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Optimal treatment and vaccination control strategies for the dynamics of pulmonary tuberculosis

Research Article

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Abstract: In this article we apply optimal control theory to one-strain tuberculosis model that incorporates vaccination and treatment. In this model the control mechanisms associated with chemoprophylaxis of latently infected with TB and education campaign are incorporated in order to reduce the number of latently and actively infected population with TB through application of Pontryagin's Maximum Principle. Numerical simulations are carried out by using both forward and backward in time fourth order Runge-Kutta schemes. The results show that education campaign control measure alone is more effective in curbing TB transmissions and infections than chemoprophylaxis of latently infected. Furthermore the combination of the two measures has desirable effect of reducing the number of infected individuals with TB than when a single control is used. We suggest that for total eradication of TB from the community, the emphasis of education campaign should be the focal point and chemoprophylaxis of latently infected individuals control strategy has to be paired with treatment of actively infected TB individuals.

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Keywords: Tuberculosis • Optimal control theory • Chemoprophylaxis • Education campaign.

1. Introduction

Tuberculosis (TB) is a chronic airborne disease caused by pathogen Mycobacterium tuberculosis with more than one-third of the world human population as its reservoir [4, 11, 19]. A global annual estimate of 8.6 million people develop Tuberculosis, of which 1.3 million die from disease. It is reported in [29] that, the burden of disease caused by TB is high in developing world where poor nutrition, congested accommodation and emergency of HIV are manifested. The global estimates of incidence, prevalence and mortality rates per 100,000 population in 2012 were respectively 255, 303 and 26 and Tanzania incidence, prevalence and mortality rates per 100,000 population were 165, 176 and 13 respectively as per [29]. It therefore raises a quest to find desirable means to curtail TB morbidity and mortality rates.

Tuberculosis disease is mainly of two types: pulmonary and extra-pulmonary TB. Pulmonary TB is a common form of TB that affects lung while extra-pulmonary TB affects other parts of body and organs including central nervous

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system and bone [28]. This particular study focuses on pulmonary TB. Tuberculosis is a disease that spreads in the air when the infectious person with pulmonary TB expel bacteria by coughing, singing, sneezing, speaking and so on [8]. An individual with active TB has usual symptoms which are general weakness or tiredness, fever, weight loss, loss of appetite and night sweats. Further symptoms are coughing, coughing up of sputum and/ or blood, shortness of breath and chest pains if the infection in the lung get worse [9]. TB draws back economics of the world and Tanzania in particular as it affects men than women and especially the productive working group [28]. A small proportion of about 10% of infected individuals with Mycobacterium tuberculosis develop TB and become infectious within two years upon infected [25]. Most become latent for the rest of their lives as long as their immune system is not compromised [8]. The recovered individuals from TB do not acquire the permanent immunity. Some of them become latently infected again. Even with treatment interventions, the rates of reinfection TB are higher than those of new TB [25]. Unlike other diseases, TB has complex dynamics to the extent that even reducing the threshold, effective reproduction number, R_e below one does not guarantee clearance of the disease from the community [30]. Mathematical modeling of epidemiology of Tuberculosis has recently become the powerful tool to study the dynamics of the disease and impact of various intervention strategies in order to advise public health policy makers to construct suitable intervention programs to combat TB infections. Agusto [2] formulated a tuberculosis model that incorporates treatment of infectious and chemoprophylaxis (administration of medication to prevent latently infected individual to progress to active TB) of latently infected individuals. In his modeling, he introduced the controls in treatment, chemoprophylaxis and relapse in order to reduce the number of active TB and latently infected individuals. His study shows that the control programs which follow these strategies can effectively reduce the population that is actively and latently infected with TB. Adekunle [1] incorporates controls representing chemoprophylaxis and treatment to SEIR model of TB proposed by Bhunu et al. [3] in order to reduce latently infected as well as actively infected population by using Pontryagin Maximum Principle of optimal control theory. The results of work show that chemoprophylaxis is more effective in controlling disease in population when used alone than applying treatment only. Furthermore, results suggest that the use of both controls concurrently stand out as an effective strategy of reducing the number of infected individuals than to use only one measure at a time. Bowong [7] introduced the control term to the basic SEI (Susceptible-Exposed-Infectious) model of TB for 'case finding' that represents the effort on chemoprophylaxis parameter on reducing the number of individuals who may become infectious. The results show that the control mechanism boosts up the efforts of chemoprophylaxis in controlling exogenous reinfection an hence reduces the number of actively infected individuals with TB. In this article we consider time dependent control mechanisms associated with education campaign and chemoprophylaxis of latently infected individual to one-strain tuberculosis model that incorporates treatment and vaccination as intervention strategies so as to boost their efforts toward reducing the number of latently and actively infected with TB. The optimality system is derived by aid of Pontryagin's Maximum Principle [24]. Numerical simulation is carried out by using forward and backward in time fourth order Runge-Kutta schemes.

2. Optimal Control Model Formulation

In this section we construct a continuous time deterministic one-strain tuberculosis model with control term by modifying the model of Mlay et al. [20]. The control terms u_1 and u_2 are added as shown in Fig. 1. The full descriptions of variables and parameters which appear in Fig. 1 are in Table 1 and Table 2 respectively.

Table 1. Description of variables of the model

Variable	Descriptions
$S(t)$	The Susceptible individuals who are at risk of being infected at time t
$L(t)$	The latently infected individuals at time t
$V(t)$	Vaccinated individuals at time t
$I_1(t)$	Individuals who are severely infected with TB at time t
$I_2(t)$	Individuals who are mildly infected with TB at time t
$T(t)$	Individuals Treated against TB at time t

We aim at introducing control measures which are education campaign and chemoprophylaxis of latently infected individuals to the basic model of Mlay et al. [20] to boost the efforts played by intervention strategies (vaccination and treatment) so as to lower TB infections in the community as well as minimizing the cost of administering these controls.

Education campaign denoted by $u_1(t)$ is introduced to the basic model as a control term that will sensitize parents and guardians to vaccinate more babies and hence increasing the proportion of vaccinated babies by $(1+u_1)\rho$. That is if education campaign is 100% effective then proportion of vaccinated babies will be doubled. Consequently education campaign provides awareness to community on how the disease is transmitted and ways to reduce the probability of being infected. This information in turn reduces the number of susceptible

Table 2. Description of Parameters of the model

Parameter	Descriptions
λ	Per capita birth rate.
β	Per capita infection rate.
ρ	Proportional of babies who are being vaccinated at birth.
θ	The rate at which a vaccinated individual looses immunity.
ϵ	The rate of progression from Latent class to both severely and mildly Infected classes.
η	Proportional of Latently infected population progressing to mild infected class.
μ	Per capita natural death rate.
δ_1	Per capita additional death rate of severely infected class.
δ_2	Per capita additional death rate of mildly infected class.
ϕ	Proportional of mildly infected class who are treated.
ω	The transferring rate of mildly infected to both severely infected and treatment classes.
ν	The rate at which a severely infected candidate is transferred to treatment class.
γ	The factor that reduces the level of reinfection.

individuals who join the class of latently infected individuals by decreasing the transmission rate to $(1-u_1)\beta$. In addition the education campaign will reduce the number of mildly infected individuals who join severely infected class as a result increases the rate of both infectious classes to treatment and reducing individuals who relapse back to Latent group after treatment. That means if u_1 is a control mechanism indicating the efforts played by education campaign to curtail TB infections and transmissions then $(1-u_1)$ is a failure of the control mechanism.

On the other hand chemoprophylaxis of latently infected individuals denoted by control term u_2 is introduced to the basic model presented in Mlay et al. [20] so as to lower active TB cases of latently infected individuals. That is $1-u_2(t)$ is a failure of chemoprophylaxis to prevent the latent infected group from progressing to active TB. Jung et al. [14] claim that, if $u_2(t)$ is near to 1 then there is low treatment failure of chemoprophylaxis and high implementation cost. The compartmental diagram with control mechanisms, education campaign, $u_1(t)$ and chemoprophylaxis of latently infected individuals with TB, $u_2(t)$ is shown in Fig. 1.

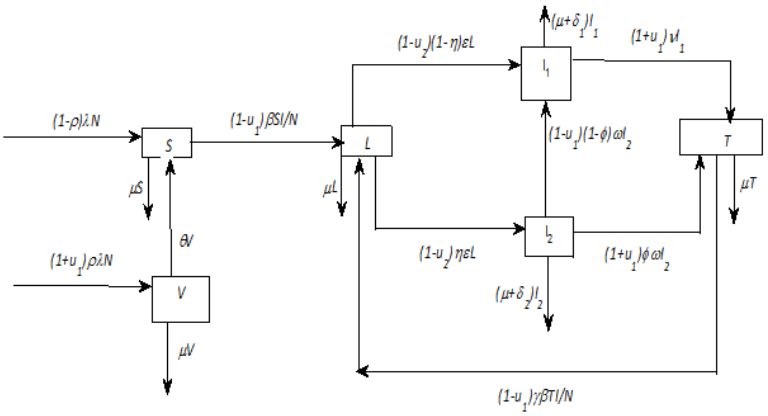

Fig. 1. Schematic flow diagram showing dynamics of tuberculosis and control mechanisms u_1 and u_2 respectively, whereby $I = I_1 + I_2$.

The state system that is one-strain tuberculosis model with two control variables u_1 and u_2 is obtained from Figure 1 as follows:

$$\frac{dS}{dt} = (1-\rho)\lambda N - (1-u_1(t))\beta S\frac{(I_1+I_2)}{N} - \mu S + \theta V, \tag{1a}$$

$$\frac{dV}{dt} = (1+u_1(t))\rho\lambda N - (\mu+\theta)V, \tag{1b}$$

$$\frac{dL}{dt} = (1-u_1(t))\beta\frac{(I_1+I_2)}{N}(S+\gamma T) - ((1-u_2(t))\epsilon+\mu)L, \tag{1c}$$

$$\frac{dI_1}{dt} = (1-u_2(t))(1-\eta)\epsilon L + (1-u_1(t))(1-\phi)\omega I_2 - (\mu+\delta_1+(1+u_1(t))\nu)I_1, \tag{1d}$$

$$\frac{dI_2}{dt} = ((1-u_2(t))\eta\epsilon L - ((1-(1-2\phi)u_1(t))\omega+\mu+\delta_2)I_2, \tag{1e}$$

$$\frac{dT}{dt} = (1+u_1(t))(\nu I_1 + \phi\omega I_2) - \left(\mu + (1-u_1(t))\gamma\beta\frac{(I_1+I_2)}{N}\right)T. \tag{1f}$$

2.1. Optimal Control Problem

In model (1) we assume that control functions $u_1(t)$ and $u_2(t)$ are Lebesgue integrable functions with $0 < u_1, u_2$. Our objective functional to be minimized is:

$$J(u_1,u_2) = \int_0^{tf}\left[A_1L(t) + A_2I_1(t) + A_3I_2(t) + \frac{B_1}{2}{u_1}^2 + \frac{B_2}{2}{u_2}^2\right]dt \tag{2}$$

where we want to minimize latent and infectious (severely and mildly infected) groups with drug-sensitive strain TB while keeping the costs of education campaign and chemoprophylaxis of latently infected group low. From equation (2), tf is fixed final time, A_1, A_2 and A_3 are positive weight constants of latently infected, severely infected and mildly infected groups respectively while B_1 and B_2 are positive weight constants which balance the cost factors associated with control mechanisms u_1 and u_2. The cost of each control mechanism is assumed to be non-linear and take quadratic form. That is, $\frac{B_1}{2}{u_1}^2$ is cost of control mechanism associated with educating the public (i.e. education campaign) about vaccinating their newly born children with TB vaccine, symptoms of active TB and the need of sending infectious individuals to hospital while $\frac{B_2}{2}{u_2}^2$ is a cost of control mechanism in latently infected group associated with administering of chemoprophylaxis that prevent them suffer the active TB.

We aim to find control pair, ${u_1}^\star$ and ${u_2}^\star$, such that

$$J({u_1}^\star, {u_2}^\star) = \min_{\Gamma} J(u_1,u_2) \tag{3}$$

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

As basic framework, after formulating model (1) and the corresponding objective functional (2) the remaining tasks according to Macki and Strauss [17], Sethi and Thompson [26] and Joshi et al. [13] is to:

1. prove existence of optimal control,
2. characterize the optimal control,
3. prove uniqueness of optimal control,
4. compute optimal control numerically,
5. investigate how optimal control depends on various parameters of the model.

2.2. Existence of an optimal control

In this section we state and prove the existence of an optimal control. We note that our objective functional in (2) has no salvage term (i.e. the value of state at the fixed final time is zero). It falls under category of Mayer optimization problem [6]. Therefore by applying the results in Theorem 4.1 of Fleming and Rishel [12] [pages 68-70], Lukes [16], Lashari et al. [15] and proof outline presented by Mpeshe et al. [22] is sufficient enough to prove that an optimal control exists. Before proving an existence of an optimal control, let us state the following theorem:

Theorem 2.1.
Consider an optimal control problem with state equations (1). There exists optimal control pair $(u_1^\star, u_2^\star) \in \Gamma$ *such that*

$$\min_{\Gamma} J(u_1, u_2) = J(u_1^\star, u_2^\star) \tag{4}$$

Proof. We begin our proof by following properties of existence of an optimal control presented in Mpeshe et al [22]. The control set together with corresponding state variables is non-empty by existential results in Lukes [16] [Theorem 9.2.1 pg. 182]. Set of all control variables $(u_1, u_2) \in \Gamma$ is convex by definition. Convexity of objective functional in u_1 and u_2 is satisfied. Our optimal system is compact (i.e. closed and bounded) as a necessary condition for existence of optimal control. That means state solution of state system (1) are bounded by a linear function. The integrand of objective functional (2),$A_1 L(t) + A_2 I_1(t) + A_3 I_2(t) + \frac{B_1}{2} {u_1}^2 + \frac{B_2}{2} {u_2}^2$ is convex on control set Γ. In addition, according to Lashari et al. [15], there exists a constant $p > 1$ and positive numbers q_1, q_2 such that objective functional is bounded below by $q_1 \left(|u_1|^2 + |u_2|^2\right)^{p/2} - q_2$. That is:

$$J(u_1, u_2) \geq q_1 \left(|u_1|^2 + |u_2|^2\right)^{p/2} - q_2,$$

because, state variables are bounded, that completes the proof of existence of optimal control following the result in Theorem 4.1 of Fleming and Rishel [12] [pages 68-70]. □

2.3. Characterization of the optimal control

In this section we derive necessary conditions on an optimal control, characterizing optimal control using upper and lower bound technique and formulating optimality system that characterizes the optimal control. The optimal pair should satisfy the necessary conditions that come from Pontryagin Maximum Principle [24], and which are also discussed in [21]. This principle converts state system (1), objective functional (2) and control set (3) into minimal value of Lagrangian of optimal problem. The Lagrangian of the optimal problem is given by:

$$\mathscr{L} = A_1 L(t) + A_2 I_1(t) + A_3 I_2(t) + \frac{B_1}{2} {u_1}^2 + \frac{B_2}{2} {u_2}^2 \tag{5}$$

In order to seek for minimum Lagrangian of optimal problem we define the Hamilitonian H for the control problem with respect to u_1 and u_2 as

$$H = A_1 L(t) + A_2 I_1(t) + A_3 I_2(t) + \frac{B_1}{2} {u_1}^2 + \frac{B_2}{2} {u_2}^2 + \sum_{i=1}^{6} \lambda_i f_i \tag{6}$$

where f_i is right hand side of the differential equation of ith state variable in system (1) and λ_i for $i = 1, 2, \cdots, 6$ is the set of adjoint functions. That means the Hamiltonian consists of integrand of objective functional and the inner product of right hand side of state equations and corresponding adjoint variables $(\lambda_1, \lambda_2, \cdots \lambda_6)$. The expanded form of Hamiltonian H in (6) is given by:

$$\begin{aligned}
H = {} & A_1 L(t) + A_2 I_1(t) + A_3 I_2(t) + \frac{B_1}{2} {u_1}^2 + \frac{B_2}{2} {u_2}^2 \\
& + \lambda_1 \left[(1-\rho)\lambda N - (1-u_1(t))\beta S \frac{(I_1 + I_2)}{N} - \mu S + \theta V \right] \\
& + \lambda_2 \left[(1+u_1(t))\rho\lambda N - (\mu + \theta)V \right] \\
& + \lambda_3 \left[(1-u_1(t))\beta \frac{(I_1 + I_2)}{N} (S + \gamma T) - ((1-u_2(t))\epsilon + \mu)L \right] \\
& + \lambda_4 \left[(1-u_2(t))(1-\eta)\epsilon L + (1-u_1(t))(1-\phi)\omega I_2 - (\mu + \delta_1 + (1+u_1(t))\nu) I_1 \right] \\
& + \lambda_5 \left[((1-u_2(t))\eta\epsilon L - ((1-(1-2\phi)u_1(t))\omega + \mu + \delta_2) I_2 \right] \\
& + \lambda_6 \left[(1+u_1(t))(\nu I_1 + \phi\omega I_2) - \left(\mu + (1-u_1(t))\gamma\beta \frac{(I_1 + I_2)}{N} \right) T. \right]
\end{aligned} \tag{7}$$

Theorem 2.2.
There exists an optimal control pair $(u_1^\star, u_2^\star)$ *and the corresponding state solutions* $S^\star, V^\star, L^\star, I_1^\star, I_2^\star$ *and* $T^\star$, *that minimizes* $J(u_1, u_2)$ *over* Γ. *Furthermore there exists adjoint functions,* $\lambda_1, \lambda_2, \cdots \lambda_6$ *such that*

$$\frac{d\lambda_1}{dt} = -\frac{\partial H}{\partial S}, \frac{d\lambda_2}{dt} = -\frac{\partial H}{\partial V}, \cdots, \frac{d\lambda_6}{dt} = -\frac{\partial H}{\partial T} \text{ adjoint conditions,} \tag{8}$$

$$\lambda_1(tf)=\lambda_2(tf)=\cdots=\lambda_6(tf)=0 \text{ transversality conditions.} \tag{9}$$

and $N=S^\star+V^\star+L^\star+I_1{}^\star+I_2{}^\star+T^\star$.

In addition,

$$\frac{\partial H}{\partial u_i}=0 \text{ at } u_i{}^\star=0,\ i=1,2 \text{ optimality conditions.} \tag{10}$$

Proof. The adjoint system is obtained by taking the negative partial derivative of Hamiltonian H with respect to state variables. By using Pontryagin's Maximum Principle the following adjoint system evaluated at optimal control pair and corresponding state variables is hereunder:

$$\begin{aligned}
\frac{d\lambda_1}{dt}&=-\frac{\partial H}{\partial S}=(\lambda_1-\lambda_3)(1-u_1{}^\star(t))\beta\frac{I_1{}^\star+I_2{}^\star}{N}+\mu\lambda_1,\\
\frac{d\lambda_2}{dt}&=-\frac{\partial H}{\partial V}=\mu\lambda_2+\theta(\lambda_2-\lambda_1),\\
\frac{d\lambda_3}{dt}&=-\frac{\partial H}{\partial L}=-A_1+\mu\lambda_3+(1-u_2{}^\star(t))(\lambda_3-\lambda_4+\eta(\lambda_4-\lambda_5))\epsilon,\\
\frac{d\lambda_4}{dt}&=-\frac{\partial H}{\partial I_1}=-A_2+\lambda_4(\mu+\delta_1)+(1-u_1{}^\star(t))\left[\frac{\beta}{N}(S^\star(\lambda_1-\lambda_3)+\gamma T^\star(\lambda_6-\lambda_3)\right]\\
&\quad+(\lambda_4-\lambda_6)(1+u_1{}^\star(t))\nu,\\
\frac{d\lambda_5}{dt}&=-\frac{\partial H}{\partial I_2}=-A_3+\lambda_5(2\phi\omega u_1{}^\star(t)+\mu+\delta_2)-\lambda_6)(1+u_1{}^\star(t))\phi\omega\\
&\quad+(1-u_1{}^\star(t))\left[\frac{\beta}{N}(S^\star(\lambda_1-\lambda_3)+\gamma T^\star(\lambda_6-\lambda_3)+(\lambda_5-\lambda_4(1-\phi))\omega\right],\\
\frac{d\lambda_6}{dt}&=-\frac{\partial H}{\partial T}=(\lambda_6-\lambda_3)(1-u_1{}^\star(t))\gamma\beta\frac{I_1{}^\star+I_2{}^\star}{N}+\mu\lambda_6.\\
N&=S^\star+V^\star+L^\star+I_1{}^\star+I_2{}^\star+T^\star.
\end{aligned} \tag{11}$$

The optimal solution of Hamiltonian is obtained by taking partial derivative of H with respect to control $u_i,\ i=1,2$ and set it to zero. That is,

$$\begin{aligned}
\frac{\partial H}{\partial u_1}&=B_1u_1+\beta\frac{I_1+I_2}{N}\left[(\lambda_1-\lambda_3)S+(\lambda_6-\lambda_3)\gamma T\right]+\lambda_2\rho\lambda N\\
&\quad+\omega I_2\left[(\lambda_6+\lambda_4-2\lambda_5)\phi+(\lambda_5-\lambda_4)\right]+\nu I_1(\lambda_6-\lambda_4),
\end{aligned} \tag{12a}$$

$$\frac{\partial H}{\partial u_2}=B_2u_2+\left(\lambda_3-\lambda_4+\eta(\lambda_4-\lambda_5)\epsilon L\right) \tag{12b}$$

If we set $\dfrac{\partial H}{\partial u_i}=0$ at $u_i{}^\star$ we find that:

$$\begin{aligned}
u_1{}^\star&=\frac{1}{B_1}\left[\beta\frac{I_1+I_2}{N}\{(\lambda_3-\lambda_1)S+(\lambda_3-\lambda_6)\gamma T\}-\lambda_2\rho\lambda N\right.\\
&\quad\left.+\omega I_2\{(2\lambda_5-\lambda_6-\lambda_4)\phi+(\lambda_4-\lambda_5)\}+\nu I_1(\lambda_4-\lambda_6)\right],
\end{aligned} \tag{13a}$$

$$u_2{}^\star=\frac{1}{B_2}\left[\lambda_4-\lambda_3+\eta(\lambda_5-\lambda_4)\epsilon L\right] \tag{13b}$$

Characterization of an optimal control is done by using technique involving control bounds $a_i\le u_i\le b_i$ and by setting $S=S^\star, V=V^\star, L=L^\star, I_1=I_1{}^\star, I_2=I_2{}^\star$ and $T=T^\star$.

Consider the control bound $a_1\le u_1\le b_1$. That means our control u_1 is bounded below by a_1 and above by b_1. Then the characterization of an optimal control $u_1{}^\star$ is given by:

$$u_1{}^\star=\begin{cases}a_1 & \text{if } X\le a_1\\ X & \text{if } a_1<X<b_1\\ b_1 & \text{if } X\ge b_1\end{cases} \tag{14}$$

whereby;

$$X = \frac{1}{B_1}\Big[\beta\frac{{I_1}^\star + {I_2}^\star}{N}\{(\lambda_3-\lambda_1)S^\star + (\lambda_3-\lambda_6)\gamma T^\star\} - \lambda_2\rho\lambda N + \omega {I_2}^\star\{(2\lambda_5-\lambda_6-\lambda_4)\phi + (\lambda_4-\lambda_5)\} + \nu {I_1}^\star(\lambda_4-\lambda_6)\Big].$$

In more compact form ${u_1}^\star$ can be written as

$${u_1}^\star = \min\Big\{\max\Big\{a_1, \frac{1}{B_1}\Big[\beta\frac{{I_1}^\star + {I_2}^\star}{N}\{(\lambda_3-\lambda_1)S^\star + (\lambda_3-\lambda_6)\gamma T^\star\} - \lambda_2\rho\lambda N + \omega {I_2}^\star\{(2\lambda_5-\lambda_6-\lambda_4)\phi + (\lambda_4-\lambda_5)\} + \nu {I_1}^\star(\lambda_4-\lambda_6)]\Big], b_1\Big\} \quad (15)$$

Likewise considering the control bound $a_2 \le u_2 \le b_2$, the control u_2 is bounded below by a_2 and bounded above by b_2. The characterization of an optimal control ${u_2}^\star$ is given by

$${u_2}^\star = \begin{cases} a_2 & \text{if } Y \le a_2 \\ Y & \text{if } a_2 < X < b_2 \\ b_2 & \text{if } Y \ge b_2 \end{cases} \quad (16)$$

where $Y = \frac{1}{B_2}\big[\lambda_4-\lambda_3+\eta(\lambda_5-\lambda_4)\epsilon L^\star\big]$. In more compact form ${u_2}^\star$ can be written as

$${u_2}^\star = \min\Big\{\max\Big\{a_2, \frac{1}{B_2}\big[\lambda_4-\lambda_3+\eta(\lambda_5-\lambda_4)\epsilon L^\star\big]\Big\}, b_2\Big\}. \quad (17)$$

Our optimality system comprises of the state system (1) coupled with adjoint system (11) with initial and transversal conditions together with characterization of optimal control.

We note that both $\frac{\partial H}{\partial {u_1}^2} = B_1 > 0$ and $\frac{\partial H}{\partial {u_2}^2} = B_2 > 0$. That means the second partial derivative of our Hamiltonian H with respect to controls u_1 and u_2 are positive. Therefore the optimal problem is minimum at controls ${u_1}^\star$ and ${u_2}^\star$.

2.4. Uniqueness of an optimal control

In this section we prove the uniqueness of an optimal control. According to Joshi et al. [13], to show the uniqueness of an optimal control is the same as to show the uniqueness of an optimality system. From (1) our system with properties of optimality system can be written as:

$$\begin{cases} S' &= p_1(t,S,V,L,I_1,I_2,T) \\ V' &= p_2(t,S,V,L,I_1,I_2,T) \\ L' &= p_3(t,S,V,L,I_1,I_2,T) \\ {I_1}' &= p_4(t,S,V,L,I_1,I_2,T) \\ {I_2}' &= p_5(t,S,V,L,I_1,I_2,T) \\ T' &= p_6(t,S,V,L,I_1,I_2,T) \\ & S(0), V(0), L(0), I_1(0), I_2(0), T(0) \text{ given}, \\ & S(tf), V(tf), L(tf), I_1(tf), I_2(tf), T(tf) \text{ given and } tf \text{ fixed}. \end{cases} \quad (18)$$

where $S \in \mathbb{R}^{m_1}, V \in \mathbb{R}^{m_2}, L \in \mathbb{R}^{m_3}, I_1 \in \mathbb{R}^{m_4}, I_2 \in \mathbb{R}^{m_5}, T \in \mathbb{R}^{m_6}$, m_i for $i = 1,2,\cdots,6$ is a dimension of vector space $\mathbb{R}^{m_i}$ and

$$\begin{aligned} p_1 &: \mathbb{R}\times\mathbb{R}^{m_1}\times\mathbb{R}^{m_2}\times\mathbb{R}^{m_3}\times\mathbb{R}^{m_4}\times\mathbb{R}^{m_5}\times\mathbb{R}^{m_6} \to \mathbb{R}^{m_1} \\ p_2 &: \mathbb{R}\times\mathbb{R}^{m_1}\times\mathbb{R}^{m_2}\times\mathbb{R}^{m_3}\times\mathbb{R}^{m_4}\times\mathbb{R}^{m_5}\times\mathbb{R}^{m_6} \to \mathbb{R}^{m_2} \\ p_3 &: \mathbb{R}\times\mathbb{R}^{m_1}\times\mathbb{R}^{m_2}\times\mathbb{R}^{m_3}\times\mathbb{R}^{m_4}\times\mathbb{R}^{m_5}\times\mathbb{R}^{m_6} \to \mathbb{R}^{m_3} \\ p_4 &: \mathbb{R}\times\mathbb{R}^{m_1}\times\mathbb{R}^{m_2}\times\mathbb{R}^{m_3}\times\mathbb{R}^{m_4}\times\mathbb{R}^{m_5}\times\mathbb{R}^{m_6} \to \mathbb{R}^{m_4} \\ p_5 &: \mathbb{R}\times\mathbb{R}^{m_1}\times\mathbb{R}^{m_2}\times\mathbb{R}^{m_3}\times\mathbb{R}^{m_4}\times\mathbb{R}^{m_5}\times\mathbb{R}^{m_6} \to \mathbb{R}^{m_5} \\ p_6 &: \mathbb{R}\times\mathbb{R}^{m_1}\times\mathbb{R}^{m_2}\times\mathbb{R}^{m_3}\times\mathbb{R}^{m_4}\times\mathbb{R}^{m_5}\times\mathbb{R}^{m_6} \to \mathbb{R}^{m_6} \end{aligned}$$

are continuous. Before proving for uniqueness of an optimal control we state the following theorem:

Theorem 2.3.
Assume $p_1, p_2, \cdots p_6$ are bounded and satisfy Lipschitz condition relative to S, V, L, I_1, I_2 and T with constant $A > 0$. Then the solutions of system (18) are unique if the final time tf is sufficiently small.

Proof. Suppose (18) has two solutions $(S_1(t), V_1(t), L_1(t), I_{1\star}(t), I_{2\star}(t), T_1(t))$ and $(S_2(t), V_2(t), L_2(t), I_{1\star\star}(t), I_{2\star\star}(t), T_2(t))$. Applying Lipschitz condition implied in [18] on p_1 results to:

$$\|S_1(t)-S_2(t)\| \leq \int_0^{t_1} A(\|S_1(r)-S_2(r)\|+\|V_1(r)-V_2(r)\|+\|L_1(r)-L_2(r)\|+\|I_{1\star}(r)-I_{1\star\star}(r)\| + \|I_{2\star}(r)-I_{2\star\star}(r)\|+\|T_1(r)-T_2(r)\|)dr \quad (19)$$

A similar inequality holds for solutions $V_1(t)$ and $V_2(t)$ as follows:

$$\|V_1(t)-V_2(t)\| \leq \int_{t_1}^{t_2} A(\|S_1(r)-S_2(r)\|+\|V_1(r)-V_2(r)\|+\|L_1(r)-L_2(r)\|+\|I_{1\star}(r)-I_{1\star\star}(r)\| + \|I_{2\star}(r)-I_{2\star\star}(r)\|+\|T_1(r)-T_2(r)\|)dr \quad (20)$$

Lipschitz condition on solutions $L_1(t)$ and $L_2(t)$ implies:

$$\|L_1(t)-L_2(t)\| \leq \int_{t_2}^{t_3} A(\|S_1(r)-S_2(r)\|+\|V_1(r)-V_2(r)\|+\|L_1(r)-L_2(r)\|+\|I_{1\star}(r)-I_{1\star\star}(r)\| + \|I_{2\star}(r)-I_{2\star\star}(r)\|+\|T_1(r)-T_2(r)\|)dr \quad (21)$$

Lipschitz condition on solutions $I_{1\star}(t)$ and $I_{1\star\star}(t)$ results to:

$$\|I_{1\star}(t)-I_{1\star\star}(t)\| \leq \int_{t_3}^{t_4} A(\|S_1(r)-S_2(r)\|+\|V_1(r)-V_2(r)\|+\|L_1(r)-L_2(r)\|+\|I_{1\star}(r)-I_{1\star\star}(r)\| + \|I_{2\star}(r)-I_{2\star\star}(r)\|+\|T_1(r)-T_2(r)\|)dr \quad (22)$$

Lipschitz condition on solutions $I_{2\star}(t)$ and $I_{2\star\star}(t)$ implies:

$$\|I_{2\star}(t)-I_{2\star\star}(t)\| \leq \int_{t_4}^{t_5} A(\|S_1(r)-S_2(r)\|+\|V_1(r)-V_2(r)\|+\|L_1(r)-L_2(r)\|+\|I_{1\star}(r)-I_{1\star\star}(r)\| + \|I_{2\star}(r)-I_{2\star\star}(r)\|+\|T_1(r)-T_2(r)\|)dr \quad (23)$$

Finally Lipschitz condition on solutions $T_1(t)$ and $T_2(t)$, where tf is final time is given by:

$$\|T_1(t)-T_2(t)\| \leq \int_{t_5}^{tf} A(\|S_1(r)-S_2(r)\|+\|V_1(r)-V_2(r)\|+\|L_1(r)-L_2(r)\|+\|I_{1\star}(r)-I_{1\star\star}(r)\| + \|I_{2\star}(r)-I_{2\star\star}(r)\|+\|T_1(r)-T_2(r)\|)dr \quad (24)$$

Adding (19), (20), (21), (22), (23) and (24) together yields:

$$\|S_1(t)-S_2(t)\|+\|V_1(t)-V_2(t)\|+\|L_1(t)-L_2(t)\|+\|I_{1\star}(t)-I_{1\star\star}(t)\|+\|I_{2\star}(t)-I_{2\star\star}(t)\| + \|T_1(t)-T_2(t)\| \leq \int_0^{tf} A(\|S_1(r)-S_2(r)\|+\|V_1(r)-V_2(r)\|+\|L_1(r)-L_2(r)\|+\|I_{1\star}(r)-I_{1\star\star}(r)\| + \|I_{2\star}(r)-I_{2\star\star}(r)\|+\|T_1(r)-T_2(r)\|)dr$$

Applying Mean Value Theorem (MVT) for Integrals, there exists a ξ, $0 \leq \xi \leq tf$, such that

$$\|S_1(t)-S_2(t)\|+\|V_1(t)-V_2(t)\|+\|L_1(t)-L_2(t)\|+\|I_{1\star}(t)-I_{1\star\star}(t)\|+\|I_{2\star}(t)-I_{2\star\star}(t)\| + \|T_1(t)-T_2(t)\| \leq A\cdot tf\cdot(\|S_1(\xi)-S_2(\xi)\|+\|V_1(\xi)-V_2(\xi)\|+\|L_1(\xi)-L_2(\xi)\|+\|I_{1\star}(\xi)-I_{1\star\star}(\xi)\| + \|I_{2\star}(\xi)-I_{2\star\star}(\xi)\|+\|T_1(\xi)-T_2(\xi)\|)$$

for all $t \in [0, tf]$. If tf is small enough that $A\cdot tf < 1$ we arrive at a contradiction, completing our proof. □

3. Numerical Analysis of Optimal Control Model

In this section we analyze numerically optimal chemoprophylaxis of latently infected population and education campaign strategies of our one-strain tuberculosis model (1). We solve the optimality system consisting of twelve ordinary differential equations from state and adjoint equations by using iterative method known as Runge-Kutta scheme.

State system is solved first by using forward in time fourth order Runge-Kutta method with initial conditions $N(0) = 240, S(0) = 144, V(0) = 12, L(0) = 24, I_1(0) = 24, I_2(0) = 24$ and $T(0) = 12$. These initial conditions are estimates implied from Jung et al. [14] for the purpose of demonstrations. Since the terminal condition of our optimality system is $\lambda_1(tf) = \lambda_2(tf) = \cdots \lambda_6(tf) = 0$, where $tf = 10$ years then the adjoint system is solved by backward fourth order Runge-Kutta scheme by using current iterated solution of state system. The time step during the simulation process will be $h = 0.02$ years. We then update controls by using suitable convex combination of previous controls and the values of characterization of optimal controls $u_1{}^\star$ and $u_2{}^\star$. We repeat this process several times with stopping criteria that the previous solution is very close to the current iterative solution. We assume our controls to be bounded in the interval $[0, 1]$. The weights of objective functional are theoretically chosen to be $A_1 = 0.1, A_2 = A_3 = 1000, B_1 = 1000$ and $B_2 = 500$. The theoretical choice of weights is purposeful for this particular intended study because calculation of real weights is very demanding and need to be acquainted with a lot of information. Parameters used in simulation together with their descriptions are shown in Table 3. We investigate the impact of one control at a time and both controls u_1 and u_2 in reducing the infected population with TB.

Table 3. Parameter values for optimal model (1) of Tuberculosis

Symbol	**Value/range**(yr^{-1})	**Source**
λ	0.05	Estimated.
β	2.58	Estimated.
ρ	0.4	Estimated.
θ	0.1	Estimated.
ϵ	0.03	[10]
η	0.7 (0.7-0.95)	[23]
μ	0.01923 (0.01-0.04)	[5]
δ_1	0.3 (0.07-0.365)	[27]
δ_2	0.2 (0.07-0.365)	[27]
ϕ	0.6	Estimated.
ω	0.2	Estimated.
ν	0.3	Estimated.
γ	0.2	Estimated.

3.1. Optimal education campaign strategy

With education campaign strategy, the optimal control u_1 associated with an increase of public awareness of tuberculosis disease and means of eradicating it from community is used to optimize the objective functional (2). In this case the optimal control u_2 is set to zero. The panel D of Fig. 2 shows that the trajectory $u_1(t)$ is at upper bound from $t = 0$ to 4.98 years and gradually decreases to lower bound zero at final time $t = 10$. At this period from $t = 0$ to $t = 4.98$ years, substantial investment in educating the public about tuberculosis disease and means of curbing it is highly needed due to presence of large number of infected individuals in the community. Onwards from $t = 4.98$ to final time $t = 10$, less investment in educating public can be used since the number of infected will be considerably reduced by earlier investment within the period of $t = 0$ to $t = 4.98$ years. Panels A, B and C of Fig. 2 show that there is significant difference in the number of infected with and without control u_1. This means that effective use of education campaign may be valuable even without use of chemoprophylaxis of latently infected with TB strategy.

3.2. Optimal Chemoprophylaxis of Latently Infected with TB strategy

With this strategy, the optimal control u_2 associated with administering of chemoprophylaxis to Latently infected individuals with TB, preventing them to progress to active TB is used to optimize the objective functional J in (2) while setting u_1 to zero. The panel D of Fig. 3 shows that the control u_2 is at upper bound for the period of 9.84 years. According to Jung et al. [14], if $u_2(t)$ is near to upper bound 1 for a long period of time then there is low treatment failure of chemoprophylaxis and high implementation cost. This means that although it reduces significantly the number of severely and mildly infected individuals as shown in panel B and C respectively with time, it is not alone regarded as effective control to curb TB if not coupled with other controls.

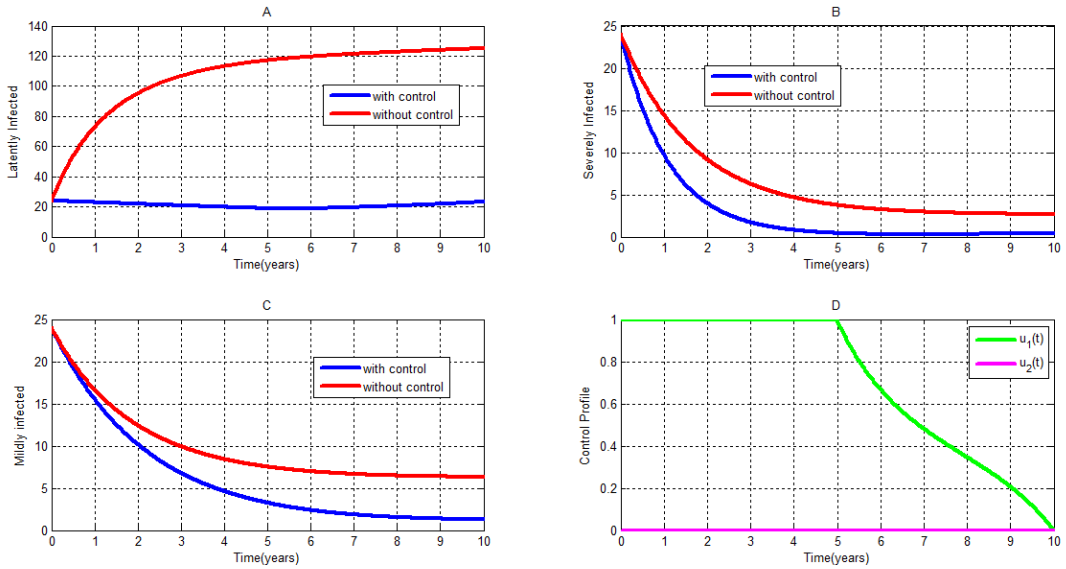

Fig. 2. Infected with control u_1

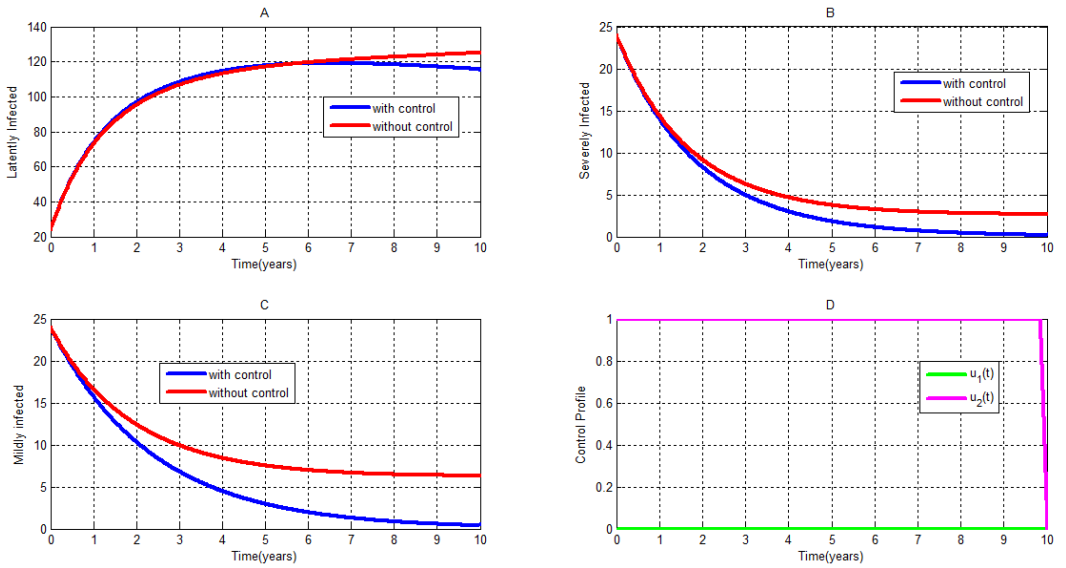

Fig. 3. Infected with control u_2

3.3. Optimal education campaign and Chemoprophylaxis of Latently Infected strategy

With this strategy, both controls u_1 and u_2 are used to optimize the objective functional J in (2). The panel D of Fig. 4 shows that, the control u_1 is at upper bound for a period of 3.66 years before gradually drops to zero at final time while control u_2 is at upper bound for a period of 9.14 years before sharply drops to zero at final time. This is improved trend compared to those in Fig. 2D and Fig. 3D respectively. In addition, panels A,B and C of Fig. 4 show that there is significant difference in the number of infected with and without control. This is similar numerical result as when education campaign strategy is used alone in Section 3.1. That is the optimal combination of controls u_1 and u_2 is effective in reducing the number of infected individuals with TB as well as minimizing the cost of implementing them.

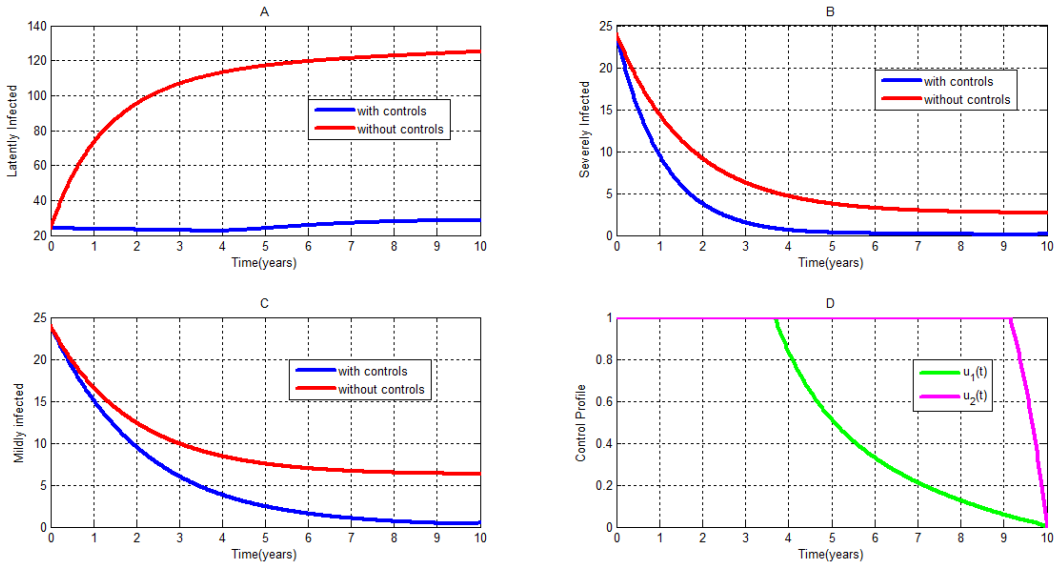

Fig. 4. Infected with controls u_1 and u_2

4. Conclusion

In this article we intended to assess the impact of education campaign and chemoprophylaxis of latently infected individuals as control measures in dynamics of TB by using optimal control techniques. The results show that these control measures have enviable effect of reducing the number of infected individuals with TB and the combination of the two controls has desirable effect than when one control is taken at a time. However, results show that the use of education campaign alone has desirable effect of reducing the number of infected individuals from community than when chemoprophylaxis of latently infected is used alone. This is due to the fact that chemoprophylaxis of latently infected individuals is not cost effective. For positive impact, chemoprophylaxis of latently infected strategy has to be coupled with other control measures such as treatment of active TB individuals.

References

[1] A.I. Adekunle, Application of Optimal Control to the Epidemiology of Tuberculosis Transmission, International Conference in memory of Late Prof. C. O. A. Sowunmi, 15th January, 2009. Ibadan, Nigeria.
[2] F.B. Agusto, Optimal chemoprophylaxis and treatment control strategies of a tuberculosis transmission model, World Journal of Modelling and Simulation 5(3) (2009) 163-173.
[3] C.P. Bhunu, Z. Mukandavire, W. Garira, M. Zimba, Tuberculosis transmission model with chemoprophylaxis and treatment, Bull. Math. Biol. 70(2008) 1163-1191.
[4] B.R. Bloom, Tuberculosis: Pathogenesis, Protection and Control. ASM Press, Washington D.C., (1994).
[5] S.M. Blower, A.R. Mclean, T. C. Porco, P. M. Amall, M. A. Sanchez, R. Moss, The intrinsic transmission dynamics of tuberculosis epidemics, Nature Medicine 1(1995) 815-821.
[6] V. Boltyanski, Sufficient Conditions for Lagrange, Mayer, and Bolza Optimization Problems, Mathematical Problems in Engineering 7(2001) 177-203.
[7] S. Bowong, Optimal control of the transmission dynamics of tuberculosis, Nonlinear Dynamics 61(2010) 729-748.
[8] C. Castillo-Chavez, B. Song, Dynamical models of tuberculosis and their applications, Mathematical Biosciences and Engineering 1(2004) 361-404.
[9] T. Cohen, M. Murray, On modeling epidemics of multidrug-resistant M. tuberculosis of heterogeneous fitness, Nature Medicine 10(2004) 1117-1121.
[10] T. Cohen, C. Colijn, B. Finklea, M. Megan, Exogenous Re-infection and the Dynamics of Tuberculosis Epidemics: Local Effects in a Network Model of Transmission, J. R. Soc. Interface 4(2007) 523-531.
[11] Z. Feng, C. Castillo-Chavez, A. F. Capurro, A model for tuberculosis with exogenous reinfection, Theor. Popul. Biol. 57(2000) 235-247.
[12] W.H. Fleming, R.W. Rishel, Deterministic and stochastic optimal control. Springer-Verlag, New York, 1975.
[13] H.R. Joshi, S. Lenhart, M.Y. Li, L. Wang, Optimal control methods applied to disease models. In Mathematical Studies on Human Disease Dynamics, volume 410 of Contemporary Mathematics, American Mathematical

Society, Providence, RI, USA (2006) 187-207.
[14] E. Jung, S. Lenhart, Z. Feng, Optimal control of Treatments in a two-strain Tuberculosis Model, Discrete and Continuous Dynamical Systems- Series B, 2(4) (2002) 473-482.
[15] A.A. Lashari, K. Hattaf, G. Zaman, X. Li, Backward bifurcation and optimal control of a vector borne disease, Appl. Math. Inf. Sci. 7(1) (2013) 301-309.
[16] D.L. Lukes, Differential Equations: Classical to Controlled. Academic Press, New York, 1982.
[17] J. Macki, A. Strauss, Introduction to Optimal Control Theory. Springer-Verlag, New York, 1982.
[18] V.I. Maksimov, On an algorithm of the dynamic reconstruction of inputs in systems with time-delay, International Journal of Advances in Applied Mathematics and Mechanics 1(2) (2013) 53-64.
[19] B. Miller, Preventive therapy for tuberculosis, Med. Clin. North Am. 77(1993), 1263-1275.
[20] G.M. Mlay, L.S. Luboobi, D. Kuznetsov, F. Shahada, Dynamics of one-strain pulmonary tuberculosis model with vaccination and treatment, Communications in Mathematical Biology and Neuroscience (2014), Article ID 6.
[21] J.P. Mpele, Y. Nkasah-Gyekye, O.D. Makinde, A model of a fishery resource in the presence of water hyacinth, the case of lake Victoria, International Journal of Advances in Applied Mathematics and Mechanics 2(1) (2014) 34-41.
[22] S.C. Mpeshe, L.S. Luboobi, Y. Nkansah-Gyekye, Optimal Control Strategies for the Dynamics of Rift Valley Fever, Communications in Optimization Theory, (2014), Article ID 5.
[23] D. Okuonghae, V. Aihie, Case detection and Direct Observation Therapy Strategy (DOTS) in Nigeria: its effect on TB dynamics, Journal of Biological Systems 16(1) (2008) 1-31.
[24] L. Pontryagin, V. Boltyanski, R. Gamkrelidze, E. Mishchenko, The mathematical theory of optimal processes. John Wiley & Sons, New York, 1962.
[25] P. Rodrigues, Modeling tuberculosis: a compromise between biological realism and mathematical tractability, Unpublished PhD thesis, University of Lisbon, (2009).
[26] S.P. Sethi, G.L. Thompson, Optimal Control Theory: Application to Management Science and Economics. Kluwer, 2nd edition, Boston, (2000).
[27] A. Ssematimba, J.Y.T. Mugisha, L. S. Luboobi, Mathematical Models for the Dynamics of Tuberculosis in Density-dependent Populations: The Case of Internally Displaced Peoples' Camps (IDPCs) in Uganda, Journal of Mathematics and Statistics 1(2005) 217-224.
[28] World Health Organization (WHO) Global Tuberculosis Report (2012), 2010/2011 Tuberculosis Global Facts.
[29] World Health Organization (WHO) Global Tuberculosis Report (2013), 2011/2012 Tuberculosis Global Facts.
[30] X. Zhou, Q. Sun, Stability analysis of a fractional-order HBV infection model, Int. J. Adv. Appl. Math. and Mech. 2(2) (2014) 1-6.