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Optimal chemoprophylaxis and treatment control strategies of a tuberculosis transmission model

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Abstract. A tuberculosis model which incorporates treatment of infectives and chemoprophylaxis is considered. For this model, controls on treatment, chemoprophylaxis and disease relapse are incorporated to reduce the latently infected and actively infected individual populations, via application of the Pontryagins Maximum Principle of optimal control theory.

Keywords: optimal control, chemoprophylaxis, tuberculosis, relapse, optimality system

1 Introduction

At present, about 95% of the estimated 8 million new cases of tuberculosis (TB) occurring each year are in developing countries, where 80% occur among people between the ages of 15-59 years[18]. In sub-Saharan Africa, TB is the leading cause of mortality and in developing countries, it accounts for an estimated 2 million deaths which accounts for a quarter of avoidable adult deaths[37]. TB was assumed to be on its way out in developed countries until the number of TB cases began to increase in the 1980s. With this return, we face the paradox of a well-known bacteria, fully treatable with efficient and affordable drugs according to internationally recommended guidelines, which yet causes increasing human suffering and death. As the world is experiencing the devasting effects of HIV/AIDS epidemic, it is now necessary to ask why we have so far failed to control TB and define the limits of the global TB control programs[36]. Currently, half of the people living with HIV are TB co-infected and three quarters of all dually infected people live in sub-Saharan Africa. In sub-Saharan Africa, the face of HIV/AIDS is TB, HIV/AIDS and TB fuel one another. Preventive therapy of TB in HIV infected individuals is highly recommended[44] and could dramatically reduce the impact of HIV on TB epidemiology, but its implementation is limited in developing countries because of complex logistical and practical difficulties[23]. Control programs have continued to function as if the TB epidemiological situation is stable and indeed all approaches including Directly Observed Treatment Short Course strategy have so far failed to control TB in areas of high HIV/AIDS prevalence[15]. The implementation of a universal strategy is thus challenged on operational, epidemiological, economic, and social grounds. The question posed is whether TB control should remain a biomedical strategy only, focusing on treatment without efforts to understand and fulfill patient needs (social and economic needs). The causes behind recent observed increases of active TB cases are the source of many studies[3, 8, 14, 35]. Active TB cases may be pulmonary or extra pulmonary, but pulmonary cases are more infectious and form the bulk of most cases of active TB. The usual symptoms of active TB include tiredness, high fever, and a cough, but confirmation of active TB requires a positive sputum culture. Extra pulmonary accounts for between 5% and 30% of the total cases and may affect any part of the body. Pulmonary cases affect the lungs. Recently infected individuals have a high chance of developing active TB within 5 years and these are classified as primary TB cases, and those who progress to active TB

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many years after infection as a result of endogenous reactivation and/or exogenous re-infection are classified as secondary active TB cases.

In human beings, TB is caused by Mycobacterium tuberculosis bacteria (Mtb) and it is an airborne transmitted disease. Mtb droplets are released into the air by sneezing and/or coughing infectious individuals. Tubercle bacillus carried by such droplets live in the air for a short period of time[40], (about 2 hours), and, therefore, it is believed that occasional contacts with an infectious individual rarely lead to transmission. TB is not highly infectious and so occasional contacts with the infectious case rarely leads to infection[40]. Most people are assumed to mount an effective immune response to the initial infection that limits the proliferation of the bacilli and leads to long lasting partial immunity both to further infection and to the reactivation of latent bacilli remaining from the original infection (Smith and Moss, 1994). TB is described as a slow disease because of its long and variable latency period distribution and its short and relatively narrow infectious period distribution. Individuals who are latently infected are neither clinically ill nor capable of transmitting TB[33]. Most latently infected individuals do not become infectious (active TB). About 5%-10% of the latently infected individuals develop active TB, that is, about 90%-95% remain latently infected. Most secondary infections are a result of prolonged and sustained close contacts with a primary case or exogenous re-infection[19, 42]. However, the risk of developing TB as a result of exogenous reinfection is lower than that of developing the first primary episode for most age groups[43]. There is strong evidence that TB transmission occurs in groups of close associates of infectious individuals and that such a risk is limited to the life of the epidemiologically active cluster to which they belong. Incomplete treatment can lead to relapse, but relapse can also occur in patients who took a full course of treatment and were declared cured[16]. Most tuberculosis in human adults in the USA results from reactivation of latent infection[13]. In a clinical study in 1999 in Malawi, 7.5% of patients registered with new tuberculosis were found to have had previous tuberculosis, with recurrence due to reactivation or reinfection[24]. Tuberculosis patients infected with HIV are signicantly more likely to relapse compared with patients uninfected with HIV[17]. Specifically, it is reported that with HIV disease, individuals exposed to tuberculosis can reactivate as frequently as 10% per year, as compared with 10% per lifetime without HIV disease[1].

Some past models of tuberculosis, particularly the predictive models attempting to calculate a threshold for the basic reproductive number R_0, have incorporated drug treatment and/or vaccination, and have discussed control of the disease by looking at the role of disease transmission parameters in the reduction of R_0 and the prevalence of the disease (see [7–9, 11, 12, 35, 39, 40, 43]). However, these models did not account for time dependent control strategies since their discussions are based on prevalence of the disease at equilibria. The time dependent control strategies have been applied for the studies of HIV models[21, 28], two strain tuberculosis models[26] and SARS[45]. Both approaches of studying control strategies produce valuable theoretical results which can be used to suggest or design epidemic control programs. Depending on a chosen goal (or goals) various objective criteria may be adopted. In this paper, we consider (time dependent) optimal control strategies associated with chemoprophylaxis and treatment of latently and actively infected individuals with TB as well as disease relapse in individuals recovered from TB for a tuberculosis transmission model developed in [5]. Introduced into the model are control mechanisms on chemoprophylaxis, treatment and disease relapse for individuals latently and actively infected with TB and for individuals recovered from TB.

The paper is organized as follows: Section 2 describes the tuberculosis transmission model with control terms. Our objective functional is also introduced in this section. The analysis of optimal controls is given in Section 3. Section 4 includes some numerical studies of the optimal controls and discuss our results.

2 Tuberculosis transmission model with chemoprophylaxis

The tuberculosis model from [5] divides the total human population into the following sub-groups that are susceptible individuals S_T, those exposed to TB E_T (latently infected), those infected with Mtb and displaying symptoms of TB I_T, and those who have recovered from sickness, R_T. It is assumed that susceptible humans are recruited into the population at per capita rate Λ. The total variable population size at time t is given by, $N(t) = S_T(t) + E_T(t) + I_T(t) + R_T(t)$. Susceptible individuals acquire TB infection following contact with an active infectious individual at rate

$$\lambda = \frac{\beta c I_T}{N}$$

where β is the probability that one susceptible individual becomes infected by an infectious individual, and c is the per capita contact rate. Susceptible individuals infected with Mtb are moved to latently infected class at a rate $f\lambda$, where f is the probability that the infected enters the latent stage. The latently infected progress to active TB at rates k for endogenous reactivation and $\delta_1\lambda$ for exogenous re-infection respectively. Susceptible individuals infected with Mtb are moved into the infective class at a rate, $(1-f)\lambda$ and these form the primary active TB cases. Once in active stage of the disease, an individual may recover naturally at rate p and move into the recovered class R_T (though they may contain some live bacilli). Individuals in R_T are not totally immune to Mtb infection and are infected at rate $\delta_2\lambda$ and move into E_T, since primary infection confers some immunity. Some individuals in R_T relapse back into the infective state at rate q. The natural death rate in each class is assumed to be $\mu > 0$ and infectives have an additional TB induced death rate, $d > 0$. The treatment rates for the latently infected and the infectives are assumed to be r_1 and r_2, respectively. With chemoprophylaxis and treatment of infectives the model system in [5] is given as:

$$\frac{\mathrm{d}S_T}{\mathrm{d}t} = \Lambda - \lambda S_T - \mu S_T, \tag{1}$$

$$\frac{\mathrm{d}E_T}{\mathrm{d}t} = f\lambda S_T - \delta_1\lambda E_T - (k + r_1 + \mu)E_T + \delta_2\lambda R_T, \tag{2}$$

$$\frac{\mathrm{d}I_T}{\mathrm{d}t} = (1-f)\lambda S_T + \delta_1\lambda E_T + kE_T - (p + r_2 + \mu + d)I_T + qR_T, \tag{3}$$

$$\frac{\mathrm{d}R_T}{\mathrm{d}t} = r_1 E_T + (p + r_2)I_T - (q + \mu)R_T - \delta_2\lambda R_T. \tag{4}$$

Introducing the controls on treatment, chemoprophylaxis and disease relapse, the model (1) $\sim$ (4) becomes

$$\frac{\mathrm{d}S_T}{\mathrm{d}t} = \Lambda - \lambda S_T - \mu S_T, \tag{5}$$

$$\frac{\mathrm{d}E_T}{\mathrm{d}t} = f\lambda S_T - \delta_1\lambda E_T - (k + u_1 r_1 + \mu)E_T + \delta_2\lambda R_T, \tag{6}$$

$$\frac{\mathrm{d}I_T}{\mathrm{d}t} = (1-f)\lambda S_T + \delta_1\lambda E_T + kE_T - (p + u_2 r_2 + \mu + d)I_T + (1-u_3)qR_T, \tag{7}$$

$$\frac{\mathrm{d}R_T}{\mathrm{d}t} = u_1 r_1 E_T + (p + u_2 r_2)I_T - ((1-u_3)q + \mu)R_T - \delta_2\lambda R_T. \tag{8}$$

Where $S_T(0), E_T(0), I_T(0), R_T(0)$ are given, the definitions of above model parameters are listed in Tab. 1. The control functions, $u_1(t), u_2(t)$, and $u_3(t)$ are bounded, Lebesgue integrable functions. The control, $u_1(t)$, represents the effort on treatment (r_1) of latently infected individuals to reduce the number of individuals that may be infectious. While the control $u_2(t)$ is the effort on treatment (r_2) of actively infected individuals to increase the number of recovered individuals. The coefficient, $1 - u_3(t)$, represents the effort that prevents the disease relapse of recovered individuals so as to reduce the number of individuals developing active TB. Our control problem involves that in which the number of individuals with latent and active tuberculosis infections and the cost of applying chemoprophylaxis, treatment and relapse controls $u_1(t), u_2(t)$ and $u_3(t)$ are minimized subject to the differential Eqs. (5) $\sim$ (8). This performance specification involves the numbers of individuals with latent and active infections respectively, as well as the cost for applying chemoprophylaxis control (u_1), treatment control (u_2) and disease relapse control (u_3), in individuals with tuberculosis. The objective functional is defined as:

$$J = \min_{u_1,u_2,u_3} \int_0^{t_f} \left[A_1 E_T + A_2 I_T + C_1 u_1^2 + C_2 u_2^2 + C_3 u_3^3\right] \mathrm{d}t \tag{9}$$

where t_f is the final time and the coefficients, A_1, A_2, C_1, C_2, C_3 are balancing cost factors due to scales and importance of the five parts of the objective function. We seek to find an optimal control, u_1^*, u_2^* and u_3^*, such that

Table 1. Description of variables and parameters of the tuberculosis model (5) ∼ (8)

Parameter	Description	Baseline value	Reference
Λ	Recruitment rate	3000 per year	assumed
μ	Natural mortality rate	0.01 per year	[5]
c	Contact rate	21 per day	assumed
d	TB induced mortality rate	0.3 per year	[5]
β	Transmission probabilities	0.35 $(0.1 - 0.6)$ per year	[5]
k	Natural rate of progression to active TB	$0.00013 - (0.0001 - 0.0003)$ per year	[5]
p	Natural recovery rate	0.2 $(0.15 - 0.25)$ per year	[5]
q	Relapsing rate	0.005 per year	assumed
r_1	Treatment rate for the latently infected	0.7 per year	[5]
r_2	Treatment rate for the infectives	0.55 per year	[5]
δ_1	Modification parameters	0.7 per year	[5]
δ_2	Modification parameters	0.9 per year	[5]
f	Probability that the infected will enter the latent stage of the disease	0.99 per year	[5]

$$\begin{aligned}\mathcal{U} = \{(u_1(t), u_2(t), u_3(t)) \mid (u_1(t), u_2(t), u_3(t)) \text{ measurable},\\ a_i \leq (u_1(t), u_2(t), u_3(t)) \leq b_i, \;\; i = 1, 2, 3, \;\; t \in [0, t_f]\}\end{aligned} \tag{10}$$

where $\mathcal{U} = \{(u_1(t), u_2(t), u_3(t)) \mid (u_1(t), u_2(t), u_3(t))$ measurable, $a_i \leq (u_1(t), u_2(t), u_3(t)) \leq b_i, i = 1, 2, t \in [0, t_f]\}$ is the control set.

3 Analysis of optimal control

The necessary conditions that an optimal control must satisfy come from the Pontryagin's Maximum Principle[34]. This principle converts (5) ∼ (8) and (9) into a problem of minimizing pointwise a Hamiltonian H, with respect to (u_1, u_2, u_3). First we formulate the Hamiltonian from the cost functional (9) and the governing dynamics (5) ∼ (8) to obtain the optimality conditions.

$$\begin{aligned}H = {} & A_1 E_T + A_2 I_T + C_1 u_1^2 + C_2 u_2^2 + C_3 u_3^3 + \lambda_{S_T} (\Lambda - \lambda S_T - \mu S_T)\\ & + \lambda_{E_T} (f\lambda S_T - \delta_1 \lambda E_T - (k + u_1 r_1 + \mu) E_T + \delta_2 \lambda R_T)\\ & + \lambda_{L_T} ((1 - f)\lambda S_T + \delta_1 \lambda E_T + k E_T - (p + u_2 r_2 + \mu + d) I_T + (1 - u_3) q R_T)\\ & + \lambda_{R_T} (u_1 r_1 E_T + (p + u_2 r_2) I_T - ((1 - u_3) q + \mu) R_T - \delta_2 \lambda R_T)\end{aligned} \tag{11}$$

where the $\lambda_{S_T}, \lambda_{E_T}, \lambda_{I_T}, \lambda_{R_T}$ are the associated adjoints for the states S_T, E_T, I_T, R_T. The system of equations is found by taking the appropriate partial derivatives of the Hamiltonian (11) with respect to the associated state variable.

Theorem 1. *Given optimal control u_1^*, u_2^*, u_3^* and solutions $S_T^*, E_T^*, I_T^*, R_T^*$ of the corresponding state system (5) ∼ (8) that minimizes $J(u_1, u_2, u_3)$ over $\mathcal{U}$. Then there exists adjoint variables $\lambda_{S_T}, \lambda_{E_T}, \lambda_{I_T}, \lambda_{R_T}$ satisfying*

$$-\frac{d\lambda_i}{dt} = \frac{\partial H}{\partial i} \tag{12}$$

and with transversality conditions

$$\lambda_i(t_f) = 0, \text{ where } i = S_T, E_T, I_T, R_T \tag{13}$$

$$u_1^* = \min\left\{b_1, \max\left[a_1, \frac{r_1 E_T(\lambda_{E_T} - \lambda_{R_T})}{2C_1}\right]\right\}, \quad u_2^* = \min\left\{b_2, \max\left[a_2, \frac{r_2 I_T(\lambda_{I_T} - \lambda_{R_T})}{2C_2}\right]\right\}$$

and

$$u_3^* = \min\left\{b_3, \max\left[a_3, \frac{q R_T(\lambda_{I_T} - \lambda_{R_T})}{2C_3}\right]\right\}. \tag{14}$$

Proof. Corollary 4.1 of [22] gives the existence of an optimal control due to the convexity of the integrand of J with respect to u_1, u_2 and u_3, a *priori* boundedness of the state solutions, and the *Lipschitz* property of the state system with respect to the state variables. The differential equations governing the adjoint variables are obtained by differentiation of the Hamiltonian function, evaluated at the optimal control. Then the adjoint system can be written as,

$$-\frac{\mathrm{d}\lambda_{S_T}}{\mathrm{d}t} = \frac{\partial H}{\partial S_T}, \quad \lambda_{S_T}(t_f) = 0 \; ; \; \cdots \; ; \; -\frac{\mathrm{d}\lambda_{R_T}}{\mathrm{d}t} = \frac{\partial H}{\partial R_T}, \quad \lambda_{R_T}(t_f) = 0,$$

evaluated at the optimal control and corresponding states, which result in the stated adjoint system (12) and (13). By considering the optimality conditions,

$$0 = \frac{\partial H}{\partial u_1}, \qquad 0 = \frac{\partial H}{\partial u_2} \quad \text{and} \quad 0 = \frac{\partial H}{\partial u_3}.$$

Solving for u_1^*, u_2^* and u_3^* subject to the constraints, the characterization (14) can be derived and we have

$$\begin{aligned} 0 = \frac{\partial H}{\partial u_1} &= 2C_1 u_1^* - r_1 E_T(\lambda_{E_T} - \lambda_{R_T}) \\ 0 = \frac{\partial H}{\partial u_2} &= 2C_2 u_2^* - r_2 I_T(\lambda_{I_T} - \lambda_{R_T}), \\ 0 = \frac{\partial H}{\partial u_3} &= 2C_2 u_3^* - q R_T(\lambda_{I_T} - \lambda_{R_T}). \end{aligned} \tag{15}$$

hence, we obtain (see [30])

$$u_1^* = \frac{r_1 E_T(\lambda_{E_T} - \lambda_{R_T})}{2C_1}, \quad u_2^* = \frac{r_2 I_T(\lambda_{I_T} - \lambda_{R_T})}{2C_2}, \quad u_3^* = \frac{q R_T(\lambda_{I_T} - \lambda_{R_T})}{2C_3}. \tag{16}$$

Then, by Standard control arguments involving the bounds on the controls, we conclude for control u_1:

$$u_1^* = \begin{cases} a_1 & \dfrac{r_1 E_T(\lambda_{E_T} - \lambda_{R_T})}{2C_1} \le a_1, \\ \dfrac{r_1 E_T(\lambda_{E_T} - \lambda_{R_T})}{2C_1} & a_1 < \dfrac{r_1 E_T(\lambda_{E_T} - \lambda_{R_T})}{2C_1} < b_1, \\ b_1 & \dfrac{r_1 E_T(\lambda_{E_T} - \lambda_{R_T})}{2C_1} \ge b_1. \end{cases} \tag{17}$$

In compact form

$$u_1^* = \min\left\{1, \; \frac{r_1 E_T(\lambda_{E_T} - \lambda_{R_T})}{2C_1}\right\}, \tag{18}$$

Similarly, for u_2 and u_3 in compact form, we have

$$u_2^* = \min\left\{1, \; \frac{r_2 I_T(\lambda_{I_T} - \lambda_{R_T})}{2C_2}\right\}, \quad u_3^* = \min\left\{1, \; \frac{q R_T(\lambda_{I_T} - \lambda_{R_T})}{2C_3}\right\}.$$

Next we discuss the numerical solutions of the optimality system and the corresponding results of varying the optimal controls u_1, u_2 and u_3, the parameter choices, and the interpretations from various cases.

4 Numerical illustrations and conclusions

Numerical solutions to the optimality system comprising of the state Eqs. (5) $\sim$ (8) and adjoint Eq. (12) are carried out using MATLAB and using parameters in Tab. 1 and the following weight factors and initial

conditions: $A_1 = 10, A_2 = 10, C_1 = 20, C_2 = 45, C_3 = 55, S_T(0) = 95703, E_T(0) = 13670, I_T(0) = 1950, R_T(0) = 0$. The algorithm is the forward-backward scheme; starting with an initial guess for the optimal controls u_1, u_2 and u_3, the state variables are then solved forward in time from the dynamics (5) $\sim$ (8) using a Runge Kutta method of the fourth order. Then those state variables and initial guess u_1, u_2 and u_3 are used to solve the adjoint Eq. (12) backward in time with given final condition (13), again employing a fourth order Runge Kutta method. The controls u_1, u_2 and u_3 are updated and used to solve the state and then the adjoint system. This iterative process terminates when current state, adjoint, and control values converge sufficiently[30].

4.1 Constant chemoprophylaxis

With this strategy, a constant chemoprophylaxis is used while the controls on treatment (u_2) and disease relapse (u_3) are optimized, with weight factors $A_1 = 0, A_2 = 10, C_1 = 0, C_2 = 45, C_3 = 55$, in other words, the control (u_1) is not optimized. For this strategy, we observed that the total number of individuals susceptible (S_T) to TB is $1.2293e + 005$ at time $t_f = 25$ (years), while the susceptible individuals with constant treatment and disease relapse is $1.0083e + 005$. Latently infected (E_T) and actively infected (I_T) individuals with optimal treatment (u_2), disease relapse (u_3) and constant chemoprophylaxis are respectively 0.0864 and 1.8166, while the individuals latently infected and actively infected under constant strategy are $E_T = 2.3822e + 003, I_T = 251.1753$. The recovered individuals with optimal treatment and disease relapse is

$$R_T = 2.9174e + 004, \quad R_T = 4.7311e + 004$$

is the recovered individuals under constant strategy. This results in higher S_T than that obtained with constant chemoprophylaxis. Also, there are far less E_T and I_T with optimal treatment and optimal disease relapse than what holds with constant strategy.

4.2 Constant treatment

Here the control (u_2) on treatment is not optimized but held constant while the controls on chemoprophylaxis (u_1) and disease relapse (u_3) are optimized, with weight factors $A_1 = 10$, $A_2 = 0$, $C_1 = 20$, $C_2 = 0$, $C_3 = 55$. For this strategy we observed that the total number of individuals susceptible to TB, S_T is $1.2293e{+}005$ at time $t_f = 25$ (years). Latently infected and actively infected individuals with optimal chemoprophylaxis (u_1), disease relapse (u_3) and constant treatment are respectively $E_T = 0.0893$ and $I_T = 1.8083$. The recovered individuals with optimal chemoprophylaxis and disease relapse is $R_T = 2.9174e + 004$. A similar trend as with the case of constant chemoprophylaxis above was observed with constant treatment. There are more S_T and less E_T, I_T and R_T when compared with the constant strategy.

4.3 Optimal chemoprophylaxis and treatment

With this strategy, a constant disease relapse is used while the controls on chemoprophylaxis (u_1) and treatment (u_2) are optimized, with weight factors

$$A_1 = 0, A_2 = 10, C_1 = 10, C_2 = 45, C_3 = 0.$$

Here, we observed that the total number of individuals susceptible (S_T) to TB is $1.0082e{+}005$ at time $t_f = 25$ (years), while the susceptible individuals with constant treatment and disease relapse is $1.0083e{+}005$. Latently infected and actively infected individuals with optimal chemoprophylaxis (u_1) treatment (u_2), and constant disease relapse are respectively $E_T = 2.3814e + 003$ and $I_T = 251.0674$, while the individuals latently infected and actively infected under constant strategy are

$$E_T = 2.3807e + 003, \quad I_T = 251.0062.$$

The recovered individuals with optimal chemoprophylaxis and treatment is

$$R_T = 4.7288e + 004, \quad R_T = 4.7279e + 004$$

is the recovered individuals under the constant strategy. The chemoprophylaxis control u_1 and treatment control u_2 are at the upper bound $b_1 = b_2 = 1$ all through the 25 years of simulation. The result here shows a negligible difference in S_T, E_T, I_T and R_T when compared with constant strategy. The controls u_1 and u_2 here are at the upper bound for the 25 years of simulation. Setting the upper bound $b_1 = b_2 = 0.9$ on optimal chemoprophylaxis and treatment control, it is observed from Fig. 1 that S_T with constant strategy is higher than in the optimal strategy resulting in a reduced E_T, I_T and R_T as observed in Fig. 2, Fig. 3 and Fig. 4.

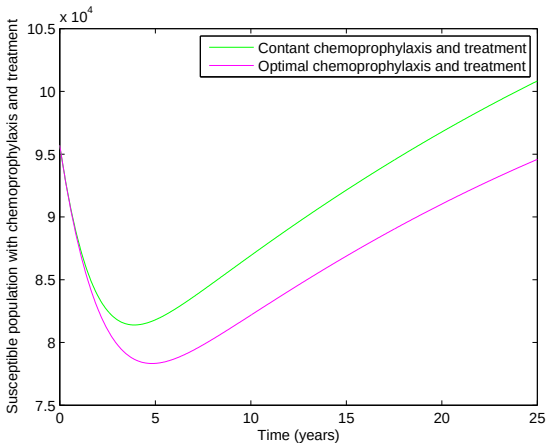

Fig. 1. Simulations of the TB model (5) ∼ (8) showing the effect of optimal chemoprophylaxis and treatment rates against constant chemoprophylaxis and treatment rates on the susceptible population

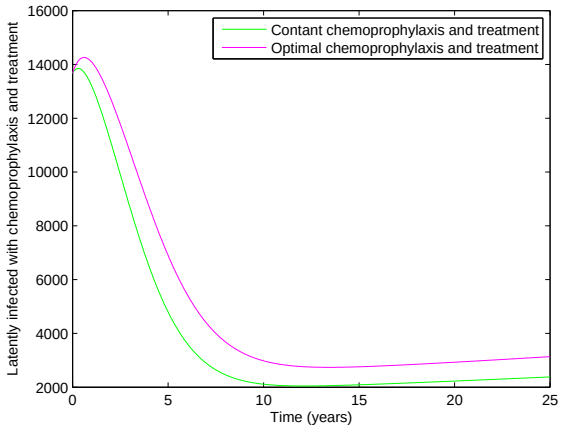

Fig. 2. Simulations of the TB model (5) ∼ (8) showing the effect of optimal chemoprophylaxis and treatment rates against constant chemoprophylaxis and treatment rates on the latently infected

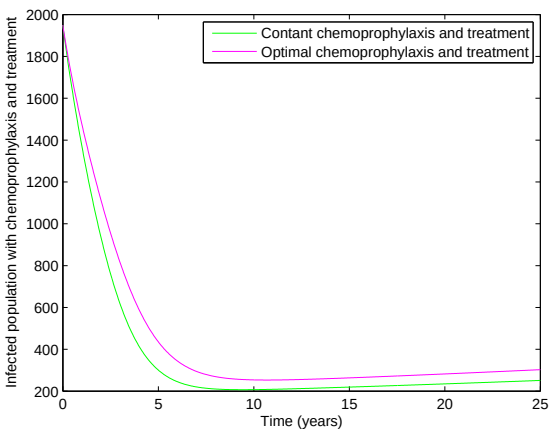

Fig. 3. Simulations of the TB model (5) ∼ (8) showing the effect of optimal chemoprophylaxis and treatment rates against constant chemoprophylaxis and treatment rates on the infected population

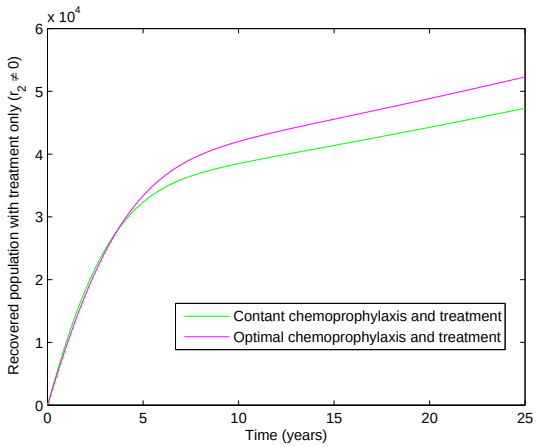

Fig. 4. Simulations of the TB model (5) ∼ (8) showing the effect of optimal chemoprophylaxis and treatment rates against constant chemoprophylaxis and treatment rates on the recovered population

4.4 Optimal chemoprophylaxis, treatment and relapse

With this strategy, the controls on chemoprophylaxis (u_1), treatment (u_2) and disease relapse (u_3) are optimized, with weight factors

$$A_1 = 10, A_2 = 10, C_1 = 20, C_2 = 45, C_3 = 55.$$

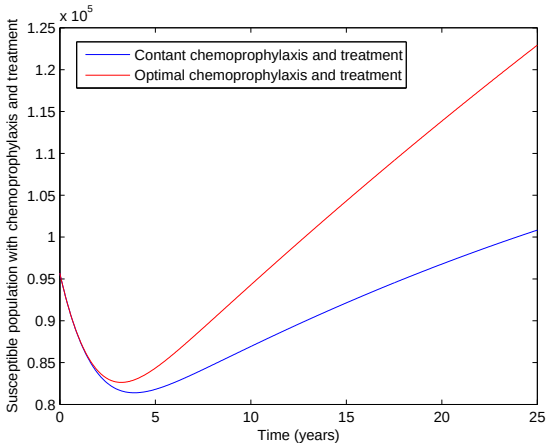

Fig. 5. Simulations of the TB model (5) ∼ (8) showing the effect of optimal chemoprophylaxis and treatment rates against constant chemoprophylaxis and treatment rates on the susceptible population

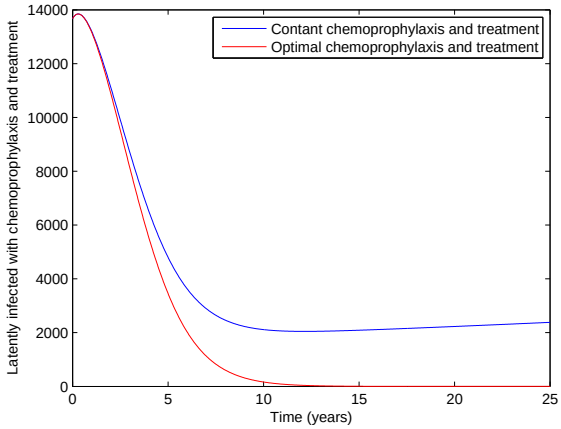

Fig. 6. Simulations of the TB model (5) ∼ (8) showing the effect of optimal chemoprophylaxis and treatment rates against constant chemoprophylaxis and treatment rates on the latently infected

For this strategy we observed in Fig. 5, that the total number of individuals susceptible to tuberculosis, S_T is $1.2293e + 005$ at time $t_f = 25$ (years), while the susceptible individuals with constant strategy is $1.0083e + 005$. Latently infected and actively infected individuals given in Fig. 6 and Fig. 7, with optimal chemoprophylaxis (u_1), treatment (u_2) and disease relapse (u_3) are respectively $E_T = 0.0897$ and $I_T = 1.8165$, while the individuals latently infected and actively infected under constant strategy are

$$E_T = 2.3822e + 003, \quad I_T = 251.1753.$$

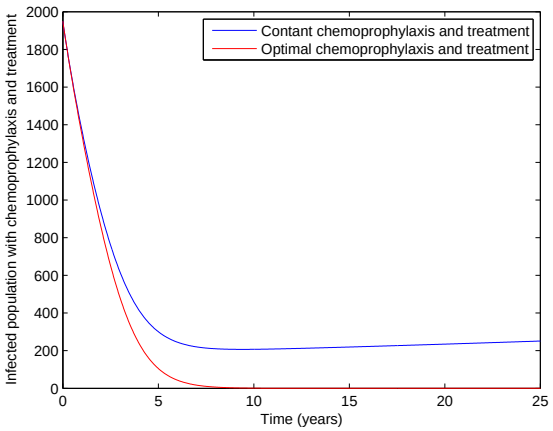

Fig. 7. Simulations of the TB model (5) ∼ (8) showing the effect of optimal chemoprophylaxis and treatment rates against constant chemoprophylaxis and treatment rates on the infected population

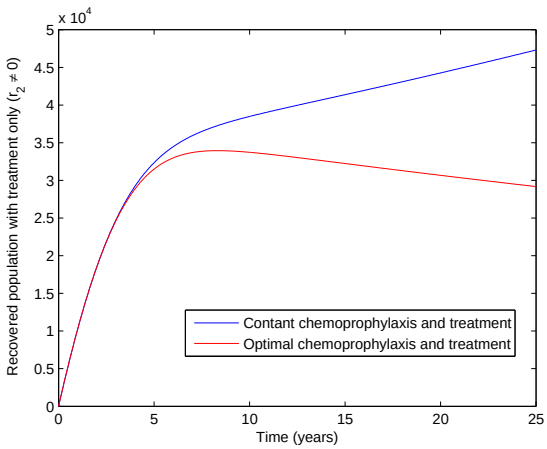

Fig. 8. Simulations of the TB model (5) ∼ (8) showing the effect of optimal chemoprophylaxis and treatment rates against constant chemoprophylaxis and treatment rates on the recovered population

Fig. 8 shows the recovered individuals $R_T = 2.9174e + 004$ with optimal strategy. $R_T = 4.7311e + 004$ is the recovered individuals under constant strategy. Controls u_1 of chemoprophulaxis in Fig. 9 is at the upper

bound $b_1 = 1$ for 23.5 years before dropping to the lower bound $a_1 = 0$. In Fig. 10, the treatment control u_2 is at the upper bound $b_2 = 1$ for 19.35 years and drops gradually until reaching the lower bound $a_2 = 0$. Disease relapse control u_1 is at the upper bound $b_3 = 1$ all through the 25 years of the simulations in Fig. 11. The result here shows that S_T is higher for the optimal strategy than in the constant strategy. E_T, I_T and R_T is far reduced in the optimal strategy than in the constant strategy.

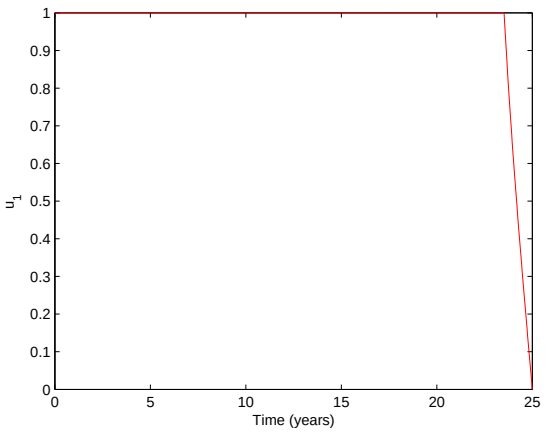

Fig. 9. Optimal chemoprophylaxis control (u_1)

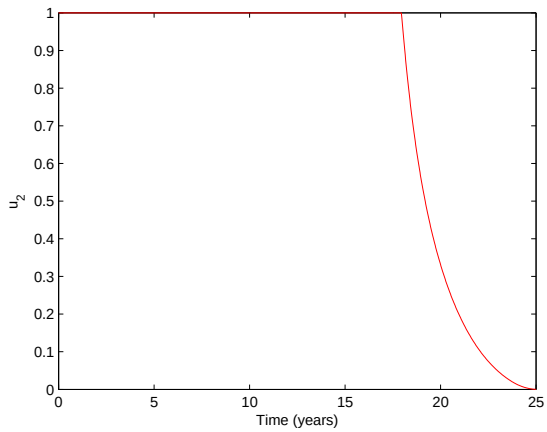

Fig. 10. Optimal treatment control (u_2)

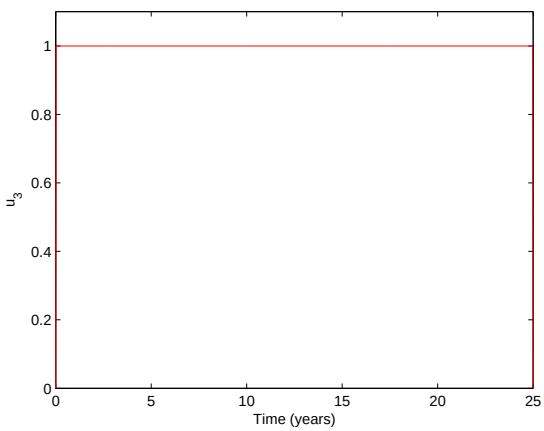

Fig. 11. Optimal relapse control (u_3)

4.5 Concluding remarks

In conclusion, our optimal control shows the result of optimally controlling chemoprophylaxis, treatment and disease relapse in individuals infected with tuberculosis. The result further emphasized the importance of controlling disease relapse in reducing the number of latently infected and actively infected individuals with tuberculosis. Control programs that follow these strategies can effectively reduce the population of latently infected and actively infected TB cases.

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