Mathematical Biology

Analysis of an age-structured tuberculosis model with treatment and relapse

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Abstract

A new tuberculosis model consisting of ordinary differential equations and partial differential equations is established in this paper. The model includes latent age (i.e., the time elapsed since the individual became infected but not infectious) and relapse age (i.e., the time between cure and reappearance of symptoms of tuberculosis). We identify the basic reproduction number $\mathcal{R}_0$ for this model, and show that the $\mathcal{R}_0$ determines the global dynamics of the model. If $\mathcal{R}_0 < 1$, the disease-free equilibrium is globally asymptotically stable, which means that tuberculosis will disappear, and if $\mathcal{R}_0 > 1$, there exists a unique endemic equilibrium that attracts all solutions that can cause the spread of tuberculosis. Based on the tuberculosis data in China from 2007 to 2018, we use Grey Wolf Optimizer algorithm to find the optimal parameter values and initial values of the model. Furthermore, we perform uncertainty and sensitivity analysis to identify the parameters that have significant impact on the basic reproduction number. Finally, we give an effective measure to reach the goal of WHO of reducing the incidence of tuberculosis by 80% by 2030 compared to 2015.

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1 Introduction

Tuberculosis (TB), one of the top 10 causes of death worldwide, is an infectious disease caused by the bacillus mycobacterium tuberculosis. The bacillus can attack any part of the body such as the lungs (pulmonary TB), kidney, spine and brain (extra-pulmonary TB). The disease is spread through the air from one person to another, when people who are sick with pulmonary TB expel the bacillus into the air, for example, by coughing, speaking and so on, people nearby may breathe in these bacillus and become infected. The extrapulmonary TB is usually not infectious. About 5–10% of people who infected with the bacillus will develop TB during their lifetime. However, people with weak immune systems have a much higher risk of TB, such as people living with HIV, malnutrition or diabetes, or people who smoke. TB occurs in every part of the world. In 2017, there were an estimated 10 million new cases of TB worldwide, the majority of them were concentrated in the African, South-East Asia and Western Pacific regions. The following eight countries accounted for two thirds of the new TB cases: India, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh and South Africa (WHO 2019; CDC 2019).

Prevention and treatment have always been considered as important means of controlling the spread of TB, they mainly include: treatment of latent TB infection, vaccination of children with the bacille Calmette–Guérin (BCG) vaccine, people with TB take the drugs exactly as prescribed for 6–9 months, and so on. These measures are considered to have made a major contribution to the reduction in TB burden since 2000. TB incidence has fallen 1.5% per year since 2000, for a total reduction of 18% worldwide. However, as the WHO notes, TB kills millions of people worldwide each year, which is unacceptable in an era when you can diagnose and cure nearly every person with TB. At this rate, the WHO 2030 goal (the new TB cases will reduce by 80% by 2030 compared to 2015) will not be achieved. If the world is to end TB, it needs to scale up services and invest in research. Unfortunately, the gap between the funding available and the requirement has widened over the past 2 years, this is not a good sign for TB control. Therefore, increasing investment and developing the most effective control measures are crucial for the current control of TB (WHO 2019; CDC 2019).

Mathematical modeling has always been a very useful and important tool in studying the transmission mechanism of epidemic disease, drinking or other behavior, through mathematical analysis and numerical simulation of the model, effective control measures can be designed and evaluated (Ullah et al. 2019; Wang et al. 2019; Agusto and Khan 2018; Rebaza 2019; Ngeleja et al. 2018; Zhao et al. 2019; Huo et al. 2019b; Xiang et al. 2019; Ma 2019; Shi and Wang 2019; Cai et al. 2018; Du and Feng 2018; Zhang and Xing 2019; Meng et al. 2018; Meng and Wu 2018; Zhang et al. 2018; Bao et al. 2020; Bao and Li 2020; Huang and Tian 2019; Li and Huang 2019; Huo et al. 2019a; Zhang et al. 2019a, b; Huo et al. 2020; Huang 2020). Due to the complexity of the pathogenesis of tuberculosis, there have been many articles to establish different models to study TB and incorporate certain factors, such as treatment, drug resistance, HIV/TB co-infection, relapse, vaccination and so on (Whang et al. 2011; Zhao et al. 2017; Ozcaglar et al. 2012; Liu and Zhang 2011; Ren 2017; Choi et al. 2015). Liu and Zhang (2011) argued that vaccination can only reduce infection, not

eliminate it entirely, and treatment can also only reduce the infectivity of treated TB cases (compared to untreated cases). According to this, they investigated the effects of vaccination and treatment on the spread of TB. Agusto and Adekunle (2014) formulated a mathematical model of the transmission of TB-HIV/AIDS co-infection. By using treatment of infected individuals with TB as the system control variable, they investigated optimal strategies for controlling the spread of the disease. Most of the models are qualitative analysis of tuberculosis transmission, and few are quantitative analysis based on actual data. Recently, more and more researchers are beginning to combine data to study the spread of diseases (Jing et al. 2020; Ullah et al. 2019; Zhao et al. 2017; Ghosh et al. 2018; Liu et al. 2020). Ullah et al. (2019) studied a TB model and used the actual data to estimate the model parameters, then they analyzed the effect of various parameters to define the importance of these parameters to disease transmission. Based on tuberculosis data from China, Zhao et al. (2017) evaluated the parameters by the Least Square method. Then, they gave two effective measures to achieve WHO's goal through numerical simulation.

During the spread of tuberculosis, it is worth noting that after becoming infected, some people develop TB disease soon (within weeks), before their immune system can fight the TB bacteria. Other people may get sick years later, when their immune system becomes weak for some reason. Many people with TB infection never develop TB disease. Iannelli and Milner (2017) argued that age structure is important when modeling a long-lasting disease, because the chance of infected individuals becoming infectious individuals and recovering patients relapsing is variable.

Motivated by these factors, in this paper, we formulate a new age-structured TB model to study the effects of relapse and treatment on transmission dynamics of TB. We not only introduce the treatment individuals as a class but also assume that the treatment class is also infectious. The article is organized as follows. In Sect. 2, we introduce an age-structured TB model and present some basic properties. In Sect. 3, we define the basic reproductive number and prove the local stability of the disease-free equilibrium and the unique endemic equilibrium. In Sect. 4, we present the uniform persistence result and prove the global stability of the disease-free equilibrium and the unique endemic equilibrium. In Sect. 5, we perform data fitting and sensitivity analysis of the basic reproductive number, and assess the feasibility of the WHO End TB Strategy by 2030. In Sect. 6, we give a brief discussion.

2 TB model and basic properties

2.1 Model formulation

The model divides the total population at time t into five mutually-exclusive subgroups: susceptible class, latent class (those who are infected but not yet infectious), infectious class, treatment and recovered class denoted by $S(t)$, $e(t, a)$, $I(t)$, $T(t)$ and $r(t, \theta)$, respectively. Here the parameter a denotes the latent age of the infected individuals, θ denotes the relapse age of the recovered individuals. We assume that people during treatment may still be re-infected due to contact with TB patients. If some people have been treated successfully, but in the process of treatment, they re-contact with
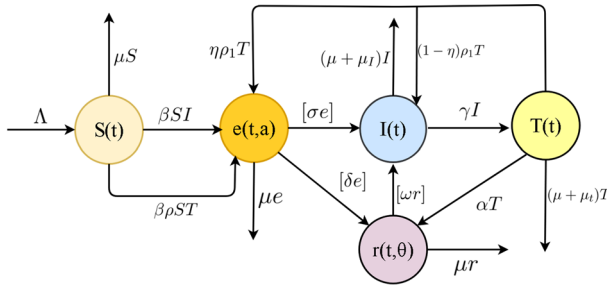
Fig. 1 Flowchart of the TB transmission

tuberculosis patients, they will enter the latent class, and those who are re-infected in other situations will enter the infectious class. Burman et al. (2009) argued that recurrent TB can develop in some patients after they complete therapy. This shows that people who have recovered may have a relapse. The flow among those subgroups is shown in the following flowchart (Fig. 1).

Base on the above notations and the flowchart (Fig. 1), we formulate the TB model as follows:

$$
\begin{cases}
\dfrac{dS(t)}{dt} = \Lambda - \beta S(I + \rho T) - \mu S, \\[2mm]
\dfrac{dI(t)}{dt} = \displaystyle\int_0^{+\infty} \sigma(a)e(t,a)da + \int_0^{+\infty} \omega(\theta)r(t,\theta)d\theta \\[2mm]
\qquad\quad + (1-\eta)\rho_1 T - (\gamma + \mu + \mu_I)I(t), \\[2mm]
\dfrac{dT(t)}{dt} = \gamma I(t) - (\mu + \mu_t + \alpha + \rho_1)T(t), \\[2mm]
\dfrac{\partial e(t,a)}{\partial t} + \dfrac{\partial e(t,a)}{\partial a} = -(\mu + \delta(a) + \sigma(a))e(t,a), \\[2mm]
\dfrac{\partial r(t,\theta)}{\partial t} + \dfrac{\partial r(t,\theta)}{\partial \theta} = -(\mu + \omega(\theta))r(t,\theta),
\end{cases}
\tag{1}
$$

with the following boundary conditions

$$
e(t,0) = \beta S(I + \rho T) + \eta \rho_1 T, \quad r(t,0) = \int_0^{+\infty} \delta(a)e(t,a)da + \alpha T, \tag{2}
$$

and initial conditions

$$
e(0,a) = e_0(a), \quad r(0,\theta) = r_0(\theta), \ S(0) = s_0, \ I(0) = i_0, \ T(0) = t_0, \tag{3}
$$

where $e_0(a), r_0(\theta) \in L^1_+(0, +\infty)$, and $s_0, i_0, t_0 \in \mathbb{R}_+$. The meanings of the parameters in (1) are explained in Table 1.

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

$(A1): \Lambda, \mu, \beta, \rho_1, \eta, \gamma, \rho, \alpha, \mu_I, \mu_t > 0$;

Table 1 Description of parameters of the model (1)

Parameters	Description
Λ	The recruitment rate of the susceptible class
μ	The natural death rate of the population
β	The transmission coefficient of TB
ρ	Parameters that reduce the rate of transmission due to treatment
$\delta(a)$	The rate at which latent individuals progress into recovered class due to treatment
$\sigma(a)$	The rate at which latent individuals progress into infectious class
γ	The treatment rate of infectious class
μ_I	The death rate due to TB
μ_t	The death rate due to treatment
α	The rate at which treatment individuals progress into recovered class due to
	complete treatment
ρ_1	The rate of developing a new infections due to exposure to tuberculosis
	during treatment
η	The proportion of individuals who become the latent class due to re-infection
$\omega(\theta)$	The age-dependent relapse rate

$(A2): \omega(\theta), \delta(a), \sigma(a) \in L^\infty_+(0, +\infty)$ with essential upper bounds $\bar{\omega}, \bar{\delta}, \bar{\sigma} > 0$, respectively;

For $a, \theta \geq 0$, we denote

$$k_1(a) = e^{-\int_0^a (\mu+\delta(s)+\sigma_1(s))ds}, \quad k_2(\theta) = e^{-\int_0^\theta (\mu+\omega(s))ds}, \quad \mathscr{K}_1 = \int_0^{+\infty} \sigma_1(a)k_1(a)da,$$

$$\mathscr{K}_2 = \int_0^{+\infty} \omega(\theta)k_2(\theta)d\theta, \quad \mathscr{K}_3 = \int_0^{+\infty} \delta(a)k_1(a)da,$$

$\mathscr{Y} = \mathbb{R}^3_+ \times (L^1_+(0, +\infty))^2$, with norm

$$\| (x_1, x_2, x_3, x_4, x_5) \|_{\mathscr{Y}} = \sum_{i=1}^3 | x_i | + \sum_{i=4}^5 \int_0^{+\infty} | x_i(s) | \, ds.$$

2.2 Well-posedness

Base on above assumptions, we can verify the local existence of unique and nonnegative solution of the model (1) with the nonnegative initial conditions (see Webb 1985 and Iannelli (1994)), thus we obtain the following proposition.

Proposition 1 *Let $x_0 \in \mathscr{Y}$, then there exists $\epsilon > 0$ and neighborhood $B_0 \subset \mathscr{Y}$ with $x_0 \in B_0$ such that there exists a unique continuous function, $\Phi : [0, \epsilon] \times B_0 \to \mathscr{Y}$, where $\Phi(t, x_0)$ is the solution to (1) with $\Phi(0, x_0) = x_0$.*

For $t \in [0, \epsilon]$, $\| \Phi(t, x_0) \|_{\mathscr{Y}} = S(t) + I(t) + T(t) + \int_0^{+\infty} e(t, a) da + \int_0^{+\infty} r(t, \theta) d\theta$, we deduce that $\| \Phi(t, x_0) \|_{\mathscr{Y}}$ satisfies the following inequality:

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

According to the comparison principle, we have

$$\| \Phi(t, x_0) \|_{\mathscr{Y}} \leq \frac{\Lambda}{\mu} - e^{-\mu t}(\frac{\Lambda}{\mu} - \| x_0 \|_{\mathscr{Y}}), \tag{4}$$

which yields

$$\| \Phi(t, x_0) \|_{\mathscr{Y}} \leq max\{\frac{\Lambda}{\mu}, \| x_0 \|_{\mathscr{Y}}\}. \tag{5}$$

Boundedness is a direct consequence of nonnegativity of solution. Then we have the following proposition.

Proposition 2 *Let $x_0 \in \mathscr{Y}$, then there exists a unique continuous semiflow, $\Phi : \mathbb{R}_+ \times \mathscr{Y} \to \mathscr{Y}$, where $\Phi(t, x_0)$ is the solution to (1) with $\Phi(0, x_0) = x_0$, and (4),(5) are satisfied for $t \in \mathbb{R}_+$. The following set is positively invariant for system (1)*

$$\Omega = \{x = (S(t), I(t), T(t), e(t, a), r(t, \theta)) \in \mathscr{Y} : \| x \|_{\mathscr{Y}} \leq \frac{\Lambda}{\mu}\}.$$

From Proposition 2 and inequality (4), we obtain the following proposition.

Proposition 3 (i) *The solution of (1), $\Phi(t, \cdot)$, is point dissipative, and Ω attracts all points in $\mathscr{Y}$;*
(ii) *Let $B \subset \mathscr{Y}$ be bounded, then $\Phi(t, B)$ is bounded;*
(iii) *If $x_0 \in \mathscr{Y}$ and $\| x_0 \|_{\mathscr{Y}} \leq A$ for some $A \geq \frac{\Lambda}{\mu}$, then $S(t)$, $I(t)$, $T(t)$, $\| e(t, \cdot) \|_{L_+^1}$, $\| r(t, \cdot) \|_{L_+^1} \leq A$.*

2.3 Asymptotic smoothness

Integrating the equations for $e(t, a), r(t, \theta)$ in (1) along the characteristic lines, $t - a$=const., $t - \theta$=cost., respectively, we deduce that

$$e(t, a) = \begin{cases} e(t - a, 0)k_1(a), & 0 \leq a \leq t, \\ e_0(a - t)\dfrac{k_1(a)}{k_1(a - t)}, & 0 \leq t < a, \end{cases}$$

$$r(t, \theta) = \begin{cases} r(t - \theta, 0)k_2(\theta), & 0 \leq \theta \leq t, \\ r(\theta - t)\dfrac{k_2(\theta)}{k_2(\theta - t)}, & 0 \leq t < \theta. \end{cases} \tag{6}$$

The continuous semiflow $\{\Phi(t, \cdot)\}_{t \geq 0}$ is said to be asymptotically smooth, if each positively invariant bounded closed set is attracted by a nonempty compact set.

We will use the following two lemmas proposed by Smith and Thieme (2011) to prove the asymptotic smoothness of the semiflow.

Lemma 1 *The semiflow* $\Phi : \mathbb{R}_+ \times \mathscr{Y} \to \mathscr{Y}$ *is asymptotically smooth if there are maps* $U_1, U_2 : \mathbb{R}_+ \times \mathscr{Y} \to \mathscr{Y}$ *such that* $\Phi(t, x) = U_1(t, x) + U_2(t, x)$, *and the following hold for any bounded closed set* $\mathscr{A} \subset \mathscr{Y}$ *that is forward invariant under* Φ:
 (i) $\lim\limits_{t \to +\infty} diam\, U_2(t, \mathscr{A}) = 0$;
 (ii) *there exists* $t_{\mathscr{A}} \geq 0$ *such that* $U_1(t, \mathscr{A})$ *has compact closure for each* $t \geq t_{\mathscr{A}}$.

Since $\mathscr{Y}$ is an infinite dimensional space, space $L_+^1(0, +\infty)$ is a component of $\mathscr{Y}$. For infinite dimensional space, we cannot deduce precompactness only from boundedness. Thus, to derive the precompactness of $\mathscr{Y}$, we apply the following lemma:

Lemma 2 *Let* $\mathscr{B}$ *be a bounded subset of* $L_+^1(0, +\infty)$. *Then* $\mathscr{B}$ *has compact closure if and only if the following conditions hold:*
 (i) $\sup\limits_{f \in \mathscr{B}} \int_0^{+\infty} | f(s) | \, ds < +\infty$;
 (ii) $\lim\limits_{h \to +\infty} \int_h^{+\infty} | f(s) | \, ds = 0$ *uniformly in* $f \in \mathscr{B}$;
 (iii) $\lim\limits_{h \to 0+} \int_0^{+\infty} | f(s + h) - f(s) | \, ds = 0$ *uniformly in* $f \in \mathscr{B}$;
 (iv) $\lim\limits_{h \to 0+} \int_0^h | f(s) | \, ds = 0$ *uniformly in* $f \in \mathscr{B}$.

We are now ready to prove a result on the semiflow Φ generated by system (1) is asymptotically smooth.

Theorem 1 *The semiflow* Φ *generated by system (1) is asymptotically smooth.*

Proof We first decompose Φ into the following two parts: U_1, U_2 defined respectively by

$$U_1(t, x) = (S(t), I(t), T(t), \widetilde{e}(t, \cdot), \widetilde{r}(t, \cdot)), \quad U_2(t, x) = (0, 0, 0, 0, \psi_e(t, \cdot), \psi_r(t, \cdot)),$$

where

$$\psi_e(t, a) = \begin{cases} 0, & 0 \leq a \leq t, \\ e_0(a - t)\dfrac{k_1(a)}{k_1(a - t)}, & 0 \leq t < a, \end{cases}$$

$$\psi_r(t, \theta) = \begin{cases} 0, & 0 \leq \theta \leq t, \\ r_0(\theta - t)\dfrac{k_2(\theta)}{k_2(\theta - t)}, & 0 \leq t < \theta, \end{cases}$$

$$\widetilde{e}(t, a) = \begin{cases} e(t - a, 0)k_1(a), \ 0 \le a \le t, \\ 0, \qquad\qquad\qquad 0 \le t < a, \end{cases}$$

$$\widetilde{r}(t, \theta) = \begin{cases} r(t - \theta, 0)k_2(\theta), \ 0 \le \theta \le t, \\ 0, \qquad\qquad\qquad 0 \le t < \theta, \end{cases}$$

for $x = (S(0), I(0), T(0), e_0(a), r_0(\theta))$, clearly, we have $\Phi(t, x) = U_1(t, x) + U_2(t, x)$.

Let $\mathscr{A} \subset \mathscr{Y}$, r is a constant greater than $\frac{\Lambda}{\mu}$, for each $x \in \mathscr{A}$, we set $\| x \|_{\mathscr{Y}} \le r$. So we can derive

$$\| U_2(t, x) \|_{\mathscr{Y}} = \int_t^{+\infty} e_0(a - t)\frac{k_1(a)}{k_1(a - t)}da + \int_t^{+\infty} r_0(\theta - t)\frac{k_2(\theta)}{k_2(\theta - t)}d\theta$$

$$= \int_0^{+\infty} e_0(s)\frac{k_1(s + t)}{k_1(s)}ds + \int_0^{+\infty} r_0(s)\frac{k_2(s + t)}{k_2(s)}ds$$

$$= \int_0^{+\infty} e_0(s)e^{-\int_s^{s+t}(\mu+\delta(l)+\sigma(l))dl}ds + \int_0^{+\infty} r_0(s)e^{-\int_s^{s+t}(\mu+\omega(l))dl}ds$$

$$\le e^{-\mu t} \| x \|_{\mathscr{Y}} \le re^{-\mu t}.$$

Thus, $\lim_{t \to +\infty} diam\, U_2(t, \mathscr{A}) = 0$. In the following we will show that $U_1(t, \mathscr{A})$ has compact closure for each $t \ge 0$.

From Proposition 3, we know that $S(t), I(t), T(t)$ remain in the compact set $[0, r]$ for all $t \ge 0$. Next, we will show that $\widetilde{e}(t, a)$ and $\widetilde{r}(t, \theta)$ remain in a precompact subset of $L_+^1(0, +\infty)$ which is independent of x. According to

$$0 \le \widetilde{e}(t, a) = \begin{cases} e(t - a, 0)k_1(a), & 0 \le a \le t, \\ 0, & 0 \le t < a, \end{cases}$$

and (2), it is easy to show that

$$0 \le \widetilde{e}(t, a) \le (\beta(1 + \rho)r + \eta\rho_1)re^{-\mu a}.$$

Therefore, the conditions $(i), (ii)$ and (iv) of Lemma 2 are satisfied. Now, we only need to check the condition (iii) of Lemma 2.

$$\int_0^{+\infty} | \widetilde{e}(t, a + h) - \widetilde{e}(t, a) | \, da$$

$$= \int_0^{t-h} | \widetilde{e}(t, a + h) - \widetilde{e}(t, a) | \, da + \int_{t-h}^t | \widetilde{e}(t, a) | \, da$$

$$= \int_0^{t-h} | \widetilde{e}(t - a - h, 0)k_1(a + h) - \widetilde{e}(t - a, 0)k_1(a) | \, da$$

$$+ \int_{t-h}^t | \widetilde{e}(t - a, 0)k_1(a) | \, da$$

$$\leq \int_0^{t-h} | \, \widetilde{e}(t-a-h,0) \, || \, k_1(a+h) - k_1(a) \, | \, da$$

$$+ \int_0^{t-h} | \, \widetilde{e}(t-a-h,0) - \widetilde{e}(t-a,0) \, || \, k_1(a) \, | \, da + (\beta(1+\rho)r + \eta\rho_2)rh,$$

where

$$\int_0^{t-h} | \, \widetilde{e}(t-a-h,0) \, || \, k_1(a+h) - k_1(a) \, | \, da$$

$$\leq (\beta(1+\rho)r + \eta\rho_1)r \left(\int_0^{t-h} k_1(a)da - \int_0^{t-h} k_1(a+h)da \right)$$

$$= (\beta(1+\rho)r + \eta\rho_1)r \left(\int_0^{t-h} k_1(a)da - \int_h^t k_1(s)ds \right)$$

$$= (\beta(1+\rho)r + \eta\rho_1)r \left(\int_0^{t-h} k_1(a)da - \int_h^{t-h} k_1(s)ds - \int_{t-h}^t k_1(s)ds \right)$$

$$= (\beta(1+\rho)r + \eta\rho_1)r \left(\int_0^h k_1(a)da - \int_{t-h}^t k_3(s)ds \right) \leq (\beta(1+\rho)r + \eta\rho_2)rh$$

Notice that $| \, \dfrac{dI(t)}{dt} \, | \leq (\bar{\omega} + \bar{\sigma})r + (1-\eta)\rho_1 r + (\gamma + \mu + \mu_I)r$, $| \, \dfrac{dS(t)}{dt} \, | \leq \Lambda + \beta(1+\rho)r^2 + \mu r$, $| \, \dfrac{dT(t)}{dt} \, | \leq \gamma r + (\mu + \mu_T + \alpha + \rho_1)r$, then

$$| \, \widetilde{e}(t-a-h,0) - \widetilde{e}(t-a,0) \, |$$
$$\leq \beta \, | \, S(t-a-h)I(t-a-h) - S(t-a)I(t-a) \, |$$
$$+ \beta\rho \, | \, S(t-a-h)T(t-a-h) - S(t-a)T(t-a) \, |$$
$$+ \eta\rho_1 \, | \, T(t-a-h) - T(t-a) \, |$$
$$= \beta(\, | \, S(t-a-h) \, || \, I(t-a-h) - I(t-\tau) \, |$$
$$+ \, | \, I(t-a) \, || \, S(t-a-h) - S(t-a) \, | \,)$$
$$+ \beta\rho(\, | \, S(t-a-h) \, || \, T(t-a-h) - T(t-\tau) \, |$$
$$+ \, | \, T(t-a) \, || \, S(t-a-h) - S(t-a) \, | \,)$$
$$+ \eta\rho_1 \, | \, T(t-a-h) - T(t-a) \, | \leq \Delta h,$$

where

$$\Delta = (\beta + \beta\rho)r(\Lambda + \beta(1+\rho)r^2 + \mu r) + (\beta\rho r + \eta\rho_1)(\gamma r + (\mu + \mu_T + \alpha + \rho_1)r)$$
$$+ \beta r((\bar{\omega} + \bar{\sigma})r + (1-\eta)\rho_1 r + (\gamma + \mu + \mu_I)r).$$

Then

$$\int_0^{t-h} | \, \widetilde{e}(t-a-h,0) - \widetilde{e}(t-a,0) \, || \, k_1(a) \, | \, da \leq \Delta h \int_0^{t-h} e^{-\mu s} ds \leq \frac{\Delta}{\mu} h.$$

Hence,

$$\int_0^{+\infty} | \widetilde{e}(t, a + h) - \widetilde{e}(t, a) | \, da \le (2(\beta(1 + \rho)r + \eta\rho_1)r + \frac{\Lambda}{\mu})h.$$

Thus, the condition (iii) of Lemma 2 holds, then we can get that $\widetilde{e}(t, a)$ satisfies the conditions of Lemma 2. In a similar way, $\widetilde{r}(t, \theta)$ also satisfies the conditions of Lemma 2. Therefore, we obtain $U_1(t, \mathscr{A})$ has compact closure for each $t \ge 0$, Using Lemma 1, we know semiflow Φ is asymptotically smooth. This completes the proof. □

Combining Proposition 3 and Φ is asymptotically smooth, as well as the existence theory of global attractors, the following result is immediate from Theorem 2.6 in Magal and Zhao (2005) and Theorem 2.4 in D'Agata et al. (2006).

Theorem 2 *The semiflow Φ has a global attractor $\mathcal{A}$ in $\mathscr{Y}$, which attracts any bounded subset of $\mathscr{Y}$.*

3 Equilibria and their local stability

3.1 Existence of equilibria

System (1) always has a disease free equilibrium $E_0 = (\frac{\Lambda}{\mu}, 0, 0, 0_{L^1(0,+\infty)}, 0_{L^1(0,+\infty)})$. One can obtain the reproduction number from system (1)

$$\mathscr{R}_0 = \beta \frac{(\mathscr{K}_1 + \mathscr{K}_2\mathscr{K}_3)}{\gamma + \mu + \mu_I} \frac{\Lambda}{\mu} + \frac{\gamma(\alpha\mathscr{K}_2 + (1 - \eta)\rho_1 + (\beta\rho\frac{\Lambda}{\mu} + \eta\rho_1)(\mathscr{K}_1 + \mathscr{K}_2\mathscr{K}_3))}{(\gamma + \mu + \mu_I)(\mu + \mu_T + \alpha + \rho_1)}. \tag{7}$$

$\mathscr{R}_0$ represents the average number of secondary infected individuals produced by a primary infected individual.

Next, we investigate the endemic equilibria of system (1). A endemic equilibrium $(S^*, I^*, T^*, e^*(a), r^*(\theta))$ of system (1) satisfies the following equations:

$$\begin{cases} \Lambda - \beta S^*(I^* + \rho T^*) - \mu S^* = 0, \\ \int_0^{+\infty} \sigma(a)e^*(a)da + \int_0^{+\infty} \omega(\theta)r^*(\theta)d\theta = (\mu + \mu_I + \gamma)I^* - (1 - \eta)\rho_1 T^*, \\ \gamma I^* - (\mu + \mu_T + \alpha + \rho_1)T^* = 0, \\ \dfrac{de^*(a)}{da} = -(\mu + \delta(a) + \sigma(a))e^*(a), \\ \dfrac{dr^*(\theta)}{d\theta} = -(\mu + \omega(\theta))r^*(\theta), \\ e^*(0) = \beta S^*(I^* + \rho T^*) + \eta\rho_1 T^*, \quad r^*(0) = \int_0^{+\infty} \delta(a)e^*(a)da + \alpha T^*. \end{cases} \tag{8}$$

From (8) we can easily find that if $\mathscr{R}_0 > 1$, system (1) has a endemic equilibrium $E^* = (S^*, I^*, T^*, e^*(a), r^*(\theta))$, where

$$I^* = \frac{\mathscr{R}_0 - 1}{1 - \dfrac{\alpha\gamma\mathscr{K}_2 + \eta\rho_1\gamma(\mathscr{K}_1 + \mathscr{K}_2\mathscr{K}_3) + (1-\eta)\rho_1\gamma}{(\mu+\mu_I+\gamma)(\mu+\mu_T+\alpha+\rho_1)}},$$

$$T^* = \frac{\gamma}{\mu+\mu_T+\alpha+\rho_1}I^*,$$

$$S^* = \frac{\Lambda}{\mu+\beta(I^*+\rho T^*)}, \quad e^*(a) = e^*(0)k_1(a), \quad r^*(\theta) = r^*(0)k_2(\theta).$$

Summarizing the discussions above, we have the following theorem.

Theorem 3 *System (1) always has the disease free equilibrium E_0. Moreover, apart from E_0, if $\mathscr{R}_0 > 1$, system (1) exists a unique endemic equilibrium E^*.*

3.2 Local stability of the equilibria

Now we consider the linearized system of (1) at an equilibrium $\widetilde{E} = (\widetilde{S}, \widetilde{I}, \widetilde{T}, \widetilde{e}(a), \widetilde{r}(\theta))$. Let $\overline{S}(t) = S(t) - \widetilde{S}$, $\overline{I}(t) = I(t) - \widetilde{I}$, $\overline{T}(t) = T(t) - \widetilde{T}$, $\overline{e}(a,t) = e(a,t) - \widetilde{e}(a)$, $\overline{r}(t,\theta) = r(t,\theta) - \widetilde{r}(\theta)$, then removing the bar, we obtain the following linearized system:

$$\begin{cases} \dfrac{dS(t)}{dt} = -\beta\widetilde{S}(I+\rho T) - \beta(\widetilde{I}+\rho\widetilde{T})S - \mu S, \\[2mm] \dfrac{dI(t)}{dt} = \displaystyle\int_0^{+\infty} \sigma(a)e(t,a)da + \int_0^{+\infty} \omega(\theta)r(t,a)da \\[2mm] \qquad\qquad + (1-\eta)\rho_1 T - (\mu+\mu_I+\gamma)I(t), \\[2mm] \dfrac{dT(t)}{dt} = \gamma I - (\mu+\mu_T+\alpha+\rho_1)T, \\[2mm] \dfrac{\partial e(t,a)}{\partial t} + \dfrac{\partial e(t,a)}{\partial a} = -(\mu+\delta(a)+\sigma(a))e(t,a), \\[2mm] \dfrac{\partial r(t,\theta)}{\partial t} + \dfrac{\partial r(t,\theta)}{\partial \theta} = -(\mu+\omega(\theta))r(t,\theta), \end{cases} \tag{9}$$

with the following boundary conditions

$$e(t,0) = \beta\widetilde{S}(I+\rho T) + \beta(\widetilde{I}+\rho\widetilde{T})S + \eta\rho_1 T,$$

$$r(t,0) = \int_0^{+\infty} \delta(a)e(t,a)da + \alpha T.$$

Let

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

$$k_2(\lambda) = \int_0^{+\infty} \omega(\theta) e^{-\int_0^\theta (\lambda+\mu+\omega(s))ds} d\theta,$$

$$k_3(\lambda) = \int_0^{+\infty} \delta(a) e^{-\int_0^a (\lambda+\mu+\sigma(s)+\delta(s))ds} da.$$

For (9), let $S(t) = S^0 e^{\lambda t}$, $I(t) = I^0 e^{\lambda t}$, $T(t) = T^0 e^{\lambda t}$, $e(t,a) = e^0(a)e^{\lambda t}$, $r(t,\theta) = r^0(\theta)e^{\lambda t}$, we have

$$
\begin{cases}
\lambda S^0 = -\beta \widetilde{S}(I^0 + \rho T^0) - \beta(\widetilde{I} + \rho \widetilde{T})S^0 - \mu S^0, \\
(\lambda + \mu + \mu_I + \gamma)I^0 = \displaystyle\int_0^{+\infty} \sigma(a)e^0(a)da + \int_0^{+\infty} \omega(\theta)r^0(a)da + (1-\eta)\rho_1 T^0, \\
(\lambda + \mu + \mu_T + \alpha + \rho_1)T^0 = \gamma I^0, \\
\dot{e}^0(a) = -(\lambda + \mu + \delta(a) + \sigma(a))e^0(a), \\
\dot{r}_h^0(\theta) = -(\lambda + \mu + \omega(\theta))r^0(\theta),
\end{cases}
\tag{10}
$$

with initial conditions

$$
\begin{cases}
e^0(0) = \beta \widetilde{S}(I^0 + \rho T^0) + \beta(\widetilde{I} + \rho \widetilde{T})S^0 + \eta\rho_1 T^0, \\
r^0(0) = e^0(0)k_3(\lambda) + \alpha T^0.
\end{cases}
\tag{11}
$$

We obtain from the system (10) that

$$(\lambda + \mu + \mu_I + \gamma)I^0 = k_1(\lambda)e^0(0) + k_2(\lambda)(k_3(\lambda)(e^0(0) + \alpha T^0) + (1-\eta)\rho T^0,$$

$$e^0(0) = (\lambda + \mu)\frac{\beta \widetilde{S}(I^0 + \rho T^0)}{\lambda + \mu + \beta(\widetilde{I} + \rho \widetilde{T})} + \eta\rho_1 T_0.$$

Combined with the third equation of system (10), and by simple calculation, we have

$$(\lambda + \mu + \mu_I + \gamma)I^0 = [k_1(\lambda) + k_2(\lambda)k_3(\lambda)]\{(\lambda + \mu)\frac{\beta \widetilde{S}(1 + \rho\frac{\gamma}{\lambda+\mu+\mu_T+\alpha+\rho_1})}{\lambda + \mu + \beta(\widetilde{I} + \rho \widetilde{T})}$$

$$+ \eta\rho_1 \frac{\gamma}{\lambda + \mu + \mu_T + \alpha + \rho_1}\}I^0$$

$$+ [(1-\eta)\rho_1 + k_2(\lambda)\alpha]\frac{\gamma}{\lambda + \mu + \mu_T + \alpha + \rho_1}I^0.$$

We obtain the characteristic equation of system (1) at an equilibrium $\widetilde{E}$ as follows:

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

where

$$f(\lambda) = \frac{[k_1(\lambda) + k_2(\lambda)k_3(\lambda)]\{(\lambda + \mu)\dfrac{\beta \widetilde{S}(1 + \rho\frac{\gamma}{\lambda+\mu+\mu_T+\alpha+\rho_1})}{\lambda + \mu + \beta(\widetilde{I} + \rho \widetilde{T})} + \eta\rho_1 \frac{\gamma}{\lambda+\mu+\mu_T+\alpha+\rho_1}\}}{\lambda + \mu + \mu_I + \gamma}$$

$$+ \frac{[(1-\eta)\rho_1 + k_2(\lambda)\alpha]\frac{\gamma}{\lambda+\mu+\mu_T+\alpha+\rho_1}}{\lambda+\mu+\mu_I+\gamma}.$$

Next we will analyze the local stability of the equilibria. Rigorous proof of local stability require more thorough spectral analysis, which be referred to in Liu et al. (2017). Liu et al. (2017) formulated an age-structured model as an abstract non-densely defined Cauchy problem, and Lemma 3.4 in Liu et al. (2017) 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 (1).

Theorem 4 (Local stability) *(i) The disease-free equilibrium E_0 of system (1) is locally stable if $\mathscr{R}_0 < 1$ and is unstable if $\mathscr{R}_0 > 1$.*
(ii) The endemic equilibrium E^* of system (1) is locally stable if it exists.

Proof We first consider the local stability of the disease-free equilibrium E_0. The characteristic equation corresponding to E_0 is

$$f(\lambda) = \frac{[k_1(\lambda) + k_2(\lambda)k_3(\lambda)]}{\lambda+\mu+\mu_I+\gamma} \left\{ \beta\frac{\Lambda}{\mu}\left(1 + \frac{\rho\gamma}{\lambda+\mu+\mu_T+\alpha+\rho_1}\right) + \frac{\eta\rho_1\gamma}{\lambda+\mu+\mu_T+\alpha+\rho_1} \right\}$$
$$+ \frac{[(1-\eta)\rho_1 + k_2(\lambda)\alpha]\gamma}{(\lambda+\mu+\mu_I+\gamma)(\lambda+\mu+\mu_T+\alpha+\rho_1)}.$$

Clearly, we have $f(0) = \mathscr{R}_0$, $f'(\lambda) < 0$ and $\lim_{\lambda\to\infty} f(\lambda) = 0$. Hence, if $\mathscr{R}_0 > 1$, then $f(\lambda) = 1$ has a unique positive real root. That is, if $\mathscr{R}_0 > 1$, the disease-free equilibrium E_0 is unstable.

If $\mathscr{R}_0 < 1$, the disease-free equilibrium E_0 is locally stable. Otherwise, $f(\lambda_0) = 1$ has at least one root $\lambda_0 = a_1 + ib_1$ satisfying $a_1 \geq 0$. But

$$\mid f(\lambda_0) \mid \leq \mathscr{R}_0 < 1.$$

Hence, if $\mathscr{R}_0 < 1$, all roots of $f(\lambda) = 1$ have negative real parts, then the disease-free equilibrium E_0 is locally stable if $\mathscr{R}_0 < 1$.

Next, we consider the local stability of the endemic equilibrium E^*. The characteristic equation corresponding to E^* is

$$f(\lambda) = \frac{[k_1(\lambda) + k_2(\lambda)k_3(\lambda)]\left\{(\lambda+\mu)\frac{\beta S^*\left(1+\rho\frac{\gamma}{\lambda+\mu+\mu_T+\alpha+\rho_1}\right)}{\lambda+\mu+\beta(I^*+\rho T^*)} + \eta\rho_1\frac{\gamma}{\lambda+\mu+\mu_T+\alpha+\rho_1}\right\}}{\lambda+\mu+\mu_I+\gamma}$$
$$+ \frac{[(1-\eta)\rho_1 + k_2(\lambda)\alpha]\frac{\gamma}{\lambda+\mu+\mu_T+\alpha+\rho_1}}{\lambda+\mu+\mu_I+\gamma}.$$

If $\mathscr{R}_0 > 1$, the endemic equilibrium E^* is locally stable. Otherwise, $f(\lambda^*) = 1$ has at least one root $\lambda^* = a_2 + ib_2$ satisfying $a_2 \geq 0$. We notice that

$$(\mathcal{K}_1 + \mathcal{K}_2\mathcal{K}_3) \left\{ \beta S^* \left(1 + \frac{\rho\gamma}{\mu + \mu_T + \alpha + \rho_1} \right) + \frac{\eta\rho_1\gamma}{\mu + \mu_T + \alpha + \rho_1} \right\} + \frac{((1-\eta)\rho_1 + \mathcal{K}_2\alpha)\gamma}{\mu + \mu_T + \alpha + \rho_1}$$
$$-(\mu + \mu_I + \gamma) = 0,$$

and

$$|f(\lambda^*)| < \frac{(\mathcal{K}_1 + \mathcal{K}_2\mathcal{K}_3) \left\{ \beta S^* \left(1 + \rho\frac{\gamma}{\mu+\mu_T+\alpha+\rho_1} \right) + \eta\rho_1 \frac{\gamma}{\mu+\mu_T+\alpha+\rho_1} \right\}}{\mu + \mu_I + \gamma}$$
$$+ \frac{[(1-\eta)\rho_1 + \mathcal{K}_2\alpha]\frac{\gamma}{\mu+\mu_T+\alpha+\rho_1}}{\mu + \mu_I + \gamma} = 1.$$

Hence, if $\mathcal{R}_0 > 1$, all roots of $f(\lambda) = 1$ have negative real parts, then the endemic equilibrium E^* is locally stable if $\mathcal{R}_0 > 1$. This completes the proof. $\square$

4 Uniform persistence and global stability

4.1 Uniform persistence

In this subsection, our purpose is to show that system (1) is uniformly persistent when $\mathcal{R}_0 > 1$. Define

$$M_0 = \{(x_1, x_2, x_3, x_4, x_5) \in \mathscr{Y} : x_2 + x_3 + \int_0^{+\infty} x_4(a)da + \int_0^{+\infty} x_5(a)da > 0\},$$

let $\partial M_0 = \mathscr{Y} \backslash M_0$. Then, we have $\mathscr{Y} = M_0 \cup \partial M_0$.

Theorem 5 *The sets M_0 and ∂M_0 are forward invariant under the semiflow $\Phi(t, \cdot)$. Also, the disease-free equilibrium E_0 of system (1) is globally asymptotically stable for the semiflow $\Phi(t, \cdot)$ restricted to ∂M_0.*

Proof First we prove M_0 is forward invariant under the semiflow $\Phi(t, \cdot)$. Let $\Phi(0, x_0) \in M_0$, $U(t) = I(t) + T(t) + \int_0^{+\infty} e(t, a)da + \int_0^{+\infty} r(t, \theta)d\theta$,

$$\frac{dU(t)}{dt} \geq -(\mu + \mu_I + \mu_T)U(t),$$
$$U(t) \geq e^{-(\mu+\mu_I+\mu_T)t}U(0) > 0.$$

This implies the fact that $\Phi(t, M_0) \subset M_0$, i.e. M_0 is forward invariant under the semiflow $\Phi(t, \cdot)$.

Next, we will prove ∂M_0 is forward invariant under the semiflow $\Phi(t, \cdot)$. Let $\Phi(0, x_0) \in \partial M_0$, we consider the following system

$$
\begin{cases}
\dfrac{dI(t)}{dt} = \displaystyle\int_0^{+\infty} \sigma(a)e(t,a)da + \int_0^{+\infty} \omega(\theta)r(t,\theta)d\theta + (1-\eta)\rho_1 T - (\gamma+\mu+\mu_I)I(t), \\[2ex]
\dfrac{dT(t)}{dt} = \gamma I(t) - (\mu+\mu_T+\alpha+\rho_1)T(t), \\[2ex]
\dfrac{\partial e(t,a)}{\partial t} + \dfrac{\partial e(t,a)}{\partial a} = -(\mu+\delta(a)+\sigma(a))e(t,a), \\[2ex]
\dfrac{\partial r(t,\theta)}{\partial t} + \dfrac{\partial r(t,\theta)}{\partial \theta} = -(\mu+\omega(\theta))r(t,\theta), \\[2ex]
e(t,0) = \beta S(I+\rho T) + \eta\rho_1 T, \quad r(t,0) = \displaystyle\int_0^{+\infty} \delta(a)e(t,a)da + \alpha T, \\[2ex]
e(0,a) = e_0(a), \quad r(0,\theta) = r_0(\theta), \ I(0) = 0, \ T(0) = 0.
\end{cases}
\tag{12}
$$

Since $S(t) \le \Delta_1$, where $\Delta_1 = max\{\dfrac{\Lambda}{\mu}, \| x_0 \|_{\mathscr{Y}}\}$, it follows that

$$
I(t) \le \hat{I}(t), \quad T(t) \le \hat{T}(t), e(t,s) \le \hat{e}(t,s), \ r(t,s) \le \hat{r}(t,s),
\tag{13}
$$

where

$$
\begin{cases}
\dfrac{d\hat{I}(t)}{dt} = \displaystyle\int_0^{+\infty} \sigma(a)\hat{e}(t,a)da + \int_0^{+\infty} \omega(\theta)\hat{r}(t,\theta)d\theta + (1-\eta)\rho_1 \hat{T} - (\gamma+\mu+\mu_I)\hat{I}(t), \\[2ex]
\dfrac{d\hat{T}(t)}{dt} = \gamma \hat{I}(t) - (\mu+\mu_T+\alpha+\rho_1)\hat{T}(t), \\[2ex]
\dfrac{\partial \hat{e}(t,a)}{\partial t} + \dfrac{\partial \hat{e}(t,a)}{\partial a} = -(\mu+\delta(a)+\sigma(a))\hat{e}(t,a), \\[2ex]
\dfrac{\partial \hat{r}(t,\theta)}{\partial t} + \dfrac{\partial \hat{r}(t,\theta)}{\partial \theta} = -(\mu+\omega(\theta))\hat{r}(t,\theta), \\[2ex]
\hat{e}(t,0) = \beta\Delta_1(\hat{I}+\rho\hat{T}) + \eta\rho_1\hat{T}, \quad \hat{r}(t,0) = \bar{\delta}\displaystyle\int_0^{+\infty} \hat{e}(t,a)da + \alpha\hat{T}, \\[2ex]
\hat{e}(0,a) = e_0(a), \quad \hat{r}(0,\theta) = r_0(\theta), \hat{I}(0) = 0, \ \hat{T}(0) = 0.
\end{cases}
\tag{14}
$$

By the formulation (6), we have

$$
\hat{e}(t,a) = \begin{cases} \hat{e}(t-a,0)k_1(a), & 0 \le a \le t, \\[1ex] e_0(a-t)\dfrac{k_1(a)}{k_1(a-t)}, & 0 \le t < a, \end{cases} \quad
\hat{r}(t,\theta) = \begin{cases} \hat{r}(t-\theta,0)k_2(\theta), & 0 \le \theta \le t, \\[1ex] r_0(\theta-t)\dfrac{k_2(\theta)}{k_2(\theta-t)}, & 0 \le t < \theta. \end{cases}
\tag{15}
$$

Substituting (15) into the first two equations of (14) yield

$$\begin{cases} \dfrac{d\hat{I}(t)}{dt} = \displaystyle\int_0^t \sigma(a)\hat{e}(t-a,0)k_1(a)da + \int_0^t \omega(\theta)\hat{r}(t-\theta,0)k_2(\theta)d\theta + F(t) + (1-\eta)\rho_1\hat{T} \\ \qquad\qquad - (\gamma+\mu+\mu_I)\hat{I}(t), \\ \dfrac{d\hat{T}(t)}{dt} = \gamma\hat{I}(t) - (\mu+\mu_T+\alpha+\rho_1)\hat{T}(t), \\ \hat{I}(0)=0, \ \ \hat{T}(0)=0. \end{cases} \qquad (16)$$

where

$$F(t) = \int_t^{+\infty} \sigma(a)e_0(a-t)\frac{k_1(a)}{k_1(a-t)}da + \int_t^{+\infty} \omega(\theta)r_0(\theta-t)\frac{k_2(\theta)}{k_2(\theta-t)}d\theta.$$

Since

$$F(t) \le \bar{\sigma}\int_t^{+\infty} e_0(a-t)da + \bar{\omega}\int_t^{+\infty} r_0(\theta-t)d\theta = \bar{\sigma}\int_0^{+\infty} e_0(a)da + \bar{\omega}\int_0^{+\infty} r_0(\theta)d\theta,$$

due to $\Phi(0,x_0) \in \partial M_0$, then $F(t) \equiv 0$ for $t \ge 0$.

$$\int_0^t \omega(\theta)\hat{r}(t-\theta,0)k_2(\theta)d\theta$$
$$= \int_0^t \omega(\theta)k_2(\theta)\alpha\hat{T}(t-\theta)d\theta + \bar{\delta}\int_0^t \omega(\theta)k_2(\theta)d\theta \int_0^{t-\theta} \hat{e}(t-\theta-a,0)k_1(a)da$$
$$+\bar{\delta}\int_0^t \omega(\theta)k_2(\theta)d\theta \int_{t-\theta}^{+\infty} \hat{e}(0,-t+\theta+a)\frac{k_1(a)}{k_1(a-t+\theta)}da$$
$$= \int_0^t \omega(\theta)k_2(\theta)\alpha\hat{T}(t-\theta)d\theta + \bar{\delta}\int_0^t \omega(\theta)k_2(\theta)d\theta \int_0^{t-\theta} \hat{e}(t-\theta-a,0)k_1(a)da.$$

The system (16) can be written

$$\begin{cases} \dfrac{d\hat{I}(t)}{dt} = \displaystyle\int_0^t \sigma(a)k_1(a)(\beta\Delta_1(\hat{I}(t-a)+\rho\hat{T}(t-a)) + \eta\rho_1\hat{T}(t-a))da \\ \qquad + (1-\eta)\rho_1\hat{T} - (\gamma+\mu+\mu_I)\hat{I}(t) + \displaystyle\int_0^t \omega(\theta)k_2(\theta)\alpha\hat{T}(t-\theta)d\theta \\ \qquad + \bar{\delta}\displaystyle\int_0^t \omega(\theta)k_2(\theta)d\theta \int_0^{t-\theta}(\beta\Delta_1(\hat{I}(t-\theta-a)+\rho\hat{T}(t-\theta-a)) \\ \qquad + \eta\rho_1\hat{T}(t-\theta-a))k_1(a)da, \\ \dfrac{d\hat{T}(t)}{dt} = \gamma\hat{I}(t) - (\mu+\mu_T+\alpha+\rho_1)\hat{T}(t), \\ \hat{I}(0)=0, \ \ \hat{T}(0)=0. \end{cases}$$

Thus, (16) has a unique solution $\hat{I}(t) \equiv 0$, $\hat{T}(t) \equiv 0$ for $t \ge 0$.

From (14), (15), we know that $\hat{e}(t, s) = 0, \hat{r}(t, s) = 0$ for $0 \le s \le t$, thus,

$$\| \hat{e}(t, a) \|_{L_+^1} = \int_t^{+\infty} e_0(a - t) \frac{k_1(a)}{k_2(a - t)} da \le \| e_0(s) \|_{L_+^1} = 0.$$

Similarly, we have $\| \hat{r}(t, \theta) \|_{L_+^1} = 0$.

By using (13) we can obtain that $I(t) = 0, \ T(t) = 0, \| e(t, a) \|_{L_+^1} = 0, \| r(t, \theta) \|_{L_+^1} = 0$ for $t \ge 0$. Thus, ∂M_0 is forward invariant under the semiflow $\Phi(t, \cdot)$.

Finally, we prove the disease-free equilibrium E_0 of system (1) is globally asymptotically stable for the semiflow $\Phi(t, \cdot)$ restricted to ∂M_0. In ∂M_0, system (1) can be written as follows

$$\frac{dS(t)}{dt} = \Lambda - \mu S(t), \tag{17}$$

Obviously, $\lim_{t \to +\infty} S(t) = \frac{\Lambda}{\mu}$. Hence, the equilibrium E_0 is globally asymptotically stable restricted to ∂M_0. The proof of Theorem 5 is complete. □

Theorem 6 *If $\mathscr{R}_0 > 1$, then semiflow $\{\Phi(t, \cdot)\}_{t \ge 0}$ generated by system (1) is uniformly persistent with respect to the decomposition $(M_0, \ \partial M_0)$. Moreover, there is a compact subset $\mathcal{A}_0 \subset M_0$, which is a global attractor for $\{\Phi(t, \cdot)\}_{t \ge 0}$ in M_0.*

Proof Since the disease-free equilibrium E_0 is globally asymptotically stable restricted to ∂M_0, applying Theorem 4.2 in Hale and Waltman (1989), we only need to prove

$$W_s(E_0) \cap M_0 = \emptyset,$$

where $W_s(E_0) = \{x \in \mathscr{Y} : \lim_{t \to +\infty} \Phi(t, x) = E_0\}$. By way of contradiction, we assume that there exists a $x_0 \in M_0$ such that $x_0 \in W_s(E_0)$. Then we can find a list of $\{x_n\} \subset M_0$ such that

$$\| \Phi(t, x_n) - E_0 \|_{\mathscr{Y}} < \frac{1}{n}, t \ge 0.$$

Denote $\Phi(t, x_n) = (S_n(t), I_n(t), T_n(t), e_n(t, \cdot), r_n(t, \cdot))$. Then for all $t \ge 0$, we have

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

and $\Phi(t, x_n) \subset M_0$. From the system (1), we know that there exists $t_0 \ge 0$ such that $I(t) > 0$ for $t \ge t_0$ or $T(t) > 0$ for $t \ge t_0$, so without loss of generality, we can take $t_0 = 0$ and $I(0) > 0$. Since $\mathcal{R}_0 > 1$, we can choose sufficiently large n such that $\frac{\Lambda}{\mu} > \frac{1}{n}$ and

$$f(n) = \frac{\beta(\frac{\Lambda}{\mu} - \frac{1}{n})}{\gamma + \mu + \mu_I}(\mathscr{K}_1 + \mathscr{K}_2 \mathscr{K}_3)$$

$$+ \frac{\gamma(\alpha\mathcal{K}_2 + (1-\eta)\rho_1 + (\beta\rho(\frac{\Lambda}{\mu} - \frac{1}{n}) + \eta\rho_1)(\mathcal{K}_1 + \mathcal{K}_2\mathcal{K}_3))}{(\gamma + \mu + \mu_I)(\mu + \mu_T + \alpha + \rho_1)} > 1$$

Now we construct the following system

$$\begin{cases} \dfrac{d\hat{I}(t)}{dt} = \displaystyle\int_0^{+\infty} \sigma(a)\hat{e}(t,a)da + \int_0^{+\infty} \omega(\theta)\hat{r}(t,\theta)d\theta + (1-\eta)\rho_1\hat{T} - (\gamma + \mu + \mu_I)\hat{I}(t), \\[2mm] \dfrac{d\hat{T}(t)}{dt} = \gamma\hat{I}(t) - (\mu + \mu_T + \alpha + \rho_1)\hat{T}(t), \\[2mm] \dfrac{\partial\hat{e}(t,a)}{\partial t} + \dfrac{\partial\hat{e}(t,a)}{\partial a} = -(\mu + \delta(a) + \sigma(a))\hat{e}(t,a), \\[2mm] \dfrac{\partial\hat{r}(t,\theta)}{\partial t} + \dfrac{\partial\hat{r}(t,\theta)}{\partial \theta} = -(\mu + \omega(\theta))\hat{r}(t,\theta), \\[2mm] \hat{e}(t,0) = \beta(\dfrac{\Lambda}{\mu} - \dfrac{1}{n})(\hat{I} + \rho\hat{T}) + \eta\rho_1\hat{T}, \ \ \hat{r}(t,0) = \displaystyle\int_0^{+\infty}\delta(a)\hat{e}(t,a)da + \alpha\hat{T}, \\[2mm] \hat{e}(0,a) = e_0(a), \ \ \hat{r}(0,\theta) = r_0(\theta), \hat{I}(0) = i_0, \ \ \hat{T}(0) = t_0. \end{cases} \tag{18}$$

Using similar analysis as in Sect. 2, we can get existence, uniqueness and nonnegative of solution to system (18). By the comparison principle, we know

$$I(t) \geq \hat{I}(t), \ \ T(t) \geq \hat{T}(t), e(t,s) \geq \hat{e}(t,s), \ r(t,s) \geq \hat{r}(t,s). \tag{19}$$

By use of Volterra formulation (6), we have

$$\hat{e}(t,\theta) = \begin{cases} \hat{e}(t-a,0)k_1(a), & 0 \leq a \leq t, \\[2mm] e_0(a-t)\dfrac{k_1(a)}{k_1(a-t)}, & 0 \leq t < a, \end{cases} \ \ \ \hat{r}(t,\theta) = \begin{cases} \hat{r}(t-\theta,0)k_2(\theta), & 0 \leq \theta \leq t, \\[2mm] r_0(\theta-t)\dfrac{k_2(\theta)}{k_2(\theta-t)}, & 0 \leq t < \theta. \end{cases} \tag{20}$$

Substituting (20) into the first two equations of (18) yield

$$\begin{cases} \dfrac{d\hat{I}(t)}{dt} \geq \displaystyle\int_0^t \sigma(a)k_1(a)[\beta(\dfrac{\Lambda}{\mu} - \dfrac{1}{n})(\hat{I}(t-a) + \rho\hat{T}(t-a)) + \eta\rho_1\hat{T}(t-a)]da \\[2mm] \qquad\quad + \displaystyle\int_0^t \omega(\theta)k_2(\theta)\alpha\hat{T}(t-\theta)d\theta + (1-\eta)\rho_1\hat{T}(t) - (\gamma + \mu + \mu_I)\hat{I}(t) \\[2mm] \qquad\quad + \displaystyle\int_0^t \omega(\theta)k_2(\theta)\int_0^{t-\theta}\delta(a)k_1(a)[\beta(\dfrac{\Lambda}{\mu} - \dfrac{1}{n})(\hat{I}(t-\theta-a) + \rho\hat{T}(t-\theta-a)) \\[2mm] \qquad\quad + \eta\rho_1\hat{T}(t-\theta-a)]d\theta, \\[2mm] \dfrac{d\hat{T}(t)}{dt} = \gamma\hat{I}(t) - (\mu + \mu_T + \alpha + \rho_1)\hat{T}(t), \\[2mm] \hat{I}(0) = i_0, \ \ \hat{T}(0) = t_0. \end{cases} \tag{21}$$

We can claim that at least one of $\hat{I}(t)$, $\hat{T}(t)$ is unbounded. Otherwise, we can use Laplace transform in the first two inequations of (21) yield

$$
\begin{cases}
-\hat{I}(0) + \lambda\mathcal{L}[\hat{I}](\lambda) \geq \mathcal{L}[u_1](\lambda)\mathcal{L}[\hat{I}](\lambda) + \mathcal{L}[u_2](\lambda)\mathcal{L}[\hat{T}](\lambda) - (\gamma + \mu + \mu_I)\mathcal{L}[\hat{I}](\lambda) \\
\quad + (1 - \eta)\rho_1\mathcal{L}[\hat{T}](\lambda) + \mathcal{L}[\omega](\lambda)\mathcal{L}[u_3](\lambda)\mathcal{L}[\hat{I}](\lambda) \\
\quad + \mathcal{L}[\omega](\lambda)\mathcal{L}[u_4](\lambda)\mathcal{L}[\hat{T}](\lambda) + \mathcal{L}[\omega](\lambda)\alpha\mathcal{L}[\hat{T}](\lambda) \\
-\hat{T}(0) + \lambda\mathcal{L}[\hat{T}](\lambda) = \gamma\mathcal{L}[\hat{I}](\lambda) - (\mu + \mu_T + \alpha + \rho_1)\mathcal{L}[\hat{T}](\lambda),
\end{cases}
\tag{22}
$$

where

$$
\mathcal{L}[\hat{I}](\lambda) = \int_0^{+\infty} e^{-\lambda t}\hat{I}(t)dt, \quad \mathcal{L}[\hat{T}](\lambda) = \int_0^{+\infty} e^{-\lambda t}\hat{T}(t)dt,
$$

$$
\mathcal{L}[u_1](\lambda) = \int_0^{\infty} \sigma(a)k_1(a)\beta(\frac{\Lambda}{\mu} - \frac{1}{n})e^{-\lambda a}da, \mathcal{L}[u_3](\lambda) = \int_0^{\infty} \delta(a)k_1(a)\beta(\frac{\Lambda}{\mu} - \frac{1}{n})e^{-\lambda a}da,
$$

$$
\mathcal{L}[u_2](\lambda) = \int_0^{\infty} \sigma(a)k_1(a)[\beta(\frac{\Lambda}{\mu} - \frac{1}{n})\rho + \eta\rho_1]e^{-\lambda a}da,
$$

$$
\mathcal{L}[u_4](\lambda) = \int_0^{\infty} \delta(a)k_1(a)[\beta(\frac{\Lambda}{\mu} - \frac{1}{n})\rho + \eta\rho_1]e^{-\lambda a}da, \quad \mathcal{L}[\omega](\lambda) = \int_0^{+\infty} \omega(\theta)k_2(\theta)e^{-\lambda\theta}d\theta.
$$

After a simple calculation, we obtain

$$
((\lambda + \gamma + \mu + \mu_I) - \mathcal{L}[u_1](\lambda) - \frac{\gamma}{\lambda + \mu + \mu_T + \alpha + \rho_1}(\mathcal{L}[u_2](\lambda) + (1 - \eta)\rho_1
$$

$$
+ \mathcal{L}[\omega](\lambda)\mathcal{L}[u_4](\lambda) + \mathcal{L}[\omega](\lambda)\alpha) - \mathcal{L}[\omega](\lambda)\mathcal{L}[u_3](\lambda))\mathcal{L}[\hat{I}](\lambda)
\tag{23}
$$

$$
\geq \hat{I}(0) + \frac{\mathcal{L}[u_2](\lambda) + (1 - \eta)\rho_1 + \mathcal{L}[\omega](\lambda)\mathcal{L}[u_4](\lambda) + \mathcal{L}[\omega](\lambda)\alpha}{\lambda + \mu + \mu_T + \alpha + \rho_1}\hat{T}(0) > 0
$$

$\mathcal{L}[u_i](\lambda) \to \mathcal{L}[u_i](0)$, $(i = 1, 2, 3, 4)$, $\mathcal{L}[\omega](\lambda) \to \mathcal{L}[\omega](0)$ as $\lambda \to 0$ by the Dominated Convergence Theorem.

Since

$$
((\lambda + \gamma + \mu + \mu_I) - \mathcal{L}[u_1](\lambda) - \frac{\gamma}{\lambda + \mu + \mu_T + \alpha + \rho_1}(\mathcal{L}[u_2](\lambda) + (1 - \eta)\rho_1
$$

$$
+ \mathcal{L}[\omega](\lambda)\mathcal{L}[u_4](\lambda) + \mathcal{L}[\omega](\lambda)\alpha) - \mathcal{L}[\omega](\lambda)\mathcal{L}[u_3](\lambda)) |_{\lambda=0} = (\gamma + \mu + \mu_I)(1 - f(n)) < 0,
$$

then there exists $\varepsilon > 0$ such that

$$
(\lambda + \gamma + \mu + \mu_I) - \mathcal{L}[u_1](\lambda) - \frac{\gamma}{\lambda + \mu + \mu_T + \alpha + \rho_1}(\mathcal{L}[u_2](\lambda) + (1 - \eta)\rho_1
$$

$$
+ \mathcal{L}[\omega](\lambda)\mathcal{L}[u_4](\lambda) + \mathcal{L}[\omega](\lambda)\alpha) - \mathcal{L}[\omega](\lambda)\mathcal{L}[u_3](\lambda) < 0,
$$

for all $\lambda \in [0, \varepsilon)$. According to (23), we have $\mathcal{L}[\hat{I}](\lambda) < 0$ for all $\lambda \in (0, \varepsilon)$. But this contradicts the nonnegative of $\hat{I}(t)(t \geq 0)$. Hence, at least one of $\hat{I}(t)$, $\hat{T}(t)$ is unbounded. Since $I(t) \geq \hat{I}(t)$, $T(t) \geq \hat{T}(t)$, we get that at least one of $I(t)$, $T(t)$

is unbounded. This contradicts the Proposition 3. Therefore, $W_s(E_0) \cap M_0 = \emptyset$. By Theorem 4.2 in Hale and Waltman (1989) , we get that semiflow $\{\Phi(t, \cdot)\}_{t \geq 0}$ generated by system (1) is uniformly persistent. By Theorem 3.7 in Magal and Zhao (2005), we get that there exists a compact subset $\mathcal{A}_0 \subset M_0$ which is a global attractor for $\{\Phi(t, \cdot)\}_{t \geq 0}$ in M_0. □

4.2 Global stablility

Theorem 7 *The disease-free equilibrium E_0 of system (1) is globally asymptotically stable if $\mathcal{R}_0 < 1$.*

Proof Let $g(x) = x - \ln x - 1$, note that $g(x)$ is non-negative and continuous in $(0, +\infty)$ with a unique root at $x = 1$. Using similar arguments to the proof of Lemma 4.2 in Browne and Pilyugin (2013), we can get that any solution in $\mathcal{A}$ satisfies that $S(t) > 0$ for $t \in \mathbb{R}$ (In Theorem 2, we have proved that $\mathcal{A}$ exists). Next, we construct the following Lyapunov function $L = L_0 + L_1 + L_2 + L_3 + L_4$ on the global attractor $\mathcal{A}$, by the compactness of $\mathcal{A}$, we can easily deduce L is bounded on $\mathcal{A}$, where

$$L_0 = (\mathcal{K}_1 + \mathcal{K}_2 \mathcal{K}_3) S^0 g(\frac{S}{S^0}), \quad S^0 = \frac{\Lambda}{\mu},$$

$$L_1 = \int_0^{+\infty} F_1(a)e(t, a)da, \quad F_1(a) = \int_a^{+\infty} (\sigma(u) + \mathcal{K}_2 \delta(u)) e^{-\int_a^u (\mu + \sigma(s) + \delta(s))ds} du,$$

$$L_2 = I, \quad L_3 = \int_0^{+\infty} F_2(\theta)r(t, \theta)d\theta, \quad F_2(\theta) = \int_\theta^{+\infty} \omega(u) e^{-\int_\theta^u (\mu + \omega(s))ds} du,$$

$$L_4 = AT, \quad A = \frac{(\mathcal{K}_1 + \mathcal{K}_2 \mathcal{K}_3)(\beta \frac{\Lambda}{\mu} \rho + \eta \rho_1) + \alpha \mathcal{K}_2 + (1 - \eta)\rho_1}{\mu + \mu_T + \alpha + \rho_1}.$$

Calculating the derivative of L_0, L_1, L_2, L_3, L_4 along solutions of system (1), respectively. We can deduce

$$\dot{L}_0 = (\mathcal{K}_1 + \mathcal{K}_2 \mathcal{K}_3)(-\mu \frac{(S - S^0)^2}{S} - (S - S^0)\beta(I + \rho T)),$$

$$\dot{L}_1 = -\int_0^{+\infty} F_1(a)((\mu + \sigma(a) + \delta(a))e(t, a) + \frac{\partial e}{\partial a})da$$

$$= F_1(0)e(t, 0) - \int_0^{+\infty} (\sigma(a) + \mathcal{K}_2 \delta(a))e(t, a)da$$

$$= (\mathcal{K}_1 + \mathcal{K}_2 \mathcal{K}_3)(\beta S(I + \rho T) + \eta \rho_1 T) - \int_0^{+\infty} (\sigma(a) + \mathcal{K}_2 \delta(a))e(t, a)da,$$

$$\dot{L}_2 = \int_0^{+\infty} \sigma(a)e(t, a)da + \int_0^{+\infty} \omega(\theta)r(t, \theta)d\theta + (1 - \eta)\rho_1 T - (\gamma + \mu + \mu_I)I(t),$$

$$\dot{L}_3 = \mathcal{K}_2(\int_0^{+\infty} \delta(a)e(t, a)da + \alpha T) - \int_0^{+\infty} \omega(\theta)r(t, \theta)d\theta,$$

$$\dot{L}_4 = A(\gamma I(t) - (\mu + \mu_t + \alpha + \rho_1)T(t)).$$

Therefore,

$$\frac{dL}{dt} = -(\mathcal{K}_1 + \mathcal{K}_2 \mathcal{K}_3)\mu \frac{(S - S^0)^2}{S} + \frac{I}{\gamma + \mu + \mu_I}(\mathcal{R}_0 - 1).$$

Notice that if $\mathcal{R}_0 < 1$, then $\frac{dL}{dt} \leq 0$ holds. According to the proof of the Theorem 4.3 in Guo et al. (2019), we can easily obtain that $\mathcal{A} = \{E_0\}$. This proves that E_0 is globally asymptotically stable. The proof is complete. □

If $\mathcal{R}_0 > 1$, we have know that the system (1) is uniformly persistent and has a global attractor $\mathcal{A}_0$ in M_0. Let $x \in \mathcal{A}_0$, we can find a complete orbit $\{\Phi(t, \cdot)\}_{t \in \mathbb{R}}$ through x in $\mathcal{A}_0$. By similar analytical method used in [Browne and Pilyugin (2013), subsection 3.2], system (1) can be written as

$$
\begin{cases}
\dfrac{dS(t)}{dt} = \Lambda - \beta S(I + \rho T) - \mu S, \\[2mm]
\dfrac{dI(t)}{dt} = \displaystyle\int_0^{+\infty} \sigma(a)e(t,a)da + \int_0^{+\infty} \omega(\theta)r(t,\theta)d\theta + (1-\eta)\rho_1 T \\[2mm]
\qquad - (\gamma + \mu + \mu_I)I(t), \\[2mm]
\dfrac{dT(t)}{dt} = \gamma I(t) - (\mu + \mu_T + \alpha + \rho_1)T(t), \\[2mm]
e(t,a) = k_1(a)(\beta S(t-a)(I(t-a) + \rho(t-a)T(t-a)) + \eta\rho_1 T(t-a)), \\[2mm]
r(t,\theta) = k_2(\theta)\displaystyle\int_0^{+\infty} \delta(a)e(t-\theta,a)da + \alpha T(t-\theta), \\[2mm]
(S(0),\ I(0),\ T(0),\ e(0,a),\ r(0,\theta)) \in \mathcal{A}_0.
\end{cases}
\tag{24}
$$

In order to study the global stability of E^*, we first prove the following lemma.

Lemma 3 *There exist $\epsilon, M > 0$ such that all solutions in $\mathcal{A}_0$ for $t \in \mathbb{R}$, the following inequalities are satisfied*

$$
\epsilon \leq S(t),\ I(t),\ T(t) \leq M,\ (\beta\epsilon^2(1+\rho) + \eta\rho_1\epsilon)k_1(a) \leq e(t,a)
$$
$$
\leq (\beta M^2(1+\rho) + \eta\rho_1 M)k_1(a),
$$
$$
((\beta\epsilon^2(1+\rho) + \eta\rho_1\epsilon)\mathcal{K}_3 + \alpha\epsilon)k_2(\theta) \leq r(t,\theta) \leq ((\beta M^2(1+\rho)
$$
$$
+\eta\rho_1 M)\mathcal{K}_3 + \alpha M)k_2(\theta).
$$

Proof Let $(S(t), I(t), T(t), e(t,a), r(t,\theta)) \in \mathcal{A}_0$. First we prove that $S(t) > 0$ for $t \in \mathbb{R}$. We assume that there exists $t_1 \in \mathbb{R}$ such that $S(t_1) = 0$. From (24) we have $\dfrac{dS(t_1)}{dt} \geq \Lambda > 0$, then $\exists\ \eta_1 > 0$ such that $S(t_1 - \eta_1) < 0$. This contradicts the $\mathcal{A}_0 \subset M_0$. Thus $S(t) > 0$ for $t \in \mathbb{R}$.

Next we prove that $I(t) > 0$, $T(t) > 0$ for $t \in \mathbb{R}$. First we assume that there exists $t_0 \in \mathbb{R}$ such that $I(t_0) = 0$ and $T(t_0) = 0$, then according to $I(t)$, $T(t)$ equations in (24), we can deduce that $I(t) = 0$, $T(t) = 0$ for $t \leq t_0$. Next, form (24) we know $\int_0^{+\infty} e(t,a)da = 0$, $\int_0^{+\infty} r(t,\theta)d\theta = 0$ for all $t \leq t_0$. This contradicts the $\mathcal{A}_0 \subset M_0$.

On the other hand, we assume that there exists $t_0 \in \mathbb{R}$ such that one of $I(t_0)$, $T(t_0)$ is positive, so without loss of generality we assume that $I(t_0) = 0$, $T(t_0) > 0$. From (24) we have $\dfrac{dI(t_0)}{dt} \geq (1-\eta)\rho_1 T(t_0) > 0$, then $\exists\ \eta_2 > 0$ such that $I(t_0 - \eta_2) < 0$.

This contradicts the $\mathcal{A}_0 \subset M_0$. Hence, $I(t) > 0$, $T(t) > 0$ for all $t \in \mathbb{R}$. In addition, from (24), we deduce that $e(t, a) > 0$, $r(t, \theta) > 0$ for $t \in \mathbb{R}$, $a, \theta \in \mathbb{R}_+$.

According to the compactness of $\mathcal{A}_0$, we know there exist $\epsilon, M > 0$ such that

$$\epsilon \le S(t), \ I(t), \ T(t) \le M, \ (\beta\epsilon^2(1+\rho) + \eta\rho_1\epsilon)k_1(a) \le e(t, a)$$
$$\le (\beta M^2(1+\rho) + \eta\rho_1 M)k_1(a),$$
$$((\beta\epsilon^2(1+\rho) + \eta\rho_1\epsilon)\mathcal{K}_3 + \alpha\epsilon)k_2(\theta) \le r(t, \theta) \le ((\beta M^2(1+\rho) + \eta\rho_1 M)\mathcal{K}_3$$
$$+\alpha M)k_2(\theta).$$

The proof is complete. $\qquad\square$

Theorem 8 *If $\mathcal{R}_0 > 1$, then endemic equilibrium E^* of system (1) is globally asymptotically stable in M_0.*

Proof We define the following Lyapunov function $V = V_1 + V_2 + V_3 + V_4 + V_5$ on the global attractor $\mathcal{A}_0$ (In Theorem 6, we have proved that $\mathcal{A}_0$ exists), using Lemma 3, we can easily deduce V is bounded on $\mathcal{A}_0$, where

$$V_1 = (\mathcal{K}_1 + \mathcal{K}_2\mathcal{K}_3)S^*g\left(\frac{S}{S^*}\right), \ V_2 = \int_0^{+\infty} A(a)e^*(a)g\left(\frac{e(t, a)}{e^*(a)}\right)da,$$

$$V_3 = I^*g\left(\frac{I}{I^*}\right), \ V_4 = AT^*g\left(\frac{T}{T^*}\right), \ V_5 = \int_0^{+\infty} B(\theta)r^*(\theta)g\left(\frac{r(t, \theta)}{r^*(\theta)}\right)d\theta,$$

and

$$A(a) = \int_a^{+\infty}(\sigma(u) + \mathcal{K}_2\delta(u))e^{-\int_a^u(\mu+\sigma(s)+\delta(s))ds}da,$$

$$B(\theta) = \int_\theta^{+\infty}\omega(u)e^{-\int_\theta^u(\mu+\omega(s))ds}d\theta,$$

$$A = \frac{(1-\eta)\rho_1 T^*}{\gamma I^*} + \frac{(\mathcal{K}_1 + \mathcal{K}_2\mathcal{K}_3)(\beta\rho S^*T^* + \eta\rho_1 T^*) + \mathcal{K}_2\alpha T^*}{\gamma I^*}.$$

Calculating the derivative of V along a solution in $\mathcal{A}_0$. When calculate the time derivative of V_1, we notice that $\Lambda = \beta S^*(I^* + \rho T^*) + \mu S^*$.

$$\frac{dV_1}{dt} = (\mathcal{K}_1 + \mathcal{K}_2\mathcal{K}_3)\left(1 - \frac{S^*}{S}\right)(\beta S^*(I^* + \rho T^*) + \mu S^* - \beta S(I + \rho T) - \mu S)$$

$$= -(\mathcal{K}_1 + \mathcal{K}_2\mathcal{K}_3)\mu\frac{(S - S^*)^2}{S} + (\mathcal{K}_1 + \mathcal{K}_2\mathcal{K}_3)\beta S^*I^*\left(1 - \frac{SI}{S^*I^*} - \frac{S^*}{S} + \frac{I}{I^*}\right)$$

$$+(\mathcal{K}_1 + \mathcal{K}_2\mathcal{K}_3)\beta\rho S^*T^*\left(1 - \frac{SI}{S^*I^*} - \frac{S^*}{S} + \frac{T}{T^*}\right)$$

$$\frac{dV_2}{dt} = \int_0^{+\infty} A(a)(1 - \frac{e^*(a)}{e(t, a)})\frac{\partial e(t, a)}{\partial t}da$$

$$= -\int_0^{+\infty} A(a)(1 - \frac{e^*(a)}{e(t, a)})(\frac{\partial e(t, a)}{\partial a} + (\mu + \delta(a) + \sigma(a))e(t, a))da$$

By using

$$\frac{\partial}{\partial a} g\left(\frac{e(t,a)}{e^*(a)}\right) = \frac{1}{e^*(a)}\left(1 - \frac{e^*(a)}{e(t,a)}\right)\left(\frac{\partial e(t,a)}{\partial a} + (\mu + \delta(a) + \sigma(a))e(t,a)\right),$$
$$A'(a) = -(\sigma(a) + \mathcal{K}_2\delta(a)) + A(a)(\mu + \sigma(a) + \delta(a))$$

we have

$$\frac{dV_2}{dt} = -\int_0^{+\infty} A(a)e^*(a)\frac{\partial}{\partial a} g\left(\frac{e(t,a)}{e^*(a)}\right) da$$
$$= A(0)e^*(0)g\left(\frac{e(t,0)}{e^*(0)}\right) - \int_0^{+\infty}(\sigma(a) + \mathcal{K}_2\delta(a))e^*(a)g\left(\frac{e(t,a)}{e^*(a)}\right) da$$
$$= (\mathcal{K}_1 + \mathcal{K}_2\mathcal{K}_3)(\beta SI + \beta \rho ST + \eta\rho_1 T - \beta S^* I^* - \beta\rho S^* T^* - \eta\rho_1 T^* - (\beta S^* I^*$$
$$+ \beta\rho S^* T^* + \eta\rho_1 T^*) \ln\frac{e(t,0)}{e^*(0)}) - \int_0^{+\infty}(\sigma(a) + \mathcal{K}_2\delta(a))e^*(a)g\left(\frac{e(t,a)}{e^*(a)}\right) da.$$

When calculate the time derivative of V_3, we notice that

$$\gamma + \mu + \mu_I = \frac{1}{I^*}\left(\int_0^{+\infty}\sigma(a)e^*(a)da + \int_0^{+\infty}\omega(\theta)r^*(\theta)d\theta + (1-\eta)\rho_1 T^*)\right).$$
$$\frac{dV_3}{dt} = \left(1 - \frac{I^*}{I}\right)(\int_0^{+\infty}\sigma(a)e(t,a)da + \int_0^{+\infty}\omega(\theta)r(t,\theta)d\theta + (1-\eta)\rho_1 T$$
$$- \frac{I}{I^*}(\int_0^{+\infty}\sigma(a)e^*(a)da + \int_0^{+\infty}\omega(\theta)r^*(\theta)d\theta + (1-\eta)\rho_1 T^*))$$
$$= \int_0^{+\infty}\sigma(a)e^*(a)(\frac{e(t,a)}{e^*(a)} - \frac{I}{I^*} - \frac{e(t,a)I^*}{e^*(a)I} + 1)da$$
$$+ \int_0^{+\infty}\omega(\theta)r^*(\theta)(\frac{r(t,\theta)}{r^*(\theta)} - \frac{I}{I^*} - \frac{r(t,\theta)I^*}{r^*(\theta)I} + 1)d\theta$$
$$+ (1-\eta)\rho_1 T^*(\frac{T}{T^*} - \frac{I}{I^*} - \frac{I^* T}{IT^*} + 1).$$

Notice that $\mu + \mu_T + \alpha + \rho_1 = \frac{I^*}{T^*}\gamma$, we can get

$$\frac{dV_4}{dt} = A\gamma I^*\left(\frac{I}{I^*} - \frac{T}{T^*} - \frac{T^* I}{TI^*} + 1\right).$$
$$\frac{dV_5}{dt} = \int_0^{+\infty} B(\theta)\left(1 - \frac{r^*(\theta)}{r(t,\theta)}\right)\frac{\partial r(t,\theta)}{\partial t}d\theta$$
$$= -\int_0^{+\infty} B(\theta)\left(1 - \frac{r^*(\theta)}{r(t,\theta)}\right)\left(\frac{\partial r(t,\theta)}{\partial \theta} + (\mu + \omega(\theta))r(t,\theta)\right)d\theta$$

By using

$$\frac{\partial}{\partial a} g(\frac{r(t,\theta)}{r^*(\theta)}) = \frac{1}{r^*(\theta)}\left(1 - \frac{r^*(\theta)}{r(t,\theta)}\right)\left(\frac{\partial r(t,\theta)}{\partial \theta} + (\mu + \omega(\theta))r(t,\theta)\right),$$
$$B'(\theta) = -\omega(\theta) + B(\theta)(\mu + \omega(\theta)),$$

we have

$$\frac{dV_5}{dt} = -\int_0^{+\infty} B(\theta)r^*(\theta)\frac{\partial}{\partial\theta}g\left(\frac{r(t,\theta)}{r^*(\theta)}\right)d\theta$$

$$= B(0)r^*(0)g\left(\frac{r(t,0)}{r^*(0)}\right) - \int_0^{+\infty}\omega(\theta)r^*(\theta)g\left(\frac{e(t,\theta)}{e^*(\theta)}\right)d\theta$$

$$= \mathscr{K}_2\left(-\int_0^{+\infty}\delta(a)e^*(a)da - \alpha T^* + \int_0^{+\infty}\delta(a)e(t,a)da + \alpha T\right.$$
$$\left. -\left(\int_0^{+\infty}\delta(a)e^*(a)da\right.\right.$$
$$\left.\left. +\alpha T^*\right)\ln\frac{r(t,0)}{r^*(0)}\right) - \int_0^{+\infty}\omega(\theta)r^*(\theta)g\left(\frac{e(t,\theta)}{e^*(\theta)}\right)d\theta.$$

Thus, $\dfrac{d\sum\limits_{i=1}^{5} V_i}{dt} = H_1 + H_2 + H_3 + H_4 + H_5 + H_6 + H_7,$
where

$$H_1 = -(\mathscr{K}_1 + \mathscr{K}_2\mathscr{K}_3)\mu\frac{(S-S^*)^2}{S} \le 0$$

$$H_2 = (\mathscr{K}_1 + \mathscr{K}_2\mathscr{K}_3)\beta S^*\left(I^*\left(-\frac{S^*}{S} + \frac{I}{I^*} - \ln\frac{e(t,0)}{e^*(0)}\right) + \rho T^*\left(-\frac{S^*}{S} + \frac{T}{T^*} - \ln\frac{e(t,0)}{e^*(0)}\right)\right)$$

$$+(\mathscr{K}_1 + \mathscr{K}_2\mathscr{K}_3)\eta\rho_1\left(T - T^* - T^*\ln\frac{e(t,0)}{e^*(0)}\right)$$

$$= (\mathscr{K}_1 + \mathscr{K}_2\mathscr{K}_3)\beta S^* I^*\left(-g\left(\frac{S^*}{S}\right) + g\left(\frac{I}{I^*}\right) - g\left(\frac{SIe^*(0)}{S^*I^*e(t,0)}\right) - 1 + \frac{SIe^*(0)}{S^*I^*e(t,0)}\right)$$

$$+(\mathscr{K}_1 + \mathscr{K}_2\mathscr{K}_3)\beta\rho S^* T^*\left(-g\left(\frac{S^*}{S}\right) + g\left(\frac{T}{T^*}\right) - g\left(\frac{STe^*(0)}{S^*T^*e(t,0)}\right) - 1 + \frac{STe^*(0)}{S^*T^*e(t,0)}\right)$$

$$+(\mathscr{K}_1 + \mathscr{K}_2\mathscr{K}_3)\eta\rho_1\left(T - T^* - T^*\ln\frac{e(t,0)}{e^*(0)}\right)$$

$$= (\mathscr{K}_1 + \mathscr{K}_2\mathscr{K}_3)\beta S^*\left(I^*\left(-g\left(\frac{S^*}{S}\right) + g\left(\frac{I}{I^*}\right) - g\left(\frac{SIe^*(0)}{S^*I^*e(t,0)}\right)\right) + \rho T^*\left(-g\left(\frac{S^*}{S}\right) + g\left(\frac{T}{T^*}\right)\right.\right.$$
$$\left.\left. -g\left(\frac{STe^*(0)}{S^*T^*e(t,0)}\right)\right)\right) + (\mathscr{K}_1 + \mathscr{K}_2\mathscr{K}_3)\left(\eta\rho_1 T^* - \eta\rho_1 T\frac{e^*(0)}{e(t,0)}\right)$$

$$+(\mathscr{K}_1 + \mathscr{K}_2\mathscr{K}_3)\eta\rho_1\left(T - T^* - T^*\ln\frac{e(t,0)}{e^*(0)}\right)$$

$$= (\mathscr{K}_1 + \mathscr{K}_2\mathscr{K}_3)\beta S^*\left(I^*\left(-g\left(\frac{S^*}{S}\right) + g\left(\frac{I}{I^*}\right) - g\left(\frac{SIe^*(0)}{S^*I^*e(t,0)}\right)\right) + \rho T^*\left(-g\left(\frac{S^*}{S}\right) + g\left(\frac{T}{T^*}\right)\right.\right.$$
$$\left.\left. -g\left(\frac{STe^*(0)}{S^*T^*e(t,0)}\right)\right)\right) + (\mathscr{K}_1 + \mathscr{K}_2\mathscr{K}_3)\eta\rho_1 T^*\left(g\left(\frac{T}{T^*}\right) - g\left(\frac{e^*(0)T}{e(t,0)T^*}\right)\right)$$

$$H_3 = \int_0^{+\infty}\sigma(a)e^*(a)\left(1 + \ln\frac{e(t,a)}{e^*(a)} - \frac{I}{I^*} - \frac{e(t,a)I^*}{e^*(a)I} + 1\right)da$$

$$= \int_0^{+\infty}\sigma(a)e^*(a)\left(-g\left(\frac{I}{I^*}\right) - g\left(\frac{e(t,a)I^*}{e^*(a)I}\right)\right)da$$

$$= -\int_0^{+\infty}\sigma(a)e^*(a)g\left(\frac{e(t,a)I^*}{e^*(a)I}\right)da - \mathscr{K}_1\left(\beta S^* I^* g\left(\frac{I}{I^*}\right) + \beta\rho S^* T^* g\left(\frac{I}{I^*}\right) + \eta\rho_1 T^* g\left(\frac{I}{I^*}\right)\right)$$

$$H_4 = \mathscr{K}_2\int_0^{+\infty}\delta(a)e^*(a)\left(\ln\frac{e(t,a)}{e^*(a)} - \ln\frac{r(t,0)}{r^*(0)}\right)da + \mathscr{K}_2\alpha T - \mathscr{K}_2\alpha T^* - \mathscr{K}_2\alpha T^*\ln\frac{r(t,0)}{r^*(0)}$$

$$= \mathscr{K}_2 \int_0^{+\infty} \delta(a)e^*(a)(-g(\frac{e(t,a)r^*(0)}{e^*(a)r(t,0)}) - 1 + \frac{e(t,a)r^*(0)}{e^*(a)r(t,0)})da$$

$$+ \mathscr{K}_2\alpha(T - T^* - T^* \ln \frac{r(t,0)}{r^*(0)})$$

$$= -\mathscr{K}_2 \int_0^{+\infty} \delta(a)e^*(a)g(\frac{e(t,a)r^*(0)}{e^*(a)r(t,0)})da - \mathscr{K}_2\alpha T \frac{r^*(0)}{r(t,0)} + \mathscr{K}_2\alpha T - \mathscr{K}_2\alpha T^* \ln \frac{r(t,0)}{r^*(0)}$$

$$= -\mathscr{K}_2 \int_0^{+\infty} \delta(a)e^*(a)g(\frac{e(t,a)r^*(0)}{e^*(a)r(t,0)})da + \mathscr{K}_2\alpha T^*(g(\frac{T}{T^*}) - g(\frac{Tr^*(0)}{T^*r(t,0)}))$$

$$H_5 = \int_0^{+\infty} \omega(\theta)r^*(\theta)(-\frac{I}{I^*} - \frac{r(t,\theta)I^*}{r^*(\theta)I} + 1 + 1 + \ln \frac{r(t,\theta)}{r^*(\theta)})d\theta$$

$$= \int_0^{+\infty} \omega(\theta)r^*(\theta)(-g(\frac{I}{I^*}) - g(\frac{r(t,\theta)I^*}{r^*(\theta)I}))d\theta$$

$$= -\int_0^{+\infty} \omega(\theta)r^*(\theta)g(\frac{r(t,\theta)I^*}{r^*(\theta)I})d\theta - \mathscr{K}_2\alpha T^*g(\frac{I}{I^*}) - \mathscr{K}_2\mathscr{K}_3\beta S^*I^*g(\frac{I}{I^*})$$

$$- \mathscr{K}_2\mathscr{K}_3\beta\rho S^*T^*g(\frac{I}{I^*}) - \mathscr{K}_2\mathscr{K}_3\eta\rho_1 T^*g(\frac{I}{I^*})$$

$$H_6 = ((\mathscr{K}_1 + \mathscr{K}_2\mathscr{K}_3)(\beta\rho S^*T^* + \eta\rho_1 T^*) + \mathscr{K}_2\alpha T^*)(\frac{I}{I^*} - \frac{T}{T^*} - \frac{IT^*}{I^*T} + 1)$$

$$H_7 = (1-\eta)\rho_1 T^*(-\frac{I^*T}{IT^*} - \frac{T^*I}{TI^*} + 2) \le 0$$

$$\sum_{i=2}^6 H_i = -(\mathscr{K}_1 + \mathscr{K}_2\mathscr{K}_3)\beta S^*(I^*(g(\frac{S^*}{S}) + g(\frac{SIe^*(0)}{S^*I^*e(t,0)})) - \rho T^*(g(\frac{S^*}{S}) + g(\frac{STe^*(0)}{S^*T^*e(t,0)})))$$

$$- (\mathscr{K}_1 + \mathscr{K}_2\mathscr{K}_3)\eta\rho_1 T^*g(\frac{e^*(0)T}{e(t,0)T^*}) - \int_0^{+\infty} \sigma(a)e^*(a)g(\frac{e(t,a)I^*}{e^*(a)I})da -$$

$$\mathscr{K}_2(\int_0^{+\infty} \delta(a)e^*(a)g(\frac{e(t,a)r^*(0)}{e^*(a)r(t,0)})da + \alpha T^*g(\frac{Tr^*(0)}{T^*r(t,0)}))$$

$$- \int_0^{+\infty} \omega(\theta)r^*(\theta)g(\frac{r(t,\theta)I^*}{r^*(\theta)I})d\theta$$

$$+ ((\mathscr{K}_1 + \mathscr{K}_2\mathscr{K}_3)(\beta\rho S^*T^* + \eta\rho_1 T^*) + \mathscr{K}_2\alpha T^*)(g(\frac{T}{T^*}) - g(\frac{I}{I^*}))$$

$$+ ((\mathscr{K}_1 + \mathscr{K}_2\mathscr{K}_3)(\beta\rho S^*T^* + \eta\rho_1 T^*) + \mathscr{K}_2\alpha T^*)(\frac{I}{I^*} - \frac{T}{T^*} - \frac{IT^*}{I^*T} + 1)$$

$$= -(\mathscr{K}_1 + \mathscr{K}_2\mathscr{K}_3)\beta S^*(I^*(g(\frac{S^*}{S}) + g(\frac{SIe^*(0)}{S^*I^*e(t,0)})) - \rho T^*(g(\frac{S^*}{S}) + g(\frac{STe^*(0)}{S^*T^*e(t,0)})))$$

$$- (\mathscr{K}_1 + \mathscr{K}_2\mathscr{K}_3)\eta\rho_1 T^*g(\frac{e^*(0)T}{e(t,0)T^*}) - \int_0^{+\infty} \sigma(a)e^*(a)g(\frac{e(t,a)I^*}{e^*(a)I})da -$$

$$\mathscr{K}_2(\int_0^{+\infty} \delta(a)e^*(a)g(\frac{e(t,a)r^*(0)}{e^*(a)r(t,0)})da + \alpha T^*g(\frac{Tr^*(0)}{T^*r(t,0)}))$$

$$- \int_0^{+\infty} \omega(\theta)r^*(\theta)g(\frac{r(t,\theta)I^*}{r^*(\theta)I})d\theta$$

$$- ((\mathscr{K}_1 + \mathscr{K}_2\mathscr{K}_3)(\beta\rho S^*T^* + \eta\rho_1 T^*) + \mathscr{K}_2\alpha T^*)g(\frac{T^*I}{TI^*}).$$

Table 2 New TB cases from 2007 to 2018 in China (persons)

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

It follows from the non-negativity of g, we know that $\dfrac{dV}{dt} \leq 0$, and according to the proof of the Theorem 4.3 in Guo et al. (2019), we can easily obtain that $\mathcal{A}_0 = \{E^*\}$. This proves that E^* is globally asymptotically stable. The proof is complete. $\square$

5 Study on TB control strategy in China

5.1 Data fitting

In this section, we firstly use the system (1) to simulate the annual new TB cases data of China from 2007 to 2018, then we predict whether current tuberculosis control measures in China will be able to achieve the WHO End TB Strategy in 2030. To do so, we need to estimate the parameters of system (1). Some of the parameters in our model are distributed, which is different from ODE models, and we believe that the parameter values may be different due to different research groups and different time units. According to the WHO (2019) report in 2018, the TB incidence rate is falling, and the treatment success rate is also falling. Through the analysis of these data, it can be found that the parameter values in system (1) are related to the time of the study. Thus, some of parameters are fitted. According to the data from the National Bureau of Statistics of China (2019), the average birth population and the average natural mortality rate between 2007 and 2018 are $\Lambda = 16,439,333$ persons year^{-1} and $\mu = 1/74.83$ year^{-1}, respectively, and the number of the initial susceptible population $S(0) = 1,314,480,000$ person. The number of new TB cases (Table 2) come from the Chinacdc (2019).

Next, we estimate the unknown parameters and initial values

$$\hat{\theta} = (\beta, \delta, \rho, \sigma_1, \sigma_2, \delta_1, \delta_2, \omega_1, \omega_2, \eta, \rho_1, \mu_I, \mu_T, \alpha, e(0), I(0), T(0), r(0))$$

of system (1), where we assume $\delta(a) = \delta_1 e^{-\delta_2 a}$, $\sigma(a) = \sigma_1 e^{-\sigma_2 a}$, $\omega(a) = \omega_1 e^{-\omega_2 a}$, $e_0(a) = e(0)\delta_2 e^{-\delta_2 a}$, $r_0(\theta) = r(0)\omega_2 e^{-\omega_2 \theta}$.

Let $P(t, \hat{\theta})$ be the number of new TB cases from model (1) at the tth year, then $P(t, \hat{\theta})$ can be written as

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

Table 3 The parameter values of model (1)

Parameter	Value	Units	Source	Parameter	Value	Units	Source
β	1.1479×10^{-10}	Persons^{-1} Year^{-1}	Fitting	δ_1	0.0890	None	Fitting
δ_2	0.2393	None	Fitting	σ_1	0.1804	None	Fitting
σ_2	0.2390	None	Fitting	ω_1	0.1861	None	Fitting
ω_2	0.0710	None	Fitting	η	0.4027	None	Fitting
ρ_1	0.0153	Year^{-1}	Fitting	μ_I	0.0056	Year^{-1}	Fitting
μ_t	0.0225	Year^{-1}	Fitting	α	0.0013	Year^{-1}	Fitting
ρ	0.4387	None	Fitting	γ	1.0363	Year^{-1}	Fitting
$e(0)$	5221333	None	Fitting	$I(0)$	5011912	Persons	Fitting
$T(0)$	8995935	Persons	Fitting	$r(0)$	7493719	None	Fitting

where $X(t)$ represents the cumulative number of people infected with TB by the tth year, and satisfies the following equation

$$\frac{dX(t)}{dt} = \int_0^{+\infty} \sigma(a)e(t,a)da + \int_0^{+\infty} \omega(\theta)r(t,\theta)d\theta + (1-\eta)\rho_1 T.$$

Thus, we use $P(t,\hat{\theta})$ to simulate the new TB cases per year. We are attracted by the advantages of algorithms mentioned in Seyedali Mirjalili (2014) when reading it, and we find that the convergence was good and the error was small after combining with the model (1) (the mean absolute percentage error of TB cases is 0.75%). By Grey Wolf Optimizer (GWO) algorithm, we estimate the optimal parameters and initial values for model (1) (Table 3).

The comparison between the new TB cases in China from 2007 to 2018 and the simulation of $P(t,\hat{\theta})$ from model (1) is given in Fig. 2. Moreover, we also find the basic reproduction numbers $\mathcal{R}_0 = 1.0608$.

Remark 1 By comparison with Moualeu et al. (2015), it can be found that the transmission rate of the Moualeu et al. (2015) is $\beta_3 = 6.33563 \times 10^{-6}$, while that of this paper is $\beta = 1.1479 \times 10^{-10}$. Analysis shows that the Moualeu et al. (2015) studies the transmission of TB in Cameroon from 1994 to 2010, and the new cases of TB in Cameroon increased rapidly during this period. In this paper, we used new TB cases in China from 2007 to 2018, during which the number of new TB cases in China decreased gradually. Therefore, the transmission rate of this paper is much lower than that of Moualeu et al. (2015). This is also why some parameters in this paper need to be estimated. Parameter estimation is very important for studying the transmission of TB. Arregui et al. (2018) and Dowdy et al. (2013) also provide some methods to analyze the parameters in tuberculosis models.

Remark 2 The GWO algorithm mimics the leadership hierarchy and hunting mechanism of grey wolves in nature. Four types of grey wolves such as alpha, beta, delta, and omega are employed for simulating the leadership hierarchy. In addition, the three main steps of hunting, searching for prey, encircling prey, and attacking prey, are
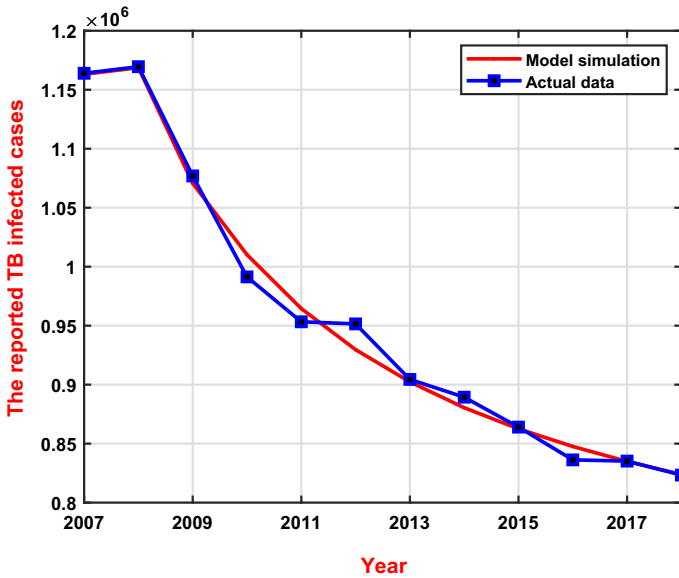
Fig. 2 Fitting for the annual new TB cases in China for model (1)

implemented. Twenty nine test functions were employed in order to benchmark the performance of the proposed algorithm in terms of exploration, exploitation, local optima avoidance, and convergence. The goal of this paper is to minimize the target function

$$\min z = \sum_{i=1}^{12} (P(t, \hat{\theta}) - r(t))^2$$

where $r(t)$ represents the actual number of new TB cases at the tth year.

5.2 Uncertainty and sensitivity analysis of $\mathcal{R}_0$

The outputs of system (1) is governed by the system input parameters and the initial values, but some of these parameters and initial values are obtained by data fitting, which may exhibit some uncertainty in their selection. The purpose of uncertainty analysis (UA) (Samsuzzoha et al. 2013; Ghosh et al. 2018; Marino et al. 2008) is to determine the reliability of parameter estimates. To ensure the reliability of the estimates of β, ρ_1, γ, μ_I, μ_t, α, ρ, η obtained through the GWO, we employ Markov Chain Monte Carlo (MCMC) method with Delayed Rejection and Adaptive Metropolis (DRAM) algorithm (DRAM is an algorithm combining DR and AM in MCMC method, and the efficiency of the combination is demonstrated with various examples in Haario et al. (2006)). The convergence of the chain is confirmed by using the Geweke's Z-scores (According to the MCMC program (MCMC 2019), the closer the Geweke's Z-score is to 1, the better the convergence of Markov Chain) . The mean,

Table 4 The parameters values and initial values of the model (1)

Parameter	Mean	Std	95% CI	Z-score
β	1.14635×10^{-10}	1.32761×10^{-11}	$[1.14577 \times 10^{-10}, 1.14694 \times 10^{-10}]$	0.99422
ρ_1	0.015330451	0.001763365	[0.015322723, 0.015338179]	0.99863
γ	1.035277047	0.119263161	[1.03475436, 1.035799735]	0.99937
μ_I	0.005602792	0.000652192	[0.005599933, 0.00560565]	0.99368
μ_t	0.022586015	0.002593855	[0.022574647,0.022597383]	0.97873
α	0.001254131	0.000145602	[0.001253493, 0.001254769]	0.99564
ρ	0.438536591	0.050638075	[0.438314662, 0.438758519]	0.99905
η	0.402338568	0.046376585	[0.402135316, 0.40254182]	0.99973
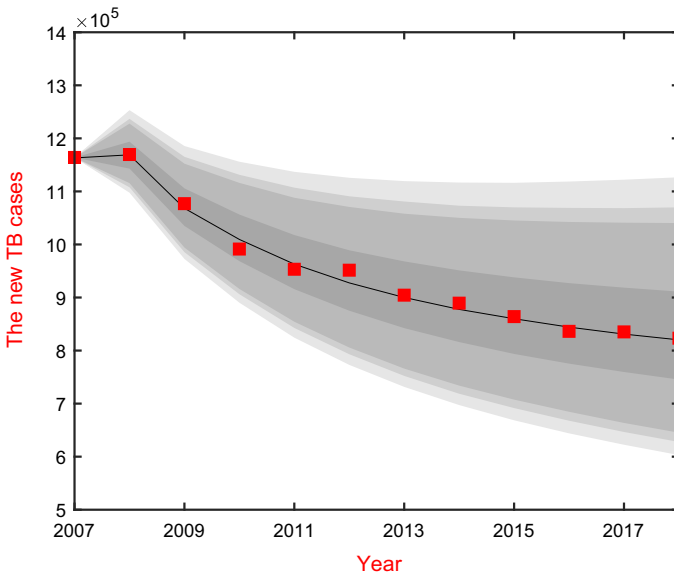
Fig. 3 The fitting results of the number of new TB cases reported from 2007 to 2018. The solid black line represents the fitted data, and the red dots represent the actual data. The areas from the darkest to the lightest correspond to the 50%, 90%, 95% and 99% posterior limits of the model uncertainty

standard deviation and 95% confidence interval of the estimated parameters are shown in Table 4, and the fitting result can be seen in Fig. 3.

Sensitivity analysis (SA) is to identify critical parameters that have significant impact on the basic reproduction numbers $\mathcal{R}_0$ and to quantify how parameters uncertainty impact $\mathcal{R}_0$. Now, a global sensitivity analysis is usually implemented by using sampling-based methods. We will use partial rank correlation coefficient (PRCC) method to study SA. For the parameters in Table 3, we fix $\sigma_1, \sigma_2, \delta_1, \delta_2, \omega_1, \omega_2, e(0), I(0), T(0), r(0)$, other parameters are considered to obey normal distribution, their mean and standard deviation are shown in Table 4. The sampling method is Latin hypercube sampling(LHS). We draw 1000 samples and
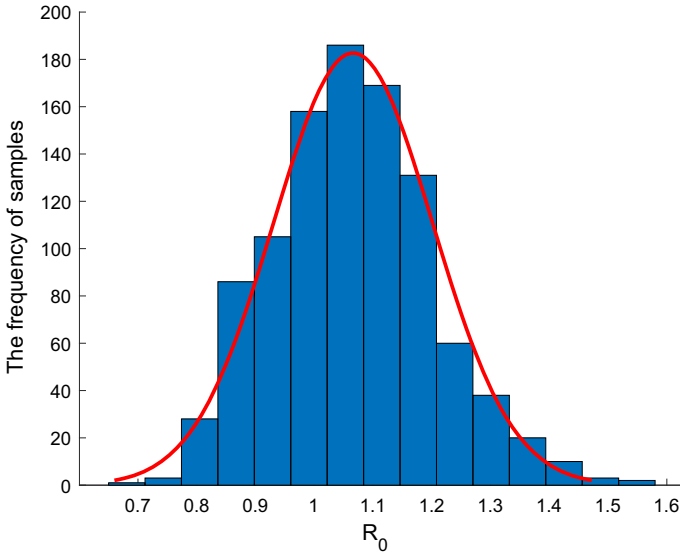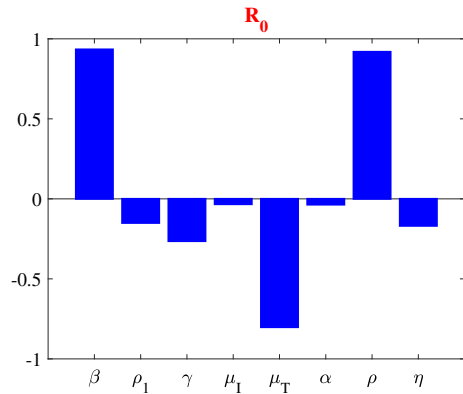
Fig. 4 The distribution histogram of the basic reproduction number $\mathcal{R}_0$

Fig. 5 The PRCC values

obtain distribution histogram of the basic reproduction number $\mathcal{R}_0$ (see Fig. 4). From Fig. 4, we know that the distribution of the basic reproduction number in the range [0.6838, 1.5672], and the average is 1.0660. Combined with the analysis in Sect. 4, we can conclude that under current control measures, the possibility of extinction of TB is small. We calculate the PRCC between the parameters and the basic reproduction number $\mathcal{R}_0$ (see Fig. 5).

From the PRCC values, we can know that β, μ_t, ρ have the most important impact on $\mathcal{R}_0$, β represents the transmission rate coefficient of TB, and β is in direct proportion to bc, b represents the number of times an infected person has contact with other person per unit time, c represents the probability of infection per contact. ρ represents reduce the rate of transmission due to treatment. μ_t represents the death rate due to treatment.
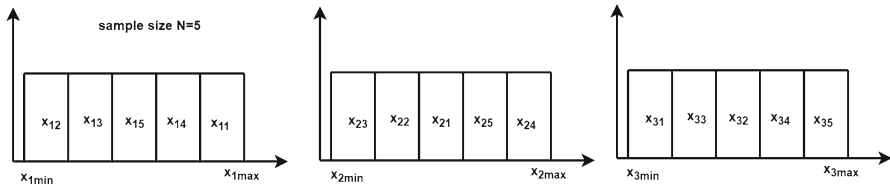
Fig. 6 The LHS scheme

The major software packages we used for our analysis were GWO, LHS, PRCC and MCMC, all of which can be found on the websites GWO (2019), LHS (2019), MCMC (2019).

Remark 3 We explain the specific steps of the LHS-PRCC scheme by studying the relationship between parameters parameters x_1, x_2, x_3 and output $y = f(x_1, x_2, x_3)$.

Step 1 Take uniform distribution as an example, the parameter distributions are divided into N equal probability intervals, which are then sampled. N represents the sample size (see Fig. 6).

$$x_i \sim Unif(x_{imin}, x_{imax}), i = 1, 2, 3.$$

Step 2 We set up the LHS matrix by assembling the samples from each probability density functions. Each row of the LHS matrix represents a unique combination of parameter values sampled.

$$X = \begin{pmatrix} x_{11} & x_{21} & x_{31} \\ x_{12} & x_{22} & x_{32} \\ x_{13} & x_{23} & x_{33} \\ x_{14} & x_{24} & x_{34} \\ x_{15} & x_{25} & x_{35} \end{pmatrix} \longrightarrow Y = \begin{pmatrix} y_1 = f(x_{11}, x_{21}, x_{31}) = 2.1 \\ y_2 = f(x_{12}, x_{22}, x_{32}) = 3.2 \\ y_3 = f(x_{13}, x_{23}, x_{33}) = 2.4 \\ y_4 = f(x_{14}, x_{24}, x_{34}) = 1.7 \\ y_5 = f(x_{15}, x_{25}, x_{35}) = 2.2 \end{pmatrix}$$

Step 3 Next, X and Y are rank transformed to X_R and Y_R in order from small to large.

$$X_R = (X_{R1}, X_{R2}, X_{R3}) = \begin{pmatrix} 5 & 3 & 1 \\ 1 & 2 & 3 \\ 2 & 1 & 2 \\ 4 & 5 & 4 \\ 3 & 4 & 5 \end{pmatrix} \longrightarrow Y_R = \begin{pmatrix} y_1 = f(x_{11}, x_{21}, x_{31}) = 2 \\ y_2 = f(x_{12}, x_{22}, x_{32}) = 5 \\ y_3 = f(x_{13}, x_{23}, x_{33}) = 4 \\ y_4 = f(x_{14}, x_{24}, x_{34}) = 1 \\ y_5 = f(x_{15}, x_{25}, x_{35}) = 3 \end{pmatrix}$$

Step 4 We calculate the residuals $X_1 = X_{R1} - \hat{X}_{R1}$ and $Y_1 = Y_R - \hat{Y}_R$, where $\hat{X}_{R1}$ and $\hat{Y}_R$ are the following linear regression models:

$$\hat{X}_{R1} = c_0 + k_2 X_{R2} + k_3 X_{R3}, \qquad \hat{Y}_R = b_0 + p_2 X_{R2} + p_3 X_{R3}.$$

Then

$$r_{x_1 y} = \frac{Cov(X_1, Y_1)}{\sqrt{Var(X_1)Var(Y_1)}}$$

is the PRCC between x_1 and y. In the same way, we can calculate the PRCC between x_2 and y, and the PRCC between x_1 and y.

5.3 Feasible measures of reaching WHO End TB strategy

Over the past few decades, China has made great efforts to control the spread of TB, such as vaccination of newborns with BCG and active treatment of tuberculosis patients and so on. However, based on the above theoretical analysis and numerical simulation results, by using the current TB control measures, China may not reach the WHO's goal by 2030. To do so, China should give more feasible control measures. In the above analysis, we know that β, μ_t, ρ are the most important factors for TB control. Next, we adjust β, ρ to predict whether an optimal control measure can be given to achieve the WHO's goal by 2030.

We use the parameter values in Table 2 as the baseline to compare the following control effects. First, we only consider changing the value of parameter β (see Fig. 7), we can find that the value of β needs to be reduced by 90% to reach the WHO 2030 target. Next, we only consider changing the value of parameter ρ (see Fig. 8), we can find the value of ρ needs to be reduced by 95% to reach the WHO 2030 target. Finally, we consider changing both parameter β and parameter ρ (see Fig. 9), we can find that if we can reduce parameter β by 70%, and reduce parameter ρ by 70%, then we will reach the WHO 2030 target. Parameters β and ρ represent the TB transmission coefficient and the reduction of infectiousness of treated individuals infected with TB, respectively. Some researchers mentioned that media coverage and public education campaigns can reduce the transmission coefficient β of disease (Barbara et al. 2020). Barbara et al. (2020) suggests that the following measure can accelerate progress toward TB elimination: maintaining awareness of both the incidence of TB disease for the public through news releases and posting of information online. Take the COVID-19 pandemic as an example, media coverage and public education campaigns play very important role in the process of controlling the pandemic. People know more about the COVID-19 and enhance their self-protecting awareness by the media report about the COVID-19, and will change their behaviours and take correct precautions such as frequent hand-washing, wearing masks, reducing the party, keeping social distances, and even quarantining themselves at home to avoid contacting with others (CDC 2021). Therefore, if the media strengthen the publicity of tuberculosis and COVID-19, it will certainly have a good effect (Saunders and Evans 2020; The Lancet Infectious Diseases 2021). Reducing the contact between treated patients and susceptible individuals can reduce the parameter ρ.

Currently, the treatment of TB patients in China includes hospitalization and home treatment, and they are not forced to be hospitalized, so these people may still infect susceptible individuals. Based on the above analysis, China should strengthen the publicity of tuberculosis knowledge so that susceptible people can know how to avoid being infected. Also, patients who are treated with TB should be given longer hospital stays to reduce their chances of contact with susceptible people. By using these control measures, China may reach the WHO End TB Strategy in 2030.
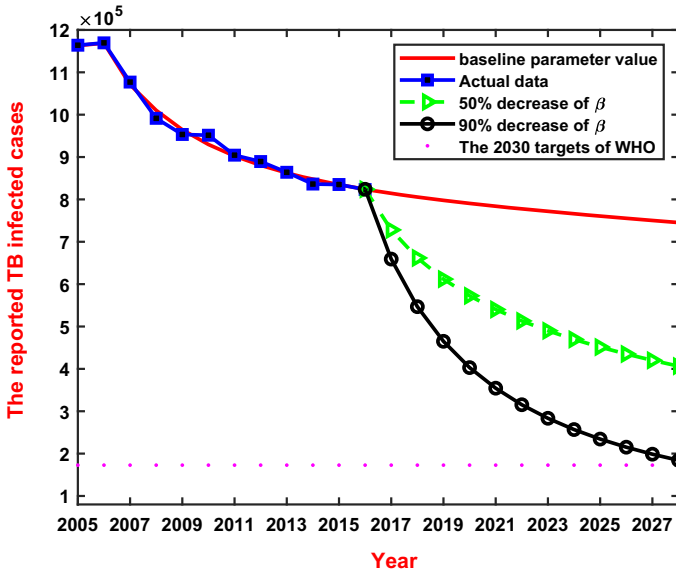
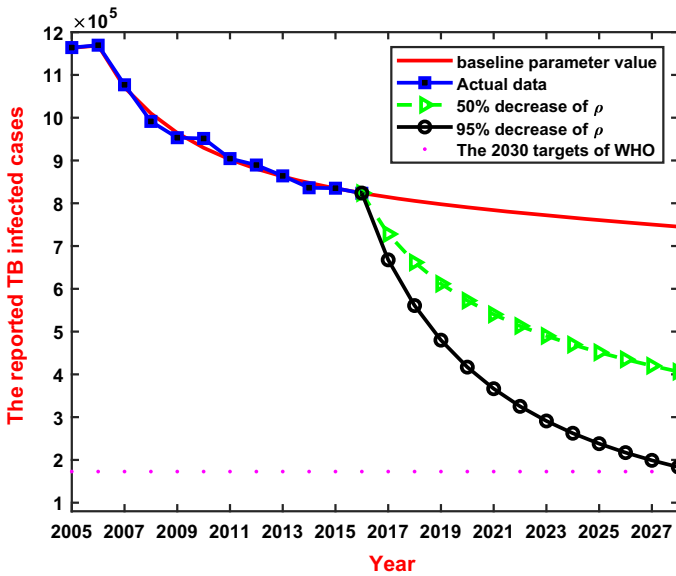**Fig. 7** Prediction of the new TB case with different values of β

Fig. 8 Prediction of the new TB case with different values of ρ
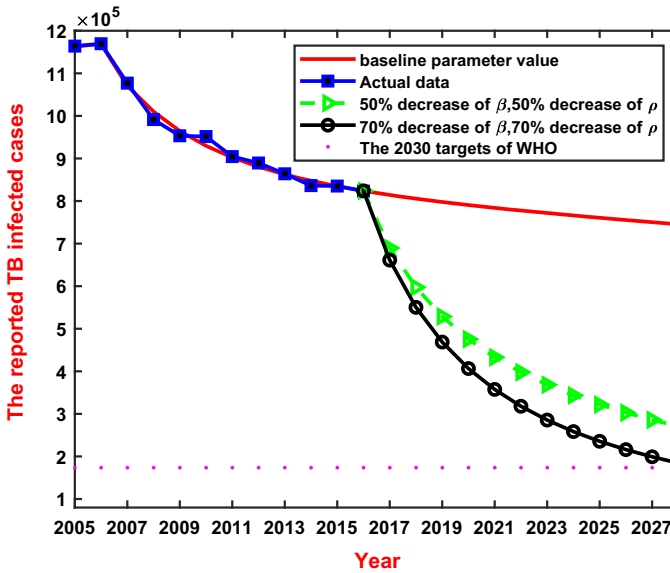
Fig. 9 Prediction of the new TB case with different values of β and ρ

6 Discussion

In this study, we used an age-structured mathematical model with treatment and relapse to study the transmission dynamics of TB. Sufficient conditions were derived for the global asymptotic stability of TB-free equilibrium and the endemic equilibrium. We estimated model parameters by fitting the annual new TB cases data of China, and concluded that, by using current tuberculosis control measures, China may not reach the WHO's goal by 2030. In order to achieve the WHO's goal, China needs to develop more practical control measures. PRCC values of the basic reproduction number, $\mathcal{R}_0$, with respect to some important model parameters demonstrate that the control measures for the spread of TB include reduction of the TB transmission coefficient β and reduction of the TB transmission coefficient $\beta\rho$ of treated individuals infected with TB. These can be achieved through media coverage, public education campaigns and increased hospital stays for TB patients.

TB is prevalent in many countries including China (Creswell et al. 2014). The transmission mechanism of TB in different countries is the same, so the TB model in this paper can be used in the research of TB in other countries, and some feasible measures to control the transmission of TB can also be put forward by using local data of TB and some population data such as birth rate and death rate.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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