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TRANSMISSION DYNAMICS AND OPTIMAL CONTROL OF AN AGE-STRUCTURED TUBERCULOSIS MODEL*

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Abstract Tuberculosis (TB) is still a serious threat to global public health, approximately 2 billion people worldwide are infected with TB. It is urgent to develop an optimal control strategy for TB. In this study, we propose an age-structured TB model taking into account vaccination, treatment, and relapse. We define the basic reproduction number $\mathcal{R}_0$ of the proposed model. Mathematical analyses show that the disease-free equilibrium state is globally asymptotically stable if $\mathcal{R}_0 < 1$, and the endemic equilibrium state is globally asymptotically stable if $\mathcal{R}_0 > 1$. We combined TB data in China between 2007 and 2020 and the Markov-chain Monte-Carlo method to obtain the parameters and initial values of the model. Through the partial rank correlation coefficient method, we find the most sensitive parameters to $\mathcal{R}_0$. In light of the actual controllability, the transmission coefficient of TB and the treatment rate of the infectious population are chosen as controlled parameters to study the least cost-deviation problem. By using Pontryagin's maximum principle, we obtain the necessary conditions for optimal control. We also perform numerical simulations based on the forward-backward sweep method. Finally, we present optimal strategies that may help China achieve the End Tuberculosis Strategy by 2035 proposed by World Health Organization (WHO).

Keywords Tuberculosis, age structure, global stability, optimal control, numerical simulation.

MSC(2010) 35B35, 35B40.

1. Introduction

TB is an ancient and persistent chronic infectious disease caused by a bacterium called Mycobacterium tuberculosis, the bacillus is spread from one person to another through the air, it can attack any part of the body. Pulmonary TB can be infectious, TB in other parts of the body is usually not infectious. Therefore, TB mentioned in our study refers to pulmonary TB. Although about 2 billion people are infected

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with TB bacillus, only a relatively small proportion (5-10%) of them will show symptoms of TB. As a result, we divide TB infection into two stages: latent TB infection (noninfectious stage) and TB disease (infectious stage). In general, the length of the latent period can range from weeks to several years. TB is a curable and preventable communicable disease. According to the TB Report 2021 of the World Health Organization, around 9.9 million new TB cases and about 1.5 million deaths are estimated to occur in the world in 2020 [1, 5]. It shows that the TB pandemic is one of the greatest challenges in the field of global public health. China has the third-highest TB burden worldwide, and in 2021, there were an estimated 780,000 new TB cases and 32,000 TB-related deaths [5]. Therefore, it is imperative to address the urgent issue of controlling the spread of tuberculosis in China.

Important means of preventing and controlling the spread of TB mainly include vaccination of young children and treatment of TB disease. Trollfors et al. [35] showed that the vaccine has a significant effect on latent TB infection, the estimate of vaccine effectiveness was 59 %. Without treatment, the mortality rate from TB disease is high. As a result, it is very important to treat people with TB disease, about 85 % of people with TB disease can be successfully treated. Meanwhile, treatment of latent TB infection is also essential to control the spread of TB because it substantially reduces the risk that latent TB infection progress to TB disease [1,5]. In addition, the pathogenesis of TB is complex. Burman et al. [9] believed that there was still the possibility of relapse after some TB patients were completely cured.

Theoretical analysis of mathematical models combined with numerical experiments gives us a better understanding of the characteristics of epidemic disease transmission and can help us find feasible and effective control strategies for some diseases. White et al. [38] argued that researchers don't fully understand the transmission dynamics of TB, this can be seen from the differences in mathematical models of TB [10,12,17,22,25,27,32,33,40], various factors are considered in these models, such as relapse, vaccination, treatment, drug resistance, and so on. Differences in these models in turn produce differences in the predicted impacts of interventions. This attracted researchers to develop mathematical models that are more consistent with the characteristics of TB transmission to gain insight into the transmission dynamics of TB. In 1962, Waaler et al. [37] established no-linear ordinary differential equations dividing the population into three compartments: susceptible, exposed, and infective. Based on the proposed model, they studied the spread of TB. In [40], Zhang analyzed a four-dimensional in-host TB model and obtained the analytical formula for the basic reproduction number and the threshold for forward and backward bifurcations. In recent years, many researchers have begun to combine data to characterize the spread of many real-world diseases [11,14,19,24,26,29,36]. Li et al. [26] proposed an SVEITR model with vaccination, fast and slow progression, incomplete treatment, and relapse to study TB control strategies based on case data in the United States. They believed that TB prevention and control education, timely treatment, and enhanced efficacy could effectively curb the spread of TB in the United States. A large number of TB models are applied to understand the dynamics of TB transmission, but there are few studies on infection cases and cost optimization control by age-structured tuberculosis model. Iannelli and Milner [23] believed that the age structure factor should be taken into account when modeling chronic infectious diseases such as TB and AIDS. Therefore, in this study, we will propose an age-structured TB transmission model with vaccination, relapse, and treatment of latent TB infection and TB disease. Further, the model is applied to

curb the spread of TB in China. Our objective is that the control cost is as low as possible and the final size of new TB cases falls to the given target as much as possible. Based on the findings of our study, we develop mitigation measures that may help to achieve the WHO target, that is, the incidence of tuberculosis was reduced to 10% or less by 2035 compared to 2015.

The rest of the paper is organized as follows. In the next section, we propose an age-structured TB transmission model and discuss the fundamental properties of the solution of the model. In Sections 3 and 4, we study the local and global stability of steady states respectively. In Section 5, to find the significant parameters relative to the basic reproductive number, we present numerical simulations and sensitivity analysis. In Section 6, we study the least cost-deviation optimal control problem and derive the necessary condition of optimal control. Then we perform numerical simulations based on the forward-backward sweep method. A brief conclusion is given in the last section.

2. The example of inserting a figure

The population at time t is divided into five distinct subclasses, including susceptible class $(S(t))$, vaccinated class $(V(t))$, latent class $(e(t,a))$, infectious class $(I(t))$, and recovered class $(R(t))$, the a in $e(t,a)$ represents the latent age of the exposed individuals, $e(t,a)$ is the density of the latent class at time t with latent age a, then the total number of latent individuals at time t is $\int_0^{+\infty} e(t,a)da$. The flow among these subclasses is visualized in the following flowchart (Figure 1).

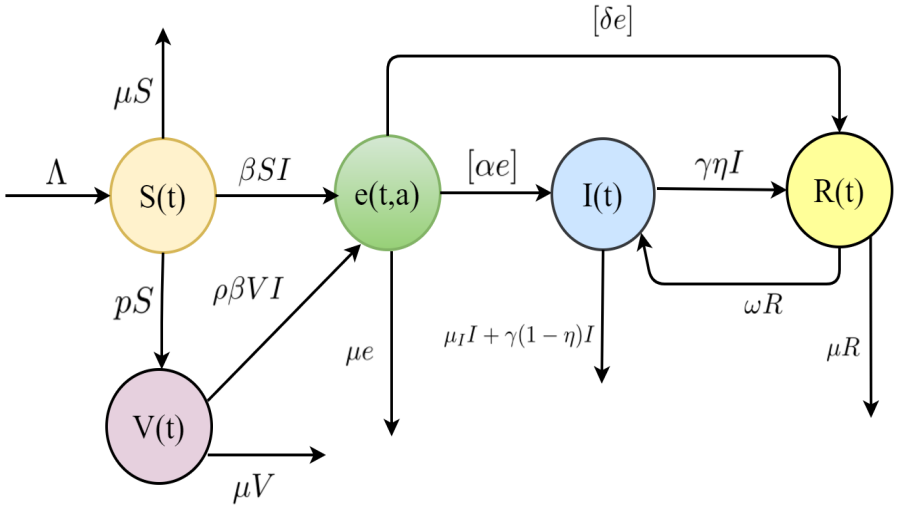

Figure 1. Flowchart of the spread of TB.

According to the above flowchart (Figure 1), we construct the following TB

transmission model:

$$\begin{cases} \dfrac{dS(t)}{dt} = \Lambda - \beta SI - \mu S - pS, \\ \dfrac{dV(t)}{dt} = pS - \rho\beta VI - \mu V, \\ \dfrac{\partial e(t,a)}{\partial t} + \dfrac{\partial e(t,a)}{\partial a} = -(\mu + \delta(a) + \alpha(a))e(t,a), \\ \dfrac{dI(t)}{dt} = \displaystyle\int_0^{+\infty} \alpha(a)e(t,a)da + \omega R - \mu_I I - \gamma I, \\ \dfrac{dR(t)}{dt} = \gamma\eta I + \displaystyle\int_0^{+\infty} \delta(a)e(t,a)da - \mu R - \omega R, \\ e(t,0) = \beta SI + \rho\beta VI, \\ e(0,a) = e_0(a),\ S(0) = s_0, V(0) = v_0,\ I(0) = i_0, R(0) = r_0, \end{cases} \tag{2.1}$$

here $e_0(a) \in L^1_+(0,+\infty)$, and $s_0, v_0, i_0, r_0 \in \mathbb{R}_+$. We summarize the list of parameters used in model (2.1) in Table 1.

Table 1. The meanings of parameters of the model (2.1).

Notations	Definitions
Λ	the recruitment number of the susceptible population per unit of time
μ	the constant natural death rate of individuals in every compartment
β	the contagion rate of tuberculosis
p	the vaccination rate of the susceptible population
ρ	the reduction coefficient of contagion rate
$\alpha(a)$	the rate distribution of latent individuals entering infectious subclass
$\delta(a)$	the rate distribution of latent individuals entering recovered subclass
γ	the rate of treatment
μ_I	the death rate of the infectious individuals
η	the proportion of effective treatment
ω	the relapse rate

To study the actual situation of TB transmission, some assumptions and notations are given:

(1) : $\mu, \beta, p, \eta, \gamma, \rho, \mu_I, \omega, \Lambda > 0$;

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

For $a \geq 0$, we let

$$k(a) = e^{-\int_0^a (\mu+\delta(s)+\alpha(s))ds}, \quad \mathscr{K}_1 = \int_0^{+\infty} \alpha(a)k(a)da, \quad \mathscr{K}_2 = \int_0^{+\infty} \delta(a)k(a)da,$$

$\mathscr{X} = \mathbb{R}^2_+ \times L^1_+(0,+\infty) \times \mathbb{R}^2_+$, its norm is

$$\| (x_1, x_2, x_3, x_4, x_5) \|_{\mathscr{X}} = \sum_{i=1,2,4,5} | x_i | + \int_0^{+\infty} | x_3(s) | ds.$$

Remark 2.1. (1) $k(a)$ denotes the probability of still being noninfectious stage at latent age a after becoming infected. $\mathscr{K}_1$ represents the number of infectious individuals produced by an infected person. $\mathscr{K}_2$ represents the number of recovered individuals produced by an infected person.

(2) $L^1_+(0,+\infty) = \{u \text{ is nonnegative and measurable in } (0,+\infty); \int_0^{+\infty} \mid u(a) \mid da < \infty\}$. $L^\infty_+(0,+\infty) = \{u \text{ is nonnegative and measurable in } (0,+\infty); |u(a)| < K \text{ a. e. in } (0,+\infty)\}$, where K is a constant. $\mathbb{R}_+ = [0,+\infty)$.

2.1. Well-posedness

Using a similar analysis of Subsection 2.2 in [19], we can show that the system (2.1) has a unique nonnegative solution. The following proposition is immediate.

Proposition 2.1. *For $x_0 \in \mathscr{X}$, the system (2.1) has a unique continuous semi-flow $\Psi(t,x_0) : \mathbb{R}_+ \times \mathscr{X} \to \mathscr{X}$, and $\Psi(0,x_0) = x_0$. In addition, the following set Υ is positively invariant for system (2.1):*

$$\Upsilon = \{x = (S(t), V(t), e(t,a), I(t), R(t)) \in \mathscr{X} : \ \| x \|_{\mathscr{X}} \leq \frac{\Lambda}{\mu}\}.$$

Using simple calculations, we arrive at the following proposition.

Proposition 2.2. *(1) For system (2.1), the semi-flow $\Psi(t,\cdot)$ is point dissipative and Υ can attract all points in the set $\mathscr{X}$;*

(2) If $C \subset \mathscr{X}$ is bounded, then $\Psi(t,C)$ is also bounded;

(3) For $x_0 \in \mathscr{X}$ with $\| x_0 \|_{\mathscr{X}} \leq r$, $S(t)$, $V(t)$, $I(t)$, $R(t)$, $\| e(t,\cdot) \|_{L^1_+} \leq \max\{r, \frac{\Lambda}{\mu}\}$.

Proof. $\| \Psi(t,x_0) \|_{\mathscr{Y}} = S(t)+V(t)+I(t)+R(t)+\int_0^{+\infty} e(t,a)da$, the time derivative of $\| \Psi(t,x_0) \|_{\mathscr{X}}$ is satisfied with the following differential inequality.

$$\frac{d}{dt} \| \Psi(t,x_0) \|_{\mathscr{X}} \leq \Lambda - \mu \| \Phi(t,x_0) \|_{\mathscr{X}} .$$

It follows from the comparison principle that

$$\| \Psi(t,x_0) \|_{\mathscr{X}} \leq \frac{\Lambda}{\mu} - e^{-\mu t}(\frac{\Lambda}{\mu} - \| x_0 \|_{\mathscr{X}}), \tag{2.2}$$

namely

$$\| \Psi(t,x_0) \|_{\mathscr{X}} \leq max\{\frac{\Lambda}{\mu}, \| x_0 \|_{\mathscr{X}}\}. \tag{2.3}$$

From inequality (2.2), we know that conclusions (1) and (2) of Proposition 2.2 hold. From inequality (2.3), we know that conclusion (3) of Proposition 2.2 holds. □

2.2. Asymptotic smoothness

Along characteristic line $t - a$=const., we integrate the third equation of system (2.1), and derive that

$$e(t,a) = \begin{cases} e_0(a-t)\dfrac{k(a)}{k(a-t)}, & 0 \leq t < a, \\ e(t-a,0)k(a), & 0 \leq a \leq t. \end{cases} \tag{2.4}$$

The following lemmas [34] will be used to prove that the semi-flow $\{\Psi(t,\cdot)\}_{t\geq 0}$ is asymptotically smooth.

Lemma 2.1. *For any bounded closed set $\mathscr{B}\subset\mathscr{X}$ that satisfies $\Psi(t,\mathscr{B})\subset\mathscr{B}$, when the following two conditions hold, the semi-flow $\Psi(t,x)=K_1(t,x)+K_2(t,x):\mathbb{R}_+\times\mathscr{X}\to\mathscr{X}$ is asymptotically smooth.*

(1) $\lim\limits_{t\to+\infty} diam K_2(t,\mathscr{B})=0$;

(2) for some $t_{\mathscr{B}}\geq 0$, $K_1(t,\mathscr{B})$ has compact closure for each $t\geq t_{\mathscr{B}}$.

For space $L^1_+(0,+\infty)$, the precompactness cannot be deduced from boundedness. Thus, we need to use the following lemma to deduce the precompactness of $L^1_+(0,+\infty)$:

Lemma 2.2. *For bounded set $\mathscr{A}\subset L^1_+(0,+\infty)$, if the following four conditions hold, then $\mathscr{A}$ is compact closure.*

(1) $\sup\limits_{g\in\mathscr{A}}\int_0^{+\infty}\mid g(s)\mid ds<+\infty$;

(2) $\lim\limits_{\theta\to+\infty}\int_\theta^{+\infty}\mid g(s)\mid ds=0$ *uniformly in* $g\in\mathscr{A}$;

(3) $\lim\limits_{\theta\to 0^+}\int_0^{+\infty}\mid g(s+\theta)-g(s)\mid ds=0$ *uniformly in* $g\in\mathscr{A}$;

(4) $\lim\limits_{\theta\to 0^+}\int_0^{\theta}\mid g(s)\mid ds=0$ *uniformly in* $g\in\mathscr{A}$.

According to the above two lemmas, we can arrive at the following theorem:

Theorem 2.1. *The continuous semi-flow $\{\Psi(t,\cdot)\}_{t\geq 0}$ generated by model* (2.1) *is asymptotically smooth.*

Proof. Define the following two semi-flows:

$$K_1(t,x)=(S(t),V(t),\widetilde{e}(t,\cdot),I(t),R(t)),\qquad K_2(t,x)=(0,0,\phi_e(t,\cdot),0,0),$$

where

$$\phi_e(t,a)=\begin{cases} e_0(a-t)\dfrac{k(a)}{k(a-t)}, & 0\leq t<a,\\ 0, & 0\leq a\leq t,\end{cases}\qquad \widetilde{e}(t,a)=\begin{cases} 0, & 0\leq t<a,\\ e(t-a,0)k(a), & 0\leq a\leq t,\end{cases}$$

for $x=(S(0),V(0),e_0(a),I(0),R(0))\in\mathscr{X}$, we can state $\Psi(t,x)=K_1(t,x)+K_2(t,x)$.

Let $\mathscr{B}\subset\mathscr{X}$ be bounded, that is, there exists a positive number $c\geq\frac{\Lambda}{\mu}$ such that $\parallel x\parallel_{\mathscr{X}}\leq c$ for each $x\in\mathscr{B}$, then we have

$$\begin{aligned}\parallel K_2(t,x)\parallel_{\mathscr{X}}&=\int_t^{+\infty}e_0(\theta-t)\frac{k(\theta)}{k(\theta-t)}d\theta\\ &=\int_0^{+\infty}e_0(u)\frac{k(u+t)}{k(u)}du\\ &=\int_0^{+\infty}e_0(u)e^{-\int_u^{u+t}(\mu+\alpha(l)+\delta(l))dl}du\\ &\leq e^{-\mu t}\parallel x\parallel_{\mathscr{X}}\leq ce^{-\mu t}.\end{aligned}$$

Thus, $\lim\limits_{t\to+\infty} diam\ K_2(t,\mathscr{B})=0$. Next, we will discuss that $K_1(t,\mathscr{B})$ is compact closure for each $t\geq 0$.

It follows from Proposition 2.2 that $S(t), V(t), I(t), R(t)$ remain in the compact set $[0, c]$ for each $t \geq 0$. In the following part, we will try to prove that $\widetilde{e}(t, a)$ remain in a precompact subset of $L^1_+(0, +\infty)$ which is not dependent on x. It follows from

$$0 \leq \widetilde{e}(t, a) = \begin{cases} 0, & 0 \leq t < a, \\ e(t-a, 0)k(a), & 0 \leq a \leq t, \end{cases}$$

and system (2.1) that

$$0 \leq \widetilde{e}(t, a) \leq \beta(1+\rho)c^2 e^{-\mu a}.$$

Consequently, conditions (1),(2) and (4) of Lemma 2.2 hold. Now, we need to show

$$\begin{aligned}
&\lim_{\theta \to 0^+} \int_0^{+\infty} \mid \widetilde{e}(t, a+\theta) - \widetilde{e}(t, a) \mid da = 0, \\
&\int_0^{+\infty} \mid \widetilde{e}(t, a+\theta) - \widetilde{e}(t, a) \mid da \\
=&\int_0^{t-\theta} \mid \widetilde{e}(t, a+\theta) - \widetilde{e}(t, a) \mid da + \int_{t-\theta}^{t} \mid \widetilde{e}(t, a) \mid da \\
=&\int_0^{t-\theta} \mid e(t-a-\theta, 0)k(a+\theta) - e(t-a, 0)k(a) \mid da + \int_{t-\theta}^{t} \mid e(t-a, 0)k(a) \mid da \\
\leq&\int_0^{t-\theta} \mid e(t-a-\theta, 0) \mid\mid k(a+\theta) - k(a) \mid da \\
&+ \int_0^{t-\theta} \mid e(t-a-\theta, 0) \mid e(t-a-\theta, 0) - e(t-a, 0) \mid\mid k(a) \mid da \\
&+ \beta(1+\rho)c^2\theta,
\end{aligned}$$

where

$$\begin{aligned}
&\int_0^{t-\theta} \mid e(t-a-\theta, 0) \mid\mid k(a+\theta) - k(a) \mid da \\
\leq&\beta(1+\rho)c^2 \Big(\int_0^{t-\theta} k(a) - k(a+\theta) da\Big) \\
=&\beta(1+\rho)c^2 \Big(\int_0^{t-\theta} k(a) da - \int_{\theta}^{t} k(s) ds\Big) \\
=&\beta(1+\rho)c^2 \Big(\int_0^{\theta} k(a) da - \int_{t-\theta}^{t} k(s) ds\Big) \\
\leq&\beta(1+\rho)c^2\theta.
\end{aligned}$$

Notice that

$$\begin{aligned}
&\mid \frac{dS(t)}{dt} \mid \leq \Lambda + \beta c^2 + (\mu + p)c, \quad \mid \frac{dV(t)}{dt} \mid \leq (p+\mu)c + \rho\beta c^2, \\
&\mid \frac{dI(t)}{dt} \mid \leq (\bar{\alpha} + \mu_I + \omega + \gamma)c,
\end{aligned}$$

then

$$\mid e(t-a-\theta, 0) - e(t-a, 0) \mid$$

$$
\begin{aligned}
&\leq \beta \mid S(t-a-\theta)I(t-a-\theta) - S(t-a)I(t-a) \mid \\
&\quad + \beta\rho \mid V(t-a-\theta)I(t-a-\theta) - V(t-a)I(t-a) \mid \\
&= \beta(\mid S(t-a-\theta) \mid\mid I(t-a-\theta) - I(t-a) \mid \\
&\quad + \mid I(t-a) \mid\mid S(t-a-\theta) - S(t-a) \mid) \\
&\quad + \beta\rho(\mid V(t-a-\theta) \mid\mid I(t-a-\theta) - I(t-a) \mid \\
&\quad + \mid I(t-a) \mid\mid V(t-a-\theta) - V(t-a) \mid) \\
&\leq \Xi\theta,
\end{aligned}
$$

where

$$\Xi = (\beta + \beta\rho)c(\bar{\alpha} + \mu_I + \omega + \gamma)c + \beta c(\Lambda + \beta c^2 + (\mu + p)c) + \beta\rho c((p + \mu)c + \rho\beta c^2).$$

Then

$$\int_0^{t-\theta} \mid e(t-a-\theta,0) - e(t-a,0) \mid\mid k(a) \mid da \leq \Xi\theta \int_0^{t-\theta} e^{-\mu s} ds \leq \frac{\Xi}{\mu}\theta.$$

Hence,

$$\int_0^{+\infty} \mid \widetilde{e}(t,a+\theta) - \widetilde{e}(t,a) \mid da \leq (2\beta(1+\rho)c^2 + \frac{\Xi}{\mu})\theta,$$

which means that condition (3) of Lemma 2.2 holds, then we can state that $\widetilde{e}(t,a)$ satisfies all conditions of Lemma 2.2 . As a consequence, we know that $K_1(t,\mathscr{B})$ has compact closure for all $t \geq 0$. It follows from Lemma 2.1 that the continuous semi-flow $\{\Psi(t,\cdot)\}_{t\geq 0}$ is asymptotically smooth. □

By using Proposition 2.2, Theorem 2.1, and Theorem 2.6 in [30], we have the following theorem.

Theorem 2.2. *For the continuous semi-flow $\{\Psi(t,\cdot)\}_{t\geq 0}$, there exists a global attractor $\mathcal{B}$ in $\mathscr{X}$ that can attract any bounded set in $\mathscr{X}$.*

3. Equilibrium states and their local stability

3.1. Existence of equilibrium states

The dynamic system characterized by (2.1) has a disease-free equilibrium state $E_0 = (S^0, V^0, 0_{L^1(0,+\infty)}, 0, 0)$, where $S^0 = \frac{\Lambda}{\mu+p}, V^0 = \frac{pS^0}{\mu}$. Define the mathematical expression of the basic reproduction number by

$$\mathscr{R}_0 = \frac{\gamma\eta\omega + (\beta S^0 + \rho\beta V^0)(\mathscr{K}_1(\mu+\omega) + \mathscr{K}_2\omega)}{(\mu_I + \gamma)(\mu + \omega)}. \tag{3.1}$$

$\mathscr{R}_0$ measures the expected number of secondary infectious individuals that a primary infectious individual may produce during the entire infection period in a completely susceptible population. Ref. [16] provides a detailed derivation of $\mathscr{R}_0$.

The endemic equilibrium state $(S^*, V^*, e^*(a), I^*, R^*)$ of system (2.1) should sat-

isfy the following equations:

$$\begin{cases} \Lambda - \beta S^* I^* - \mu S^* - pS^* = 0, \\ pS^* - \beta\rho V^* I^* - \mu V^* = 0, \\ \dfrac{de^*(a)}{da} = -(\mu + \delta(a) + \alpha(a))e^*(a), \\ e^*(0) = \beta S^* I^* + \rho\beta V^* I^*, \\ e^*(0)\mathscr{K}_1 - \mu_I I^* - \gamma I^* + \omega R^* = 0, \\ \gamma\eta I^* + e^*(0)\mathscr{K}_2 - (\mu + \omega)R^* = 0. \end{cases} \tag{3.2}$$

By doing a simple calculation, we find that I^* is the root of the following equation

$$g(I^*) = 1, \text{ where } g(I^*) = \frac{\gamma\eta\omega + (\beta S^* + \rho\beta V^*)(\mathscr{K}_1(\mu+\omega) + \mathscr{K}_2\omega)}{(\mu_I + \gamma)(\mu + \omega)}.$$

In this equation, $S^* = \frac{\Lambda}{\beta I^* + \mu + p}$, $V^* = \frac{p\Lambda}{(\beta I^* + \mu + p)(\beta\rho I^* + \mu)}$ and $e^*(a) = e^*(0)k(a)$. Clearly, we have $g(0) = \mathscr{R}_0$ and $g(+\infty) = \frac{\gamma\omega\eta}{(\mu+\omega)(\mu_I+\gamma)} < \eta \leq 1$, and it is not difficult to find $g'(I^*) < 0$. Hence, $g(I^*) = 1$ has only a positive real root if $\mathscr{R}_0 > 1$, namely, if $\mathscr{R}_0 > 1$, system (2.1) has only a endemic equilibrium state $E^* = (S^*, V^*, e^*(a), I^*, R^*)$. For the system (2.1), we arrive at the following result.

Theorem 3.1. *The disease-free equilibrium state E_0 of the system* (2.1) *is always feasible. In addition, the endemic equilibrium state E^* of the system* (2.1) *is also feasible if $\mathscr{R}_0 > 1$.*

3.2. Local stability of the equilibria

At equilibrium state $\widetilde{E} = (\widetilde{S}, \widetilde{V}, \widetilde{e}(a), \widetilde{I}, \widetilde{R})$, the linearized system of system (2.1) can be written as the following equations:

$$\begin{cases} \dfrac{ds(t)}{dt} = -\beta\widetilde{S}i(t) - \beta\widetilde{I}s(t) - \mu s(t) - ps(t), \\ \dfrac{dv(t)}{dt} = ps(t) - \beta\rho\widetilde{V}i(t) - \rho\beta\widetilde{I}v(t) - \mu v(t), \\ \dfrac{\partial \mathbf{e}(t,a)}{\partial t} + \dfrac{\partial \mathbf{e}(t,a)}{\partial a} = -(\mu + \delta(a) + \alpha(a))\mathbf{e}(t,a), \\ \dfrac{di(t)}{dt} = \displaystyle\int_0^{+\infty} \alpha(a)\mathbf{e}(t,a)da - (\mu_I + \gamma)i(t) + \omega r(t), \\ \dfrac{dr(t)}{dt} = \gamma\eta i(t) + \displaystyle\int_0^{+\infty} \delta(a)\mathbf{e}(t,a)da - (\mu + \omega)r(t), \\ \mathbf{e}(t,0) = \beta\widetilde{S}i(t) + \beta\widetilde{I}s(t) + \beta\rho\widetilde{V}i(t) + \beta\rho\widetilde{I}v(t), \end{cases} \tag{3.3}$$

where $s(t) = S(t) - \widetilde{S}$, $v = V(t) - \widetilde{V}$, $\mathbf{e}(t,a) = e(t,a) - \widetilde{e}(a)$, $i(t) = I(t) - \widetilde{I}$, , $r(t) = R(t) - \widetilde{R}$.

Let

$$k_1(\lambda) = \int_0^{+\infty} \alpha(a)e^{-\int_0^a (\lambda+\mu+\alpha(s)+\delta(s))ds}da,$$

$$k_2(\lambda) = \int_0^{+\infty} \delta(a)e^{-\int_0^a (\lambda+\mu+\alpha(s)+\delta(s))ds}da.$$

In system (3.3), we set $s(t) = S_0 e^{\lambda t}$, $v(t) = V_0 e^{\lambda t}$, $\mathbf{e}(t,a) = e_0(a)e^{\lambda t}$, $i(t) = I_0 e^{\lambda t}$, $r(t) = R_0 e^{\lambda t}$ and derive the following equations:

$$\begin{cases} \lambda S_0 = -\beta \widetilde{S} I_0 - \beta \widetilde{I} S_0 - (\mu + p) S_0, \\ \lambda V_0 = p S_0 - \beta \rho \widetilde{V} I_0 - \beta \rho \widetilde{I} V_0 - \mu V_0, \\ \dot{e}_0(a) = -(\lambda + \mu + \delta(a) + \alpha(a)) e_0(a), \\ (\lambda + \mu_I + \gamma) I_0 = \int_0^{+\infty} \alpha(a) e_0(a) da + \omega R_0, \\ (\lambda + \mu + \omega) R_0 = \gamma \eta I_0 + \int_0^{+\infty} \delta(a) e_0(a) da, \\ e_0(0) = \beta \widetilde{S} I_0 + \beta \widetilde{I} S_0 + \beta \rho \widetilde{V} I_0 + \beta \rho \widetilde{I} V_0. \end{cases} \tag{3.4}$$

By solving the system (3.4), we have

$$S_0 = \frac{-\beta \widetilde{S} I_0}{\lambda + \beta \widetilde{I} + \mu + p}, \quad V_0 = \frac{p S_0 - \rho \beta \widetilde{V} I_0}{\lambda + \mu + \rho \beta \widetilde{I}}, \quad R_0 = \frac{\gamma \eta I_0 + e_0(0) k_2(\lambda)}{\lambda + \mu + \omega},$$
$$e_0(0) = \frac{\lambda + \mu_I + \gamma - \frac{\omega \gamma \eta}{\lambda + \mu + \omega}}{k_1(\lambda) + \frac{\omega k_2(\lambda)}{\lambda + \mu + \omega}} I_0.$$

Combined the above expressions with the last equation of system (3.4), we get the following equation

$$\beta(\widetilde{S} + \widetilde{I} \frac{-\beta \widetilde{S}}{\lambda + \widetilde{I} + \mu + p} + \rho \widetilde{V} + \rho \widetilde{I} \frac{\frac{-p \beta \widetilde{S}}{(\lambda + \beta \widetilde{I} + \mu + p)} - \rho \beta \widetilde{V}}{\lambda + \mu + \rho \beta \widetilde{I}}) I_0 = \frac{(\lambda + \mu_I + \gamma) - \frac{\omega \gamma \eta}{\lambda + \mu + \omega}}{k_1(\lambda) + \frac{\omega k_2(\lambda)}{\lambda + \mu + \omega}} I_0.$$

The implies that, at equilibrium state $\widetilde{E}$, the characteristic equation of system (3.3) can be written in the following form:

$$f(\lambda) = 1,$$

where

$$f(\lambda) = \frac{A + B}{(\lambda + \beta \widetilde{I} + \mu + p)(\lambda + \beta \rho \widetilde{I} + \mu)(\lambda + \mu + \omega)(\lambda + \mu_I + \gamma)},$$
$$A = (\lambda + \mu)[\beta \widetilde{S}(\lambda + \beta \rho \widetilde{I} + \mu + p) + \beta \rho \widetilde{V}(\lambda + \beta \widetilde{I} + \mu + p)]$$
$$\times [(\lambda + \mu + \omega) k_1(\lambda) + \omega k_2(\lambda)],$$
$$B = \omega \gamma \eta (\lambda + \beta \widetilde{I} + \mu + p)(\lambda + \beta \rho \widetilde{I} + \mu).$$

Next, we will give the local stability results of the equilibria. Rigorous proof of local stability require more thorough spectral analysis, which be referred to in [28]. [28] formulated an age-structured model as an abstract non-densely defined Cauchy problem, and Lemma 3.4 in [28] shows that point spectrum and spectrum are equal. Thus, the growth rate of solutions is given by the point spectrum, so we only need to study the eigenvalues of the characteristic equation of system (2.1).

Theorem 3.2. *(i) The disease-free equilibrium state E_0 is locally asymptotically stable (unstable) for $\mathscr{R}_0 < 1$ (for $\mathscr{R}_0 > 1$).*

(ii) If the endemic equilibrium state E^* exists, then it is locally asymptotically stable.

Proof. First, let us prove the local stability of the equilibrium state E_0.

$$f(\lambda) = \frac{[\beta\frac{\Lambda}{\mu+p} + \beta\rho\frac{p}{\mu}\frac{\Lambda}{\mu+p}][(\lambda+\mu+\omega)k_1(\lambda) + \omega k_2(\lambda)] + \omega\gamma\eta}{(\lambda+\mu+\omega)(\lambda+\mu_I+\gamma)}.$$

It is easy to find $f'(\lambda) < 0$, $f(0) = \mathscr{R}_0$ and $\lim\limits_{\lambda\to+\infty} f(\lambda) = 0$. Hence, for $\mathscr{R}_0 > 1$, the equation $f(\lambda) = 1$ exists positive real root. In other words, for $\mathscr{R}_0 > 1$, the equilibrium state E_0 is unstable.

For $\mathscr{R}_0 < 1$, if $\lambda_0 = a_0 + ib_0$ is a root of $f(\lambda) = 1$ with $a_0 \geq 0$. However

$$\mid f(a_0 + ib_0) \mid \leq \mathscr{R}_0 < 1.$$

As a consequence, for $\mathscr{R}_0 < 1$, the real parts of all the eigenvalues of $f(\lambda) = 1$ are negative. That is, E_0 is locally asymptotically stable for $\mathscr{R}_0 < 1$.

Now, we are going to prove the endemic equilibrium state E^* is locally asymptotically stable.

$$\begin{aligned} f(\lambda) =& \frac{C}{(\lambda+\beta I^*+\mu+p)(\lambda+\beta\rho I^*+\mu)(\lambda+\mu+\omega)(\lambda+\mu_I+\gamma)} \\ &+ \frac{\omega\gamma\eta}{(\lambda+\mu+\omega)(\lambda+\mu_I+\gamma)}, \end{aligned}$$

where

$$C = (\lambda+\mu)[\beta S^*(\lambda+\beta\rho I^*+\mu+p)+\beta\rho V^*(\lambda+\beta I^*+\mu+p)][(\lambda+\mu+\omega)k_1(\lambda)+\omega k_2(\lambda)].$$

The equilibrium state E^* exists when $\mathscr{R}_0 > 1$, if $\lambda^* = a^* + ib^*$ is a root of $f(\lambda) = 1$ with $a^* \geq 0$. By calculating the characteristic equation $f(\lambda) = 1$, we have

$$\mid f(a^* + ib^*) \mid < g(I^*) = 1.$$

From this, we might conclude that the real parts of all the eigenvalues of $f(\lambda) = 1$ are negative if $\mathscr{R}_0 > 1$. That is, E^* is locally asymptotically stable for $\mathscr{R}_0 > 1$. □

4. Uniform persistence and global stability

4.1. Uniform persistence

In this section of the paper, we are going to analyze the uniform persistence of the system (2.1). Let us define

$$\begin{aligned} \Gamma =& \{(x_1,x_2,x_3,x_4,x_5) \in \mathscr{X} \mid \exists\ t_1,t_2 \in \mathbb{R}_+ :\ \int_0^{+\infty} \alpha(a+t_1)x_3(a)da \\ &+ \int_0^{+\infty} \delta(a+t_2)x_3(a)da + x_4 + x_5 > 0\}, \end{aligned}$$

and $\partial\Gamma = \mathscr{X} \setminus \Gamma$. We know $\mathscr{X} = \Gamma \cup \partial\Gamma$.

Theorem 4.1. *For semi-flow $\Psi(t,\cdot)$, Γ and $\partial\Gamma$ are both positively invariant sets. In addition, on set $\partial\Gamma$, the equilibrium state E_0 is globally asymptotically stable.*

Proof. Let $\Psi(0,x_0)\in\Gamma$, if $I(0)>0$ or $R(0)>0$, based on the system (2.1), it is easy to verify that $I(t)>I(0)e^{-(\gamma+\mu_I)t}>0$ or $R(t)>R(0)e^{-(\omega+\mu)t}>0$, then Γ is positively invariant set of the semi-flow $\Psi(t,\cdot)$. If $I(0)=0$ and $R(0)=0$, without loss of generality, we assume $\exists\ t_1\in\mathbb{R}_+$ such that $\int_0^{+\infty}\alpha(a+t_1)e(0,a)da>0$, then $\forall t\in[0,t_1]$, $s=t_1-t\geq 0$ such that

$$\begin{aligned}\int_0^{+\infty}\alpha(a+s)e(t,a)da&\geq\int_t^{+\infty}\alpha(a+s)e(t,a)da\\&=\int_0^{+\infty}\alpha(a+t+s)e(t,a+t)da\\&=\int_0^{+\infty}\alpha(a+t_1)e(0,a)\frac{k(a+t)}{k(a)}da\\&\geq e^{-(\mu+\bar{\alpha}+\bar{\delta})t}\int_0^{+\infty}\alpha(a+t_1)e(0,a)da\\&>0.\end{aligned}\tag{4.1}$$

If $\exists\ t_2\in(0,t_1]$ such that $I(t_2)>0$, then $I(t)>0$ for $\forall t>t_2$. Otherwise, according to (4.1), we have

$$\frac{dI(t_1)}{dt}\geq\int_0^{+\infty}\alpha(a)e(t_1,a)da>0,$$

then $I(t)>0$ for $\forall t>t_1$. It means that $\Psi(t,\Gamma)\subset\Gamma$ for all $t\geq 0$. That is to say, Γ is positively invariant set of the semi-flow $\Psi(t,\cdot)$.

Let $\Psi(0,x_0)\in\partial\Gamma$, we construct the following model

$$\begin{cases}\dfrac{\partial e(t,a)}{\partial t}+\dfrac{\partial e(t,a)}{\partial a}=-(\mu+\delta(a)+\alpha(a))e(t,a),\\ \dfrac{dI(t)}{dt}=\displaystyle\int_0^{+\infty}\alpha(a)e(t,a)da+\omega R-(\gamma+\mu_I)I(t),\\ \dfrac{dR(t)}{dt}=\displaystyle\int_0^{+\infty}\delta(a)e(t,a)da+\gamma\eta I(t)-(\mu+\omega)R(t),\\ e(t,0)=\beta SI+\beta\rho VI,\\ e(0,a)=e_0(a),\ I(0)=0,\quad R(0)=0.\end{cases}\tag{4.2}$$

Since $S(t),V(t)\leq\mathcal{C}$, where $\mathcal{C}=\max\{\parallel x_0\parallel_{\mathscr{X}},\dfrac{\Lambda}{\mu}\}$, it is easy to verify that

$$I(t)\leq\hat{I}(t),\quad R(t)\leq\hat{T}(t),\parallel e(t,s)\parallel_{L^1_+}\leq\parallel\hat{e}(t,s)\parallel_{L^1_+},\tag{4.3}$$

where

$$\begin{cases}\dfrac{\partial\hat{e}(t,a)}{\partial t}+\dfrac{\partial\hat{e}(t,a)}{\partial a}=-(\mu+\delta(a)+\alpha(a))\hat{e}(t,a),\\ \dfrac{d\hat{I}(t)}{dt}=\displaystyle\int_0^{+\infty}\alpha(a)\hat{e}(t,a)da+\omega\hat{R}-(\gamma+\mu_I)\hat{I}(t),\\ \dfrac{d\hat{R}(t)}{dt}=\displaystyle\int_0^{+\infty}\delta(a)\hat{e}(t,a)da+\gamma\eta\hat{I}(t)-(\mu+\omega)\hat{R}(t),\\ \hat{e}(t,0)=\mathcal{C}(\beta\hat{I}+\beta\rho\hat{I}),\\ \hat{e}(0,a)=e_0(a),\ \hat{I}(0)=0,\quad\hat{R}(0)=0.\end{cases}\tag{4.4}$$

Similar to the formulation (2.4), we derive

$$\hat{e}(t,a)=\begin{cases} e_0(a-t)\dfrac{k(a)}{k(a-t)}, & 0\le t<a,\\ \hat{e}(t-a,0)k(a), & 0\le a\le t. \end{cases} \tag{4.5}$$

We substitute (4.5) into the second and third equations of (4.4) and obtain the following equations

$$\begin{cases} \dfrac{d\hat{I}(t)}{dt}=\displaystyle\int_0^t \alpha(a)\hat{e}(t-a,0)k(a)da+G_1(t)+\omega\hat{R}-(\gamma+\mu_I)\hat{I}(t),\\ \dfrac{d\hat{R}(t)}{dt}=\gamma\eta\hat{I}(t)+\displaystyle\int_0^t \delta(a)\hat{e}(t-a,0)k(a)da+G_2(t)-(\mu+\omega)\hat{R}(t),\\ \hat{I}(0)=0,\quad \hat{R}(0)=0, \end{cases} \tag{4.6}$$

where

$$G_1(t)=\int_t^{+\infty}\alpha(a)e_0(a-t)\frac{k(a)}{k(a-t)}da,\ G_2(t)=\int_t^{+\infty}\delta(a)e_0(a-t)\frac{k(a)}{k(a-t)}da.$$

Since

$$G_1(t)\le\int_t^{+\infty}\alpha(a)e_0(a-t)da=\int_0^{+\infty}\alpha(a+t)e_0(a)da,$$
$$G_2(t)\le\int_t^{+\infty}\delta(a)e_0(a-t)da=\int_0^{+\infty}\delta(a+t)e_0(a)da.$$

Based on $\Psi(0,x_0)\in\partial\Gamma$, we know $G_1(t),G_2(t)\equiv 0$ for $t\ge 0$, then the system (4.6) can be rewritten in the following equations:

$$\begin{cases} \dfrac{d\hat{I}(t)}{dt}=\displaystyle\int_0^t \alpha(a)k(a)\mathcal{C}(\beta+\beta\rho)\hat{I}(t-a)da+\omega\hat{R}-(\gamma+\mu_I)\hat{I}(t),\\ \dfrac{d\hat{R}(t)}{dt}=\gamma\eta\hat{I}(t)+\displaystyle\int_0^t \delta(a)k(a)\mathcal{C}(\beta+\beta\rho)\hat{I}(t-a)da-(\mu+\omega)\hat{R}(t),\\ \hat{I}(0)=0,\quad \hat{R}(0)=0. \end{cases}$$

It is easy to conclude that the system (4.6) exists a unique solution $\hat{I}(t)\equiv 0,\hat{R}(t)\equiv 0$ for $t\ge 0$. Depending on (4.4),(4.5), we know that $\hat{e}(t,s)=0$ for $0\le s\le t$, thus,

$$\begin{aligned} \|\,\alpha(a+u)\hat{e}(t,a)\,\|_{L^1_+}&=\int_t^{+\infty}\alpha(a+u)e_0(a-t)\frac{k(a)}{k(a-t)}da\\ &\le\|\,\alpha(t+u+s)e_0(s)\,\|_{L^1_+}=0,\\ \|\,\delta(a+u)\hat{e}(t,a)\,\|_{L^1_+}&=\int_t^{+\infty}\delta(a+u)e_0(a-t)\frac{k(a)}{k(a-t)}da\\ &\le\|\,\delta(t+u+s)e_0(s)\,\|_{L^1_+}=0. \end{aligned}$$

According to (4.3), we can conclude that $I(t)=0,\ R(t)=0,$

$$\|\,\alpha(a+t_1)e(t,a)\,\|_{L^1_+}=0,\|\,\delta(a+t_2)e(t,a)\,\|_{L^1_+}=0,\ \text{for all } t,t_1,t_2\ge 0.$$

Thus, $\partial\Gamma$ is positively invariant set of the semi-flow $\Psi(t,\cdot)$.

On set $\partial\Gamma$, system (2.1) reduces to the following system:

$$\begin{cases} \dfrac{dS(t)}{dt} = \Lambda - \mu S(t) - pS, \\ \dfrac{dV(t)}{dt} = pS - \mu V(t). \end{cases} \tag{4.7}$$

We can easily find that $\lim\limits_{t\to+\infty} S(t) = \frac{\Lambda}{\mu+p}$ and $\lim\limits_{t\to+\infty}(S(t)+V(t)) = \frac{\Lambda}{\mu}$. Hence, $\lim\limits_{t\to+\infty} V(t) = \frac{\Lambda p}{\mu(\mu+p)}$. In other words, on set $\partial\Gamma$, the equilibrium state E_0 is globally asymptotically stable. □

Theorem 4.2. *the semi-flow $\{\Psi(t,\cdot)\}_{t\geq 0}$ is uniformly persistent with respect to $(\Gamma,\ \partial\Gamma)$ when $\mathscr{R}_0 > 1$. Apart from this, there is a global attractor $\mathcal{B}_0 \subset \Gamma$ for $\{\Psi(t,\cdot)\}_{t\geq 0}$.*

Proof. Theorem 4 has proved that 4.1 that E_0 is globally stable on set $\partial\Gamma$. It follows from Theorem 4.2 in [21] that we need only to verify

$$\omega_s(E_0) \cap \Gamma = \emptyset,$$

where $\omega_s(E_0) = \{x \in \mathscr{X} \mid \lim\limits_{t\to+\infty} \Psi(t,x) = E_0\}$. Assume that there is a $x_0 \in \Gamma \cap \omega_s(E_0)$, then there exists a sequence $\{x_n\} \subset \Gamma$ such that

$$\parallel \Psi(t,x_n) - E_0 \parallel_{\mathscr{X}} < \frac{1}{n}, t \geq 0.$$

Let us define $\Psi(t,x_n) = (S_n(t), V_n(t), e_n(t,\cdot), I_n(t), R_n(t))$. Then

$$\frac{\Lambda}{\mu+p} - \frac{1}{n} < S_n(t) < \frac{\Lambda}{\mu+p} + \frac{1}{n}, \qquad \frac{\Lambda p}{\mu(\mu+p)} - \frac{1}{n} < V_n(t) < \frac{\Lambda p}{\mu(\mu+p)} + \frac{1}{n},$$

and $\Psi(t,x_n) \subset \Gamma$, for all $t \geq 0$. Similar to the analysis that Γ is positively invariant set in Theorem 4.1, we know that there exists $t_0 \geq 0$ such that $I(t) > 0$ or $R(t) > 0$ for all $t \geq t_0$, we may as well let $t_0 = 0$ and $I(0) > 0$. If n is sufficiently large, we can assume that $\frac{\Lambda}{\mu+p} > \frac{1}{n}$, $\frac{\Lambda p}{\mu(\mu+p)} > \frac{1}{n}$ and

$$f(n) = \frac{\gamma\eta\omega + (\beta(S^0 - \frac{1}{n}) + \rho\beta(V^0 - \frac{1}{n}))(\mathscr{K}_1(\mu+\omega) + \mathscr{K}_2\omega)}{(\mu_I+\gamma)(\mu+\omega)} > 1 \tag{4.8}$$

when $\mathcal{R}_0 > 1$.

Next, we build the following system

$$\begin{cases} \dfrac{\partial\hat{e}(t,a)}{\partial t} + \dfrac{\partial\hat{e}(t,a)}{\partial a} = -(\mu + \delta(a) + \alpha(a))\hat{e}(t,a), \\ \dfrac{d\hat{I}(t)}{dt} = \displaystyle\int_0^{+\infty} \alpha(a)\hat{e}(t,a)da + \omega\hat{R} - (\gamma+\mu_I)\hat{I}(t), \\ \dfrac{d\hat{R}(t)}{dt} = \displaystyle\int_0^{+\infty} \delta(a)\hat{e}(t,a)da + \gamma\eta\hat{I}(t) - (\mu+\omega)\hat{R}(t), \\ \hat{e}(t,0) = (\beta(\dfrac{\Lambda}{\mu+p} - \dfrac{1}{n}) + \beta\rho(\dfrac{\Lambda p}{\mu(\mu+p)} - \dfrac{1}{n}))\hat{I}, \\ \hat{e}(0,a) = e_0(a),\ \hat{I}(0) = i_0,\quad \hat{R}(0) = r_0. \end{cases} \tag{4.9}$$

Similar to the analysis in Subsection 2.2, we know that the system (4.9) has a unique nonnegative solution. It follows from the comparison principle that

$$I(t) \geq \hat{I}(t), \quad R(t) \geq \hat{R}(t), e(t,s) \geq \hat{e}(t,s). \tag{4.10}$$

Similar to the formulation (2.4), we can obtian

$$\hat{e}(t,\theta) = \begin{cases} e_0(a-t)\dfrac{k(a)}{k(a-t)}, & 0 \leq t < a, \\ \hat{e}(t-a,0)k(a), & 0 \leq a \leq t. \end{cases} \tag{4.11}$$

We substitute (4.11) into the second and third equations of (4.9) and obtain the following inequations

$$\begin{cases} \dfrac{d\hat{I}(t)}{dt} \geq \displaystyle\int_0^t \alpha(a)k(a)(\beta(\frac{\Lambda}{\mu+p} - \frac{1}{n}) + \beta\rho(\frac{\Lambda p}{\mu(\mu+p)} - \frac{1}{n}))\hat{I}(t-a)da \\ \qquad\qquad - (\mu_I + \gamma)\hat{I}(t) + \omega\hat{R}(t), \\ \dfrac{d\hat{R}(t)}{dt} \geq \gamma\eta\hat{I}(t) + \displaystyle\int_0^t \delta(a)k(a)(\beta(\frac{\Lambda}{\mu+p} - \frac{1}{n}) + \beta\rho(\frac{\Lambda p}{\mu(\mu+p)} - \frac{1}{n}))\hat{I}(t-a)da \\ \qquad\qquad - (\mu+\omega)\hat{R}(t), \\ \hat{I}(0) = i_0, \quad \hat{R}(0) = r_0. \end{cases} \tag{4.12}$$

If $\hat{I}(t)$ and $\hat{R}(t)$ are bounded, we take the Laplace transform of both sides of (4.12) and obtain the following inequations

$$\begin{cases} -\hat{I}(0) + \lambda\mathcal{L}[\hat{I}](\lambda) \geq \mathcal{L}[u_1](\lambda)\mathcal{L}[\hat{I}](\lambda) - (\gamma+\mu_I)\mathcal{L}[\hat{I}](\lambda) + \omega\mathcal{L}[\hat{R}](\lambda), \\ -\hat{R}(0) + \lambda\mathcal{L}[\hat{R}](\lambda) \geq \gamma\eta\mathcal{L}[\hat{I}](\lambda) + \mathcal{L}[u_2](\lambda)\mathcal{L}[\hat{I}](\lambda) - (\mu+\omega)\mathcal{L}[\hat{R}](\lambda), \end{cases} \tag{4.13}$$

where

$$\begin{aligned} &\mathcal{L}[\hat{I}](\lambda) = \int_0^{+\infty} e^{-\lambda t}\hat{I}(t)dt, \quad \mathcal{L}[\hat{R}](\lambda) = \int_0^{+\infty} e^{-\lambda t}\hat{R}(t)dt, \\ &\mathcal{L}[u_1](\lambda) = \int_0^{\infty} \alpha(a)k(a)(\beta(\frac{\Lambda}{\mu+p} - \frac{1}{n}) + \beta\rho(\frac{\Lambda p}{\mu(\mu+p)} - \frac{1}{n}))e^{-\lambda a}da, \\ &\mathcal{L}[u_2](\lambda) = \int_0^{\infty} \delta(a)k(a)(\beta(\frac{\Lambda}{\mu+p} - \frac{1}{n}) + \beta\rho(\frac{\Lambda p}{\mu(\mu+p)} - \frac{1}{n}))e^{-\lambda a}da. \end{aligned}$$

From inequations (4.13), we can derive

$$\begin{aligned} &\frac{(\lambda+\mu+\omega)(\lambda+\mu_I+\gamma)}{\omega}[1 - \frac{\omega\gamma\eta + \omega\mathcal{L}[u_2](\lambda) + \mathcal{L}[u_1](\lambda)(\lambda+\mu+\omega)}{(\lambda+\mu+\omega)(\lambda+\mu_I+\gamma)}]\mathcal{L}[\hat{I}](\lambda) \\ \geq &\hat{R}(0) + \frac{\lambda+\mu+\omega}{\omega}\hat{I}(0) > 0. \end{aligned} \tag{4.14}$$

Applying the Dominated Convergence Theorem, we know $\mathcal{L}[u_i](\lambda) \to \mathcal{L}[u_i](0), (i = 1, 2)$ as $\lambda \to 0$. Since

$$\frac{(\lambda+\mu+\omega)(\lambda+\mu_I+\gamma)}{\omega}[1 - \frac{\omega\gamma\eta + \omega\mathcal{L}[u_2](\lambda) + \mathcal{L}[u_1](\lambda)(\lambda+\mu+\omega)}{(\lambda+\mu+\omega)(\lambda+\mu_I+\gamma)}] \mid_{\lambda=0}$$

$$=\frac{(\mu+\omega)(\mu_I+\gamma)}{\omega}(1-f(n))<0,$$

which means that there exists a positive number ε such that

$$\frac{(\lambda+\mu+\omega)(\lambda+\mu_I+\gamma)}{\omega}[1-\frac{\omega\gamma\eta+\omega\mathcal{L}[u_2](\lambda)+\mathcal{L}[u_1](\lambda)(\lambda+\mu+\omega)}{(\lambda+\mu+\omega)(\lambda+\mu_I+\gamma)}]<0,$$

for each $\lambda\in[0,\varepsilon)$. It follows from (4.14) that $\mathcal{L}[\hat{I}](\lambda)<0$ for each $\lambda\in(0,\varepsilon)$. But there is a contradiction with the nonnegative of $\hat{I}(t)(t\geq 0)$. that is to say, $\hat{I}(t)$ and $\hat{R}(t)$ cannot both be bounded. It follows from $I(t)\geq\hat{I}(t)$ and $R(t)\geq\hat{R}(t)$ that $I(t),R(t)$ cannot both be bounded. It is a contradiction with Proposition 2.2. Thus, $\omega_s(E_0)\cap\Gamma=\emptyset$ holds. With Theorem 4.2 [21], it is easy to show that semiflow $\{\Psi(t,\cdot)\}_{t\geq 0}$ of system (2.1) is uniformly persistent. With Theorem 3.7 [30], we know that there is a global attractor $\mathcal{B}_0\subset\Gamma$ for $\{\Psi(t,\cdot)\}_{t\geq 0}$. □

4.2. Global stability

Theorem 4.3. *For system* (2.1)*, if* $\mathcal{R}_0<1$*, the disease-free equilibrium state* E_0 *is globally asymptotically stable.*

Proof. Let us define $h(x)=x-\ln x-1$. It is easy to conclude that $h(x)$ achieves a global minimum at $x=1$ and $h(1)=0$. Thus $h(x)>0$ for all $x>0$ and $x\neq 1$. By following the same reasoning as Lemma 4.2 [8], we can verify that any solution of system (2.1) on $\mathcal{B}$ is satisfied that $S(t),V(t)>0$ for any $t\in\mathbb{R}$. Next, we define the Lyapunov function $W=W_0+W_1+W_2+W_3$ on $\mathcal{B}$, It follows from the compactness of $\mathcal{B}$ that W is bounded on $\mathcal{B}$, where

$$W_0=(\mathscr{K}_1+\frac{\omega}{\mu+\omega}\mathscr{K}_2)S^0h(\frac{S}{S^0}),\ S^0=\frac{\Lambda}{\mu+p},\ W_2=I,\ W_3=\frac{\omega}{\mu+\omega}R,$$
$$W_1=\int_0^{+\infty}F(a)e(t,a)da,\ F(a)=\int_a^{+\infty}(\alpha(u)+\frac{\omega}{\mu+\omega}\delta(u))e^{-\int_a^u(\mu+\alpha(s)+\delta(s))ds}du.$$

The derivatives of W_0, W_1, W_2, W_3 along solutions of system (2.1) are calculated as

$$\begin{aligned}
\dot{W}_0&=(\mathscr{K}_1+\frac{\omega}{\mu+\omega}\mathscr{K}_2)(-(\mu+p)\frac{(S-S^0)^2}{S}-\beta(S-S^0)I),\\
\dot{W}_1&=-\int_0^{+\infty}F(a)((\mu+\alpha(a)+\delta(a))e(t,a)+\frac{\partial e}{\partial a})da\\
&=F(0)e(t,0)-\int_0^{+\infty}(\alpha(a)+\frac{\omega}{\mu+\omega}\delta(a))e(t,a)da\\
&=(\mathscr{K}_1+\frac{\omega}{\mu+\omega}\mathscr{K}_2)(\beta SI+\rho\beta VI)-\int_0^{+\infty}(\alpha(a)+\frac{\mu}{\mu+\omega}\delta(a))e(t,a)da,\\
\dot{W}_2&=\int_0^{+\infty}\alpha(a)e(t,a)da-(\gamma+\mu_I)I(t)+\omega R,\\
\dot{W}_3&=\frac{\omega}{\mu+\omega}(\int_0^{+\infty}\delta(a)e(t,a)da+\gamma\eta I-(\mu+\omega)R).
\end{aligned}$$

Further, we can obtian

$$\frac{dW}{dt} = (\mathscr{K}_1 + \frac{\omega}{\mu+\omega}\mathscr{K}_2)(\beta S^0 I + \rho\beta V I) - (\mu_I + \gamma)I + \frac{\omega}{\mu+\omega}\gamma\eta I$$
$$-(\mathscr{K}_1 + \frac{\omega}{\mu+\omega}\mathscr{K}_2)(\mu+p)\frac{(S-S^0)^2}{S}.$$

Thus

$$\frac{dW}{dt} \le -(\mathscr{K}_1 + \tfrac{\omega}{\mu+\omega}\mathscr{K}_2)(\mu+p)\frac{(S-S^0)^2}{S} + (\gamma+\mu_I)I(\mathcal{R}_0 - 1)$$
$$+(\mathscr{K}_1 + \tfrac{\omega}{\mu+\omega}\mathscr{K}_2)\rho\beta(V-V^0)I.$$

Notice that $V(t) \le V^0$ on $\mathcal{B}$. As a consequence, if $\mathcal{R}_0 < 1$, then $\frac{dW}{dt} \le 0$ holds. Let T is the largest invariant subset of $\{\frac{dW}{dt}|_{(2.1)} = 0\}$, the equality holds only if $S(t) = S^0, I = 0, V = V^0$. In T, $S(t) = S^0, I = 0, V = V^0$, for all $t \in \mathbb{R}$, then we have $e(t,a) = 0$, Combining this with system (2.1), it follows that $R(t) = 0$, for all $t \in \mathbb{R}$. Hence, $T = \{E_0\}$. It follows from the LaSalle invariance principle and Theorem 3.2 that E_0 is globally asymptotically stable. □

When $\mathcal{R}_0 > 1$, the system (2.1) has a global attractor $\mathcal{B}_0 \subset \Gamma$. Let $x \in \mathcal{B}_0$, then there exists a total trajectory $\{\Psi(t,x)\}_{t\in\mathbb{R}}$ in $\mathcal{B}_0$. By following the same reasoning as Subsection 3.2 in [8], the system (2.1) reduces to the following total trajectory system:

$$\begin{cases} \dfrac{dS(t)}{dt} = \Lambda - \beta SI - \mu S - pS, \\ \dfrac{dV(t)}{dt} = pS - \beta\rho VI - \mu V, \\ e(t,a) = k(a)(\beta S(t-a)(I(t-a) + \beta\rho V(t-a)I(t-a)), \\ \dfrac{dI(t)}{dt} = \displaystyle\int_0^{+\infty} \alpha(a)e(t,a)da + \omega R - (\gamma+\mu_I)I(t), \\ \dfrac{dR(t)}{dt} = \gamma\eta I(t) + \displaystyle\int_0^{+\infty} \delta(a)e(t,a)da - (\mu+\omega)R(t), \\ (S(0),\ V(0),\ e(0,a),\ I(0),\ R(0)) \in \mathcal{B}_0. \end{cases} \tag{4.15}$$

To prove that E^* is globally stable, it is mandatory to prove that

$$S(t),\ V(t),\ e(t,a),\ I(t),\ R(t) > 0.$$

Lemma 4.1. *All solutions of system* (2.1) *or* (4.15) *on* $\mathcal{B}_0$ *satisfy the following inequalities:*

$$\epsilon \le S(t),\ V(t),\ I(t),\ R(t) \le M,\ (\beta+\beta\rho)\epsilon^2 k(a) \le e(t,a) \le (\beta+\beta\rho)M^2 k(a),$$

for all $t \in \mathbb{R},\ a \in \mathbb{R}_+$, *where* ϵ *and* M *are positive constants.*

Proof. Let $\Psi(t,x) = (S(t), V(t), e(t,a), I(t), R(t)) \subset \mathcal{B}_0$.

Now, we are going to prove that $S(t) > 0$ for all $t \in \mathbb{R}$. We assume $S(t_0) = 0$ for some $t_0 \in \mathbb{R}$. Clearly, $\dfrac{dS(t_0)}{dt} \ge \Lambda > 0$, we can know from here, $S(t_0 - \eta_0) < 0$

for some $\eta_0 > 0$. This is a contradiction with $\mathcal{B}_0 \subset \Gamma$. Hence, $S(t) > 0$ for all $t \in \mathbb{R}$. Similarly, we can also derive $V(t) > 0$ for any $t \in \mathbb{R}$.

Next, we are going to prove that $I(t) > 0,\ R(t) > 0$ for any $t \in \mathbb{R}$. We assume $I(t_0) = 0$ and $R(t_0) = 0$ for some $t_0 \in \mathbb{R}$. From (4.15), it is easy to derive that $I(t) = 0,\ R(t) = 0$ when $t \le t_0$. Furthermore, we have $\int_0^{+\infty} e(t,a)da = 0$ for all $t \le t_0$. This is a contradiction with $\Psi(t,x) \subset \mathcal{B}_0$. Further, we assume that $I(t_0) = 0,\ R(t_0) > 0$ for some $t_0 \in \mathbb{R}$. It follows from (4.15) that $\frac{dI(t_0)}{dt} \ge \omega R(t_0) > 0$, we can know from here, $I(t_0 - \eta_1) < 0$ for some $\eta_1 > 0$. This is a contradiction with $\mathcal{B}_0 \subset \Gamma$. Similarly, the assumption that $I(t_0) > 0,\ R(t_0) = 0$ for some $t_0 \in \mathbb{R}$ is not true. Hence, $I(t) > 0,\ R(t) > 0$ for any $t \in \mathbb{R}$. Furthermore, it follows from (4.15) that $e(t,a) > 0$ for any $(t,a) \in (\mathbb{R},\ \mathbb{R}_+)$. Then it follows from the compactness of $\mathcal{B}_0$ that the conclusions of Lemma 4.1 hold. □

Theorem 4.4. *For system* (2.1) *or* (4.15) *in* Γ*, if* $\mathcal{R}_0 > 1$*, the equilibrium state* E^* *is globally asymptotically stable.*

Proof. Let us define the Lyapunov function $G(t) = G_1 + G_2 + G_3 + G_4 + G_5$ on $\mathcal{B}_0$. It follows from Lemma 4.1 that $G(t)$ is bounded, where

$$G_1 = (\mathscr{K}_1 + \frac{\omega}{\mu+\omega}\mathscr{K}_2)S^* h(\frac{S}{S^*}),\ G_2 = (\mathscr{K}_1 + \frac{\omega}{\mu+\omega}\mathscr{K}_2)V^* h(\frac{V}{V^*}),$$

$$G_3 = \int_0^{+\infty} F(a)e^*(a)h(\frac{e(t,a)}{e^*(a)})da,\ G_4 = I^* h(\frac{I}{I^*}),\ G_5 = \frac{\omega}{\mu+\omega}R^* h(\frac{R}{R^*}),$$

and

$$h(x) = x - lnx - 1,\quad F(a) = \int_a^{+\infty} (\alpha(u) + \frac{\omega}{\mu+\omega}\delta(u))e^{-\int_a^u (\mu+\alpha(s)+\delta(s))ds}du.$$

Along any solution in $\mathcal{B}_0$, we take the derivative versus time of G.

$$\begin{aligned}
\dot{G}_1 =& -(\mathscr{K}_1 + \frac{\omega}{\mu+\omega}\mathscr{K}_2)(\mu+p)S^*(\frac{S^*}{S} + \frac{S}{S^*} - 2)\\
&+ (\mathscr{K}_1 + \frac{\omega}{\mu+\omega}\mathscr{K}_2)\beta S^* I^*(1 - \frac{SI}{S^*I^*} - \frac{S^*}{S} + \frac{I}{I^*})\\
=&(\mathscr{K}_1 + \frac{\omega}{\mu+\omega}\mathscr{K}_2)[(\mu+p)S^*(-h(\frac{S}{S^*}) - h(\frac{S^*}{S}))\\
&+ \beta S^* I^*(h(\frac{I}{I^*}) - h(\frac{S^*}{S}) - h(\frac{SI}{S^*I^*}))],\\
\dot{G}_2 =&(\mathscr{K}_1 + \frac{\omega}{\mu+\omega}\mathscr{K}_2)pS^*(\frac{S}{S^*} - 1 - \frac{V^*S}{VS^*} + \frac{V^*}{V})\\
&- (\mathscr{K}_1 + \frac{\omega}{\mu+\omega}\mathscr{K}_2)\mu V^*(\frac{V^*}{V} + \frac{V}{V^*} - 2)\\
&+ (\mathscr{K}_1 + \frac{\omega}{\mu+\omega}\mathscr{K}_2)\beta\rho V^* I^*(1 - \frac{VI}{V^*I^*} - \frac{V^*}{V} + \frac{I}{I^*})\\
=&(\mathscr{K}_1 + \frac{\omega}{\mu+\omega}\mathscr{K}_2)[pS^*(h(\frac{S}{S^*}) + h(\frac{V^*}{V}) - h(\frac{V^*S}{S^*V})) + \mu V^*(-h(\frac{V}{V^*}) - h(\frac{V^*}{V}))
\end{aligned}$$

$$+\rho\beta V^*I^*(h(\frac{I}{I^*})-h(\frac{V^*}{V})-h(\frac{VI}{V^*I^*}))],$$

$$\begin{aligned}\dot{G}_3=&F(0)\beta S^*I^*(\frac{SI}{S^*I^*}-1-\ln\frac{e(t,0)}{e^*(0)})+F(0)\beta\rho V^*I^*(\frac{VI}{V^*I^*}-1-\ln\frac{e(t,0)}{e^*(0)})\\&-\int_0^{+\infty}(\alpha(a)+\frac{\omega}{\mu+\omega}\delta(a))e^*(a)h(\frac{e(t,a)}{e^*(a)})da\\=&F(0)\beta S^*I^*(h(\frac{SI}{S^*I^*})-h(\frac{e^*(0)SI}{e(t,0)S^*I^*}))\\&+F(0)\rho\beta V^*I^*(h(\frac{VI}{V^*I^*})-h(\frac{e^*(0)VI}{e(t,0)V^*I^*}))\\&-\int_0^{+\infty}(\alpha(a)+\frac{\omega}{\mu+\omega}\delta(a))e^*(a)h(\frac{e(t,a)}{e^*(a)})da.\end{aligned}$$

Where, we use $\Lambda=\beta S^*I^*+(\mu+p)S^*$ and $pS^*-\rho\beta V^*I^*-\mu V^*$.

$$\begin{aligned}\dot{G}_4=&\int_0^{+\infty}\alpha(a)e^*(a)(\frac{e(t,a)}{e^*(a)}-\frac{I}{I^*}-\frac{e(t,a)I^*}{e^*(a)I}+1)da+\omega R^*(\frac{R}{R^*}-\frac{I}{I^*}-\frac{I^*R}{IR^*}+1)\\=&\int_0^{+\infty}\alpha(a)e^*(a)(h(\frac{e(t,a)}{e^*(a)})-h(\frac{I}{I^*})-h(\frac{e(t,a)I^*}{e^*(a)I}))da\\&+\omega R^*(h(\frac{R}{R^*})-h(\frac{I}{I^*})-h(\frac{I^*R}{R^*I})),\\\dot{G}_5=&\frac{\omega}{\mu+\omega}\int_0^{+\infty}\delta(a)e^*(a)(\frac{e(t,a)}{e^*(a)}-\frac{R}{R^*}-\frac{e(t,a)R^*}{e^*(a)R}+1)da\\&+\frac{\omega}{\mu+\omega}\gamma\eta I^*(\frac{I}{I^*}-\frac{R}{R^*}-\frac{R^*I}{RI^*}+1)\\=&\frac{\omega}{\mu+\omega}\int_0^{+\infty}\delta(a)e^*(a)(h(\frac{e(t,a)}{e^*(a)})-h(\frac{R}{R^*})-h(\frac{e(t,a)R^*}{e^*(a)R}))da\\&+\frac{\omega}{\mu+\omega}\gamma\eta I^*(h(\frac{I}{I^*})-h(\frac{R}{R^*})-h(\frac{IR^*}{I^*R})).\end{aligned}$$

Where, we use

$$\gamma+\mu_I=\frac{1}{I^*}(\int_0^{+\infty}\alpha(a)e^*(a)da+\omega R^*),\quad \mu+\omega=\frac{1}{R^*}(\int_0^{+\infty}\delta(a)e^*(a)da+\gamma\eta I^*).$$

Further, we can get

$$\begin{aligned}\dot{G}=&\sum_{i=1}^{5}\dot{G}_i\\=&-(\mathscr{K}_1+\frac{\omega}{\mu+\omega}\mathscr{K}_2)((\mu+p)S^*+\beta S^*I^*)h(\frac{S^*}{S})-(\mathscr{K}_1+\frac{\omega}{\mu+\omega}\mathscr{K}_2)\mu S^*h(\frac{S}{S^*})\end{aligned}$$

$$
\begin{aligned}
&-(\mathscr{K}_1+\frac{\omega}{\mu+\omega}\mathscr{K}_2)[pS^*h(\frac{V^*S}{S^*V})+\mu V^*h(\frac{V}{V^*})]-F(0)\beta S^*I^*h(\frac{e^*(0)SI}{e(t,0)S^*I^*})\\
&-F(0)\rho\beta V^*I^*h(\frac{e^*(0)VI}{e(t,0)V^*I^*})-\int_0^{+\infty}\alpha(a)e^*(a)h(\frac{e(t,a)I^*}{e^*(a)I})da-\omega R^*h(\frac{I^*R}{R^*I})\\
&-\frac{\omega}{\mu+\omega}\int_0^{+\infty}\delta(a)e^*(a)h(\frac{e(t,a)R^*}{e^*(a)R})da-\frac{\omega}{\mu+\omega}\gamma\eta I^*h(\frac{IR^*}{I^*R})\\
\leq&0.
\end{aligned}
$$

It follows from the analysis of Theorem 4.3 [16] that $\mathcal{B}_0=\{E^*\}$. Therefore, the global asymptotic stability of E^* is derived. □

5. Parameters estimation and sensitivity analysis

5.1. Parameters estimation

In this subsection of the paper, based on the annual tuberculosis patients' data of China from 2007 to 2020, we will estimate the parameters of the system (2.1). Based on the data from the National Bureau of Statistics of China (NBSC) [4], we can deduce that between 2007 and 2020, the average newborn population in China is $16,289,670$ $persons\ year^{-1}$, and the average life expectancy in China is 76.34 $years\ old$. Thus, we take $\Lambda=16,289,670$ and $\mu=1/76.34$. The World Health Organization estimates about a quarter of the world's population has been infected with TB and about 85 % of people who develop TB disease can be successfully treated with a 6-month drug regimen. Thus, we take $S(0)=0.75*1,314,480,000$ $persons$, $\int_0^{+\infty}e(0,a)da=0.25*1,314,480,000$ $persons$, $\eta=0.85$. Trollfors et al. [35] suggested that the BCG vaccine has a significant effect on LTBI. The effectiveness was 59%. Thus, parameter $\rho=0.41$. Guo et al. [19] suggested that the death rate due to TB was 0.056 $year^{-1}$,thus parameter $\mu_I=\mu+0.0056$ $year^{-1}$. The initial infectious population $I(0)=5011912$ $persons$, and the initial recovered population $R(0)=7493719$ $persons$. The annual tuberculosis patients' data (Table 2) came from the Chinese Center for Disease Control and Prevention [2].

Table 2. The data of TB cases in China (persons).

Year	2007	2008	2009	2010	2011	2012	2013
Cases	1,163,959	1,169,540	1,076,938	991,350	953,275	951,508	904,434
Year	2014	2015	2016	2017	2018	2019	2020
Cases	889,381	864,015	836,236	835,193	823,342	775,764	670,538

After being infected with TB, some infected people will soon show symptoms of TB (about a few weeks) because of a lack of immunity to the bacillus. Over time, the immune system of infected people can fight off the bacillus, they are less and less likely to show symptoms of TB and more and more likely to recover [1, 5]. We use the year as the unit and the time length of a few weeks is negligible. Thus, we create the following monotone functions to represent $\alpha(a)$ and $\delta(a)$, respectively

$$\alpha(a)=\alpha_1e^{-\alpha_2a},\quad \delta(a)=\delta_1(1-e^{-\delta_2a}).$$

We also assume that $e_0(a) = e(0)\mu e^{-\mu a}$.

Next, we simulate the following parameters and initial condition of system (2.1)

$$\hat{\Theta} = (\alpha_1, \alpha_2, \delta_1, \delta_2, p, \beta, \rho, \omega, V(0)).$$

We use $P(t, \hat{\Theta})$ to represent the number of new tuberculosis patients at the t^{th} year, then $P(t, \hat{\Theta})$ can be expressed as follows:

$$P(t, \hat{\Theta}) = X(t) - X(t-1),$$

here $X(t)$ denotes the cumulative number of patients with TB disease by the t^{th} year. We can derive the expression for $X(t)$ as:

$$\frac{dX(t)}{dt} = \int_0^{+\infty} \alpha(a)e(t,a)da + \omega R(t).$$

Next, we will use $P(t, \hat{\Theta})$ to simulate the annual tuberculosis patients data of China. We use MATLAB 2018b software to estimate $\hat{\Theta}$. In this study, we employ the Delayed Rejection and Adaptive Metropolis (DRAM) algorithm to carry out the Markov chain Monte Carlo (MCMC) procedure [20]. We estimate the convergence of the Markov chain by using Geweke's Z-scores [3]. The expectations, standard deviations, and confidence intervals of the parameters and initial values are listed in Table 3. Based on the expectations of parameters in Table 3, we find that China will not achieve the WHO target of 2035 without a new control strategy (see Figure 2).

Table 3. The parameters values and initial values of the system (1).

Parameters	Mean	Std	95% CI	Gewekes Z-score	Source
Λ	16289670	-	-	-	[4]
μ	1/76.34	-	-	-	[4]
$S(0)$	0.75*1314480000	-	-	-	[4]
$e(0)$	0.25*1314480000	-	-	-	[4]
$I(0)$	5011912	-	-	-	[19]
$R(0)$	7493719	-	-	-	[19]
μ_I	0.015599	-	-	-	[19]
η	0.85	-	-	-	[35]
ρ	0.41	-	-	-	[5]
α_1	0.021253299	0.002457035	[0.02124, 0.02126]	0.99532217	MCMC
α_2	0.060170011	0.006924137	[0.0601, 0.0602]	0.988589519	MCMC
δ_1	0.367737936	0.042197186	[0.3675, 0.3679]	0.993649912	MCMC
δ_2	0.052697579	0.006082301	[0.0526, 0.0527]	0.998609138	MCMC
p	0.092698114	0.010674527	[0.0926, 0.0927]	0.997274947	MCMC
β	1.70853×10^{-9}	1.97×10^{-10}	$[1.707 \times 10^{-9}, 1.709 \times 10^{-9}]$	0.997600778	MCMC
ω	0.000358884	4.127×10^{-5}	[0.000358, 0.000359]	0.997742014	MCMC
γ	0.195569335	0.022714474	[0.1954, 0.1956]	0.998434275	MCMC
$V(0)$	1.917110131×10^{8}	22247154.49	$[1.916 \times 10^{8}, 1.918 \times 10^{8}]$	0.995765272	MCMC

5.2. Sensitivity analysis

Sensitivity analysis (SA) is to find the most sensitive parameter relative to $\mathcal{R}_0$. We are going to use the partial rank correlation coefficient (PRCC) to analyze sensitivity, which is based on Latin hypercube sampling(LHS). For the parameters

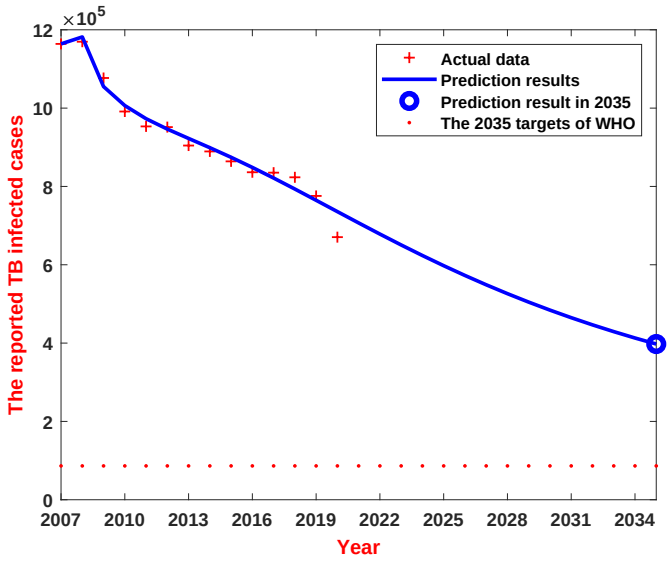

Figure 2. The comparison chart of the data of new TB cases in the China and simulation results by system (2.1).

in Table 3, we let $V(0)$ take the expectation value, and we assume that other parameters are normal distributions, the expectations and standard deviations are the estimated values in Table 3. Figure 3 shows the values of PRCC for $\mathcal{R}_0$. It follows from the values of PRCC that β, $\alpha(a)$, $\delta(a)$, γ have significant influence on $\mathcal{R}_0$.

6. Optimal control analysis

China is a country with a high TB burden. Although the treatment coverage in China is very high in recent years, according to the analysis above in this paper, it is difficult for China to achieve the WHO target of 2035. To do this, we should explore more mitigation measures that may curb the spread of TB. In the sensitivity analysis, we found that β, $\alpha(a)$, $\delta(a)$, γ have important influence on TB transmission. Based on the actual controllability, we choose the transmission coefficient of TB β and the treatment rate of infectious population γ as controlled parameters. Apart from that, the rate $\alpha(a)$ of latent class entering infectious class and the rate $\delta(a)$ of latent individuals entering recovered class are very sensitive. But we think it difficult to take control measures on these two parameters in China's public health at present. Now we consider the following two mitigation measures: one is TB prevention and control education and the other is the treatment of patients with TB disease. These two mitigation measures are implemented in system (2.1) by decreasing β and increasing γ. Our goal is one that the control cost is as low as possible and the final number of infectious individuals falls to the given goal as much as possible.

Therefore, after considering the above two mitigation measures, the system (2.1)

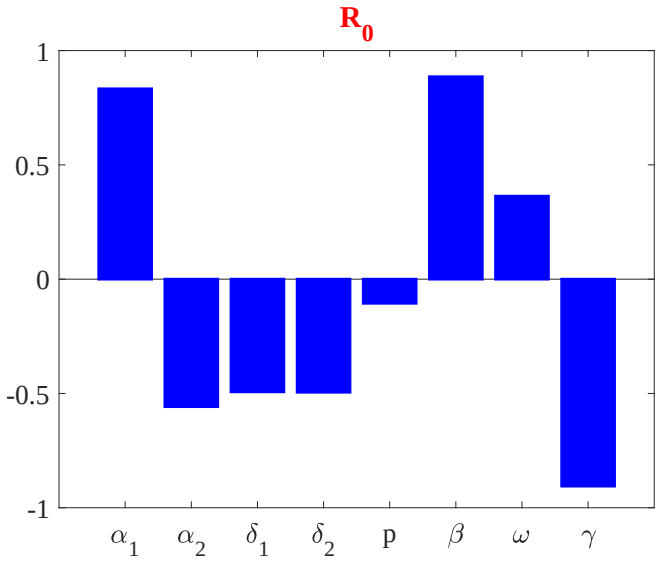

Figure 3. The PRCC values.

is rewritten as the following system:

$$\begin{cases} \dfrac{dS(t)}{dt} = \Lambda - \beta(1-u_1(t))SI - \mu S - pS, \\ \dfrac{dV(t)}{dt} = pS - \rho\beta(1-u_1(t))VI - \mu V, \\ \dfrac{\partial e(t,a)}{\partial t} + \dfrac{\partial e(t,a)}{\partial a} = -(\mu + \delta(a) + \alpha(a))e(t,a), \\ \dfrac{dI(t)}{dt} = \displaystyle\int_0^A \alpha(a)e(t,a)da + \omega R - \mu_I I - \gamma(1+u_2(t))I, \\ \dfrac{dR(t)}{dt} = \gamma(1+u_2(t))\eta I + \displaystyle\int_0^A \delta(a)e(t,a)da - \mu R - \omega R, \\ e(t,0) = \beta(1-u_1(t))SI + \rho\beta(1-u_1(t))VI, \\ e(0,a) = e_0(a),\ S(0) = s_0, V(0) = v_0,\quad I(0) = i_0, R(0) = r_0, \end{cases} \tag{6.1}$$

where $(t,a) \in Q = (0,T)\times(0,A)$, A is the maximum latent age and T is the length of the control period. $u_1(t), u_2(t)$ are the control variables and belong to

$$\mathcal{U} = \{(u_1(t), u_2(t)) \in (L_+^\infty(0,T))^2 : 0 \le u_1(t) \le \overline{u}_1 < 1, 0 \le u_2(t) \le \overline{u}_2\},$$

a.e. in $(0,T)$.

The control variable $u_1(t)$ implies the effort of preventing susceptible population from becoming TB latent population, including paying attention to personal protection, accepting TB treatment and prevention education, avoiding unhealthy living habits, and so on. The control variable $u_2(t)$ represents the effort of treatment of

patients with TB disease. The objective function is defined as:

$$\min_{(u_1(t),u_2(t))\in\mathcal{U}} J(u_1(t),u_2(t)) = \frac{1}{2}\Big(\int_0^A \alpha(a)e(T,a)da + \omega R(T) - \bar{u}(T)\Big)^2 + \frac{\rho_1}{2}\int_0^T u_1(t)^2dt + \frac{\rho_2}{2}\int_0^T u_2(t)^2dt, \tag{6.2}$$

subject to the system (6.1). Here ρ_1 and ρ_2 are positive weights that balance the relative importance of the terms in J. $\int_0^A \alpha(a)e(T,a)da + \omega R(T)$ represents the number of new tuberculosis patients at the T^{th} year, $\bar{u}(T)$ is a specified-in-advance target value. $\frac{\rho_1 u_1(t)^2}{2}$ and $\frac{\rho_2 u_2(t)^2}{2}$ denote costs of disease prevention and treatment programs. Prevention and treatment are considered nonlinear functions since any public health intervention does not have a linear cost, but rather, implementation costs increase with reaching higher population fractions [7]. In this paper, a quadratic function is taken by reference to many papers on epidemic control [13,39]. Hence, our goal is one that the control cost is as low as possible and the number of infectious individuals at the T^{th} year is close to the target value $\bar{u}(T)$ as much as possible.

Remark 6.1. Similar to the method in [18], we can prove the well-posedness of the system (6.1), including non-negativity, existence, and uniqueness of the solution as well as the continuous dependence of system state variables $S(t), V(t), e(t,a), I(t), R(t)$ concerning control variables $(u_1(t), u_2(t))$.

6.1. The solution of the optimal control problem

The sensitivity equations of system (6.1) can be derived from the following theorem:

Theorem 6.1. *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 $\frac{x^\varepsilon - x}{\varepsilon} \to z$, as $\varepsilon \to 0^+$, where x^ε and x are the solutions of system (6.1) corresponding to $u + \varepsilon v$ and u, respectively. And sensitivity functions $z \in (L^\infty(0,T))^2 \times L^\infty(0,T;L^1(0,A)) \times (L^\infty(0,T))^2$ satisfy*

$$\begin{cases}
\frac{dz_1(t)}{dt} = \beta l(t)SI - \beta(1-u_1(t))z_1(t)I - \beta(1-u_1(t))z_4(t)S - (\mu+p)z_1(t),\\
\frac{dz_2(t)}{dt} = pz_1(t) + \rho\beta l(t)VI - \rho\beta(1-u_1(t))z_2(t)I - \rho\beta(1-u_1(t))z_4(t)V - \mu z_2(t),\\
\frac{\partial z_3(t,a)}{\partial t} + \frac{\partial z_3(t,a)}{\partial a} = -(\mu+\alpha(a)+\delta(a))z_3(t,a),\\
\frac{dz_4(t)}{dt} = \int_0^A \alpha(a)z_3(t,a)da - \mu_I z_4(t) - \gamma h(t)I - \gamma(1+u_2(t))z_4(t) + \omega z_5(t),\\
\frac{dz_5(t)}{dt} = \int_0^A \delta(a)z_3(t,a)da - (\mu+\omega)z_5(t) + \eta\gamma h(t)I + \eta\gamma(1+u_2(t))z_4(t),\\
z_3(t,0) = -\beta l(t)SI + \beta(1-u_1(t))z_1(t)I + \beta(1-u_1(t))z_4(t)S\\
\qquad - \rho\beta l(t)VI + \rho\beta(1-u_1(t))z_2(t)I + \rho\beta(1-u_1(t))z_4(t)V,\\
z_3(0,a) = 0,\ z_1(0) = 0,\ z_2(0) = 0,\ z_4(t) = 0,\quad z_5(0) = 0\ t \in (0,T),\quad a \in (0,A).
\end{cases} \tag{6.3}$$

Proof. Since the map $(u_1(t), u_2(t)) \in \mathcal{U} \to (S(t), V(t), e(t,a), I(t), R(t))$ is Lipschitz in L^∞, we have the existence of the Gâteaux derivatives z by Barbu [6] and Fister et al. [15]. Passing to the limit in the representation of the quotients, the sensitivity functions $z = (z_1(t), z_2(t,a), z_3(t,\theta), z_4(t))$ satisfy system (6.3), where

$$z_1(t) = \lim_{\varepsilon\to 0^+} \frac{S^\varepsilon - S}{\varepsilon}, \quad z_2(t) = \lim_{\varepsilon\to 0^+} \frac{V^\varepsilon - V}{\varepsilon}, \quad z_3(t,a) = \lim_{\varepsilon\to 0^+} \frac{e^\varepsilon(t,a) - e(t,a)}{\varepsilon},$$
$$z_4(t) = \lim_{\varepsilon\to 0^+} \frac{I^\varepsilon - I}{\varepsilon}, \quad z_5(t) = \lim_{\varepsilon\to 0^+} \frac{R^\varepsilon - R}{\varepsilon}.$$

□

To derive an adjoint system, we define a Lagrangian $\mathcal{L}$ as follows:

$$\begin{aligned}
&\mathcal{L}(S, V, e, I, R, \lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5)\\
=&J(u_1(t), u_2(t))\\
&- \int_0^T \lambda_1(t)(\frac{dS(t)}{dt} - \Lambda + \beta(1-u_1(t))SI + (\mu+p)S)dt\\
&- \int_0^T \lambda_2(t)(\frac{dV(t)}{dt} - pS + \rho\beta(1-u_1(t))VI + \mu V)dt\\
&- \int_0^T \int_0^A \lambda_3(t,a)(\frac{\partial e(t,a)}{\partial t} + \frac{\partial e(t,a)}{\partial a} + (\mu + \delta(a) + \alpha(a))e(t,a))dadt\\
&- \int_0^T \lambda_4(t)(\frac{dI(t)}{dt} - \int_0^A \alpha(a)e(t,a)da - \omega R + \mu_I I + \gamma(1+u_2(t))I)dt\\
&- \int_0^T \lambda_5(t)(\frac{dR(t)}{dt} - \gamma(1+u_2(t))\eta I - \int_0^A \delta(a)e(t,a)da + (\mu+\omega)R)dt\\
&- \int_0^T \lambda_3(t,0)(e(t,0) - \beta(1-u_1(t))SI - \rho\beta(1-u_1(t))VI)dt.
\end{aligned}$$

The adjoint system can be got by solving $\frac{\partial \mathcal{L}}{\partial S} = 0, \frac{\partial \mathcal{L}}{\partial V} = 0, \frac{\partial \mathcal{L}}{\partial e} = 0, \frac{\partial \mathcal{L}}{\partial I} = 0$, and $\frac{\partial \mathcal{L}}{\partial R} = 0$. That is

$$\begin{cases}
-\dfrac{d(\lambda_1(t))}{dt} = (-\beta(1-u_1(t))I - \mu - p)\lambda_1(t) + p\lambda_2(t) + \lambda_3(t,0)\beta(1-u_1(t))I,\\
-\dfrac{d(\lambda_2(t))}{dt} = (-\rho\beta(1-u_1(t))I - \mu)\lambda_2(t) + \lambda_3(t,0)\beta\rho(1-u_1(t))I,\\
-\dfrac{\partial\lambda_3(t,a)}{\partial t} - \dfrac{\partial\lambda_3(t,a)}{\partial a} = -(\mu + \alpha(a) + \delta(a))\lambda_3(t,a) + \alpha(a)\lambda_4(t) + \delta(a)\lambda_5(t),\\
-\dfrac{d\lambda_4(t)}{dt} = -\beta(1-u_1(t))S\lambda_1(t) - \beta\rho(1-u_1(t))V\lambda_2(t)\\
\qquad\qquad - (\mu_I + \gamma(1+u_2(t)))\lambda_4(t) + \gamma(1+u_2(t))\eta\lambda_5(t)\\
\qquad\qquad + \beta(1-u_1(t))S\lambda_3(t,0) + \rho\beta(1-u_1(t))V\lambda_3(t,0),\\
-\dfrac{d\lambda_5(t)}{dt} = \omega\lambda_4(t) - (\mu+\omega)\lambda_5(t),
\end{cases} \tag{6.4}$$

with transversality conditions

$$\begin{aligned}
&\lambda_1(T)=0,\lambda_2(T)=0,\lambda_4(T)=0,\lambda_3(t,A)=0,\\
&\lambda_3(T,a)=(\int_0^A \alpha(a)e(T,a)da+\omega R(T)-\bar{u}(T))\alpha(a),\\
&\lambda_5(T)=(\int_0^A \alpha(a)e(T,a)da+\omega R(T)-\bar{u}(T))\omega.
\end{aligned} \tag{6.5}$$

Similar to the proof of Theorem 3.4 of [31], we can prove the existence of solutions to the adjoint equations (6.4). Similar results for the adjoint equations can also be seen in [6].

Next, we present the optimality conditions of the control problem (6.2).

Theorem 6.2. *Assume there is an optimal control pair* $(u_1^*(t),u_2^*(t))\in\mathcal{U}$ *which minimizes* (6.2)*, and the corresponding optimal state solution is* $(S^*(t),V^*(t),e^*(t,a),I^*(t),R^*(t))$*, and* $(\lambda_1(t),\lambda_2(t),\lambda_3(t,a),\lambda_4(t),\lambda_5(t))$ *is the solution of adjoint system* (6.4) *corresponding to* $(S^*(t),V^*(t),e^*(t,a),I^*(t),R^*(t))$*, then the optimal control pair* $(u_1^*(t),u_2^*(t))$ *can be written in the following expressions:*

$$\begin{aligned}
u_1^*(t)&=F_1\Big(\frac{(-\lambda_1(t)\beta S^*I^*-\lambda_2(t)\beta\rho V^*I^*+\lambda_3(t,0)\rho\beta V^*I^*+\lambda_3(t,0)\beta S^*I^*)}{\rho_1}\Big),\\
u_2^*(t)&=F_2\Big(\frac{\lambda_4(t)\gamma I^*-\lambda_5(t)\gamma\eta I^*}{\rho_2}\Big),\ a.\ e.\ in\ (0,T),
\end{aligned} \tag{6.6}$$

where

$$F_i(x)=\begin{cases}0, x\le 0,\\ x, 0\le x\le \overline{u}_i,\quad i=1,2.\\ \overline{u}_i, x\ge \overline{u}_i.\end{cases}$$

Proof. Using the sensitivity equations (6.3), adjoint system (6.4), transversality condition (6.5), and integration by parts, we get

$$\begin{aligned}
&\int_0^T 0\cdot z_1(t)+0\cdot z_2(t)+\int_0^A 0\cdot z_3(t,a)da+0\cdot z_4(t)+0\cdot z_5(t)dt\\
=&\int_0^T z_1(t)\times\{-\frac{d(\lambda_1(t))}{dt}-(-\beta(1-u_1(t))I-\mu-p)\lambda_1(t)\\
&-p\lambda_2(t)-\lambda_3(t,0)\beta(1-u_1(t))I\}dt\\
&+\int_0^T z_2(t)\{-\frac{d(\lambda_2(t))}{dt}-(-\rho\beta(1-u_1(t))I-\mu)\lambda_2(t)-\lambda_3(t,0)\beta\rho(1-u_1(t))I\}dt\\
&+\int_0^T\int_0^A z_3(t,a)\{-\frac{\partial\lambda_3(t,a)}{\partial t}-\frac{\partial\lambda_3(t,a)}{\partial a}+(\mu+\alpha(a)+\delta(a))\lambda_3(t,a)\\
&-\alpha(a)\lambda_4(t)-\delta(a)\lambda_5(t)\}dadt\\
&+\int_0^T z_4(t)\{-\frac{d\lambda_4(t)}{dt}+\beta(1-u_1(t))S\lambda_1(t)+\beta\rho(1-u_1(t))V\lambda_2(t)\\
&+(\mu_I+\gamma(1+u_2(t)))\lambda_4(t)-\gamma(1+u_2(t))\eta\lambda_5(t)-\beta(1-u_1(t))S\lambda_3(t,0)\\
&-\rho\beta(1-u_1(t))V\lambda_3(t,0)\}dt
\end{aligned}$$

$$
\begin{aligned}
&+\int_0^T z_5(t)\{-\frac{d\lambda_5(t)}{dt}-\omega\lambda_4(t)+(\mu+\omega)\lambda_5(t)\}dt\\
=&\int_0^T \lambda_1(t)\{\frac{dz_1(t)}{dt}-(-\beta(1-u_1(t))I-\mu-p)z_1(t)+\beta(1-u_1(t))Sz_4(t)\}dt\\
&+\int_0^T \lambda_2(t)\{\frac{dz_2(t)}{dt}-(-\beta\rho(1-u_1(t))I-\mu)z_2(t)-pz_1(t)\\
&+\rho\beta(1-u_1(t))Vz_4(t)\}dt\\
&+\int_0^T\int_0^A \lambda_3(t,a)\{\frac{\partial z_3(t,a)}{\partial t}+\frac{\partial z_3(t,a)}{\partial a}+(\mu+\alpha(a)+\delta(a))z_3(t,a)\}dadt\\
&+\int_0^T \lambda_4(t)\{\frac{dz_4(t)}{dt}+(\mu_I+\gamma(1+u_2(t))z_4(t)-\int_0^A\alpha(a)z_3(t,a)da-\omega z_5(t)\}dt\\
&+\int_0^T \lambda_5(t)\{\frac{dz_5(t)}{dt}+(\mu+\omega)z_5(t)-\int_0^A\delta(a)z_3(t,a)da-\gamma\eta(1+u_2(t))z_4(t)\}dt\\
&-\int_0^T \lambda_3(t,0)(\beta(1-u_1(t))z_1(t)I+\beta(1-u_1(t))z_4(t)S+\rho\beta(1-u_1(t))z_2(t)I\\
&+\rho\beta(1-u_1(t))z_4(t)V)dt\\
&-\int_0^A \lambda_3(T,a)z_3(T,a)da-\lambda_5(T)z_5(T)+\int_0^T\lambda_3(t,0)z_3(t,0)dt\\
=&\int_0^T\lambda_1(t)\beta l(t)SIdt+\int_0^T\lambda_2(t)\beta\rho l(t)VIdt-\int_0^A\lambda_3(T,a)z_3(T,a)da-\lambda_5(T)z_5(T)\\
&-\int_0^T\lambda_4(t)\gamma h(t)Idt+\int_0^T\lambda_5(t)\eta\gamma h(t)Idt-\int_0^T\lambda_3(t,0)\rho\beta l(t)VIdt\\
&-\int_0^T\lambda_3(t,0)\beta l(t)SIdt.
\end{aligned}
$$

Since $(u_1^*(t),u_2^*(t))\in\mathcal{U}$ is an optimal control strategy that minimizes the control problem (6.2), and we omit the asterisks for simplicity in subsequent calculations, then we have

$$
\begin{aligned}
0\le&\lim_{\varepsilon\to0^+}\frac{J(u_1^*+\varepsilon l,u_2^*+\varepsilon h)-J(u_1^*,u_2^*)}{\varepsilon}\\
=&(\int_0^A\alpha(a)e(T,a)da+\omega R(T)-\bar{u}(T))(\int_0^A\alpha(a)z_3(T,a)da+\omega z_5(T))\\
&+\rho_1\int_0^T u_1(t)l(t)dt+\rho_2\int_0^T u_2(t)h(t)dt\\
=&(\int_0^A\alpha(a)e(T,a)da+\omega R(T)-\bar{u}(T))(\int_0^A\alpha(a)z_3(T,a)da+\omega z_5(T))\\
&+\rho_1\int_0^T u_1(t)l(t)dt+\rho_2\int_0^T u_2(t)h(t)dt\\
&+\int_0^T 0\cdot z_1(t)+0\cdot z_2(t)+\int_0^A 0\cdot z_3(t,a)da+0\cdot z_4(t)+0\cdot z_5(t)dt\\
=&\int_0^T l(t)(\rho_1u_1+\lambda_1(t)\beta SI+\lambda_2(t)\beta\rho VI-\lambda_3(t,0)\rho\beta VI-\lambda_3(t,0)\beta SI)dt
\end{aligned}
$$

$$+\int_0^T h(t)(\rho_2 u_2(t) - \lambda_4(t)\gamma I + \lambda_5(t)\gamma\eta I)dt.$$

By standard optimality arguments, we get the expressions in (6.6). □

6.2. Numerical simulations

We use the algorithm in [18], which is based on finite-difference schemes for ordinary differential equations and partial differential equations. Next, we present numerical experiments of optimal control. The optimal control measures were taken from 2023 to 2035. In addition, we take $A = 100, T = 13, \overline{u}_1 = 0.3$, and $\overline{u}_2 = 3$, and use the expectation values in Table 3 as parameter values in the system (6.1).

In Figure 4, we depict the optimal control and the corresponding optimal solution for new tuberculosis cases. It follows from Figure 4 that the number of new tuberculosis patients was reduced to 30% by 2035 compared to 2015 in the case of optimal control. Without control, the number of new tuberculosis patients was reduced to 44%. Therefore, it is easy to conclude that optimal control is essential for curbing TB in China. When this control strategy is applied, the effort of treatment of people with TB disease decreases gradually from 2023 to 2035 and has not reached the upper limit of the effort. The effort of preventing susceptible population from becoming TB latent population increases gradually and almost full effort is applied between 2032 and 2035.

The assignment of weight coefficients ρ_1 and ρ_2 are directly related to the budget for TB control. Regrettably, this relation is not specific, but it is easy to know that the weights ρ_1 and ρ_2 should decrease if the available budget is plentiful, and the weights ρ_1 and ρ_2 should increase if the available budget is scarce. It can be observed from Figure 5 that when the weight ρ_1 and ρ_2 are reduced, which implies that there is a sufficient budget for TB control, a full effort of treatment of people with TB disease is applied from 2023 and 2035. The effort of preventing susceptible population from becoming TB latent population decreases gradually from 2023 to 2026 then increases gradually. The final number of new tuberculosis patients is also reduced compared with Figure 4. This shows that the available budget is important to TB control. Table 4 provides a summary of the two different control schemes. Through this table, we can also find that the control effectiveness of the second group of weight coefficients is more satisfactory.

In fact, in both control schemes, at the beginning of the simulated time, the effort of treatment of people with TB disease u_2 is staying at a high level to isolate as many patients as possible with TB disease (I) to prevent the increase of the number of the infected individuals. In the case of insufficient budget shown in Figure 4, the steady decrease of u_2 is determined by the balance between the number of new tuberculosis patients and the cost of treatment programs.

Remark 6.2. The weight coefficients ρ_1 and ρ_2 are very hard to obtain in practice. It needs a lot of work on data mining, analyzing, and fitting. Hence, the acquisition of appropriate practical weights is a difficult problem and it remains for further investigation. It should be pointed out that the weights in the simulations here are of only theoretical interest to illustrate the control strategies proposed in this paper.

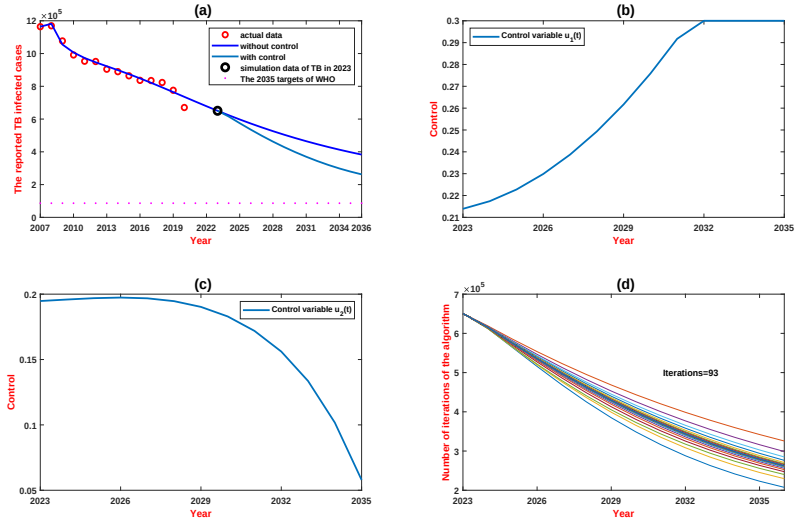

Figure 4. Optimal controls of the system (6.1) with the weight coefficients $\rho_1 = 10^{10}, \rho_2 = 10^{10}$. **(a)** The number of new tuberculosis patients with and without control. **(b),(c)** Diagrams of time-varying control variables. **(d)** The number of iterations for the forward-backward sweep method

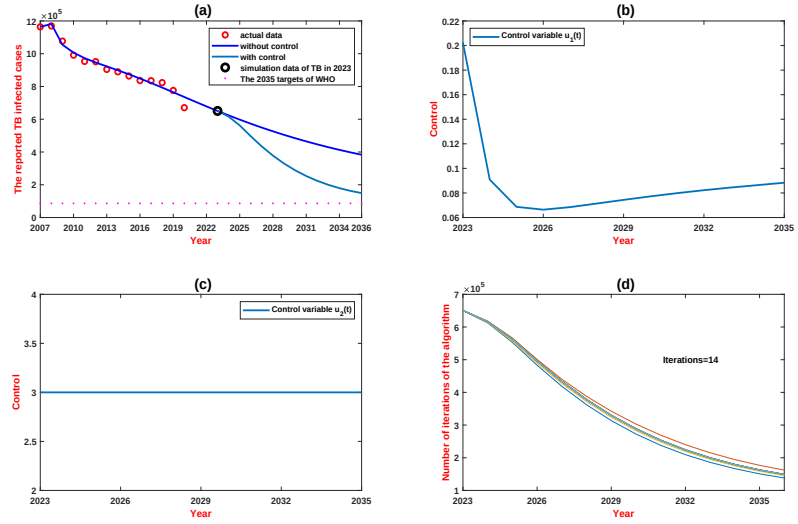

Figure 5. Optimal controls of the system (6.1) with the weight coefficients $\rho_1 = 2 \times 10^9, \rho_2 = 1.1 \times 10^7$. **(a)** The number of new tuberculosis patients with and without control from 2023 to 2035. **(b),(c)** Diagrams of time-varying control variables. **(d)** The number of iterations for the forward-backward sweep method

7. Conclusion

In this paper, based on the characteristics of TB transmission, we proposed and analyzed an age-structured TB infection mathematical model for understanding the

Table 4. Summary of the two different control schemes.

weight coefficients		The new TB cases in 2035	The value of objective functional
$\rho_1 = 10^{10}$	without control	3.8934×10^5	4.5887×10^{10}
$\rho_2 = 10^{10}$	control	2.5968×10^5	2.0739×10^{10}
$\rho_1 = 2 \times 10^9$	without control	3.8934×10^5	4.5887×10^{10}
$\rho_2 = 1.1 \times 10^7$	control	1.4713×10^5	2.5195×10^9

spread of TB in China. The goal of our research was to propose control strategies for mitigating the risk of TB. We defined the basic reproduction number $\mathcal{R}_0$ and showed that $\mathcal{R}_0$ completely determines the global dynamics of the proposed model. Based on the annual data of TB in China from 2007 to 2020, we estimated model parameters by the MCMC method and concluded that, by using the current TB control measures, it is difficult for China to achieve the WHO target of 2035. To do this, we should explore more mitigation measures that may help to curb the spread of TB. We calculated the PRCC between the parameters and the basic reproduction number $\mathcal{R}_0$. From the PRCC values, we can know that β, $\alpha(a)$, $\delta(a)$, γ have the most important influence on $\mathcal{R}_0$. In light of the actual controllability, we chose the transmission coefficient of TB and the treatment rate of infectious population as controlled parameters to study the least cost-deviation problem. Using Pontryagin's maximum principle, we got the necessary conditions for optimal control. 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 different values to the weight coefficients to indicate the different budget levels. Our study provides guidance for public health authorities on how to utilize limited resources effectively to mitigate the spread of TB.

TB is still spreading in many developing countries, and the characteristics of TB transmission in these countries are the same, so our model and the research framework will also be of value to the mitigation of the risk of TB in other developing countries.

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