Cost-Effectiveness Analysis of Optimal Control Measures for Tuberculosis

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Abstract We propose and analyze an optimal control problem where the control system is a mathematical model for tuberculosis that considers reinfection. The control functions represent the fraction of early latent and persistent latent individuals that are treated. Our aim was to study how these control measures should be implemented, for a certain time period, in order to reduce the number of active infected individuals, while minimizing the interventions implementation costs. The optimal intervention is compared along different epidemiological scenarios, by varying the transmission coefficient. The impact of variation of the risk of reinfection, as a result of acquired immunity to a previous infection for treated individuals on the optimal controls and associated solutions, is analyzed. A cost-effectiveness analysis is done, to compare the application of each one of the control measures, separately or in combination.

Keywords Tuberculosis · Optimal control · Post-exposure interventions · Efficacy function · Cost effort

Mathematics Subject Classification 92D30 · 49M05

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1 Introduction

Tuberculosis (TB) detection and treatment saved 22 million of lives, between 1995 and 2012, following the 2013 report of the World Health Organization (WHO 2013). However, in 2012, there were 8.6 million of new TB cases and 1.3 million of TB deaths (WHO 2013). TB prevention, diagnosis and treatment, requires adequate funding, sustained over many years, which represents a worldwide scale challenge.

Mathematical dynamic models are an important tool in analyzing the spread and control of infectious diseases. Many TB mathematical models have been developed—see, e.g., (Blower et al. 1996; Castillo-Chavez and Feng 1998; Cohen and Murray 2004; Dye et al. 1998; Gomes et al. 2004; Vynnycky and Fine 1997) and the references cited therein. The main differences of the models proposed in (Castillo-Chavez and Feng 1997; Cohen et al. 2007; Cohen and Murray 2004; Dye et al. 1998; Gomes et al. 2004, 2007; Rie et al. 2005; Rodrigues et al. 2007; Vynnycky and Fine 1997; Warren et al. 2004) are the way they represent reinfection, since there is no consensus on whether a previous infection gives or not protection. The way recently infected individuals progress to active disease is not the same in all models: They can be “fast progressors” or “slow progressors.” In some models, it is assumed that only 5–10% of the infected individuals are fast progressors. The remaining models consider that individuals are able to contain the infection asymptomatic and non-infectiously (latent individuals), having a much lower probability of developing active disease by endogenous reactivation. More recent models also assume exogenous reinfection of latent and treated individuals, based on the fact that infection and/or disease do not confer full protection (Verver et al. 2005). This assumption has an important impact on the efficacy of interventions (Cohen and Murray 2004; Gomes et al. 2004; Rodrigues et al. 2007, 2013; Silva and Torres 2012, 2013; Vynnycky and Fine 1997). In this paper, we consider a TB mathematical model from Gomes et al. (2007), where exogenous reinfection is considered.

Without treatment, TB mortality rates are high (WHO 2013). Different interventions are available for TB prevention and treatment: vaccination to prevent infection; treatment to cure active TB; and treatment of latent TB to prevent endogenous reactivation. In this work, we study the implementation of two post-exposure 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 prophylactic treatment/vaccination of the persistent latent individuals. We propose an optimal control problem that consists in analyzing how these two control measures should be implemented, for a certain time period, in order to reduce the number of active infected individuals, while controlling the interventions implementation costs.

Optimal control is a branch of mathematics developed to find optimal ways to control a dynamic system (Cesari 1983; Fleming and Rishel 1975; Pontryagin et al. 1962). Other authors applied optimal control theory to TB models (see, e.g., Jung et al. 2002; Moualeu et al. 2015; Silva and Torres 2012). 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 (Gomes et al. 2007).
The paper is organized as follows. In Sect. 2, we present the mathematical model for TB that will be studied in this paper. Two control functions $u_1$ and $u_2$ are then added to the original model from Gomes et al. (2007). Section 3 is dedicated to the formulation of the optimal control problem. We prove the existence of a unique solution and derive the expression for the optimal controls according to the Pontryagin maximum principle (Pontryagin et al. 1962). Section 4 has five subsections dedicated to a numerical and cost-effectiveness analysis of the optimal control problem. We start by illustrating the problem solutions for a particular case (Sect. 4.1). We then introduce some summary measures in Sect. 4.2 to describe how the results change when varying transmission intensity (Sect. 4.3) and protection against reinfection (Sect. 4.4). In Sect. 4.5, we analyze the cost-effectiveness of three intervention strategies: applying $u_1$ or $u_2$ separately and applying the two control measures simultaneously. We end with Sect. 5 of discussion.

2 Mathematical Model

Following the model proposed in Gomes et al. (2007), population is divided into five categories: susceptible ($S$); early latent ($L_1$), i.e., individuals recently infected (less than 2 years) but not infectious; infected ($I$), i.e., individuals who have active TB and are infectious; persistent latent ($L_2$), 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 rates of birth and death, $\mu$, are equal [corresponding to a mean lifetime of 70 years (Gomes et al. 2007)], and no disease-related deaths are considered, keeping the total population, $N$, constant with $N = S(t) + L_1(t) + I(t) + L_2(t) + R(t)$.

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 $I$; $\omega$ and $\omega_R$ are the rates of endogenous reactivation for persistent latent infections (untreated latent infections) and for treated individuals (for those who have undergone a therapeutic intervention), respectively. Parameters $\sigma$ and $\sigma_R$ are factors that reduce the risk of infection, as a result of acquired immunity to a previous infection, for persistent latent individuals and for treated patients, respectively. These factors affect the rate of exogenous reinfection. As in Gomes et al. (2007), in our simulations, we consider three different cases for the protection against reinfection conferred by treatment: same protection as natural infection ($\sigma_R = \sigma$); lower protection than conferred by infection ($\sigma_R = \sigma/2$); and higher protection than conferred by infection ($\sigma_R = 2\sigma$), see Sect. 4.4. Parameter $\tau_0$ is the rate of recovery under standard treatment of active TB, assuming an average duration of infectiousness of 6 months. The values of the rates $\delta$, $\phi$, $\omega$, $\omega_R$, $\sigma$ and $\tau_0$ are taken from Gomes et al. (2007) and the references cited therein (see Table 1 for the values of the parameters).

Additional to standard treatment of infectious individuals, we consider two post-exposure interventions targeting different subpopulations: early detection and treatment of recently infected individuals ($L_1$) and chemotherapy or post-exposure vaccine of persistent latent individuals ($L_2$). These interventions are applied at rates $\tau_1$ and $\tau_2$. We consider, without the 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, $\tau_1 = 2$ year$^{-1}$, and greater than the rate of recovery of persistent latent individuals under post-exposure interventions, $\tau_2 = 1$ year$^{-1}$ (Gomes et al. 2007). Since we are interested in studying these interventions along time, we add to the original model two control functions, $u_1(\cdot)$ and $u_2(\cdot)$, which represent the intensity at which these post-exposure interventions are applied at each time step.

The dynamical control system that we propose is given by

\[
\begin{align*}
\dot{S}(t) &= \mu N - \frac{\beta}{N} I(t) S(t) - \mu S(t) \\
\dot{L}_1(t) &= \frac{\beta}{N} I(t) (S(t) + \sigma L_2(t) + \sigma_R R(t)) - (\delta + \tau_1 u_1(t) + \mu) L_1(t) \\
\dot{I}(t) &= \phi \delta L_1(t) + \omega L_2(t) + \omega_R R(t) - (\tau_0 + \mu) I(t) \\
\dot{L}_2(t) &= (1 - \phi) \delta L_1(t) - \frac{\beta}{N} I(t) L_2(t) - (\omega + \tau_2 u_2(t) + \mu) L_2(t) \\
\dot{R}(t) &= \tau_0 I(t) + \tau_1 u_1(t) L_1(t) + \tau_2 u_2(t) L_2(t) - \sigma_R \frac{\beta}{N} I(t) R(t) - (\omega_R + \mu) R(t).
\end{align*}
\]

\textbf{Remark 2.1} The assumption that the total population $N$ is constant allows to reduce the control system (1) from five to four state variables. We decided to maintain the TB model in form (1), using relation $S(t) + L_1(t) + I(t) + L_2(t) + R(t) = N$ as a test to confirm the numerical results.

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 (1) in the

| Symbol | Description | Value |
|--------|-------------|-------|
| $\beta$ | Transmission coefficient | Variable |
| $\mu$ | Death and birth rate | $1/70$ year$^{-1}$ |
| $\delta$ | Rate at which individuals leave $L_1$ | $12$ year$^{-1}$ |
| $\phi$ | Proportion of individuals going to $I$ | $0.05$ |
| $\omega$ | Rate of endogenous reactivation for persistent latent infections | $0.0002$ year$^{-1}$ |
| $\omega_R$ | Rate of endogenous reactivation for treated individuals | $0.00002$ year$^{-1}$ |
| $\sigma$ | Factor reducing the risk of infection as a result of acquired immunity to a previous infection for $L_2$ | $0.25$ |
| $\sigma_R$ | Rate of exogenous reinfection of treated patients | $\sigma; 2\sigma; \sigma/2$ |
| $\tau_0$ | Rate of recovery under treatment of active TB | $2$ year$^{-1}$ |
| $\tau_1$ | Rate of recovery under treatment of latent individuals $L_1$ | $2$ year$^{-1}$ |
| $\tau_2$ | Rate of recovery under treatment of latent individuals $L_2$ | $1$ year$^{-1}$ |
| $N$ | Total population | $30,000$ |
| $t_f$ | Total simulation duration | $5$ years |
| $W_0$ | Weight constant on active infectious individuals $I(t)$ | $50$ |
| $W_1$ | Weight constant on control $u_1(t)$ | $50$ |
| $W_2$ | Weight constant on control $u_2(t)$ | $50$ |

Table 1 Parameter values for the control system (1)
absence of post-exposure interventions, i.e., in the case \( u_1 = u_2 = 0 \), is proportional to the transmission coefficient \( \beta \) (see Gomes et al. 2007) and is given by

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

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 and post-exposure interventions, the reinfection threshold \( RT \) becomes important. It corresponds to critical transmissibility values above which there is a steep nonlinear increase in disease prevalence, corresponding to the increase in contribution of reinfection cases to the disease load. The \( RT \) for the system (1), in the absence of post-exposure interventions, has been computed in Gomes et al. (2007).

3 Optimal Control Problem

TB control is still a common problem around the world. In order to have the desire impact, TB control measures must be timely applied. However, economical, social and environmental constraints are imposed to 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 make decisions in this situation (Kar and Jana 2013).

We consider the state system (1) of ordinary differential equations in \( \mathbb{R}^5 \) with the set of admissible control functions given by

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

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 the constants \( W_i, i = 1, 2 \), are a measure of the relative cost of the interventions associated with 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 with an admissible control pair \( (u_1^*(\cdot), u_2^*(\cdot)) \) \( \in \Omega \) on the time interval \( [0, t_f] \), satisfying (1), given initial conditions \( S(0), L_1(0), I(0), L_2(0) \) and \( R(0) \) and minimizing the cost functional (2), i.e.,

\[
J(u_1^*(\cdot), u_2^*(\cdot)) = \min_{\Omega} J(u_1(\cdot), u_2(\cdot)).
\]
In Appendix 1, we prove the following existence and uniqueness result.

**Theorem 3.1** Problem (1)–(3) with given initial conditions $S(0), L_1(0), I(0), L_2(0)$ and $R(0)$ and fixed final time $t_f$, admits an unique optimal solution $(S^*(·), L_1^*(·), I^*(·), L_2^*(·), R^*(·))$ associated to an optimal control pair $(u_1^*(·), u_2^*(·))$ on $[0, t_f]$.

The optimal control pair predicted by Theorem 3.1 represents the optimal intervention strategy, given the cost constraints, and can be found by the application of the celebrated Pontryagin maximum principle (Pontryagin et al. 1962) (Lemma in Appendix 1) and appropriate numerical methods (Rodrigues et al. 2014).

**4 Numerical Results and Cost-Effectiveness Analysis**

Different approaches were used to obtain and confirm the numerical results. One approach consisted in using IPOPT and the algebraic modeling language AMPL. A second approach was to use the PROPT Matlab Optimal Control Software. The results coincide with the ones obtained by an iterative method that consists in solving the system of ten ODEs given by (1) and (11) (Lemma in Appendix 1). For that, first we solve system (1) with a guess for the controls over the time interval $[0, t_f]$ using a forward fourth-order Runge–Kutta scheme and the transversality conditions $\lambda_i(t_f) = 0, i = 1, \ldots, 5$. Then, system (11) is solved by a backward fourth-order Runge–Kutta scheme using the current iteration solution of (1). The controls are updated by using a convex combination of the previous controls and the values from (12). The iteration is stopped when the values of the unknowns at the previous iteration are very close to the ones at the present iteration.

In the following sections, all parameters are fixed according to Table 1, with exception to the transmission parameter $\beta$ and the reinfection parameter for treated individuals $\sigma_R$, which are varied to illustrate different scenarios. The initial conditions are obtained as the non-trivial equilibria values for the system (1) with no controls ($u_1 = 0 = u_2$), corresponding to the population state before the introduction of post-exposure interventions.

**4.1 An Example of Optimal Control for a Period of 5 Years**

For illustration, we fix all parameters according to Table 1. We start by considering $\beta = 100$ and the simplest case where latent ($L_1$ and $L_2$) and recovered ($R$) individuals have the same protection against reinfection, i.e., $\sigma_R = \sigma$. Both these assumptions will be relaxed latter on, in Sects. 4.3 and 4.4. Initial conditions are given in Table 2. The solution for the optimal control problem is illustrated in Fig. 1a, b. During the 5 years, for which the interventions lasts, the number of infectious individuals decreases and both interventions can be relaxed along time. Treatment intensity of the persistent latent individuals $u_2$ must be maximum during the initial 2 years and then can be progressively reduced. Treatment of early latent individuals $u_1$ should stay longer at its maximum intensity, for approximately 4 years. Figure 1c shows the efficacy function defined by
**Table 2** Initial conditions for system (1) with parameters according to Table 1 and for $\beta = 100$ and $\sigma_R = \sigma$. The values are obtained as the endemic equilibria values for (1) before the introduction of post-exposure interventions (i.e., $u_1 = 0 = u_2$)

|    | $S(0)$ | $L_1(0)$ | $I(0)$ | $L_2(0)$ | $R(0)$ |
|----|--------|----------|--------|----------|--------|
|    | 4,554  | 72       | 24     | 23,950   | 1,400  |

**Fig. 1** Solution for the optimal control problem (1)–(3), assuming $t_f = 5$, $\beta = 100$ and $\sigma_R = \sigma$.

- a Optimal control pair $u_1$ (continuous line) and $u_2$ (dashed line).
- b Number of infectious individuals along time.
- c Efficacy function $E(t)$, defined by (4)

$$E(t) = \frac{I(0) - I^*(t)}{I(0)} = 1 - \frac{I^*(t)}{I(0)}, \quad (4)$$

where $I^*(t)$ is the optimal solution associated with the optimal controls and $I(0)$ is the corresponding initial condition. This function measures the proportional decrease in the number of infectious individuals imposed by the intervention with controls $(u_1^*, u_2^*)$, by comparing the number of infected individuals at time $t$ with the initial value $I(0)$ for which there are no controls implemented ($u_1 = u_2 = 0$).
\( E(t) \in [0, 1] \) for all time \( t \) and the efficacy is highest when \( E(t) \) is one. Note that \( E(t) \) has the contrary tendency of \( I(t) \).

Naturally, the results depend on the objective functional \( J \) given by (2). In particular, they depend on the duration of the intervention \( t_f \) and on the weight constants associated with the amount of infectious individuals \( W_0 \) and with the costs of controls \( W_i, i = 1, 2 \). WHO goals are usually fixed for 5 years periods, so in what follows, we assume \( t_f = 5 \) years. Moreover, for higher values of \( t_f \) \((t_f \in \{10, \ldots, 25\})\), we can observe that the number of infected individuals starts to increase toward the end of the intervention (Appendix 2). In practical terms, this would mean that the intervention should be revised before its end. Results do not change qualitatively by varying constants \( W_i, i = 0, 1, 2 \). However, the magnitude of the efficacy changes more significantly in the cases where \( W_0 \) and \( W_1 = W_2 \) are varied independently. Generally, efficacy decreases when the costs \( W_1 \) and \( W_2 \) increase, corresponding to earlier relaxation of the intensity of treatment \((u_1(t), u_2(t))\) in the optimal solution. More details can be found in Appendix 3.

More importantly, these results will change depending on the epidemiological scenario we consider. In the next subsections, we vary the transmission coefficient \( \beta \) and on the protection conferred by treatment \( \sigma_R \).

### 4.2 Summary Measures

We introduce some summary measures to evaluate the cost and the effectiveness of the proposed control measures for the entire intervention period, for different epidemiological scenarios.

For each \( \beta \) and \( \sigma_R \) fixed, the total cases averted by the intervention during the time period \( t_f \) is given by

\[
A(\beta, \sigma_R) = t_f I(0; \beta, \sigma_R) - \int_0^{t_f} I^*(t; \beta, \sigma_R) dt, \tag{5}
\]

where, for each \( \beta \) and \( \sigma_R \) fixed, \( I^*(t; \beta, \sigma_R) = I^*(t) \) is the optimal solution associated with the optimal controls \((u_1^*, u_2^*)\) and \( I(0; \beta, \sigma_R) = I(0) \) is the corresponding initial condition. Note that this initial condition is obtained as the equilibrium proportion \( \bar{T}(\beta, \sigma_R) \) of system (1) with no post-exposure intervention \((u_1 = u_2 = 0)\), which does not depend on time, so \( t_f I(0; \beta, \sigma_R) = \int_0^{t_f} \bar{T}(\beta, \sigma_R) dt \) represents the total infectious cases over a period of \( t_f \) years.

We define effectiveness as the proportion of cases averted on the total cases possible under no intervention:

\[
\bar{E}(\beta, \sigma_R) = \frac{A(\beta, \sigma_R)}{t_f I(0; \beta, \sigma_R)} = 1 - \frac{\int_0^{t_f} I^*(t; \beta, \sigma_R) dt}{t_f I(0; \beta, \sigma_R)}. \tag{6}
\]

We choose dimensionless measures for effectiveness to be able to compare different epidemiological scenarios.
The total cost associated with the intervention is

\[ TC(\beta, \sigma_R) = \int_0^{t_f} C_1 u_1^*(t)L_1^*(t) + C_2 u_2^*(t)L_2^*(t) dt, \]  

where \( C_i \) correspond to the per person unit cost of the two possible interventions: detection and treatment of early latent individuals (\( C_1 \)) and chemotherapy/vaccination of persistent latent individuals (\( C_2 \)). Following Okosun et al. (2013), we define the average cost-effectiveness ratio by

\[ ACER = \frac{TC}{A}. \]  

Typically, optimal solutions correspond to maximum intensity of intervention for a certain period followed by relaxation, as in the example in Sect. 4.1. So, we use the time at which the intensity of each intervention is relaxed as another way to evaluate the effort associated with an optimal solution:

\[ t_{ri} = t_{ri}(\beta, \sigma_R) = \max\{t \in [0, t_f] : u_i(t; \beta, \sigma_R) = 1\}, \quad i = 1, 2. \]

We refer to these as relaxation-times. Table 3 summarizes the particular case analyzed in the previous section, \( \beta = 100 \) and \( \sigma_R = \sigma \).

### 4.3 Impact of Transmission Intensity on Optimal Control Interventions

First, we compare model results for different epidemiological scenarios in terms of transmission intensity, by varying parameter \( \beta \). For now, we assume that protection conferred by natural infection or by treatment is the same (\( \sigma_R = \sigma \)). The remaining parameters are fixed according to Table 1.

Figure 2 represents effectiveness \( \bar{E} \) and relaxation-times \( t_{ri}, i = 1, 2 \), for the optimal control measures, when varying transmission intensity \( \beta \). Effectiveness is a monotonically decreasing function on \( \beta \). The reinfection threshold \( RT \), marked by the dotted vertical line, coincides with a change in curvature of \( \bar{E}(\beta) \) from concave to convex (Fig. 2a). For all endemic scenarios, maximum intensity of treatment of early latent individuals is required for longer periods than treatment of persistent latent individuals (Fig. 2b). Below the \( RT \), the relaxation-times of both post-exposure interventions increase with \( \beta \). However, above the \( RT \), treatment of early latent individuals is required at its maximum intensity for almost the entire 5 year period (\( t_f \)) and the intervention on persistent latent individuals is needed for shorter periods. For very high transmission intensity, relaxation-time for intervention on persistent latent individuals is zero (\( t_{r2} = 0 \)), corresponding to a singular control.
Depending on the background epidemiological scenario, we can have different optimal intervention strategies. For example, for $\beta = 100$, the optimal solution corresponds to both interventions with relaxation-times of $t_{r_1} = 4.1765$ and $t_{r_2} = 2.0$ years and for $\beta = 250$, the optimal solution corresponds to treatment of early latent individuals for approximately the entire intervention period, $t_{r_1} = 4.941$ years and treat persistent individuals at intensity always below the maximum $u_2^*(t) < 1$, for $t \in [0, t_f]$ (results not shown). These interventions are associated with very different effectiveness, $47\%$ ($E(100) = 0.4691$) and $20\%$ ($E(250) = 0.2005$), respectively.

### 4.4 Impact of Protection Against Reinfection of the Treated Individuals ($\sigma_R \neq \sigma$) on Optimal Control Interventions

In this section, we relax the assumption that latent ($L_1$ and $L_2$) and treated ($R$) individuals have the same protection to reinfection. Given the lack of published studies supporting on of the hypothesis, we explore both possibilities, as in Gomes et al. (2007): Treatment enhances protection against reinfection ($\sigma_R < \sigma$), or protection is impaired by treatment ($\sigma_R > \sigma$). To illustrate, we will use $\sigma_R = \sigma/2$ and $\sigma_R = 2\sigma$, respectively. Results are very different for the two scenarios. If protection against reinfection is enhanced by treatment ($\sigma_R = \sigma/2$), then the optimal solution corresponds to treat both early and persistent latent individuals at maximum intensity for a certain period, ranging from 1.5 to 5 years, followed by relaxation of the intervention intensity (full lines in Fig. 3b, c). The relaxation-times increase with $\beta$. However, if treatment impairs protection, then the optimal intervention would be to treat early latent at maximum intensity for longer periods and to treat persistent latent individuals almost always below the maximum intensity (dashed lines in Fig. 3b, c). Actually, in this case, the optimal solution can impose not to treat persistent latent individuals ($u_2^* = 0$ for $t \in [0, t_f]$) as illustrated in Fig. 4 for the case $\beta = 100$. In both cases, effectiveness peaks close to the reinfection threshold $RT$ (see Fig. 3a).
4.5 Optimal Controls Strategy and Cost-Effectiveness Analysis

In this section, we analyze the cost-effectiveness of alternative combinations of the two possible control measures: strategy a—implementing both controls $u_1$ and $u_2$, corresponding to intervene on both early and persistent latent individuals, as in previous sections; strategy b—implementing only control measure $u_1$ and strategy c—only control measure $u_2$, separately.

For each value of $\beta$, we compute the optimal solution for the three strategies and calculate the associated effectiveness $E$. In Fig. 5a, we can see that, below the reinfection threshold $RT$, the strategy using interventions on both population groups has higher effectiveness. However, above the $RT$, this advantage is marginal, comparing with the intervention on early latent individuals, only. From Fig. 5b, we can have one idea of the time design of the optimal intervention for each case. Intervention on early
latent individuals only corresponds to a control at maximum intensity for long periods (very high $t_{r_1}$). When intervening on persistent latent individuals only, maximum intensity of control is required for shorter periods which are close to zero for very high transmission intensity, corresponding to singular controls.

For a particular epidemiological scenario (fixed $\beta$ and $\sigma_R$), we can use a more classical approach to analyze the cost-effectiveness of the three alternative strategies by using the incremental cost-effectiveness ratio (ICER) in Okosun et al. (2013). This ratio is used to compare the differences between the costs and health outcomes of two alternative intervention strategies that compete for the same resources, and it is generally described as the additional cost per additional health outcome. First, we
Table 4 Incremental cost-effectiveness ratio for alternative strategies a, b and c, with $\beta = 100$. Parameters according to Table 1, $C_1 = C_2 = 1$ and $\sigma_R = \sigma$

| Strategy | $A$ | $TC$ | ACER | ICER |
|----------|-----|------|------|------|
| c        | 24  | 35,640 | 1,485 | 1,485 |
| b        | 37  | 211   | 5.7  | -1.721 |
| a        | 56  | 23,374 | 417.4 | 1,207 |

must rank the strategies in order of increasing effectiveness, here measured as the total infections averted $A(\beta, \sigma_R)$, defined in (8). Given two competing strategies $a$ and $b$, the ICER of the strategy with the least effectiveness is its ACER and for the following strategies is given by

$$ICER(b) = \frac{A(b) - A(a)}{TC(b) - TC(a)}.$$ 

For illustration, we focus on an epidemiological scenario of moderate transmission with $\beta = 100$. Results are shown in Table 4. Strategy c has a unit cost of 1,485, and it is more costly and less effective than strategy b, so we exclude strategy c from the set of alternatives. We align the remaining alternative strategies by increasing effectiveness and recompute the ICER: $ICER(b) = ACER(b) = 5.7$ and $ICER(a) = 1,207$. Hence, we conclude that strategy b has the least ICER and therefore is more cost-effective than strategy a. For this illustration, we have considered the same cost for both interventions ($C_1 = C_2 = 1$). Results should depend strongly on the choice of these parameters; however, this discussion is out of the scope of our present work.

5 Discussion

In this work, we study the potential of widespread of two post-exposure interventions that are not widely used: treatment of early latent individuals and prophylactic treatment/vaccination of persistent latent individuals. We propose an optimal control problem that consists in analyzing how these two control measures should be implemented, for a certain time period, in order to reduce the number of active infected individuals, while controlling the interventions implementation costs. This approach differs from others (Blower et al. 1996; Castillo-Chavez and Feng 1998; Dye et al. 1998; Gomes et al. 2007) since it allows intensity of intervention to be changed along time.

As previously suggested (Gomes et al. 2004, 2007), interventions impact can be sensitive to transmission intensity and reinfection. We choose a dimensionless measure of effectiveness to compare different scenarios: assuming different transmission intensity ($\beta$) or assuming different assumptions on protection against reinfection conferred by treatment ($\sigma_R$).

Effectiveness of optimal intervention decreases with transmission. There is a change in the intervention profile from low to high transmission. In high transmission settings, the intensity of treatment of persistent latent individuals $u_{R2}^*$ for the optimal solution is reduced. Since treatment of persistent latent individuals reduces the reactivation
rate (from $\omega$ to $\omega_R$), when reinfection is very common and it overcomes reactivation impact, the advantage of treating this population group is less pronounced.

The susceptibility to reinfection after treatment is still an open question. In one hand, treatment can reduce the risk of TB by reducing the amount of bacteria present in the lungs. On the other hand, we can argue that latent infection boosts immunity by constant stimulation of the immune system, so treatment could reduce protection. We vary parameter $\sigma_R$ to explore these two possible scenarios: $\sigma_R = \sigma/2$ when treatment enhances protection and $\sigma_R = 2\sigma$ when treatment impairs protection. Results show that treatment of persistent latent individuals should be less intense or even absent for the case where treatment impairs protection. Similar results were obtained for the case of constant treatment rates in Gomes et al. (2007). In fact, for the correspondent case with maximum intensity ($u_1 \equiv 1$ and $u_2 \equiv 1$), we can have an increase in the equilibrium proportion of infectious individuals ($t \to \infty$).

We can conclude that reinfection has an important role in the determination of the optimal control strategy, by diminishing the intervention intensity on persistent latent individuals: first when transmission is very high corresponding to a very high reinfection rate and secondly when this population group has a lower susceptibility to reinfection ($\sigma < \sigma_R$). Interestingly, the reinfection threshold $RT$ of the model with no controls still marks a change in the model behavior. Even though, we are comparing equilibrium results to transient short time interventions.

Cost-effectiveness analysis of alternative combinations of the two interventions is conducted. For $\beta = 100$, treatment of only early latent individuals is the more cost-effective strategy, despite of the treatment of both early latent and persistent latent individuals having a higher effectiveness. The total cost associated with the treatment of persistent latent individuals is very high, especially because this population group can be very big in comparison with the others. It is believed that about one-third of world’s population is latent infected with TB. Here, for simplicity, we have considered the cost parameters both equal to one. However, this depends greatly on the type of intervention used and results can be changed. For example, if intervention on persistent latent individuals could be done by vaccination, then the per person unit cost could be significantly reduced. In addition, treatment of early latent individuals implies contact tracing of index cases and prophylactic treatment, which can also be very expensive.

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Appendix 1: Proof of Theorem 3.1

The Hamiltonian $H$ associated with the problem (1)–(3) is given by

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

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 (Pontryagin et al. 1962), if \((u_1^*(\cdot), u_2^*(\cdot)) \in \Omega\) is optimal for problem (1)–(3) with the initial conditions given in Table 2 and fixed final time \(t_f\), then there exists a non-trivial 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

\[ \dot{\lambda}_1 = -\frac{\partial H}{\partial S}, \quad \dot{\lambda}_2 = -\frac{\partial H}{\partial L_1}, \quad \dot{\lambda}_3 = -\frac{\partial H}{\partial I}, \quad \dot{\lambda}_4 = -\frac{\partial H}{\partial L_2}, \quad \dot{\lambda}_5 = -\frac{\partial H}{\partial R}. \quad (9) \]

The minimality condition

\[ H(S^*(t), L_1^*(t), I^*(t), L_2^*(t), R^*(t), \lambda^*(t), u_1^*(t), u_2^*(t)) = \min_{0 \leq u_1, u_2 \leq 1} H(S^*(t), L_1^*(t), I^*(t), L_2^*(t), R^*(t), \lambda^*(t), u_1, u_2) \quad (10) \]

holds almost everywhere on \([0, t_f]\). Moreover, the transversality conditions

\[ \lambda_i(t_f) = 0, \quad i = 1, \ldots, 5, \]

hold.

**Lemma** For problem (1)–(3) with fixed initial conditions \(S(0), L_1(0), I(0), L_2(0)\) and \(R(0)\) and fixed final time \(t_f\), there exists adjoint functions \(\lambda_1^*(\cdot), \lambda_2^*(\cdot), \lambda_3^*(\cdot), \lambda_4^*(\cdot)\) and \(\lambda_5^*(\cdot)\) such that
\[
\begin{align*}
\dot{\lambda}_1^* (t) &= \lambda_1^* (t) \left( \frac{\beta}{N} I^*(t) + \mu \right) - \lambda_2^* (t) \frac{\beta}{N} I^*(t) \\
\dot{\lambda}_2^* (t) &= \lambda_2^* (t) (\delta + \tau_1 + \mu) - \lambda_3^* (t) \phi \delta - \lambda_4^* (t) (1 - \phi) \delta - \lambda_5^* (t) \tau_1 u_1^* (t) \\
\dot{\lambda}_3^* (t) &= -W_0 + \lambda_1^* (t) \frac{\beta}{N} S^* (t) - \lambda_2^* (t) \frac{\beta}{N} (S^* (t) + \sigma L_2^* (t)) + \sigma R R^* (t) \\
&\quad + \lambda_3^* (t) (\tau_0 + \mu) + \lambda_4^* (t) \sigma \frac{\beta}{N} L_2^* (t) - \lambda_5^* (t) \left( \tau_0 - \sigma \frac{\beta}{N} R^* (t) \right) \\
\dot{\lambda}_4^* (t) &= -\lambda_2^* (t) \frac{\beta}{N} I^*(t) \sigma - \lambda_3^* (t) \omega + \lambda_4^* (t) \left( \sigma \frac{\beta}{N} I^*(t) + \omega + \tau_2 u_2^* (t) + \mu \right) \\
&\quad - \lambda_5^* (t) \left( \tau_2 u_2^* (t) \right) \\
\dot{\lambda}_5^* (t) &= -\lambda_2^* (t) \sigma R \frac{\beta}{N} I^*(t) - \lambda_3^* (t) \omega_R + \lambda_5^* (t) \left( \sigma R \frac{\beta}{N} I^*(t) + \omega_R + \mu \right),
\end{align*}
\]

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

Furthermore,
\[
\begin{align*}
u_1^* (t) &= \min \left\{ \max \left\{ 0, \frac{\tau_1 L_1^* (\lambda_2^* - \lambda_5^*)}{W_1} \right\}, 1 \right\}, \\
u_2^* (t) &= \min \left\{ \max \left\{ 0, \frac{\tau_2 L_2^* (\lambda_4^* - \lambda_5^*)}{W_2} \right\}, 1 \right\}.
\end{align*}
\]

**Proof** System (11) is derived from the Pontryagin maximum principle (see (9), Pontryagin et al. 1962) and the optimal controls (12) come from the minimality condition (10). For small final time \(t_f\), the optimal control pair given by (12) is unique due to the

**Fig. 6** Proportion of infectious individuals for the optimal solution \(I (t)\) with \(t_f \in \{5, 7, 10, 12, 15, 17, 20, 22, 25\}\). Parameters according to Table 1, \(\beta = 100\) and \(\sigma_R = \sigma\)
boundedness of the state and adjoint functions and the Lipschitz property of systems (1) and (11) (see Jung et al. 2002 and references cited therein).

Proof of Theorem 3.1 Existence of an optimal solution \((S^*, L_1^*, I^*, L_2^*, R^*)\) associated with an optimal control pair \((u_1^*, u_2^*)\) comes from the convexity of the integrand of the cost functional \(\mathcal{J}\) 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., Cesari 1983; Fleming and Rishel 1975). For small final time \(t_f\), the optimal control pair is given by (12) that is unique by the Lemma above. Because the problem (1)–(3) is autonomous, uniqueness is valid for any time \(t_f\) and not only for small time \(t_f\).

Appendix 2: Sensitivity Analysis to the Duration of Intervention \(t_f\)

We fix \(\beta = 100\) and \(\sigma_R = \sigma\) and the remaining parameters according to Table 1 and vary \(t_f\). Results for the proportion of infectious individuals are shown in the Fig. 6.
The general behavior do not change significantly with $t_f$. The proportion of infected individuals slightly increases toward the end of the intervention for $t_f > 7$. This tendency is more pronounced for higher $t_f$.

**Appendix 3: Sensitivity Analysis to the Weight Constants on the Objective Functional $J$**

Figure 7 shows the results for different combination of the weight constants on the objective functional $J$. We fix $\beta = 100$ and $\sigma_R = \sigma$ and the remaining parameters according to Table 1 and vary $W_0$, $W_1$ and $W_2$. Efficacy decreases when the costs $W_1$ and $W_2$ increase, corresponding to an earlier relaxation of the intensity of treatment $(u_1(t), u_2(t))$ in the optimal solution due to cost restrictions. The change in efficacy is more pronounced for the cases where the weight associated with infectious individuals $W_0$ change in comparison with the weights associated with the controls $W_1 = W_2$ (Fig. 7a, b). Results are less sensitive to the variation between the weight controls $W_1$ and $W_2$ (Fig. 7c, d).

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