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Optimal intervention strategies for tuberculosis

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ABSTRACT

This paper deals with the problem of optimal control of a deterministic model of tuberculosis (abbreviated as TB for tubercle bacillus). We first present and analyze an uncontrolled tuberculosis model which 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 co-exists with one or more stable endemic equilibria when the associated basic reproduction number is less than the unity. Based on this continuous model, the tuberculosis control is formulated and solved as an optimal control problem, indicating how control terms on the chemoprophylaxis and detection should be introduced in the population to reduce the number of individuals with active TB. Results provide a framework for designing the cost-effective strategies for TB with two intervention methods.

1. Introduction

More than 36 million patients have been successfully treated via the World Health Organization (WHO) strategy for tuberculosis control since 1995. Despite predictions of a decline in global incidence, the number of new cases continues to grow, approaching 10 million in 2010 [1,2]. This rise has been attributed to the spread of HIV, the collapse of public health programs, the emergence of drug-resistant strains of *Mycobacterium tuberculosis* [3–5] and exogenous re-infections, where a latently-infected individual acquires a new infection from another infectious (see [6,7] and references therein). 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 (see [8–12] and references therein). A number of theoretical studies have been carried out on the mathematical modelling of TB transmission dynamics [13–21].

Mathematical models can provide a powerful tool for investigating the dynamics and control of infectious diseases. Optimal control theory provides a valuable tool to begin to assess the trade-offs between vaccination and treatment strategies [22,23]. Optimal control is a mathematical technique derived from the calculus of variations. Anyhow we can give suggestions to the public health authorities about the effects of a particular control policy with respect to others, and in this context the analysis and simulation of mathematical models may become a powerful tool in the hands of the above authorities. However, the control of epidemic systems is not usually an easy task since in real situations it is rather difficult to implement the control policies suggested by the mathematical analysis [24,27]. There are a number of different methods for calculating the optimal control for a specific mathematical model [23,25,26,30]. For example, Pontryagin's maximum principle [26] allows

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the calculation of the optimal control for an ordinary equation model system with a given constraint. Variations of Pontryagin's maximum principle have been derived for other types of models including partial differential equations and difference equations [23,25]. These techniques are powerful when applied to disease models and can provide great insight into the best pathway to reduce disease burden. For example, with a given mathematical model for a disease, one can calculate the best vaccination schedule balancing the cost of the vaccine and the cost of the disease burden [23]. There have been several articles considering optimal control applied to specific diseases [27–31].

The present contribution considers the optimal control problem of the dynamical transmission of tuberculosis. We first formulate and analyze an uncontrolled tuberculosis model that incorporates the essential biological and epidemiological features of the disease such as constant recruitment, slow and fast progression, effective chemoprophylaxis, diagnostic and treatment of infectious and exogenous reinfections of latently-infected 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. Moreover, despite the development of a number of effective treatments over the past half century, TB remains one of the most destructive bacteria infections in humans. All levels of government and public health officials are searching for answers to identify the best strategies for intervention. We sound to determine optimal control strategies that would minimize not only infectious but also latently-infected individuals. We completely characterize the optimal controls and compute a numerical solution of the optimality system via analytic continuation. An important result of this analysis is that a cost-effective balance of chemoprophylaxis and treatment methods can successfully control a TB, but that the balance of treatment is specific to the population.

The organization of the paper is as follows. In the next section, a model for the dynamics of TB is formulated and rigorously analyzed. Section 3 presents the optimal control problem in which chemoprophylaxis of latently-infected individuals and detection of infectious rates are the controls. We seek to minimize the number of individuals with active TB. We characterize the optimal control using Pontryagin's Maximum Principle. The resulting optimality have been solved numerically. Section 4 discusses the epidemiological implications of the results established in this paper.

2. The model

2.1. Model construction

In this section, we process with the construction of a mathematical model for the spread of tuberculosis. Based on epidemiological status, the simplest models include classes of susceptible, infected and infective individuals, and hence are known as SEI (Susceptible-Infected-Infective) models [27–38].

We consider a finite population of N people. The infective class is divided into two subclasses with different properties: diagnosed and undiagnosed infectious. At any given time, an individual is therefore in one of the following states: susceptible, latently infected (exposed to TB but not infectious), diagnosed infectious (has an active TB confirmed after a sputum examination in the hospital), undiagnosed infectious (i.e., have an active TB not confirmed by a sputum examination in hospital) and we will denote these states by S, E, I and J, respectively.

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. Diagnosed and undiagnosed infectious have addition death rates due to the disease with constant rates d_1 and d_2, respectively. Transmission of *M. tuberculosis* occurs due to adequate contacts between susceptible, diagnosed and undiagnosed infectious. Then, susceptible individuals acquire TB infection from individuals with active TB at a rate λ, given by

$$\lambda = \beta \frac{(I + \varepsilon J)}{N}, \tag{1}$$

where β is the effective contact rate of diagnosed or undiagnosed infectious that is sufficient to transmit infection to a susceptible, and the parameter $\varepsilon > 1$ accounts for the high infectiousness of undiagnosed infectious with respect to diagnosed infectious. On adequate contacts with active TB, a susceptible individual becomes infected but not yet infectious. Fraction p of newly infected individuals is assumed to undergo a fast progression to TB, while the remainder is latently infected and enters the latent class E. Among the newly infected individuals that undergo a fast progression to TB, a fraction f of them is detected and will enter the diagnosed infectious class I and the remaining fraction $1 - f$ is undetected and will be transferred in the undiagnosed infectious class J. Once latently infected with *M. tuberculosis*, an individual will remain so for life unless reactivation occurs. Latently infected individuals are assumed to acquire some immunity as a result of infection, which reduces the risk of subsequent infection but does not fully prevent it. To account for treatment, we define by $r_1 E$, latently infected individuals that receive effective chemoprophylaxis, and r_2 as the rate of effective per capita therapy of diagnosed infectious. We assume that the chemoprophylaxis of latently infected individuals reduces their reactivation at a constant rate r_1 and that the initiation of therapeutics of diagnosed infectious immediately removes individuals from the active status I and places them into a latent state E. We also assume that undiagnosed infectious can naturally recover and will be transfer in the latent class E at a constant rate $r_3 < r_2$. Indeed, there is a resistance to tuberculosis in human beings which is called immunity. Most people possess it in some degree, but some to a much greater degree than others. Some races possess it in a greater degree than others and some families possess it in a greater degree than others. The

probabilities are that immunity is gradually developed by resistance to the disease, and that for this reason families and races which have been fighting the disease in some of their members for long periods have great resistance. Note that there is no permanence in immunity against tuberculosis in the individual, the family or in the race. It may be lost after many generations in the family and it may be lost in the individual through depression in health. Racial immunity is probably the most durable of all. Due to endogenous reactivation, a fraction $1-r_1$ of latently infected individuals who did not received effective chemoprophylaxis become infectious at a constant rate k, and reinfected (exogenously) after effective contacts with individuals in the active TB classes at a rate $\sigma\lambda$, where σ is the factor reducing the risk of infection as a result of acquiring immunity for latently infected individuals. Among latently infected individuals who become infectious, the fraction h of them is diagnosed and treated, while the remaining $1-h$ is not diagnosed and enters the undiagnosed infectious class J. The model flow diagram is shown in Fig. 1.

This yields the following differential equations:

$$\begin{cases} \dot{S} = \Lambda - \lambda S - \mu S, \\ \dot{E} = (1-p)\lambda S + r_2 I + r_3 J - \sigma(1-r_1)\lambda E - A_1 E, \\ \dot{I} = pf\lambda S + h(1-r_1)(k+\sigma\lambda)E - A_2 I, \\ \dot{J} = p(1-f)\lambda S + (1-h)(1-r_1)(k+\sigma\lambda)E - A_3 J, \end{cases} \tag{2}$$

where $A_1 = \mu + k(1-r_1), A_2 = \mu + d_1 + r_2$, and $A_3 = \mu + d_2 + r_3$.

System (2) can be written in the following compact form:

$$\begin{cases} \dot{x} = \varphi(x) - \lambda x, \\ \dot{y} = \lambda[B_1 x + B_2\langle e_2|y\rangle] + Ay, \end{cases} \tag{3}$$

where $x = S \in \mathbb{R}_{\geqslant 0}$ is a state representing the compartment of non transmitting individuals (susceptible), $y = (y_1, y_2, y_3) = (E, I, J)^T \in \mathbb{R}^3_{\geqslant 0}$ is the vector representing the state compartment of different infected individuals (latently-infected individuals, diagnosed and undiagnosed infectious), $\varphi(x) = \Lambda - \mu x$ is a function that depends on x, $\lambda = \langle e_1|y\rangle/N$ is the force of infection, $N = x + y_1 + y_2 + y_3$ is the size of the total population, $e_1 = (0, \beta, \beta\varepsilon) \in \mathbb{R}^3, e_2 = (1,0,0) \in \mathbb{R}^3$, $B_1 = (1-p, pf, p(1-f))^T \in \mathbb{R}^3, B_2 = (-\sigma(1-r_1), \sigma h(1-r_1), \sigma(1-h)(1-r_1))^T \in \mathbb{R}^3$, $\langle .|. \rangle$ is the usual scalar product and A is the 3×3 constant matrix:

$$A = \begin{bmatrix} -A_1 & r_2 & r_3 \\ kh(1-r_1) & -A_2 & 0 \\ k(1-h)(1-r_1) & 0 & -A_3 \end{bmatrix},$$

with A_1, A_2 and A_3 defined as in Eq. (2).

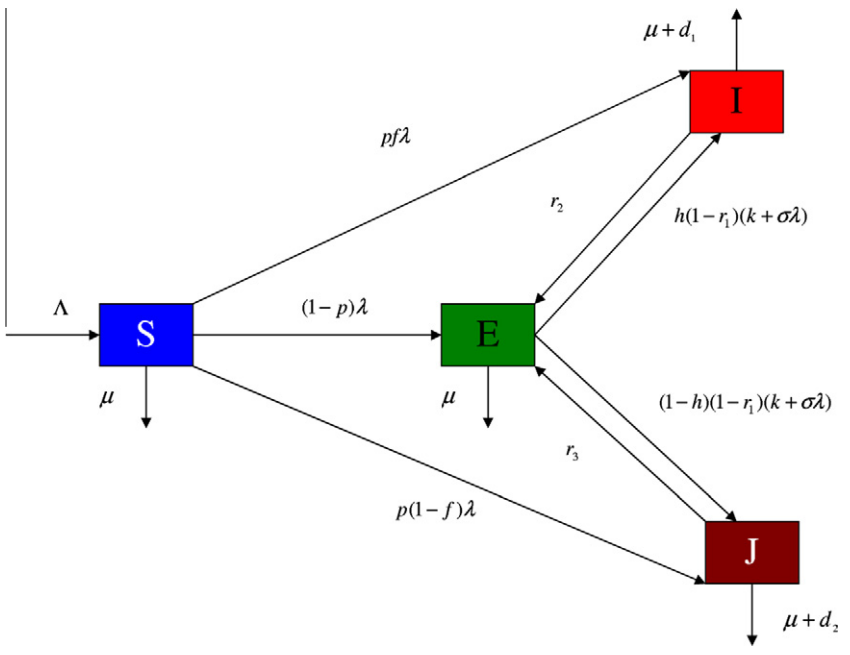

Fig. 1. Transfer diagram for a dynamical transmission of tuberculosis where $\lambda = \beta(I + \varepsilon J)/N$.

We give the explicit expression of $-A^{-1}$ since we will need it later.

$$-A^{-1}=\frac{1}{\tau}\begin{bmatrix} A_2A_3 & r_2A_3 & r_3A_2 \\ hk(1-r_1)A_3 & A_1A_3-kr_3(1-h)(1-r_1) & -hkr_3(1-r_1) \\ kA_2(1-h)(1-r_1) & kr_2(1-h)(1-r_1) & A_1A_2-hkr_2(1-r_1) \end{bmatrix},$$

where

$$\tau=A_1A_2A_3-k(1-r_1)[hr_2A_3+A_2r_3(1-h)].$$

The TB model (2) was simulated with the parameters given in Table 1.

2.2. Properties of the model

2.2.1. Positivity and boundedness of solutions

For model system (2) 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 model system (2) with positive initial data remain positive for all time $t>0$.

Suppose, for example that, the variable E becomes zero for some time $\bar{t}>0$, i.e., $E(\bar{t})=0$, while all other variables are positive. Then, from the E equation, we have $dE(\bar{t})/dt>0$. Thus, $E(t)\geqslant 0$ for all $t>0$. Similarly, it can be shown that $S(t)>0, I(t)>0$ and $J(t)>0$ for all $t>0$.

Now, adding all equations in the differential system (2) yields

$$\dot{N}=\Lambda-\mu N(t)-d_1I(t)-d_2J(t). \tag{4}$$

Thus, one can deduce that $\dot{N}\leqslant\Lambda-\mu N(t)$. It then follows that $\lim_{t\to+\infty}N(t)\leqslant\frac{\Lambda}{\mu}$, which implies that the trajectories of model system (2) are bounded. On the other hand, solving the differential inequality $\dot{N}\leqslant\Lambda-\mu N(t)$ gives $N(t)\leqslant N(0)e^{-\mu t}+\frac{\Lambda}{\mu}(1-e^{-\mu t})$. In particular $N(t)\leqslant\frac{\Lambda}{\mu}$ if $N(0)\leqslant\frac{\Lambda}{\mu}$. Then, the region:

$$\Omega=\left\{(S,E,I,J)\in\mathbb{R}^4_{\geqslant 0},\quad N(t)\leqslant\frac{\Lambda}{\mu}\right\}, \tag{5}$$

is a compact forward invariant set for model system (2). So, we limit our study to this region.

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

System (2) has a DFE given by $Q_0=\left(\frac{\Lambda}{\mu},0,0,0\right)$. The stability of this equilibrium will be investigated using the next generation operator [34]. Using the notations in [34] on model system (2), the matrices F and V, for the new infection terms and the remaining transfer terms are, respectively, given by

$$F=\begin{bmatrix} 0 & \beta & \beta\varepsilon \\ 0 & \beta pf & \beta\varepsilon pf \\ 0 & \beta p(1-f) & \beta\varepsilon p(1-f) \end{bmatrix} \quad \text{and} \quad V=-A.$$

Then, the basic reproduction ratio is defined, following [34], as the spectral radius of the next generation matrix, FV^{-1}:

$$\mathcal{R}_0=\rho(FV^{-1})=\frac{\beta[(1-p)\mathcal{R}_{01}+pf\mathcal{R}_{02}+p(1-f)\mathcal{R}_{03}]}{A_1A_2A_3-k(1-r_1)[hr_2A_3+A_2r_3(1-h)]}, \tag{6}$$

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

Table 1
Numerical values for the parameters of model system (2).

Parameters	Symbol	Estimate	Source
Recruitment rate of susceptible	Λ	397800/year	[32]
Transmission rate	β	Variable	Assumed
Fast route to active TB	p	0.015	Assumed
Fast route to diagnosed infectious class	f	0.7/year	Assumed
Infectivity of undiagnosed infectious	ε	1.5	Assumed
Reinfection parameter of latently infected individuals	σ	2	Assumed
Slow route to active TB	k	0.05/year	Assumed
Natural mortality	μ	0.019896/year	[32]
TB mortality of diagnosed infectious	d_1	0.0575/year	[33]
TB mortality of undiagnosed infectious	d_2	0.24/year	Assumed
Chemoprophylaxis of latently infected individuals	r_1	0.001/year	[33]
Detection rate of active TB	h	0.69/year	[33]
Treatment rate of diagnosed infectious	r_2	0.8625/year	[33]
Recovery rate of undiagnosed infectious	r_3	0.49/year	Assumed

$$\mathcal{R}_{01} = hk(1-r_1)A_3 + \varepsilon A_2(1-h)(1-r_1),$$
$$\mathcal{R}_{02} = A_1A_3 - kr_3(1-h)(1-r_1) + \varepsilon kr_2(1-h)(1-r_1),$$
$$\mathcal{R}_{03} = -hkr_3(1-r_1) + \varepsilon[A_1A_2 - hkr_2(1-r_1)].$$

The basic reproductive number measures the average number of new infections generated by a single infected individual in a completely susceptible population.

Now, let us analyze the effects of the transmission rate β and the detection rate h on the basic reproduction ratio $\mathcal{R}_0$.

Fig. 2 shows the effects of β and h 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 for large values of h. This means that if the transmission coefficient β is sufficiently small, TB infection could be eliminated even if $h = 0$. However, it is difficult to control β. Therefore, detection of infectious is an efficient intervention. Thus, combining detection of infectious with the reduction of contacts can reduce $\mathcal{R}_0$ to be less than 1. Then, the optimal control strategy should be a combination of detection of infectious, chemoprophylaxis of latently-infected individuals, and reduction of contacts.

The following result is established (from Theorem 2 of [34]):

Lemma 1. *The disease-free equilibrium Q_0 of model system (2) is locally asymptotically stable whenever $\mathcal{R}_0 < 1$, and instable if $\mathcal{R}_0 > 1$.*

Biologically speaking, Lemma 1 implies that TB can be eliminated from the community (when $\mathcal{R}_0 < 1$) if the initial size of the population of model system (2) are in the basin of attraction of Q_0. Since TB models may undergo the phenomenon of backward bifurcation (see [6]), it is instructive to determine whether the present model exhibits this phenomenon.

2.3. Equilibria and bifurcation

Model system (2) has one disease-free equilibrium, $Q_0 = (S_0,\ 0,\ 0,\ 0)$ with $S_0 = \Lambda/\mu$ and one or two endemic equilibria of the form $Q^* = (S^*, E^*, I^*, J^*)$. On the other hand, from Lemma 1, the DFE of model system (2) is locally asymptotically stable (LAS) if $\mathcal{R}_0 < 1$. However, this equilibrium may not be globally asymptotically stable (GAS) in Ω for $\mathcal{R}_0 < 1$, owing to the possibility of the backward bifurcation phenomenon, where the stable DFE co-exists with a stable endemic equilibrium when $\mathcal{R}_0 < 1$ (see for instance [35–38] and the references therein). The public health implication of the backward bifurcation phenomenon is that the classical requirement of having the basic reproductive ratio less than the unity, although necessary, is no longer sufficient for curtailing the outbreak of the disease [38]. The possibility of this phenomenon in model system (2) is investigated below.

Let $Q^* = (x^*, y^*)$ be any arbitrary equilibrium point of model system (3). To find conditions for the existence of an equilibrium for which TB is endemic in the population (steady state with y^* non zero), all equations in model system (3) are set at zero, i.e.,

$$\begin{cases} \varphi(x^*) - \lambda^* x^* = 0, \\ \lambda^*[B_1 x^* + B_2\langle e_2|y^*\rangle] + Ay^* = 0, \end{cases} \tag{7}$$

where

$$\lambda^* = \frac{\langle e_1|y^*\rangle}{N^*}, \tag{8}$$

is the force of infection at the steady state. Multiplying the second equation of (7) by $-A^{-1}$, one obtains

$$y^* = \lambda^*[x^*(-A^{-1})B_1 + (-A^{-1})B_2\langle e_2|y^*\rangle]. \tag{9}$$

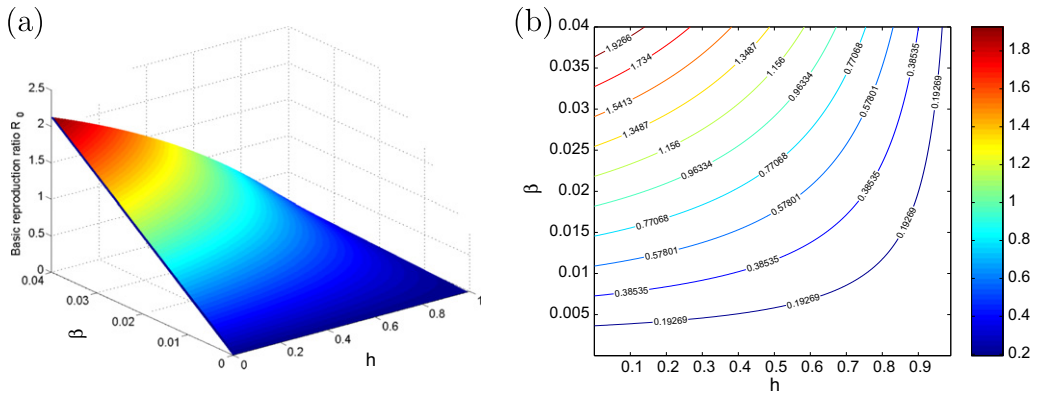

Fig. 2. Graphs of the basic reproduction number $\mathcal{R}_0$ of model system (2) in dependence of h and β. All other parameters are as in Table 1.

From Eq. (9), one has

$$\langle e_1|y^*\rangle = \lambda^*[x^*a_1 + a_2\langle e_2|y^*\rangle] \qquad \text{and} \qquad \langle e_2|y^*\rangle = \lambda^*[a_3x^* + a_4\langle e_2|y^*\rangle], \tag{10}$$

where

$$a_1 = \langle e_1|(-A^{-1})B_1\rangle = \mathcal{R}_0, \qquad a_2 = \langle e_1|(-A^{-1})B_2\rangle,$$
$$a_3 = \langle e_2|(-A^{-1})B_1\rangle \qquad \text{and} \qquad a_4 = \langle e_2|(-A^{-1})B_2\rangle.$$

From Eq. (10), one can deduce that

$$\langle e_1|y^*\rangle = \frac{x^*\lambda^*[\mathcal{R}_0 + (a_2a_3 - a_4\mathcal{R}_0)\lambda^*]}{1 - a_4\lambda^*} \qquad \text{and} \qquad \langle e_2|y^*\rangle = \frac{a_3\lambda^*x^*}{1 - a_4\lambda^*}. \tag{11}$$

Combining the first equation of (11) and the force of infection at the steady state (8) yields

$$N^* = \frac{x^*[\mathcal{R}_0 + (a_2a_3 - a_4\mathcal{R}_0)\lambda^*]}{1 - a_4\lambda^*}. \tag{12}$$

Now, let $e_3 = (0, 1, 0)$ and $e_4 = (0, 0, 1)$. Then, from Eq. (9), one has

$$I^* = \langle e_3|y^*\rangle = \lambda^*[a_5x^* + a_6\langle e_2|y^*\rangle] \qquad \text{and} \qquad J^* = \langle e_4|y^*\rangle = \lambda^*[a_7x^* + a_8\langle e_2|y^*\rangle]. \tag{13}$$

where

$$a_5 = \langle e_3|(-A^{-1})B_1\rangle, \qquad a_6 = \langle e_3|(-A^{-1})B_2\rangle,$$
$$a_7 = \langle e_4|(-A^{-1})B_1\rangle \qquad \text{and} \qquad a_8 = \langle e_4|(-A^{-1})B_2\rangle.$$

Combining Eqs. (11) and (13) gives

$$I^* = \frac{x^*\lambda^*}{1 - a_4\lambda^*}[a_5 + (a_3a_6 - a_4a_5)\lambda^*] \qquad \text{and} \qquad J^* = \frac{x^*\lambda^*}{1 - a_4\lambda^*}[a_7 + (a_3a_8 - a_4a_7)\lambda^*].$$

Now, using Eq. (4) at the endemic equilibrium and the above expressions of I^* and J^*, the size of the total population at the endemic equilibrium can be written as

$$N^* = \frac{\Lambda(1 - a_4\lambda^*) - d_1x^*\lambda^*[a_5 + (a_3a_6 - a_4a_5)\lambda^*] - d_2x^*\lambda^*[a_7 + (a_3a_8 - a_4a_7)\lambda^*]}{\mu(1 - a_4\lambda^*)}. \tag{14}$$

Moreover, using the first equation of (7), one has

$$x^* = \frac{\Lambda}{\mu + \lambda^*}. \tag{15}$$

Equalizing Eqs. (12) and (14), and using Eq. (15), it can be shown that the non-zero equilibria of model system (3) satisfy the following quadratic equation in term of λ^*:

$$c_2(\lambda^*)^2 + c_1(\lambda^*) + c_0 = 0, \tag{16}$$

where

$$c_2 = d_1(a_4a_5 - a_3a_6) + d_2(a_4a_7 - a_3a_8) - a_4,$$
$$c_1 = 1 + \mu a_4(\mathcal{R}_0 - 1) - d_1a_5 - d_2a_7 - \mu a_2a_3,$$
$$c_0 = \mu(1 - \mathcal{R}_0).$$

Thus, positive endemic equilibria Q^* are obtained by solving for λ^* from the quadratic Eq. (16) and substituting the result (positive values of λ^*) into the expressions of the variables of model system (2) at the steady state. Clearly, c_0 is positive or negative depending whether $\mathcal{R}_0$ is less than or greater than the unity, respectively. Thus, the number of possible real roots of the polynomial (16) depends on the signs of c_2, c_1 and c_0. This can be analyzed using the Descartes Rule of Signs on the quadratic polynomial $f(\lambda^*) = c_2(\lambda^*)^2 + c_1(\lambda^*) + c_0$. 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 2. *The TB model (2)*

(i) Could have a unique endemic equilibrium if $\mathcal{R}_0 > 1$ and whenever Cases 2 and 4 are satisfied.
(ii) Could have more than one endemic equilibrium if $\mathcal{R}_0 > 1$ and whenever Case 3 is satisfied.
(iii) Could have one or more unique endemic equilibria if $\mathcal{R}_0 < 1$ and whenever Cases 1, 2 and 3 are satisfied.
(iv) No endemic equilibria in all other cases.

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

Cases	c_2	c_1	c_0	$\mathcal{R}_0$	Number of sign changes	Number of possible positive real roots
1	−	−	−	$\mathcal{R}_0 > 1$	0	0
	−	−	+	$\mathcal{R}_0 < 1$	1	1
2	+	−	−	$\mathcal{R}_0 > 1$	1	1
	+	−	+	$\mathcal{R}_0 < 1$	2	0,2
3	−	+	−	$\mathcal{R}_0 > 1$	2	0,2
	−	+	+	$\mathcal{R}_0 < 1$	1	1
4	+	+	−	$\mathcal{R}_0 > 1$	1	1
	+	+	+	$\mathcal{R}_0 < 1$	0	0

It should be pointed out that the case (iii) indicates the possibility of the backward bifurcation phenomenon (where the locally asymptotically stable DFE co-exists with a locally asymptotically stable endemic equilibrium when $\mathcal{R}_0 < 1$, see for instance, [45–49]) in the TB model (2) when $\mathcal{R}_0 < 1$. To check for this, the discriminant $c_1^2 - 4c_2c_0$ is set to zero and solved for the critical value of $\mathcal{R}_0$, denoted by $\mathcal{R}_c$, given by

$$\mathcal{R}_c = 1 - \frac{c_1^2}{4\mu c_2}. \tag{17}$$

Thus, the backward bifurcation phenomenon would occur for values of $\mathcal{R}_0$ such that $\mathcal{R}_c < \mathcal{R}_0 < 1$.

The backward bifurcation phenomenon is illustrated by simulating model system (2) with the parameters values of Table 1. The associated backward bifurcation diagram is depicted in Fig. 3. Fig. 4 presents the time series of model system (2) when $\beta = 0.35$ (so that $\mathcal{R}_0 = 0.8733$). It clearly appears that 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 noting that, for the set of parameter values used, the simulations have be performed for a long-time period (in hundred of years). We point out that the backward bifurcation is due to exogenous reinfections. Indeed, if $\sigma = 0$, the coefficients c_2, c_1 and c_0 of Eq. (16) are reduced to $c_2 = 0, c_1 = 1 - d_1a_5 - d_2a_7$ and $c_0 = \mu(1 - \mathcal{R}_0)$. Then, one can easily prove that model system (2) has a unique endemic equilibrium. Hence, when $\sigma = 0$, no endemic equilibrium exists whenever $\mathcal{R}_0 < 1$. It then follows that, owing to the absence of multiple endemic equilibria for model system (2) with $\sigma = 0$ and $\mathcal{R}_0 < 1$, a backward bifurcation is unlikely for model system (2) with $\sigma = 0$ and $\mathcal{R}_0 < 1$.

One important parameter that forms the core of this work is investigated numerically.

Fig. 5 shows the impact of varying the detection parameter h in model system (2) when $\beta = 0.5$ (so that $\mathcal{R}_0 > 1$). The initial conditions and parameters are as in Fig. 4. From this figure, one can see that as the value of h increases, the population of diagnosed infectious increases (Fig. 5(b)), while the populations of undiagnosed and latently infected individuals decrease (Fig. 5(a) and (c)). This is due to the fact that diagnosis leads to the treatment of patients, resulting in less latently infected individuals and undiagnosed infectious, that do not lead to an epidemic. This demonstrates the importance of diagnosis. Care then should be taken to prevent a failure of treatment and a relapse of the disease after treatment.

3. Optimal control

Several kinds of interesting nonlinear dynamics behavior of model system (2) such as the backward bifurcation phenomenon has been studied in the previous section. Since, the backward bifurcation is due to exogenous reinfections, it is then

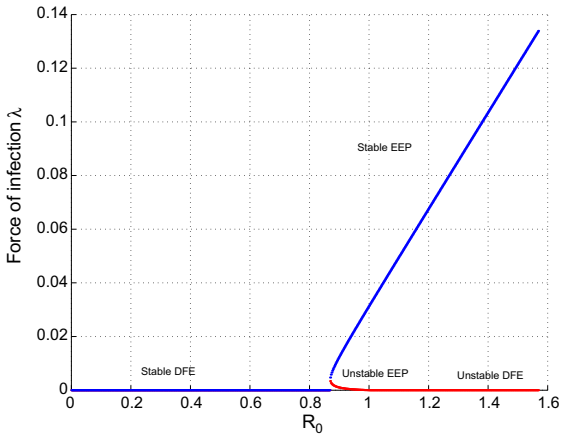

Fig. 3. Bifurcation diagram for the model (2). The notation EEP stands for endemic equilibrium point. All other parameters are as in Table 1.

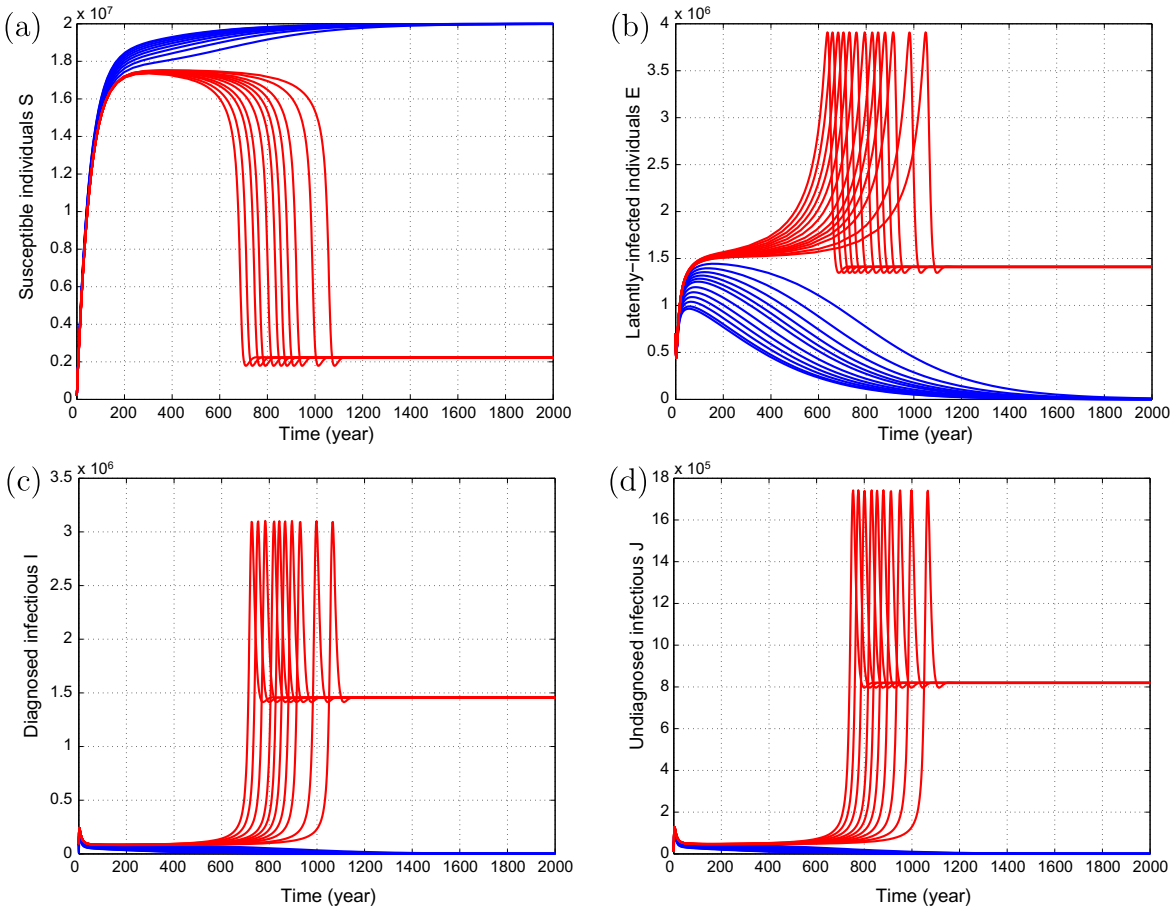

Fig. 4. Simulation of system (2). Time series of (a) susceptible individuals, (b) latently infected individuals, (c) diagnosed infectious and (d) undiagnosed infectious when $\beta = 0.35$ (so that $\mathcal{R}_0 = 0.8733$). All other parameters are as in Table 1.

desirable to reduce exogenous reinfections in model system (2) so that the number of latently infected individuals that may develop an active TB will be lower. Moreover, it is important to point out that one of the main goal of a TB program is to detect the maximum of infectious. This will certainly increase the treatment rate of infectious and reduce the source of infection. The aim of this section is to propose an optimal control strategy to reduce the burden of the disease.

3.1. Optimal control problem

Two intervention methods, called controls, are included in model system (2). Controls are represented as functions of time and assigned reasonable upper and lower bounds. First, $u(t)$ represents the effort on the chemoprophylaxis parameter (r_1) of latently infected individuals to reduce the number of individuals that may develop an active TB. Second, $v(t)$ is the effort on detection (h) of infectious. This will certainly increase the treatment rate of infectious and consequently, will reduce the number of infectious and the source of infection.

Using the same parameters and class names as in model system (2), the system of differential equations describing the controlled model is

$$\begin{cases} \dot{S} = \Lambda - \lambda S - \mu S, \\ \dot{E} = (1-p)\lambda S + r_2 I + r_3 J - (1-ur_1)(k+\sigma\lambda)E - \mu E, \\ \dot{I} = pf\lambda S + vh(1-ur_1)(k+\sigma\lambda)E - A_2 I, \\ \dot{J} = p(1-f)\lambda S + (1-vh)(1-ur_1)(k+\sigma\lambda)E - A_3 J, \end{cases} \tag{18}$$

where λ, A_2 and A_3 are defined as in Eq. (2).

A control scheme is assumed to be optimal if it minimizes the objective functional:

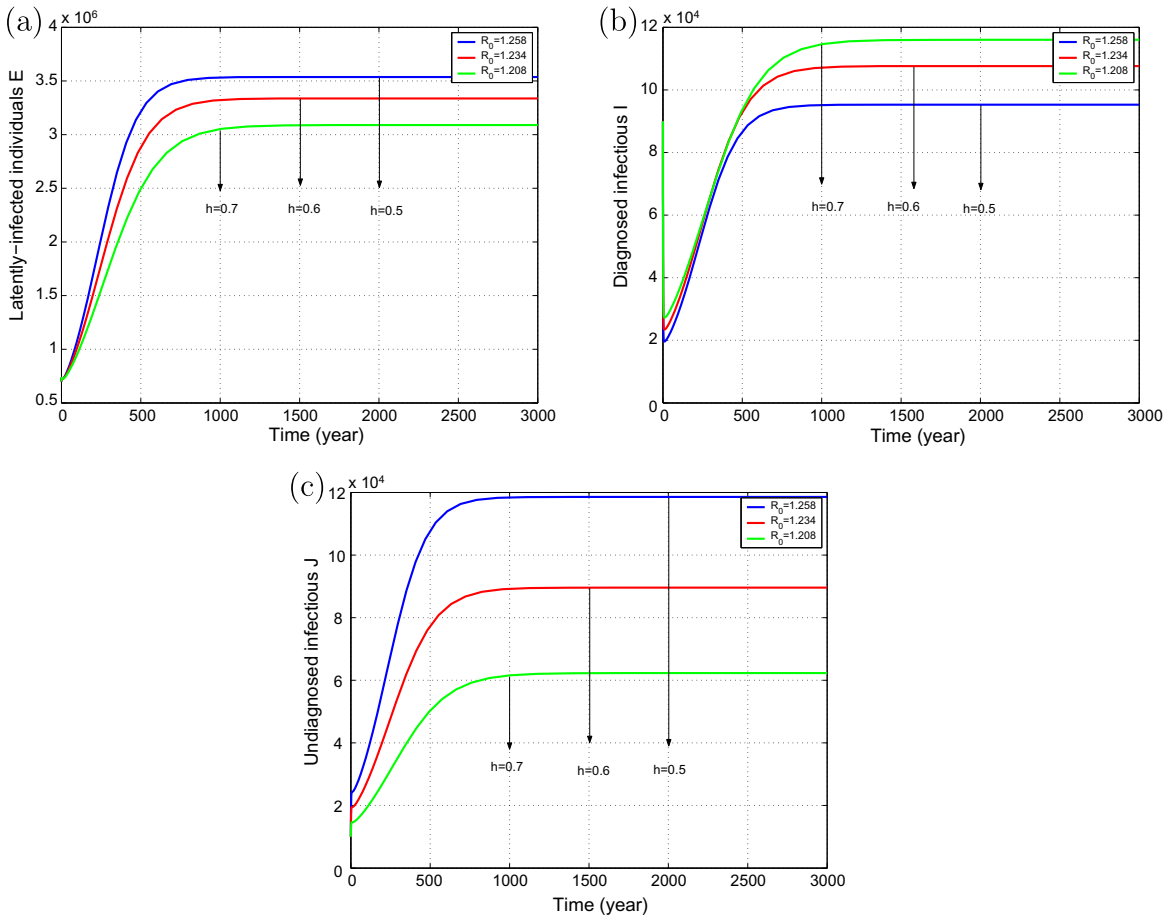

Fig. 5. Time series of (a) latently infected individuals, (b) diagnosed infectious and (c) undiagnosed infectious of model (2) showing the impact of varying h for $\beta = 0.5$ (so that $\mathcal{R}_0 > 1$). Initial conditions and all other parameters are as in Fig. 4.

$$L(u, v) = \int_0^T [B_1 I(t) + C_1 J(t) + B_2 u^2(t) + C_2 v^2(t)]dt, \tag{19}$$

where the constants B_1, B_2, C_1 and C_2 have a dual role. They are needed to balance the units in the integrand because the number of diagnosed and undiagnosed infectious will be measured in the hundreds in this paper. We assume that there are practical limitations on the maximum rate at which latently-infected individuals that may treated via chemoprophylaxis or infectious that may be detected in a given time period and we define positive constants $u_{\max}$ and $v_{\max}$ accordingly.

Pontryagin's Maximum principle [26] introduces adjoint functions that allow us to attach our state system, i.e., the S, E, I and J differential equations, to our objective functional. After first showing the existence of optimal controls [24], this principle can be used to obtain the differential equations for the adjoint variables, corresponding boundary conditions and the characterization of an optimal control double $\bar{u}$ and $\bar{v}$. This characterization gives a representation of an optimal control in terms of the state and adjoint functions. Also, this principle converts the problem of minimizing the objective functional subject to the state system into minimizing the Hamiltonian with respect to the controls (bounded measurable functions) at each time t.

Forming the Hamiltonien, H, we have

$$\begin{aligned} H = {} & B_1 I(t) + C_1 J(t) + B_2 u^2(t) + C_2 v^2(t) + w_S[\Lambda - \lambda(t)S(t) - \mu S(t)] + w_E[(1-p)\lambda(t)S(t) + r_2 I(t) + r_3 J(t) - (1 \\ & - u(t)r_1)(k + \sigma\lambda(t))E(t) - \mu E(t)] + w_I[pf\lambda(t)S(t) + v(t)h(1 - u(t)r_1)(k + \sigma\lambda(t))E(t) - A_2 I(t)] + w_J[p(1 \\ & - f)\lambda(t)S(t) + (1 - v(t)h)(1 - u(t)r_1)(k + \sigma\lambda(t))E(t) - A_3 J(t)], \end{aligned} \tag{20}$$

where w_S, w_E, w_I and w_J are the adjoint functions associated with their respective states. Note that in H, each adjoint function multiplies the right-hand side of the differential equation of its corresponding state function. The first terms in H comes from the integrand of the objective functional. Thus, the adjoint variable $w_j, j = S, E, I, J$ together with our state system determine our optimality system.

Given an optimal control double $(\bar{u}, \bar{v})$ and the corresponding states $(\bar{S}, \bar{E}, \bar{I}, \bar{J})$, there exist adjoint functions satisfying

$$\begin{cases} \frac{dw_S}{dt} = \frac{(N-S)\lambda}{N}[w_S - (1-p)w_E - pfw_I - p(1-f)w_J] + \mu w_S + \frac{\sigma(1-r_1u)\lambda E}{N}[vh(w_I - w_J) + w_J - w_E], \\ \frac{dw_E}{dt} = \frac{\lambda S}{N}[-w_S + (1-p)w_E + pfw_I + p(1-f)w_J] + \mu w_E + (1-r_1u)(k+\sigma\lambda)[w_E - vhw_I - (1-vh)w_J] + \frac{\sigma(1-r_1u)\lambda E}{N}[-w_E + vhw_I + (1-vh)w_J], \\ \frac{dw_I}{dt} = B_1 - r_2w_E + A_2w_I + \frac{(\beta-\lambda)S}{N}[w_S - (1-p)w_E - pfw_I - p(1-f)w_J] + \frac{\sigma(1-r_1u)(\beta-\lambda)E}{N}[w_E - vhw_I - (1-vh)w_J], \\ \frac{dw_J}{dt} = C_1 - r_3w_E + A_3w_J + \frac{(\beta\varepsilon-\lambda)S}{N}[w_S - (1-p)w_E - pfw_I - p(1-f)w_J] + \frac{\sigma(1-r_1u)(\beta\varepsilon-\lambda)E}{N}[w_E - vhw_I - (1-vh)w_J], \end{cases} \tag{21}$$

with the transversality conditions

$$w_S(T) = 0, \qquad w_E(T) = 0, \qquad w_I(T) = 0 \qquad \text{and} \qquad w_J(T) = 0. \tag{22}$$

Note that the right-hand side of w_S differential equation is $-\frac{\partial H}{\partial S}$, and similarly for the other adjoint functions. The final time boundary conditions (transversality conditions) are zero since there is no dependence on the states at the final time in the objective functional.

Furthermore, the optimal controls are characterized by

$$\bar{u} = \max(0, \min(\hat{u}(t), u_{\max})) \qquad \text{and} \qquad \bar{v} = \max(0, \min(\hat{v}(t), v_{\max})), \tag{23}$$

where

$$\begin{aligned} \hat{u}(t) &= \frac{r_1(k+\sigma\lambda)[2C_2(w_E+w_J) - h^2(k+\sigma\lambda)(w_I-w_J)^2E]E}{4B_2C_2 - r_1^2h^2(k+\sigma\lambda)^2(w_I-w_J)^2E^2}, \\ \hat{v}(t) &= \frac{h(k+\sigma\lambda)(w_I-w_J)[-2B_2 + r_1^2(k+\sigma\lambda)(w_J+w_E)E]E}{4B_2C_2 - r_1^2h^2(k+\sigma\lambda)^2(w_I-w_J)^2E^2}. \end{aligned} \tag{24}$$

The control characterization for $\bar{u}$ comes from $\frac{\partial H}{\partial u} = 0$ whenever $0 < \bar{u}(t) < u_{\max}$ and taking bounds into account, and similarly for the control v.

The state system of differential equations and the adjoint system of differential equations together with the control characterization above form the optimality system to be solved numerically. Since the state equations have initial conditions and the adjoint equations have final time conditions, we cannot solve the optimality system directly by only sweeping forward in time. Thus, an iterative algorithm, "forward–backward sweep method" [23], is used. An initial estimate for the controls is made. The state system is then solved forward in time from the dynamics using a Runge–Kutta method of fourth order. Resulting state values are placed in the right-hand sides of the adjoint differential equations. Then, the adjoint system with the given initial conditions is solved backward in time, again employing a fourth order Runge–Kutta method. Both state and adjoint values are used to update the control using the characterization, and then the process is repeated. This iterative process terminates when the current state, adjoint, and control values converge sufficiently.

3.2. Optimal control numerical simulations

Numerical solutions to the optimality system comprising the state system (18) and the adjoint system (21) are carried out using parameters and initial conditions of Fig. 4. With this strategy, the controls on chemoprophylaxis u and detection v are optimized, with weight factors $B_1 = 50, B_2 = 10, C_1 = 40$ and $C_2 = 20$. Also, we take $u_{\max} = v_{\max} = 1$. Cost coefficients are fixed within the integral expression (19) and the optimal schedule of the two controls over $T = 5$ year is simulated. We note that this is not necessarily the only or most efficient homotopy path possible; however, it was sufficient to produce an accurate answer in an acceptable amount of time. Numerical simulations are depicted in Figs. 6–8.

From Fig. 6, we can see that the optimal chemoprophylaxis and detection protocol have a very desirable effect upon the population of infectious which decreases while the population of susceptible which increases for almost the entire length of treatment and detection. Also, from Fig. 6(b) one can observe that the population of latently infected individuals decreases during the 0.6 year of the beginning of the treatment and detection protocols and after begin to increase slowly. The inverse phenomenon has been observed for the population of undiagnosed infectious (see Fig. 6(d)) who increases as the controls start and begin to decrease after the 0.6 year of simulations. This is presumably because at the beginning of the optimal chemoprophylaxis and detection protocol, the chemoprophylaxis control is at it upper bound (see Fig. 7(a)), while the detection control is at its lower value 0 (see Fig. 7(b)).

As Fig. 7 illustrates, the optimal control results provide clearly different strategies for relative application of chemoprophylaxis of latently-infected individuals and detection of infectious in the host population. The optimal chemoprophylaxis and detection protocol were applied on the interval $[0, 5]$. This means that the two controls will start at zero and after 5 years, they will converge to zero. Fig. 7(a) illustrates that if one want to reduce the burden of the disease, the chemoprophylaxis of latently infected individuals need to be apply intensively at the beginning of the proposed strategy of control. Note that when the chemoprophylaxis control u is at its upper bound $u_{max} = 1$ through the 4.7 years of the simulations, very few latently infected individuals will develop an active TB. This implies that the detection rate of patients will be low since there will be no infectious to diagnose. This can be seen in Fig. 7(b) where the detection control v starts to converge to zero and after 4.7 years of the simulations, grow rapidly at its upper bound $v_{max} = 1$. Also, from Fig. 7(a), the chemoprophylaxis control drops rapidly to zero after 4.7 years and then converges to zero until the end of the simulations because the strategy of control has been applied over 5 years so that it remains to zero when $T = 5$ years. Thus, when the chemoprophylaxis

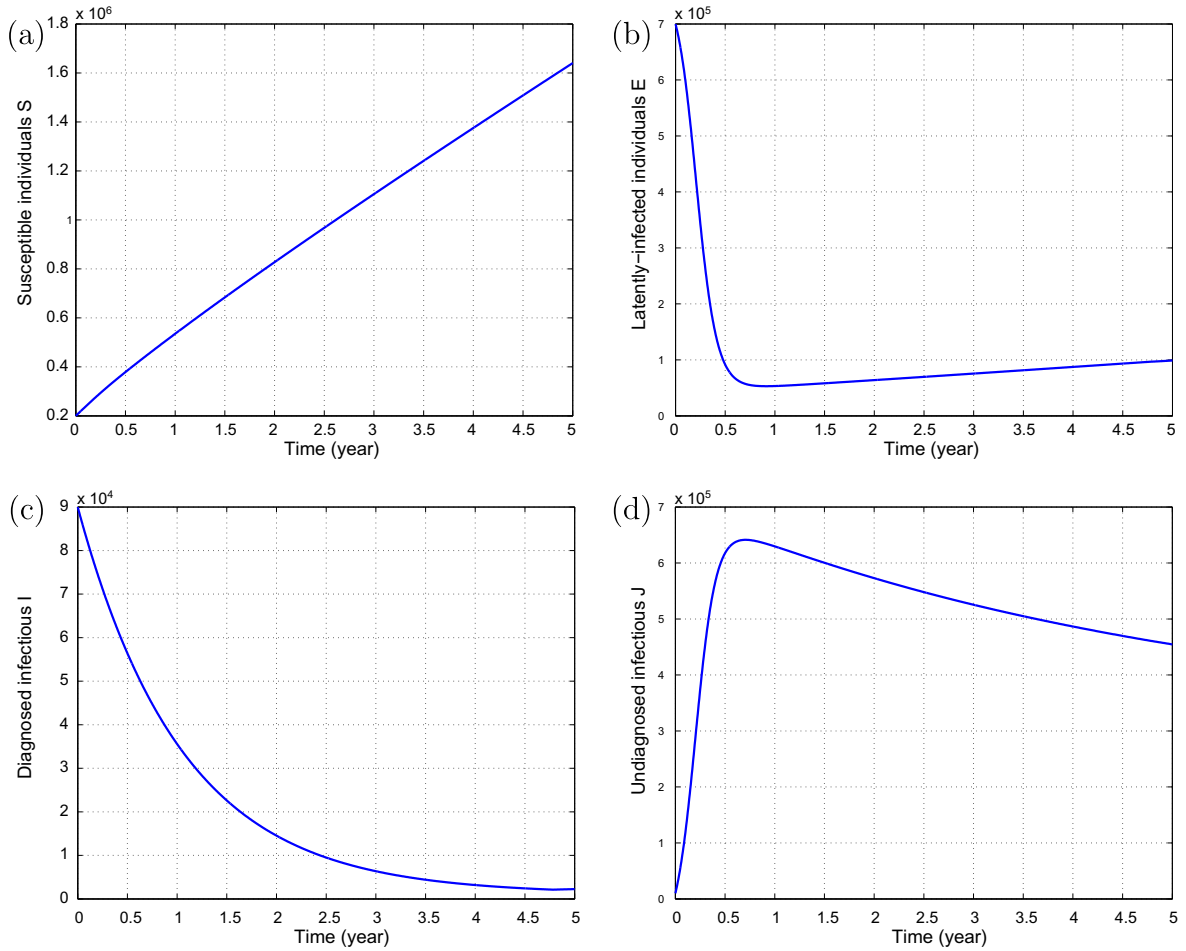

Fig. 6. Dynamics of the model (18) showing the effect of chemoprophylaxis and detection rates on the host population. Time series of (a) susceptible individuals, (b) latently infected individuals, (c) diagnosed infectious and (d) undiagnosed infectious.

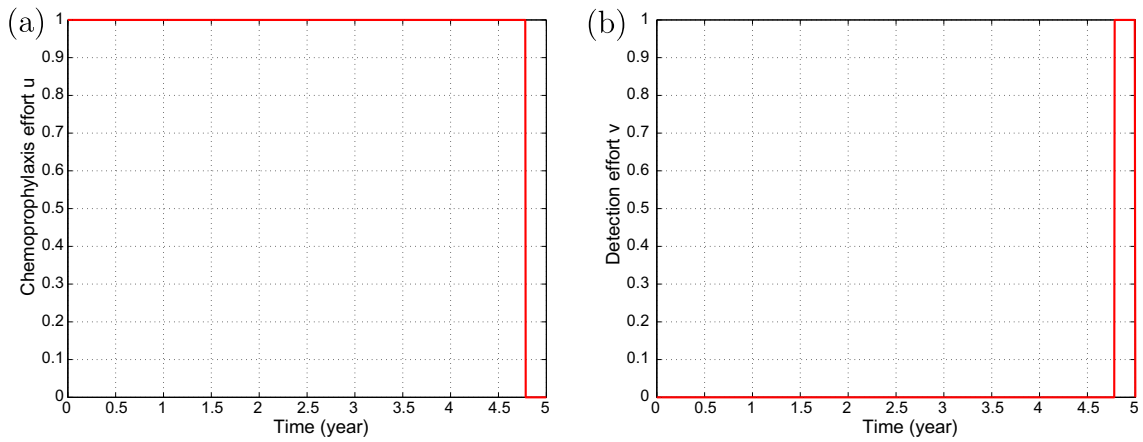

Fig. 7. Optimal balance of controls for the model (18). (a) Optimal chemoprophylaxis control u and (b) optimal detection control v.

control converges to zero after 4.7 years, more people will develop an active TB and the maximum of them should be diagnosed if we want to fight against disease. This can be observed in Fig. 7(b) where the optimal detection control v is at its upper bound $v_{max} = 1$ after 4.7 years of the simulations and then drop rapidly to zero at the final time because the proposed

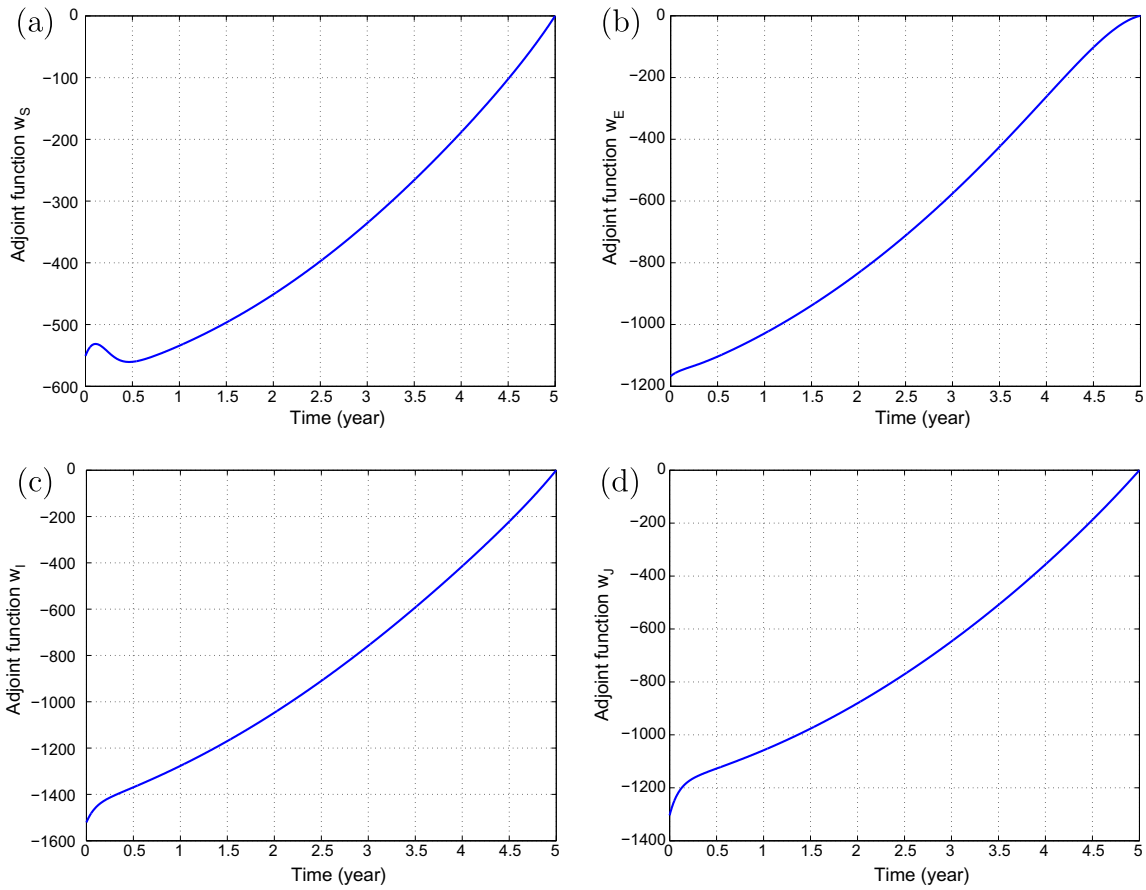

Fig. 8. The adjoint variables (a) w_S, (b) w_E, (c) w_I and (d) w_J of the optimality system.

strategy of control has been applied over 5 years. We believe that these phenomena are certainly due to the structure of the terms that contain the chemoprophylaxis and detection controls in model system (18). Biologically speaking, with the proposed model and parameter values, the chemoprophylaxis of latently infected individuals should be applied intensively at the beginning of the control strategy so that it is not necessary to apply the detection protocol at the same time. However, the detection of infectious should be applied just before the end of the control strategy. This will avoid many states to expend too much money for the fight against a single disease.

In summary, for this population, chemoprophylaxis and detection greatly reduces death due to disease. Consequently, fewer funds can be allow for chemoprophylaxis and detection in the optimal scheme; however, temporary maximum treatment is advantageous at the onset of infection. In combination with other controls, high level of chemoprophylaxis is most beneficial at the beginning of a TB control program to decrease the rate at which latently-infected individuals become infectious, providing more time to effectively implement the diagnosis and the treatment. Recall that our analysis on the basic reproduction ratio revealed that chemoprophylaxis, detection and treatment play a strong role on controlling the total number of infectious.

The time evolution of the adjoint variables w_S, w_E, w_I and w_J associated to the state variables S, E, I and J are depicted in Fig. 8(a)–(d), respectively. It clearly appears that the adjoint variables converge to the origin after 5 years.

4. Discussions

This paper presents a comprehensive, continuous and more realistic deterministic model for the transmission dynamics of tuberculosis. In contrast to many TB models in the literature, we have included two infective classes emanating from diagnosed and undiagnosed infectious. The undiagnosed subclass is of particular importance in modeling TB in developing countries like sub-Saharan Africa where public health is under developed. In particular the proportion of individuals that present themselves to medical facilities, h, is worth noting. This parameter can be used to measure successes of educational campaigns that encourage individuals to go for TB screening. It can also be a measure of the level of awareness of the implications of not having TB diagnosis.

The model has been rigourously analyzed to gain insight into its qualitative dynamics. We have mainly found that the model exhibits the phenomenon of backward bifurcation, where the stable disease-free equilibrium co-exists with a stable endemic equilibrium, when the basic reproduction ratio is less than the unity. It is shown that this (backward bifurcation) dynamics feature is caused by the re-infections of latently infected individuals.

An optimal control strategy has been presented. The proposed optimal control shows the result of optimally controlling exogenous reinfections using chemoprophylaxis and detection of infectious in the reduction of the number of individuals with active TB. Thought numerical simulations, we found that the infection level decreases, but is never eradicated. However, at the end of the chemoprophylaxis and detection, the infection level cannot rise again. Also, the chemoprophylaxis control is at its upper bound while, the detection control is at its lower bound at the beginning of the chemoprophylaxis and detection protocol. We believe that these phenomena is directly dependent upon the action of the response of the treatment of diagnosed infectious, which occurs shortly after treatment initiation in response to the high infection level. An important result of this analysis is that a cost-effective balance of chemoprophylaxis and detection methods can successfully control TB. Treatment strategies such as interruption of drug therapy should also be considered. This can be tested clinically via drug trails, but also mathematically using a periodic control.

From the practical viewpoint, the model formulated in this paper can be used to understand the transmission behaviors of the disease and to forecast the disease trends, which can help health program planners to implement more preventive interventions in TB control during the period of higher risk of infection.

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