Journal of Applied Analysis and Computation
Volume 15, Number 6, December 2025, 3246–3269
Website:http://www.jaac-online.com
DOI:10.11948/20240575

OPTIMAL CONTROL OF A TUBERCULOSIS TRANSMISSION MODEL WITH AGE STRUCTURE AND TIME DELAYS*

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Abstract Tuberculosis remains a critical global health challenge. We develop an age-structured delayed model to identify cost-effective control strategies, proving the existence and uniqueness of a non-negative solution to the model and demonstrating the continuous dependence of solutions on control variables. Through optimal control theory, we derive necessary conditions for minimizing intervention costs during the implementation of treatment programs for active tuberculosis cases and public health education campaigns. By combining theoretical analysis with simulations, we propose integrated interventions to accelerate China's progress toward achieving the WHO 2035 target (90% reduction in new cases compared to 2015).

Keywords Tuberculosis, age structure, time delays, optimal control.

MSC(2010) 35B35, 35B40.

1. Introduction

Tuberculosis (TB), one of the oldest infectious diseases, is caused by Mycobacterium tuberculosis (M.tb). Within the initial two-year period following infection, approximately 5 % of these individuals will develop active TB disease and have the potential to transmit M.tb to others through airborne. The discovery of effective drugs to treat TB in the 1940s led to a significant decline in infections and raised hopes for eradicating the disease. However, with the emergence of drug resistance, the number of people infected with TB started to increase again. Despite recent advances in the diagnosis and treatment of TB, it continues to be one of the diseases with the highest global incidence. The World Health Organization (WHO) estimates that approximately one-fourth of the global population has been infected with TB, and more than one million people die from it each year. Therefore, controlling the TB epidemic is an urgent task in the field of global public health [3]. To combat the TB epidemic, governments and international organizations allocate billions of dollars annually towards the prevention, diagnosis, treatment, care and research of tuberculosis. However, there is a significant gap between the available funds and the funding required for the WHO End TB Strategy [3,13]. The primary

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objective of this paper is to explore control strategies aimed at optimizing the utilization of existing resources in order to maximize progress towards implementing the End TB Strategy.

Theoretical analysis and numerical simulations of compartmental mathematical models play a crucial role in understanding the transmission characteristics of infectious diseases and identifying effective control strategies [7, 19, 29–33]. Bashier and Patidar [7] developed an SIR model incorporating time delays and a saturated incidence rate to investigate the optimal control problem involving vaccination and treatment as control variables. The objective was to maximize the recovered population while minimizing both the infected and susceptible populations and reducing the costs associated with implementing vaccination and treatment strategies. The efficacy of these control strategies is discussed through numerical simulation. Kang et al. [19] proposed a delayed avian influenza model with avian slaughter, and discussed the effects of time delays and avian slaughter on the disease transmission. They then investigated the optimal control problem by considering slaughter intensity and the effectiveness of education campaigns as control variables, aiming to minimize the disease outbreak and control costs. Over the years, many researchers have developed various compartment models to study the dynamics of TB transmission and strategies for its control. These models consider different characteristics of TB transmission, such as relapse, latency, drug resistance, HIV/TB co-infection, etc., as well as diverse control strategies for TB, such as vaccination, treatment, and education campaigns, etc. [4,5,8–10,12,14,16,17,20–23,25–28,34,35]. Baba et al. [5] developed a tuberculosis model that incorporates both slow and fast progression, as well as a saturated incidence rate. The control measures include screening for latent infection cases and the treatment of active tuberculosis cases. The objective was to minimize the prevalence of tuberculosis as well as the cost of treatments. Given the wide range of incubation periods for tuberculosis, ranging from a few weeks to several years, Iannelli and Milner [18] suggested that the age structure equation should be used to characterize the incubation period compartment. Guo et al. [17] developed a tuberculosis model with age structure to investigate the effects of endogenous relapse of TB, treatment for latent infection cases, and treatment for active TB cases on TB transmission. They presented effective measures for achieving the WHO's End TB Strategy through theoretical analysis and numerical simulations. The successful treatment for active TB cases typically lasts about three months or longer. Therefore, when considering treatment measures in tuberculosis models, delays in treatment are often taken into account. In [16], we developed a TB model incorporating age-dependent latency and treatment delay. Through theoretical analysis and numerical simulation of the model, we gained a deeper understanding of the spread of TB in China.

To the best of our knowledge, there is limited literature on optimal control for mathematical models that include age structure and time delays. The aim of this paper is to study the optimal control strategy using the TB model with age structure and time delays established in [16], with treatment for active TB cases and public education campaigns as control variables. The objective of this paper is to minimize control costs while ensuring that the final number of new TB cases remains as close as possible to the specified target value, which is a 90% reduction in new tuberculosis cases by 2035 relative to the 2015 baseline.

The remaining part of the paper is structured as follows: In Section 2, we introduce a TB model with control variables and prove the existence and uniqueness of the nonnegative solution of the model. Additionally, we demonstrate the continuous dependence of the solution on the control variables. In Section 3, we study the least cost-deviation problem and give the necessary conditions of optimal control through detailed derivation. In Section 4, we conduct numerical simulations by integrating the state system and the adjoint system. The simulation results demonstrate how implementing optimal control strategies with varying available funds affects the spread of TB in China. The final section provides a concise summary of the paper's conclusions.

2. Model and its basic properties

2.1. TB model with control variables

At time t, we categorize the population into five distinct compartments: susceptible individuals, whose number is denoted as $S(t)$; vaccinated individuals, whose number is denoted as $V(t)$; latent individuals (non-infectious), whose number is denoted as $\int_0^{+\infty} e(a,t)da$, where $e(a,t)$ is the density of latent individuals at latent age a; active TB individuals (infectious), whose number is denoted as $I(t)$; and recovered individuals, whose number is denoted as $R(t)$. To illustrate the interaction among these compartments, we make the following assumptions and present them in Figure 1, while Table 1 provides the meaning of related parameters.

(1) All recruitment is into the susceptible compartment.

(2) Vaccine does not always provide protection against TB. The bilinear incidence functions, $\beta(1-u_1(t))S(t)I(t)$ and $\rho\beta(1-u_1(t))V(t)I(t)$, are used to model the transmission of TB from susceptible and vaccinated compartments to the latent compartment.

(3) Many latent individuals never progress to active TB. Therefore, the latent individuals can either transition into the active TB compartment or move to the recovered compartment.

(4) The time spent in treatment, denoted as τ, is represented by the probability distribution function $\phi(\tau)$.

(5) Individuals who have recovered may experience endogenous relapse and re-enter the active TB compartment.

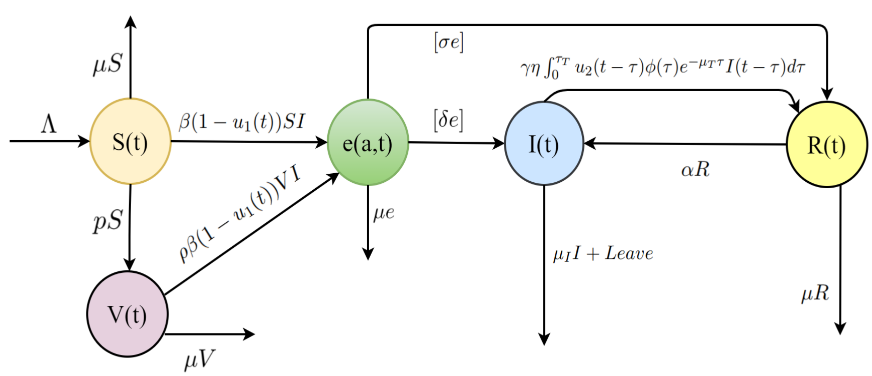

Figure 1. Schematic diagram of TB model with control variables.

Remark 2.1. The "*Leave*" in Figure 1 represents individuals who have either died during treatment or require further treatment due to unsuccessful outcomes. Also, $[\sigma e]$ stands for $\int_0^A \sigma(a)e(a,t)da$, $[\delta e]$ stands for $\int_0^A \delta(a)e(a,t)da$.

Table 1. Parameters and control variables used in Figure 1 or the model (2.1).

Notations	Description
Parameters	
Λ	the recruitment rate of the susceptible compartment
μ	the natural death rate
β	the transmission rate from active TB individuals to susceptible individuals
ρ	the parameter that reduces the transmission rate due to vaccination
p	the vaccination rate
$\delta(a), \sigma(a)$	the rate at which latent individuals progress to active TB or recovery at latent age a, respectively
μ_I, μ_T	the mortality rates for individuals with active TB and those receiving treatment, respectively, where $\mu_I > \mu, \mu_T > \mu$
α	the endogenous relapse rate of recovered individuals
γ	the treatment rate for individuals with active TB
η	the treatment success rate
τ_T	the maximal duration spent in treatment
Control variables	
$u_1(t)$	the effort of preventing susceptible individuals from developing latent cases, such as public education campaigns
$u_2(t)$	the effort of treatment for active TB cases

Based on the assumptions and the flow diagram (Figure 1), we develop the following TB model:

$$\begin{cases} \dfrac{dS(t)}{dt} = \Lambda - \beta(1-u_1(t))SI - (\mu+p)S, \\ \dfrac{dV(t)}{dt} = pS - \rho\beta(1-u_1(t))VI - \mu V, \\ \dfrac{\partial e(a,t)}{\partial t} + \dfrac{\partial e(a,t)}{\partial a} = -(\mu+\delta(a)+\sigma(a))e(a,t), \\ \dfrac{dI(t)}{dt} = \displaystyle\int_0^A \delta(a)e(a,t)da + \alpha R - (\gamma u_2(t)+\mu_I)I, \\ \dfrac{dR(t)}{dt} = \gamma\eta \displaystyle\int_0^{\tau_T} u_2(t-\tau)\phi(\tau)e^{-\mu_T\tau}I(t-\tau)d\tau + \int_0^A \sigma(a)e(a,t)da - (\mu+\alpha)R, \end{cases} \tag{2.1}$$

with the following boundary condition

$$e(0,t) = \beta(1-u_1(t))SI + \rho\beta(1-u_1(t))VI, \tag{2.2}$$

and initial conditions

$$S(0) = s_0, V(0) = v_0, e(a,0) = e_0(a), I(\theta) = i_\theta, R(0) = r_0. \tag{2.3}$$

In system (2.1), $a \in [0, A], t \in [0, T]$, $e_0(a) \in L^1_+(0, A)$, $s_0, v_0, r_0 \in R_+$ and $i_\theta \in C_+$, where A represents the maximum latent age, T denotes the control period, $C_+ = C([-\tau_T, 0], R_+)$ represents a Banach space of continuous mappings from $[-\tau_T, 0]$ to R_+, equipped with norm $\|\cdot\|$ defined by

$$\|\psi\| = \sup_{-\tau_T \le \theta \le 0} |\, \psi(\theta) \,|, \ \ \psi \in C_+, \tag{2.4}$$

and $u_1(t), u_2(t)$ are control variables belonging to the following control set

$$\begin{aligned}\mathcal{U} =&\{(u_1(t), u_2(t)) \in (L^\infty_+(0,T))^2 : 0 \le u_1(t) \le \overline{u}_1 < 1, 1 \le u_2(t) \le \overline{u}_2, \\ &\text{a.e. in } (0,T)\}.\end{aligned} \tag{2.5}$$

Remark 2.2. $u_2(t) = 1$ for $t \in [-\tau_T, 0]$.

In this paper, we make the following assumptions and notations.

(1) $\mu, \beta, p, \eta, \gamma, \rho, \mu_I, \mu_T, \alpha, \Lambda > 0$.

(2) $\delta(a), \sigma(a) \in L^\infty_+(0, +\infty)$, their essential upper bounds are $\bar{\delta} > 0$ and $\bar{\sigma} > 0$, respectively.

(3) $e(0, 0) = \beta(1 - u_1(0))S(0)I(0) + \rho\beta(1 - u_1(0))V(0)I(0)$.

2.2. Existence and uniqueness of non-negative solution

Following the approach in [24], we employ integrating factors and characteristics to derive the solution expression for system (2.1), and obtain the following representation formula for system (2.1).

$$\begin{cases} S(t) = s_0 e^{-\int_0^t(\mu+p+\beta(1-u_1(s))I(s))ds} + \Lambda \displaystyle\int_0^t e^{-\int_\xi^t(\mu+p+\beta(1-u_1(s))I(s))ds} d\xi, \\ V(t) = v_0 e^{-\int_0^t(\mu+\rho\beta(1-u_1(s))I(s))ds} + \displaystyle\int_0^t pS(\xi) e^{-\int_\xi^t(\mu+\rho\beta(1-u_1(s))I(s))ds} d\xi, \\ e(a,t) = \begin{cases} e(0, t-a) e^{-\int_0^a(\mu+\delta(s)+\sigma(s))ds}, & a \le t, \\ e_0(a-t) e^{-\int_{a-t}^a(\mu+\delta(s)+\sigma(s))ds}, & a > t, \end{cases} \\ I(t) = \begin{cases} i_t, \quad -\tau_T \le t \le 0, \\ \displaystyle\int_0^t (\alpha R(\xi) + \int_0^A \delta(a) e(a,\xi) da) e^{-\int_\xi^t(\mu_I+\gamma u_2(s))ds} d\xi \\ + i_0 e^{-\int_0^t(\mu_I+\gamma u_2(s))ds}, \quad t \ge 0, \end{cases} \\ R(t) = r_0 e^{-(\mu+\alpha)t} + \displaystyle\int_0^t (\gamma\eta \int_0^{\tau_T} u_2(\xi-\tau)\phi(\tau) e^{-\mu_T\tau} I(\xi-\tau) d\tau \\ \qquad + \displaystyle\int_0^A \sigma(a) e(a,\xi) da) e^{-\int_\xi^t(\mu+\alpha)ds} d\xi. \end{cases} \tag{2.6}$$

Take a positive number M, such that

$$\begin{aligned} &0 \le s_0, \ v_0, r_0 \le M, 0 \le e_0(a), \text{a.e. in } (0, A), \text{and } \int_0^A e_0(a) da \le M, \\ &0 \le i_t \le M, t \in [-\tau_T, 0]. \end{aligned} \tag{2.7}$$

We define the following state space

$$
\begin{aligned}
X = \{&(S(t), V(t), e(a,t), I_t(\theta), R(t)) \in L_+^\infty(0,T)^2 \times L_+^\infty(0,T; L_+^1(0,A)) \\
&\times L_+^\infty(0,T; C_+) \times L_+^\infty(0,T): \\
&S(t) \leq 2M, V(t) \leq 2M, \int_0^A e(a,t)da \leq 2M, \|I_t\| \leq 2M, R(t) \leq 2M\},
\end{aligned} \tag{2.8}
$$

where $t \in [0,T], \theta \in [-\tau_T, 0], I_t(\theta) = I(t+\theta)$ and $\|I_t\| = \sup\limits_{-\tau_T \leq \theta \leq 0} | I(t+\theta) |$.

Theorem 2.1. *For $(u_1(t), u_2(t)) \in \mathcal{U}$ and sufficiently small T, the system* (2.1) *has a unique non-negative solution $(S(t), V(t), e(a,t), I_t(\theta), R(t))$ in X.*

Proof. Define a mapping $\mathcal{L} : X \to X$, such that

$$
\begin{aligned}
\mathcal{L}(S,V,e,I,R) =&(L_1(S,V,e,I,R), L_2(S,V,e,I,R), L_3(S,V,e,I,R), \\
&L_4(S,V,e,I,R), L_5(S,V,e,I,R)),
\end{aligned} \tag{2.9}
$$

where

$$
\begin{cases}
L_1(S,V,e,I,R) = s_0 e^{-\int_0^t (\mu+p+\beta(1-u_1(s))I(s))ds} \\
\qquad\qquad + \Lambda \int_0^t e^{-\int_\xi^t (\mu+p+\beta(1-u_1(s))I(s))ds} d\xi, \\
L_2(S,V,e,I,R) = v_0 e^{-\int_0^t (\mu+\rho\beta(1-u_1(s))I(s))ds} \\
\qquad\qquad + \int_0^t pS(\xi) e^{-\int_\xi^t (\mu+\rho\beta(1-u_1(s))I(s))ds} d\xi, \\
L_3(S,V,e,I,R) = \begin{cases} e(0, t-a) e^{-\int_0^a (\mu+\delta(s)+\sigma(s))ds}, & a \leq t, \\ e_0(a-t) e^{-\int_{a-t}^a (\mu+\delta(s)+\sigma(s))ds}, & a > t, \end{cases} \\
L_4(S,V,e,I,R) = \begin{cases} i_t, \quad -\tau_T \leq t \leq 0, \\ i_0 e^{-\int_0^t (\mu_I+\gamma u_2(s))ds} \\ \quad + \int_0^t (\alpha R(\xi) + \int_0^A \delta(a) e(a,\xi) da) e^{-\int_\xi^t (\mu_I+\gamma u_2(s))ds} d\xi, \ t \geq 0, \end{cases} \\
L_5(S,V,e,I,R) = r_0 e^{-(\mu+\alpha)t} + \int_0^t (\gamma\eta \int_0^{\tau_T} u_2(\xi-\tau)\phi(\tau) e^{-\mu_T \tau} I(\xi-\tau) d\tau \\
\qquad\qquad + \int_0^A \sigma(a) e(a,\xi) da) e^{-\int_\xi^t (\mu+\alpha)ds} d\xi.
\end{cases} \tag{2.10}
$$

First, we will demonstrate that the mapping $\mathcal{L}$ maps X onto itself. Based on the properties of space X and the nature of the representations of $L_i(S,V,e,I,R), i = 1,2,3,4,5$, it is established that $L_i(S,V,e,I,R) \geq 0, i = 1,2,3,4,5$. Through a simple calculation, we obtain

$$|L_1(S,V,e,I,R)(t)| \leq |s_0| + \Lambda T.$$

Similarly, we can also deduce that

$$|L_2(S,V,e,I,R)(t)| \leq |v_0| + 2MpT.$$

Thus, when T sufficiently small, we may infer that $|L_1(S,V,e,I,R)(t)| \leq 2M$ and $|L_2(S,V,e,I,R)(t)| \leq 2M$. By performing a simple calculation, we obtain

$$\int_0^A |L_3(S,V,e,I,R)(a,t)|da \leq (\beta+\rho\beta)(2M)^2T + M.$$

Therefore, when T is sufficiently small, we can deduce that

$$\begin{aligned} L_1(S,V,e,I,R)(t) \leq 2M, L_2(S,V,e,I,R)(t) &\leq 2M, \int_0^A L_3(S,V,e,I,R)(a,t)da \\ &\leq 2M \end{aligned}$$

for $t \in [0,T]$. When $t \in [-\tau_T, 0]$,

$$|L_4(S,V,e,I,R)(t)| \leq \sup_{-\tau_T \leq t \leq 0} |i_t|,$$

by conducting a simple calculation, we know when $t \in (0,T]$

$$|L_4(S,V,e,I,R)(t)| \leq |i_0| + (\alpha 2M + \bar{\delta}2M)T.$$

For sufficiently small T, we can deduce that $|L_4(S,V,e,I,R)(t)| \leq 2M$ for $t \in [-\tau_T, T]$. Thus,

$$\|L_4(S,V,e,I,R)_t\| = \sup_{-\tau_T \leq \theta \leq 0} |L_4(S,V,e,I,R)(t+\theta)| \leq 2M, \text{for } t \in [0,T].$$

Similarly, we can also deduce that

$$|L_5(S,V,e,I,R)(t)| \leq |r_0| + (\gamma\eta\bar{u}_2 2M + \bar{\sigma}2M)T.$$

When T is sufficiently small, we have $|L_5(S,V,e,I,R)(t)| \leq 2M$. Therefore, when $(u_1(t), u_2(t)) \in \mathcal{U}$ and T is sufficiently small, we know that $\mathcal{L}$ maps X to X.

Next, we will demonstrate that the mapping $\mathcal{L}$ has a unique fixed point. To achieve this, we define the following iterative sequence

$$\begin{aligned} &(S^{(n+1)}(t), V^{(n+1)}(t), e^{(n+1)}(a,t), I_t^{(n+1)}(\theta), R^{(n+1)}(t)) \\ =&\mathcal{L}(S^{(n)}(t), V^{(n)}(t), e^{(n)}(a,t), I_t^{(n)}(\theta), R^{(n)}(t)), \end{aligned} \tag{2.11}$$

where

$$\begin{aligned} S^{(n+1)}(t) &= s_0 e^{-\int_0^t (\mu+p+\beta(1-u_1(s))I^{(n)}(s))ds} \\ &\quad + \Lambda \int_0^t e^{-\int_\xi^t (\mu+p+\beta(1-u_1(s))I^{(n)}(s))ds} d\xi, \\ V^{(n+1)}(t) &= v_0 e^{-\int_0^t (\mu+\rho\beta(1-u_1(s))I^{(n)}(s))ds} \\ &\quad + \int_0^t pS^{(n)}(\xi) e^{-\int_\xi^t (\mu+\rho\beta(1-u_1(s))I^{(n)}(s))ds} d\xi, \\ e^{(n+1)}(a,t) &= \begin{cases} e^{(n)}(0,t-a)e^{-\int_0^a (\mu+\delta(s)+\sigma(s))ds}, & a \leq t, \\ e_0(a-t)e^{-\int_{a-t}^a (\mu+\delta(s)+\sigma(s))ds}, & a > t, \end{cases} \\ I^{(n+1)}(t) &= \begin{cases} i_t, \quad -\tau_T \leq t \leq 0, \\ i_0 e^{-\int_0^t (\mu_I+\gamma u_2(s))ds} \\ + \displaystyle\int_0^t (\alpha R^{(n)}(\xi) + \int_0^A \delta(a)e^{(n)}(a,\xi)da) e^{-\int_\xi^t (\mu_I+\gamma u_2(s))ds} d\xi, \quad t \geq 0, \end{cases} \end{aligned}$$

$$R^{(n+1)}(t) = r_0 e^{-(\mu+\alpha)t} + \int_0^t (\gamma\eta \int_0^{\tau_T} u_2(\xi-\tau)\phi(\tau)e^{-\mu_T \tau} I^{(n)}(\xi-\tau)d\tau$$
$$+ \int_0^A \sigma(a)e^{(n)}(a,\xi)da)e^{-\int_\xi^t (\mu+\alpha)ds} d\xi,$$

where $e^{(n)}(0, t-a) = \beta(1-u_1(t-a))S^{(n)}(t-a)I^{(n)}(t-a) + \rho\beta(1-u_1(t-a))V^{(n)}(t-a)I^{(n)}(t-a)$, and we set $(S^{(0)}(t), V^{(0)}(t), e^{(0)}(a,t), I_t^{(0)}(\theta), R^{(0)}(t)) = 0_{L_+^\infty(0,T)^2 \times L_+^\infty(0,T;L_+^1(0,A)) \times L_+^\infty(0,T;C_+) \times L_+^\infty(0,T)} \in X$.

$$\begin{aligned} |S^{(n+1)}(t) - S^{(n)}(t)| \leq & |s_0| \int_0^t \beta(1-u_1(s))|I^{(n)}(s) - I^{(n-1)}(s)|ds \\ & + \Lambda \int_0^t \int_\xi^t \beta(1-u_1(s))|I^{(n)}(s) - I^{(n-1)}(s)|dsd\xi \\ \leq & K_S \int_0^t |I^{(n)}(s) - I^{(n-1)}(s)|ds \\ \leq & K_S \int_0^t \|I_s^{(n)} - I_s^{(n-1)}\|ds, \end{aligned} \tag{2.12}$$

where $K_S = M\beta + \Lambda\beta T$ and $\|I_s^{(n)} - I_s^{(n-1)}\| = \sup_{-\tau_T \leq \theta \leq 0} | I^{(n)}(s+\theta) - I^{(n-1)}(s+\theta) |$. Similarly, we can also deduce that

$$\begin{aligned} |V^{(n+1)}(t) - V^{(n)}(t)| \leq & |v_0| \int_0^t \rho\beta(1-u_1(s))|I^{(n)}(s) - I^{(n-1)}(s)|ds \\ & + \int_0^t pS^{(n)}(\xi) \int_\xi^t \rho\beta(1-u_1(s))|I^{(n)}(s) - I^{(n-1)}(s)|dsd\xi \\ & + p\int_0^t |S^{(n)}(s) - S^{(n-1)}(s)|ds \\ \leq & K_V \int_0^t \|I_s^{(n)} - I_s^{(n-1)}\|ds + K_V \int_0^t |S^{(n)}(s) - S^{(n-1)}(s)|ds, \end{aligned} \tag{2.13}$$

where $K_V = \max\{M\rho\beta(1+2pT), p\}$. Likewise, we can also infer that

$$\begin{aligned} & \int_0^A |e^{(n+1)}(a,s) - e^{(n)}(a,s)|da \\ \leq & \int_0^t | e^{(n)}(0,t-a) - e^{(n-1)}(0,t-a) | da \\ = & \int_0^t | e^{(n)}(0,s) - e^{(n-1)}(0,s) | ds \\ \leq & \int_0^t | \beta(S^{(n)}(s)I^{(n)}(s) - S^{(n-1)}(s)I^{(n-1)}(s)) \\ & + \rho\beta(V^{(n)}(s)I^{(n)}(s) - V^{(n-1)}(s)I^{(n-1)}(s)) | ds \\ \leq & K_e \int_0^t | (S^{(n)}(s) - S^{(n-1)}(s) | ds + K_e \int_0^t \|(I_s^{(n)} - I_s^{(n-1)}\|ds \\ & + K_e \int_0^t | (V^{(n)}(s) - V^{(n-1)}(s) | ds, \end{aligned} \tag{2.14}$$

where $K_e = (\beta + \rho\beta)2M$.

When $t \in [-\tau_T, 0]$,

$$|I^{(n+1)}(t) - I^{(n)}(t)| = 0,$$

when $t \in [0, T]$,

$$\begin{aligned}
&|I^{(n+1)}(t) - I^{(n)}(t)| \\
\le& \int_0^t |\alpha(R^{(n)}(\xi) - R^{(n-1)}(\xi)) + \int_0^A \delta(a)(e^{(n)}(a,\xi) - e^{(n-1)}(a,\xi))da| d\xi \\
\le& K_I \int_0^t |R^{(n)}(s) - R^{(n-1)}(s)|ds + K_I \int_0^t \int_0^A |e^{(n)}(a,s) - e^{(n-1)}(a,s)|dads,
\end{aligned}$$

where $K_I = max\{\alpha, \bar{\delta}\}$. Furthermore, we can infer that when $s \le t$,

$$\begin{aligned}
&|I^{(n+1)}(s) - I^{(n)}(s)| \\
\le& K_I \int_0^t |R^{(n)}(s) - R^{(n-1)}(s)|ds + K_I \int_0^t \int_0^A |e^{(n)}(a,s) - e^{(n-1)}(a,s)|dads.
\end{aligned}$$

Thus,

$$\begin{aligned}
&\|I_t^{(n+1)} - I_t^{(n)}\| \\
\le& K_I \int_0^t |R^{(n)}(s) - R^{(n-1)}(s)|ds + K_I \int_0^t \int_0^A |e^{(n)}(a,s) - e^{(n-1)}(a,s)|dads.
\end{aligned} \tag{2.15}$$

Finally we can deduce that

$$\begin{aligned}
&|R^{(n+1)}(t) - R^{(n)}(t)| \\
\le& \gamma\eta\bar{u}_2 \int_0^t \int_0^{\tau_T} \phi(\tau)|I^{(n)}(s-\tau) - I^{(n-1)}(s-\tau)|d\tau ds \\
&+ \bar{\sigma} \int_0^t \int_0^A |e^{(n)}(a,\xi) - e^{(n-1)}(a,\xi)|dad\xi \\
\le& K_R \int_0^t \|I_s^{(n)} - I_s^{(n-1)}\|ds + K_R \int_0^t \int_0^A |e^{(n)}(a,s) - e^{(n-1)}(a,s)|dads,
\end{aligned} \tag{2.16}$$

where $K_R = \max\{\gamma\eta\bar{u}_2, \bar{\sigma}\}$. Note:

$$\begin{aligned}
W_n(t) =& |S^{(n)}(t) - S^{(n-1)}(t)| + |V^{(n)}(t) - V^{(n-1)}(t)| + |R^{(n)}(t) - R^{(n-1)}(t)| \\
&+ \int_0^A |e^{(n)}(a,t) - e^{(n-1)}(a,t)|da + \|I_t^{(n)} - I_t^{(n-1)}\|, \quad n = 1, 2, \cdots.
\end{aligned} \tag{2.17}$$

According to inequalities (2.12) – (2.16), it is easy to deduce that

$$W_1(t) \le 8M \text{ and } W_{n+1}(t) \le K \int_0^t W_n(s)ds \text{ for } t \in [0, T], \tag{2.18}$$

where $K = K_S + K_V + K_e + K_I + K_R$. Further, we can deduce that

$$W_2(t) \le 8MKt,\ W_3(t) \le 8MK^2\frac{t^2}{2},\ \text{and } W_{n+1}(t) \le 8MK^n\frac{t^n}{n!} \le 8MK^n\frac{T^n}{n!}.$$

Applying a similar analysis approach as demonstrated in [24], we can conclude that there exists $(S(t), V(t), e(a,t), I_t(\theta), R(t)) \in X$, which is the limit of the sequence

$$(S^{(n)}(t), V^{(n)}(t), e^{(n)}(a,t), I_t^{(n)}(\theta), R^{(n)}(t)),\ n = 0, 1, 2, \cdots,$$

namely,

$$(S(t), V(t), e(a,t), I_t(\theta), R(t)) = \mathcal{L}(S(t), V(t), e(a,t), I_t(\theta), R(t)). \tag{2.19}$$

This means that $(S(t), V(t), e(a,t), I_t(\theta), R(t))$ is the solution of the system (2.1).

In order to prove the uniqueness of the solution of system (2.1), we assume that system (2.10) has two fixed points denoted by $(S(t), V(t), e(a,t), I_t(\theta), R(t))$ and $(\bar{S}(t), \bar{V}(t), \bar{e}(a,t), \bar{I}_t(\theta), \bar{R}(t))$, namely

$$(S(t), V(t), e(a,t), I_t(\theta), R(t)) = \mathcal{L}(S(t), V(t), e(a,t), I_t(\theta), R(t))$$

and

$$(\bar{S}(t), \bar{V}(t), \bar{e}(a,t), \bar{I}_t(\theta), \bar{R}(t)) = \mathcal{L}(\bar{S}(t), \bar{V}(t), \bar{e}(a,t), \bar{I}_t(\theta), \bar{R}(t)).$$

We replace

$$\begin{aligned}&(S^{(n+1)}(t), V^{(n+1)}(t), e^{(n+1)}(a,t), I_t^{(n+1)}(\theta), R^{(n+1)}(t)),\\&(S^{(n)}(t), V^{(n)}(t), e^{(n)}(a,t), I_t^{(n)}(\theta), R^{(n)}(t))\end{aligned}$$

in inequalities (2.12) $-$ (2.16) with

$$(S(t), V(t), e(a,t), I_t(\theta), R(t)), (\bar{S}(t), \bar{V}(t), \bar{e}(a,t), \bar{I}_t(\theta), \bar{R}(t)),$$

respectively. Setting

$$\begin{aligned}\bar{W}(t) = &|S(t) - \bar{S}(t)| + |V(t) - \bar{V}(t)| + \int_0^A |e(a,t) - \bar{e}(a,t)| da\\&+ \|I_t - \bar{I}_t\| + |R^{(n)}(t) - \bar{R}(t)|.\end{aligned} \tag{2.20}$$

Similar to the analysis presented in (2.18), we can infer that

$$\bar{W}(t) \le \bar{K} \int_0^t \bar{W}(s) ds, \tag{2.21}$$

where $\bar{K}$ is a constant. Using the classical Gronwall's lemma we may infer that $\bar{W}(t) = 0$ for all $t \in [0,T]$. Namely, $S(t) = \bar{S}(t)$, $V(t) = \bar{V}(t)$, $e(a,t) = \bar{e}(a,t), I_t(\theta) = \bar{I}_t(\theta)$, $R(t) = \bar{R}(t)$. Hence, for $(u_1(t), u_2(t)) \in \mathcal{U}$ and sufficiently small T, the system (2.1) has a unique non-negative solution

$$(S(t), V(t), e(a,t), I_t(\theta), R(t))$$

within the space X. This completes the proof of Theorem 2.1. □

Now, we investigate the Lipschitz properties of state variables

$$(S(t), V(t), e(a,t), I_t(\theta), R(t))$$

in relation to control variables $(u_1(t), u_2(t))$, which will be utilized to establish the existence of sensitivity equations.

Theorem 2.2. *In the case of sufficiently small* T*,*

$$(u_1(t), u_2(t)) \in \mathcal{U} \to (S(t), V(t), e(a,t), I_t(\theta), R(t)) \in X$$

is Lipschitz in the following sense:

$$\begin{aligned} &\| S - \widetilde{S} \|_{L^\infty(0,T)} + \| V - \widetilde{V} \|_{L^\infty(0,T)} + \| e - \widetilde{e} \|_{L^\infty(0,T;L^1(0,A))} \\ &+ \| I_t - \widetilde{I}_t \|_{L^\infty(0,T;C_+)} + \| R - \widetilde{R} \|_{L^\infty(0,T)} \\ \le & C(\| u_1 - \widetilde{u}_1 \|_{L^\infty(0,T)} + \| u_2 - \widetilde{u}_2 \|_{L^\infty(0,T)}), \end{aligned} \tag{2.22}$$

where C *represents a positive constant, the state variables of* $(u_1(t), u_2(t))$ *and* $(\widetilde{u}_1(t), \widetilde{u}_2(t))$ *are* $(S(t), V(t), e(a,t), I_t(\theta), R(t))$ *and* $(\widetilde{S}(t), \widetilde{V}(t), \widetilde{e}(a,t), \widetilde{I}_t(\theta), \widetilde{R}(t))$*, respectively.*

Proof. By employing similar arguments as the proof of the mapping $\mathcal{L}$ having a unique fixed point, we have the following inequalities, where C_1,C_2 are constants.

$$\begin{aligned} &|S(t) - \widetilde{S}(t)| \\ \le & |s_0| |e^{-\int_0^t (\mu + p + \beta(1-u_1(s))I(s))ds} - e^{-\int_0^t (\mu + p + \beta(1-\widetilde{u}_1(s))\widetilde{I}(s))ds}| \\ &+ \Lambda| \int_0^t e^{-\int_\xi^t (\mu+p+\beta(1-u_1(s))I(s))ds} d\xi \\ &- \int_0^t e^{-\int_\xi^t (\mu+p+\beta(1-\widetilde{u}_1(s))\widetilde{I}(s)ds} d\xi| \\ \le & C_1 \int_0^t |u_1(s) - \widetilde{u}_1(s)| ds + C_1 \int_0^t |I(s) - \widetilde{I}(s)| ds \\ \le & C_1 T \|u_1 - \widetilde{u}_1\|_{L^\infty(0,T)} + C_1 \int_0^t \|I_s - \widetilde{I}_s\| ds, \\ &|V(t) - \widetilde{V}(t)| \\ \le & |v_0| |e^{-\int_0^t (\mu + \rho\beta(1-u_1(s))I(s))ds} - e^{-\int_0^t (\mu + \rho\beta(1-\widetilde{u}_1(s))\widetilde{I}(s))ds}| \\ &+ | \int_0^t pS(\xi) e^{-\int_\xi^t (\mu+\rho\beta(1-u_1(s))I(s))ds} d\xi \\ &- \int_0^t p\widetilde{S}(\xi) e^{-\int_\xi^t (\mu+\rho\beta(1-\widetilde{u}_1(s))\widetilde{I}(s)ds} d\xi| \\ \le & C_2 \int_0^t |u_1(s) - \widetilde{u}_1(s)| ds + C_2 \int_0^t |S(s) - \widetilde{S}(s)| ds \\ &+ C_2 \int_0^t |I(s) - \widetilde{I}(s)| ds \\ \le & C_2 T \|u_1 - \widetilde{u}_1\|_{L^\infty(0,T)} + C_2 \int_0^t |S(s) - \widetilde{S}(s)| ds + C_2 \int_0^t \|I_s - \widetilde{I}_s\| ds, \end{aligned}$$

Similarly, we can also deduce that

$$\begin{aligned} &\int_0^A |e(a,s) - \widetilde{e}(a,s)| da \\ \le & \int_0^t | \ e(0, t-a) - \widetilde{e}(0, t-a) \ | \ da \end{aligned}$$

$$
\begin{aligned}
&\leq \int_0^t \mid \beta((1-u_1(s))S(s)I(s)-(1-\widetilde{u}_1(s))\widetilde{S}(s)\widetilde{I}(s)) \mid ds \\
&\quad + \int_0^t \mid \rho\beta((1-u_1(s))V(s)I(s)-(1-\widetilde{u}_1(s))\widetilde{V}(s)\widetilde{I}(s)) \mid ds \\
&\leq C_3(\int_0^t |u_1(s)-\widetilde{u}_1(s)|ds + \int_0^t |S(s)-\widetilde{S}(s)|ds + \int_0^t |V(s)-\widetilde{V}(s)|ds \\
&\quad + \int_0^t |I(s)-\widetilde{I}(s)|ds) \\
&\leq C_3T\|u_1-\widetilde{u}_1\|_{L^\infty(0,T)} + C_3\int_0^t |S(s)-\widetilde{S}(s)|ds \\
&\quad + C_3\int_0^t |V(s)-\widetilde{V}(s)|ds + C_3\int_0^t \|I_s-\widetilde{I}_s\|ds,
\end{aligned}
$$

where C_3 is a constant. When $t \in [-\tau_T, 0]$,

$$
|I(t)-\widetilde{I}(t)| = 0,
$$

when $t \in [0,T]$,

$$
\begin{aligned}
&|I(t)-\widetilde{I}(t)| \\
&\leq |i_0||e^{-\int_0^t(\mu_I+\gamma u_2(s))ds} - e^{-\int_0^t(\mu_I+\gamma\widetilde{u}_2(s))ds}| \\
&\quad + \int_0^t |\alpha(R(\xi)e^{-\int_\xi^t(\mu_I+\gamma u_2(s))ds} - \widetilde{R}(\xi)e^{-\int_\xi^t(\mu_I+\gamma\widetilde{u}_2(s))ds})|d\xi \\
&\quad + \int_0^t\int_0^A |\delta(a)(e(a,\xi)e^{-\int_\xi^t(\mu_I+\gamma u_2(s))ds} - \widetilde{e}(a,\xi)e^{-\int_\xi^t(\mu_I+\gamma\widetilde{u}_2(s))ds})da|d\xi \\
&\leq C_4\int_0^t |R(s)-\widetilde{R}(s)|ds + C_4\int_0^t\int_0^A |e(a,s)-\widetilde{e}(a,s)|dads \\
&\quad + C_4\int_0^t |u_2(s)-\widetilde{u}_2(s)|ds \\
&\leq C_4\int_0^t |R(s)-\widetilde{R}(s)|ds + C_4\int_0^t\int_0^A |e(a,s)-\widetilde{e}(a,s)|dads \\
&\quad + C_4T\|u_2-\widetilde{u}_2\|_{L^\infty(0,T)},
\end{aligned}
$$

where C_4 is a positive constant. Following the analysis in (2.15), we can derive the following inequality

$$
\begin{aligned}
&\|I_t-\widetilde{I}_t\| \\
&\leq C_4\int_0^t |R(s)-\widetilde{R}(s)|ds + C_4\int_0^t\int_0^A |e(a,s)-\widetilde{e}(a,s)|dads \\
&\quad + C_4T\|u_2-\widetilde{u}_2\|_{L^\infty(0,T)}, \\
&|R(t)-\widetilde{R}(t)| \\
&\leq \gamma\eta\int_0^t\int_0^{\tau_T} \phi(\tau)|u_2(s-\tau)I(s-\tau)-\widetilde{u}_2(s-\tau)\widetilde{I}(s-\tau)|d\tau ds \\
&\quad + \bar{\sigma}\int_0^t\int_0^A |e(a,\xi)-\widetilde{e}(a,\xi)|dad\xi
\end{aligned}
$$

$$\begin{aligned}&\leq C_5(\int_0^t \|I_s-\widetilde{I}_s\|ds+\int_0^t\int_0^A|e(a,s)-\widetilde{e}(a,s)|dads\\&\quad+\|u_2-\widetilde{u}_2\|_{L^\infty(0,T)}),\end{aligned}$$

where C_5 represents a constant. Note:

$$\begin{aligned}U(t)=&|S(t)-\widetilde{S}(t)|+|V(t)-\widetilde{V}(t)|+\int_0^A|e(a,t)-\widetilde{e}(a,t)|da+\|I_t-\widetilde{I}_t\|\\&+|R(t)-\widetilde{R}(t)|,\end{aligned}$$

we can deduce that

$$U(t)\leq C_6\int_0^t U(s)ds+C_6(\|u_1-\widetilde{u}_1\|_{L^\infty(0,T)}+\|u_2-\widetilde{u}_2\|_{L^\infty(0,T)}),$$

where C_6 is a constant. Thus, by Gronwall's inequality in integral form, we obtain

$$U(t)\leq C_0(\| u_1-\widetilde{u}_1 \|_{L^\infty(0,T)}+\| u_2-\widetilde{u}_2 \|_{L^\infty(0,T)}), \tag{2.23}$$

where C_0 is a positive constant. Finally, by taking the essential supremum over all $t\in[0,T]$, we can deduce from (2.23) that (2.22) holds. □

3. The least cost-deviation problem

In this section, we will consider the following optimal control problem

$$\min_{(u_1(t),u_2(t))\in\mathcal{U}} J(u_1(t),u_2(t)), \tag{3.1}$$

subject to the equations (2.1), and the objective functional $J(u_1(t),u_2(t))$ is defined as

$$\begin{aligned}J(u_1(t),u_2(t))=&\frac{1}{2}(\int_0^A\delta(a)e(a,T)da+\alpha R(T)-\bar{u}(T))^2\\&+\frac{\rho_1}{2}\int_0^T u_1(t)^2dt+\frac{\rho_2}{2}\int_0^T u_2(t)^2dt,\end{aligned} \tag{3.2}$$

where ρ_1 and ρ_2 represent non-negative constants that determine the relative importance of the terms in J. The expression $\int_0^A\delta(a)e(a,T)da+\alpha R(T)$ represents the number of newly diagnosed cases of active TB in the T^{th} year, the predetermined target value $\bar{u}(T)$ represents the ideal outcome we aim to achieve. Our optimal control policy, therefore, aims to minimize the control cost while maximizing the reduction of new active TB cases at time T to reach the target value $\bar{u}(T)$.

The sensitivity equations, which represent the derivative of the control-to-state map, are derived in the following theorem for system (2.1).

Theorem 3.1. *For each $u=(u_1(t),u_2(t))\in\mathcal{U}$ and $v=(l(t),h(t))\in(L^\infty(0,T))^2$ such that $u+\varepsilon v\in\mathcal{U}$ for sufficiently small $\varepsilon>0$, we have $\dfrac{x^\varepsilon-x}{\varepsilon}\to z$, as $\varepsilon\to 0^+$, where x^ε and x are the solutions of system (2.1) corresponding to $u+\varepsilon v$*

and u, respectively. The sensitivity functions $z \in L^\infty(0,T)^2 \times L^\infty(0,T;L^1(0,A)) \times L^\infty(0,T;C_+) \times L^\infty(0,T)$ *and satisfy the following equations:*

$$\begin{cases} \dfrac{dz_1(t)}{dt} = \beta l(t)S(t)I(t) - \beta(1-u_1(t))S(t)z_4(t) - \beta(1-u_1(t))I(t)z_1(t) \\ \qquad - (\mu+p)z_1(t), \\ \dfrac{dz_2(t)}{dt} = pz_1(t) + \rho\beta l(t)V(t)I(t) - \rho\beta(1-u_1(t))V(t)z_4(t) \\ \qquad - \rho\beta(1-u_1(t))I(t)z_2(t) - \mu z_2(t), \\ \dfrac{\partial z_3(a,t)}{\partial a} + \dfrac{\partial z_3(a,t)}{\partial t} = -(\mu+\delta(a)+\sigma(a))z_3(a,t), \\ \dfrac{dz_4(t)}{dt} = \displaystyle\int_0^A \delta(a)z_3(a,t)da + \alpha z_5(t) - \gamma h(t)I(t) - \gamma u_2(t)z_4(t) - \mu_I z_4(t), \\ \dfrac{dz_5(t)}{dt} = \displaystyle\int_0^A \sigma(a)z_3(a,t)da + \gamma\eta\int_0^{\tau_T}\phi(\tau)e^{-\mu_T\tau}z_4(t-\tau)u_2(t-\tau)d\tau \\ \qquad + \gamma\eta\displaystyle\int_0^{\tau_T}\phi(\tau)e^{-\mu_T\tau}I(t-\tau)h(t-\tau)d\tau - (\mu+\alpha)z_5(t), \\ z_3(0,t) = \beta(1-u_1(t))z_1(t)I(t) + \beta(1-u_1(t))z_4(t)S(t) - \beta l(t)S(t)I(t) \\ \qquad + \rho\beta(1-u_1(t))z_2(t)I(t) + \rho\beta(1-u_1(t))z_4(t)V(t) - \rho\beta l(t)V(t)I(t), \\ z_3(a,0) = 0,\ z_1(0) = 0,\ z_2(0) = 0,\ z_4(\theta) = 0,\ z_5(0) = 0, \\ \qquad a \in [0,A],\ t \in [0,T],\ \theta \in [-\tau_T, 0]. \end{cases} \tag{3.3}$$

Proof. Since the map $(u_1(t), u_2(t)) \in \mathcal{U} \to (S(t), V(t), e(a,t), I_t(\theta), R(t))$ is Lipschitz in L^∞ by Theorem 2.2, we have the existence of the Gâteaux derivatives z by Barbu [6] and Fister et al. [11], the sensitivity functions $z = (z_1(t), z_2(t), z_3(a,t), z_{4t}(\theta), z_5(t))$ satisfy system (3.3), where

$$z_1(t) = \lim_{\varepsilon\to0^+}\frac{S^\varepsilon(t)-S(t)}{\varepsilon},\ z_2(t) = \lim_{\varepsilon\to0^+}\frac{V^\varepsilon(t)-V(t)}{\varepsilon},\ z_5(t) = \lim_{\varepsilon\to0^+}\frac{R^\varepsilon(t)-R(t)}{\varepsilon},$$
$$z_3(a,t) = \lim_{\varepsilon\to0^+}\frac{e^\varepsilon(a,t)-e(a,t)}{\varepsilon},\ z_{4t}(\theta) = \lim_{\varepsilon\to0^+}\frac{I_t^\varepsilon(\theta)-I_t(\theta)}{\varepsilon}.$$

□

Remark 3.1. $h(t) = 0$ for $t \in [-\tau_T, 0]$.

To derive adjoint system of the state system (2.1), we define a Lagrangian, $\mathcal{L}$, based on the objective functions (3.2) and system (2.1). The $\mathcal{L}$ is defined as follows:

$$\begin{aligned} &\mathcal{L}(S,V,e,I,R,\lambda_1,\lambda_2,\lambda_3,\lambda_4,\lambda_5) \\ &= J(u_1(t),u_2(t)) - \int_0^T \lambda_1(t)(\frac{dS(t)}{dt} - \Lambda + \beta(1-u_1(t))S(t)I(t) + (\mu+p)S(t))dt \\ &\quad - \int_0^T \lambda_2(t)(\frac{dV(t)}{dt} - pS(t) + \rho\beta(1-u_1(t))V(t)I(t) + \mu V(t))dt \\ &\quad - \int_0^T\int_0^A \lambda_3(a,t)(\frac{\partial e(a,t)}{\partial a} + \frac{\partial e(a,t)}{\partial t} + (\mu+\delta(a)+\sigma(a))e(t,a))dadt \end{aligned}$$

$$
\begin{aligned}
&-\int_0^T \lambda_4(t)(\frac{dI(t)}{dt}-\int_0^A \delta(a)e(a,t)da-\alpha R(t)+(\mu_I+\gamma u_2(t))I(t))dt\\
&-\int_0^T \lambda_5(t)(\frac{dR(t)}{dt}-\gamma\eta\int_0^{\tau_T}\phi(\tau)u_2(t-\tau)e^{-\mu_T\tau}I(t-\tau)d\tau\\
&-\int_0^A \sigma(a)e(a,t)da+(\mu+\alpha)R(t))dt\\
&-\int_0^T \lambda_3(0,t)(e(0,a)-\beta(1-u_1(t))S(t)I(t)-\rho\beta(1-u_1(t))V(t)I(t))dt. \quad (3.4)
\end{aligned}
$$

From $\frac{\partial\mathcal{L}}{\partial S}, \frac{\partial\mathcal{L}}{\partial V}, \frac{\partial\mathcal{L}}{\partial e}=0,\ \frac{\partial\mathcal{L}}{\partial I(t)}+\chi_{[0,T-\tau]}(t)\frac{\partial\mathcal{L}}{\partial I(t-\tau)}|_{t=t+\tau}=0,\ \frac{\partial\mathcal{L}}{\partial R}=0$, we have

$$
\begin{cases}
-\dfrac{d\lambda_1(t)}{dt}=-(\beta(1-u_1(t))I(t)+\mu+p)\lambda_1(t)+p\lambda_2(t)+\beta(1-u_1(t))I(t)\lambda_3(0,t),\\
-\dfrac{d\lambda_2(t)}{dt}=-(\rho\beta(1-u_1(t))I(t)+\mu)\lambda_2(t)+\rho\beta(1-u_1(t))I(t)\lambda_3(0,t),\\
-\dfrac{\partial\lambda_3(a,t)}{\partial a}-\dfrac{\partial\lambda_3(a,t)}{\partial t}=\delta(a)\lambda_4(t)+\sigma(a)\lambda_5(t)-(\mu+\delta(a)+\sigma(a))\lambda_3(a,t),\\
-\dfrac{d\lambda_4(t)}{dt}=-\beta(1-u_1(t))S(t)\lambda_1(t)-\rho\beta(1-u_1(t))V(t)\lambda_2(t)\\
\qquad-(\gamma u_2(t)+\mu_I)\lambda_4(t)+(\beta(1-u_1(t))S(t)+\rho\beta(1-u_1(t))V(t))\lambda_3(0,t)\\
\qquad+\displaystyle\int_0^{\tau_T}\chi_{[0,T-\tau]}(t)\gamma\eta\phi(\tau)e^{-\mu_T\tau}u_2(t)\lambda_5(t+\tau)d\tau,\\
-\dfrac{d\lambda_5(t)}{dt}=\alpha\lambda_4(t)-(\mu+\alpha)\lambda_5(t),
\end{cases}
\tag{3.5}
$$

with transversality conditions

$$
\begin{aligned}
&\lambda_1(T)=0,\ \lambda_2(T)=0,\ \lambda_4(T)=0,\\
&\lambda_3(a,T)=\delta(a)(\int_0^A \delta(a)e(a,T)da+\alpha R(T)-\bar{u}(T)),\\
&\lambda_5(T)=\alpha(\int_0^A \delta(a)e(a,T)da+\alpha R(T)-\bar{u}(T)),\\
&\lambda_3(A,t)=0.
\end{aligned}
\tag{3.6}
$$

Where

$$
\chi_{[a,b]}(t)=\begin{cases}1,\ t\in[a,b],\\ 0,\ \text{otherwise.}\end{cases}
$$

Similar methods to Theorem 3.4 of [24] can be employed to establish the existence of solutions for the adjoint system (3.5). For similar results on the existence of solutions for the adjoint system, refer also to [6]. Next, we will present the optimality conditions for our control problem (3.2).

Theorem 3.2. *If* $(u_1^*(t),u_2^*(t))\in\mathcal{U}$ *is an optimal control pair that minimizes* (3.2), *and the corresponding optimal state solution is* $(S^*(t),V^*(t),e^*(a,t),I_t^*(\theta),R^*(t))$, *while* $(\lambda_1(t),\lambda_2(t),\lambda_3(a,t),\lambda_4(t),\lambda_5(t))$ *represents the solution of adjoint system* (3.5) *corresponding to* $(S^*(t),V^*(t),e^*(a,t),I_t^*(\theta),R^*(t))$, *then* $(u_1^*(t),u_2^*(t))$ *can be* *expressed as follows*

$$
\begin{aligned}
&u_1^*(t) = F_1(\frac{W}{\rho_1}),\ u_2^*(t) = F_2(\frac{V}{\rho_2}), a.\ e. \in (0,T),\ \textit{where},\\
&W = -\beta\lambda_1(t)S^*(t)I^*(t) - \rho\beta\lambda_2(t)V^*(t)I^*(t) + \beta S^*(t)I^*(t)\lambda_3(0,t)\\
&\qquad + \rho\beta V^*(t)I^*(t)\lambda_3(0,t),\\
&V = \gamma\lambda_4(t)I^*(t) - \gamma\eta I^*(t)\int_0^{\tau_T}\chi_{[0,T-\tau]}(t)\phi(\tau)e^{-\mu_T\tau}\lambda_5(t+\tau)d\tau,
\end{aligned}
\tag{3.7}
$$

and

$$
F_1(x) = \begin{cases} 0, x \le 0,\\ x, 0 \le x \le \overline{u}_1,\\ \overline{u}_1, x \ge \overline{u}_1, \end{cases} \qquad F_2(x) = \begin{cases} 1, x \le 1,\\ x, 1 \le x \le \overline{u}_2,\\ \overline{u}_2, x \ge \overline{u}_2. \end{cases}
$$

Proof. By utilizing the sensitivity equations (3.3), adjoint system (3.5), transversality condition (3.6) and employing integration by parts, we can derive

$$
\begin{aligned}
&\int_0^T 0\cdot z_1(t)dt + \int_0^T 0\cdot z_2(t)dt + \int_0^T\int_0^A 0\cdot z_3(a,t)dadt + \int_0^T 0\cdot z_4(t)dt\\
&+ \int_0^T 0\cdot z_5(t)dt\\
=&\int_0^T z_1(t)\{-\frac{d\lambda_1(t)}{dt} + (\beta(1-u_1(t))I(t)+\mu+p)\lambda_1(t) - p\lambda_2(t)\\
&-\beta(1-u_1(t))I(t)\lambda_3(0,t)\}dt\\
&+\int_0^T z_2(t)\{-\frac{d\lambda_2(t)}{dt} + (\rho\beta(1-u_1(t))I(t)+\mu)\lambda_2(t)\\
&-\rho\beta(1-u_1(t))I(t)\lambda_3(0,t)\}dt\\
&+\int_0^T\int_0^A z_3(a,t)\{-\frac{\partial\lambda_3(a,t)}{\partial a} - \frac{\partial\lambda_3(a,t)}{\partial t} + (\mu+\delta(a)+\sigma(a))\lambda_3(a,t) - \delta(a)\lambda_4(t)\\
&-\sigma(a)\lambda_5(t)\}dadt\\
&+\int_0^T z_4(t)\{-\frac{d\lambda_4(t)}{dt} + \beta(1-u_1(t))S(t)\lambda_1(t) + \rho\beta(1-u_1(t))V(t)\lambda_2(t)\\
&+(\gamma u_2(t)+\mu_I)\lambda_4(t) - (\beta(1-u_1(t))S(t)+\rho\beta(1-u_1(t))V(t))\lambda_3(0,t)\\
&-\int_0^{\tau_T}\chi_{[0,T-\tau]}(t)\gamma\eta\phi(\tau)e^{-\mu_T\tau}u_2(t)\lambda_5(t+\tau)d\tau\}dt\\
&+\int_0^T z_5(t)\{-\frac{d\lambda_5(t)}{dt} - \alpha\lambda_4(t) + (\mu+\alpha)\lambda_5(t)\}dt\\
=&\int_0^T \lambda_1(t)\{\frac{dz_1(t)}{dt} + (\beta(1-u_1(t))I(t) + (\mu+p))z_1(t) + \beta(1-u_1(t))S(t)z_4(t)\}dt\\
&+\int_0^T \lambda_2(t)\{\frac{dz_2(t)}{dt} + (\rho\beta(1-u_1(t))I(t)+\mu)z_2(t) - pz_1(t)\\
&+\rho\beta(1-u_1(t))V(t)z_4(t)\}dt\\
&+\int_0^T\int_0^A \lambda_3(a,t)\{\frac{\partial z_3(a,t)}{\partial a} + \frac{\partial z_3(a,t)}{\partial t} + (\mu+\delta(a)+\sigma(a))z_3(a,t)\}dadt
\end{aligned}
$$

$$
\begin{aligned}
&+\int_0^T \lambda_4(t)\{\frac{dz_4(t)}{dt}-\int_0^A \delta(a)z_3(a,t)da+(\gamma u_2(t)+\mu_I)z_4(t)-\alpha z_5(t)\}dt\\
&+\int_0^T \lambda_5(t)\{\frac{dz_5(t)}{dt}-\int_0^A \sigma(a)z_3(a,t)da+(\mu+\alpha)z_5(t)\}dt\\
&-z_1(T)\lambda_1(T)-\int_0^T z_1(t)\lambda_3(0,t)\beta(1-u_1(t))I(t)dt\\
&-z_2(T)\lambda_2(T)-\int_0^T z_2(t)\lambda_3(0,t)\rho\beta(1-u_1(t))I(t)dt\\
&-\int_0^T z_3(A,t)\lambda_3(A,t)dt+\int_0^T z_3(0,t)\lambda_3(0,t)dt-\int_0^A z_3(a,T)\lambda_3(a,T)da\\
&+\int_0^A z_3(a,0)\lambda_3(a,0)dt\\
&-z_4(T)\lambda_4(T)-\int_0^T z_4(t)\lambda_3(0,t)(\beta(1-u_1(t))S(t)+\rho\beta(1-u_1(t))V(t))dt\\
&-\gamma\eta\int_0^T z_4(t)\int_0^{\tau_T}\chi_{[0,T-\tau]}(t)\phi(\tau)e^{-\mu_T\tau}u_2(t)\lambda_5(t+\tau)d\tau dt-z_5(T)\lambda_5(T).\\
=&\int_0^T \lambda_1(t)\beta l(t)S(t)I(t)dt+\int_0^T \lambda_2(t)\rho\beta l(t)V(t)I(t)dt-\int_0^T \lambda_4(t)\gamma h(t)I(t)dt\\
&+\int_0^T \chi_{[0,T-\tau]}(t)\gamma\eta\int_0^{\tau_T}\phi(\tau)e^{-\mu_T\tau}h(t)I(t)\lambda_5(t+\tau)d\tau dt\\
&-\int_0^A \lambda_3(a,T)z_3(a,T)da-\lambda_5(T)z_5(T)\\
&-\int_0^T \lambda_3(0,t)(\beta l(t)S(t)I(t)+\rho\beta l(t)V(t)I(t))dt.
\end{aligned}
$$

Remark 3.2. The following equations were utilized in deriving the aforementioned equation

$$
\begin{aligned}
&\int_0^T \chi_{[0,T-\tau]}(t)\gamma\eta\int_0^{\tau_T}\phi(\tau)e^{-\mu_T\tau}u_2(t)z_4(t)\lambda_5(t+\tau)d\tau dt\\
=&\int_0^T \gamma\eta\int_0^{\tau_T}\phi(\tau)e^{-\mu_T\tau}u_2(t-\tau)z_4(t-\tau)\lambda_5(t)d\tau dt,\\
&\int_0^T \chi_{[0,T-\tau]}(t)\gamma\eta\int_0^{\tau_T}\phi(\tau)e^{-\mu_T\tau}h(t)I(t)\lambda_5(t+\tau)d\tau dt\\
=&\int_0^T \gamma\eta\int_0^{\tau_T}\phi(\tau)e^{-\mu_T\tau}h(t-\tau)I(t-\tau)\lambda_5(t)d\tau dt.
\end{aligned}
$$

Thus,

$$
\begin{aligned}
&\int_0^A \lambda_3(a,T)z_3(a,T)da+\lambda_5(T)z_5(T)\\
=&\int_0^T \lambda_1(t)\beta l(t)S(t)I(t)dt+\int_0^T \chi_{[0,T-\tau]}(t)\gamma\eta\int_0^{\tau_T}\phi(\tau)e^{-\mu_T\tau}h(t)I(t)\lambda_5(t+\tau)d\tau dt\\
&-\int_0^T \lambda_4(t)\gamma h(t)I(t)dt+\int_0^T \lambda_2(t)\rho\beta l(t)V(t)I(t)dt
\end{aligned}
$$

$$- \int_0^T \lambda_3(0,t)(\beta l(t)S(t)I(t) + \rho\beta l(t)V(t)I(t))dt.$$

Since $(u_1^*(t), u_2^*(t)) \in \mathcal{U}$ is an optimal control pair and we seek to minimize our control problem (3.2), and ignoring the asterisks for notational simplicity in the following calculation.

$$\begin{aligned}
0 \leq & \lim_{\varepsilon \to 0^+} \frac{J(u_1^* + \varepsilon l, u_2^* + \varepsilon h) - J(u_1^*, u_2^*)}{\varepsilon} \\
=& (\int_0^A \delta(a)e(a,T)da + \alpha R(T) - \bar{u}(T))(\int_0^A \delta(a)z_3(a,T)da + \alpha z_5(T)) \\
& + \rho_1 \int_0^T u_1(t)l(t)dt + \rho_2 \int_0^T u_2(t)h(t)dt \\
=& \int_0^A \lambda_3(a,T)z_3(a,T)da + \lambda_5(T)z_5(T) + \rho_1 \int_0^T u_1(t)l(t)dt + \rho_2 \int_0^T u_2(t)h(t)dt \\
=& \int_0^T \lambda_1(t)\beta l(t)S(t)I(t)dt + \int_0^T \lambda_2(t)\rho\beta l(t)V(t)I(t)dt - \int_0^T \lambda_4(t)\gamma h(t)I(t)dt \\
& + \int_0^T \chi_{[0,T-\tau]}(t)\gamma\eta \int_0^{\tau_T} \phi(\tau)e^{-\mu_T \tau}h(t)I(t)\lambda_5(t+\tau)d\tau dt \\
& - \int_0^T \lambda_3(0,t)(\beta l(t)S(t)I(t) + \rho\beta l(t)V(t)I(t))dt \\
& + \rho_1 \int_0^T u_1(t)l(t)dt + \rho_2 \int_0^T u_2(t)h(t)dt \\
=& \int_0^T l(t)(\rho_1 u_1(t) + \beta\lambda_1(t)S(t)I(t) + \rho\beta\lambda_2(t)V(t)I(t) - \beta S(t)I(t)\lambda_3(0,t) \\
& - \rho\beta V(t)I(t)\lambda_3(0,t))dt \\
& + \int_0^T h(t)(\rho_2 u_2(t) - \lambda_4(t)\gamma I(t) + \chi_{[0,T-\tau]}(t)\gamma\eta I(t) \int_0^{\tau_T} \phi(\tau)e^{-\mu_T \tau} \\
& \times \lambda_5(t+\tau)d\tau)dt.
\end{aligned}$$

By standard optimality arguments, we obtain the representations in (3.7). □

4. Study on TB control strategy in China

4.1. Data sources

In reference [16], we provided estimated values for some parameters and initial values in (2.1) based on statistical data from relevant institutions such as the National Bureau of Statistics of China (NBSC) and the Centers for Disease Control and Prevention (CDC) in the U. S. For the remaining parameters and initial values in (2.1), we utilized Grey Wolf Optimizer (GWO) algorithm and Markov chain Monte Carlo (MCMC) method to estimate them.

According to the methods in [16], we use the month as the unit to present numerical simulations and take $\tau_T = 9$, and we propose that the distribution function

$\phi(\tau)$ takes the following form:

$$\phi(\tau) = \begin{cases} \dfrac{x^2(9-x)e^{-\frac{x}{10}}}{A}, & 0 \le \tau \le \tau_T, \\ 0, & \text{others}, \end{cases} \tag{4.1}$$

where $A = \int_0^{\tau_T} x^2(9-x)e^{-\frac{x}{10}}dx$. Also, we define the following monotone functions to represent $\alpha(a)$ and $\delta(a)$, respectively

$$\delta(a) = \delta_1 e^{-\delta_2 a}, \quad \sigma(a) = \sigma_1(1 - e^{-\sigma_2 a}).$$

We take $S(0) = 0.75 * 1,314,480,000$ persons, $\int_0^{+\infty} e(0,a)da =$ $0.25 * 0.95 * 1,314,480,000$ persons, $I(0) = 0.25 * 0.05 * 1,314,480,000$ persons, $\Lambda = 16,289,670/12$ persons per month and $\mu = 0.0011$ per month, where we assume $e_0(a) = e(0)\mu e^{-\mu a}$. In [16], we gave estimates of the following parameters and initial values of the system (2.1) through numerical simulations

$$\hat{\Theta} = (p, \beta, \mu_T, \mu_I, \delta_1, \delta_2, \sigma_1, \sigma_2, \alpha, \gamma, V(0), R(0)),$$

and the estimated parameters and initial values are shown in Table 2.

Table 2. The estimated parameters and initial values of the system (2.1).

Parameters	Mean	Std	Parameters	Mean	Std
p	0.0014911	0.00016965	β	1.9817×10^{-1}	2.2861×10^{-12}
μ_T	0.0014518	0.00016051	μ_I	0.004051	0.00046482
δ_1	0.77362	0.08849	δ_2	0.98422	0.11407
σ_1	0.26582	0.030671	σ_2	0.49356	0.057128
α	0.00073445	8.5971×10^{-5}	γ	0.010993	0.0013183
$V(0)$	1.0556×10^{8}	6.183×10^{6}	R(0)	2.0624×10^{6}	1.1691×10^{5}

Remark 4.1. In [16], we described in detail the sources and estimates of parameters and initial values in (2.1). Since our main purpose in this paper is to optimize the formulation of control measures, we only listed the parameter values and initial values. Readers interested in the sources of parameters and initial values may refer to Reference [16].

4.2. Numerical simulations

We now present numerical simulations of the optimal control strategy. The optimal control measures were implemented from 2025 to 2035. For these simulations, we utilized the algorithm described in [15], which is based on finite-difference schemes for ordinary differential equations and partial differential equations. We take $A = 100, T = 132, \overline{u}_1 = 0.3, \overline{u}_2 = 3$, and use the population data in the subsection 4.1 and the expectation values in Table 2 as initial values and the parameter values of the system (2.1).

In the following research on the control strategy, we compare the results of the controlled scenario with those of the uncontrolled scenario and the 2035 target set by the World Health Organization (a 90 % reduction in new TB cases by 2035 compared to 2015).

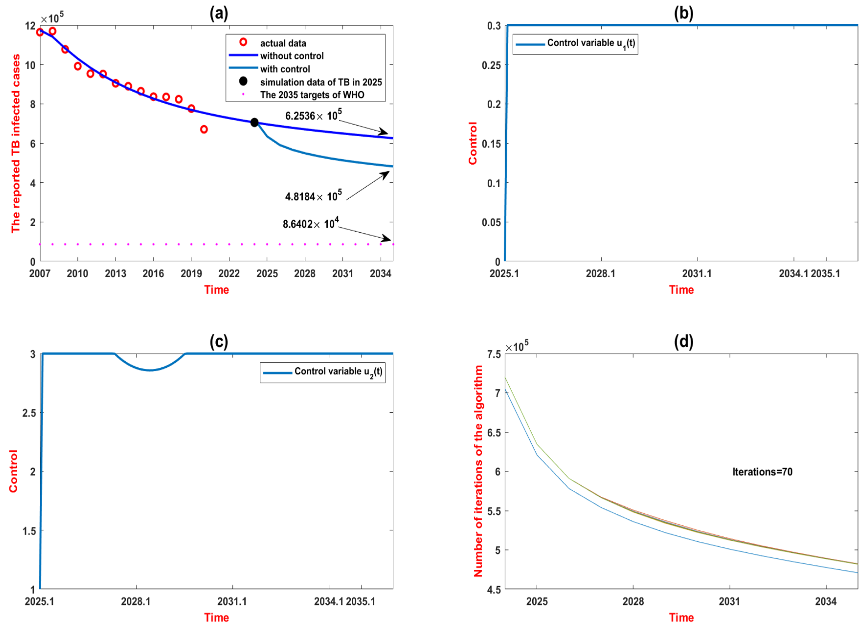

Figure 2. Optimal controls with the weight coefficients $\rho_1 = 10^6, \rho_2 = 9 \times 10^4$. **(a)** The comparison of the number of new TB cases with and without control from 2025 to 2035. **(b), (c)** Optimal control strategy. **(d)** The number of iterations of the algorithm.

Figure 2 illustrates the optimal control strategy and its corresponding impact on reducing new TB cases. Under this control strategy, almost full efforts are applied from 2025 to 2035 (see Figure 2 **(b)**, **(c)**). Specifically, Figure 2 **(a)** demonstrates that with optimal control measures in place, new TB cases are projected to decrease by 44 % by 2035 relative to 2015 levels. In contrast, without such control measures, the reduction is estimated to be only 28 % over the same period. The results in Figure 2 show that optimal control plays a significant role in TB control in China. However, the outcome of implementing the optimized control measures is far from the WHO 2035 target. This also underscores the importance of considering additional measures beyond those discussed in this paper for the effective control of tuberculosis. While treating tuberculosis patients and promoting public awareness and education are crucial, it is equally important to develop more effective vaccines and address other factors influencing the spread of tuberculosis that have not been addressed in this paper and [15].

The coefficients ρ_1 and ρ_2 are associated with the cost of implementing the control strategy. Although it is not possible to express this relationship in a functional form, it is evident that ρ_1 and ρ_2 should decrease when sufficient funds are available, and they should increase when available funds are limited. Figure 3 illustrates that as the coefficients ρ_1 and ρ_2 increase, indicating a reduction in available funds for TB control, the duration for which $u_1(t)$ and $u_2(t)$ remain at their upper bounds decreases, and the number of new TB cases at the end of the period is higher compared to Figure 2. This demonstrates the critical importance of adequate funding for effective TB control.

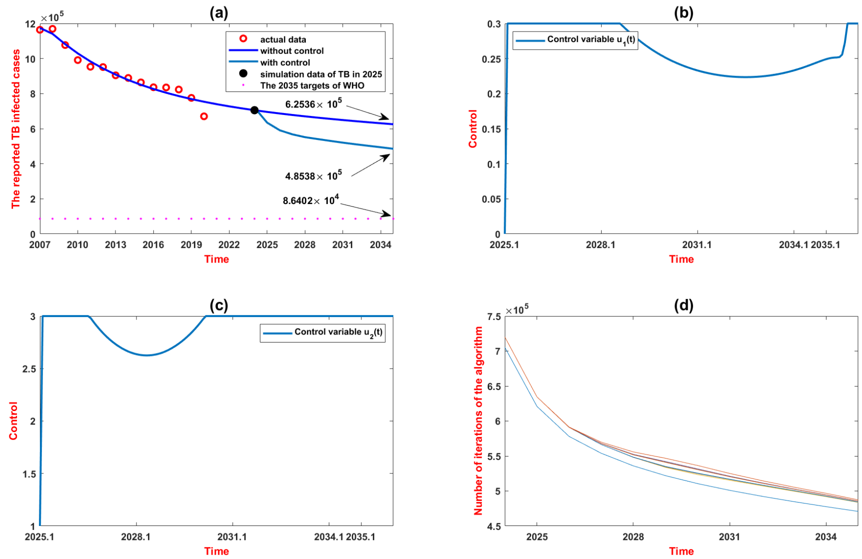

Figure 3. Optimal controls with the weight coefficients $\rho_1 = 3 \times 10^6, \rho_2 = 1 \times 10^5$. **(a)** The comparison of the number of new TB cases with and without control from 2025 to 2035. **(b), (c)** Optimal control strategy. **(d)** The number of iterations of the algorithm.

5. Conclusion

In this paper, we developed an age-structured mathematical model of TB infection to investigate the transmission dynamics of TB in China. The initial conditions and parameter values were derived from the literature [1, 2, 15]. Our objective was to propose optimal control strategies for TB based on a mathematical modeling approach. We established the existence of a unique non-negative solution and demonstrated its continuous dependence on control parameters, which is essential for deriving the necessary conditions for optimal control strategies. Due to the serious shortage of funds available for TB control, we proposed the least cost-deviation optimization problem and got the necessary conditions for optimal control. In order to demonstrate the effectiveness of the control strategies, we used forward-backward finite difference approximation and iterative methods to solve the optimality system numerically. We assigned varying values to the weight coefficients to quantitatively reflect the adequacy and insufficiency of available funds. Our study offers valuable guidance for public health authorities on optimizing the allocation of limited resources to effectively mitigate the spread of tuberculosis. Also, since the effect of the implemented optimized control measures is far from the goal of the World Health Organization in 2035, it indicates the importance of considering taking other measures beyond those discussed in this paper to effectively control tuberculosis.

Tuberculosis is endemic in numerous developing countries, including China. Given that the transmission mechanisms of TB are similar across these regions, the model and research methods established in this paper can be applicable to TB control efforts in other developing countries. However, when collecting data, it is essential to utilize country-specific data, such as the recruitment rate of the susceptible population, mortality rate, and TB transmission rate, among others.

Acknowledgements

The authors thank the referees for their comments and detailed suggestions. These have significantly improved the presentation of this paper.

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Received December 2024; Accepted April 2025; Available online May 2025.