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OPTIMAL CONTROL AND COST-EFFECTIVENESS ANALYSIS OF TUBERCULOSIS MODEL WITH FAST AND SLOW PROGRESSION

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ABSTRACT

Designing feasible and cost-effective control interventions for the eradication of epidemic diseases is a daunting task. Mathematical modelling and control system theory provide efficient tools that can be employed to analyse and understand the dynamics of the disease and its control. Nevertheless, finding optimal control strategies for epidemic models is cumbersome, owing to the stringent need for balancing the dissenting demands of the control goal and minimising the cost of implementing the control actions. This study proposed the application of optimal control theory to a Tuberculosis (TB) model with slow and fast progression, seeking to reduce or eliminate the prevalence of TB and minimise the cost of implementation of the control. The optimal controls are characterised using the Pontryagin maximum principle and solved numerically. Moreover, a cost-effectiveness analysis is performed by using an incremental cost-effectiveness ratio (ICER). The results indicated that disease control policy that combined vaccine, case finding and case holding interventions would successfully curtail the prevalence of TB.

Disciplinary: Epidemiology, Biocomputing, Medical Science (Public Health).

1. INTRODUCTION

Over the decades, epidemic diseases have been a leading cause of billions of deaths. For this purpose, the entire world is making an effort to avoid the outbreak of the disease, such as the new Corona Covid19 pandemic. Improving public health is among the priority of the united nation's 2030 sustainable development goals (SDGs) (UN, 2019).

Tuberculosis, also known as TB is one of the world's life-threatening diseases, with over 10 million cases of infection as of 2018, and an estimate of 1.2 million incidences of death among the infected population. SDG goal 3.3 contains a plan to end the TB epidemic by 2030 (WHO, 2019). TB

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disease usually starts in the body of a susceptible person with infection by Mycobacterium tuberculosis (MTB) (Jumbo et al., 2013). The transmission of the disease is mostly through air breath between healthy and infected individuals. Common symptoms of TB include fever, weight loss and coughing blood (Baba et al., 2019). TB can also be contracted through co-infection with other diseases such as HIV (WHO, 2015). The understanding of TB epidemiology is cumbersome, which makes the design and implementation of control measures complicated (Nematollahi et al. 2020).

The frequently used method for the treatment of TB includes vaccination of the susceptible individuals to prevent infection and further spread of the disease; treatment of latently infected individuals through "case finding" to avoid reactivation and treatment of the patient with active TB through "case holding" to guarantee adherence to treatment (Gomes et al., 2007).

Mathematical modelling and control system theory provide efficient tools that can be employed to analyse and understand the dynamics of the disease and its control. Also, to access the performance and cost-effectiveness of several control strategies employed in eradicating the diseases (Metcalf et al., 2015; Xin et al., 2019; Zaman et al., 2017). In this regard, a large number of mathematical models have been proposed in the literature (Chalub & Souza, 2011; Giamberardino & Iacoviello, 2018; Heesterbeek et al., 2015; Li, 2015; Matthew & Keeling, 2008; Metcalf et al. 2015; Zhang & Zhou, 2012). However, modelling and control of epidemic diseases like other natural phenomena are quite challenging. Developing reliable control algorithm for epidemic models is cumbersome due to the inherent non-linearity, system complexity, modelling uncertainties, parameter variations. Moreover, finding optimal control strategies for epidemic models is cumbersome, owing to the stringent need for balancing the dissenting demands of the control goal and minimising the cost of implementing the control actions. (Bather et al., 1976).

In 2006, Mccluskey (2006) introduced a nonlinear TB model, considering the fact that TB transmission exhibit slow and fast progression from susceptible to infected class. The system uses SEI compartmental epidemic model as

$$\begin{cases} \frac{dS}{dt} = \Lambda - \beta SI - \mu S \\ \frac{\mathrm{dE}}{dt} = (1-p)\beta SI - \kappa E - \mu \mathrm{E} \\ \frac{dI}{dt} = p\beta SI + \kappa E - \mathrm{dI} - \mu \mathrm{I} \end{cases} \quad (1),$$

where the population is separated into three compartments depending on the epidemiological status: individuals that are healthy but can contract the disease categorised as susceptible class $S(t)$, exposed class $E(t)$ containing individuals that have been in contact with the infected class but did not yet show any symptoms and the infectious class $I(t)$ representing the individuals with active TB. It is assumed that the rate of the disease transmission to susceptible individuals is bilinear βSI, with a fraction p undergoing fast progression to the infectious compartment, and the remaining $(1-p)$ exhibiting slow progress into the exposed class. It is considered that the time taken by the exposed individuals to move to the infectious class follows an exponential distribution, with average waiting time $1/k$. The exposed class is assumed to have latent TB which can be cured and removed upon receiving adequate treatment; else they will progress to the infectious class. The system parameters, along with their meanings, are summarized in Table 1.

Table 1: Parameter description as presented in (Mccluskey, 2006)

Parameter Symbol	Parameter description
Λ	Overall recruitment into a susceptible compartment
μ	Natural death rate
d	Disease induced death rate
β	Disease transmission coefficient
p	A fraction of newly infected individuals that exhibit fast progression to infectious compartment
κ	The rate at which exposed individuals moved to the infectious compartment

For model (1) using the concept of a next-generation matrix (Brauer, 2017), the basic reproduction number was found to be

$$\mathcal{R}_0 = \frac{\Lambda\beta(\kappa+p\mu)}{\mu(\mu+d)(\mu+\kappa)} \quad (2).$$

They showed and proved that the disease would be eradicated by itself if $\mathcal{R}_0 < 1$ and linger otherwise. Based on that, the basic reproduction number, $\mathcal{R}_0$, helps in understanding the dynamics of the disease and can be used to recommend or plan TB control programs. Nevertheless, they did not examine time-dependent control strategies and cost-effectiveness of the control methods, since their study had been focused on the global stability analysis and prevalence of TB at equilibria.

The current study explores the potential application of optimal control theory and cost-effectiveness analysis on a TB model with slow and fast progression. Hence, the research aimed at finding the most suitable and cost-effective control interventions for the eradication of the TB epidemic. The optimal control analysis is based on the indirect application of Pontryagin's maximum principle, and the cost-effective analysis is expressed through the use of incremental cost-effectiveness ratio (ICER).

2. OPTIMAL CONTROL PROBLEM

This section described the optimal control system for the SEI model of TB transmission with fast and slow progression studied in Mccluskey (2006). The optimal control theory is applied along with time-dependent controls to identify the best control strategies under which the TB could be controlled or eliminated. Three control interventions $u_1(t)$, $u_2(t)$ and $u_3(t)$ are incorporated into the system model (1). The control $u_1(t)$, denote the vaccination given to a fraction of the susceptible individuals to provide them with immunity from the disease. The control $u_2(t)$, denotes a "case finding" control effort that is applied to identify and cure a fraction of exposed populations, to minimise the rate of migration from the exposed compartment to infectious. And finally, "case holding control" $u_3(t)$, signifies the control effort that ensures the effective treatment of the infected. The optimal controls $u_1(t)$, $u_2(t)$ and $u_3(t)$ are assumed to be bounded, integrable, Lesbesgue functions with values in the closed set $[0,1]$. By employing similar parameters as in model (1), the optimal control model can be written as

$$\begin{cases} \frac{dS}{dt} = \Lambda - \beta SI - \left(\mu + u_1(t)\right)S \\ \frac{dE}{dt} = (1-p)\beta SI - \kappa E - \left(\mu + u_2(t)\right)E \\ \frac{dI}{dt} = p\beta SI + \kappa E - dI - \left(\mu + u_3(t)\right)I \end{cases} \quad (3),$$

with a set of system state variables $X(t) = \left(S(t), E(t), I(t)\right)$ and the objective functional to be minimised, defined as

$$J(u_1, u_2, u_3) = \int_0^{t_f} \left(a_1 E(t) + a_2 I(t) + \frac{w_1}{2}u_1^2(t) + \frac{w_2}{2}u_2^2(t) + \frac{w_3}{2}u_3^2(t)\right) dt \quad (4).$$

The main objective is to reduce or eliminate the prevalence of TB in both the latent and active classes, also minimise the cost of implementation of the control actions. As indicated in (4), the total cost of the control includes the disease-induced cost and the cost of vaccination and control interventions. It is assumed that the cost of the interventions is nonlinear and quadratic, as in (Baba et al., 2019; Gao & Huang, 2018). The positive coefficients a_1, a_2, w_1, w_2 and w_3 are nonnegative weights related to the exposed population, infected population and control measures, respectively.

The problem is to find the optimal controls u_1^*, u_2^* and u_3^* along with an equivalent set of state variables $X^* = (S^*, E^*, I^*)$ over the fixed time interval $[0, t_f]$, that minimises the objective functional (5) subject to the control systems dynamic constraints (3) as:

$$J(X^*, u_1^*, u_2^*) = \min_{\Psi} J(X, u_1, u_2, u_2) \quad (5),$$

with

$$\Psi = \left\{X \in W^{1.1}\left([0, t_f]; \mathbb{R}^3\right), (u_1, u_2, u_3) \in L^1\left([0, t_f];\ \mathbb{R}\right) \middle| X(0) \geq 0, and\ (3)\ are\ satisfied\right\}$$

3. OPTIMAL CONTROL ANALYSIS

3.1 EXISTENCE OF THE OPTIMAL CONTROL

Theorem 1. There exist optimal controls $u_1^*, u_2^*\ and\ u_3^*$ and associated optimal solution, S^*, E^*, I^* to the problem (5).

Proof: This theorem can be proved by adopting the conditions stated in Theorem 4.1 and Corollary 4.1 from Bather et al. (1976) and verifying the nontrivial conditions. Let $\varphi\left(\vec{X}, \vec{u}, t\right)$ represent the right-hand side of (3), the following conditions should be satisfied to prove the existence of the optimal control solutions.

I. φ is of class C^1 and there exists a constant ζ such that
$|\varphi(0,0,t)| \leq \eta,$
$\left|\varphi_{\vec{X}}\left(\vec{X},,\vec{u},t\right)\right| \leq \eta(1 + |\vec{u}|)$, and
$\left|\varphi_{\vec{u}}\left(\vec{X},,\vec{u},t\right)\right| \leq \eta;$

II. The admissible set $\mathcal{F}$ of all solutions to system (3) along with associated control in Ψ is nonempty;

III. $\varphi\left(\vec{X}, \vec{u}, t\right) = a\left(\vec{X}, t\right) + b\left(\vec{X}, t\right)\vec{u};$

IV. The optimal control set $U = [0, u_{1_{max}}] \times [0, u_{2_{max}}] \times [0, u_{3_{max}}]$ is closed, compact and convex;

V. Th the objective functional integrand is convex in U.

By writing $\varphi(\vec{X}, \vec{u}, t)$ as in (6), it is evident that $\varphi(\vec{X}, \vec{u}, t)$ is of class C^1 and $|\varphi(0,0,t)| = \Lambda$.

$$\varphi(\vec{X}, \vec{u}, t) = \begin{pmatrix} \Lambda - \beta SI - (\mu + u_1(t))S \\ (1-p)\beta SI - \kappa E - (\mu + u_2(t))E \\ p\beta SI + \kappa E - dI - (\mu + u_3(t))I \end{pmatrix} \quad (6).$$

Also,

$$|\varphi_{\vec{X}}(\vec{X}, \vec{u}, t)| = \left| \begin{pmatrix} -\beta I - \mu - u_1 & 0 & -\beta S \\ (1-p)\beta I & -\kappa - \mu - u_2 & (1-p)\beta S \\ p\beta I & \kappa & p\beta S - d - \mu - u_3 \end{pmatrix} \right|, \text{ and}$$

$$|\varphi_{\vec{u}}(\vec{X}, \vec{u}, t)| = \left| \begin{pmatrix} -S & 0 & 0 \\ 0 & -E & 0 \\ 0 & 0 & -I \end{pmatrix} \right|.$$

Owing to the boundedness of the state variables S, E and I, there exist a constant η such that

$$|\varphi(0,0,t)| \leq \eta, \ |\varphi_{\vec{X}}(\vec{X},, \vec{u}, t)| \leq \eta(1 + |\vec{u}|), \text{ and } |\varphi_{\vec{u}}(\vec{X},, \vec{u}, t)| \leq \eta.$$

Hence, the first condition is satisfied.

It can be deduced from condition (I), for constant control, there exists a unique solution to the system (3). It follows that condition (II) holds.

Furthermore, $\varphi(\vec{X}, \vec{u}, t)$ can be expanded as

$$\varphi(\vec{X}, \vec{u}, t) = \begin{pmatrix} \Lambda - \beta SI - (\mu + u_1(t))S \\ (1-p)\beta SI - \kappa E - (\mu + u_2(t))E \\ p\beta SI + \kappa E - dI - (\mu + u_3(t))I \end{pmatrix}$$
$$= \begin{pmatrix} \Lambda - \beta SI - \mu S \\ (1-p)\beta SI - \kappa E - \mu E \\ p\beta SI + \kappa E - dI - \mu I \end{pmatrix} + \begin{pmatrix} -S & 0 & 0 \\ 0 & -E & 0 \\ 0 & 0 & -I \end{pmatrix} \times \begin{pmatrix} u_1 \\ u_2 \\ u_3 \end{pmatrix}$$

Therefore, condition (III) also holds. Conditions (IV) and (V) can be investigated by verifying the convexity of the integrand over the objective functional $r(\vec{X}, \vec{u}, t)$. The convexity is satisfied if for any two control vectors $\vec{u}$ and $\vec{v}$ and a constant $\rho \in [0, 1]$

$$(1-\rho)r(\vec{X}, \vec{u}, t) + \rho r(\vec{X}, \vec{v}, t) \geq r(\vec{X}, (1-\rho)\vec{u} + \rho\vec{v}, t) \quad (7)$$

Where

$$r(\vec{X}, \vec{u}, t) = a_1 E(t) + a_2 I(t) + \frac{w_1}{2} u_1^2(t) + \frac{w_2}{2} u_2^2(t) + \frac{w_3}{2} u_3^2(t)$$

Considering the LHS of (7), we have

$$(1-\rho)r\left(\vec{X},\vec{u},t\right)+\rho r\left(\vec{X},\vec{v},t\right)=a_1E(t)+a_2I(t)+$$
$$(1-\rho)\left[\frac{w_1}{2}u_1^2(t)+\frac{w_2}{2}u_2^2(t)+\frac{w_3}{2}u_3^2(t)\right]+\rho\left[\frac{w_1}{2}v_1^2(t)+\frac{w_2}{2}v_2^2(t)+\frac{w_3}{2}v_3^2(t)\right]$$

And the RHS of Equation (7) gives

$$r\left(\vec{X},(1-\rho)\vec{u}+\rho\vec{v},t\right)=a_1E(t)+a_2I(t)+\frac{w_1}{2}[(1-\rho)u_1+\rho v_1]^2+$$
$$\frac{w_2}{2}[(1-\rho)u_2+\rho v_2]^2+\frac{w_3}{2}[(1-\rho)u_3+\rho v_3]^2$$

It follows that

$$\begin{aligned}
&(1-\rho)r\left(\vec{X},\vec{u},t\right)+\rho r\left(\vec{X},\vec{v},t\right)-r\left(\vec{X},(1-\rho)\vec{u}+\rho\vec{v},t\right)\\
&=\frac{w_1}{2}[(1-\rho)u_1^2+\rho v_1^2]+\frac{w_2}{2}[(1-\rho)u_2^2+\rho v_2^2]+\frac{w_3}{2}[(1-\rho)u_3^2+\rho v_3^2]\\
&\quad-\frac{w_1}{2}[(1-\rho)u_1+\rho v_1]^2-\frac{w_2}{2}[(1-\rho)u_2+\rho v_2]^2-\frac{w_3}{2}[(1-\rho)u_3+\rho v_3]^2\\
&=\frac{w_1}{2}\{(1-\rho)u_1^2+\rho v_1^2-[(1-\rho)u_1+\rho v_1]^2\}+\frac{w_2}{2}\{(1-\rho)u_1^2+\rho v_1^2-[(1-\rho)u_1+\rho v_1]^2\}\\
&\quad+\frac{w_3}{2}\{(1-\rho)u_2^2+\rho v_2^2-[(1-\rho)u_3+\rho v_3]^2\}\\
&=\frac{w_1}{2}\{\rho(1-\rho)(u_1-v_1)^2\}+\frac{w_2}{2}\{\rho(1-\rho)(u_2-v_2)^2\}+\frac{w_3}{2}\{\rho(1-\rho)(u_3-v_3)^2\}\\
&\geq 0,
\end{aligned}$$

Consequently, both conditions (IV) and (V) are satisfied, and the proof is completed.

3.2 OPTIMAL CONTROL SYSTEM CHARACTERISATION

It has been proved in Section 3.1 that there exist the optimal controls that minimise the functional (5) subject to the system dynamic (3). The necessary conditions for this control can be drive by employing the Pontryagin's Maximum Principle (PMP) (Pontryagin et al., 1962). Following PMP, the control u_1^*, u_2^* and u_3^* with equivalent states variables X^* are optimal and minimises the objective functional (5) for a fixed final time t_f, if the following conditions hold:

1. The optimality condition

$$\begin{cases}\frac{\partial H(X,u_1,u_2,u_3,\lambda)}{\partial u_1}=0\\ \frac{\partial H(X,u_1,u_2,u_3,\lambda)}{\partial u_2}=0\\ \frac{\partial H(X,u_1,u_2,u_3,\lambda)}{\partial u_3}=0\end{cases} \tag{8}$$

2. The optimal control system

$$\begin{cases}\frac{dS}{dt}=\frac{\partial H(X,u_1,u_2,u_3,\lambda)}{\partial \lambda_1}\\ \frac{dE}{dt}=\frac{\partial H(X,u_1,u_2,u_3,\lambda)}{\partial \lambda_2}\\ \frac{dI}{dt}=\frac{\partial H(X,u_1,u_2,u_3,\lambda)}{\partial \lambda_3}\end{cases}$$

3. The co-state system

$$\begin{cases} \frac{d\lambda_1}{dt} = -\frac{\partial H(X,u_1,u_2,u_3,\lambda)}{\partial S} \\ \frac{d\lambda_2}{dt} = -\frac{\partial H(X,u_1,u_2,u_3,\lambda)}{\partial E} \\ \frac{d\lambda_3}{dt} = -\frac{\partial H(X,u_1,u_2,u_3,\lambda)}{\partial I} \end{cases} \tag{9}$$

4. The minimisation conditions

$$H(X^*, u_1^*, u_2^*, u_3^*, \lambda^*) = \min_{0\le u\le 1} H(X^*, u_1, u_2, u_3, \lambda^*), \text{holds for } t \in [0, t_f].$$

5. And the transversality conditions are also holds

$$\lambda_i(t_f) = 0, \ i = 1,2,3 \tag{10}$$

With the function H (Hamiltonian function) defined as

$$\begin{aligned} H(X,u_1,u_2,u_3,\lambda) = a_1E(t) + a_2I(t) + \tfrac{w_1}{2}u_1^2(t) + \tfrac{w_2}{2}u_2^2(t) + \tfrac{w_3}{2}u_3^2(t) \\ +\lambda_1\left[\Lambda - \beta SI - \left(\mu + u_1(t)\right)S\right] \\ + \lambda_2\left[(1-p)\beta SI - kE - \left(\mu + u_2(t)\right)E\right] \\ + \lambda_3\left[p\beta SI + kE - dI - \left(\mu + u_3(t)\right)I\right] \end{aligned}$$

Theorem 2: There exist co-state variables $\lambda_1^*(t)$, $\lambda_2^*(t)$, $\lambda_3^*(t)$, given the optimal solution, S^*, E^*, I^* and associated control $u_1^*, u_2^* \text{ and } u_3^*$ that minimises $J(X,u_1,u_2,u_3)$ over Ψ, such that

$$\begin{cases} \frac{d\lambda_1}{dt} = \lambda_1^*(t)[\beta I^*(t) + \mu + u_1^*(t)] - \lambda_2^*(t)(1-p)\beta I^*(t) - \lambda_3^*(t)p\beta I^*(t) \\ \frac{d\lambda_2}{dt} = \lambda_2^*(t)[\mu + k + u_2^*(t)] - a_1 \\ \frac{d\lambda_3}{dt} = \lambda_1^*(t)\beta S^*(t) - \lambda_2^*(t)(1-p)\beta S^*(t) - \lambda_3^*(t)[p\beta S^*(t) - d - \mu - u_3^*(t)] - a_2 \end{cases} \tag{11}.$$

Together with transversality conditions

$$\lambda_i^*(t_f) = 0, \ i = 1,2,3 \tag{12}$$

Equally, the piecewise characterization of the continuous optimal control function is given as:

$$\begin{aligned} u_1^*(t) &= min\left\{max\left\{0, \frac{\lambda_1^*(t)S^*(t)}{B_1}\right\}, 1\right\} \\ u_2^*(t) &= min\left\{max\left\{0, \frac{\lambda_2^*(t)E^*(t)}{B_2}\right\}, 1\right\} \\ u_3^*(t) &= min\left\{max\left\{0, \frac{\lambda_3^*(t)I^*(t)}{B_3}\right\}, 1\right\} \end{aligned} \tag{13}$$

Proof: The co-state system (11) and the optimal control characterisation (13) are obtained from the explicit application of conditions (9) and (8) of the Pontryagin's Maximum Principle,

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respectively. The optimal control (13) is unique over an adequately short final time t_f, the Lipschitz property and boundedness of the state (3) and co-state (11) systems (3) and (9) and boundedness of the state and co-state functions (Bather et al., 1976).

The overall optimality system encompasses the system (3) and its initial conditions, the co-state system (11) along with transversality conditions (12), and the optimal control characterisation (13):

$$\begin{cases} \frac{dS}{dt} = \Lambda - \beta SI - \left(\mu + u_1(t)\right)S \\ \frac{dE}{dt} = (1-p)\beta SI - kE - \left(\mu + u_2(t)\right)E \\ \frac{dI}{dt} = p\beta SI + kE - dI - \left(\mu + u_3(t)\right)I \\ \frac{d\lambda_1}{dt} = \lambda_1^*(t)[\beta I^*(t) + \mu + u_1^*(t)] - \lambda_2^*(t)(1-p)\beta I^*(t) - \lambda_3^*(t)p\beta I^*(t) \\ \frac{d\lambda_2}{dt} = \lambda_2^*(t)[\mu + k + u_2^*(t)] - a_1 \\ \frac{d\lambda_3}{dt} = \lambda_1^*(t)\beta S^*(t) - \lambda_2^*(t)(1-p)\beta S^*(t) - \lambda_3^*(t)[p\beta S^*(t) - d - \mu - u_3^*(t)] - a_2 \\ S(0), E(0), I(0) \geq 0, \\ \lambda_i^*(t_f) = 0, \ i = 1,2,3 \\ u_1^*(t) = min\left\{max\left\{0, \frac{\lambda_1^*(t)S^*(t)}{B_1}\right\}, 1\right\} \\ u_2^*(t) = min\left\{max\left\{0, \frac{\lambda_2^*(t)E^*(t)}{B_2}\right\}, 1\right\} \\ u_3^*(t) = min\left\{max\left\{0, \frac{\lambda_3^*(t)I^*(t)}{B_3}\right\}, 1\right\} \end{cases} \quad (14)$$

4. NUMERICAL SIMULATION

In this section, numerical simulations are implemented to validate the analytic results. The epidemiological parameters used for the simulation are reflected in Table 2. The optimality system (14), is solved by employing the forward-backward sweep technique. In this technique, the state equations are first solved forward in time using an initial guess of the control variables and state variables' initial conditions. The co-state equations are solved backward in time using the values of the states and control variables from the current iteration and transversality conditions. The control variables are then updated by using the values of the states and co-states obtained from the current iteration. The process is repeated until the results converged. The initial values of the state variables are assumed to be as $S(0) = 3800$, $E(0) = 1800$ and $I(0) = 200$.

Table 2: Simulation parameters

Parameter Symbol	Value	Unit	Source
Λ	1000	person year^{-1}	(Baba et al., 2019)
μ	$\frac{1}{70}$	year^{-1}	(Castillo-chavez, 2004)
d	0.17	year^{-1}	(Gao & Huang, 2018)
β	0.003	person^{-1} year^{-1}	(Yang et al., 2016)
p	0.3	None	
κ	0.003	year^{-1}	(Castillo-chavez, 2004)

Figure 1 illustrated the trajectories of the optimal control functions, which indicated that to curtail the prevalence of the TB, both the case finding $u_2(t)$ and case holding $u_3(t)$ control efforts should be maintained at the top bound throughout the entire period of the control intervention. In Figs. 2-3, the comparison of the populations in the case with optimal control (with u_1, u_2 and u_3) and without the application of the control are depicted. Solid-blue lines identify the population without control interventions whereas the populations with optimal control are indicated with dashed-red lines. In Figure 2, the population of the susceptible to optimal control is higher than the case without control. Similarly, from Figs. 3 and 4 it is clear that the optimal control intervention is very effective as both the exposed and infected populations are successfully contained.

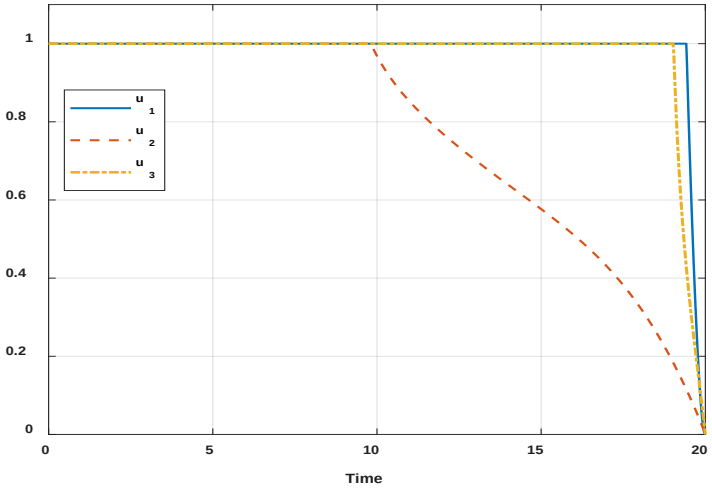

Figure 1: Profiles of the optimal control functions. Weight constants $a_1 = 100, a_2 = 100, w_1 = 1000, w_2 = 500$ and $w_3 = 500$.

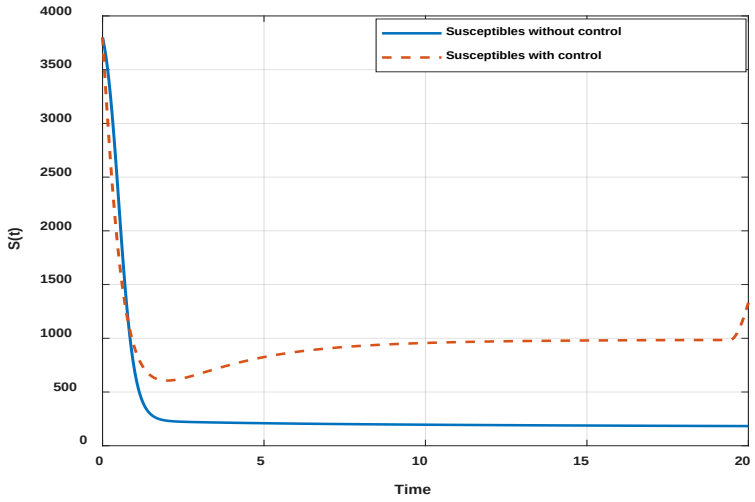

Figure 2: Significance of the optimal control of the susceptible population.

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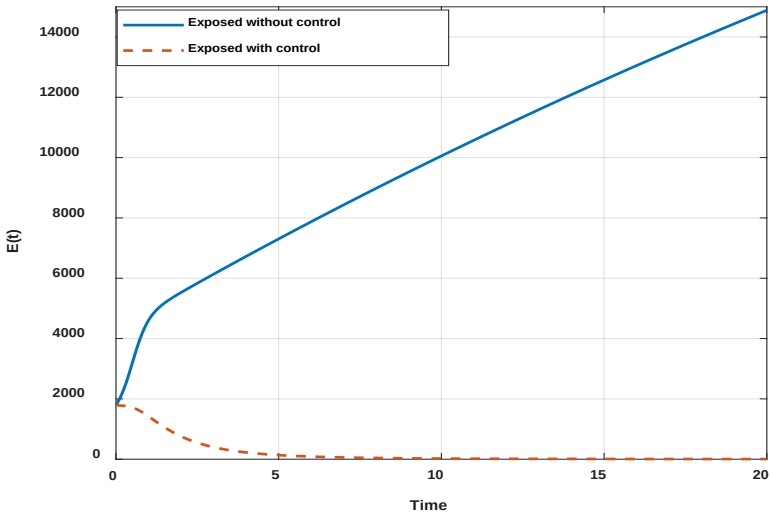

Figure 3: Significance of the optimal control of the exposed population.

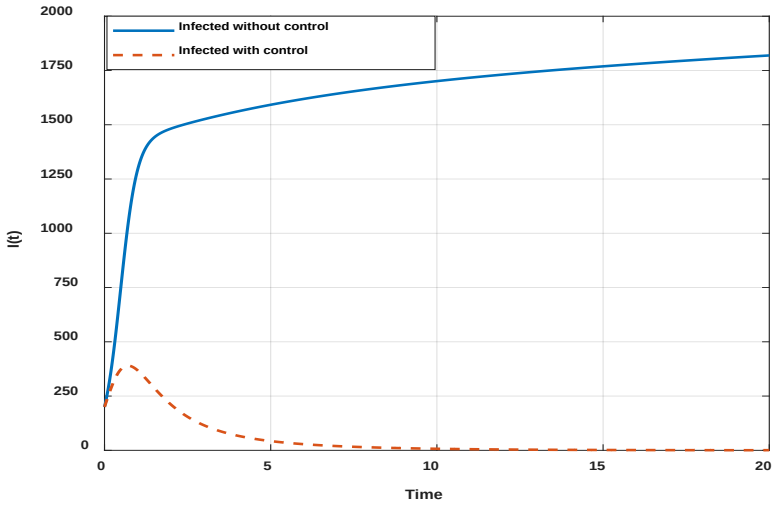

Figure 4: Significance of the optimal control of the infected population.

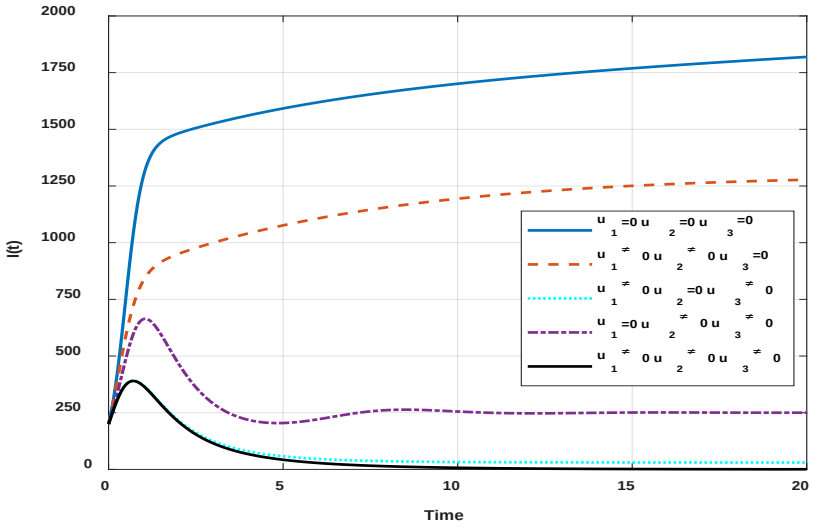

Figure 5: Infected population trajectory under different control strategies.

Figure 5 illustrates the effects of different control strategies on the infected group. It can be

vividly seen that the best performance is achieved by considering the three controls simultaneously. The least performance occurs when only u_1 *and* u_2 are considered. From the numerical result at the final time, the total number of the infected without control is approximately 1820, and 0 when all the three control interventions are considered simultaneously.

5. COST-EFFECTIVENESS ANALYSIS

This section discussed the cost-effectiveness analysis, using an incremental cost-effectiveness ratio (ICER), as described in (Tilahun et al., 2017). The investigation is performed to identify the most suitable control strategy that balances the stringent needs of the control actions and the need to minimise the cost of implementation of the control interventions compared to other policies. An ICER gives a degree of the economic value of a particular intervention strategy in comparison to alternative approaches. ICER is computed as a ratio of incremental cost (difference in costs between two strategies) to incremental effect (difference in a total number of prevented incidences) (York, 2016).

As illustrated in Table 3, four control strategies are considered, with at least two control interventions in each (considering that single intervention is not reliable in eradicating the disease). These strategies are compared pairwise. The total cost of each strategy is assumed to be equal to the objective function cost value associated with it. Moreover, the total number of prevented cases for each strategy is estimated by subtracting the number of infected populations with control from those without control at the final time.

Comparing the cost-effectiveness of strategies, I and II,

$$ICER(I) = \frac{41435}{542} = 76$$

$$ICER(II\ wth\ repect\ to\ I) = \frac{(41435-80013)}{(542-1790)} = 31$$

Which indicated that strategy II (with less ICER) is more effective compared to strategy I. Next strategy II is compared with strategy III as follows:

$$ICER(II) = \frac{80013}{1790} = 45$$

$$ICER(III\ with\ respect\ to\ II) = \frac{(80013-31953)}{(1790-1568)} = 216$$

Similarly, a comparison between strategies II and III revealed that strategy II is more effective. Finally, by comparing strategies II and IV, strategy IV with ICER of -2203 appeared to be the best among all the four strategies.

Table 3: comparison of the control's combination

Controls Strategies	Infected populations at final time $I(t_f)$	Number of cases saved at t_f	Objective cost function value (J)
No control	1820	NA	NA
Strategy I (u_1 *and* u_2)	1278	542	41435
Strategy II (u_1 *and* u_3)	30	1790	80013
Strategy III (u_2 *and* u_3)	252	1568	31953
Strategy IV (u_1, u_2 *and* u_3)	0	1820	13917

6. CONCLUSION

The study proposed the potential application of optimal control theory and cost-effectiveness

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analysis for a tuberculosis model with slow and fast progression. For this purpose, a basic TB model is modified by adding three optimal control functions representing vaccination, case finding and case holding control interventions. The objective of the control is to reduce or eliminate the prevalence of TB in both the latent and active classes, while simultaneously minimizing the cost of executing the control intervention. The uniqueness and existence of the resulting optimal control model have been proved using Pontryagin's Maximum Principle. Numerical simulations were conducted using the fourth-order Runge Kutta method to validate the analytical results. Moreover, different control strategies were proposed, and their economic value and effectiveness were investigated using the incremental cost-effectiveness ratio. The optimal control results indicated how the use of effective control strategies would help in eradicating the disease. Also, the cost-effectiveness analysis implies that the best way to curtail the epidemic is to implement the three control interventions concurrently. The study can serve as a reliable tool to inform practical disease management strategies.

7. AVAILABILITY OF DATA AND MATERIAL

The code can be made available upon reasonable request to the corresponding author.

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