Optimal control strategies for reducing the number of active infected individuals with tuberculosis

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Abstract
We propose and analyze an optimal control problem where the control system is a mathematical model for tuberculosis (TB) with different post-exposure interventions considered. We analyze the impact of transmission intensity on the control interventions and show that optimal control solutions reduce the number of active TB cases.

1 Introduction.
Tuberculosis (TB) care and control is responsible for saving 20 million people all over the world, following the 2012 report of the World Health Organization (WHO) [17]. However WHO warned that the global fight against TB remains fragile and it continues to be a major killer infectious disease. The number of infected individuals continues to decrease but the global burden of disease amounted to 8.7 millions of new cases in 2011. Support for TB prevention and care must be guaranteed, yet the current progress is at risk from underfunding [17].

There are many mathematical dynamic models for TB, see, e.g., [1, 2, 4, 5, 7, 16] and the references cited therein. Most models consider that there are two different ways to progress to active disease after infection: “fast progressors” and “slow progressors”. It is also considered that only 5 to 10% of the infected individuals are fast progressors. The remaining are able to contain the infection (latent infected individuals) and have a much lower probability to develop active disease by endogenous reactivation. More recent models also consider the possibility of latent and treated individuals being reinfected, since it was already recognized that infection and/or disease do not confer full protection [15]. Models show that reinfection can be an important component of TB transmission and can have impact on the efficacy of interventions [4, 7, 13, 16]. We consider the model from [8], where exogenous reinfection is taken into account.

TB control is still a challenging task, despite the several interventions available: vaccination to prevent infection; treatment to cure active TB; treatment of latent TB to prevent endogenous reactivation. Here, we study the implementation of two of these interventions that are not widely used: treatment of early latent individuals with anti-TB drugs (e.g., treatment of recent contacts of index cases) and for the prophylactic vaccination of the persistent latent individuals.

Our aim is to analyze how these control measures should be implemented, for a certain time period, to reduce the number of active infected individuals, while controlling their costs. To do this we propose and analyze an optimal control problem. This approach allows the study of the most cost-effective intervention design by generating an implementation design that minimizes an objective function. The intensity of interventions can be relaxed along time which is not the case considered in most models for which interventions are modeled by constant rates [8].

Optimal control is a branch of mathematics developed to find optimal ways to control a dynamic system [3, 6, 12]. Other authors applied optimal control theory to TB models [10, 14], but in this paper the model and the objective functional are different.

2 Mathematical model.
Following [8], population is divided into five categories: susceptible (S); early latent (L1), i.e., individuals recently infected (less than two years) but not infectious; infected (I), i.e., individuals who have active TB and are infectious; persistent latent (L2), i.e., individuals who...
were infected and remain latent; and recovered (R), i.e., individuals who were previously infected and treated.

We assume that at birth all individuals are equally susceptible and differentiate as they experience infection and respective therapy. The rate of birth and death, \( \mu \), are equal (corresponding to a mean life time of 70 years [8]) and no disease-related deaths are considered, keeping the total population, \( N \), constant with \( N = S(t) + L_1(t) + I(t) + L_2(t) + R(t) \).

The parameter \( \delta \) denotes the rate at which individuals leave \( L_1 \) compartment; \( \phi \) is the proportion of infected individuals progressing directly to the active disease compartment \( I \); \( \omega \) is the rate of endogenous reactivation for persistent latent infections (untreated latent infections); \( \omega_R \) is the rate of endogenous reactivation for treated individuals (for those who have undergone a therapeutic intervention). The parameter \( \sigma \) is the factor that reduces the risk of infection, as a result of acquired immunity to a previous infection, for persistent latent individuals, i.e., this factor affects the rate of exogenous reinfection of untreated individuals; while \( \sigma_R \) represents the same parameter factor but for treated patients. The parameter \( \tau_0 \) is the rate of recovery under treatment of active TB (assuming an average duration of infectiousness of six months). The values of the rates \( \delta, \phi, \omega, \omega_R, \sigma \) and \( \tau_0 \) are taken from [8] and the references cited therein (see Table 1 for the values of the parameters).

In this first approach we consider only the case where the protection against reinfection conferred by infection or by treatment is the same, i.e., \( \sigma_R = \sigma = 0.25 \).

The parameters \( \tau_1 \) and \( \tau_2 \) apply to latent individuals \( L_1 \) and \( L_2 \), respectively, and are the rates at which chemotherapy or a post-exposure vaccine is applied. In [8] different values for these rates are considered: the case where no treatment of latent infections occur \( (\tau_1 = \tau_2 = 0) \); the case where there is an immediate treatment of persistent latent infections \( (\tau_2 \to \infty) \); or there is a moderate treatment of persistent latent infections \( (\tau_2 \in [0.1, 1]) \). In our paper we consider, without loss of generality, that the rate of recovery of early latent individuals under post-exposure interventions is equal to the rate of recovery under treatment of active TB, \( \tau_1 = 2 \text{ yr}^{-1} \), and greater than the rate of recovery of persistent latent individuals under post-exposure interventions, \( \tau_2 = 1 \text{ yr}^{-1} \).

We add to the original model two control functions \( u_1 \) and \( u_2 \), which represent the intensity at which the post-exposure interventions are applied to early latent individuals \( L_1 \) and persistent latent individuals \( L_2 \), respectively. Namely, the control \( u_1 \) represents the intensity of treatment of early latent individuals with anti-TB drugs and the control \( u_2 \) represents the intensity of the prophylactic vaccination of the persistent latent individuals. The dynamical system that we propose is given by

\[
\begin{align*}
S(t) &= \mu N - \frac{\beta}{N} I(t) S(t) - \mu S(t) \\
L_1(t) &= \frac{\beta}{N} I(t) (S(t) + \sigma L_2(t) + \sigma_R R(t)) \\
&\quad - (\delta + \tau_1 u_1(t) + \mu) L_1(t) \\
I(t) &= \phi \delta L_1(t) + \omega L_2(t) + \omega_R R(t) - (\tau_0 + \mu) I(t) \\
L_2(t) &= (1 - \phi) \delta L_1(t) - \sigma \frac{\mu}{N} I(t) L_2(t) \\
&\quad - (\omega + \tau_2 u_2(t) + \mu) L_2(t) \\
\dot{R}(t) &= \tau_0 I(t) + \tau_1 u_1(t) L_1(t) + \tau_2 u_2(t) L_2(t) \\
&\quad - \sigma_R \frac{\mu}{N} I(t) R(t) - (\omega_R + \mu) R(t).
\end{align*}
\]

The assumption that the total population \( N \) is constant, allows to reduce the control system (2.1) from five to four state variables. We decided to maintain the TB model in form (2.1), using relation \( S(t) + L_1(t) + I(t) + L_2(t) + R(t) = N \) as a test to confirm the numerical results.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \beta )</td>
<td>Transmission coefficient</td>
<td>50; 100; 200</td>
</tr>
<tr>
<td>( \mu )</td>
<td>Death and birth rate</td>
<td>1/70 yr(^{-1} )</td>
</tr>
<tr>
<td>( \delta )</td>
<td>Rate at which individuals leave ( L_1 )</td>
<td>12 yr(^{-1} )</td>
</tr>
<tr>
<td>( \phi )</td>
<td>Proportion of individuals going to ( I )</td>
<td>0.05</td>
</tr>
<tr>
<td>( \omega )</td>
<td>Rate of endogenous reactivation for persistent latent infections</td>
<td>0.0002 yr(^{-1} )</td>
</tr>
<tr>
<td>( \omega_R )</td>
<td>Rate of endogenous reactivation for treated individuals</td>
<td>0.00002 yr(^{-1} )</td>
</tr>
<tr>
<td>( \sigma )</td>
<td>Factor reducing the risk of infection as a result of acquired immunity to a previous infection for ( L_2 )</td>
<td>0.25</td>
</tr>
<tr>
<td>( \sigma_R )</td>
<td>Rate of exogenous reactivation of treated patients</td>
<td>0.25</td>
</tr>
<tr>
<td>( \tau_0 )</td>
<td>Rate of recovery under treatment of active TB</td>
<td>2 yr(^{-1} )</td>
</tr>
<tr>
<td>( \tau_1 )</td>
<td>Rate of recovery under treatment of latent individuals ( L_1 )</td>
<td>2 yr(^{-1} )</td>
</tr>
<tr>
<td>( \tau_2 )</td>
<td>Rate of recovery under treatment of latent individuals ( L_2 )</td>
<td>1 yr(^{-1} )</td>
</tr>
<tr>
<td>( N )</td>
<td>Total population</td>
<td>30000</td>
</tr>
<tr>
<td>( t_f )</td>
<td>Total simulation duration</td>
<td>5 yr</td>
</tr>
<tr>
<td>( W_0 )</td>
<td>Weight constant on active infections individuals ( I(t) )</td>
<td>50</td>
</tr>
<tr>
<td>( W_1 )</td>
<td>Weight constant on control ( u_1(t) )</td>
<td>50</td>
</tr>
<tr>
<td>( W_2 )</td>
<td>Weight constant on control ( u_2(t) )</td>
<td>50</td>
</tr>
</tbody>
</table>

Table 1: Parameter values.

It is assumed that the rate of infection of susceptible individuals is proportional to the number of infectious individuals and the constant of proportionality is \( \beta \), which is the transmission coefficient. The basic reproduction number \( R_0 \), for system (2.1) in the absence of
controls, is proportional to the transmission coefficient \( \beta \) (see [8]) and is given by

\[
R_0 = \frac{\delta(\omega + \phi \mu)(\omega R + \mu)}{\mu(\omega R + \tau_0 + \mu)(\delta + \mu)(\omega + \mu)}.
\]

The endemic threshold \( ET \) at \( R_0 = 1 \) indicates the minimal transmission potential that sustains endemic disease, i.e., when \( R_0 < 1 \) the disease will die out and for \( R_0 > 1 \) the disease may become endemic. Since our model considers reinfection, it becomes important to consider another threshold in transmission, the re-infection threshold \( RT \) [9]. It corresponds to the critical transmissibility value, above which there is a steep nonlinear increase in disease prevalence, corresponding to the increased contribution of re-infection cases to the disease load. The \( RT \) for the model presented here has been computed in [8]. In Section 4 we take various values for \( \beta \). For \( \beta = 50; 100 \) we are between \( ET \) and \( RT \), and for \( \beta = 200 \) we are above \( RT \) [8].

The total simulation duration, \( t_f \), is fixed. Future work will address the impact of relaxing the assumption \( t_f = 5 \) years.

### 3 Optimal control problem.

TB control is still an unresolved issue around the world. In order to have the desired impact, TB control measures must be timely applied. However, economical, social and environmental obstacles prevent implementation of TB control measures. The ideal situation would be a minimization of active infected individuals with the lowest cost possible. Optimal control theory is a powerful mathematical tool that can be used to aid decision making in this situation [11].

We consider the state system (2.1) of ordinary differential equations in \( \mathbb{R}^5 \) with the set of admissible control functions given by

\[
\Omega = \{(u_1(\cdot), u_2(\cdot)) \in (L^\infty(0, t_f))^2 | 0 \leq u_1(t), u_2(t) \leq 1, \forall t \in [0, t_f] \}.
\]

Our aim is to minimize the number of active infected individuals \( I \) as well as the costs required to control the disease by treating early and persistent latent individuals \( L_1 \) and \( L_2 \). The objective functional is given by

\[
J(u_1(\cdot), u_2(\cdot)) = \int_0^{t_f} \left[ W_0 I(t) + \frac{W_1}{2} u_1^2(t) + \frac{W_2}{2} u_2^2(t) \right] dt,
\]

where we want to minimize the active infectious individuals while controlling the cost of the treatment interventions. The constants \( W_i, i = 1, 2, \) are a measure of the relative cost of the interventions associated to the controls \( u_1 \) and \( u_2 \), respectively, and the constant \( W_0 \) is the weight constant for class \( I \). We consider the optimal control problem of determining \( (S^*(\cdot), L_1^*(\cdot), I^*(\cdot), L_2^*(\cdot), R^*(\cdot)) \), associated to an admissible control pair \( (u_1^*(\cdot), u_2^*(\cdot)) \) in \( \Omega \) on the time interval \([0, t_f] \), satisfying (2.1), the initial conditions \( S(0), L_1(0), I(0), L_2(0) \) and minimizing the cost function (3.2), i.e.,

\[
J(u_1^*(\cdot), u_2^*(\cdot)) = \min_{\Omega} J(u_1(\cdot), u_2(\cdot)).
\]

The initial conditions are obtained as the nontrivial equilibrium values for the system (2.1) with no controls.

The Hamiltonian \( H \) is given by

\[
H = H(S(t), L_1(t), I(t), L_2(t), R(t), \lambda(t), u_1(t), u_2(t))
\]

\[
= W_0 I(t) + \frac{W_1}{2} u_1^2(t) + \frac{W_2}{2} u_2^2(t) + \lambda_1(t)(\mu N - \frac{\beta}{\mu} I(t) S(t) - \mu S(t)) + \lambda_2(t)(\frac{\beta}{N} I(t) (S(t) + \sigma L_2(t) + \sigma R(t)) - (\delta + \tau_1 u_1(t) + \mu)L_1(t)) + \lambda_3(t)(\phi \delta L_1(t) + \omega L_2(t) + \omega R(t) - (\tau_0 + \mu)I(t)) + \lambda_4(t)((1 - \phi)\delta L_1(t) - \frac{\beta}{N} I(t) L_2(t) - (\omega + \tau_2 u_2(t) + \mu)L_2(t)) + \lambda_5(t)(\tau_0 I(t) + \tau_1 u_1(t)L_1(t) + \tau_2 u_2(t)L_2(t)) - \sigma R \frac{\beta}{N} I(t)(R(t) - (\omega R + \mu)R(t)),
\]

where \( \lambda(t) = (\lambda_1(t), \lambda_2(t), \lambda_3(t), \lambda_4(t), \lambda_5(t)) \) is the adjoint vector. According to the Pontryagin Maximum Principle [12], if \( (u_1^*(\cdot), u_2^*(\cdot)) \) in \( \Omega \) is optimal for the problem (2.1), (3.3) with the initial conditions given in Table 2 and fixed final time \( t_f \), then there exists a nontrivial absolutely continuous mapping \( \lambda: [0, t_f] \to \mathbb{R}^5, \lambda(t) = (\lambda_1(t), \lambda_2(t), \lambda_3(t), \lambda_4(t), \lambda_5(t)) \), such that

\[
\dot{S} = \frac{\partial H}{\partial \lambda_1}, \quad \dot{L}_1 = \frac{\partial H}{\partial \lambda_2}, \quad \dot{I} = \frac{\partial H}{\partial \lambda_3}, \quad \dot{L}_2 = \frac{\partial H}{\partial \lambda_4}, \quad \dot{R} = \frac{\partial H}{\partial \lambda_5},
\]

and

\[
\dot{\lambda}_1 = -\frac{\partial H}{\partial S}, \quad \dot{\lambda}_2 = -\frac{\partial H}{\partial L_1}, \quad \dot{\lambda}_3 = -\frac{\partial H}{\partial I}, \quad \dot{\lambda}_4 = -\frac{\partial H}{\partial L_2}, \quad \dot{\lambda}_5 = -\frac{\partial H}{\partial R}.
\]

The minimization condition

\[
J(u_1^*(\cdot), u_2^*(\cdot)) = \min_{0 \leq u_1, u_2 \leq 1} H(S^*(t), L_1^*(t), I^*(t), L_2^*(t), R^*(t), \lambda^*(t), u_1^*(t), u_2^*(t))
\]

\[
= \min_{0 \leq u_1, u_2 \leq 1} H(S^*(t), L_1^*(t), I^*(t), L_2^*(t), R^*(t), \lambda^*(t), u_1, u_2)
\]
holds almost everywhere on \([0,t_f]\). Moreover, the transversality conditions \(\lambda_i(t_f) = 0, \ i = 1, \ldots, 5\), hold.

**Theorem 3.1.** Problem (2.1), (3.3) with fixed initial conditions \(S(0), \ L_1(0), \ I(0), \ L_2(0)\) and fixed final time \(t_f\), admits a unique optimal solution \((S^*(\cdot), L_1^*(\cdot), I^*(\cdot), L_2^*(\cdot), R^*(\cdot))\) associated to an optimal control pair \((u_1^*(\cdot), u_2^*(\cdot))\) on \([0, t_f]\). Moreover, there exist adjoint functions \(\lambda_1^*(\cdot), \lambda_2^*(\cdot), \lambda_3^*(\cdot), \lambda_4^*(\cdot), \lambda_5^*(\cdot)\) such that

\[
\begin{align*}
\dot{\lambda}_1^*(t) &= \lambda_1^*(t) \left( \frac{\beta}{N} I^*(t) + \mu \right) - \lambda_2^*(t) \frac{\beta}{N} I^*(t) \\
\dot{\lambda}_2^*(t) &= \lambda_2^*(t) (\delta + \tau_1 + \mu) - \lambda_3^*(t) \phi \delta - \lambda_1^*(t) (1 - \phi) \delta - \lambda_5^*(t) \tau_1 u_1^*(t) \\
\dot{\lambda}_3^*(t) &= -W_0 + \lambda_1^*(t) \frac{\beta}{N} S^*(t) - \lambda_2^*(t) \frac{\beta}{N} S^*(t) + \lambda_4^*(t) (\tau_0 + \mu) + \lambda_5^*(t) \sigma \frac{\beta}{N} L_2^*(t) \\
&\quad + \lambda_3^*(t) (\tau_0 - \sigma R^* R^*(t)) \\
\dot{\lambda}_4^*(t) &= -\lambda_3^*(t) \frac{\beta}{N} I^*(t) \sigma - \lambda_5^*(t) \omega + \lambda_1^*(t) (\sigma \frac{\beta}{N} I^*(t)) \\
&\quad + \omega + \tau_2 u_2^*(t) + \mu - \lambda_3^*(t) (\tau_2 u_2^*(t)) \\
\dot{\lambda}_5^*(t) &= \lambda_3^*(t) \frac{\sigma R}{N} I^*(t) + \lambda_4^*(t) \omega_R + \mu
\end{align*}
\]

with transversality conditions

\[\lambda_i^*(t_f) = 0, \ i = 1, \ldots, 5.\]

Furthermore,

\[
\begin{align*}
u_1^*(t) &= \min \left\{ \max \left\{ \frac{\tau_1 L_1^* (\lambda_2 - \lambda_5^*)}{W_1}, 1 \right\}, 1 \right\}, \\
u_2^*(t) &= \min \left\{ \max \left\{ \frac{\tau_2 L_2^* (\lambda_3 - \lambda_5^*)}{W_2}, 1 \right\}, 1 \right\}.
\end{align*}
\]

**Proof.** Existence of an optimal solution \((S^*, L_1^*, I^*, L_2^*, R^*)\) comes from the convexity of the integrand of the cost function \(J\) with respect to the controls \((u_1, u_2)\) and the Lipschitz property of the state system with respect to state variables \((S, L_1, I, L_2, R)\) (see, e.g., [3, 6]). System (3.6) is derived from the Pontryagin maximum principle (see (3.4), [12]) and the optimal controls (3.7) come from the minimization condition (3.5). For small final time \(t_f\), the optimal control pair given by (3.7) is unique due to the boundedness of the state and adjoint functions and the Lipschitz property of systems (2.1) and (3.6) (see [10] and references cited therein). Because the state system (2.1) is autonomous, uniqueness is valid for any time \(t_f\) and not only for small time \(t_f\).

### 4 Numerical results and cost effectiveness analysis.

In this section, we start analyzing the impact of transmission intensity on the interventions. Secondly, we analyze the cost effectiveness of three control strategies: apply \(u_1\) and \(u_2\) separately; apply the two control measures simultaneously.

Different approaches were used to obtain and confirm the numerical results. One approach consisted in using IPOPT [18] and the algebraic modeling language AMPL [19]. A second approach was to use the PROPT Matlab Optimal Control Software [20]. The results coincide with the ones obtained by an iterative method that consists in solving the system of ten ODEs given by (2.1) and (3.6). For that, first we solve system (2.1) with a guess for the controls over the time interval \([0, T]\) using a forward fourth-order Runge–Kutta scheme and the transversality conditions \(\lambda_i(T) = 0, \ i = 1, \ldots, 5\). Then, system (3.6) is solved by a backward fourth-order Runge–Kutta scheme using the current iteration solution of (2.1). The controls are updated by using a convex combination of the previous controls and the values from (3.7). The iteration is stopped when the values of the unknowns at the previous iteration are very close to the ones at the present iteration.

#### 4.1 Impact of transmission intensity on the control interventions.

We take three different values for the transmission coefficient \(\beta\): 50; 100; 200. For these values of \(\beta\) the initial conditions of the optimal control problem are given in Table 2.

<table>
<thead>
<tr>
<th>(\beta)</th>
<th>(S(0))</th>
<th>(L_1(0))</th>
<th>(I(0))</th>
<th>(L_2(0))</th>
<th>(R(0))</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>16467</td>
<td>19</td>
<td>7</td>
<td>12689</td>
<td>818</td>
</tr>
<tr>
<td>100</td>
<td>4554</td>
<td>72</td>
<td>24</td>
<td>23950</td>
<td>1400</td>
</tr>
<tr>
<td>200</td>
<td>47</td>
<td>4605</td>
<td>1374</td>
<td>22781</td>
<td>1193</td>
</tr>
</tbody>
</table>

Table 2: State variables initial values for system (2.1) for different values of the transmission coefficient \(\beta\).

When the transmission coefficient \(\beta\) increases, both control \(u_1\) and \(u_2\) reach their maximum value for a longer period of time, that is, when the transmission intensity increases a bigger control effort is required (see Figures 1–2). We can also observe that, for all values of \(\beta\), control \(u_1\) is required for a longer period.

We consider an efficacy function in order to measure the impact of the control measures in the reduction of the number of infected individuals:

\[
E(t) = 1 - \frac{I_n(t; \beta)}{I(0; \beta)},
\]

where \(I_n(t)\) is the optimal solution \(I^*\) associated to the optimal controls \((u_1^*, u_2^*)\) for time \(t\) and \(I(0)\) is the

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initial value of $I$, for each transmission coefficient $\beta$ (see Table 2). This function measures the efficacy of the control interventions $(u_1, u_2)$, comparing the number of infected individuals at time $t$ with the initial value $I(0)$ for which there are no controls implemented ($u_1 = u_2 = 0$). Note that $E(t) \in [0, 1]$ for all time $t$ and that the efficacy is highest when $E(t)$ is close to one.

As expected, for all values of $\beta$ the fraction of infected individuals decreases. This effect is stronger for low transmission settings. In Figure 3, we can see that interventions for transmission intensities below the reinfection threshold ($\beta = 50$ or 100) have a much higher efficacy, for all time $t$.

We now present two summary measures to evaluate the efficacy of the proposed control measures. First, a time independent measure of efficacy,

$$\overline{E} = 1 - \frac{\int_{t_f}^{t_f} I_n(t; \beta) dt}{t_f I(0; \beta)},$$

which measures the average efficacy in the treatment time interval $t_f$; second, the average proportion of cost per unit of time,

$$\overline{C} = \frac{1}{t_f(W_1^2 + W_2^2)} \int_0^{t_f} \frac{W_1}{2} u_1^2(t) + \frac{W_2}{2} u_2^2(t) dt.$$

Note that both $\overline{E}$ and $\overline{C}$ vary between zero and one. Table 3 shows the summary measures for cost and efficacy. Cost of implementation of the control measures increases with $\beta$ and efficacy decreases. The ratio between these two measures (third column) also increases with $\beta$ indicating that both cost and efficacy change at similar rates. This intervention obtains the best results for low endemic regions where its cost-effectiveness ratio $\overline{C}/\overline{E}$ is higher.
Table 3: Summary of cost-effectiveness measures for different values of $\beta$: 50; 100; 200.

<table>
<thead>
<tr>
<th>$\beta$</th>
<th>$C$</th>
<th>$E$</th>
<th>$C/E$</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>0.39436</td>
<td>0.49801</td>
<td>0.79187</td>
</tr>
<tr>
<td>100</td>
<td>0.70238</td>
<td>0.46778</td>
<td>1.50152</td>
</tr>
<tr>
<td>200</td>
<td>0.52225</td>
<td>0.29699</td>
<td>1.75848</td>
</tr>
</tbody>
</table>

4.2 Optimal control strategies. In what follows we analyze the cost effectiveness of the following control strategies: implement only the control measure $u_1$; implement only control $u_2$; apply the two control measures $u_1$ and $u_2$ simultaneously.

We consider $\beta = 100$ and the parameter values of Table 1. In this case the most effective strategy is to apply $u_1$ and $u_2$ simultaneously. Between only $u_1$ and only $u_2$, the best choice is only $u_2$ during all the treatment period of time, see Figure 4.

Figure 4: Efficacy function.

The implementation of the two controls $u_1$ and $u_2$ at the same time implies a reduction on the effort of each measure, compared to the case when only one of the measures is applied, see Figures 5–7.

The biggest cost of implementation occurs when the two controls are applied simultaneously. The cost of implementation of the control measure $u_2$ is lower than control $u_1$, see Table 4.

Table 4: Summary of cost-effectiveness measures for different control strategies.

<table>
<thead>
<tr>
<th></th>
<th>$C$</th>
<th>$E$</th>
<th>$C/E$</th>
</tr>
</thead>
<tbody>
<tr>
<td>only $u_1$</td>
<td>0.46915</td>
<td>0.31026</td>
<td>1.51212</td>
</tr>
<tr>
<td>only $u_2$</td>
<td>0.27088</td>
<td>0.19664</td>
<td>1.37754</td>
</tr>
<tr>
<td>$u_1$ and $u_2$</td>
<td>0.70238</td>
<td>0.46778</td>
<td>1.50152</td>
</tr>
</tbody>
</table>

5 Discussion.

Optimal control theory is a powerful mathematical tool that can be used to make decisions in the situation described by problem (2.1), (3.3). The intensity of interventions can be relaxed along time, which is not the case considered in most models for which interventions are modeled by constant rates [8].

Numerical results indicate that the optimal solution is able to reduce the number of active TB cases. Below the reinfection threshold, efficacy of the interventions is higher, the cost is lower, and both controls can be relaxed sooner indicating a lower effort. Above the reinfection threshold, reinfection is very common which
impairs the success of the control measures, as described before for different contexts [7, 8, 13].

Future work must address important questions like the impact of relaxing the assumptions on the treatment duration $t_f$ and the weight constants on the objective functional. Also the analysis of the contribution of each control independently can be extended. Following [8], the relative partial protection to reinfection by acquired immunity through infection or conferred by treatment of a TB active case can be different. This can have significant impact on the results and should be investigated further.

References

[18] https://projects.coin-or.org/Ipopt