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MODELING AND PARAMETER ESTIMATION OF TUBERCULOSIS WITH APPLICATION TO CAMEROON

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This paper deals with the problem of modeling and parameter estimation of a deterministic model of tuberculosis (abbreviated as TB for *tubercle bacillus*). We first propose and analyze a tuberculosis model without seasonality that incorporates the essential biological and epidemiological features of the disease. The model is shown to exhibit the phenomenon of backward bifurcation, where a stable disease-free equilibrium coexists with one or more stable endemic equilibria when the associated basic reproduction number is less than unity. The statistical data of new TB cases show seasonal fluctuations in many countries. Then, we extend the proposed TB model by incorporating seasonality. We propose a numerical study to estimate unknown parameters according to demographic and epidemiological data in Cameroon. Simulation results are in good accordance with the seasonal variation of the reported new cases of active TB in Cameroon.

Keywords: Dynamical systems; epidemiological models; tuberculosis; season pattern; parameter estimation.

1. Introduction

Tuberculosis is a common deadly infectious disease caused mainly by *Mycobacterium tuberculosis*. It basically attacks the lungs (pulmonary TB), but can also affect the central nervous system, circulatory system, the genital-urinary system, bones, joints and even the skin. Tuberculosis can spread through cough, sneeze, speak, kiss or spit from active pulmonary TB persons. It can also spread through use of an infected person's unsterilized eating utensils and in rare cases a pregnant woman with active TB can infect her foetus (vertical transmission) [Dye & Williams, 2010; World Health Organization, 2009]. More than 36 million patients have been successfully treated via the World Health Organization strategy for tuberculosis control since 1995. Despite predictions of a decline in global incidence, the number of new cases continues to grow,

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approaching 10 million in 2010 [Dye & Williams, 2010; World Health Organization, 2009]. This rise has been attributed to the spread of HIV, the collapse of public health programs and the emergence of drug-resistant strains of *M. tuberculosis*. It is worth emphasizing that mathematical analysis of biomedical and disease transmission models can contribute to the understanding of the mechanisms of those processes and to design potential therapies [Anderson & May, 1992; Capasso, 1993; Thieme, 2003]. A number of theoretical studies have been carried out on the mathematical modeling of TB transmission dynamics [Castillo-Chavez & Song, 2004; Bowong & Tewa, 2009; Bowong, 2010; Murphy *et al.*, 2003; Blower *et al.*, 1998; Feng *et al.*, 2000]. A lot of glorious results have appeared. The basic and important research subjects for these models are the existence of a threshold value which distinguishes whether TB disease will die out, the local and global stability of the disease-free equilibrium and endemic equilibria, the existence of periodic solutions, the persistence and extinction of the disease, etc.

Although TB is not widely recognized as having seasonal trends like measles, diphtheria, chickenpox, cholera, malaria, and even sexually transmitted gonorrhea [Grassly & Fraser, 2006; Hethcote & Yorke, 1984], some studies have shown variable periods of peak seasonality in TB incidence rates in late winter to early spring in South Africa [Schaaf *et al.*, 1996], during summer in United Kingdom [Douglas *et al.*, 1996] and Hong Kong [Leung *et al.*, 2005], during summer and autumn in Spain [Rios *et al.*, 2000], and during spring and summer in Japan [Nagayama & Ohmori, 2006]. In northern India, it was indicated that TB diagnosis peaked between April and June, and reached a nadir between October and December, and the magnitude of seasonal variation had important positive correlation with rates of new smear-positive TB cases [Thorpe *et al.*, 2004].

The real causes of seasonal patterns of TB remain unknown, but the seasonal trend, with higher incidence rate in winter, may be relevant to the increased periods spent in overcrowded, poorly ventilated housing conditions, these phenomena much more easily seen than in warm seasons [Schaaf *et al.*, 1996; Rios *et al.*, 2000], and/or vitamin D deficiency leading to reactivation of latent/exposed infection, which may have been the basic causes for observed TB seasonality [Thorpe *et al.*, 2004]. Furthermore, in winter and spring, the viral infections like flu are more frequent and cause immunological deficiency leading to reactivation of the *M. tuberculosis* [Aron & Schwartz, 1984]. There is a growing awareness that seasonality can cause population fluctuations ranging from annual cycles to multiyear oscillations, and even chaotic dynamics [Rios *et al.*, 2000]. From an applied perspective, clarifying the mechanisms that link seasonal environmental changes to diseases dynamics may aid in forecasting the long-term health risks, in developing an effective public health program, and in setting objectives and utilizing limited resources more effectively [Rios *et al.*, 2000; Nagayama & Ohmori, 2006; Altizer *et al.*, 2006]. For these reasons, we need to identify possible seasonal patterns in the incidence rate for pulmonary tuberculosis. In addition, a systematic construction of a TB model that best matches parameter estimation of the model equations from real data is needed. However, relating a model to observed data is not a straightforward matter due to the complexity of the model and noise in the data. Unfortunately, nothing has been done in terms of estimating all or some parameters of tuberculosis in developing countries.

In this paper, motivated by the usefulness of and the current investigation on the spread of infectious diseases, we intend to systematically investigate the analysis and parameter estimation of tuberculosis in the modeling framework. We first formulate and analyze a tuberculosis model without seasonality which incorporates the essential biological and epidemiological features of the disease such as exogenous reinfection of latently infected and recovered individuals, chemoprophylaxis of latently infected individuals, treatment of infectious and relapse of recovered individuals. We show that the model exhibits the phenomenon of backward bifurcation, where a stable disease-free equilibrium co-exists with one or more stable endemic equilibria when the associated basic reproduction number is less than unity. Then, the extension of our TB model by incorporating seasonality is proposed. Based on this model, we suggest a simulation method to parameter estimation by exploiting information obtained from only real data in Cameroon, which is crucial for many practical application such as the prediction and the control of TB. Our results point out that from the quarterly reported data (2003–2007) of the National Committee to Fight against Tuberculosis [National Committee of Fight Against Tuberculosis, 2001], there is a seasonal pattern in new TB cases. An advantage of the proposed

simulation study is that it is less computationally intensive and easier to implement. It is our view, this study represents the first work that provides an in-depth TB seasonality and parameter estimation using real demographic and epidemiological data of the situation of TB in a developing country like Cameroon.

The rest of the paper is organized as follows. In Sec. 2, a model without seasonality for the dynamics of TB is formulated and rigorously analyzed. Section 3 extends the model formulated in Sec. 2 to describe seasonal incidence rate by incorporating periodic coefficients. Numerical results are presented to illustrate analytical results. Finally, Sec. 4 contains concluding remarks.

2. Model

TB is an old disease whose world-wide prevalence had been diminishing even before vaccination and prophylaxis strategies were first accomplished [Wilson, 1990; Styblo *et al.*, 1969; Daniel *et al.*, 1994]. Its recent return in developing countries, mainly in Southeast Asia, has attracted renewed interest. The current world estimate of prevalence is about 33% while the number of deaths per year that it is causing reaches more than 3 million people [World Health Organization, 2009]. Depending on the kind and the intensity of immune response that the host immune system performs after initial infection with *M. tuberculosis bacillus*, the individual can suffer latent infection, in which the bacteria are under a growth-arrest regime and the individual neither suffers any clinical symptom nor becomes infectious or actively infected, where the host suffers clinical symptoms and can transmit the pathogen by air [Bleed *et al.*, 1982; Styblo, 1986]. Latently infected individuals can, generally after an immune-depression episode, reach the active phase. Estimating the probability of developing direct active infection after a contact, or alternatively, the lifetime's risk for a latent infected individual to evolve into the active phase, are not easy tasks. However, it is generally accepted that only 5–10% of the infections directly produce active TB [Bleed *et al.*, 1982; Styblo, 1986], while the ranges concerning the estimation of typical "half-life" of latent state rounds about 500 years [Murphy *et al.*, 2002].

2.1. *Model formulation*

We assume that individuals in a population are compartmentalized into four groups: healthy or susceptible $S(t)$, infected but not infectious or latently infected $E(t)$, sick individuals $I(t)$ which are infected and are infectious as well and recovered individuals $R(t)$. The transition between these subpopulations proceeds in such a way that a susceptible individual acquires the bacteria through a contact with an infectious subject with the transmission rate β. In its turn, this newly infected individual may develop the disease directly with probability p. However, the most common case is the establishment of a dynamical equilibrium between the bacillus and the host's immune system, which allows the survival of the former inside the latter. When this happens, newly infected individuals become latently infected, because despite harboring the bacteria in their blood, neither becomes sick nor is able to infect others. Once latently infected, an individual can follow a chemoprophylaxis. We assume that chemoprophylaxis of latently infected individuals reduces their reactivation. On the other hand, after a certain period of time (which may be several years) and usually following an episode of immunosuppression, the balance between the bacterium and its host can be broken. In this case, the bacteria grow and the individual falls ill beginning to develop the clinical symptoms of the disease. It is also possible that latently infected individuals who did not receive effective chemoprophylaxis can be reinfected (exogenously) through a contact with an infectious subject with the same transmission rate β. In addition, if the infection attacks the lungs (pulmonary TB), the bacillus is present in the sputum, making the guest infectious. After receiving effective therapy, the infectious spontaneously recovers from the disease. Recovered individuals can only have partial immunity, and hence, they can undergo a reactivation of the disease or be reinfected against with the same transmission rate β. The model flow diagram is shown in Fig. 1.

The dynamics of the disease, in a well-mixed population, is then described by the following system of nonlinear differential equations:

$$\begin{cases} \dot{S} = \Lambda - \lambda S - \mu S, \\ \dot{E} = (1-p)\lambda S + \theta I + \sigma_2(1-\gamma)\lambda R \\ \qquad - \sigma_1(1-r_1)\lambda E - A_1 E, \\ \dot{I} = p\lambda S + \gamma R + (1-r_1)(k+\sigma_1\lambda)E - A_2 I, \\ \dot{R} = \alpha(1-\theta)I - \sigma_2(1-\gamma)\lambda R - A_3 R, \end{cases} \tag{1}$$

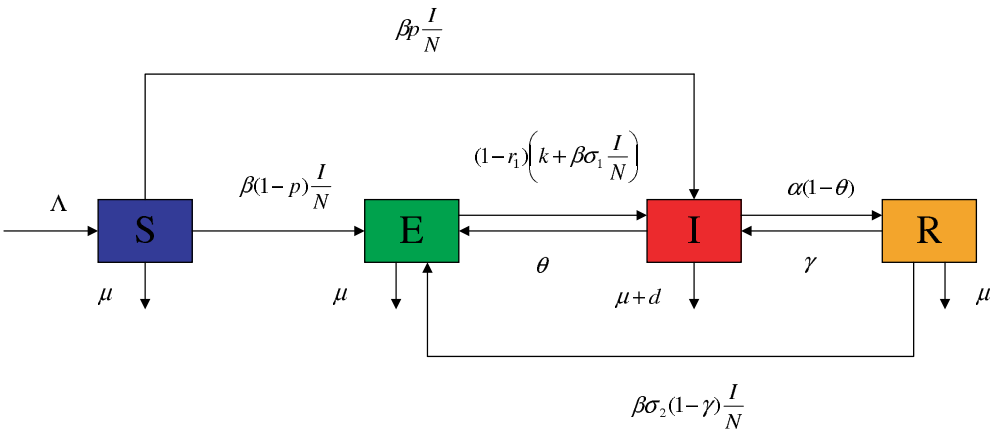


Fig. 1. Flowchart of the dynamical transmission of tuberculosis.

where

$$\lambda = \beta\frac{I}{N}, \quad A_1 = \mu + k(1-r_1),$$

$$A_2 = \mu + d + \theta + \alpha(1-\theta) \quad \text{and} \quad A_3 = \mu + \gamma.$$

In Eq. (1), $N(t) = S(t) + E(t) + I(t) + R(t)$ represents the total population at time t, $\lambda = \beta I/N$ is the force of the infection; β is the effective contact rate of the infectious that is sufficient to transmit the infection to the susceptible; Λ is the recruitment (immigration and birth) rate; μ is the natural death rate per capital; d is the rate of disease-related death; r_1 is the chemoprophylaxis rate of latently-infected individuals; k is the transition frequency of latent infection (i.e. the probability that a latently infected individual becomes infectious); σ_1 and σ_2 are respectively, the probabilities that the bacteria are transmitted to an old latent and recovered host after a contact with a infectious subject; α is the recovery rate of infectious (i.e. the probability that an infectious person recovered from the disease after a therapy of treatment); θ is the natural recovery rate (i.e. the probability that an infectious person recovered from the disease without therapy of treatment) and γ is the relapse rate (i.e. the probability that a recovered individual becomes infectious again). We point out that parameters β and k are generally difficult to estimate and the rest of the parameters can be estimated using real data of the situation of TB.

For model (1) to be epidemiologically meaningful, it is important to prove that all its state variables are non-negative for all time. In other words, solutions of the model (1) with positive initial data have to remain positive for all time $t > 0$. This can be verified as follows.

Assume that $\bar{t} = \sup\{t > 0 : S > 0, E > 0, I > 0, R > 0\} \in [0, t]$. Thus, $\bar{t} > 0$ and it follows from the first equation of system (10), that

$$\frac{dS}{dt} = \Lambda - (\mu + \lambda)S,$$

which can be rewritten as,

$$\frac{d}{dt}\left[S(t)\exp\left\{\mu t + \int_0^t \lambda(s)ds\right\}\right] \geq \Lambda\exp\left\{\mu t + \int_0^t \lambda(s)ds\right\}.$$

Hence,

$$S(\bar{t})\exp\left\{\mu\bar{t} + \int_0^{\bar{t}} \lambda(s)ds\right\} - S(0) \geq \int_0^{\bar{t}} \Lambda\exp\left\{\mu u + \int_0^u \lambda(w)dw\right\}du,$$

so that

$$S(\bar{t}) \geq S(0)\exp\left\{-\left(\mu\bar{t} + \int_0^{\bar{t}} \lambda(s)ds\right)\right\} + \exp\left\{-\left(\mu\bar{t} + \int_0^{\bar{t}} \lambda(s)ds\right)\right\} \times \int_0^{\bar{t}} \Lambda\exp\left\{\mu u + \int_0^u \lambda(w)dw\right\}du > 0.$$

Thus, $S(t) \geq 0$ for all $t > 0$. Similarly, it can be shown that the remaining variables are also positive for all time $t > 0$.

Now, we will show that all feasible solutions are uniformly-bounded in a proper subset of Ω.

Let, $S, E, I, R \geq 0$ be any solution of the system with non-negative initial conditions. Adding all equations in the differential system (1) yields

$$\dot{N} = \Lambda - \mu N - dI.$$

Thus, we can deduce that $\dot{N} \leq \Lambda - \mu N$. It then follows that $\lim_{t\to+\infty} N(t) \leq (\Lambda/\mu)$ which implies that the trajectories of model (1) are bounded. On the other hand, from the differential inequality $\dot{N} \leq \Lambda - \mu N$, one can deduce that $N(t) \leq N(0)e^{-\mu t} + (\Lambda/\mu)(1 - e^{-\mu t})$. In particular $N(t) \leq (\Lambda/\mu)$, if $N(0) \leq (\Lambda/\mu)$. Therefore, all feasible solutions of the components of the system (1) enter the region

$$\Omega = \left\{(S, E, I, R) \in \mathbb{R}^4_{\geq 0}, N(t) \leq \frac{\Lambda}{\mu}\right\}. \qquad (2)$$

It then follows from (2) that all possible solutions of system (1) will enter the region Ω. Hence, the region Ω, of biological interest, is positively-invariant under the flow induced by system (1). Further, it can be shown using the theory of permanence [Hutson & Schmitt, 1992] that all solutions on the boundary of Ω will eventually enter the interior of Ω. Furthermore, in Ω, the usual existence, uniqueness and continuation results hold for system (1). Hence, system (1) is well posed mathematically and epidemiologically and it is sufficient to consider the dynamics of the flow generated by system (1) in Ω.

2.2. *Local stability of the disease-free equilibrium (DFE)*

For the analysis of the infection's spread, the so-called disease-free equilibrium is particularly relevant. By definition, this is obtained by taking $I = 0$ in equations of system (1) at the equilibrium. Then, the disease-free equilibrium is given by $Q_0 = (\Lambda/\mu, 0, 0, 0)$.

Linearizing all equations in system (1) around the disease-free equilibrium, it follows that the Jacobian matrix of the system is

$$J = \begin{pmatrix} -\mu & 0 & -\beta & 0 \\ 0 & -A_1 & \beta(1-p)+\theta & 0 \\ 0 & k(1-r_1) & \beta p - A_2 & \gamma \\ 0 & 0 & \alpha(1-\theta) & -A_3 \end{pmatrix}.$$

Since $-\mu < 0$, the triangular structure of the Jacobian matrix implies that its stability is associated with the stability of the following submatrix:

$$J_0 = \begin{pmatrix} -A_1 & \beta(1-p)+\theta & 0 \\ k(1-r_1) & \beta p - A_2 & \gamma \\ 0 & \alpha(1-\theta) & -A_3 \end{pmatrix}.$$

Now let

$$A = -A_1, \quad B = [\beta(1-p)+\theta \quad 0],$$

$$C = \begin{bmatrix} k(1-r_1) \\ 0 \end{bmatrix} \quad \text{and} \quad D = \begin{bmatrix} \beta p - A_2 & \gamma \\ \alpha(1-\theta) & -A_3 \end{bmatrix}.$$

Then, using the results of [Kamgang & Sallet, 2005] on the computation of the eigenvalues of a matrix of dimension n, one can show that the stability of the submatrix J_0 is associated with the stability of the following matrix of dimension 2:

$$J_1 = D - CA^{-1}B = \begin{bmatrix} \beta p - A_2 + \dfrac{k(1-r_1)}{A_1}[\beta(1-p)+\theta] & \gamma \\ \alpha(1-\theta) & -A_3 \end{bmatrix}.$$

The matrix J_1 is stable if its trace is negative and its determinant non-negative. Therefore, a sufficient condition for this equilibrium to be stable is given by

$$\frac{\beta(\mu+\gamma)[p\mu + k(1-r_1)]}{(\mu+\gamma)[\mu(\mu+d+\theta)+k(1-r_1)(\mu+d)] + \mu\alpha(1-\theta)[\mu+k(1-r_1)]} \leq 1. \qquad (3)$$

Model of this type demonstrates clearly the infection threshold. In the presence of a threshold, disease eradication requires the reduction of the infection rate below a critical level where a stable infection-free equilibrium is guaranteed. In epidemiological terminology, the infection threshold may be expressed in terms of the basic reproductive number $\mathcal{R}_0$, the average number of infections produced by a single infected individual in a population of susceptible individuals. From this definition, it is clear that TB infection cannot spread in a population only if $\mathcal{R}_0 < 1$. It then follows that the basic reproduction number $\mathcal{R}_0 < 1$ is given by

Table 1. Numerical values for the parameters of model.

Parameters	Symbol	Estimate	Source
Recruitment rate of susceptible	Λ	397800/yr	NIS[1]
Transmission rate	β	Variable	Assumed
Fast route to active TB	p	0.015	NCFAT[2]
Reinfection parameter of latently infected individuals	σ_1	3	Assumed
Reinfection parameter of recovered individuals	σ_2	3	Assumed
Slow route to active TB class	k	0.00013/yr	Assumed
Natural mortality	μ	0.019896/yr	NIS
TB mortality of infectious	d	0.0575/yr	NCFAT
Chemoprophylaxis rate of latently infected individuals	r_1	0/yr	NCFAT
Recovery rate of infectious	α	0.7311/yr	NCFAT
Natural recovery	θ	0.1828/yr	Assumed
Relapse of recovered individuals	γ	0.0986/yr	NCFAT

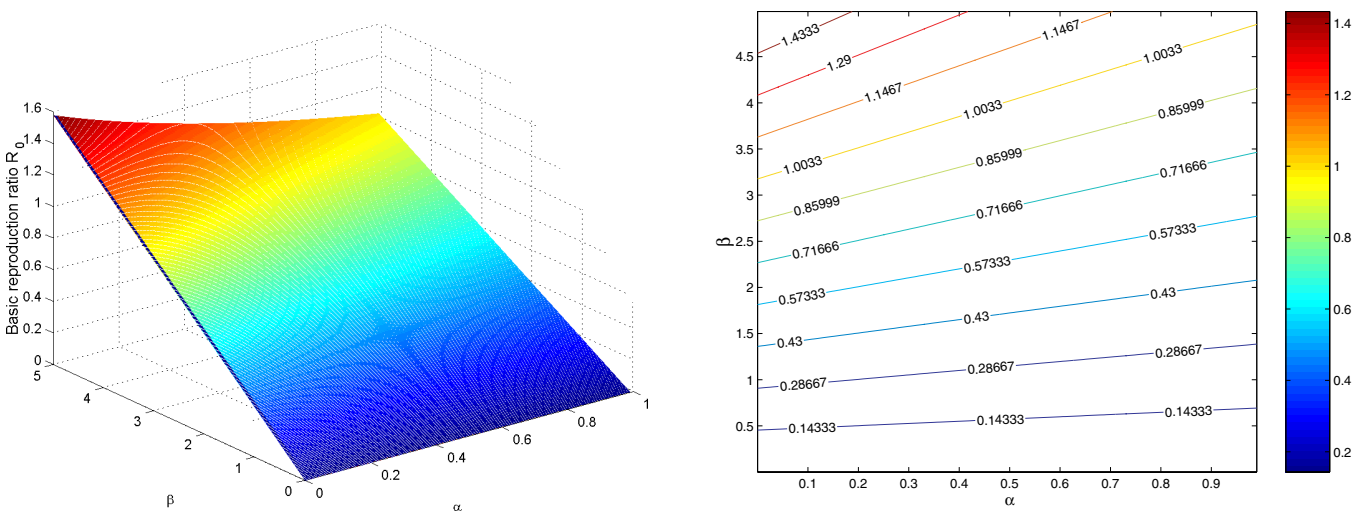
[1]National Institute of Statistics.
[2]National Committee of Fight Against Tuberculosis.

$$\mathcal{R}_0 = \frac{\beta(\mu+\gamma)[p\mu + k(1-r_1)]}{(\mu+\gamma)[\mu(\mu+d+\theta)+k(1-r_1)(\mu+d)] + \mu\alpha(1-\theta)[\mu+k(1-r_1)]}. \tag{4}$$

In conclusion, crossing the threshold reduces the basic reproductive number $\mathcal{R}_0$ below unity and the infection is prevented from propagating.

The TB model (1) was simulated with the parameter values using demographic and epidemiological data of Cameroon and summarized in Table 1.

Now, let us analyze the effects of the transmission rate β and the recovery rate α on the basic reproduction ratio $\mathcal{R}_0$. Figure 2 shows the effects of β and α on the basic reproduction ratio $\mathcal{R}_0$. All other parameters are as in Table 1. From this figure, one can see that $\mathcal{R}_0$ decreases if β decreases even in the case of large values of α. This means that if the transmission coefficient β is sufficiently small, TB infection could be eliminated even if $\alpha = 0$. However, it is difficult to control β. Therefore, the recovery of infectious individuals is an efficient intervention. Thus, combining recovery of infectious with reduction of contacts can reduce $\mathcal{R}_0$ to be less than 1. Then, the optimal control strategy will be a



(a) (b)

Fig. 2. Graphs of the basic reproduction number $\mathcal{R}_0$ of system (1) depending on β and α. All other parameters are as in Table 1.

combination of recovery of infectious, chemoprophylaxis of latently-infected individuals, and reduction of contacts.

2.3. *Equilibria and bifurcation*

Herein, we investigate the number of equilibrium solutions that model (1) can have. To this end, let $Q^* = (S^*, E^*, I^*, R^*)$ be any arbitrary equilibrium of model (1). To find conditions for the existence of an equilibrium for which tuberculosis is endemic in the population (steady state with I^* nonzero), the equations in model (1) are set at zero, i.e.

$$\begin{cases} \Lambda - \lambda^* S^* - \mu S^* = 0, \\ (1-p)\lambda^* S^* + \sigma_2(1-\gamma)\lambda^* R^* \\ \qquad - \sigma_1(1-r_1)\lambda^* E^* + \theta I^* - A_1 E^* = 0, \\ p\lambda^* S^* + \sigma_1(1-r_1)\lambda^* E^* + k(1-r_1)E^* \\ \qquad + \gamma R^* - A_2 I^* = 0, \\ \alpha(1-\theta)I^* - \sigma_2(1-\gamma)\lambda^* R^* - A_3 R^* = 0, \end{cases} \tag{5}$$

where

$$\lambda^* = \beta \frac{I^*}{N^*}, \tag{6}$$

is the force of infection at the steady state. Solving the above equations in (5) at the steady state gives

$$S^* = \frac{\Lambda}{\mu + \lambda^*}, \quad I^* = \frac{\Lambda\lambda^*}{\beta\mu + d\lambda^*}, \quad R^* = \frac{\alpha\Lambda(1-\theta)\lambda^*}{(\beta\mu + d\lambda^*)[A_3 + \sigma_2(1-\gamma)\lambda^*]} \quad \text{and}$$
$$E^* = \frac{\Lambda\lambda^*[(1-p)(\beta\mu + d\lambda^*) + \theta(\mu+\lambda^*)][A_3 + \sigma_2(1-\gamma)\lambda^*] + \sigma_2\alpha(1-\gamma)(1-\theta)(\mu+\lambda^*)\lambda^*}{(\mu+\lambda^*)(\beta\mu + d\lambda^*)[A_1 + \sigma_1(1-r_1)\lambda^*][A_3 + \sigma_2(1-\gamma)\lambda^*]}. \tag{7}$$

Substituting (7) in (6), it can be shown that the nonzero equilibria of system (5) satisfy the following cubic equation in terms of λ^*:

$$a_3(\lambda^*)^3 + a_2(\lambda^*)^2 + a_1(\lambda^*) + a_0 = 0, \tag{8}$$

where

$$\begin{aligned} a_3 &= \sigma_1\sigma_2(1-r_1)(1-\gamma)\mu, \\ a_2 &= \sigma_1\sigma_2(1-r_1)(1-\gamma)\mu(\mu + d - \beta) \\ &\quad + \sigma_1(1-r_1)\mu[\mu + \gamma + \alpha(1-\theta)] \\ &\quad + \sigma_2(1-\gamma)\mu[\mu + \theta + \alpha(1-\theta) + k(1-r_1)], \\ a_1 &= \sigma_1(1-r_1)\mu[\mu\alpha(1-\theta) + (\mu+\gamma)(\mu + d - \beta)] \\ &\quad + \sigma_2(1-\gamma)\mu[-\beta[p\mu + k(1-r_1)] \\ &\quad + \mu[\mu + d + \theta + \alpha(1-\theta)] + k(1-r_1)(\mu + d)], \\ &\quad - d(\mu+\gamma)[p\mu + k(1-r_1)] + \mathcal{R}^*, \\ a_0 &= \mu\mathcal{R}^*(1 - \mathcal{R}_0), \end{aligned}$$

with $\mathcal{R}^* = (\mu+\gamma)[\mu(\mu + d + \theta) + k(1-r_1)(\mu + d)] + \mu\alpha(1-\theta)[\mu + k(1-r_1)]$.

The positive endemic equilibria Q^* are obtained by solving for λ^* from the cubic equation (8) and substituting the result (positive values of λ^*) into the expression of the force of infection at the steady state. Clearly, the coefficient a_3 in Eq. (8) is always positive, and a_0 is positive or negative depending on whether $\mathcal{R}_0$ is less or greater than unity, respectively. Thus, the number of possible real roots of the polynomial (8) depends on the signs of a_3, a_2, a_1 and a_0. This can be analyzed using the Descartes Rule of Signs on the cubic polynomial $f(\lambda^*) = a_3(\lambda^*)^3 + a_2(\lambda^*)^2 + a_1(\lambda^*) + a_0$ given in (8). The various possibilities for the roots of $f(\lambda^*)$ are tabulated in Table 2.

The following result follows from various possibilities enumerated in Table 2.

Lemma 1. *The TB model (1)*

(i) *has a unique endemic equilibrium if* $\mathcal{R}_0 > 1$ *and whenever Cases 1, 2, 4 and 5 are satisfied.*
(ii) *could have more than one endemic equilibrium if* $\mathcal{R}_0 > 1$ *and Case 3 is satisfied.*
(iii) *could have one or more endemic equilibria if* $\mathcal{R}_0 < 1$ *and Cases 1, 2, 3 and 5 are satisfied.*

The existence of multiple endemic equilibria when $\mathcal{R}_0 < 1$ (shown in Table 2) suggests the possibility of backward bifurcation [Dushoff *et al.*, 1998; Brauer, 2004], where the stable disease-free equilibrium co-exists with a stable endemic equilibrium when the basic reproduction number is less than unity. This is explored below via numerical simulations.

The backward bifurcation phenomenon is illustrated by simulating model (1) with the parameters

Table 2. Number of possible real roots of $f(\lambda^*)$ for $\mathcal{R}_0 < 1$ and $\mathcal{R}_0 > 1$.

Cases	a_3	a_2	a_1	a_0	$\mathcal{R}_0$	Number of Sign Changes	Number of Possible Positive Real Roots
1	+	−	−	−	$\mathcal{R}_0 > 1$	1	1
	+	−	−	+	$\mathcal{R}_0 < 1$	2	0, 2
2	+	+	−	−	$\mathcal{R}_0 > 1$	1	1
	+	+	−	+	$\mathcal{R}_0 < 1$	2	0, 2
3	+	−	+	−	$\mathcal{R}_0 > 1$	3	1, 3
	+	−	+	+	$\mathcal{R}_0 < 1$	2	0, 2
4	+	+	+	−	$\mathcal{R}_0 > 1$	1	1
	+	+	+	+	$\mathcal{R}_0 < 1$	0	0
5	+	−	−	−	$\mathcal{R}_0 > 1$	1	1
	+	−	−	+	$\mathcal{R}_0 < 1$	2	0, 2

of Table 1. The associated backward bifurcation diagrams are depicted in Figs. 3 and 4.

Figure 3 presents the backward bifurcation diagram of the force of infection as a function of the basic reproduction ratio $\mathcal{R}_0$, while the backward bifurcation diagrams of all the state variables of the model (1) as a function of the transmission rate β are depicted in Fig. 4.

A time series of the model when $\beta = 0.3$ (so that $\mathcal{R}_0 = 0.0682$) is shown in Fig. 5. This clearly shows that for the case when $\mathcal{R}_0 < 1$, the profiles can converge to either the disease-free equilibrium or an endemic equilibrium point, depending on the initial sizes of the population of the model (owing to the phenomenon of backward bifurcation). It is worth stating that, for the set of parameter values used, the simulations have to be run for a long-time period (in hundred of years).

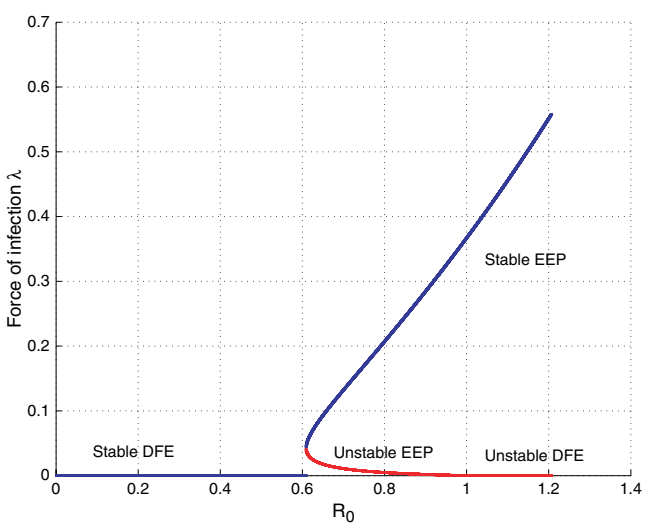


Fig. 3. Bifurcation diagram for the model (1). All other parameters are as in Table 1.

The epidemiological significance of the phenomenon of backward bifurcation is that the classical requirement of $\mathcal{R}_0 < 1$ is, although necessary, no longer sufficient for disease eradication. In such a scenario, disease elimination would depend on the initial sizes of the population (state variables) of the model. That is, the presence of backward bifurcation in the TB transmission model (1) suggests that the feasibility of controlling TB when $\mathcal{R}_0 < 1$ could depend on the initial sizes of the population. Further, as a consequence, it is instructive to try to determine the "cause" of the backward bifurcation phenomenon in the model (1). This is explored below.

Herein, the role of exogenous reinfections on the backward bifurcation phenomenon will be investigated. We consider the case where there are no exogenous reinfections in the population, that is, $\sigma_1 = \sigma_2 = 0$ in system (1). Then, the model has the same disease-free equilibrium Q_0 than system (1). Apart from this equilibrium state, the model can also have a unique positive endemic equilibrium state. In the absence of exogenous reinfections (i.e. $\sigma_1 = \sigma_2 = 0$), the coefficients a_0, a_1, a_2 and a_3 in Eq. (8) reduce to

$$a_3 = 0,$$

$$a_2 = 0,$$

$$a_1 = -d(\mu + \gamma)[p\mu + k(1 - r_1)] + \mathcal{R}^* \quad \text{and}$$

$$a_0 = \mu\mathcal{R}^*(1 - \mathcal{R}_0).$$

In this case, the force of infection at the steady state is

$$\lambda^* = \frac{\mu\mathcal{R}^*(\mathcal{R}_0 - 1)}{a_1},$$

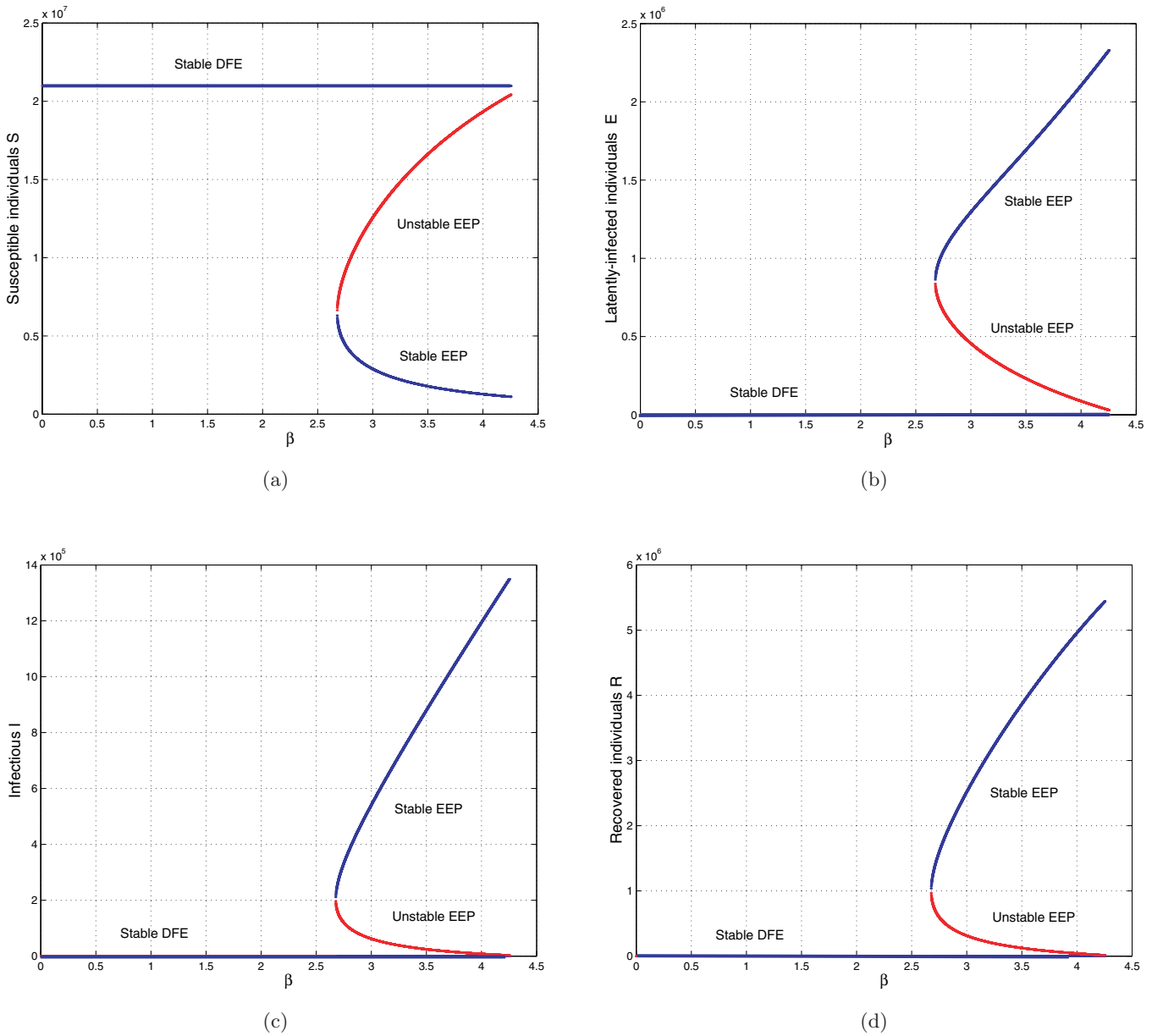


Fig. 4. Simulations of the model (1). Backward bifurcation diagrams for (a) susceptible individuals, (b) latently-infected individuals, (c) infectious and (d) recovered individuals. All other parameters are as in Table 1.

which is positive when $\mathcal{R}_0 > 1$. Then, one can tediously prove that an endemic equilibrium $Q^* = (S^*, E^*, I^*, R^*)$ exists and is unique, and, S^*, E^*, I^* and R^* are given as in Eq. (7).

Hence, in this case (with $\sigma_1 = \sigma_2 = 0$), no endemic equilibrium exists whenever $\mathcal{R}_0 \leq 1$. It then follows that, owing to the absence of multiple endemic equilibria for system (1) with $\sigma_1 = \sigma_2 = 0$ and $\mathcal{R}_0 \leq 1$, a backward bifurcation is unlikely for system (1) with $\sigma_1 = \sigma_2 = 0$ and $\mathcal{R}_0 \leq 1$.

The absence of multiple endemic equilibria suggests that the disease-free equilibrium of model (1) is globally asymptotically stable when $\mathcal{R}_0 < 1$. Then, we claim the following:

Lemma 2. *The disease-free equilibrium of model (1) with $\sigma_1 = \sigma_2 = 0$ is globally asymptotically stable in Ω whenever $\mathcal{R}_0 \leq 1$.*

Proof [Proof of Lemma]. All solutions starting in Ω remain in Ω, and all other solutions approach Ω. Thus, it may be assumed that $S/N \leq 1$, for all $t \geq 0$. Consequently, the last three equations of system (1) in the absence of exogenous reinfections

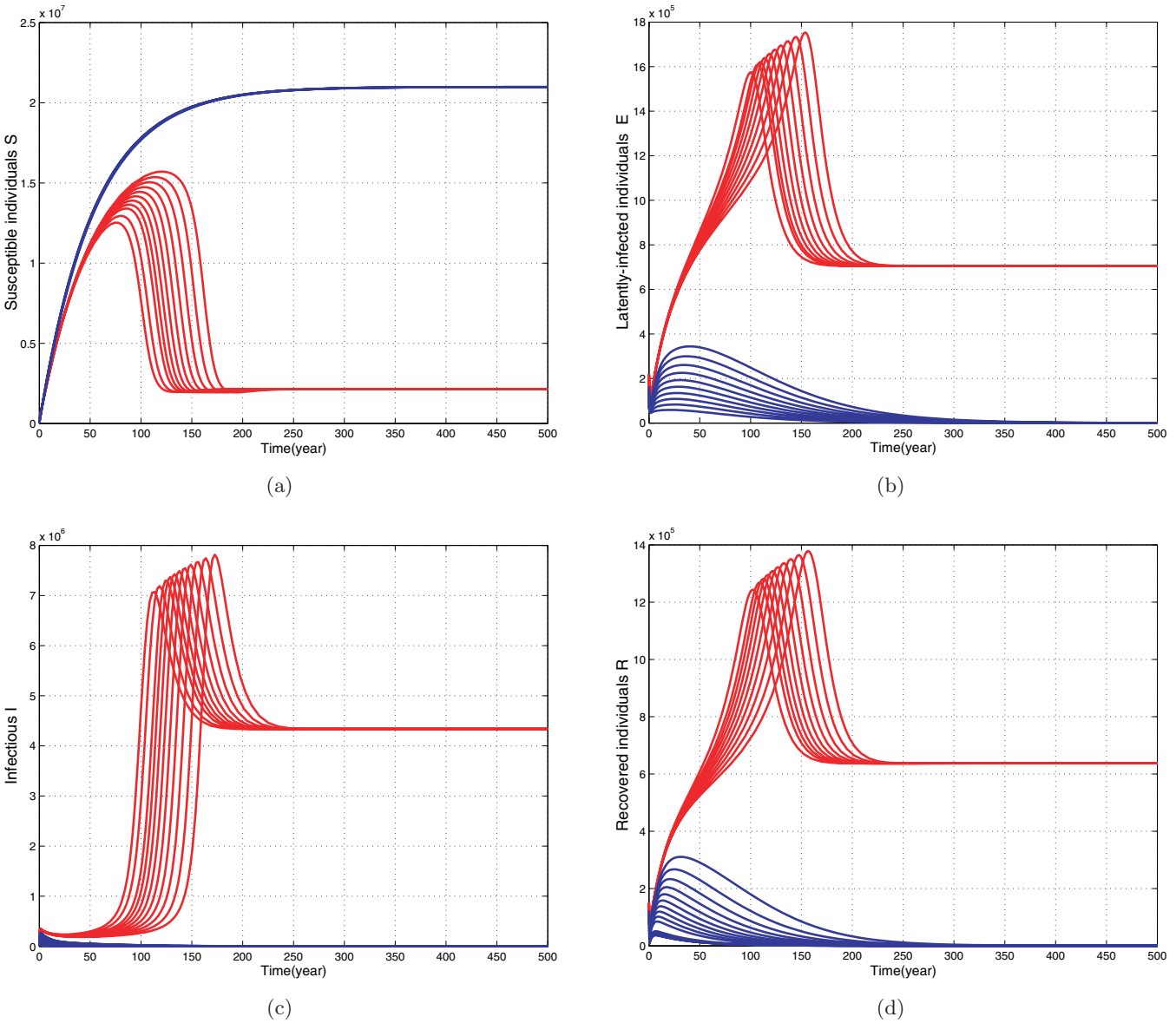


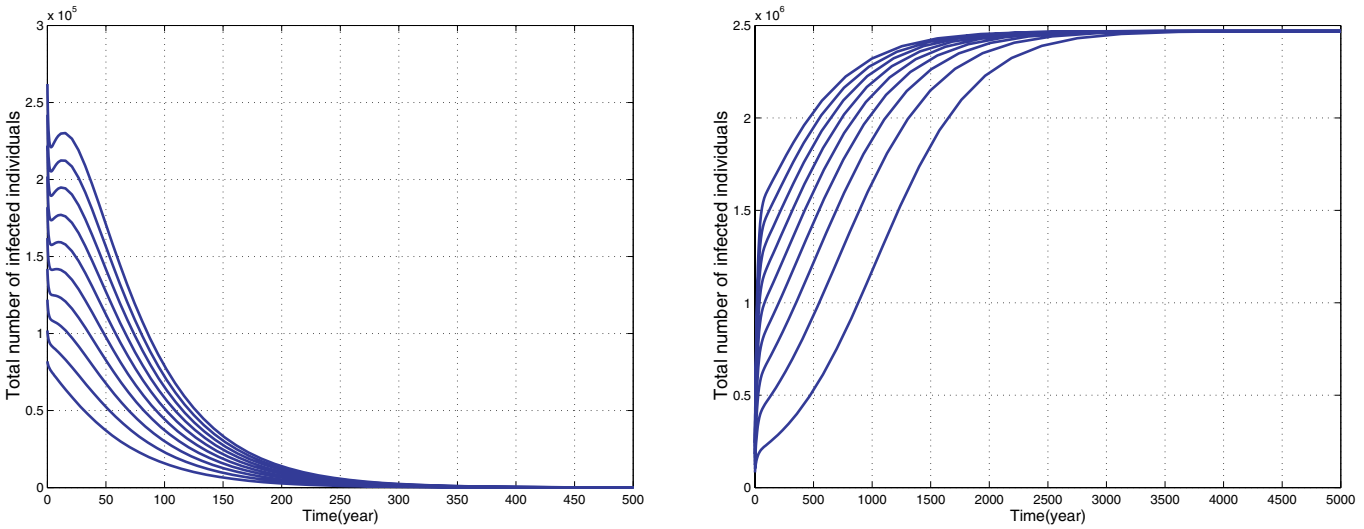
Fig. 5. Simulation of system (1). Time series of (a) susceptible individuals, (b) latently infected individuals, (c) infectious and (d) recovered individuals when $\beta = 0.3$ (so that $\mathcal{R}_0 = 0.0682$). All other parameters are as in Table 1.

can be expressed with the following differential inequality:

$$\begin{pmatrix} \dot{E} \\ \dot{I} \\ \dot{R} \end{pmatrix} \leq J_0 \begin{pmatrix} E \\ I \\ R \end{pmatrix}, \tag{9}$$

where J_0 is the submatrix of the Jacobian at the disease-free equilibrium defined as in Sec. 2.2. Consider the linear ODE system given by the inequality in (9). If $\mathcal{R}_0 < 1$, J_0 have all its eigenvalues in the left-half plane. It follows that the linear system given by the inequality (9) is stable whenever $\mathcal{R}_0 < 1$, thus $(E(t), I(t), R(t)) \to (0, 0, 0)$ as $t \to \infty$ for this linear ODE system. Consequently, after using a standard comparison theorem [Lakshmikantham *et al.*, 1989], the variables $(E(t), I(t), R(t)) \to (0, 0, 0)$ as well for the nonlinear system given by the last three equations of system (1). Returning now to the first equation of system (1) and substituting $E = I = R = 0$ in this equation gives a linear system with $S \to \Lambda/\mu$ as $t \to \infty$. Thus, $(S(t), E(t), I(t), R(t)) \to (\Lambda/\mu, 0, 0, 0)$ as $t \to \infty$ for $\mathcal{R}_0 < 1$, so that Q_0 is globally asymptotically stable if $\mathcal{R}_0 < 1$ in Ω. This concludes the proof. ■

Numerical results for system (1) without exogenous reinfections are depicted in Fig. 6. Figure 6(a) shows simulation results converging to the



(a) (b)

Fig. 6. Time series of system (1) with $\sigma_1 = \sigma_2 = 0$ showing the total number of infected individuals as a function of time, using various initial conditions. (a) When $\beta = 0.3$ (so that $\mathcal{R}_0 = 0.0682$) and (b) when $\beta = 5$ (so that $\mathcal{R}_0 = 1.1371$). All other parameters are as in Table 1.

disease-free equilibrium for the total cases of infection using various initial conditions when $\beta = 0.3$ (so that $\mathcal{R}_0 = 0.0682$). This illustrates that the disease disappears in the population. Figure 6(b) shows the convergence for the total cases of infection to the endemic equilibrium using various initial conditions when $\beta = 5$ (so that $\mathcal{R}_0 = 1.1371$). This illustrates that the disease persists in the population. Although the stability analysis of the endemic equilibrium of the model (1) without exogenous reinfections has not been carried out in this study, this result is certainly expected (since the DFE is unstable in this case, and, typically, the disease persists when the reproduction threshold ($\mathcal{R}_0$) exceeds unity; as is the case in this particular simulation).

In model (1), we have assumed that all parameters are positive and constant. Indeed, some of the parameters may vary and it will be useful to estimate these parameters using only real data. Then, we need to extend the model (1) to take into account the seasonality and to estimate unknown parameters. This is the aim of the next section.

3. A Seasonal TB Model and Parameter Estimation

In this section, we extend the model proposed in the previous section by incorporating periodic coefficients based on the possible fact that there is a seasonal trend in the new TB cases. In view of the periodic trend of quarterly new TB cases in Cameroon [National Committee of Fight Against Tuberculosis, 2001] and the possible causes of the seasonal pattern [Liu *et al.*, 2010], a model with periodic infection rate $\beta(t)$ and reactivation rate $k(t)$ may be a natural choice to describe the TB transmission. Thus, we assume that $k(t)$ and $\beta(t)$ are periodic positive continuous functions in t with period ω for some $\omega > 0$. This can be due to the fact that the seasonal trend may be mainly attributed to increasing times spent in overcrowded, poorly ventilated housing conditions [Schaaf *et al.*, 1996; Rios *et al.*, 2000; Altizer *et al.*, 2006], and/or more frequent viral infections, hence immunological deficiency leading to reactivation of the *M. tuberculosis* [Rios *et al.*, 2000]. Then, the compartmental model (1) is now described by the following system of nonautonomous differential equations:

$$\begin{cases} \dot{S} = \Lambda - \lambda(t)S - \mu S, \\ \dot{E} = \lambda(t)(1-p)S + \sigma_2(1-\gamma)\lambda(t)R + \theta I \\ \qquad - \sigma_1(1-r_1)\lambda(t)E - A_1(t)E, \\ \dot{I} = \lambda(t)pS + \gamma R \\ \qquad + (1-r_1)[k(t) + \sigma_1\lambda(t)]E - A_2 I, \\ \dot{R} = \alpha(1-\theta)I - \sigma_2(1-\gamma)\lambda(t)R - A_3 R, \end{cases} \tag{10}$$

where $\lambda(t) = \beta(t)(I/N)$, $A_1(t) = \mu + k(t)(1-r_1)$, $A_2 = \mu + d + \theta + \alpha(1-\theta)$ and $A_3 = \gamma + \mu$.

One of the most important problems in epidemiology is to reconcile the available data with the mathematical model. Indeed, in most epidemiological models discussed in the literature, the question of estimating unknown parameters has not been played a central role.

From the National Committee for Fight against Tuberculosis of Cameroon [National Committee of Fight Against Tuberculosis, 2001], we have obtained quarterly numbers of newly reported TB cases from January 2003 to December 2007. The quarterly reported TB cases in Cameroon from 2003 and 2007 show an obvious seasonal fluctuation, with a seasonality peak in the first quarter of each year. The quarterly reported TB cases in Cameroon from 2003 to 2007 are given in Table 3. The quarterly numbers of new TB cases in Table 3 correspond to the term:

$$f(t) = \lambda(t)pS(t) + (1 - r_1)[k(t) + \sigma\lambda(t)]E(t), \tag{11}$$

in the third equation of system (10).

Table 3. The number of quarterly reported new TB cases in Cameroon.

Quarter	2003	2004	2005	2006	2007
First quarter	3032	2875	3334	3703	3491
Second quarter	2778	2854	3323	3626	3160
Third quarter	2475	2655	3187	3171	3157
Fourth quarter	2624	3122	3325	3315	3208

Since the variables and parameters in system (10) are continuous functions of t, we use trigonometric functions to fit $f(t)$ as a periodic function with five years of observations. Let

$$f(t) = c_0 + \sum_{m=1}^{7} (d_m \cos mLt + e_m \sin mLt), \tag{12}$$

in order to let the expression of $f(t)$ be simpler and more exact, where $L = 2\pi/5$ is the fundamental frequency. We use the least-squares trigonometric of the software Mathematica to determine those coefficients d_m and e_m, which yield the function $f(t)$ given as follows:

$$\begin{aligned} f(t) \approx{}& 3120.75 - 232.102\cos\left(\frac{2\pi t}{5}\right) + 44.9921\cos\left(\frac{4\pi t}{5}\right) + 37.0004\cos\left(\frac{6\pi t}{5}\right) \\ & - 32.8381\cos\left(\frac{8\pi t}{5}\right) + 179\cos\left(\frac{10\pi t}{5}\right) + 19.7421\cos\left(\frac{12\pi t}{5}\right) - 68.5405\cos\left(\frac{14\pi t}{5}\right) \\ & - 313.023\sin\left(\frac{2\pi t}{5}\right) - 63.8465\sin\left(\frac{4\pi t}{5}\right) - 54.4061\sin\left(\frac{6\pi t}{5}\right) - 47.7114\sin\left(\frac{8\pi t}{5}\right) \\ & + 14.7\sin\left(\frac{10\pi t}{5}\right) - 29.9372\sin\left(\frac{12\pi t}{5}\right) + 12.4314\sin\left(\frac{14\pi t}{5}\right). \end{aligned} \tag{13}$$

The comparison of the data with the curve is shown in Fig. 7. The data and the curve match quite well.

After simulations and comparisons, the infection rate $\beta(t)$ and the reactivation rate $k(t)$ have been chosen to be $\beta(t) = \beta_0\beta_1(t)$ and $k(t) = k_0k_1(t)$, respectively, where $\beta_1(t)$ and $k_1(t)$ are the following two periodic functions:

$$\begin{aligned} \beta_1(t) = {}& 2.6006 - 0.1934\cos\left(\frac{2\pi t}{5}\right) + 0.0375\cos\left(\frac{4\pi t}{5}\right) + 0.0308\cos\left(\frac{6\pi t}{5}\right) \\ & - 0.0274\cos\left(\frac{8\pi t}{5}\right) + 0.1492\cos\left(\frac{10\pi t}{5}\right) + 0.0165\cos\left(\frac{12\pi t}{5}\right) - 0.0571\cos\left(\frac{14\pi t}{5}\right) \\ & - 0.2609\sin\left(\frac{2\pi t}{5}\right) - 0.0532\sin\left(\frac{4\pi t}{5}\right) - 0.0453\sin\left(\frac{6\pi t}{5}\right) - 0.0398\sin\left(\frac{8\pi t}{5}\right) \\ & + 0.0122\sin\left(\frac{10\pi t}{5}\right) - 0.0249\sin\left(\frac{12\pi t}{5}\right) + 0.0104\sin\left(\frac{14\pi t}{5}\right), \end{aligned} \tag{14}$$

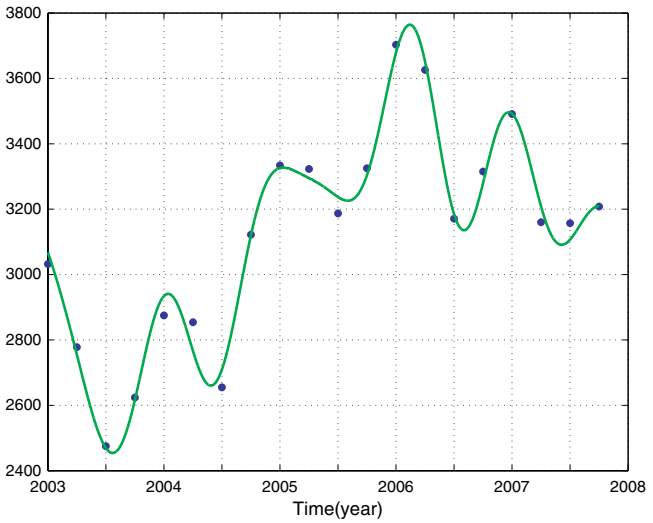


Fig. 7. The quarterly numbers of new TB cases and its fitted curve.

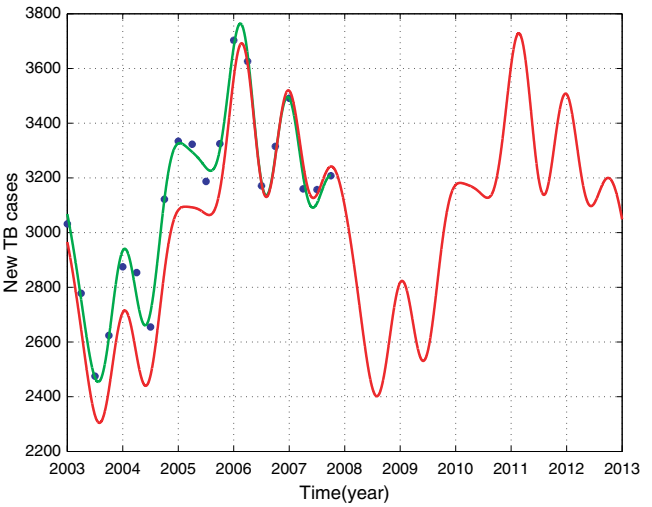


Fig. 8. New TB cases: reported number and simulation curve.

and

$$k_1(t) = (10^{-5})\left[9.3125 - 0.6926\cos\left(\frac{2\pi t}{5}\right) + 0.1343\cos\left(\frac{4\pi t}{5}\right) + 0.1104\cos\left(\frac{6\pi t}{5}\right)\right.$$
$$- 0.098\cos\left(\frac{8\pi t}{5}\right) + 0.5343\cos\left(\frac{10\pi t}{5}\right) + 0.0589\cos\left(\frac{12\pi t}{5}\right) - 0.2045\cos\left(\frac{14\pi t}{5}\right)$$
$$- 0.9341\sin\left(\frac{2\pi t}{5}\right) - 0.1905\sin\left(\frac{4\pi t}{5}\right) - 0.1624\sin\left(\frac{6\pi t}{5}\right) - 0.1424\sin\left(\frac{8\pi t}{5}\right)$$
$$\left. + 0.0439\sin\left(\frac{10\pi t}{5}\right) - 0.0893\sin\left(\frac{12\pi t}{5}\right) + 0.0371\sin\left(\frac{14\pi t}{5}\right)\right]. \tag{15}$$

Note that β_0 and k_0 are related to the magnitudes of the seasonal fluctuation. After simulations and comparisons, we choose $\beta_0 = 0.01$ and $k_0 = 0.133$. In the sensitive analysis, those two parameters are varied to see the influences of the infection rate and the reactivation rate on the new TB case numbers. All other parameter values in the simulations are as in Table 1.

Substituting those values of parameters and functions into system (10), we obtain the following TB transmission model to simulate TB infection in Cameroon:

$$\begin{cases} \dot{S} = 397800 - \beta_0\beta_1(t)\dfrac{SI}{N} - 0.019896S, \\ \dot{E} = 0.9855\beta_0\beta_1(t)\dfrac{SI}{N} + 0.81126\beta_0\beta_1(t)\dfrac{RI}{N} + 0.1828I - 0.7\beta_0\beta_1(t)\dfrac{EI}{N} - k_0k_1(t)E - 0.019896E, \\ \dot{I} = 0.015\beta_0\beta_1(t)\dfrac{SI}{N} + 0.0986R + k_0k_1(t)E + 0.7\beta_0\beta_1(t)\dfrac{EI}{N} - 0.8577I, \\ \dot{R} = 0.5975I - 0.81126\beta_0\beta_1(t)\dfrac{RI}{N} - 0.1185R, \end{cases} \tag{16}$$

We take the first quarter of 2003 as the start time of our simulation. The statistics of the National Institute of Statistics of Cameroon [National Institute of Statistics, 2007] show that the total population of the whole Cameroonian population in 2003 is $N(0) = 15\,685\,000$. According to the National Committee of Fight against Tuberculosis of Cameroon, the number of new and relapse cases of TB was 3650, then we take $I(0) = 3650$. We assume that 70% of the Cameroonian population is infected with *Mycobacterium Tuberculosis*, that is, $S(0) = 4\,705\,500$. From the average age of the active TB cases, the death rate, and the life expectation, we get the estimation that $R(0) = 2669$. Then, the direct computation implies that $E(0) = 10\,973\,681$.

The simulation results are reported in Figs. 8 and 9. Figure 8 illustrates the comparison of the quarterly reported data and the simulation curve of new TB cases in Cameroon. The stars in the curve stand for the reported new TB cases, from January 2003 to December 2007. The simulation result based on our model exhibits the seasonal fluctuation and matches the data with some small error between 2003 and 2005 but after 2005 the model matches the data well. This implies that the model

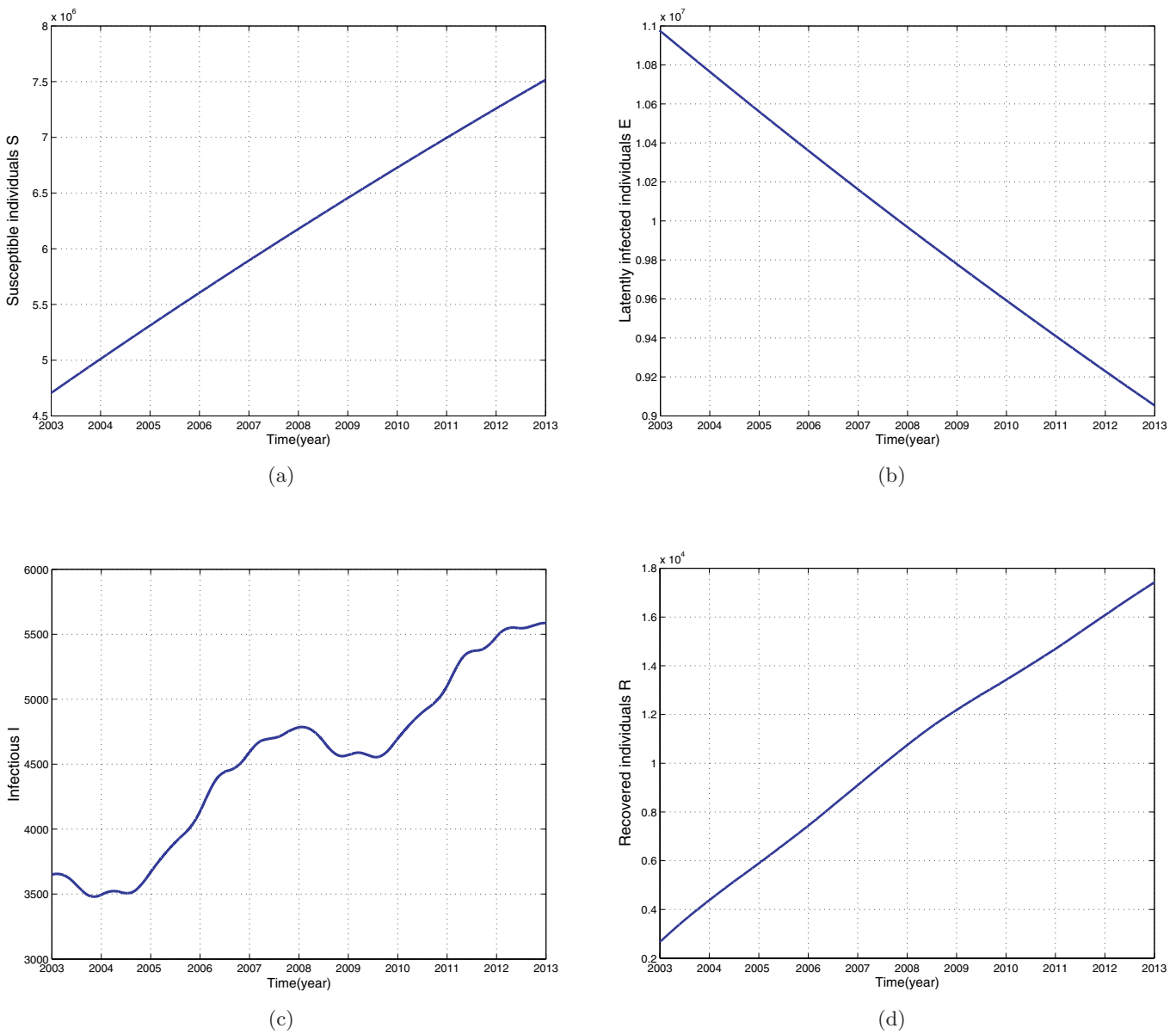
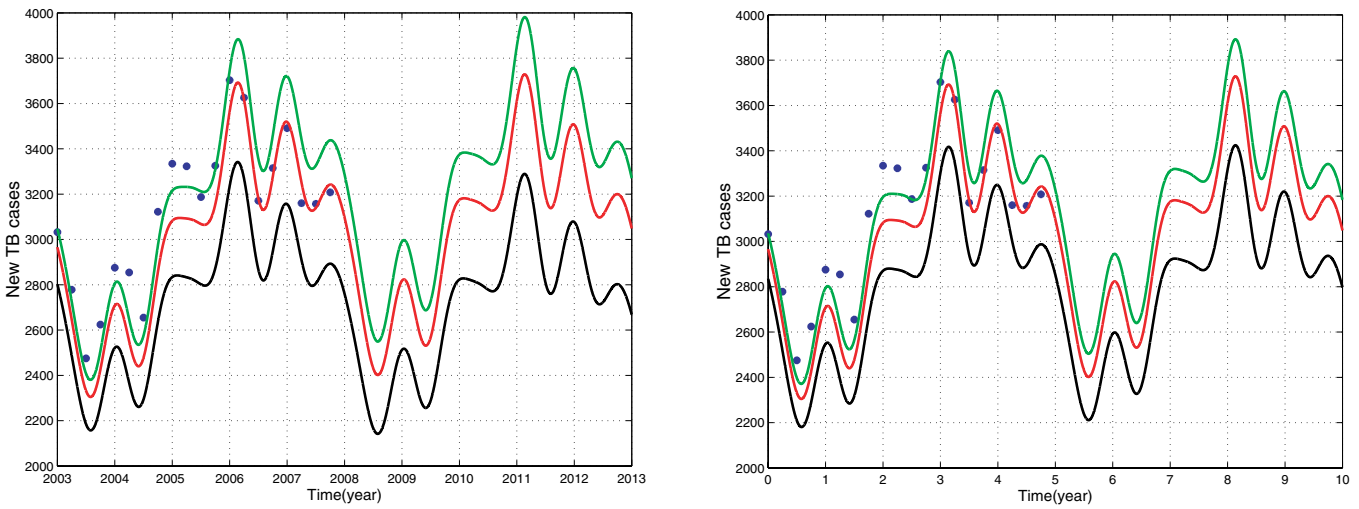


Fig. 9. Simulation of system (10) performed with $\beta_0 = 0.01$ and $k_0 = 0.133$. Time series of (a) susceptible individuals, (b) latently infected individuals, (c) infectious and (d) recovered individuals. All other parameters are as in Table 1.



(a) (b)

Fig. 10. The relationship between new TB cases for different values of β_0 and k_0. (a) In the green-line curve, $\beta_0 = 0.0105$ and in black-line curve, $\beta_0 = 0.009$ when $k_0 = 0.133$ and (b) in green-line curve $k_0 = 0.14$ and in black-line curve $k_0 = 0.12$ when $\beta_0 = 0.133$. Other parameter values are given in Table 1. Here, the stars correspond to the real data from Cameroon and the red-line curve stands for $\beta_0 = 0.01$ and $k_0 = 0.133$.

is in transient period between 2003 and 2005. We believe that this is certainly due to the choice of the initial conditions which may not be the exact initial conditions corresponding to the first quarter of 2003. To resolve this problem, we need more data. Figure 9 gives the trends of susceptible, latently-infected, infectious and recovered individuals in the future years, respectively.

Sensitivity analysis of parameters is not only critical to model verification and validation in the process of model development and refinement, but also provide insight to the robustness of the model results when making decisions [Saltelli *et al.*, 2000]. Figure 10 illustrates the impact of β_0 and k_0 on the quarterly new TB cases. From this figure, one can see that β_0 and k_0 have evident impacts on the numbers of new TB cases. The number of new TB cases increases substantially with a rise in β_0 and k_0, and fails with a decrease in β_0 and k_0.

4. Concluding Remarks

We have discussed a comprehensive, continuous deterministic model for the transmission dynamics of tuberculosis without and with seasonality. The model has been rigourously analyzed to gain insight into its qualitative dynamics. We have mainly found that the model without seasonality exhibits the phenomenon of backward bifurcation, where the stable disease-free equilibrium coexists with a stable endemic equilibrium, when the basic reproduction number is less than unity. It is shown that this (backward bifurcation) dynamics feature is caused by the reinfection of latently infected and recovered individuals. By analyzing this model without exogenous reinfections, we have found that it is globally asymptotically stable and possesses only the globally stable equilibrium state. Depending on the basic reproduction number, this steady state is either the endemic or the disease-free one. This model has been extended to describe TB seasonal incidence rate by incorporating periodic coefficients. We have proposed a numerical study to estimate unknown parameters of the model from real data of the situation of TB in Cameroon. It has been found that there is a seasonal pattern of new TB cases in the mainland of Cameroon. Throughout numerical simulations, we found that the number of new TB cases is an increasing function of β_0 or k_0 and is more sensitive to k_0 than β_0. Although, our analysis has been applied on a TB model, the basic idea and the proposed methodology can be applied to other models of infectious diseases.

Acknowledgment

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