Article

Tuberculosis in Ethiopia: Optimal Intervention Strategies and Cost-Effectiveness Analysis

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Abstract: This paper searches for optimal strategies for the minimization of the number of high-risk latent and active tuberculosis (TB) infectious individuals using real data from Ethiopia. Optimal control theory is harnessed for investigation and analysis of the optimal combination of interventions for controlling the transmission of TB using distancing, case finding, and case holding as controls. We calculate and compare the incremental cost-effectiveness ratio (ICER) for each of the strategies to determine the most effective combination of interventions for curbing the spread of the disease. Our findings suggest that, for optimal cost-effective management of the TB disease, the government of Ethiopia must focus more on prevention strategies such as isolation of infectious people, early TB patient detection, treatment, and educational programs. The optimal strategy is quantified through simulation.

Keywords: tuberculosis; TB detection; social distancing; isolation; incremental cost-effectiveness ratio

MSC: 92D30; 34K20

1. Introduction

Tuberculosis (TB) is still a significant public health problem and is one of the top 10 causes of illness and death. Globally, in 2019, 10 million people were infected with TB, and 1.4 million died [1]. In Ethiopia, tuberculosis is still a major health problem and one of the leading causes of death [2]. Furthermore, Ethiopia is one of the 30 high-burden countries, and there were an estimated 157,000 (140 per 100,000 of the population) incident cases of TB in 2019 [1]. Therefore, effective prevention measures are needed to stop the spread of tuberculosis in Ethiopia. This study aims to identify the most cost-effective combination of interventions for curbing the spread of TB in Ethiopia.

Among the many different forms of action in the fight against TB, distancing, case finding, and case holding are the most important [3]. Distancing control is an essential strategy to curb the spread of airborne contagious diseases such as TB, influenza, COVID-19, etc., by reducing the opportunities for close contact between people. Case finding is another important controlling method of TB [4], which is the process of screening and treating latent TB patients. Finally, case holding includes the activities and techniques we can apply to help patients complete the treatment they have started.

Infectious diseases can exhibit complex nonlinear dynamics, and it is possible to examine, explain, and predict the transmission dynamics of infectious diseases using mathematical models [5–11]. An optimal control problem entails the identification of a feasible scheme, policy, program, strategy, or campaign to achieve the optimal possible outcome of a system [12]. Numerous scholars (for example [3,13–17]) have applied the optimal control theory to predict suitable control strategies and to analyze their cost-effectiveness in mitigating the TB disease. Sunhwa Choi and Eunok Jung [3] developed a mathematical model for the transmission dynamics of TB in South Korea and considered three different

control strategies (distancing, case finding, and case holding efforts). The results showed that distancing control, such as isolation of infectious people, early TB patient detection, and educational programs/campaigns constitute the most effective combination of interventions for the prevention of TB transmission in South Korea. In [13] a mathematical TB model with control was developed and analysed based on the Philippines's real data. The result of their study showed that enhancing active case finding instead of the case holding control together with distancing has significant potential for curtailing the spread of TB in the Philippines. Gao and Huang [14] analyzed a TB model that incorporates vaccination, case finding, and case holding controls. Their result revealed that the combined implementation of three controls is the most effective and less expensive among different strategies. The mathematical model [15] for the transmission dynamics of TB in Angola considered two control strategies (case finding and case holding controls). Their results showed that the combined strategy that involves both controls is preferable. Doyo Kereyu and Seleshi Demie [16] developed and analyzed a TB model for Haramaya district, Ethiopia. They considered three control strategies (distancing, case finding, and treatment efforts). The results suggested that a combination of all interventions makes for the best strategy to eradicate TB disease from the community at an optimal level with minimum cost.

All the above studies showed that the strategies we use to control the spread of TB may vary depending on the situation in the country. Therefore, each government must adopt a better and more cost-effective approach based on its realities. In this study, based on Ethiopian TB data, we propose effective methods to eliminate the disease from the country.

2. TB Model with Controls

The following model (1) of TB disease dynamics was proposed and analyzed in [11]. This model forms the basis of our investigation in the current paper, and we include it for completeness.

The total population size $N(t)$ is partitioned into four subclasses: susceptible (S), high-risk latent (E), infectious (I), and low-risk latent (L). We aggregated the two groups, the recovered and the low-risk latent, in a class called low-risk individuals (L).

$$\begin{cases} \frac{dS}{dt} = \Lambda - \frac{\beta\psi SI}{1+bI} - \mu S \\ \frac{dE}{dt} = \frac{\beta\psi SI}{1+bI} + (1-p)rI + \sigma L - (k+\alpha+\mu)E \\ \frac{dI}{dt} = kE - (\mu+r+\delta)I \\ \frac{dL}{dt} = prI + \alpha E - (\mu+\sigma)L \\ N = S + E + I + L, \end{cases} \quad (1)$$

with $\psi = (1 - \varepsilon + \theta\varepsilon)$.

The recruitment rate to the susceptible population is assumed to be constant Λ. We assume that all classes have the same natural death rate μ, with disease-induced mortalities occurring only in the I-class at a rate δ. The susceptible individual acquires the TB bacteria through contact with infected individuals with a nonlinear transmission rate $\frac{\beta I}{1+bI}$. It is assumed that the BCG vaccine will be administered to susceptible individuals (at a rate εS). People who have been vaccinated can become infected because the vaccine is imperfect and does not completely protect against the disease. The vaccinated individuals are infected at a rate $\theta\varepsilon\beta SI$ where $0 \le \theta \le 1$ is the loss of vaccine protection. Newly infected individuals (with a latent level) will develop active TB (at a rate k). We assume that patients at the latent stage will move to the L-class with a rate of αE when treated. Here r is the treatment coverage rate, p represents the successful treatment rate for active TB infected individuals, and σ represents the relapse rate.

We modified the model (1) by including three control strategies, $u_i = u_i(t)$, for $i \in \{1, 2, 3\}$. The controls represent the intensities of different public health interventions. The function $u_1(t)$ is a distancing control associated with the effort to reduce susceptible individuals that become infected, and such effort includes an isolation policy, wearing a face mask, or public educational program. A case finding control ($u_2(t)$) represents the

effort of decreasing the number of latently infected individuals that may develop active TB. Such activities include screening and treatment of latent individuals who are at high risk of developing active TB. The third strategy is a case holding control, denoted by $u_3(t)$. It refers to efforts to prevent the failure of treatment in infectious individuals (e.g., patient supervision, including activities used to ensure the regularity of drug intake until the last treatment stage is attained).

This leads to the following system of ODEs, with all the parameters constant and in which we have suppressed the time variable:

$$
\begin{cases}
\frac{dS}{dt} = \Lambda - \frac{(1-u_1)\beta\psi SI}{1+bI} - \mu S \\
\frac{dE}{dt} = \frac{(1-u_1)\beta\psi SI}{1+bI} + (1 - (1+u_3)p)rI + \sigma L - (k + (1+u_2)\alpha + \mu)E \\
\frac{dI}{dt} = kE - (\mu + r + \delta)I \\
\frac{dL}{dt} = (1+u_3)prI + (1+u_2)\alpha E - (\mu + \sigma)L \\
N = S + E + I + L,
\end{cases}
\tag{2}
$$

with initial conditions $S_0, E_0, I_0, L_0 \geq 0$.

Let

$U = \{(u_1, u_2, u_3) | u_1, u_2$ and u_3 are Lebesgue integrable functions on the interval $[0, \infty)$, with $0 \leq u_i \leq 1$, $i = 1, 2, 3\}$.

We searched for an optimal control $(u_1^*, u_2^*, u_3^*) \in U$ that minimizes the objective functional $J(u_1, u_2, u_3)$

where

$$
J(u_1, u_2, u_3) = \int_{t_0}^{t_f} \left[E(t) + I + \frac{1}{2}B_1 u_1^2 + \frac{1}{2}B_2 u_2^2 + \frac{1}{2}B_3 u_3^2 \right] dt.
\tag{3}
$$

In Equation (3), the values of t_0 and t_f are taken as 0 and 20, respectively, to determine Ethiopia's 20-year (2019–2038) effective TB control strategies. The constants B_i, $i = 1, 2, 3$, are positive weight constants, which balance the cost factors associated with the controls u_1, u_2 and u_3, respectively. The functions $\frac{1}{2}B_1 u_1^2$, $\frac{1}{2}B_2 u_2^2$ and $\frac{1}{2}B_3 u_3^2$ are the costs of the controls u_1, u_2 and u_3, respectively. The cost terms are assumed to be nonlinear quadratic functions (as in [17–19]).

2.1. Existence of an Optimal Control

Theorem 1. *There exists an optimal control* (u_1^*, u_2^*, u_3^*) *that minimizes the objective functional* $J(u_1, u_2, u_3)$ *subject to the control system (2).*

Proof. Let us denote the right-hand side of the system (2) by $y(t, \vec{x}, \vec{u})$. Then following the same procedure as in [14], we prove the existence of an optimal control (u_1^*, u_2^*, u_3^*). To achieve this, we must first show that the following conditions are met.

i. y is of class C^1 and there exists a constant c such that

$$
|y(t, 0, 0)| \leq c, \left| y_{\vec{x}}\left(t, \vec{x}, \vec{u}\right) \right| \leq c\left(1 + \left| \vec{u} \right| \right), \left| y_{\vec{u}}\left(t, \vec{x}, \vec{u}\right) \right| \leq c,
$$

ii.   The set of all solutions to system (2) with corresponding control in U is nonempty,

iii. There exist functions a_1 and a_2 such that $y(t, \vec{x}, \vec{u}) = a_1(t, \vec{x}) + a_2(t, \vec{x})\vec{u}$,

iv.   The control set $U = [0,1] \times [0,1] \times [0,1]$ is closed, convex and compact,

v.   The integrand of the objective function is convex in U.

To verify the first conditions, let us write

$$
y\left(t, \vec{x}, \vec{u}\right) = \begin{pmatrix} \Lambda - \frac{(1-u_1)\beta\psi SI}{1+bI} - \mu S \\ \frac{(1-u_1)\beta\psi SI}{1+bI} + (1 - (1+u_3)p)rI + \sigma L - (k + (1+u_2)\alpha + \mu)E \\ kE - (\mu + r + \delta)I \\ (1+u_3)prI + (1+u_2)\alpha E - (\mu + \sigma)L \end{pmatrix},
$$

Then we can easily show that $y\left(t,\ \overrightarrow{x},\ \overrightarrow{u}\right)$ is of class C^1 and $|y(t,\ 0,\ 0)| = \Lambda$.
Moreover, we will have the following

$$\left|y_{\overrightarrow{x}}\left(t,\ \overrightarrow{x},\ \overrightarrow{u}\right)\right| = \left|\begin{pmatrix} -\mu - \frac{(1-u_1)\beta\psi I}{1+bI} & 0 & -\frac{(1-u_1)\beta\psi S}{(1+bI)^2} & 0 \\ \frac{(1-u_1)\beta\psi I}{1+bI} & -k-\alpha-\mu-\alpha u_2 & \frac{((1-p)r-pru_3)(1+bI)^2+(1-u_1)\beta\psi S}{(1+bI)^2} & \sigma \\ 0 & k & -(r+\delta+\mu) & 0 \\ 0 & \alpha(1+u_2) & pr(1+u_3) & -(\mu+\sigma) \end{pmatrix}\right|,$$

and

$$\left|y_{\overrightarrow{u}}(t,\ \overrightarrow{x},\ \overrightarrow{u})\right| = \left|\begin{pmatrix} \frac{\beta\psi SI}{1+bI} & 0 & 0 \\ -\frac{\beta\psi SI}{1+bI} & -\alpha E & -prI \\ 0 & 0 & 0 \\ 0 & \alpha E & prI \end{pmatrix}\right|.$$

Since $S,\ E,\ I,$ and L are bounded, there exists a constant c such that

$$|y(t,\ 0,\ 0)| \le c,\ \left|y_{\overrightarrow{x}}\left(t,\ \overrightarrow{x},\ \overrightarrow{u}\right)\right| \le c\left(1+\left|\overrightarrow{u}\right|\right),\ \left|y_{\overrightarrow{u}}\left(t,\ \overrightarrow{x},\ \overrightarrow{u}\right)\right| \le c.$$

This shows that condition (i) is satisfied.

According to condition (i), there is a unique solution for the constant controls, which will ensure that condition (ii) is met.

Besides,

$$y(t,\ \overrightarrow{x},\ \overrightarrow{u}) = \begin{pmatrix} \Lambda - S\mu - \frac{\beta\psi SI}{1+bI} \\ -(k+\alpha+\mu)E+\sigma L+I\left(r-pr+\frac{\beta\psi S}{1+bI}\right) \\ kE-I(r+\delta+\mu) \\ \alpha E+prI-L(\mu+\sigma) \end{pmatrix} + \begin{pmatrix} \frac{\beta\psi SI}{1+bI} & 0 & 0 \\ -\frac{\beta\psi SI}{1+bI} & -\alpha E & -prI \\ 0 & 0 & 0 \\ 0 & \alpha E & prI \end{pmatrix} \times \begin{pmatrix} u_1 \\ u_2 \\ u_3 \end{pmatrix}.$$

This verifies condition (iii). The subset U of $\mathbb{R}^3$ is closed and bounded, and hence compact. Thus condition (iv) is fulfilled. We proceed with verification of condition (v), the convexity of the integrand of the objective functional. We must prove that for any two values $\overrightarrow{u}$ and $\overrightarrow{v}$ of the control vector, and a constant $q \in [0,1]$, the following inequality holds:

$$(1-q)g\left(t,\ \overrightarrow{x},\ \overrightarrow{u}\right) + qg\left(t,\ \overrightarrow{x},\ \overrightarrow{v}\right) \ge g\left(t,\ \overrightarrow{x},\ (1-q)\overrightarrow{u}+q\overrightarrow{v}\right),$$

where

$$g\left(t,\ \overrightarrow{x},\ \overrightarrow{u}\right) = E+I+\frac{1}{2}B_1 u_1^2+\frac{1}{2}B_2 u_2^2+\frac{1}{2}B_3 u_3^2.$$

Further,

$$(1-q)g\left(t,\ \overrightarrow{x},\ \overrightarrow{u}\right) + qg\left(t,\ \overrightarrow{x},\ \overrightarrow{v}\right) = E \quad +I+\tfrac{1}{2}(1-q)\left[B_1 u_1^2+B_2 u_2^2+B_3 u_3^2\right] \\ +\tfrac{1}{2}q\left[B_1 v_1^2+B_2 v_2^2+B_3 v_3^2\right],$$

And

$$g\left(t,\ \overrightarrow{x},\ (1-q)\overrightarrow{u}+q\overrightarrow{v}\right) = E+I+\tfrac{1}{2}B_1[(1-q)u_1+qv_1]^2+\tfrac{1}{2}B_2[(1-q)u_2+qv_2]^2 \\ +\tfrac{1}{2}B_3[(1-q)u_3+qv_3]^2,$$

Then

$$(1-q)g\left(t,\ \vec{x},\ \vec{u}\right)+qg\left(t,\ \vec{x},\ \vec{v}\right)-g\left(t,\ \vec{x},\ (1-q)\vec{u}+q\vec{v}\right)$$

$$= (1-q)\left[\tfrac{B_1}{2}u_1^2+\tfrac{B_2}{2}u_2^2+\tfrac{B_3}{2}u_3^2\right]+q\left[\tfrac{B_1}{2}v_1^2+\tfrac{B_2}{2}v_2^2+\tfrac{B_3}{2}v_3^2\right]$$

$$-\left[\tfrac{B_1}{2}[(1-q)u_1+qv_1]^2+\tfrac{B_2}{2}[(1-q)u_2+qv_2]^2+\tfrac{B_3}{2}[(1-q)u_3+qv_3]^2\right],$$

$$= \tfrac{B_1}{2}\left\{(1-q)u_1^2+qv_1^2-[(1-q)u_1+qv_1]^2\right\}+\tfrac{B_2}{2}\left\{(1-q)u_2^2+qv_2^2-[(1-q)u_2+qv_2]^2\right\}$$

$$+\tfrac{B_3}{2}\left\{(1-q)u_3^2+qv_3^2-[(1-q)u_3+qv_3]^2\right\},$$

$$= \tfrac{B_1}{2}\left\{q(1-q)u_1^2-2q(1-q)u_1v_1+q(1-q)v_1^2\right\}$$

$$+\tfrac{B_2}{2}\left\{q(1-q)u_2^2-2q(1-q)u_2v_2+q(1-q)v_2^2\right\}$$

$$+\tfrac{B_3}{2}\left\{q(1-q)u_3^2-2q(1-q)u_3v_3+q(1-q)v_3^2\right\},$$

$$= \tfrac{B_1}{2}\left\{q(1-q)(u_1-v_1)^2\right\}+\tfrac{B_2}{2}\left\{q(1-q)(u_2-v_2)^2\right\}+\tfrac{B_3}{2}\left\{q(1-q)(u_3-v_3)^2\right\}\geq 0.$$

Consequently, condition (v) is satisfied, and this completes the proof. □

2.2. Characterization of an Optimal Control

To find the best cost-effective strategies for reducing the number of high-risk latent (E) and infectious (I), we use optimal control theory. In this section, we derive the necessary conditions for the optimal control by using Pontryagin's Maximum Principle [20,21]. We formulate the Hamiltonian

$$
\begin{aligned}
H(S,E,I,L,u_1,u_2,u_3,\lambda) &= E+I+\tfrac{1}{2}B_1u_1^2+\tfrac{1}{2}B_2u_2^2+\tfrac{1}{2}B_3u_3^2 \\
&+\lambda_1\left[\Lambda-\tfrac{(1-u_1)\beta\psi SI}{1+bI}-\mu S\right] \\
&+\lambda_2\left[\tfrac{(1-u_1)\beta\psi SI}{1+bI}+(1-(1+u_3)p)rI+\sigma L-(k+(1+u_2)\alpha+\mu)E\right] \\
&+\lambda_3[kE-(\mu+r+\delta)I] \\
&+\lambda_4[(1+u_3)prI+(1+u_2)\alpha E-(\mu+\sigma)L].
\end{aligned}
\tag{4}
$$

Here, $\lambda=(\lambda_1,\lambda_2,\lambda_3,\lambda_4)\in\mathbb{R}^4$ are the adjoint functions.

Theorem 2. *For the optimal control $(u_1^*,\ u_2^*,\ u_3^*)$ and the corresponding solutions to the variables $\overline{S},\ \overline{E},\ \overline{I},\ \overline{L}$, that minimizes the Equation (3), there exist adjoint variables $\lambda_1,\ \lambda_2,\ \lambda_3,$ and λ_4 satisfying*

$$
\begin{cases}
\frac{d\lambda_1}{dt} = \frac{(1-u_1)\beta\psi I}{1+bI}\lambda_1+\mu\lambda_1-\frac{(1-u_1)\beta\psi I}{1+bI}\lambda_2 \\
\frac{d\lambda_2}{dt} = [k+\mu+(1+u_2)\alpha]\lambda_2-k\lambda_3-(1+u_2)\alpha\lambda_4-1 \\
\frac{d\lambda_3}{dt} = (\mu+r+\delta)\lambda_3+\left[\frac{(u_1-1)\beta\psi bSI}{(1+bI)^2}+\frac{(1-u_1)\beta\psi S}{1+bI}\right]\lambda_1 \\
\quad+\left[\frac{(1-u_1)\beta\psi bSI}{(1+bI)^2}+\frac{(u_1-1)\beta\psi S}{1+bI}-(1-(1+u_3)p)r\right]\lambda_2-(1+u_3)pr\lambda_4-1 \\
\frac{d\lambda_4}{dt} = (\mu+\sigma)\lambda_4-\sigma\lambda_2
\end{cases}
\tag{5}
$$

with transversality conditions

$$\lambda_1\left(t_f\right)=\lambda_2\left(t_f\right)=\lambda_3\left(t_f\right)=\lambda_4\left(t_f\right)=0,\tag{6}$$

Furthermore,

$$
\begin{aligned}
u_1^* &= \min\left\{\max\left\{0,\tfrac{(\lambda_2-\lambda_1)\beta\psi\overline{S}\,\overline{I}}{(1+b\overline{I})B_1}\right\},1\right\}, \\
u_2^* &= \min\left\{\max\left\{0,\tfrac{(\lambda_2-\lambda_4)\alpha\overline{E}}{B_2}\right\},1\right\}, \\
u_3^* &= \min\left\{\max\left\{0,\tfrac{(\lambda_2-\lambda_4)pr\overline{I}}{B_3}\right\},1\right\}.
\end{aligned}
\tag{7}
$$

Proof. By applying Pontryagin's Maximum Principle, we obtain the adjoint system (5) as follows:

$$\frac{d\lambda_1}{dt} = -\frac{\partial H}{\partial S}, \ \frac{d\lambda_2}{dt} = -\frac{\partial H}{\partial E}, \ \frac{d\lambda_3}{dt} = -\frac{\partial H}{\partial I}, \ \frac{d\lambda_4}{dt} = -\frac{\partial H}{\partial L},$$ (8)

with

$$\lambda_i\left(t_f\right) = 0, \ i = 1, 2, 3, 4.$$ (9)

Evaluating the optimal control and corresponding state variables, we obtain the adjoint system (5) and the transversality conditions (6).

Finally, by applying the optimality condition

$$\frac{\partial H}{\partial u_1} = \frac{\partial H}{\partial u_2} = \frac{\partial H}{\partial u_3} = 0,$$

And using the bounds for the controls u_1, u_2 and u_3, we can derive the optimal control $\left(u_1^*, \ u_2^*, \ u_3^*\right)$ as in Equation (7). □

3. Numerical Results and Discussion

Using Matlab2019b, the optimal control system is solved by applying the forward-backward sweeping technique. According to [7], in the total population of Ethiopia, the classes E_0 and L_0 comprise 16.37% and 30% of the population, respectively. Based on these percentages we can deduce values for E_0 and L_0.

The values of parameters and the initial values of the variables used in our simulations are presented in Table 1. The algorithm used for the solution is based on the approach proposed in [20,22].

Table 1. Values of variables and parameters.

Symbols	Description	Units	Value	Reference
N_0	Total population	*Humans*	1.12×10^8	[23]
S_0	Susceptible	*Humans*	5.85×10^7	Estimated
E_0	High-risk latent	*Humans*	1.83×10^7	[7]
I_0	Infected	*Humans*	1.57×10^5	[23]
L_0	Low-risk latent	*Humans*	3.36×10^7	[7]
Λ	Recruitment rate	*Humans/year*	1.4×10^6	[7]
β	Effective contact rate	$\frac{1}{year}$	1.646×10^{-7}	[7]
ε	Vaccination rate of new-borns	*dimensionless*	0.715	[24]
θ	Loss of protection for vaccination	*dimensionless*	0.5	[11]
μ	Natural mortality rate	$\frac{1}{year}$	0.016	[7]
k	Transfer rate from E to I	$\frac{1}{year}$	0.023	[7]
r	Treatment rate of I	$\frac{1}{year}$	0.546	[7]
p	Recovery rate of I	*dimensionless*	0.832	[25]
α	Treatment rate of E	$\frac{1}{year}$	0.153	[7]
δ	Death rate due to TB	$\frac{1}{year}$	0.17	[26]
σ	Relapse rate	$\frac{1}{year}$	0.0013	[7]
b	Saturation constant	$\frac{1}{Humans}$	0.0004	[11]
u_1	Distancing control	*dimensionless*	$[0,1]$	Assumed
u_2	Case finding control	*dimensionless*		Assumed
u_3	Case holding control	*dimensionless*	$[0,1]$	Assumed

Studies show that applying combined strategies rather than single strategies is more effective in curbing the spread of TB [13,16]. Therefore, to examine the impact of each control on the elimination of TB, we test the following four control strategies, and we search for an optimal combination of these interventions.

Strategy A: distancing and case holding controls (u_1 and u_3), with $u_2(t) = 0$.
Strategy B: case finding and case holding controls (u_2 and u_3), with $u_1(t) = 0$.

Strategy C: distancing and case finding controls (u_1 and u_2), with $u_3(t) = 0$.

Strategy D: Using all the control efforts (u_1, u_2 and u_3).

We assume a value for the weight parameters $B_1 = B_2 = 10^5$. Since the case holding control u_3 targets active TB patients undergoing treatment, the numbers in these groups are smaller than the others. Hence it is reasonable to take B_3 as being far smaller than B_1 and B_2, and we assigned a value $B_3 = 10^3$.

The dynamics of the total infected population ($E + I$) are shown in Figure 1. It can be observed that the number of infected individuals can be significantly decreased when the three control inputs (u_1, u_2, and u_3) are used simultaneously. Like *Strategy D*, Strategies *B* and *C* play a significant role in reducing the number of high-risk latent individuals. In contrast, *Strategy A* has the least impact on reducing the number of patients. This shows that it is beneficial to use case finding control in combination with other strategies to prevent the disease.
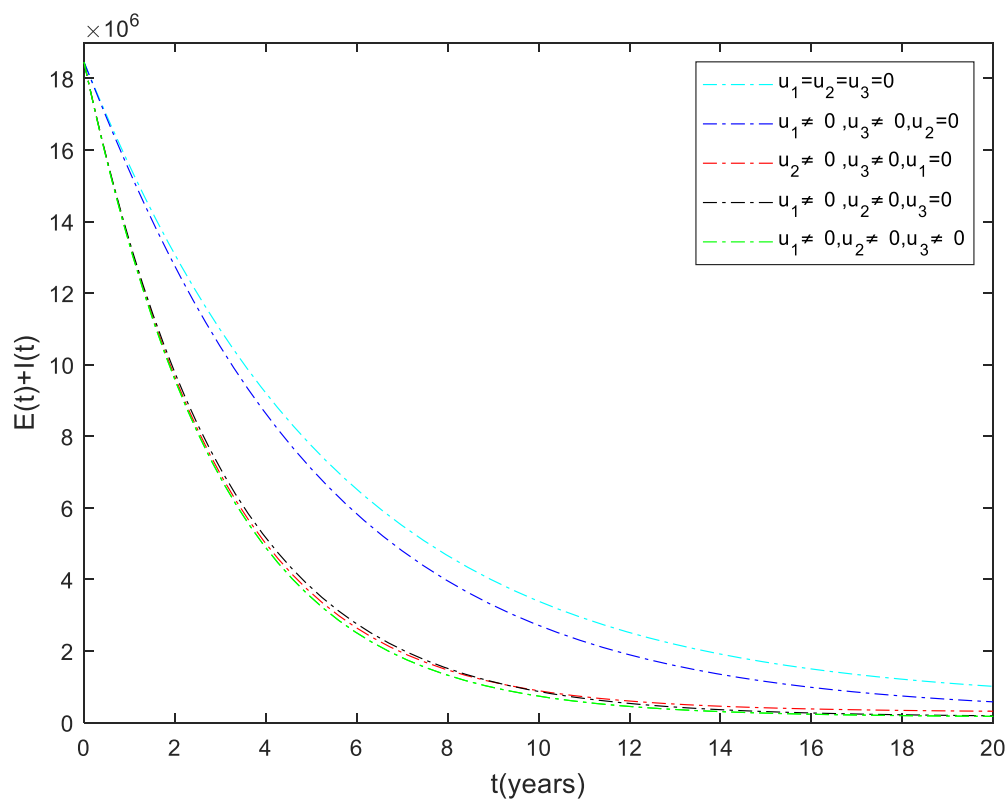
Figure 1. The dynamics of the total infected population under different control strategies.

3.1. Strategy A: Use of Distancing and Case Holding Controls

In this strategy, the distancing and the case holding controls are used to optimize the objective function J while we set case finding control (u_2) to zero. Figure 2a shows that the total number of infected people ($E + I$) has a significant difference when we compare with control and without control. Specifically, when this strategy is implemented, 4.32×10^5 total infected people are averted. The total cost for the combined effects of these two controls is given in Figure 2b. The simulation results in Figure 2c suggest that this strategy would require both distancing and case holding controls to be at maximum for almost the entire period of intervention.
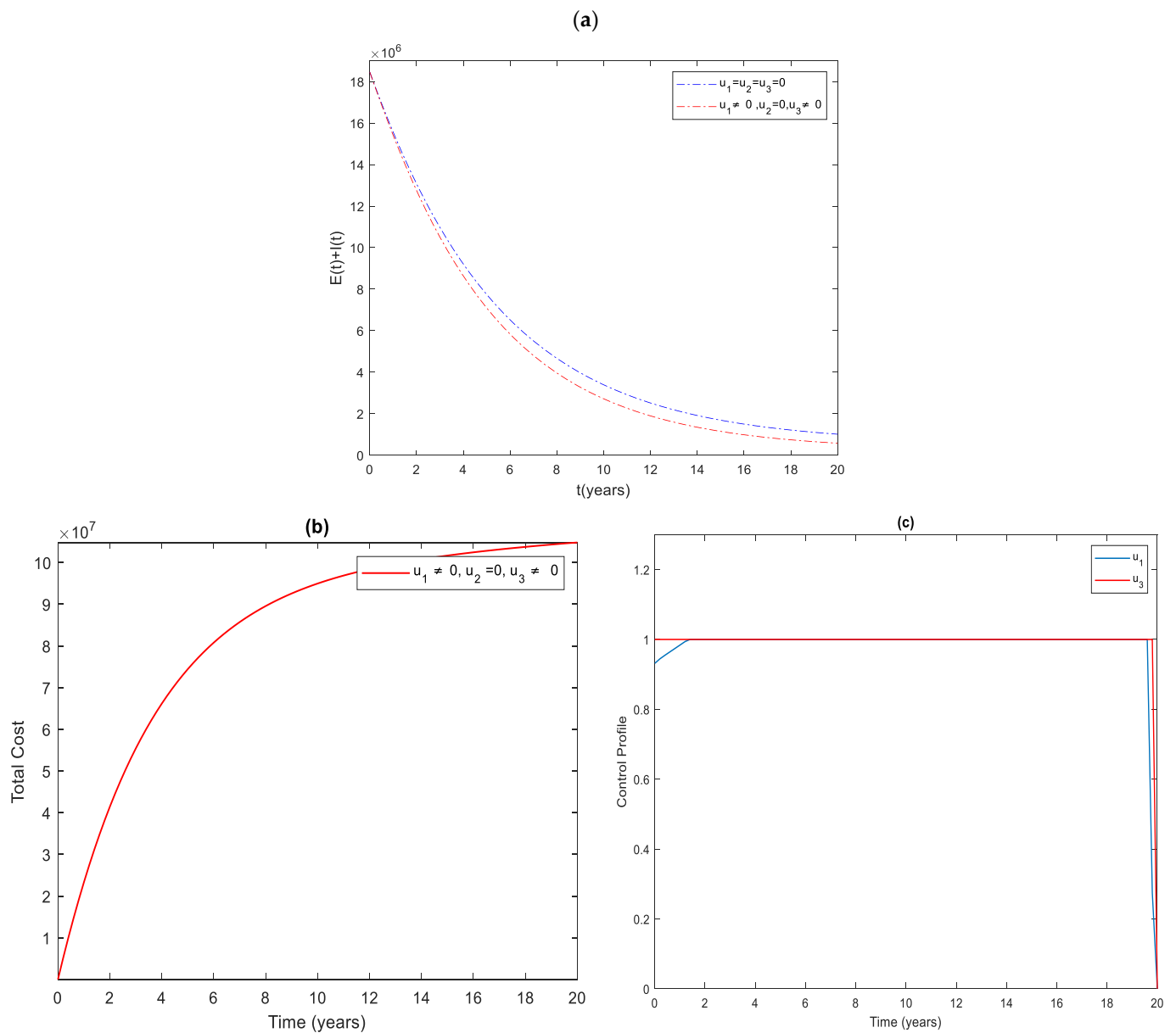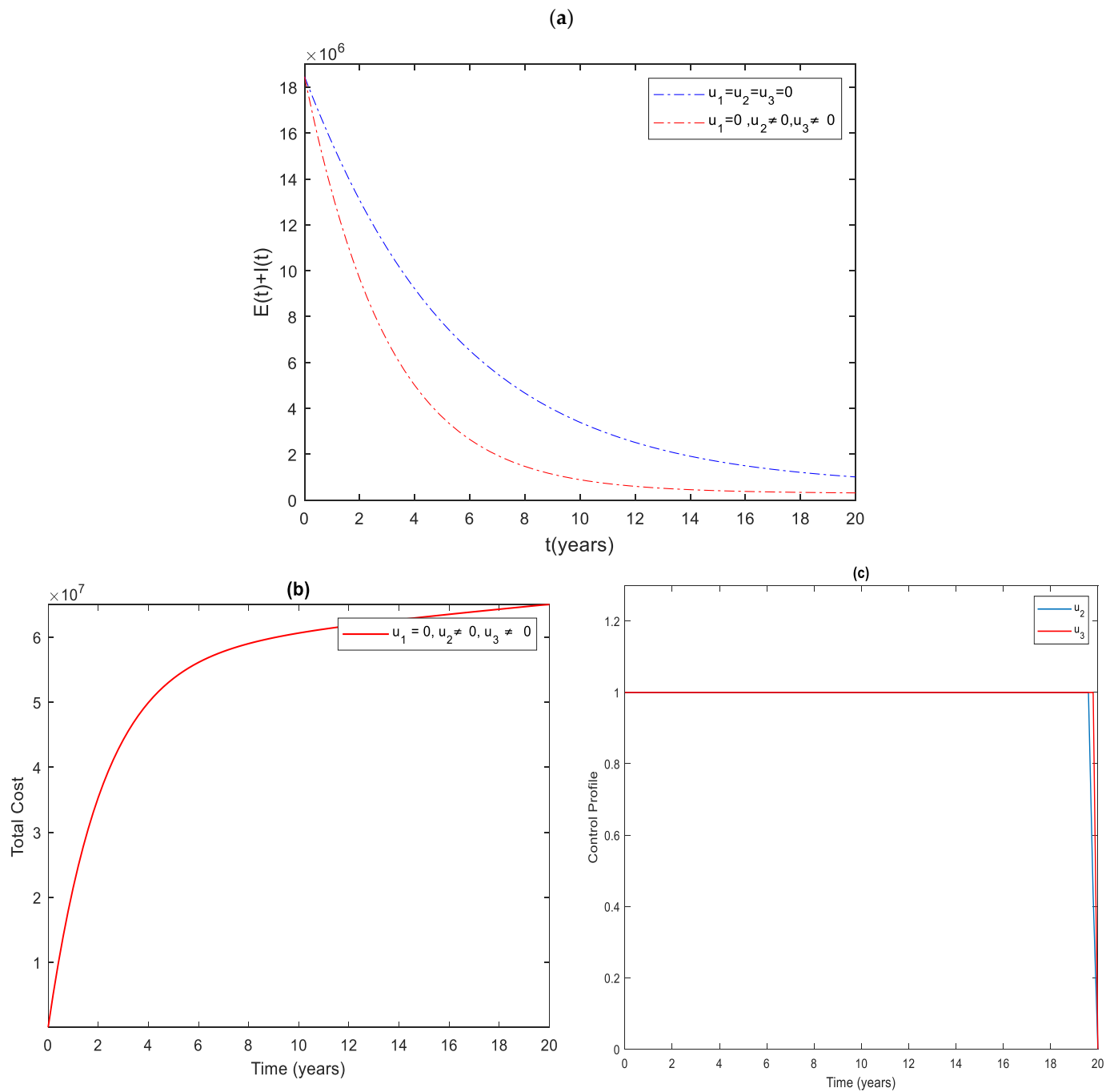
(a)

(b)

(c)

Figure 2. (**a**) The impact of distancing and case holding control on the infected population. (**b**) Cost function. (**c**) Optimal controls profile.

3.2. Strategy B: Control with Case Finding and Case Holding

Figure 3a shows the significant difference in the numbers of the total infected population with control and without control. More precisely, the total number of infected people with and without controls at the end of the simulation period is 3.16×10^5 and 1.011×10^6, respectively. To achieve this, the control profile u_2 and u_3 should be implemented at a maximum (Figure 3c). The cost function for this strategy is shown in Figure 3b. The total cost when the strategy is implemented throughout the simulated time horizon is \$6.5012 $\times 10^7$.

(a)

(b)

(c)

Figure 3. (**a**) The impact of case finding and case holding control on the infected population. (**b**) Cost function. (**c**) Optimal controls profile.

3.3. Strategy C: Use of Distancing and Case Finding Control

As shown in Figure 4a, there is a significant difference in the number of infected individuals with control and without control. By applying this strategy, 8.22×10^5 infected people are averted. The cost function for this strategy is shown in Figure 4b. The simulation result in Figure 4c shows that this strategy would require that the case finding u_2 should be at maximum for almost the entire period of intervention, while distancing controls u_1 should start at 0.4679 and gradually increase to the maximum.
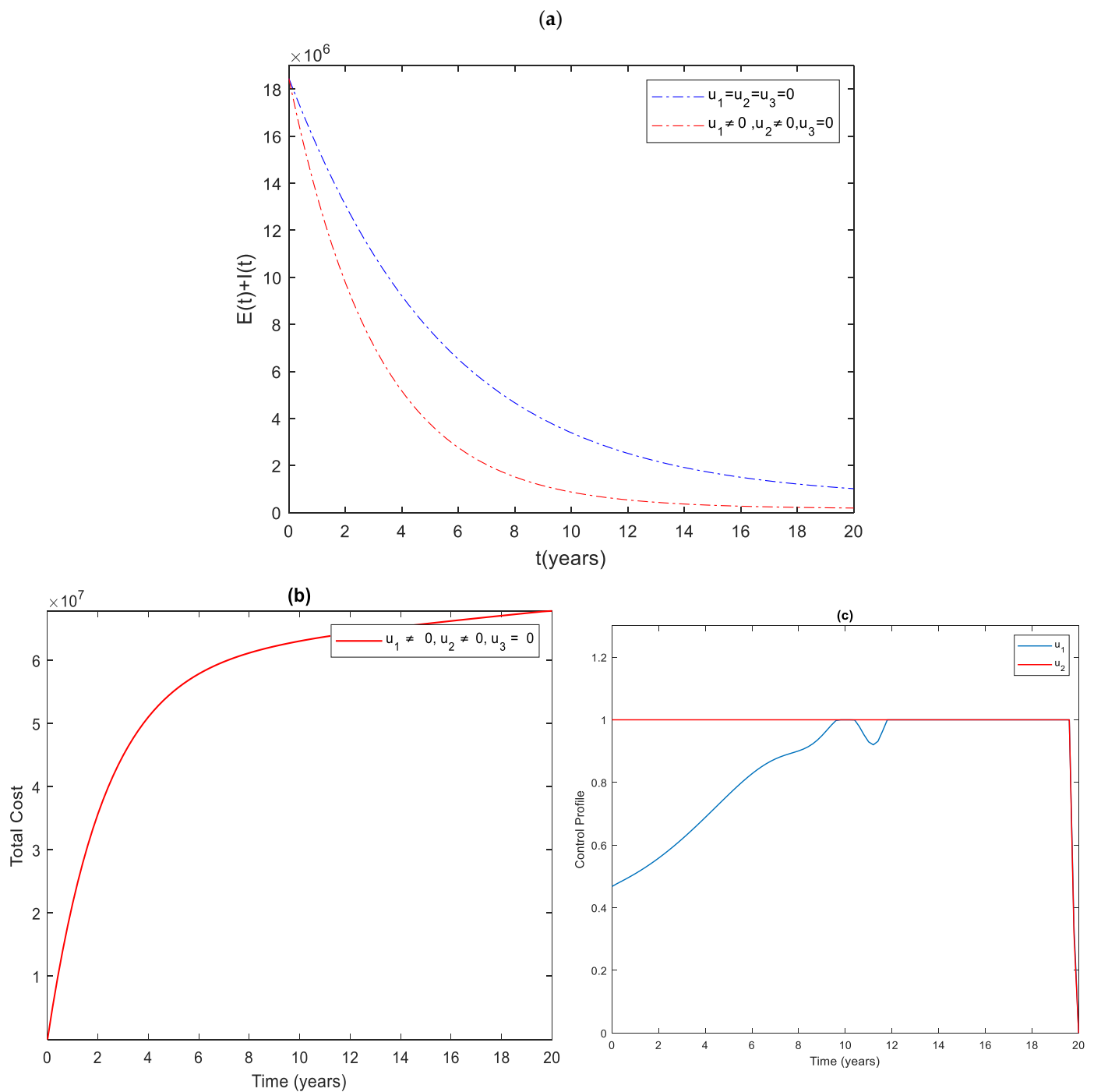
(a)

(b)

(c)

Figure 4. (**a**) The impact of distancing and case finding control on the infected population. (**b**) Cost function. (**c**) Optimal controls profile.

3.4. Strategy D: Using All the Controls

In this strategy, we have implemented a combination of all the three controls. This method helps us to save more people from disease than any other strategy. As we can see from Figure 5a, it averts about 8.38×10^5 infected people. The cost and control functions of this strategy are displayed in Figure 5b,c.

(**a**)

(**b**)

(**c**)
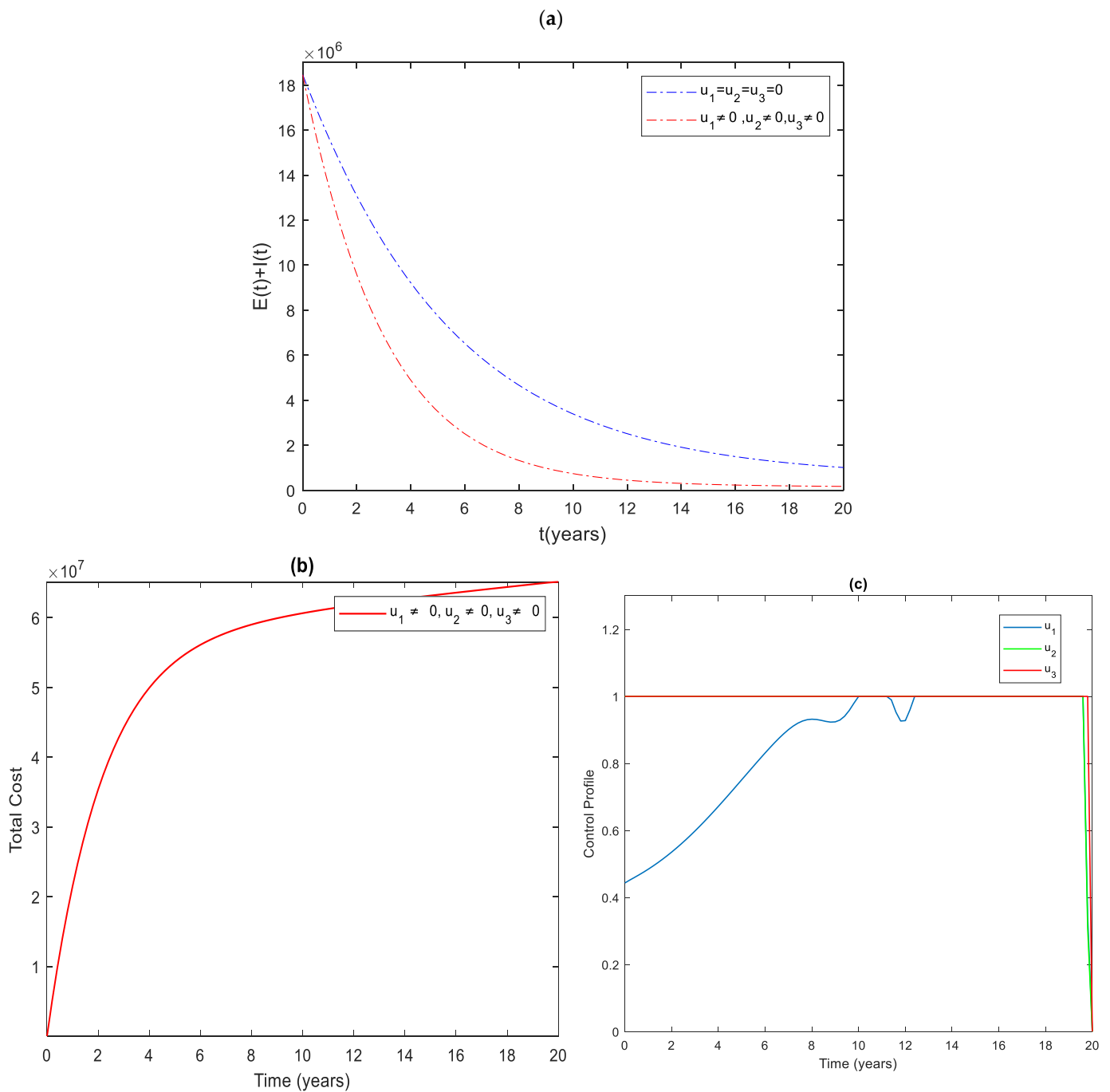
Figure 5. (**a**) The impact of the combination of all controls on the infected population. (**b**) Cost function. (**c**) Optimal controls profile.

4. Cost-Effectiveness Analysis

Controlling and eliminating the spread of infectious diseases in a community requires time and money. Therefore, it is essential to identify and implement cost-effective strategies to prevent the spread of the disease. In addition, community awareness and lifestyle are critical factors determining the spread of disease. As a result, effective methods of controlling the spread of disease may vary from country to country. In this study, we identified cost-effective ways to prevent the spread of tuberculosis in Ethiopia. We used the incremental cost-effectiveness ratio (*ICER*) to do this. The *ICER* is defined as the cost per health outcome [27], which is given by:

$$ICER = \frac{\text{The difference in cos ts between strategies}}{\text{Total number of infections averted}}.$$

Table 2 calculates the total number of infections averted by each strategy and the total cost of implementing the strategy. We calculated the number of infections averted by subtracting the number of infections with control from without control. On the other hand, the total cost of each strategy was obtained using the cost function $\frac{B_1}{2}u_1^2(t)$, $\frac{B_2}{2}u_2^2(t)$, and $\frac{B_3}{2}u_3^2(t)$.

Table 2. Cost-effectiveness of the control strategies.

Strategy	Total Infection Averted	Total Cost ($)
A (u_1 and u_3)	4.32×10^5	1.0479×10^8
B (u_1 and u_2)	6.95×10^5	6.5012×10^7
C (u_2 and u_3)	8.22×10^5	6.782×10^7
D ($u_1, u_2,$ and u_3)	8.38×10^5	6.5122×10^7

To implement the *ICER* method, we first needed to rank the control strategies based on averted infection, as shown in Table 2. Based on this rank, we first compared the *ICER* of *strategy A* and *strategy B* as follows.

$$ICER(A) = \frac{1.0479 \times 10^8}{4.32 \times 10^5} = 242.57.$$
$$ICER\ (B) = \frac{6.5012 \times 10^7 - 1.0479 \times 10^8}{6.95 \times 10^5 - 4.32 \times 10^5} = -151.25.$$

Which shows that *strategy B* is less costly than *strategy A*. *Strategy A* was then ignored, and the analysis continued by comparing *strategy* B with C as:

$$ICER(B) = \frac{6.5012 \times 10^7}{6.95 \times 10^5} = 93.54.$$
$$ICER(C) = \frac{6.782 \times 10^7 - 6.5012 \times 10^7}{8.22 \times 10^5 - 6.95 \times 10^5} = 22.11.$$

This indicates that *Strategy C* is cheaper and more effective than *Strategy B* and hence, *strategy* B was ignored, and the analysis continued by comparing *strategy C* and *strategy D* as follows:

$$ICER(C) = \frac{6.782 \times 10^7}{8.22 \times 10^5} = 82.5.$$
$$ICER(D) = \frac{6.5122 \times 10^7 - 6.782 \times 10^7}{8.38 \times 10^5 - 8.22 \times 10^5} = -168.62.$$

Finally, the comparison result revealed that *strategy D* is less costly and more effective than *strategy C*. In conclusion, of the four strategies mentioned, *strategy D* (combining the three controls simultaneously) is the most effective way in combating the spread of TB in Ethiopia.

5. Conclusions

The Ethiopian government is working with partners and the community to eliminate TB by 2035. Therefore, it is vital to identify and implement effective strategies to eradicate the disease. This paper has developed a mathematical model by including three control strategies (distancing, case finding, and case holding). After that, using Pontryagin's maximum principle, the conditions for optimal control of the disease were analyzed. The optimal solution to the system was then illustrated by numerical simulations using available data from Ethiopia. From the numerical simulation result (Figure 1), one can deduce that considering the combination of distancing and case holding controls (*Strategy A*), does not lead to the best results in decreasing the number of TB infected individuals. On the other hand, we can understand from this analysis that the combination of all the three controls (*Strategy D*) is an effective way to eradicate tuberculosis from the community.

Finally, we investigated the cost-effectiveness of the control strategies by using the ICER technique. Based on the results of these analyses, we concluded that applying the

combination of the three controls (distancing, case finding, and case holding) is less costly and more effective than other strategies. This suggested that intervention strategies, such as isolation of infectious people, early TB patient detection, treating high-risk latently infected individuals, educational campaigns, and preventing treatment failure of active TB patients are essential in Ethiopia to control the spread of the disease.

The paper [16] presents a theme similar to the theme of this paper. However, an essential difference is that the structure of the model and the control variables are not the same, and the model of [16] is calibrated to a single district in Ethiopia. In contrast, we consider Ethiopia as a whole in the current paper. It may be wise to consider more controls than the three we included in this paper. Accuracy of the dynamics of the disease may be improved by considering more compartments in the population, such as considering age structure or multi-group models, in which the smaller groups are more homogeneous.

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