the importance of contact rate in TB models, the global stability of such models with a general contact rate is an important issue.

4. The model and its properties

4.1. Model formulation

Based on epidemiological status, the population is divided into three classes: susceptible, latently infected (exposed) and infectious with the number in each class denoted by S, E, and I, respectively. The model is represented by the transfer diagram in Fig. 1. All recruitment is into the susceptible class, and occurs at a constant rate Λ. The rate constant for non-disease related death is μ, thus $1/\mu$ is the average lifetime. A fraction p of the newly infected individuals is assumed to undergo fast progression directly to the infectious class, while the remainder are latently infected and enter the latent class. Once latently infected with M. tuberculosis, an individual will remain so for life unless reactivation occurs. To account for treatments, we define r_1E as the fraction of latently infected individuals receiving effective chemoprophylaxis, and r_2 as the rate of effective per capita therapy. We assume that chemoprophylaxis of latently infected individuals reduces their reactivation at a constant rate r_1 and that the initiation of therapeutics immediately removes individuals from active status and places them into a latent state. The time before latently infected individuals who does not received effective chemoprophylaxis become infectious is assumed to satisfy an exponential distribution, with mean waiting time $1/k$. Thus, individuals leave the class E to the class I at a constant rate $k(1 - r_1)$. Also, after receiving a therapeutic treatment, individuals leave the class I to E at rate r_2. Infectious have an additional death rate due to the disease with rate constant $d > \mu \geqslant 0$. We assume that the emigration only

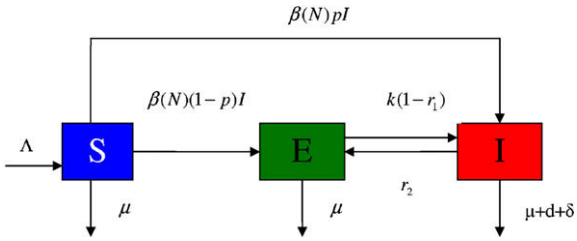

Fig. 1. Transfer diagram for the dynamics of tuberculosis with a general contact rate.

affects the class of infectious I so that the fraction δI of infectious leaves the class I without receive a therapy treatment for many reasons such as poverty, mentality, etc. Since TB latent individuals are not capable of transmitting the disease, we assume that a susceptible individual may become infected only through contacts with infectious. In each unit time, a susceptible individual has an average $\beta(N)I$ contacts that would be suffice to transmit the infection where $N = S + E + I$ is the total population size. Thus, the rate at which susceptible are infected is $\beta(N)SI$.

This leads to the following system of differential equations for the rate change with respect to time of the numbers of susceptible, latently infected and infectious individuals:

$$\begin{cases} \dot{S} = \Lambda - \beta(N)SI - \mu S, \\ \dot{E} = \beta(N)(1-p)SI + r_2 I - [\mu + k(1-r_1)]E, \\ \dot{I} = \beta(N)pSI + k(1-r_1)E - (\mu + d + \delta + r_2)I. \end{cases} \tag{2}$$

Parameters Λ, μ, d, k, r_1 and r_2 are assumed to be positive and all other parameters are non-negative with $p \in [0,1]$.

Since the model (2) monitors human populations, it is further assumed that all the state variables are non-negative at time $t = 0$. It then follows from the differential equations that the variables are non-negative for all $t \geqslant 0$. Furthermore, adding all equations in (2) gives

$$\dot{N} = \Lambda - \mu N - (d + \delta)I. \tag{3}$$

Consequently, in the absence of tuberculosis infection, $N \to \Lambda/\mu$ as $t \to \infty$ and Λ/μ is an upper bound of $N(t)$ provided that $N(0) \leqslant \Lambda/\mu$. Also, if $N(0) > \Lambda/\mu$, then N will decrease to this level. Thus, the following feasible region:

$$\mathscr{D} = \left\{ (S,E,I) \in \mathbb{R}^3_{\geqslant 0}, \quad 0 \leqslant S + E + I \leqslant \frac{\Lambda}{\mu} + \varepsilon \right\}, \tag{4}$$

is a compact forward positively invariant set for $\varepsilon > 0$ and that for $\varepsilon > 0$ this set is absorbing. Furthermore, each solution of $\mathbb{R}^3_{\geqslant 0}$ approaches $\mathscr{D}$ so that we may restrict our analysis to this region. In this region, the usual existence, uniqueness and continuation results hold for the system. In general, the model cannot be reduced to a lower dimensional model without making additional assumptions on the parameters.

4.2. Basic reproduction ratio

Many epidemiological models have a threshold condition which can be used to determine whether an infection will be eliminated from the population or become endemic. The basic reproduction number, $\mathscr{R}_0$, is defined as the average number of secondary infections produced by an infected individual in a completely susceptible population. Indeed, $\mathscr{R}_0$ is simply a normalized bifurcation (transcritical) condition for epidemiological models, such that $\mathscr{R}_0 > 1$ implies that the endemic steady state is stable (i.e., the infection persists) and, $\mathscr{R}_0 \leqslant 1$ implies that the uninfected steady state is stable (i.e., the infection can be eliminated from the population).

The model has a disease-free equilibrium (DFE), obtained by setting the right hand side of Eq. (2) to zero and $I = 0$, given by $P_0 = (S_0, 0, 0)$ with $S_0 = \Lambda/\mu$.

The stability of this equilibrium will be investigated using the next generation operator [42–45]. Using the notation in Ref. [45] on the system (2), the matrices F and V, for the new infection terms and the remaining transfer terms are, respectively, given by

$$F = \begin{bmatrix} 0 & \beta(S_0)S_0(1-p) \\ 0 & \beta(S_0)S_0 p \end{bmatrix} \quad \text{and} \quad V = \begin{bmatrix} \mu + k(1-r_1) & -r_2 \\ -k(1-r_1) & \mu + d + r_2 + \delta \end{bmatrix}.$$

The spectral radius or the largest eigenvalue of its next generation operator is given by

$$\mathscr{R}_0 = \rho(FV^{-1}) = \frac{\beta(S_0)S_0[\mu p + k(1-r_1)]}{(\mu + d + \delta)[\mu + k(1-r_1)] + \mu r_2}, \tag{5}$$

where ρ represents the spectral radius (the dominant eigenvalue in magnitude) of FV^{-1}.

The threshold quantity $\mathscr{R}_0$ is the basic reproduction number for TB infection. It measures the average number of new TB infections generated by a single infectious in a completely susceptible population. Consequently, the disease-free equilibrium P_0 of the basic model (2) is locally asymptotically stable (LAS) whenever $\mathscr{R}_0 < 1$ and unstable if $\mathscr{R}_0 > 1$. This means that TB can be eliminated from the community (when $\mathscr{R}_0 < 1$) if the sizes of the population of system (2) are in the basin of attraction of the disease-free equilibrium P_0.

4.3. Global stability of the disease-free equilibrium

The following theorem provides the global stability of the disease-free equilibrium.

Theorem 1. *The disease-free equilibrium P_0 of model (2) is globally asymptotically stable in the non-negative orthant $\mathbb{R}^3_{\geqslant 0}$ when $\mathscr{R}_0 \leqslant 1$.*

Proof. Consider the following Lyapunov–LaSalle function:

$$V(E,I) = k(1-r_1)E + [\mu + k(1-r_1)]I. \tag{6}$$

Its time derivative along the solutions of system (2) satisfies

$$\begin{aligned} \dot{V}(E,I) &= k(1-r_1)\dot{E} + [\mu + k(1-r_1)]\dot{I}, \\ &= k(1-r_1)[\beta(N)(1-p)SI + r_2 I - [\mu + k(1-r_1)]E] \\ &\quad + [\mu + k(1-r_1)][\beta(N)pSI + k(1-r_1)E - (\mu + d + \delta + r_2)I], \\ &= [\beta(N)S[p\mu + k(1-r_1)] - r_2\mu - [\mu + k(1-r_1)](\mu + d + \delta)]I. \end{aligned} \tag{7}$$

Now, using Eq. (1), one has $\beta(N)S \leqslant \beta(S_0)S_0$. With this in mind, Eq. (7) becomes

$$\begin{aligned} \dot{V}(E,I) &\leqslant [r_2\mu + [\mu + k(1-r_1)](\mu + d + \delta)]\left(\frac{\Lambda\beta(S_0)[p\mu + k(1-r_1)]}{\mu[[\mu + k(1-r_1)](\mu + d + \delta) + r_2\mu]} - 1\right)I, \\ &= [r_2\mu + [\mu + k(1-r_1)](\mu + d + \delta)](\mathscr{R}_0 - 1)I. \end{aligned} \tag{8}$$

Thus, $\dot{V}(E,I) \leqslant 0$ if $\mathscr{R}_0 \leqslant 1$. Furthermore, $\dot{V}(E,I) = 0$ if and only if $\mathscr{R}_0 = 1$ or $I = 0$. Then, the largest compact invariant set in $\{(S,E,I) \in \mathbb{R}^3_{\geqslant 0},\ \dot{V}(E,I) = 0\}$ is the singleton $\{P_0\}$. Therefore, by the LaSalle–Lyapunov theorem [39], all trajectories that start in $\mathscr{D}$ approach P_0 when $t \to \infty$. Since $\mathscr{D}$ is absorbing, this proves the global asymptotic stability on the non-negative orthant $\mathbb{R}^3_{\geqslant 0}$ for $\mathscr{R}_0 \leqslant 1$. It should be stressed that the need to consider a positively invariant compact set is to establish the stability of P_0 since $V(E,I)$ is not positive definite. Generally, the LaSalle's invariance principle only proves the attractivity of the equilibrium. Considering $\mathscr{D}$ permits to conclude for the stability [38–40]. This fact is often overlooked in the literature using LaSalle's invariance principle. This concludes the proof. □

4.4. Existence and uniqueness of endemic equilibrium

Here, we present a result concerning the existence and uniqueness of endemic equilibrium for the model formulated above. To do this, we shall make use of the basic reproduction ratio $\mathscr{R}_0$.

Let $P^* = (S^*, E^*, I^*)$ be the positive endemic equilibrium of model (2). Then, the positive endemic equilibrium (steady state with $I > 0$) can be obtained by setting the right hand side of each of the three differential equations in model (2) equal to zero, giving

$$\begin{cases} \Lambda - \beta(N^*)S^*I^* - \mu S^* = 0, \\ \beta(N^*)(1-p)S^*I^* + r_2 I^* - [k(1-r_1) + \mu]E^* = 0, \\ \beta(N^*)pS^*I^* + k(1-r_1)E^* - (\mu + d + \delta + r_2)I^* = 0, \end{cases} \tag{9}$$

and

$$\Lambda - \mu N^* - (d+\delta)I^* = 0. \tag{10}$$

Using Eq. (10), the first and second equations of (9), one can easily express S^*, E^* and I^* in terms of N^* in the form:

$$\begin{aligned} S^* &= \frac{\Lambda(d+\delta)}{\beta(N^*)(\Lambda - \mu N^*) + \mu(d+\delta)}, \quad I^* = \frac{\Lambda - \mu N^*}{d+\delta} \quad \text{and} \\ E^* &= \frac{(\Lambda - \mu N^*)}{\mu + k(1-r_1)}\left[\frac{\beta(N^*)\Lambda(1-p)}{\beta(N^*)(\Lambda - \mu N^*) + \mu(d+\delta)} + \frac{r_2}{d+\delta}\right]. \end{aligned} \tag{11}$$

Substituting (11) in the third equation of (9) yields

$$(\Lambda - \mu N^*)F(N^*) = 0, \tag{12}$$

where

$$F(N^*) = \beta(N^*)\Lambda(d+\delta)[p\mu + k(1-r_1)] - [\beta(N^*)(\Lambda - \mu N^*) + \mu(d+\delta)][r_2\mu + [\mu + k(1-r_1)](\mu + d + \delta)].$$

Clearly, $\Lambda - \mu N^* = 0$ is a fixed point of (9), which corresponds to the disease-free equilibrium P_0. Since $N^* \in [0, S_0]$, one has

$$\begin{aligned} F(0) &= -\beta(0)\Lambda(d+\delta)\mu(1-p) - \mu[\beta(0)\Lambda + \mu(d+\delta)][r_2 + \mu + k(1-r_1)] \\ &\quad - \mu(d+\delta)^2[\mu + k(1-r_1)], \\ F(S_0) &= \mu(d+\delta)[r_2\mu + (\mu + d + \delta)[\mu + k(1-r_1)]](\mathscr{R}_0 - 1). \end{aligned}$$

Clearly, it appears that $F(0) < 0$. It is now trivial matter to see that $F(S_0) > 0$ when $\mathscr{R}_0 > 1$. The existence follows from the intermediate value theorem. Now, $F(N^*)$ is monotone increasing, so that $F(N^*) = 0$ has only one positive root in the interval $[0, S_0]$.

Thus, we have established the following result.

Lemma 1. *When $\mathscr{R}_0 > 1$, the model (2) has a unique endemic equilibrium $P^* = (S^*, E^*, I^*)$ with S^*, E^* and I^* all non-negative.*

4.5. Global stability of the endemic equilibrium

Herein, we study the global stability of the endemic equilibrium P^* of system (2). We have the following result.

Theorem 2. *If $\mathscr{R}_0 > 1$, the unique endemic equilibrium P^* of the model (2) is globally asymptotically stable in $\mathscr{D} \setminus \{E = I = 0\}$ whenever*

$$\frac{S}{S^*} \leqslant \frac{E}{E^*} \quad \text{and} \quad \frac{S}{S^*} \leqslant \frac{I}{I^*}. \tag{13}$$

Proof. Consider the following Lyapunov function candidate [30–37]:

$$U(S,E,I) = (S - S^*\ln(S)) + A(E - E^*\ln(E)) + B(I - I^*\ln(I)), \tag{14}$$

where A and B are positive constants to be determined later. Differentiating this function with respect to time yields

$$\begin{aligned} \dot{U}(S,E,I) &= \left(1 - \frac{S^*}{S}\right)\dot{S} + A\left(1 - \frac{E^*}{E}\right)\dot{E} + B\left(1 - \frac{I^*}{I}\right)\dot{I}, \\ &= \left(1 - \frac{S^*}{S}\right)(\Lambda - \beta(N)SI - \mu S) \\ &\quad + A\left(1 - \frac{E^*}{E}\right)[\beta(N)(1-p)SI + r_2 I - [\mu + k(1-r_1)]E] \\ &\quad + B\left(1 - \frac{I^*}{I}\right)[\beta(N)pSI + k(1-r_1)E - (\mu + d + \delta + r_2)I]. \end{aligned} \tag{15}$$

Considering Eq. (9), one can deduce that

$$\begin{aligned} &\Lambda = \beta(N^*)S^*I^* + \mu S^*, \quad \mu + k(1-r_1) = \beta(N^*)(1-p)\frac{S^*I^*}{E^*} + r_2\frac{I^*}{E^*}, \\ &\mu + d + \delta + r_2 = \beta(N^*)pS^* + k(1-r_1)\frac{E^*}{I^*}. \end{aligned} \tag{16}$$

With this mind, Eq. (15) becomes

$$\begin{aligned} \dot{U}(S,E,I) &= \left(1 - \frac{S^*}{S}\right)[\beta(N^*)S^*I^* + \mu S^* - \beta(N)SI - \mu S] \\ &\quad + A\left(1 - \frac{E^*}{E}\right)\left[\beta(N)(1-p)SI + r_2 I - \beta(N^*)(1-p)S^*I^*\frac{E}{E^*} - r_2 I^*\frac{E}{E^*}\right] \\ &\quad + B\left(1 - \frac{I^*}{I}\right)\left[\beta(N)pSI + k(1-r_1)E - \beta(N^*)pS^*I - k(1-r_1)E^*\frac{I}{I^*}\right], \\ &= -\frac{\mu(S-S^*)^2}{S} + \beta(N^*)S^*I^*\left(1 - \frac{\beta(N)SI}{\beta(N^*)S^*I^*}\right)\left(1 - \frac{S^*}{S}\right) \\ &\quad + A\left(1 - \frac{E^*}{E}\right)\left[(1-p)\beta(N^*)S^*I^*\left(\frac{\beta(N)SI}{\beta(N^*)S^*I^*} - \frac{E}{E^*}\right) + r_2 I^*\left(\frac{I}{I^*} - \frac{E}{E^*}\right)\right] \\ &\quad + B\left(1 - \frac{I^*}{I}\right)\left[p\beta(N^*)S^*I^*\left(\frac{\beta(N)SI}{\beta(N^*)S^*I^*} - \frac{I}{I^*}\right) + k(1-r_1)E^*\left(\frac{E}{E^*} - \frac{I}{I^*}\right)\right]. \end{aligned} \tag{17}$$

Now, using Eq. (9), one has

$$E^* = \frac{1}{\mu + k(1-r_1)}[\beta(N^*)(1-p)S^*I^* + r_2 I^*].$$

Then, Eq. (17) may be rewritten as follows:

$$\begin{aligned}\dot{U}(S,E,I) = &-\frac{\mu(S-S^*)^2}{S} + \beta(N^*)S^*I^*\left[\left(1-\frac{S^*}{S}\right)\left(-\frac{\beta(N)SI}{\beta(N^*)S^*I^*}+1\right)\right.\\ &+A(1-p)\left(1-\frac{E^*}{E}\right)\left(\frac{\beta(N)SI}{\beta(N^*)S^*I^*}-\frac{E}{E^*}\right)+Bp\left(1-\frac{I^*}{I}\right)\left(\frac{\beta(N)SI}{\beta(N^*)S^*I^*}-\frac{I}{I^*}\right)\\ &\left.+\frac{Bk(1-r_1)(1-p)}{\mu+k(1-r_1)}\left(1-\frac{I^*}{I}\right)\left(\frac{E}{E^*}-\frac{I}{I^*}\right)\right]+r_2I^*\left[A\left(1-\frac{E}{E^*}\right)\left(\frac{I}{I^*}-\frac{E}{E^*}\right)\right.\\ &\left.+\frac{Bk(1-r_1)}{\mu+k(1-r_1)}\left(1-\frac{I^*}{I}\right)\left(\frac{E}{E^*}-\frac{I}{I^*}\right)\right].\end{aligned} \tag{18}$$

Now, let $(x,y,z,w) = (\frac{S}{S^*},\frac{E}{E^*},\frac{I}{I^*},\frac{N}{N^*})$ and $g(w) = \frac{\beta(wN^*)}{\beta(N^*)}$, then one gets

$$\begin{aligned}\dot{U}(S,E,I) &= -\mu\frac{(S-S^*)^2}{S} + \beta(N^*)S^*I^*\left[\left(1-\frac{1}{x}\right)(-g(w)xz+1)+A(1-p)\left(1-\frac{1}{y}\right)(g(w)xz-y)\right.\\ &\quad\left.+Bp\left(1-\frac{1}{z}\right)(g(w)xz-z)+\frac{Bk(1-r_1)(1-p)}{\mu+k(1-r_1)}\left(1-\frac{1}{z}\right)(y-z)\right]\\ &\quad+r_2I^*\left[A\left(1-\frac{1}{y}\right)(z-y)+\frac{Bk(1-r_1)}{\mu+k(1-r_1)}\left(1-\frac{1}{z}\right)(y-z)\right],\\ &= -\mu\frac{(S-S^*)^2}{S}+f(x,y,z,w),\end{aligned} \tag{19}$$

where

$$\begin{aligned}f(x,y,z,w) &= \beta(N^*)S^*I^*f_1(x,y,z,w)+r_2I^*f_2(z,w),\\ f_1(x,y,z,w) &= \left(1-\frac{1}{x}\right)(-g(w)xz+1)+A(1-p)\left(1-\frac{1}{y}\right)(g(w)xz-y)\\ &\quad+Bp\left(1-\frac{1}{z}\right)(g(w)xz-z)+\frac{Bk(1-r_1)(1-p)}{\mu+k(1-r_1)}\left(1-\frac{1}{z}\right)(y-z)\\ f_2(z,w) &= A\left(1-\frac{1}{y}\right)(z-y)+\frac{Bk(1-r_1)}{\mu+k(1-r_1)}\left(1-\frac{1}{z}\right)(y-z).\end{aligned} \tag{20}$$

The constants A and B can be choose in the form $A = A(p)$ and $B = B(p)$ such that the function f is non-positive for all $x,y,z,w \in \mathbb{R}_{\geqslant 0}$ so that the time derivative of $U(S, E, I)$ is less than zero. In order to cancel the coefficients of y and z in the expressions of f_1 and f_2, respectively, one can choose

$$A = \frac{k(1-r_1)}{\mu p + k(1-r_1)} \quad \text{and} \quad B = \frac{\mu + k(1-r_1)}{\mu p + k(1-r_1)}. \tag{21}$$

Substituting Eq. (21) into Eq. (20) and rearranging gives

$$\begin{aligned}f_1(x,y,z,w) &= 1+g(w)z-\frac{1}{x}+\frac{k(1-r_1)(1-p)}{p\mu+k(1-r_1)}\left(2-g(w)\frac{xz}{y}-z-\frac{y}{z}\right)+\frac{p[\mu+k(1-r_1)]}{p\mu+k(1-r_1)}(1-z-g(w)x),\\ f_2(y,z) &= \frac{k(1-r_1)}{p\mu+k(1-r_1)}\left(2-\frac{y}{z}-\frac{z}{y}\right).\end{aligned} \tag{22}$$

From the second equation of (22), using the arithmetic–geometric means inequality, it clearly appears that the function f_2 is less or equal to zero with equality at $y = z$. On the other hand, differentiating the function f_1 with respect to p yields

$$\frac{\partial f_1}{\partial p}(x,y,z,w) = -\frac{k(1-r_1)[\mu+k(1-r_1)]}{[\mu p+k(1-r_1)]^2}\left(1+g(w)x-g(w)\frac{xz}{y}-\frac{y}{z}\right).$$

If x, y, z, w are fixed, then $\frac{\partial f_1}{\partial p}$ has a constant sign for $p \in [0,1]$. Thus, f_1 is maximized at $p = 0$ or at $p = 1$.
Suppose that $p = 1$. Then, filling it into the first equation of (22) yields

$$f_1(x,y,z,w) = 2+(z-x)g(w)-z-\frac{1}{x}.$$

Using Eq. (1), one has $g(w) \leqslant 1$. Then, if $x \leqslant z$, the above equation becomes

$$f_1(x,w,z,w) \leqslant 2 - x - \frac{1}{x}, \tag{23}$$

which is less than or equal by the arithmetic–geometric mean inequality, with equality if and only if $x = 1$.

Similarly, if $p = 0$, then the function $f_1(x, y, z, w)$ becomes

$$f_1(x,y,z,w) = 3 + g(w)z\left(1 - \frac{x}{y}\right) - z - \frac{1}{x} - \frac{y}{z}.$$

Using Eq. (1), one has $g(w) \leqslant 1$. Then, if $x \leqslant y$, one obtains

$$f_1(x,y,z,w) \leqslant 3 - \frac{xz}{y} - \frac{1}{x} - \frac{y}{z}, \tag{24}$$

which is also less than or equal to zero by arithmetic–geometric mean inequality, with equality if and only if $x = 1$ and $y = z$.

Thus, $\dot{U}(S,E,I)$ is less or equal to zero with equality only if $S = S^*$ and $y = z$. LaSalle's extension [38–40] implies that solutions of (2) which intersect the interior of $\mathscr{D}$ limit to an invariant set contained in $\Omega = \{(S,E,I) \in \mathbb{R}^3_{\geqslant 0},\ S = S^*,\ E/E^* = I/I^*\}$. Then, it follows that the only invariant set contained in Ω is the set consisting of the endemic equilibrium point P^*. Therefore, all solutions of system (2) which intersect the interior of $\mathscr{D} \setminus \{E = I = 0\}$ limit to P^*. Then, one can conclude that the endemic equilibrium P^* is globally asymptotically stable on $\mathscr{D} \setminus \{E = I = 0\}$ for all non-negative initial conditions if inequalities (13) are satisfied. This ends the proof. □

Remark 2. It is possible for inequalities (13) to fail, in which case the global stability of the endemic equilibrium of model (2) has not been established. The local stability result and numerical simulations, however, seem to support the idea that the endemic equilibrium of model (2) is still global asymptotically stable even in these cases.

5. Numerical simulations

To illustrate the theoretical results contained in previous sections, system (2) is simulated with parameter values using real data of Cameroon [46,47] and summarize in Table 1.

Numerical results are reported in Figs. 2 and 7.

We first consider system (2) with $\beta(N) = \beta$. We choose $\beta = 0.01$ so that $\mathscr{R}_0 \leqslant 1$. Fig. 2 presents the trajectories plot and its plane figure for different initial conditions. From this figure, one can see that the trajectories of system (2) converge to the

Table 1
Description and estimation of parameters.

Parameter	Description	Estimated value	Source
Λ	Recruitment rate of susceptible individuals into the community	100 year^{-1}	[47]
$\beta(N)$	Transmission coefficient	Variable	Assumed
μ	Per capita naturally death rate	*0.0101* year^{-1}	[47]
k	Per capita rate of progression from infection to infectious	*0.005* year^{-1}	Assumed
r_1	Per capital rate of effective chemoprophylaxis	*0* year^{-1}	[46]
r_2	Per capita rate of effective therapy	*0.8182* year^{-1}	[46]
d	Per capita disease-induced mortality rate	*0.022722* year^{-1}	[46]
δ	Per capital rate of emigration	*0.16288* year^{-1}	[46]

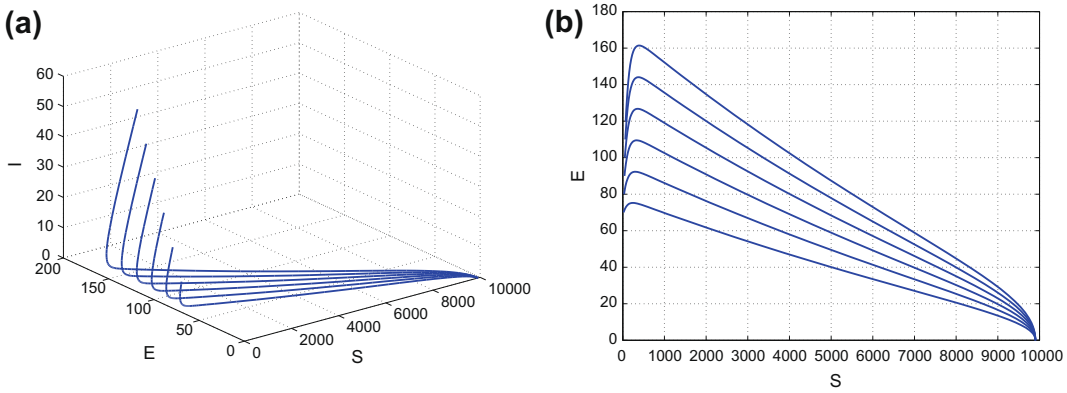

Fig. 2. Trajectories of model (2) and its plane figure for different initial conditions converge to the disease-free equilibrium P_0 when $\beta(N) = \beta = 0.001$ (so that $\mathscr{R}_0 \leqslant 1$).

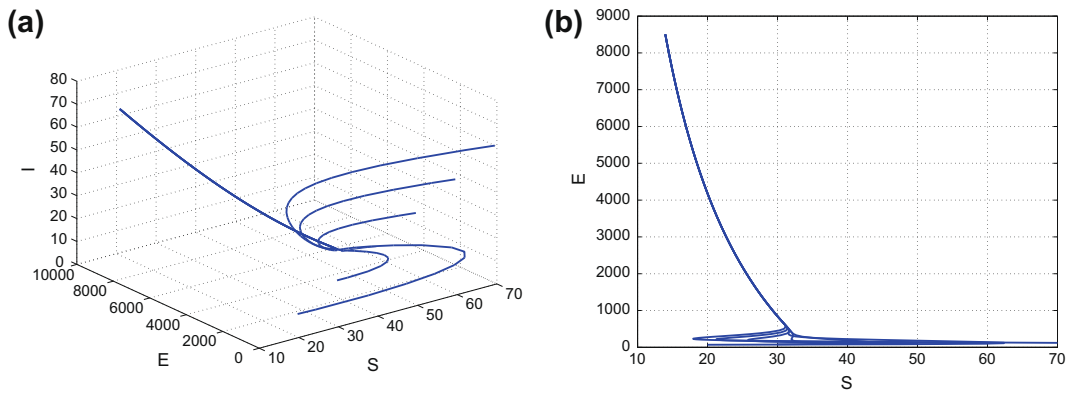

Fig. 3. Trajectories of model (2) and its plane figure for three different initial conditions converge to the unique endemic equilibrium P^* when $\beta(N) = \beta = 1$ (so that $\mathscr{R}_0 > 1$).

disease-free equilibrium. This means that the disease disappears in the host population. We also choose $\beta = 1$, so that $\mathscr{R}_0 > 1$. The trajectories plot and its plane figure are depicted in Fig. 3 for different initial conditions. One can observe that the trajectories converge to the unique endemic equilibrium point. This implies that the disease persists in the host population as shown in Theorem 2.

Consider the case when $\beta(N) = \frac{\beta}{N}$. Figs. 4 and 5 show the trajectories plot and its plane figure of system (2) for different initial conditions when $\beta = 0.001$ (so that $\mathscr{R}_0 \leqslant 1$); and $\beta = 1$ (so that $\mathscr{R}_0 > 1$), respectively. As the previous cases, one can

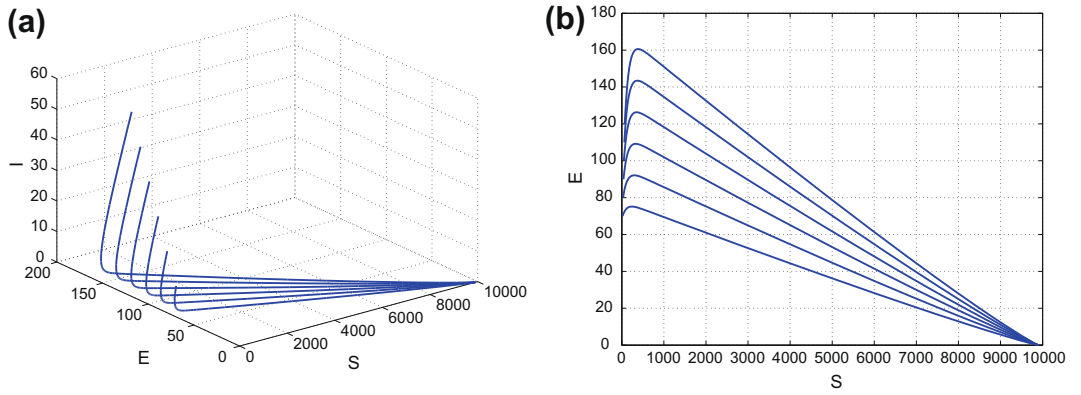

Fig. 4. Trajectories of model (2) and its plane figure for different initial conditions converge to the disease-free equilibrium P_0 when $\beta(N) = \beta/N$ and $\beta = 0.001$ (so that $\mathscr{R}_0 \leqslant 1$).

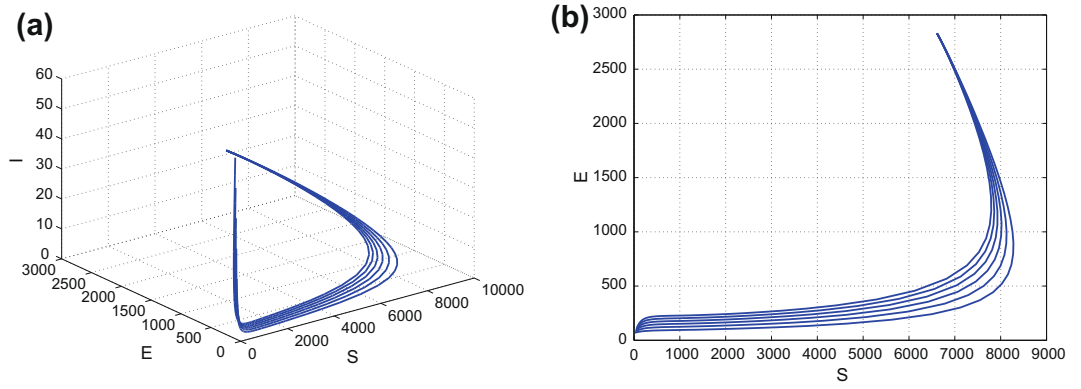

Fig. 5. Trajectory of model (2) and its plane figure for three different initial conditions converge to the unique endemic equilibrium P^* when $\beta(N) = \beta/N$ and $\beta = 2$ (so that $\mathscr{R}_0 > 1$).

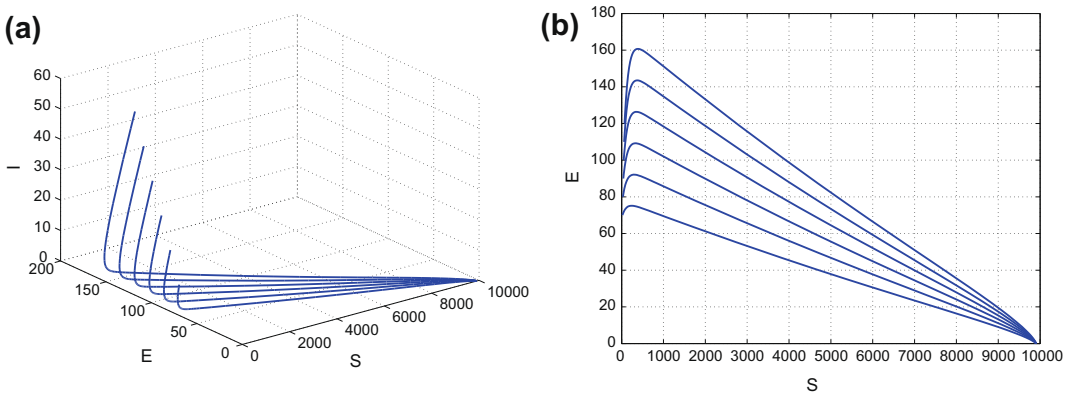

Fig. 6. Trajectories of model (2) for different initial conditions converge to the unique endemic equilibrium P_0 when $\beta(N) = bN/(1 + bN + \sqrt{1 + 2bN})$ and $b = 0.001$ (so that $\mathscr{R}_0 \leqslant 1$).

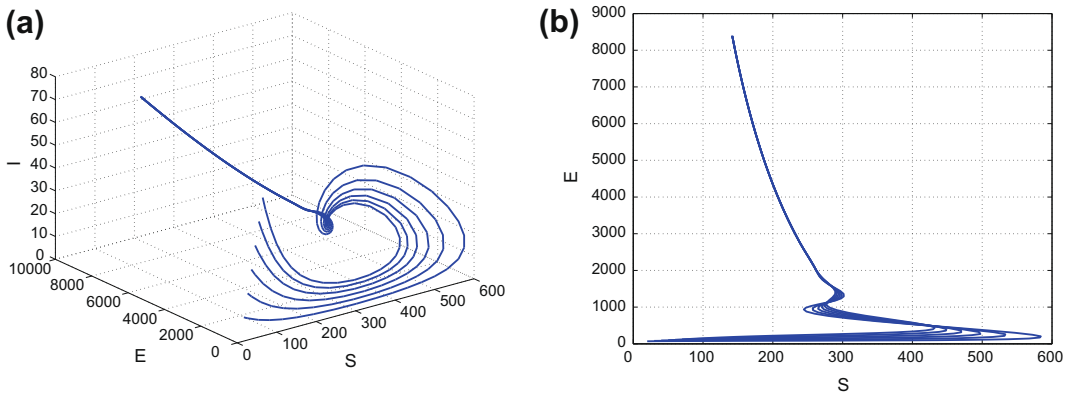

Fig. 7. Trajectories of model (2) for different initial conditions converge to the unique endemic equilibrium P^* when $\beta(N) = bN/(1 + bN + \sqrt{1 + 2bN})$ and $b = 1$ (so that $\mathscr{R}_0 > 1$).

observe that the trajectories of system (2) converge to the disease-free equilibrium when $\mathscr{R}_0 \leqslant 1$ (see Fig. 4), while the trajectories of system (2) converge to the unique endemic equilibrium point when $\mathscr{R}_0 > 1$ (see Fig. 5).

Now assume that $\beta(N) = \frac{bN}{1+bN+\sqrt{1+2bN}}$ in system (2). Numerical results are depicted in Figs. 6 and 7 for different initial conditions. Fig. 6 presents the trajectories and its plane figure when $b = 0.001$, i.e., $\mathscr{R}_0 \leqslant 1$. From this figure, it clearly appears that the disease disappears in the host population. Fig. 7 presents the time trajectories and its plane figure when $b = 1$, i.e., $\mathscr{R}_0 > 1$. Also, one can see that the disease persists in the host population.

6. Conclusion

This paper has considered a tuberculosis model that incorporate general contact rate, constant recruitment, slow and fast progression, effective chemoprophylaxis and therapeutic treatments. By using the Lyapunov stability theory, the global stability of the proposed model is completely proved. We show that the dynamics of the disease transmission model is governed by a basic reproductive ratio $\mathscr{R}_0$. When $\mathscr{R}_0 \leqslant 1$, then all solutions converge to the disease-free equilibrium, while when $\mathscr{R}_0 > 1$, then the disease-free equilibrium is unstable and there exists a unique positive equilibrium which is globally asymptotically stable under certain conditions. A fairly good agreement is obtained between the analytical and numerical results.

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References

[1] Snider D, Raviglione M, Kochi A. In: Bloom B, editor. Global burden of tuberculosis 1994;16:3.
[2] Reichman L, Tanne JH. Timebomb: the global epidemic of multi-drug-resistant tuberculosis. New York, NY: McGraw-Hill; 2002.
[3] Small P, Hopewell P, Singh S, Paz A, Parsonnet J, Ruston D, et al. The epidemiology of tuberculosis in San Francisco a population-based study using conventional and molecular methods. New Engl J Med 1994;330(24):1703–11.
[4] Enarson D, Murray J. In: Rom W, Garay, editors. Global epidemiology of tuberculosis 1996;17:57–61.
[5] Adler J, Rose D. In: Rom W, Garay, editors. Transmission and pathogenesis of tuberculosis, vol. 17, 1996.
[6] Karus C. Tuberculosis: an overview of pathogenesis and prevention. Nurse Pract 1983;8(2):21–33.
[7] Bloom B, editor. Tuberculosis: pathogenesis protection and control. Washington, BC: ASM; 1994.
[8] Rom W, Garay S, editors. Tuberculosis. New York: Little Brown; 1996.
[9] Chapman J, Dyerly M. Social and other factors in intrafamilial transmission of tuberculosis. Am Rev Respirat Dis 1964;90:48.
[10] Nardell E, Piessens W. Transmission of tuberculosis. In: Reichman L, Hershfield E, editors. Tuberculosis: a comprehensive international approach, vol. 134. New York, NY: Macrel Dekker; 2000. p. 215.
[11] Enarson D. Why not the elimination of tuberculosis? Mayo Clin Proc 1994;69:85–93.
[12] Hetcote HW. The mathematics of infectious diseases. SIAM Rev 2000;42(4):599–635.
[13] Busenberg S, Van den Driessche P. Analysis of a disease transmission model in a population with varying size. J Math Biol 1990;28:257–70.
[14] Anderson RM, May RM. Infectious disease of humans, dynamics and control. London, New York: Oxford Univ. Press; 1991.
[15] Hetcote HW. The mathematics of infectious diseases. SIAM Rev 2000;42(4):599–635.
[16] Brauer F, Castillo-Chavez C. Mathematical models in population: biology and epidemiology, text in applied mathematics. New York: Springer; 2001.
[17] Murphy BM, Singer BH, Kirschner D. Comparing epidemic tuberculosis in demographically distinct populations. Math Biosci 2002;180:161–85.
[18] Blower SM, McLean AR, Porco TC, Small PM, Hopwell PC, Sanchez MA, et al. The intrinsic transmission dynamics of tuberculosis epidemics. Nature Med 1995;1:815–21.
[19] Castillo-Chavez C, Song B. Dynamical models of tuberculosis and their applications. Math Biosci Eng 2004;1:361–404.
[20] Murphy BM, Singer BH, Kirschner D. On the treatment of tuberculosis in hetergeneous populations. J Theor Biol 2003;223:391–404.
[21] Murray C, Salomon J. Modelling the impact of global tuberculosis control strategies. Proc Nature Sci USA 1998;95:13881–6.
[22] Castillo-Chavez C, Feng Z. Global stability of an age-structured model for tuberculosis and its application to vaccine strategies. Math Biosci 1998;151:135–54.
[23] Moghadas SM, Gumel AB. Analysis of a model for transmission dynamics of TB. Can Appl Math Quart 2002;10:411–27.
[24] McCluskey CC. Lyapunov functions for tuberculosis models with fast and slow progression. Math Biosci Eng 2006;3:603–14.
[25] Castillo-Chavez C, Feng Z. To treat or not to treat: the case of tuberculosis. J Math Biol 1997;35:629–56.
[26] Connell McCluskey C, van den Driessche P. Global analysis of two tuberculosis models. J Dyn Differ Eq 2004;16:139–66.
[27] McCallum H, Barlow N, Hone J. Trends Ecol Evol 2001;6:295–300.
[28] Li MY, Muldowney JS. Global stability for the SEIR models in epidemiology. Math Biosci 2005;125:155–64.
[29] Heesterbeek JAJ, Metz JAJ. The saturating contact rate in marriage and epidemic models. J Math Biosci 1995;125:155–64.
[30] Korobeinikov A. Lyapunov functions and global properties for SIER and SEIS epidemic models. Math Med Biol 2004;21:75–83.
[31] Korobeinikov A, Maini PK. A Lyapunov function and global properties for SIR and SEIR epidemiological models with nonlinear incidence. Math Biosci Eng 2004;1:57–60.
[32] Korobeinikov A, Wake GC. Lyapunov functions and global stability for SIR, SIRS and SIS epidemiological models. Appl Math Lett 2002;15:955–61.
[33] Bame N, Bowong S, Mbang J, Sallet G, Tewa JJ. Global stability for SEIS models with n latent classes. Math Biosci Eng 2008;5:20–33.
[34] Iggidr A, Kamgang JC, Sallet G, Tewa JJ. Global analysis of new malaria intrahost models with a competitive exclusion principle. SIAM J Appl Math 2007;1:260–78.
[35] Adda P, Dimi JL, Iggidr A, Kamgang JC, Sallet G, Tewa JJ. General models of host-parasite systems. Global Anal Discrete Contin Dyn Syst Ser B 2007;8:1–17.
[36] Iggidr A, Mbang J, Sallet G, Tewa JJ. Multi-compartment models. DCDS 2007:506–19.
[37] Iggidr A, Mbang J, Sallet G. Stability analysis of within-host parasite models with delays. Math Biosci 2007;209:51–75.
[38] LaSalle JP. The stability of dynamical systems. Philadelphia, PA: Society for Industrial and Applied Mathematics; 1976. With an appendix: "Limiting equations and stability of nonautonomous ordinary differential equations" by Z. Artstein, Regional Conference Series in Applied Mathematics.
[39] LaSalle JP. Stability theory for ordinary differential equations, stability theory for ordinary differential equations. J Differ Eq 1968;41:57–65.
[40] Bhatia NP, Szegö GP. Stability theory of dynamical systems. Springer-Verlag; 1970.
[41] Thieme HR, Castillo-Chavez C. On the role of variable infectivity in the dynamics of the human immunodeficiency virus epidemic. In: Mathematical and statistical approaches to aids epidemiology, Lecture Note in Biomathematics, vol. 83. Berlin: Springer; 1999. p. 157.
[42] Diekmann O, Heesterbeek PJA, Metz JAJ. On the definition and the computation of the basic reproduction ratio R_0 in models for infectious diseases in heterogenous populations. J Math Biol 2000;28:365–82.
[43] Kamgang JC, Sallet G. Global asymptotic stability for the disease free equilibrium for epidemiological models. C.R. Math. Acad. Sci. Paris, Ser I 2005;341:433–8.
[44] Jacquez JA, Simon CP. Qualitative theory of compartmental systems. SIAM Rev 1993;35:43–79.
[45] van den Driessche P, Watmough J. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. Math Biosci 2002;180:28–9.
[46] National Committee for Fight Tuberculosis in Cameroon. Livret du personnel de la santé, 2001.
[47] National Institute of Statistics. Evolution des systèmes statistiques nationaux, 2007.