Received <day> <Month>, <year>; | Revised <day> <Month>, <year>; | Accepted <day> <Month>, <year>

DOI: xxx/xxxx

ARTICLE TYPE

Optimal Control for a Tuberculosis Model with Exogenous Reinfection under the Influence of Stigma.

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Often described as the world's most deadly infectious disease, Tuberculosis remains a serious health threat in many parts of the world, especially in the developing countries. One of the social barriers hindering TB patients to seek and complete medical attention is stigmatization. In this study, we incorporated stigmatization on a model published by Feng et al. last 2000. We obtained the basic reproduction number and showed conditions where multiple endemic equilibrium will exist depending on a reinfection threshold. The model predicted a significant increase in the basic reproduction number as the level of stigmatization increases. We used optimal control theory to investigate the effect of controls to combat stigmatization and compare these controls with the usual controls such as improving treatment and minimizing reinfection. Simulations show that although stigmatization controls are helpful, they are not enough to successfully control the disease. A combination of all the controls will be ideal and some optimal rates of doing it over time are given, depending on the perceived cost of implementation.

KEYWORDS:
Tuberculosis; Stigma ; Exogeneous Reinfection

1 | INTRODUCTION

Tuberculosis (TB) is a communicable disease caused by Mycobacterium tuberculosis which is transmitted from one person to another. According to the 2020 World Health Organization global TB report (16), there was a cumulative reduction in the TB incidence rate and the number of TB deaths of 9% and 14%, respectively, from 2015 and 2019. In 2018 and 2019, there was an increased of 14.1 and 6.3 million of people given TB treatment and TB preventive treatment, respectively. However, these progress are insufficient and in fact, far from what is needed to reach global TB targets. As such, Tuberculosis remains a serious health threat in many parts of the world, especially in developing countries.

Early diagnosis with a follow-up treatment is seen to be a key ingredient in stopping the progression of the disease that let most patients live a normal life afterwards. However, completely eradicating the disease remains a big challenge. One of the commonly identified barriers contributing to delayed diagnosis and non-adherence to treatment is stigmatization (2, 10, 14). The World Health Organization has described it as a 'hidden' burden of the disease (9). Tuberculosis is stigmatized mainly because of the perceived risk of transmission as well as being associated with poverty, malnutrition and HIV (2). As a result, people affected by Tuberculosis suffered not only from the agony of the disease but also from social isolation and avoidance, verbal abuse, discrimination, and even neglect from family (9). Hence, stigmatization may greatly influence their health-seeking behavior which may lead to the increase in the spread of the disease.

Optimal control for TB systems was studied in various articles including models with reinfection (11, 1), exogenous reinfection (5), two-strains (6), and undetected cases (8). Since it is impossible to give a comprehensive list, we refer to the review (12) and the references therein. Notwithstanding the widely use of optimal control theory in the TB models and various studies examining Tb-associated stigma and its consequences, the investigation of intervention strategies minimizing stigma on TB has not been extensively reviewed and even the formulation of tuberculosis model with stigmatization is not given enough attention. It is clearly evident that neglecting stigmatization is not a good idea because of its significant role in the effectiveness of TB control measures (13). Hence, we focus our study on the impact of stigmatization and on investigating intervention strategies to minimize stigmatization using optimal control theory. Along with treatment and reinfection controls, we consider anti-stigmatization controls that encourage TB-infected individuals to seek and complete medication. The goal of our control strategies is to minimize the number of exposed and infectious individuals with the minimum implementation cost of the control measures. We base our model on Feng et al. (4), which describe the transmission dynamics of TB with exogenous reinfection. To the best of our knowledge, this study is the first to consider stigmatization in a mathematical model with the presence of exogenous reinfection and apply optimal control theory.

2 | MATHEMATICAL MODEL

2.1 | Description of the Model

The model from (4) serves as our base model. It describes the transmission of TB with exogenous reinfection. Here, we further divide the active infected compartment into two, namely, the infectious and willing to seek medical attention and the infectious but not willing to seek medical attention due to the stigmatization of TB. The entire population is classified into five classes: susceptible (S), exposed (E), infectious and willing to seek medical attention (I_S), infectious but not willing to be treated (I_N) and those under treatment or already treated (T). We denote by N the total population, that is, $N = S + E + I_S + I_N + T$ and I the total active infected, that is, $I = I_S + I_N$. We assume that an individual can be infected only through contacts with active infected individuals. Recovered and infected but not infectious individuals are classified into a single class of exposed individuals because TB bacteria cannot be completely removed from the patient's body after treatment. Hence, we assume that previously infected individuals have no permanent immunity to TB, that is, previously infected individuals can lose their immunity and become infectious at some stage. We further assume that the natural death rate $u > 0$ and the recruitment rate $\Lambda > 0$ is given such that $\mu < \Lambda$. The level of exogeneous reinfection p is in the interval $(0, 1)$. The rest of the parameters are assumed to be nonnegative.

The dynamics is governed by the following system of ordinary differential equations:

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - \beta c S\frac{I}{N} - \mu S\\
\frac{dE}{dt} &= \beta c S\frac{I}{N} - p\beta c E\frac{I}{N} - (\mu + k)E + \sigma\beta c T\frac{I}{N}\\
\frac{dI_S}{dt} &= \alpha p\beta c E\frac{I}{N} + \alpha k E - (\mu + r + d)I_S\\
\frac{dI_N}{dt} &= (1-\alpha)p\beta c E\frac{I}{N} + (1-\alpha)kE - (\mu + d)I_N\\
\frac{dT}{dt} &= rI_S - \sigma\beta c T\frac{I}{N} - \mu T
\end{aligned} \tag{1}$$

The parameters are described in Table 1 and taken from (4), except the level of stigmatization $(1-\alpha) \in [0, 1]$. Here, $1-\alpha = 0$ means all active infected are seeking medical attention, while $1 - \alpha = 1$ means no one is seeking medical treatment.

2.2 | Model Analysis

For system (1), it can be checked that $\mathbb{R}^5_+$ is positively invariant. Moreover, adding the equations in system (1), we have

$$\frac{dN(t)}{dt} = \Lambda - \mu N(t) - dI(t).$$

Parameter	Description	Value
Λ	recruitment rate	588 humans/year
βc	transmission rate from S to E	2 /year
σ	reduction of reinfection rate from T	0.9 (dimensionless)
μ	natural death rate	0.0235 /year
k	progression rate from E to I	0.0294 /year
d	disease-induced death rate	0.05 /year
r	treatment rate	0.2906 /year
p	level of exogenous reinfection	0.4 (dimensionless)
$1-\alpha$	level of stigmatization	[0,1] (dimensionless)

TABLE 1 Model parameters

Note that $\frac{dN(t)}{dt} < 0$ for $N > \frac{\Lambda}{\mu}$. Hence, the set

$$\Omega = \left\{ (S, E, I_s, I_N, T) \in \mathbb{R}^5_+ \mid S + E + I_S + I_N + T \leq \frac{\Lambda}{\mu} \right\}$$

is also positively invariant. It can be easily seen that system (1) has a unique solution in Ω given that the initial condition is in Ω.

2.2.1 | Basic Reproduction Number

To find the disease-free equilibrium (DFE) point of system (1), we set the right-hand side of the system to zero. Since $I_{S_0} = I_{N_0} = E_0 = 0$ at the disease-free equilibrium, from the first and last equation, we have

$$S^* = \frac{\Lambda}{\mu} \qquad \text{and} \qquad T^* = 0.$$

Hence, the system has the disease-free equilibrium point given by $P_0 = \left(\frac{\Lambda}{\mu}, 0, 0, 0, 0\right)$.

Theorem 1. *The basic reproduction number of system (1) is given by*

$$R_0 = \frac{\beta c \alpha k}{(\mu + k)(\mu + r + d)} + \frac{\beta c (1-\alpha) k}{(\mu + k)(\mu + d)}.$$

Proof. We compute the basic reproduction number R_0 using the Next Generation Matrix approach (15, 3). Considering that the infected compartments are E, I_S and I_N, we let

$$\mathcal{F} = \begin{pmatrix} \beta c S \frac{I}{N} + \sigma \beta c T \frac{I}{N} \\ \alpha p \beta c E \frac{I}{N} \\ (1-\alpha) p \beta c E \frac{I}{N} \end{pmatrix}$$

and

$$\mathcal{V} = \begin{pmatrix} p \beta c E \frac{I}{N} + (\mu + k) E \\ -\alpha k E + (\mu + r + d) I_S \\ -(1-\alpha) k E + (\mu + d) I_N, \end{pmatrix}$$

where $\mathcal{F}$ is the vector of new infection rates and $\mathcal{V}$ is the vector of all the other rates. The Jacobian matrix of $\mathcal{F}$ and $\mathcal{V}$ evaluated at P_0 are given by the following matrices:

$$F = \begin{pmatrix} 0 & \beta c & \beta c \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix},$$

$$V = \begin{pmatrix} \mu + k & 0 & 0 \\ -\alpha k & \mu + r + d & 0 \\ -(1-\alpha) k & 0 & \mu + d \end{pmatrix}.$$

Then, $V^{-1} = \begin{pmatrix} \frac{1}{\mu+k} & 0 & 0 \\ \frac{\alpha k}{(\mu+k)(\mu+r+d)} & \frac{1}{\mu+r+d} & 0 \\ \frac{(1-\alpha)k}{(\mu+k)(\mu+d)} & 0 & \frac{1}{\mu+d} \end{pmatrix}$ *and*

$$FV^{-1} = \begin{pmatrix} \frac{\beta c \alpha k}{(\mu+k)(\mu+r+d)} + \frac{\beta c(1-\alpha)k}{(\mu+k)(\mu+d)} & \frac{\beta c}{\mu+r+d} & \frac{\beta c}{\mu+d} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}$$

is the Next Generation Matrix of our system. Computing for the dominant eigenvalue of FV^{-1}*, we have*

$$R_0 = \frac{\beta c \alpha k}{(\mu + k)(\mu + r + d)} + \frac{\beta c(1 - \alpha)k}{(\mu + k)(\mu + d)}. \tag{2}$$

□

The two terms in (2) show the contribution of those infected and willing to seek medical attention and those infected but are not seeking medical attention due to stigmatization, to the basic reproduction number.

From (2), we can readily see the value of reducing stigmatization. Observe that the first term corresponding to those willing to seek medical attention has an extra term r, the treatment rate, that can decrease the value of R_0.

By computing the eigenvalues of the Jacobian matrix of our system, we can deduce that the disease-free equilibrium P_0 is locally asymptotically stable when $R_0 < 1$ and unstable when $R_0 > 1$.

2.3 | Existence of Endemic Equilibrium Point(s)

For our base model (without stigmatization), Feng et.al. (4) showed that multiple endemic equilibria could exist depending on the value of the level of exogenous reinfection p. Here, we show that it is still the case even if we add stigmatization.

To simplify our analysis, in the following theorem we only consider the case when $d = 0$ and $\sigma = 1$.

Theorem 2. *Let* $\alpha \in [0, 1]$ *and* $p_0 = \frac{(1+Q)D}{1-D}$*, where* $D = \frac{k}{\mu+k}$ *and* $Q = \frac{k}{\mu+r}\frac{\mu+r(1-\alpha)}{\mu}$*. Then, we have the following:*

a) If $R_0 > 1$*, then system (1) has exactly one endemic equilibrium.*

b) If $R_0 < 1$ *and* $p > p_0$*, then for each given p there exists a positive constant* $R_p < 1$ *such that system (1) has exactly two endemic equilibria if* $R_0 > R_p$*; only one endemic equilibrium if* $R_0 = R_p$*; and no endemic equilibrium if* $R_0 < R_p$*.*

c) If $R_0 < 1$ *and* $p \leq p_0$*, then system (1) has no endemic equilibrium.*

Proof. Let $x = \frac{I^*}{N^*}$*. We want to find* $(S^*, E^*, I_S^*, I_N^*, T^*)$ *such that* $I^* = I_S^* + I_N^* > 0$*. Then, system (1) has the following endemic equilibrium point(s):*

$$\begin{aligned} S^* &= \frac{\Lambda}{\beta c x + \mu} \\ E^* &= \frac{\Lambda x(\mu + r)}{(\mu + r(1 - \alpha))(p\beta c x + k)} \\ I_S^* &= \frac{x\Lambda\alpha}{\mu + r(1 - \alpha)} \\ I_N^* &= \frac{(\mu + r)(1 - \alpha)}{\mu + r(1 - \alpha)} \frac{x\Lambda}{\mu} \\ T^* &= \frac{rx\Lambda\alpha}{(\mu + r(1 - \alpha))(\beta c x + \mu)}. \end{aligned}$$

By using the definition of R_0 *and noting that* $S^* + E^* + I_S^* + I_N^* + T^* = N^* = \frac{\Lambda}{\mu}$*, we get*

$$Ax^2 + Bx + C = 0 \tag{3}$$

where

$$A = pR_0$$

$$B = (1 + p + Q)D - pR_0$$
$$C = DQ\left(\frac{1}{R_0} - 1\right).$$

The solution is given by

$$x_{1,2} = \frac{-B \pm \sqrt{B^2 - 4AC}}{2A}.$$

We will now describe the solution in terms of p and R_0.

(*a*) *Suppose that* $R_0 > 1$. *Then,* $A > 0$ *and* $C < 0$. *Thus,* $B^2 + 4AC > 0$ *and hence, (3) has exactly one positive solution. Thus, system (1) has exactly one endemic equilibrium.*

(*b*) *Suppose that* $R_0 < 1$ *and* $p > p_0$. *Then, we can derive*

$$R_p = \frac{D(1 + p - Q)}{p} + \frac{2}{p}\sqrt{DQ(p - pD - D)}$$

such that $B^2 - 4AC > (= or <)0$ *if* $R_0 > (= or <)R_p$. *Using* p_0, *it can be checked that* $R_p < 1$ *for* $p > p_0$. *It follows that* (1) *has two (one or none) endemic equilibrium if* $R_0 > (= or <)R_p$.

(*c*) *Suppose that* $R_0 < 1$ *and* $p \leq p_0$. *Then* $AC > 0$ *and* $B > 0$. *Hence,* (3) *has no positive solution and thus,* (1) *has no endemic equilibrium.* □

3 | OPTIMAL CONTROL

3.1 | *Choice of controls*

We consider four control strategies where the first two, are controls to combat stigmatization. First, is the control minimizing the proportion of individuals going to the I_N *compartment from E, denoted by* $u_1(t)$. *Second is the control of encouraging infected people who are unwilling to get treated (in* I_N*) to change their views (to* I_S*), denoted by* $u_2(t)$. *These anti-stigmatization controls can be possibly done by advertising the positive effect of getting medically treated and downplaying the negative social connotation of being a TB patient. Another way of doing this is by directly giving money to infected people to support them and their families during the treatment. Although this method could be quite costly for the government, it may prove very effective in convincing the poor patients to seek and finish medical treatment. Examples of intervention strategies to reduce stigmatization that are applied in some communities are discussed in (2).*

The third control is increasing the treatment rate denoted by $u_3(t)$. *This could be done by increasing the budget for tuberculosis treatment. The fourth and last control minimizes the reinfection from the treated (T) compartment, denoted by* $u_4(t)$. *This control includes efforts to shield the treated population against re-exposure from TB and their own efforts to boost their immune system.*

For any time $t \geq 0$, *the controls are in the interval* $[0, 1]$, *where* 0 *means the control is not implemented at all, and* 1 *means the full implementation of the control.*

Our system with the controls is given by

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - \beta c S\frac{I}{N} - \mu S\\
\frac{dE}{dt} &= \beta c S\frac{I}{N} - p\beta c E\frac{I}{N} - (\mu + k)E + (1 - u_4(t))\sigma\beta c T\frac{I}{N}\\
\frac{dI_S}{dt} &= (1 + u_1(t))\alpha p\beta c E\frac{I}{N} + (1 + u_1(t))\alpha k E - (\mu + (1 + u_3(t))r + d)I_S + u_2(t)I_N\\
\frac{dI_N}{dt} &= (1 - (1 + u_1(t))\alpha)p\beta c E\frac{I}{N} + (1 - (1 + u_1(t))\alpha)kE - (\mu + d)I_N - u_2(t)I_N\\
\frac{dT}{dt} &= (1 + u_3(t))rI_S - (1 - u_4(t))\sigma\beta c T\frac{I}{N} - \mu T\\
\frac{dN}{dt} &= \Lambda - \mu N - dI,
\end{aligned}$$

where we add the total population N as the sixth variable.

3.2 | Pontryagin's Maximum Principle

We aim to minimize the number of exposed and infected individuals with the minimum implementation cost of the control measures. The objective function to be minimized is given by

$$J(u_1, u_2, u_3, u_4) = \int_{t_0}^{t_f} \left(E(t) + I_N(t) + I_S(t) + \sum_{i=1}^{4} \frac{C_i}{2} u_i^2(t) \right) dt$$

and the corresponding Hamiltonian H is given by

$$H = E(t) + I_N(t) + I_S(t) + \sum_{i=1}^{4} \frac{C_i}{2} u_i^2(t) + \sum_{i=1}^{6} \lambda_i g_i,$$

where g_i is the right hand side of the differential equation of the ith state variable. It is assumed that the controls are quadratic functions to incorporate nonlinear societal cost associated with the implementation of the control measures.

Applying Pontryagin's Maximum Principle, there exist adjoint variables $\lambda_1, ..., \lambda_6$ which satisfy the following system of ordinary differential equations

$$\begin{aligned}
\frac{\partial \lambda_1}{\partial t} =& \lambda_1 \left(\frac{\beta c I(N-S)}{N^2} + \mu \right) - \lambda_2 \left(\frac{\beta c I(N-S) + p\beta c E I - (1-u_4(t))\sigma \beta c T I}{N^2} \right) \\
&+ \lambda_3 \left(\frac{(1+u_1(t))\alpha p \beta c E I}{N^2} \right) + \lambda_4 \left(\frac{(1-(1+u_1(t))\alpha) p \beta c E I}{N^2} \right) \\
&- \lambda_5 \left(\frac{(1-u_4(t))\sigma \beta c T I}{N^2} \right) + \lambda_6 \mu \\
\frac{\partial \lambda_2}{\partial t} =& -1 - \lambda_1 \left(\frac{\beta c S I}{N^2} \right) + \lambda_2 \left(\frac{\beta c I(S + (1-u_4(t))\sigma T + p\beta c I(N-E)}{N^2} + u + k \right) \\
&- \lambda_3 \left(\frac{(1+u_1(t))\alpha p \beta c I(N-E)}{N^2} + (1+u_1(t))\alpha k \right) \\
&- \lambda_4 \left[(1-(1+u_1(t))\alpha) \left(k + \frac{p\beta c I(N-E)}{N^2} \right) \right] - \lambda_5 \left(\frac{(1-u_4(t))\sigma \beta c T I}{N^2} \right) + \lambda_6 \mu \\
\frac{\partial \lambda_3}{\partial t} =& -1 + \lambda_1 \left(\frac{\beta c S(N-I)}{N^2} \right) - \lambda_2 \left(\frac{(\beta c S - p\beta c E + (1-u_4(t))\sigma \beta c T)(N-I)}{N^2} \right) \\
&- \lambda_3 \left(\frac{(1+u_1(t))\alpha p \beta c E(N-I)}{N^2} - (u + (1+u_3(t))r + d) \right) \\
&- \lambda_4 \left(\frac{(1-(1+u_1(t))\alpha) p \beta c E(N-I)}{N^2} \right) \\
&- \lambda_5 \left((1+u_3(t))r - \frac{(1-u_4(t))\sigma \beta c T(N-I)}{N^2} \right) + \lambda_6(\mu + d) \\
\frac{\partial \lambda_4}{\partial t} =& -1 + \lambda_1 \left(\frac{\beta c S(N-I)}{N^2} \right) - \lambda_2 \left(\frac{(\beta c S - p\beta c E + (1-u_4(t))\sigma \beta c T)(N-I)}{N^2} \right) \\
&- \lambda_3 \left(\frac{(1+u_1(t))\alpha p \beta c E(N-I)}{N^2} + u_2(t) \right) + \lambda_4 \left(\frac{(1-(1+u_1(t))\alpha) p \beta c E(I-N)}{N^2} + \mu + d + u_2(t) \right) \\
&+ \lambda_5 \left(\frac{(1-u_4(t))\sigma \beta c T(N-I)}{n^2} \right) + \lambda_6(\mu + d)
\end{aligned}$$

$$\frac{\partial \lambda_5}{\partial t} = -\lambda_1\left(\frac{\beta c S I}{N^2}\right) - \lambda_2\left(\frac{-\beta c S I + p\beta c E I + (1-u_4(t))\sigma\beta c I(N-T)}{N^2}\right) + \lambda_3\left(\frac{(1+u_1(t))\alpha p\beta c E I}{N^2}\right) + \lambda_4\left(\frac{(1-(1+u_1(t))\alpha)p\beta c E I}{N^2}\right) + \lambda_5\left(\frac{(1-u_4(t))\sigma\beta c I(N-T)}{N^2} + \mu\right) + \lambda_6\mu$$

$$\frac{\partial \lambda_6}{\partial t} = -\lambda_1\left(\frac{\beta c S I}{N^2}\right) + \lambda_2\left(\frac{\beta c S I - p\beta c E I + (1-u_4(t))\sigma\beta c T I)}{N^2}\right) + \lambda_3\left(\frac{(1+u_1(t))\alpha p\beta c E I}{N^2}\right) + \lambda_4\left(\frac{(1-(1+u_1(t))\alpha)p\beta c E I}{N^2}\right) - \lambda_5\left(\frac{(1-u_4(t))\sigma\beta c T I}{N^2}\right) + \lambda_6\mu,$$

with transversality conditions $\lambda_i(t_f) = 0$, for $i = 1, ..., 6$. Moreover, the controls are given in the following theorem.

Theorem 3. *The optimal control variables are given by*

$$\begin{aligned}
u_1(t) &= \min\left(1, \max\left(0, \frac{(\lambda_4-\lambda_3)\left(\alpha p\beta c E\frac{I}{N} + \alpha k E\right)}{C_1}\right)\right)\\
u_2(t) &= \min\left(1, \max\left(0, \frac{(\lambda_4-\lambda_3)I_N}{C_2}\right)\right)\\
u_3(t) &= \min\left(1, \max\left(0, \frac{(\lambda_3-\lambda_5)rI_S}{C_3}\right)\right)\\
u_4(t) &= \min\left(1, \max\left(0, \frac{(\lambda_2-\lambda_5)\sigma\beta c T I}{NC_4}\right)\right).
\end{aligned}$$

Proof. Optimal controls u_1, u_2, u_3 and u_4 are derived from the following optimality conditions:

$$\begin{aligned}
\frac{\partial H}{\partial u_1(t)} &= C_1u_1(t) + (\lambda_3-\lambda_4)\left(\alpha p\beta c E\frac{I}{N} + \alpha k E\right) = 0\\
\frac{\partial H}{\partial u_2(t)} &= C_2u_2(t) + (\lambda_3-\lambda_4)I_N = 0\\
\frac{\partial H}{\partial u_3(t)} &= C_3u_3(t) + (\lambda_5-\lambda_3)rI_S = 0\\
\frac{\partial H}{\partial u_4(t)} &= C_4u_4(t) + (\lambda_5-\lambda_2)\left(\sigma\beta cT\frac{I}{N}\right) = 0.
\end{aligned}$$

□

4 | SIMULATIONS

4.1 | Parameter Values

The values of the parameters used in the following simulations are given in Table 1 . The values for the parameters μ, k, d, and r are from (7), while the values for Λ, σ, and p are from (4). We also based on (4) our choice for the initial conditions: $S(0) = 18000$, $E(0) = 5500$, $I_S(0) = 700$, $I_N(0) = 400$, and $T(0) = 400$. The parameters β and c are separate parameters in (4), denoting the average numbers of susceptible infected by one infectious individual per contact per unit of time and the per-capita contact rate, respectively. But one may interpret the product βc as just the transmission rate from S to E. Its value in Table 1 is just an estimate to have an R_0 of around 3 for the base model. In our simulations, we vary the level of stigmatization. We choose the values $\alpha = 0.3, 0.5, 0.7$ to represent high, medium, and low levels of stigmatization, respectively. Due to lack of data to differentiate the cost of the controls, we assume that $C_1 = C_2 = C_3 = C4$. But, we note that governments or implementing agencies have different capacities. For example rich countries may find implementing all of the controls very cheap while developing countries may find it very costly. We use the values 10, 10^2, and 10^3 to

denote low, medium, and high perception of the cost of implementing the controls, respectively. Moreover, in the optimal control simulations we have the following lower and upper bounds for the controls: $0.01 \leq u_1 \leq \frac{1-\alpha}{\alpha}$, $0.01 \leq u_2 \leq 0.9$, $0.01 \leq u_3 \leq \frac{1-r}{r}$, *and* $0.01 \leq u_4 \leq 0.9$. *This is because, we let the controls* u_1 *and* u_3 *increase the values of the parameters* α *and* r *up to twice its given values, but not greater than* 1.

4.2 | The Effect of Stigmatization

We simulate the effect of stigmatization by varying the values of α *in system (1). The results are given in Figure 1 and Table 2 .*

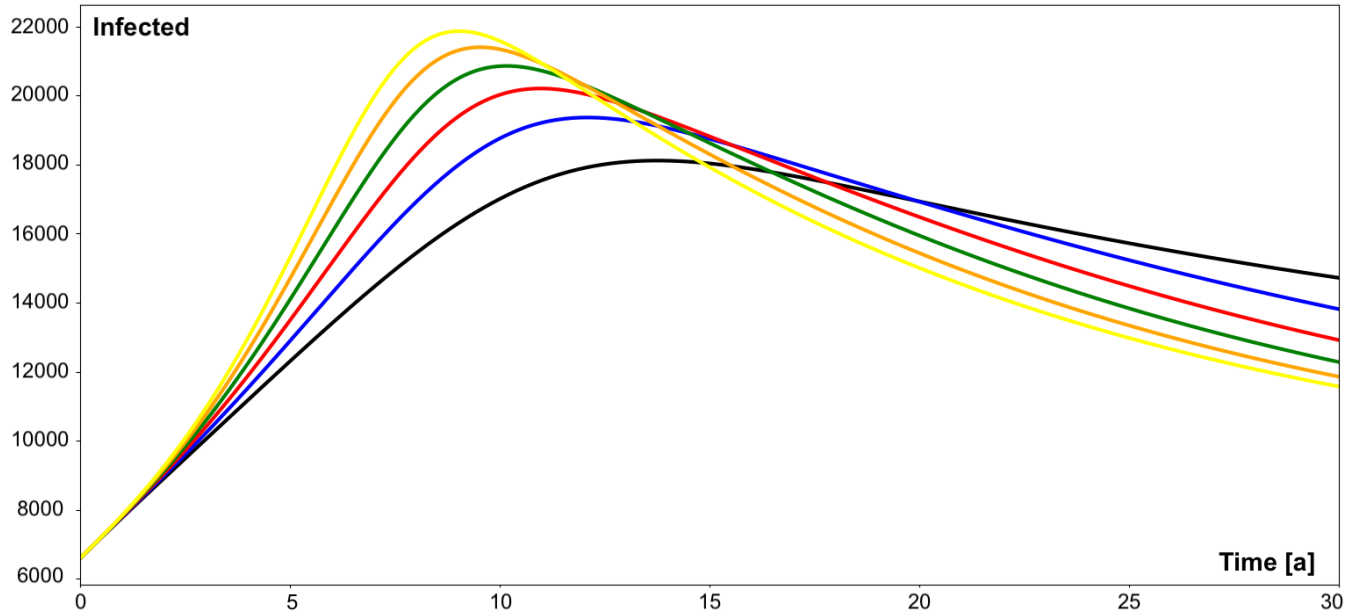

FIGURE 1 The total infected $(E + I_S + I_N)$ over time. The curves with colors black, blue, red, green, orange, and yellow are for the simulations with values of α equal to 1, 0.8, 0.6, 0.4, 0.2, and 0, respectively.

	Level of Stigmatization $(1-\alpha)$					
	0	**0.2**	**0.4**	**0.6**	**0.8**	**1**
R_0	3.053	5.467	7.88	10.295	12.709	15.123
Time of Peak *(year)*	13.7	12.1	10.9	10.1	9.5	9
At $t = 30$ $(year)$						
E	7317	3397	1825	1184	896	739
I_S	7356	4621	2232	1005	378	0
I_N	44	5792	8858	10088	10578	10829
$E + I_S + I_N$	14717	13810	12915	12277	11852	11568
T	2892	1107	449	187	67	0

TABLE 2 The effect of the various levels of stigmatization in the dynamics of the TB model (1).

4.3 | Optimal Controls

In these simulations, we seek optimal controls u_1, u_2, u_3, and u_4 considering the perceived cost of implementing all of the controls and the level of stigmatization. A bigger value for the control weights C_i, $i = 1, ..., 4$, means a higher perception on the cost of implementing the controls. Which means the government or implementing agency is having a hard time implementing the controls. On the other hand, a bigger value for α means a lesser stigmatization. The results are given in Figure 2 and Table 3 .

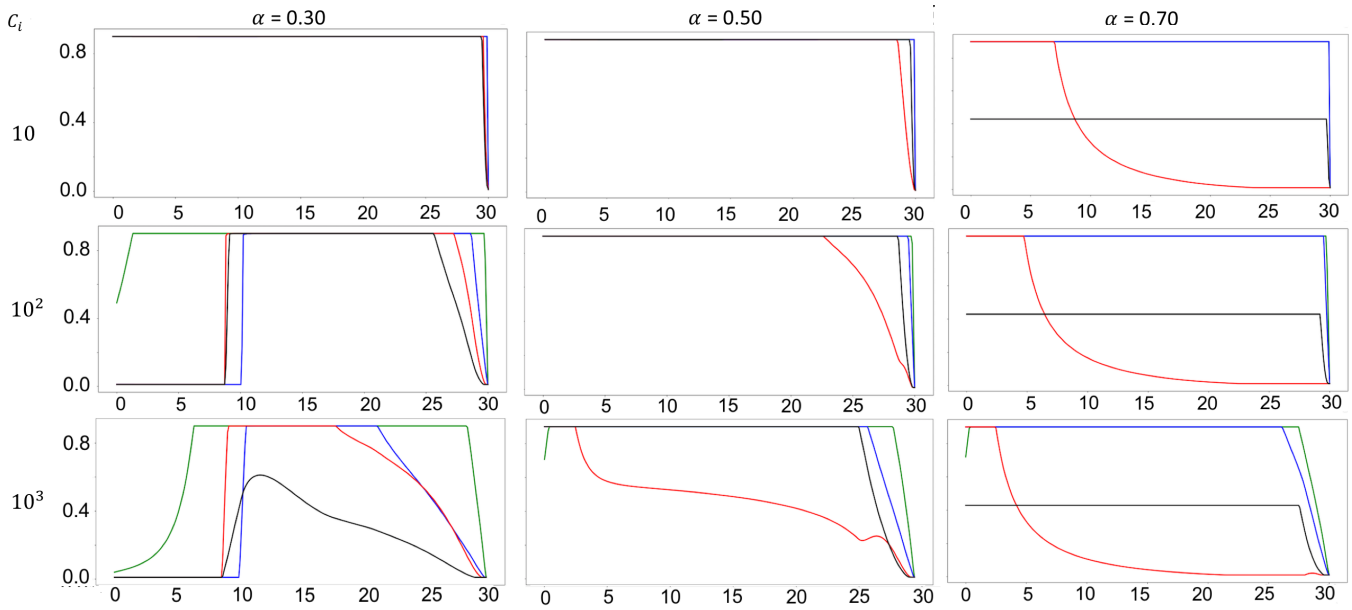

FIGURE 2 Optimal controls. Each block shows the optimal controls obtained for a particular value of all the $C_i's$ and a particular value of α. For each graph, the y-axis represents the control rate from 0 to 1 and the x-axis represents the time in years. The simulations are up to 30 years. The curves black, red, blue, and green, are for the controls u_1, u_2, u_3, and u_4, respectively.

$At\ t = 30\ (year)$		No Control	With Controls and Weights $C_i, i = 1,2,3,4$		
			$C_i = 10$	$C_i = 10^2$	$C_i = 10^3$
$\alpha = 0.30$	E	1015	7539	3727	4448
	I_S	645	743	183	258
	I_N	10383	313	211	467
	Total	12043	8595	4121	5173
$\alpha = 0.50$	E	1437	7587	7629	8345
	I_S	1510	592	546	679
	I_N	9619	81	206	607
	Total	12566	8260	8381	9631
$\alpha = 0.70$	E	2433	7477	7508	8039
	I_S	3253	597	594	724
	I_N	7644	18	58	201
	Total	13330	8092	8160	8964

TABLE 3 The values of the infected compartments at $t = 30$ for the various combination of control cost and level of stigmatization.

4.4 | *Stigma Controls vs Treatment and Reinfection Controls*

We want to answer if the stigma controls (u_1 and u_2) are enough to curb the transmission of TB and if the controls are better compared to the other controls (treatment control u_3 and reinfection control u_4). In all the simulations, we use $C_i = 10$, for $i = 1, 2, 3, 4$ (low cost) and $\alpha = 0.7$ (low level of stigmatization). The results are given in Figure 3 and Table 4 .

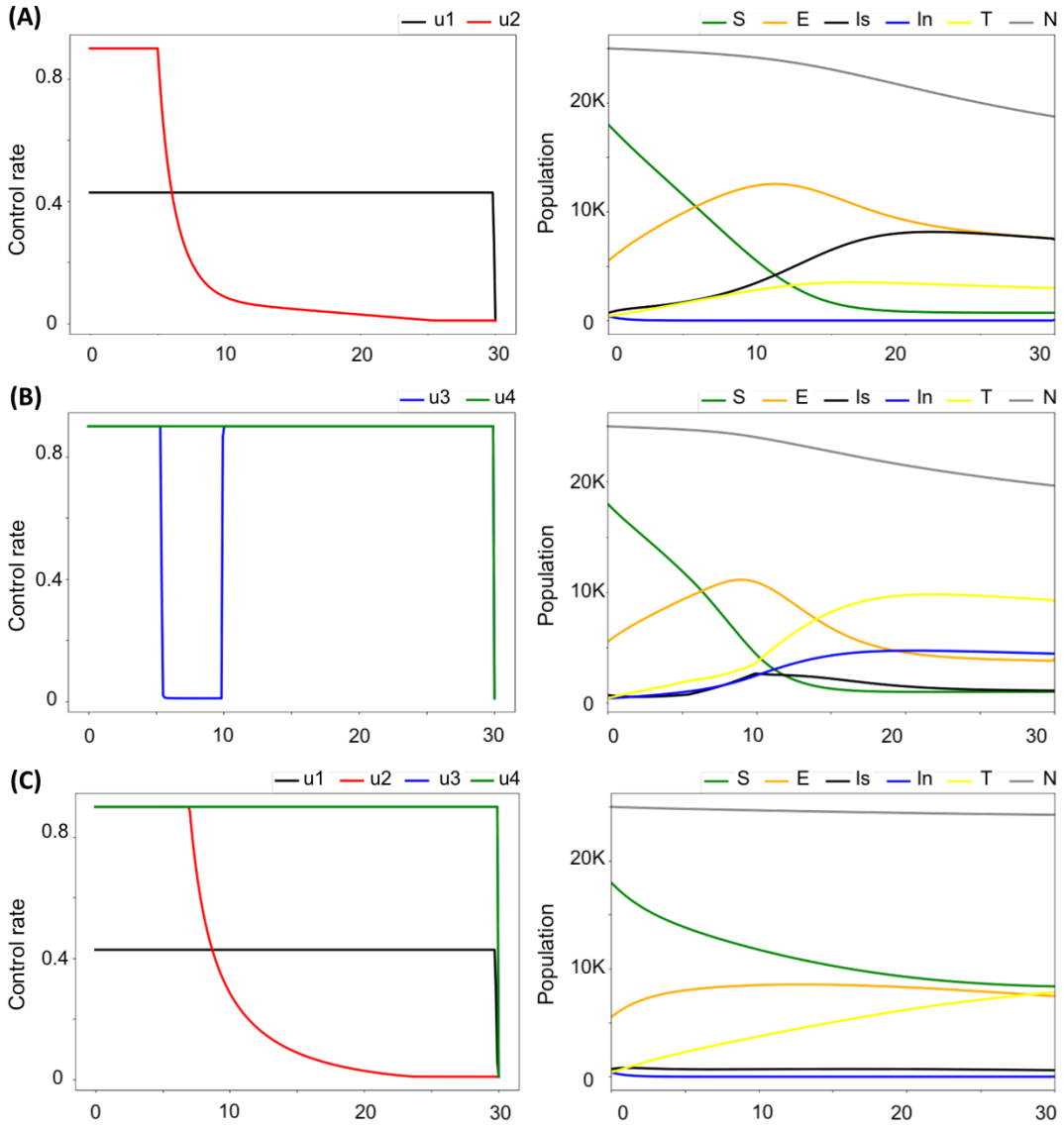

FIGURE 3 For (A), (B), and (C), the graphs on the right are for the controls while the graphs on the left are for the compartments over time. In (A), we simulate having the stigma controls only, while in (B) having the other controls only. In (C), we simulate having all of the controls.

5 | DISCUSSION

In Section 4.2, we see that as the level of stigmatization increases, the reproduction number increases considerably, showing the significant negative effect of stigmatization on the dynamics of TB transmission. Moreover, one could clearly see the

	$No\ Control$	$Stigma\ Controls\ Only$ $u_1\ and\ u_2$	$Other\ Controls\ Only$ $u_3\ and\ u_4$	$All\ Controls$ u_1, u_2, u_3, u_4
S	383	712	997	8361
E	2433	7529	4002	7477
I_S	3253	7445	1116	597
I_N	7644	69	4443	18
$E + I_S + I_N$	13330	15043	9561	8092
T	701	2978	9064	7803
N	14417	18735	19625	24258

TABLE 4 Values of the compartments at $t = 30$.

effect of minimizing stigmatization in the number of treated individuals (T compartment in Table 2). We observe that every time we decrease the level of stigmatization by 20%, the number of treated individuals more than doubled. The lowering stigmatization hence contributes to the number of treated people.

In Section 4.3, we see some optimal implementation of the controls u_1, u_2, u_3, and u_4 for a particular perception on the implementation cost and level of stigmatization. We can observe in Figure 2 that in all of the cases controls u_3 (increasing treatment rate) and u_4 (minimizing reinfection) take priority more than the stigmatization controls u_1 and u_2. As expected, when the level of stigmatization is already low (e.g. $\alpha = 0.70$), the implementation of the stigmatization controls u_1 and u_2 are also minimized. This is also the case when the perceived implementation cost is high (e.g. $C_1 = C_2 = C_3 = C_4 = 10^3$). In both cases stigmatization controls are dropped first.

In Section 4.4, we can see the relative impact of the treatment and reinfection controls u_3 and u_4 compared to the stigma controls u_1 and u_2. Table 4 clearly shows that the combination of the treatment and reinfection controls provide better result than the combined stigma controls, judging from the number of individuals treated (T) and the lives saved (the bigger the population N at the end of simulation means the lesser disease-induced deaths). A considerably bigger population N at the end of simulation can be observed when a combination of controls is used.

6 | CONCLUSION

In this study, we modeled the negative effect of stigmatization. As stigmatization increases one expects an increase in the basic reproduction number. There are already designed interventions to reduce stigmatization and in this study we evaluated them as a group and compared them with the usual treatment and reducing reinforcing controls. Simulations showed that stigmatization controls alone are not enough to curb the disease. In fact, treatment and reinfection controls only have better results compared to stigmatization controls only. However, a far more better result can be observed if the four controls are implemented together, as shown in Figure 3 . An optimal strategy is depicted in Figure 2 . Hence, stigmatization controls and the other controls should go hand in hand to ensure a stronger countermeasure against TB.

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