Optimal Control of Tuberculosis Transmission Model with Vaccination

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Abstract. Tuberculosis (TB) is a disease that causes many deaths in the world. This paper discusses optimal control strategies of TB transmission with vaccination in newborns and adults. This study aims to minimize the cost of vaccination intervention and reduce infected populations. Using the Pontryagin Principle, we obtained the optimal control characteristics of the model. Then, it transformed from a continuous to a semi-discrete function. It means that vaccination was given only at certain times. Next, numerical simulations were performed to obtain the optimal control interpretation. As a result, vaccination control was more effective in adults than newborns. Vaccination control for adults will be more optimal if given every four years because it will minimize the weight cost of vaccination and reduce the number of the infected population.

INTRODUCTION

Tuberculosis (TB) is a disease that causes many deaths in the world. In 2019, as many as 1.4 million people died from TB [1]. An estimated 10 million people were infected with TB, with 5.6 million men, 3.2 million women, and 1.2 million children [1]. The number of deaths that occur is due to the difficulty in predicting the spread of the disease. People with TB who are not reported to public health also increase TB cases [2]. TB bacteria uses air as its medium. When an infectious TB (active TB) coughs or sneezes, the bacteria in the sputum splash will be carried out into the air until inhaled by another people. There is an incubation period to become infectious TB depending on the immunity of each individual [3]. They have a 5 – 10% lifetime risk of falling ill with TB [1]. In this period, they have no symptoms and cannot spread TB bacteria even though they have a positive skin test result [4].

To successfully fight against TB needs collaboration between governmental and non-governmental [5]. The government provided the Bacillus Calmette Guerin (BCG) to control the TB transmission in the population. BCG is the only license for TB and will probably be effective against tuberculosis [6]. Generally, BCG is given to newborns or infants when they first interact with health services [7]. However, adults can also get vaccinated if they never get vaccinated or exposed [8].

In vaccination implementation, some obstacles arise, such as the cost of vaccination. Vaccination continuously requires higher costs. There is a need for vaccination strategies to minimize the cost of intervention and reduce the number of infectious more effectively. Mathematical analyses can provide the best strategy to control infectious diseases [9]. It is necessary to calculate the time of vaccination so that the effect will be maximized. To determine strategies that can reduce the cost of vaccination intervention, we established an optimal control of the TB transmission model with vaccination. Optimal control theory is a mathematical tool to minimize the cost to reduce

infected individuals [10]. Using this theory, we can obtain optimal control solutions in controlling the dynamic system of TB disease. The optimal control model will be analyzed and simulated to be interpreted in the real world.

There are many studies on the optimal control of TB disease, such as optimal control using the maximum level of individuals who can be vaccinated or treated during a given period and the maximum level of individuals who can be successfully treated [11], optimal control for a fractional tuberculosis infection [12], optimal control with undetected cases [13], vaccination and treatment [14], endogenous reactivation and exogenous reinfection [15]. Gao and Huang showed that implementing the three controls is the most effective strategy and is cheaper than others [11]. Silva, Maurer, and Torres developed a TB model with control over the interval when a person infected with TB became infectious [16].

Akman and Karaouglu formed a mathematical model to determine the optimal control strategy with re-infection intervention by active TB treatment at home and in the hospital [17]. This model used distance control, control of prevention of treatment failure at home and in hospital for active patients. The model obtains that prevention of treatment failure at home is an essential factor in eradicating TB. In addition, distance control is a supporting strategy to improve treatment success. Based on the above, this paper analyzed the optimal control model for the spread of TB with vaccination intervention to newborns and adults.

METHOD

This section consists of analyzing the model, formulation of the optimal control, numerical result, and discussion. In analyzing the model, we use the model [18] to analyze the optimal control of vaccination for newborns and adults. We present the equilibrium point of the model, basic reproduction number, and the local stability at the disease-free equilibrium (DFE). Then, we construct the optimal control formulation with make objective function, adjoint equations, and optimization conditions. We use Matlab Software to simulate the optimal control model with parameter description in TABLE 1. The numerical result provides the dynamic of the population with several strategies for vaccination control to newborns (u_1) and adults (u_2).

Analysis of the Model

This study uses a TB transmission model [18] with vaccination strategies for newborns and adults. There are five classes in the population: vaccinated (V), susceptible (S), high-risk latent (E), low-risk latent (L), and infectious (I). The total population $N(t)$ is given as $N(t) = V(t) + S(t) + E(t) + L(t) + I(t)$. It assumed that the population was closed and constant. There is no migration, the births have the same number of deaths, and no disease death is considered. The vaccine is not only given to newborns, but also to adults who have never been vaccinated or exposed with TB. When they are not vaccinated, they will become susceptible individuals (S).

Using a TB transmission model in FIGURE 1., the TB model with vaccination is as follows [18].

$$
\begin{aligned}
\frac{dV(t)}{dt} &= bN(t)u_1 + u_2 S(t) - \frac{\beta\xi V(t)I(t)}{N(t)} - \mu V(t),\\
\frac{dS(t)}{dt} &= bN(t)(1-u_1) - u_2 S(t) - \frac{\beta S(t)I(t)}{N(t)} - \mu S(t),\\
\frac{dE(t)}{dt} &= \frac{\beta\xi V(t)I(t)}{N(t)} + \frac{\beta S(t)I(t)}{N(t)} + p\gamma I(t) - \kappa E(t) - \alpha E(t) - \mu E(t),\\
\frac{dL(t)}{dt} &= \alpha E(t) + (1-p)\gamma I(t) - \mu L(t),\\
\frac{dI(t)}{dt} &= \kappa E(t) - \gamma I(t) - \mu I(t).
\end{aligned}
\tag{1}
$$

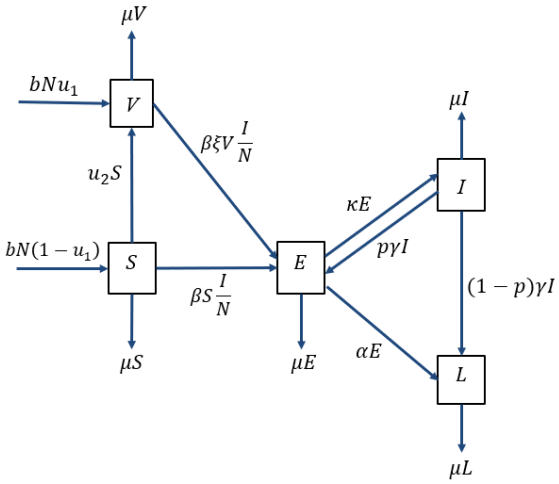

FIGURE 1. A TB transmission model

TABLE 1. Parameter description of the model [18].

Description	Parameters	Value
Total population	N	1000
Natural birth rate	b	1/70
Natural death rate	μ	1/70
Proportion vaccinated newborns	u_1	[0,1]
Proportion vaccinates of adults	u_2	[0,1]
Transmission rate	β	11.7354
Percentage of vaccine cannot protect human	ξ	[0,1]
Progression rate from E to L	α	0.2077
Progression rate from E to L	κ	0.0298
Treatment rate	γ	0.2906
Proportion treatment failure probability	p	[0,1]

Model (1) has two equilibria points, i.e., disease-free and endemic equilibrium. Disease free-equilibrium of model (1) is defined as

$$E_0 = (V_0, S_0, E_0, L_0, I_0) = \left(\frac{bN(\mu u_1 + u_2)}{(\mu + u_2)\mu}, \frac{bN(1-u_1)}{(\mu + u_2)}, 0, 0, 0 \right) \tag{2}$$

Moreover, the endemic equilibrium of model (1) is $E_1 = (V_1, S_1, E_1, L_1, I_1)$ with

$$S_1 = \frac{bN^2(1-u_1)}{(\mu + u_2)N + I_1\beta},$$

$$V_1 = \frac{b\left((\mu u_1 + u_2)N + u_1\beta I_1\right)N^2}{\left(\xi\beta I_1 + \mu N\right)\left((\mu + u_2)N + \beta I_1\right)},$$

$$E_1 = \frac{(\gamma+\mu)I_1}{\kappa},$$

$$L_1 = \frac{\left((1-p)\gamma\kappa+\alpha(\gamma+\mu)\right)I_1}{\kappa\mu},$$

$$I_1 = I_1.$$

We describe the basic reproduction number (R_0) as the number of secondary cases from primary cases [19]. If $R_0 < 1$, then an infectious individual can produce less than one new infected individual. Conversely, if $R_0 > 1$, then an infectious produce more than one new infected individual [9]. In model (1), we have the basic reproduction number below.

$$R_0 = \frac{\kappa}{\left(\mu+(1-p)\kappa+\alpha\right)\gamma+\mu(\mu+\alpha+\kappa)}.\left(\frac{b\xi\beta(\mu u_1+u_2)}{(\mu+u_2)\mu}+\frac{b\beta(1-u_1)}{\mu+u_2}\right) \quad (3)$$

The disease-free equilibrium E_0 is locally stable if $R_0 < 1$. Otherwise, it is unstable. Furthermore, endemic equilibrium is locally stable if E_1 exists and $R_0 > 1$ [20].

Formulation of the Optimal Control

In this section, we construct the objective function of the TB transmission model with two vaccination strategies. The objective function in the model (1) is a function that consists of three state variables (high-risk latent (E), low-risk latent (L), and infectious) and two control variables (vaccination to newborns (u_1) and adults (u_2)). This objective function is the cost due to the infected population and the cost of vaccination. The correlation between the cost of vaccination and the number of infected individuals is not linear. Thus, we use the quadratic function to control variables and state variables. $\omega_3 E^2$, $\omega_4 L^2$, and $\omega_5 I^2$ are the cost function due to infected individuals high-risk latent, low-risk latent, and infectious, respectively. The weight of the vaccination cost is denoted by ϕ, then ϕu_1^2 dan ϕu_2^2 are the cost function of implementing vaccination. We obtain the optimal control strategies by minimizing the following objective function below.

$$J(u_1,u_2) = \int_0^T \left(\omega_3 E^2 + \omega_4 L^2 + \omega_5 I^2 + \phi^2 u_1^2 + \phi^2 u_2^2\right) dt \quad (4)$$

Using Pontryagin's principle, the Hamiltonian function H is formed, i.e.,

$$H = \omega_3 E^2 + \omega_4 L^2 + \omega_5 I^2 + \phi^2 u_1^2 + \phi^2 u_2^2 + \sum_{i=1}^{5} z_i f_i, \quad (5)$$

where f_i denotes the right-hand side of the model (1). The adjoint variables z_i for $i = 1,2,\ldots,5$ satisfy the following co-state system

$$\dot{z}_1 = -\frac{\partial H}{\partial V} = (z_1 - z_3)\frac{\beta\xi I}{N} + z_1\mu$$

$$\dot{z}_2 = -\frac{\partial H}{\partial S} = (z_2 - z_1)u_2 + (z_2 - z_3)\frac{\beta I}{N} + z_2\mu$$

$$\dot{z}_3 = -\frac{\partial H}{\partial E} = -1 + z_3\left(\kappa + \alpha + \mu\right) - z_4\alpha - z_5\kappa$$

$$\dot{z}_4 = -\frac{\partial H}{\partial L} = -1 + z_4\mu \tag{6}$$

$$\dot{z}_5 = -\frac{\partial H}{\partial I} = -1 + \left(z_1 - z_3\right)\frac{\beta\xi V}{N} + \left(z_2 - z_3\right)\frac{\beta S}{N} + \left(z_4 - z_3\right)p\gamma + \left(z_5 - z_4\right)\gamma + z_5\mu$$

where the transversality condition $z_i\left(t\right) = 0$, for $i = 1, 2, \ldots, 5$.

To obtain the optimal controls variable, we solve the partial derivative of a Hamiltonian function concerning the controls variable $u = \left(u_1^*, u_2^*\right)$ equal to zero. Since the control variable is bounded in $\left[0,1\right]$ for all $t \in T$, then we obtain the optimal controls variable below.

$$u_1^* = \begin{cases} 0, & \text{for } u_1 \le 0 \\ \dfrac{bN\left(z_2 - z_1\right)}{2\phi}, & \text{for } 0 < u_1 < 1 \\ 1, & \text{for } u_1 \ge 0 \end{cases} \tag{7}$$

$$u_2^* = \begin{cases} 0, & \text{for } u_2 \le 0 \\ \dfrac{S\left(z_2 - z_1\right)}{2\phi}, & \text{for } 0 < u_2 < 1 \\ 1, & \text{for } u_2 \ge 0 \end{cases} \tag{8}$$

Using the initial condition x_0, we solve the variable state $\dot{x}\left(t\right) = \dfrac{\partial H}{\partial z}$, where $x = \left(V, S, E, L, I\right)$ and $z = \left(z_1, z_2, \ldots, z_5\right)$, and the co-state system $\dot{z}\left(t\right) = -\dfrac{\partial H}{\partial x}$ with transversality conditions $z_1\left(t\right) = 0,$ for $i = 1, 2, ..., 5.$ We obtain the optimal control $\left(u_1^*, u_2^*\right)$ to minimizing the cost function $J\left(u_1, u_2\right)$ as follows.

$$u_1^* = \max\left\{0, \min\left\{1, \frac{bN\left(z_2 - z_1\right)}{2\phi}\right\}\right\} \tag{9}$$

$$u_2^* = \max\left\{0, \min\left\{1, \frac{S\left(z_2 - z_1\right)}{2\phi}\right\}\right\} \tag{10}$$

In (9) and (10), the control variable is continuous. It means vaccination is given every time. If vaccination is given every few years, we transform (9) and (10) to semi-discrete function with optimal control $u^* = \left(u_1^*, u_2^*\right)$ is

$$u^*\left(t\right) = \sum_{0 \le j \le \frac{T}{h}} u^*\left(t\right)\mathbf{1}_{\left[t_j, t_j + 1\right)} \tag{11}$$

where $t_j = jh$, $\mathbf{1}_{\left[t_j, t_j + 1\right)}$ is characterization function on interval $\left[t_j, t_j + 1\right)$ and $u^*\left(t\right)$ control value that changes every h year.

Numerical Result and Discussion

This section simulates the TB model with and without control. The control used was a vaccination for newborns (u_1) and adults (u_2). Then, we compared the model simulations with different vaccination intervention times.

Vaccination was given at three different times, i.e., every two years, three years, and four years. We use parameters in TABLE 1. and initial condition $V(0)=0$, $S(0)=800$, $E(0)=50$, $L(0)=100$, and $I(0)=50$. The total population N is 1000. We assume that the cost of low-risk latent treatment is cheaper than high-risk latent. In contrast, the cost of treatment to infectious is more expensive than high-risk latent. Thus, we obtain $\omega_4 < \omega_3 < \omega_5$ with the weighting constant in the objective function are $\omega_3 = 70$, $\omega_4 = 50$, and $\omega_5 = 90$.

In the first simulation, vaccination is only given to newborns. There are four strategies for vaccination, i.e., without vaccination, vaccination every two years, three years, and four years. The dynamics of the vaccinated population are given in FIGURE 2(a), susceptible population in FIGURE 2(b), and infectious TB population in FIGURE 2(c)-(e). FIGURE 2(a). show that the number of vaccinated people with optimal control variable u_1^* every two years is higher than otherwise. The more often the vaccination is done, the vaccinated population will increase. In five years, the number of susceptible decreases from 800 to less than 100 people. It was due to the population become low-risk latent.

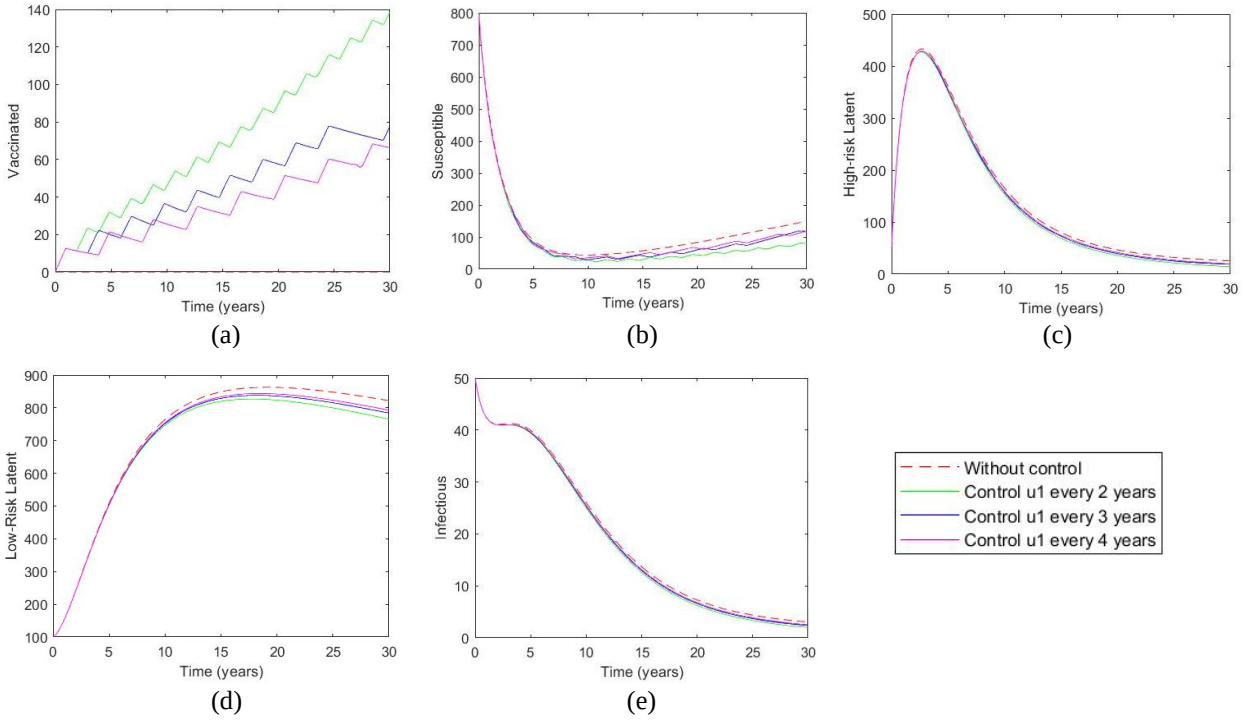

FIGURE 2. The dynamic of variable state using optimal controls variable u_1^*.

From FIGURE 2(c) and (e), the high-risk latent and infectious population decreased significantly in five to twenty years, but not with the low-risk latent population. There are more than 50% of people in the population that are low-risk latent at 20 years. Although the number of vaccinated populations increases with the increasing frequency of vaccination, the number of infected populations in each vaccination strategy is not much different from without vaccination.

In the second simulation, vaccination to adults is implemented. Meanwhile, vaccination to newborns is not used. FIGURE 3 shows the dynamic population using optimal control vaccination to adults u_2^*. In FIGURE 3(c) and (d), population of high-risk latent and infectious individuals decreases significantly for 15 years with vaccination for adults.

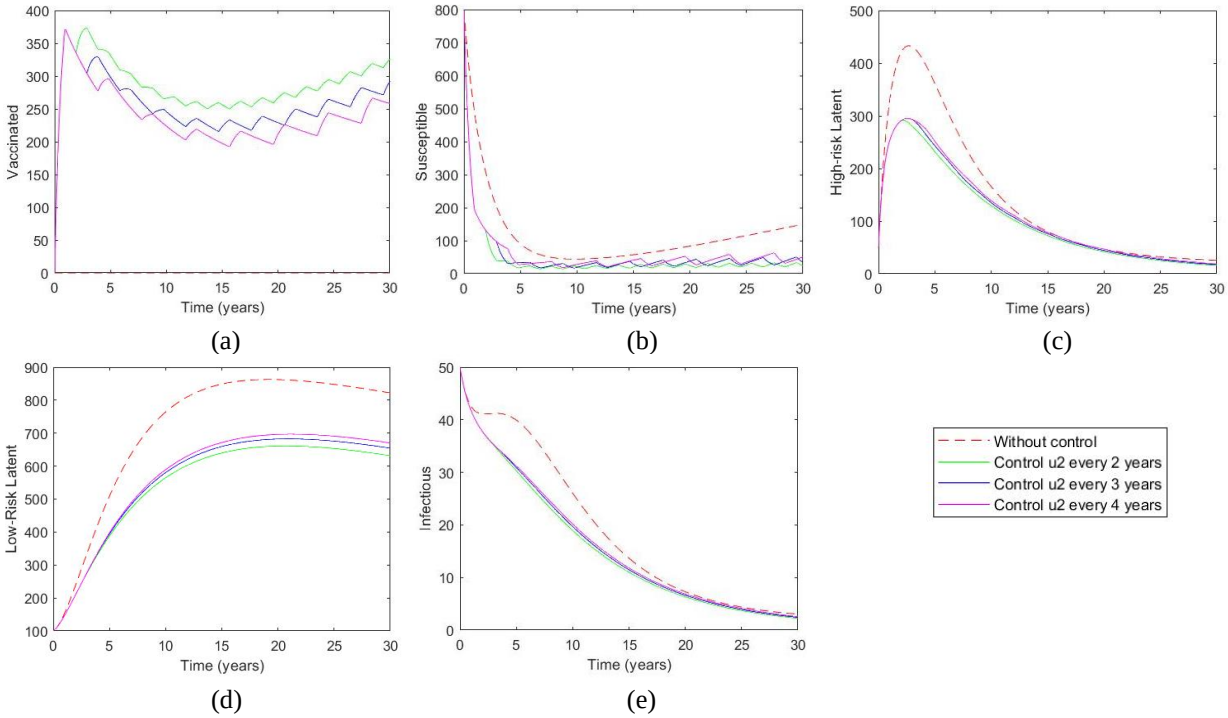

FIGURE 3. The dynamic of variable state using optimal controls u_2^*.

From FIGURE 2(c)-(e). and 3(c)-(e)., the number of infected populations in vaccination strategies to newborns at five years is more than in vaccination to adults. Control every two years makes the number of infected populations decrease. However, it did not make a big difference compared to the control every four years. It will be more effective to provide vaccinations for adults every four years because the cost of vaccination will reduce. Thus, we can conclude that vaccination to adults is more effective in reducing infected TB.

CONCLUSION

This paper simulated the optimal control of three different vaccination intervention times and without control. The result of the numerical simulation indicates that vaccination control strategies can suppress an infected population. However, vaccination control is more effective for adults than for newborns. The number of active TB using vaccination controls in adults is less than in newborns. Although the number of infected TB decreases if vaccination is given more frequently, it does not provide many different results. So, vaccination to adults will be more optimal if given every four years because it will minimize the weight cost of vaccination and reduce the number of the infected population.

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