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Local and Global Stabilities of a Viral Dynamics Model with Infection-Age and Immune Response

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Abstract In this paper, we construct an infection-age model to study the interaction between viruses and the immune system within the host. In the model, the mortality rate of infected cells, the rate that cytotoxic T lymphocytes (CTL) kill infected cells, the rate that infected cells produce new virus, and the CTL proliferate rate may depend on the infection-age. The basic reproduction number and the threshold for the existence of steady states are obtained. Local stability of both the infection-free and infection steady states is studied by analyzing the linearized systems. Global stability of the infection-free steady state is obtained by investigating a renewal integral equation and global stability of the infection steady state is obtained by constructing a Liapunov functional. Numerical simulations are presented to verify the theoretical results.

Keywords Age-structured model · Viral dynamics · Integrated solution · Liapunov functional · Local and global stabilities

1 Introduction

In the last two decades, many mathematical models have been proposed to investigate the within-host dynamics of viruses and immune cells interactions. A basic model describing the response of cytotoxic T lymphocytes (CTL) to viral infection was first proposed by Nowak and Bangham [24]. Since then, various models have been developed to study immune responses to different viral infections in vivo [3,25,27,33,34,36–39]. Wodarz et al. [37] proposed an

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ordinary differential equation model to study the important role of lytic and nonlytic immune responses in viral infections. Besides the immune response of CTL, researchers have also studied the humoral immunity response of B cells (see [38]). The purpose of constructing and studying these models is to understand how CTL responses work to fight the viral infections. These modeling studies have demonstrated that such mathematical and computational approaches are valuable when coupled with experimental work through collaborations [36].

Taking the latent period into account, delay differential equations have been employed to study the dynamical behavior of viruses and the immune system, in which viruses need times to infect susceptible cells, or the immune system needs times to make an immune response [26,29,32]. In these delay differential equations, the time period of delay is supposed to be a constant. Age-structured models have been used extensively to study the population dynamics and transmission dynamics of infectious diseases (see [9,21,31]). Most recently, age-structured models have been employed to describe viral infections based on the fact that the death rate of infected cells varies over their life span [1,8,12]. In addition, the production rate of viruses is initially low and increases with the age of the infected cells [12,40]. Therefore, it is more reasonable to assume that the mortality of infected cells and the production rate of viruses are functions depending on the age of infected cells. This type of age-structured models has drawn attention of many researchers (see [1,4,5,12,16,23,28,40]). Most studies on this topic are based on a coupled ODE–PDE system incorporating target cells, infected cells, and free viruses as the state variables. As discussed above and as in references [25,27,33,34,36–39], CTL play a crucial role in host defense against viral infections. Therefore, an introduction of the immune cells to the model is necessary in order to better understand virus infections.

In this paper, we propose an infection-age model to study the interactions of the viruses and immune response of CTL within the host. This model may be used to study the interactions between pathogens and the immune system in viral infections such as HIV, HBV, HCV and so on. The model takes the following form:

$$\begin{cases} \dfrac{dx(t)}{dt} = b - d_1 x(t) - \beta x(t) v(t), \\ \dfrac{\partial y(t,\tau)}{\partial t} + \dfrac{\partial y(t,\tau)}{\partial \tau} = -d_2(\tau) y(t,\tau) - p(\tau) y(t,\tau) z(t), \\ \dfrac{dv(t)}{dt} = \displaystyle\int_0^\infty k(\tau) y(t,\tau) d\tau - d_3 v(t), \\ \dfrac{dz(t)}{dt} = \displaystyle\int_0^\infty c(\tau) y(t,\tau) d\tau - d_4 z(t) \end{cases} \tag{1.1}$$

with initial and boundary conditions

$$y(t,0) = \beta x(t) v(t), \tag{1.2}$$

$$x(0) = x_0 > 0,\ y(0,\cdot) = y_0 \in L^1_+(\mathbb{R}_+, \mathbb{R}_+),\ v(0) = v_0 > 0,\ z(0) = z_0 > 0, \tag{1.3}$$

where $x(t)$, $v(t)$, $z(t)$ are the numbers of uninfected target cells, free viruses, and CTL at time t, respectively. $y(t,\tau)$ is the number of infected cells at time t with an infection-age τ, which is the time since the moment of being infected. Uninfected target cells are assumed to be produced at a constant rate b and die out with a rate d_1. When the susceptible cells meet free viruses, they become infected with a rate β. Infected cells at age τ die out with a rate $d_2(\tau)$. Infected cells are killed by CTL with a rate $p(\tau)$, where $p(\tau)$ represents the strength of the CTL killing the infected cells. The viruses die out with a rate d_3, and the mortality

rate of CTL is d_4. Infected cells produce new viruses with a rate $k(\tau)$. The CTL proliferate in response to antigenic stimulation with a rate $c(\tau)$. Here, $k(\tau), c(\tau) \in L^1_+(\mathbb{R}_+, \mathbb{R}_+)$.

Let

$$T(t) := x(t) + \int_0^\infty y(t,\tau)d\tau, \tag{1.4}$$

$$C(t) := \int_0^\infty k(\tau)y(t,\tau)d\tau, \tag{1.5}$$

$$E(t) := \int_0^\infty c(\tau)y(t,\tau)d\tau. \tag{1.6}$$

Thus, $T(t)$ is the total number of organ cells, $C(t)$ represents the proliferate rate of viruses at time t, and $E(t)$ represents the rate of CTL expansion at time t. We assume that all the parameters in (1.1) are positive.

The paper is organized as follows. In Sect. 2 we discuss the existence and uniqueness of solutions to the model. The existence of (both infection-free and infection) steady states is considered in Sect. 3. Section 4 deals with the local and global stabilities of the infection-free steady state. We then establish the uniform persistence of the model system in Sect. 5. Section 6 is devoted to the local and global stabilities of the infection steady state. Some numerical simulations are given in Sect. 7. The paper ends in Sect. 8 with some brief discussions.

2 Existence and Uniqueness of Solutions

In this section, we study the fundamental properties of model (1.1) including the existence and uniqueness of solutions.

In order to study the existence of solutions for system (1.1), we denote

$$\begin{aligned} X &= \mathbb{R} \times L^1(\mathbb{R}_+, \mathbb{R}) \times \mathbb{R} \times \mathbb{R} \times \mathbb{R}, \\ X_0 &= \{0\} \times L^1(\mathbb{R}_+, \mathbb{R}) \times \mathbb{R} \times \mathbb{R} \times \mathbb{R}, \\ X_+ &= \mathbb{R}_+ \times L^1_+(\mathbb{R}_+, \mathbb{R}) \times \mathbb{R}_+ \times \mathbb{R}_+ \times \mathbb{R}_+, \end{aligned}$$

and

$$X_{0+} = X_+ \cap X_0.$$

Define an operator $A : D(A) \subset X \to X$ by

$$A\begin{pmatrix} \begin{pmatrix} 0 \\ \varphi \end{pmatrix} \\ \varphi_1 \\ \varphi_2 \\ \varphi_3 \end{pmatrix} = \begin{pmatrix} \begin{pmatrix} -\varphi(0) \\ -\varphi' - d_2(\tau)\varphi \end{pmatrix} \\ -d_1\varphi_1 \\ -d_3\varphi_2 \\ -d_4\varphi_3 \end{pmatrix} \tag{2.1}$$

with $D(A) = \{0\} \times W^{1,1}(0,\infty) \times \mathbb{R} \times \mathbb{R} \times \mathbb{R}$. If $\lambda \in \mathbb{C}$ with $\mathrm{Re}(\lambda) > -d$ (here $d = \min_{0 \le \tau < \infty} \{d_2(\tau)\}$), then $\lambda \in \rho(A)$ ($\rho(A)$ is the resolvent set of A), and the resolvent of A is given by the following formula:

$$(\lambda I - A)^{-1}\begin{pmatrix}\begin{pmatrix}\alpha\\ \psi\end{pmatrix}\\ \psi_1\\ \psi_2\\ \psi_3\end{pmatrix} = \begin{pmatrix}\begin{pmatrix}0\\ \varphi\end{pmatrix}\\ \varphi_1\\ \varphi_2\\ \varphi_3\end{pmatrix} \tag{2.2}$$

$$\Leftrightarrow \begin{pmatrix}\varphi\\ \varphi_1\\ \varphi_2\\ \varphi_3\end{pmatrix}(\tau) = \begin{pmatrix}e^{-\lambda\tau}e^{-\int_0^\tau d_2(\sigma)d\sigma}\alpha + \int_0^\tau e^{-\lambda(\tau-s)}e^{-\int_s^\tau d_2(\sigma)d\sigma}\psi(s)ds\\ \frac{\psi_1(\tau)}{\lambda+d_1}\\ \frac{\psi_2(\tau)}{\lambda+d_3}\\ \frac{\psi_3(\tau)}{\lambda+d_4}\end{pmatrix}. \tag{2.3}$$

Now we rewrite system (1.1) as the following abstract Cauchy problem:

$$\begin{cases}\dfrac{du(t)}{dt} = Au(t) + F(u(t)), \qquad t \geq 0,\\ u(0) = u_0 \in \overline{D(A)},\end{cases} \tag{2.4}$$

where

$$u(t) = \begin{pmatrix}\begin{pmatrix}0\\ y(t,\cdot)\end{pmatrix}\\ x(t)\\ v(t)\\ z(t)\end{pmatrix}, \quad F(u(t))(\tau) = \begin{pmatrix}\begin{pmatrix}\beta x(t)v(t)\\ -p(\tau)y(t,\tau)z(t)\end{pmatrix}\\ b - \beta x(t)v(t)\\ \int_0^\infty k(\tau)y(t,\tau)d\tau\\ \int_0^\infty c(\tau)y(t,\tau)d\tau\end{pmatrix}. \tag{2.5}$$

F is a nonlinear map defined from $\overline{D(A)}$ to X. One can see that it is Lipschitz continuous on bounded sets. Based on this fact, we have the following theorem by applying the results given in [6,10,15,17,19].

Theorem 2.1 *There exists a uniquely determined semiflow $\{U(t)\}_{t\geq 0}$ on X_{0+}, such that for each $\zeta \in X_{0+}$, there exists a unique continuous map $U \in C([0,+\infty), X_{0+})$ which is an integrated solution of the abstract Cauchy problem (2.4); that is,*

$$\int_0^t U(s)\zeta ds \in D(A), \quad \forall t \geq 0 \tag{2.6}$$

and

$$U(t)\zeta = \zeta + A\int_0^t U(s)ds + \int_0^t F(U(s)\zeta)ds, \quad \forall t \geq 0. \tag{2.7}$$

Moreover, the semiflow $\{U(t)\}_{t\geq 0}$ is asymptotically smooth and bounded dissipative.

Let

$$\Omega = \left\{\left((0,y),x,v,z\right) \in X_{0+} \mid T(t) \leq \frac{b}{r}, v(t) \leq \frac{\bar{k}b}{rd_3}, z(t) \leq \frac{\bar{c}b}{rd_4}\right\}, \tag{2.8}$$

where $r = \min(d_1, \underline{d_2})$, $\underline{d_2} = \inf_{\tau\geq 0} d_2(\tau)$, $\bar{k} = \sup_{\tau\geq 0} k(\tau)$, $\bar{c} = \sup_{\tau\geq 0} c(\tau)$. We have the following theorem.

Theorem 2.2 *Ω is a positively invariant set under semiflow $\{U(t)\}_{t\geq 0}$; that is $U(t)\Omega \subset \Omega$. Moreover, Ω attracts all positive solutions of (2.4).*

Proof Let $\bar{d_2} = \sup_{\tau\geq 0} d_2(\tau)$, $\bar{p} = \sup_{\tau\geq 0} p(\tau)$, $a = \max(d_1, \bar{d_2} + \frac{\bar{p}\bar{c}b}{rd_4})$. For any $\big((0, y), x, v, z\big) \in \Omega$ and $t \geq 0$, we have

$$\frac{dT(t)}{dt} \leq b - d_1 x(t) - \underline{d_2}\int_0^\infty y(t,\tau)d\tau \leq b - rT(t). \tag{2.9}$$

It follows that

$$T(t) \leq \frac{b}{r} + \Big(T(0) - \frac{b}{r}\Big)e^{-rt}. \tag{2.10}$$

Therefore, $T(t) \leq \frac{b}{r}$ if $((0, y_0), x_0, v_0, z_0) \in \Omega$. Moreover,

$$-d_3 v(t) \leq \frac{dv(t)}{dt} \leq \bar{k}\int_0^\infty y(t,\tau)d\tau - d_3 v(t) \leq \bar{k}\frac{b}{r} - d_3 v(t). \tag{2.11}$$

Thus,

$$v_0 e^{-d_3 t} \leq v(t) \leq \frac{\bar{k}b}{rd_3} + \Big(v_0 - \frac{\bar{k}b}{rd_3}\Big)e^{-d_3 t}. \tag{2.12}$$

Similarly, we have

$$z_0 e^{-d_4 t} \leq z(t) \leq \frac{\bar{c}b}{rd_4} + \Big(z_0 - \frac{\bar{c}b}{rd_4}\Big)e^{-d_4 t}. \tag{2.13}$$

In addition,

$$\frac{dT(t)}{dt} = b - d_1 x(t) - \int_0^\infty \big(d_2(\tau) + p(\tau)z(t)\big)y(t,\tau)d\tau \geq -aT(t), \tag{2.14}$$

hence,

$$T(t) \geq T(0)e^{-at}. \tag{2.15}$$

Therefore, $U(t)\Omega \subset \Omega$ and Ω is a positively invariant set. Moreover, it is easy to see that Ω attracts all positive solutions of (2.4) by (2.10), (2.12) and (2.13). □

3 Existence of Steady States

System (1.1) always has an infection-free steady state $E^0 = (x^0, 0, 0, 0)$, where $x^0 = \frac{b}{d_1}$. There may exist an infection steady state $E^* = (x^*, y^*(\tau), v^*, z^*)$ satisfying the following equations

$$\begin{cases} b - d_1 x^* - \beta x^* v^* = 0, \\ \dfrac{dy^*(\tau)}{d\tau} = -(d_2(\tau) + p(\tau)z^*)y^*(\tau), \\ \displaystyle\int_0^\infty k(\tau)y^*(\tau)d\tau - d_3 v^* = 0, \\ \displaystyle\int_0^\infty c(\tau)y^*(\tau)d\tau - d_4 z^* = 0, \\ y^*(0) = \beta x^* v^*. \end{cases} \tag{3.1}$$

Calculating the first equation of (3.1) yields

$$x^* = \frac{b}{d_1 + \beta v^*}. \tag{3.2}$$

Solving the second equation of (3.1), we have

$$y^*(\tau) = y^*(0)\exp\left\{-\int_0^\tau (d_2(\tau) + p(\tau)z^*)d\tau\right\}$$
$$= \beta x^* v^* \Gamma_1(\tau)\Gamma_2(\tau, z^*), \tag{3.3}$$

where $\Gamma_1(\tau) := \exp\{-\int_0^\tau d_2(\sigma)d\sigma\}, \Gamma_2(\tau, f) := \exp\{-\int_0^\tau p(\sigma)fd\sigma\}, f(\cdot) \in L^1_+(\mathbb{R}_+, \mathbb{R})$. Next, substituting (3.3) into the third equation of (3.1), it follows that

$$v^* = \frac{\beta x^* v^*}{d_3}\int_0^\infty k(\tau)\Gamma_1(\tau)\Gamma_2(\tau, z^*)d\tau. \tag{3.4}$$

When $v^* \neq 0$, it is equivalent to

$$1 = \frac{\beta x^*}{d_3}\int_0^\infty k(\tau)\Gamma_1(\tau)\Gamma_2(\tau, z^*)d\tau. \tag{3.5}$$

This leads to

$$v^* = \frac{\beta b G(z^*) - d_1 d_3}{\beta d_3}, \tag{3.6}$$

where $G(z^*) = \int_0^\infty k(\tau)\Gamma_1(\tau)\Gamma_2(\tau, z^*)d\tau$. Similarly, substituting (3.3) into the fourth equation of (3.1), we have

$$z^* = \frac{\beta x^* v^*}{d_4}\int_0^\infty c(\tau)\Gamma_1(\tau)\Gamma_2(\tau, z^*)d\tau. \tag{3.7}$$

Substituting (3.2) and (3.6) into (3.7) yields

$$z^* = \frac{d_1 d_3 G_1(z^*)}{\beta d_4 G(z^*)}\Big(\frac{\beta b G(z^*)}{d_1 d_3} - 1\Big), \tag{3.8}$$

where $G_1(z^*) = \int_0^\infty c(\tau)\Gamma_1(\tau)\Gamma_2(\tau, z^*)d\tau$.

Let

$$\Phi(z^*) = \frac{d_1 d_3 G_1(z^*)}{\beta d_4 G(z^*)}\Big(\frac{\beta b G(z^*)}{d_1 d_3} - 1\Big) - z^*. \tag{3.9}$$

Then,

$$\Phi(0) = \frac{d_1 d_3 G_1(0)}{\beta d_4 G(0)}\Big(\frac{\beta b G(0)}{d_1 d_3} - 1\Big). \tag{3.10}$$

The basic reproduction number of system (1.1) is defined as

$$\mathcal{R}_0 = \frac{\beta b G(0)}{d_1 d_3} = \frac{\beta b\int_0^\infty k(\tau)e^{-\int_0^\tau d_2(\sigma)d\sigma}d\tau}{d_1 d_3}. \tag{3.11}$$

Remark 3.1 The basic reproduction number $\mathcal{R}_0$ is the average number of newly infected cells produced by a single infected cell during its lifetime, assuming all other cells are susceptible [2,36]. In (3.11), β is the effective infection rate; $1/d_3$ denotes the average lifespan of the virus; $e^{-\int_0^\tau d_2(\sigma)d\sigma}$ is the probability that an infected cell survives to age τ, hence $\int_0^\infty k(\tau)e^{-\int_0^\tau d_2(\sigma)d\sigma}d\tau$ represents the number of viruses that an infected cell reproduces in its lifetime; b/d_1 is the number of susceptible cells at the infection-free steady state. Therefore, the basic reproduction number has the same biological interpretation as in the non-age-structured epidemic models.

On account of $G(z^*) > 0, G_1(z^*) > 0$ and $G(z^*) \le G(0)$, we have $\Phi(z^*) \le 0$ if $\mathcal{R}_0 \le 1$, and $\Phi(z^*) = 0$ holds if and only if $z^* = 0$. Therefore, there is no infection steady state if $\mathcal{R}_0 \le 1$.

Equation (3.8) has at least one positive root z_0^* if $\mathcal{R}_0 > 1$ since $\Phi(0) > 0$ and $\lim_{z^* \to +\infty} \Phi(z^*) = -\infty$; that is, system (1.1) has at least one infection steady state if $\mathcal{R}_0 > 1$. Furthermore,

$$\Phi'(z^*) = \frac{d_1 d_3 G_1'(z^*)}{\beta d_4 G(z^*)} \Big(\frac{\beta b G(z^*)}{d_1 d_3} - 1 \Big) + \frac{d_1 d_3 G_1(z^*) G'(z^*)}{\beta d_4 G^2(z^*)} - 1. \tag{3.12}$$

By the expressions of $G(z^*)$ and $G_1(z^*)$, we know that $G(z^*) > 0, G_1(z^*) > 0, G'(z^*) < 0$ and $G_1'(z^*) < 0$. In the neighborhood of the positive root z_0^*, it is easy to see that $\frac{\beta b G(z^*)}{d_1 d_3} - 1 > 0$, hence, $\Phi'(z^*) < 0$, which means that there is no more than one positive root for (3.8). Hence, the following threshold property holds.

Theorem 3.2 *For system (1.1), there is no infection steady state if $\mathcal{R}_0 \le 1$, and there is a unique infection steady state if $\mathcal{R}_0 > 1$.*

4 Stability of the Infection-Free Steady State

In this section, we discuss the local and global stabilities of the infection-free steady state $E^0 = (x^0, 0, 0, 0)$.

4.1 Local Stability of the Infection-Free Steady State

Let $x_1(t) = x(t) - x^0$, $y_1(t, \tau) = y(t, \tau)$, $v_1(t) = v(t)$, $z_1(t) = z(t)$. We can derive the linearized equations at E^0 as follows:

$$\begin{cases} \dfrac{dx_1(t)}{dt} = -d_1 x_1(t) - \dfrac{\beta b}{d_1} v_1(t), \\ \dfrac{\partial y_1(t,\tau)}{\partial t} + \dfrac{\partial y_1(t,\tau)}{\partial \tau} = -d_2(\tau) y_1(t,\tau), \\ \dfrac{dv_1(t)}{dt} = \displaystyle\int_0^\infty k(\tau) y_1(t,\tau) d\tau - d_3 v_1(t), \\ \dfrac{dz_1(t)}{dt} = \displaystyle\int_0^\infty c(\tau) y_1(t,\tau) d\tau - d_4 z_1(t) \end{cases} \tag{4.1}$$

with boundary and initial conditions

$$y_1(t, 0) = \frac{\beta b}{d_1} v_1(t), \tag{4.2}$$

$$x_1(0) = x_{10}, y_1(0, \cdot) = y_{10}, v_1(0) = v_{10}, z_1(0) = z_{10}. \tag{4.3}$$

Let

$$B_1(t) = \frac{\beta b}{d_1} v_1(t), \tag{4.4}$$

$$C_1(t) = \int_0^\infty k(\tau) y_1(t, \tau) d\tau, \tag{4.5}$$

$$E_1(t) = \int_0^\infty c(\tau) y_1(t, \tau) d\tau. \tag{4.6}$$

Then, by formal integration of (4.1), we have

$$x_1(t) = x_{10}e^{-d_1 t} - (l_1 * B_1)(t), \tag{4.7}$$

$$v_1(t) = v_{10}e^{-d_3 t} + (l_3 * C_1)(t), \tag{4.8}$$

$$z_1(t) = z_{10}e^{-d_4 t} + (l_4 * E_1)(t), \tag{4.9}$$

where $l_j(\tau) := e^{-d_j\tau}(j = 1, 3, 4)$. The asterisk denotes the convolution operation defined by

$$(f * g)(t) := \int_0^t f(t-\sigma)g(\sigma)d\sigma. \tag{4.10}$$

Next by integrating the second equation of (4.1) along the characteristic lines, one has

$$y_1(t,\tau) = \begin{cases} B_1(t-\tau)\Gamma_1(\tau), & t \geq \tau, \\ y_{10}(\tau - t)\Gamma_1(t), & t < \tau. \end{cases} \tag{4.11}$$

Then,

$$\begin{aligned} C_1(t) &= \int_0^\infty k(\tau)y_1(t,\tau)d\tau \\ &= \int_0^t k(\tau)B_1(t-\tau)\Gamma_1(\tau)d\tau + \int_t^\infty k(\tau)y_{10}(\tau - t)\Gamma_1(\tau)d\tau \\ &= (k\Gamma_1 * B_1)(t) + F_{10}(t), \end{aligned} \tag{4.12}$$

where

$$F_{10}(t) = \int_t^\infty k(\tau)y_{10}(\tau - t)\Gamma_1(\tau)d\tau. \tag{4.13}$$

Therefore,

$$\begin{aligned} B_1(t) &= \frac{\beta b}{d_1}\big(v_{10}e^{-d_3 t} + (l_3 * C_1)(t)\big) \\ &= \frac{\beta b}{d_1}\Big(v_{10}e^{-d_3 t} + (l_3 * F_{10})(t) + \big((l_3 * k\Gamma_1) * B_1\big)(t)\Big) \\ &= G_2(t) + \int_0^t \Psi_0(\tau)B_1(t-\tau)d\tau, \end{aligned} \tag{4.14}$$

where

$$G_2(t) = \frac{\beta b}{d_1}\Big(v_{10}e^{-d_3 t} + (l_3 * F_{10})(t)\Big), \tag{4.15}$$

$$\Psi_0(\tau) = \frac{\beta b}{d_1}(l_3 * k\Gamma_1)(\tau). \tag{4.16}$$

Then, $\lim_{t\to+\infty} G_2(t) = 0$. In fact,

$$\begin{aligned} |F_{10}(t)| &= \left|\int_t^\infty k(\tau)y_{10}(\tau - t)\Gamma_1(\tau)d\tau\right| \\ &\leq \bar{k}\|y_{10}\|_{L^1}\int_t^\infty e^{-\underline{d_2}\tau}d\tau \\ &= \frac{1}{\underline{d_2}}\bar{k}\|y_{10}\|_{L^1}e^{-\underline{d_2}t}, \end{aligned} \tag{4.17}$$

when $\underline{d_2} \neq d_3$,

$$\begin{aligned} |(l_3 * F_{10})(t)| &\leq \int_0^t e^{-d_3(t-\tau)} |F_{10}(\tau)| d\tau \\ &\leq \int_0^t \frac{1}{\underline{d_2}} e^{-d_3(t-\tau)} \bar{k} \|y_{10}\|_{L^1} e^{-\underline{d_2}\tau} d\tau \\ &= \bar{k} \|y_{10}\|_{L^1} \frac{e^{-d_3 t} - e^{-\underline{d_2} t}}{\underline{d_2}(\underline{d_2} - d_3)}, \end{aligned} \tag{4.18}$$

and if $\underline{d_2} = d_3$,

$$|(l_3 * F_{10})(t)| \leq \frac{1}{\underline{d_2}} \bar{k} \|y_{10}\|_{L^1} t e^{-d_3 t}. \tag{4.19}$$

It follows that $\lim_{t\to+\infty} G_2(t) = 0$. By the Paley–Wiener Theorem [13,14], we know that $\lim_{t\to+\infty} B_1(t) = 0$ if and only if

$$\begin{aligned} \int_0^\infty \Psi_0(\tau) d\tau &= \beta \frac{b}{d_1} \int_0^\infty (l_3 * k\Gamma)(\tau) d\tau \\ &\leq \beta \frac{b}{d_1} \int_0^\infty (l_3 * k\Gamma_1)(\tau) d\tau \\ &= \beta \frac{b}{d_1 d_3} \int_0^\infty k(\tau) \Gamma_1(\tau) d\tau \\ &= \mathcal{R}_0 < 1. \end{aligned}$$

Therefore, $\lim_{t\to+\infty} y_1(t,\tau) = 0$ for any $\tau \in (0, +\infty)$, $\lim_{t\to+\infty} x_1(t) = \frac{b}{d_1}$, $\lim_{t\to+\infty} v_1(t) = 0$, and $\lim_{t\to+\infty} z_1(t) = 0$ if and only if $\mathcal{R}_0 < 1$.

By the principle of linearized stability for the evolution equation as system (1.1) (see [7], Proposition 5.2 in [14], Appendix in [20], Corollary in [30] or Theorem 4.13 in [35]), we have the following theorem.

Theorem 4.1 *The infection-free steady state E^0 is locally stable if $\mathcal{R}_0 < 1$ and unstable if $\mathcal{R}_0 > 1$.*

4.2 Global Stability of the Infection-Free Steady State

Let

$$B(t) = \beta x(t) v(t).$$

Then, by formal integration of (1.1), one obtains

$$x(t) = \frac{b}{d_1} + \left(x_0 - \frac{b}{d_1}\right) e^{-d_1 t} - (l_1 * B)(t), \tag{4.20}$$

$$v(t) = v_0 e^{-d_3 t} + (l_3 * C)(t), \tag{4.21}$$

$$z(t) = z_0 e^{-d_4 t} + (l_4 * E)(t), \tag{4.22}$$

where $C(t)$ and $E(t)$ are defined in (1.5) and (1.6) respectively. Next by integrating the second equation of (1.1) along the characteristic lines, we have

$$y(t,\tau) = \begin{cases} B(t-\tau)\Gamma_1(\tau)\Gamma_2(\tau, z(t+\sigma)), & t \geq \tau, \\ y_0(\tau - t)\Gamma_1(t)\Gamma_2(t, z(\tau+\sigma)), & t < \tau. \end{cases} \tag{4.23}$$

Therefore,

$$\begin{aligned} T(t) &= x(t) + \int_0^\infty y(t,\tau)d\tau \\ &= x(t) + \int_0^t B(t-\tau)\Gamma_1(\tau)\Gamma_2(\tau, z(t+\sigma))d\tau \\ &\quad + \int_t^\infty y_0(\tau - t)\Gamma_1(t)\Gamma_2(t, z(\tau+\sigma))d\tau. \end{aligned} \tag{4.24}$$

Thus for any fixed $t_0 > 0$, we can define operators $X(f)$, $T(f)$, $V(f)$ and $Z(f)$ for $f(\cdot) \in C([0, t_0]; \mathbb{R}_+)$ as

$$\begin{aligned} X(f)(t) &:= \frac{b}{d_1} + \left(x_0 - \frac{b}{d_1}\right) e^{-d_1 t} - (l_1 * f)(t), \\ T(f)(t) &:= X(f)(t) + F_0(t) + F_1(t), \\ V(f)(t) &:= v_0 e^{-d_3 t} + (l_3 * f)(t), \\ Z(f)(t) &:= z_0 e^{-d_4 t} + (l_4 * f)(t), \end{aligned} \tag{4.25}$$

where

$$\begin{aligned} F_0(t) &= \int_0^t B(t-\tau)\Gamma_1(\tau)\Gamma_2(\tau, z(t+\sigma))d\tau, \\ F_1(t) &= \int_t^\infty y_0(\tau - t)\Gamma_1(\tau)\Gamma_2(t, z(\tau+\sigma))d\tau. \end{aligned}$$

Hence,

$$\begin{cases} B(t) = \beta X(B)(t) V(C)(t), \\ C(t) = (k\Gamma * B)(t) + F_3(t), \\ E(t) = (c\Gamma * B)(t) + F_4(t), \end{cases} \tag{4.26}$$

where

$$\begin{aligned} \Gamma(\tau) &= \Gamma_1(\tau)\Gamma_2(\tau, Z(E)(t+\sigma)), \\ F_3(t) &= \int_t^\infty k(\tau) y_0(\tau - t)\Gamma_1(\tau)\Gamma_2(\tau, Z(E)(\tau+\sigma))d\tau, \\ F_4(t) &= \int_t^\infty c(\tau) y_0(\tau - t)\Gamma_1(\tau)\Gamma_2(\tau, Z(E)(\tau+\sigma))d\tau. \end{aligned}$$

We have the following theorem on the global stability of the infection-free steady state.

Theorem 4.2 *The infection-free steady state E^0 is globally asymptotically stable if $\mathcal{R}_0 < 1$.*

Proof Define

$$\Psi_{\varepsilon_0}(\tau) := \beta\Big(\frac{b}{d_1} + \varepsilon_0\Big)(l_3 * k\Gamma)(\tau), \qquad \varepsilon_0 \in \mathbb{R}_+.$$

Under the assumption $\mathcal{R}_0 < 1$, there exists $\varepsilon_0 > 0$ small enough, such that $\int_0^\infty \Psi_{\varepsilon_0}(\tau) < 1$. For the above ε_0, there exists a $T > 0$, such that $(x_0 - \frac{b}{d_1})e^{-d_1 t} < \varepsilon_0$ for any $t > T$. Thus, for any $t > T$, we have

$$
\begin{aligned}
B(t) &= \beta X(B)(t)V(C)(t)\\
&= \beta\Big(\frac{b}{d_1} + (x_0 - \frac{b}{d_1})e^{-d_1 t} - (l_1 * B)(t)\Big)\Big(v_0 e^{-d_3 t} + (l_3 * C)(t)\Big)\\
&\le \beta\Big(\frac{b}{d_1} + (x_0 - \frac{b}{d_1})e^{-d_1 t}\Big)\Big(v_0 e^{-d_3 t} + (l_3 * C)(t)\Big)\\
&= \beta\Big(\frac{b}{d_1} + (x_0 - \frac{b}{d_1})e^{-d_1 t}\Big)v_0 e^{-d_3 t} + \beta\Big(\frac{b}{d_1} + (x_0 - \frac{b}{d_1})e^{-d_1 t}\Big)(l_3 * C)(t)\\
&\le \beta\Big(\frac{b}{d_1} + \varepsilon_0\Big)v_0 e^{-d_3 t} + \beta\Big(\frac{b}{d_1} + \varepsilon_0\Big)(l_3 * C)(t)\\
&= \beta\Big(\frac{b}{d_1} + \varepsilon_0\Big)v_0 e^{-d_3 t} + \beta\Big(\frac{b}{d_1} + \varepsilon_0\Big)\Big((l_3 * (k\Gamma * B))(t) + (l_3 * F_3)(t)\Big)\\
&= G_3(t) + \beta\Big(\frac{b}{d_1} + \varepsilon_0\Big)\big((l_3 * k\Gamma) * B\big)(t),
\end{aligned}
\tag{4.27}
$$

where

$$
G_3(t) := \beta\Big(\frac{b}{d_1} + \varepsilon_0\Big)\Big(v_0 e^{-d_3 t} + (l_3 * F_3)(t)\Big). \tag{4.28}
$$

Similar to the proof of $\lim_{t\to+\infty} G_2(t) = 0$, we can prove that $\lim_{t\to+\infty} G_3(t) = 0$.

Let $\overline{B}(t)$ be the solution of the following renewal integral equation:

$$
\overline{B}(t) = G_3(t) + \int_0^t \Psi_{\varepsilon_0}(\tau)\overline{B}(t-\tau)d\tau, \tag{4.29}
$$

Thus $B(t) \le \overline{B}(t)$. Since $\lim_{t\to+\infty} G_3(t) = 0$ and $\int_0^\infty \Psi_{\varepsilon_0}(\tau)d\tau < 1$ if $\mathcal{R}_0 < 1$, by the Paley–Wiener Theorem [13,14], we have $\lim_{t\to+\infty} \overline{B}(t) = 0$ which implies $\lim_{t\to+\infty} B(t) = 0$. Therefore, if $\mathcal{R}_0 < 1$, by (4.11), $\lim_{t\to+\infty} y(t,\tau) = 0$ for any $\tau \in (0,+\infty)$. By (4.20), (4.21) and (4.22), $\lim_{t\to+\infty} x(t) = \frac{b}{d_1}$, $\lim_{t\to+\infty} v(t) = 0$, and $\lim_{t\to+\infty} z(t) = 0$. □

5 Uniform Persistence

From Theorem 4.1, one can see that E^0 is unstable when $\mathcal{R}_0 > 1$. In this section, we will show that system (1.1) is uniformly persistent and hence the viruses will not go extinct when $\mathcal{R}_0 > 1$. Define

$$
M_0 = \Big\{\big((0,y),x,v,z\big) \in \Omega : v + \int_0^\infty y(\tau)d\tau > 0\Big\}
$$

and $\partial M_0 = \Omega \backslash M_0$.

Lemma 5.1 *The subsets M_0 and ∂M_0 are both positively invariant under the semiflow $\{U(t)\}_{t\ge 0}$; that is, $U(t)M_0 \subset M_0$ and $U(t)\partial M_0 \subset \partial M_0$. Moreover, for each $\zeta \in \partial M_0$, $U(t)\zeta \to e^0$ as $t \to +\infty$, where*

$$
e^0 = \begin{pmatrix} \begin{pmatrix} 0_{\mathbb{R}} \\ 0_{L^1} \end{pmatrix} \\ x^0 \\ 0 \\ 0 \end{pmatrix}
$$

is the infection-free steady state of $\{U(t)\}_{t\geq 0}$.

Proof Let

$$J(t) = v(t) + \int_0^\infty y(t,\tau)d\tau. \tag{5.1}$$

For any $\big((0,y),x,v,z\big) \in M_0$, we have

$$\begin{aligned}\frac{dJ(t)}{dt} &= \int_0^\infty k(\tau)y(t,\tau)d\tau - d_3v(t) + \beta x(t)v(t) - \int_0^\infty (d_2(\tau)+p(\tau)z(t))y(t,\tau)d\tau,\\ &\geq -d_3v(t) - (\bar{d_2} + \frac{\bar{p}\bar{c}b}{rd_4})\int_0^\infty y(t,\tau)d\tau,\\ &\geq -a_1J(t),\end{aligned} \tag{5.2}$$

where $a_1 = \max\{d_3, \bar{d_2} + \frac{\bar{p}\bar{c}b}{rd_4}\}$. Then, $J(t) \geq J(0)e^{-a_1t} > 0$. It follows that $U(t)M_0 \subset M_0$.

In addition, for any $\big((0,y),x,v,z\big) \in \partial M_0$, we have

$$\begin{aligned}\int_0^\infty y(t,\tau)d\tau &= \beta\int_0^t x(t-\tau)v(t-\tau)\Gamma_1(\tau)\Gamma_2(\tau,z(t+\sigma))d\tau\\ &\quad + \int_t^\infty y_0(\tau)\Gamma_1(\tau)\Gamma_2(t,z(\tau+\sigma))d\tau = 0.\end{aligned}$$

We also have

$$-d_3v(t) \leq \frac{dv(t)}{dt} \leq \bar{k}\int_0^\infty y(t,\tau)d\tau - d_3v(t) = -d_3v(t),$$

which follows that $v(t) = 0$ if $v_0 \in \partial M_0$. Hence, $U(t)\partial M_0 \subset \partial M_0$. Furthermore, $v(t) = 0$ means that $B(t) = \beta x(t)v(t) = 0$. Using the same argument as in the proof of Theorem 4.2, we can see that for each $\zeta \in \partial M_0$, $U(t)\zeta \to e^0$ as $t \to +\infty$. □

By applying the results in [11,18], we obtain the following theorem.

Theorem 5.2 *If* $\mathcal{R}_0 > 1$, *the semiflow* $\{U(t)\}_{t\geq 0}$ *is uniformly persistent with respect to the pair* $(\partial M_0,\ M_0)$; *that is, there exists* $\varepsilon > 0$ *such that* $\liminf_{t\to\infty} d\big(U(t)\zeta, \partial M_0\big) \geq \varepsilon$ *for any* $\zeta \in M_0$.

Proof By Lemma 5.1 and Theorem 2.1, the conditions (i)–(iii) in Theorem 4.1 in [11] are satisfied. Applying Theorem 4.1 in [11], $\{U(t)\}_{t\geq 0}$ is uniformly persistent if and only if

$$W^s(\{e^0\}) \cap M_0 = \emptyset, \tag{5.3}$$

where

$$W^s(\{e^0\}) = \left\{\zeta \in \Omega : \lim_{t\to+\infty} U(t)\zeta = e^0\right\}. \tag{5.4}$$

Assume by contradiction that there exists $\zeta \in W^s(\{e^0\}) \cap M_0$, then there exists $t_0 > 0$ such that $v(t_0) + \int_0^\infty y(t_0,\tau)d\tau > 0$. Since $U(t)M_0 \subset M_0$, we have $v(t) + \int_0^\infty y(t,\tau)d\tau > 0$ for any $t \geq t_0$. Let

$$\xi(t,\tau) = \int_\tau^\infty k(\sigma)\exp\{-\int_\tau^\sigma (d_2(s)+p(s)z(t))ds\}d\sigma. \tag{5.5}$$

Then $\frac{\partial\xi(t,\tau)}{\partial\tau} = -k(\tau) + \big(d_2(\tau)+p(\tau)z(t)\big)\xi(t,\tau)$ a.e. $\tau \geq 0$. Define

$$J_1(t) = v(t) + \int_0^\infty \xi(t,\tau)y(t,\tau)d\tau. \tag{5.6}$$

Since $\zeta \in W^s(\{e^0\})$, we have $\lim_{t\to+\infty} x(t) = x^0$, $\lim_{t\to+\infty} z(t) = 0$, and hence $\lim_{t\to+\infty} \xi(t,0) = G(0)$. When $\mathcal{R}_0 > 1$, taking $\varepsilon_0 > 0$ and $\varepsilon_1 > 0$ small enough such that $0 < \frac{\beta(x^0\varepsilon_1 + G(0)\varepsilon_0)}{d_3} < \mathcal{R}_0 - 1$. For the above ε_0 and ε_1, there exists $t_1 > 0$ such that $x(t) > x^0 - \varepsilon_0$ and $\xi(t,0) > G(0) - \varepsilon_1$ for all $t \geq t_1$. Then, for $t \geq t_1$, we have

$$\begin{aligned}\frac{dJ_1(t)}{dt} &\geq (\beta\xi(t,0)x(t) - d_3)v(t)\\ &> \big(\beta(x^0-\varepsilon_0)(G(0)-\varepsilon_1) - d_3\big)v(t)\\ &= d_3\Big(R_0 - 1 - \frac{\beta(x^0\varepsilon_1 + G(0)\varepsilon_0)}{d_3} + \frac{\beta\varepsilon_0\varepsilon_1}{d_3}\Big)v(t)\\ &\geq 0,\end{aligned} \tag{5.7}$$

which implies that $J_1(t)$ is a non-decreasing function for $t \geq t_1$. Therefore, $J_1(t) \geq J_1(t_2) > 0$ for all $t \geq t_2$ with $t_2 = \max\{t_0, t_1\}$, which prevents $(y(t,\tau), v(t))$ converging to $(0_{L^1}, 0)$ as $t \to +\infty$. A contradiction with $\zeta \in W^s(\{e^0\})$. □

6 Stability of the Infection Steady State

Next, we study the stability of the infection steady state $E^* = (x^*, y^*(\tau), v^*, z^*)$ when $\mathcal{R}_0 > 1$.

6.1 Local Stability of the Infection Steady State

We first discuss the local stability of the infection steady state and have the following result.

Theorem 6.1 *The infection steady state E^* is locally stable if $\mathcal{R}_0 > 1$.*

Proof Let $x_2(t) = x(t) - x^*$, $y_2(t,\tau) = y(t,\tau) - y^*(\tau)$, $v_2(t) = v(t) - v^*$, $z_2(t) = z(t) - z^*$. Then we obtain the linearized equation at E^* as follows:

$$\begin{cases}\dfrac{dx_2(t)}{dt} = -d_1x_2(t) - \beta v^*x_2(t) - \beta x^*v_2(t),\\ \dfrac{\partial y_2(t,\tau)}{\partial t} + \dfrac{\partial y_2(t,\tau)}{\partial \tau} = -(d_2(\tau) + p(\tau)z^*)y_2(t,\tau) - p(\tau)y^*(\tau)z_2(t),\\ \dfrac{dv_2(t)}{dt} = \displaystyle\int_0^\infty k(\tau)y_2(t,\tau)d\tau - d_3v_2(t),\\ \dfrac{dz_2(t)}{dt} = \displaystyle\int_0^\infty c(\tau)y_2(t,\tau)d\tau - d_4z_2(t)\end{cases} \tag{6.1}$$

with the boundary condition

$$y_2(t,0) = \beta v^*x_2(t) + \beta x^*v_2(t). \tag{6.2}$$

We assume that $x_2(t) = x_2 e^{\varpi t}$, $y_2(t,\tau) = y_2(\tau)e^{\varpi t}$, $v_2(t) = v_2 e^{\varpi t}$, and $z_2(t) = z_2 e^{\varpi t}$, then

$$\begin{cases} v_2 = -\dfrac{(\varpi + d_1 + \beta v^*)x_2}{\beta x^*}, \\ \dfrac{dy_2(\tau)}{d\tau} = -(d_2(\tau) + p(\tau)z^* + \varpi)y_2(\tau) - p(\tau)y^*(\tau)z_2, \\ (\varpi + d_3)v_2 = \displaystyle\int_0^\infty k(\tau)y_2(\tau)d\tau, \\ (\varpi + d_4)z_2 = \displaystyle\int_0^\infty c(\tau)y_2(\tau)d\tau, \\ y_2(0) = \beta(v^*x_2 + x^*v_2). \end{cases} \tag{6.3}$$

Solving the second equation of (6.3), one has

$$\begin{aligned} y_2(\tau) &= \Gamma_1(\tau)\Gamma_2(\tau, z^*)e^{-\varpi\tau}\Big(\beta(v^*x_2 + x^*v_2) - z_2\int_0^\tau \frac{p(s)y^*(s)e^{\varpi s}}{\Gamma_1(s)\Gamma_2(s,z^*)}ds\Big) \\ &= F_5(\tau) - F_6(\tau), \end{aligned} \tag{6.4}$$

where

$$F_5(\tau) = \Gamma_1(\tau)\Gamma_2(\tau, z^*)\beta(v^*x_2 + x^*v_2)e^{-\varpi\tau}, \tag{6.5}$$

$$F_6(\tau) = z_2\int_0^\tau p(s)y^*(s)\Gamma_1(\tau - s)\Gamma_2(\tau - s, z^*)e^{-\varpi(\tau-s)}ds. \tag{6.6}$$

From the third and fourth equations of (6.3), we have

$$z_2 = \frac{\beta(x^*v_2 + v^*x_2)G_4}{\varpi + d_4 + G_3}, \tag{6.7}$$

where

$$\begin{aligned} G_3 &= \int_0^\infty\int_0^\tau k(\tau)p(s)y^*(s)\Gamma_1(\tau - s)\Gamma_2(\tau - s, z^*)e^{-\varpi(\tau-s)}dsd\tau, \\ G_4 &= \int_0^\infty c(\tau)\Gamma_1(\tau)\Gamma_2(\tau, z^*)e^{-\varpi\tau}d\tau. \end{aligned}$$

Substituting (6.4), (6.7) and the first equation of (6.3) into the third equation of (6.3), and recalling that $\beta x^* = \frac{d_3}{\int_0^\infty k(\tau)\Gamma_1(\tau)\Gamma_2(\tau,z^*)d\tau}$, we have

$$\begin{aligned} &(d_1 + \varpi + \beta v^*)(1 + \frac{\varpi}{d_3} + \frac{(d_1 + \varpi)G_4G_3}{(\varpi + d_4 + G_3)\beta x^*(d_1 + \varpi + \beta v^*)}) \\ &\quad = (d_1 + \varpi)\frac{\int_0^\infty k(\tau)\Gamma_1(\tau)\Gamma_2(\tau, z^*)e^{-\varpi\tau}d\tau}{\int_0^\infty k(\tau)\Gamma_1(\tau)\Gamma_2(\tau, z^*)d\tau}. \end{aligned} \tag{6.8}$$

It is easy to see that the modulus of left hand side of (6.8) is greater than that of the right hand side for all complex roots ϖ with non-negative real parts. Therefore, all roots of (6.3) have negative real parts. By the principle of linearized stability for the evolution equation as system (1.1), it follows that the infection steady state E^* is locally stable if $\mathcal{R}_0 > 1$. □

6.2 Global Stability of the Infection Steady State

Now, we discuss the global stability of the infection steady state by constructing a Liapunov functional.

Define a positive function

$$\alpha(\tau) = \int_\tau^\infty k(\sigma)\exp\{-\int_\tau^\sigma (d_2(s) + p(s)z^*)ds\}d\sigma. \tag{6.9}$$

Denote

$$N = \int_0^\infty k(\sigma)\exp\Big\{-\int_0^\sigma (d_2(s) + p(s)z^*)ds\Big\}d\sigma.$$

Notice that $\alpha(0) = N$, $\alpha'(\tau) = -k(\tau) + (d_2(\tau) + p(\tau)z^*)\alpha(\tau)$, and $\alpha(\tau)$ is bounded.

Theorem 6.2 *The infection steady state E^* is globally asymptotically stable if $\mathcal{R}_0 > 1$ and $c(\tau) = \epsilon p(\tau)\alpha(\tau)$ for any constant $\epsilon > 0$.*

Proof Define a function

$$g(x) = x - 1 - \ln x, \quad x \in (0, \infty). \tag{6.10}$$

Then g is nonnegative and has a unique minimum at 1 satisfying $g(1) = 0$.

Next, we define a Liapunov functional

$$H(t) = H_x(t) + H_y(t) + H_v(t) + H_z(t), \tag{6.11}$$

where,

$$\begin{aligned}
H_x(t) &= x^* g\Big(\frac{x(t)}{x^*}\Big),\\
H_y(t) &= \frac{1}{N}\int_0^\infty \alpha(\tau)y^*(\tau)g\Big(\frac{y(t,\tau)}{y^*(\tau)}\Big)d\tau,\\
H_v(t) &= \frac{1}{N}v^* g\Big(\frac{v(t)}{v^*}\Big),\\
H_v(t) &= \frac{1}{2\epsilon N}(z(t) - z^*)^2.
\end{aligned}$$

Recall that Eq. (3.1) holds at the infection steady state E^*. Calculating the time derivatives of $H_x(t)$, $H_y(t)$, $H_v(t)$ and $H_z(t)$ along (1.1), we have

$$\begin{aligned}
\frac{dH_x(t)}{dt} &= \Big(1 - \frac{x^*}{x(t)}\Big)(b - d_1x(t) - \beta x(t)v(t))\\
&= \Big(1 - \frac{x^*}{x(t)}\Big)(d_1x^* + \beta x^*v^* - d_1x(t) - \beta x(t)v(t))\\
&= -\frac{d_1}{x(t)}(x(t) - x^*)^2 + \beta x^*v^* - \beta x(t)v(t) - \beta x^*v^*\frac{x^*}{x(t)} + \beta x^*v(t),\\
\frac{dH_y(t)}{dt} &= -\frac{1}{N}\int_0^\infty \alpha(\tau)\Big(1 - \frac{y^*(\tau)}{y(t,\tau)}\Big)\Big(\frac{\partial y(t,\tau)}{\partial\tau} + d_2(\tau)y(t,\tau) + p(\tau)y(t,\tau)z(t)\Big)d\tau\\
&= -\frac{1}{N}\alpha(\tau)y^*(\tau)\Big(\frac{y(t,\tau)}{y^*(\tau)} - 1\Big)\Big|_0^\infty\\
&\quad + \frac{1}{N}\int_0^\infty \Big(1 - \frac{y^*(\tau)}{y(t,\tau)}\Big)y(t,\tau)(-k(\tau) + p(\tau)z^*\alpha(\tau))d\tau\\
&\quad - \frac{1}{N}\int_0^\infty \alpha(\tau)y^*(\tau)d\ln\frac{y^*(\tau)}{y(t,\tau)} - \frac{1}{N}\int_0^\infty \Big(1 - \frac{y^*(\tau)}{y(t,\tau)}\Big)\alpha(\tau)p(\tau)y(t,\tau)z(t)d\tau
\end{aligned}$$

$$
\begin{aligned}
&= -\frac{1}{N}\alpha(\tau)y^*(\tau)\Big(\frac{y(t,\tau)}{y^*(\tau)} - 1 - \ln\frac{y(t,\tau)}{y^*(\tau)}\Big)\Big|_0^\infty - \frac{1}{N}\int_0^\infty k(\tau)y^*(\tau)g\big(\frac{y(t,\tau)}{y^*(\tau)}\big)d\tau\\
&\quad -\frac{1}{N}\int_0^\infty p(\tau)\alpha(\tau)\Big(y(t,\tau)-y^*(\tau)\Big)(z(t)-z^*)d\tau\\
&= -\frac{1}{N}\alpha(\tau)y^*(\tau)\Big(\frac{y(t,\tau)}{y^*(\tau)} - 1 - \ln\frac{y(t,\tau)}{y^*(\tau)}\Big)\Big|_{\tau=\infty} + \beta x(t)v(t) - \beta x^*v^*\\
&\quad -\beta x^*v^*\ln\frac{x(t)v(t)}{x^*v^*} - \frac{1}{N}\int_0^\infty k(\tau)y^*(\tau)g\big(\frac{y(t,\tau)}{y^*(\tau)}\big)d\tau\\
&\quad -\frac{1}{N}\int_0^\infty p(\tau)\alpha(\tau)\Big(y(t,\tau)-y^*(\tau)\Big)(z(t)-z^*)d\tau\\
\frac{dH_v(t)}{dt} &= \frac{1}{N}\Big(1-\frac{v^*}{v(t)}\Big)\Big(\int_0^\infty k(\tau)y(t,\tau)d\tau - d_3v(t)\Big)\\
&= \frac{1}{N}\int_0^\infty k(\tau)y(t,\tau)d\tau - \frac{v^*}{Nv(t)}\int_0^\infty k(\tau)y(t,\tau)d\tau\\
&\quad -\frac{v(t)}{Nv^*}\int_0^\infty k(\tau)y^*(\tau)d\tau + \frac{1}{N}\int_0^\infty k(\tau)y^*(\tau)d\tau,
\end{aligned}
$$

and

$$
\begin{aligned}
\frac{dH_z(t)}{dt} &= \frac{1}{\epsilon N}(z(t)-z^*)\Big(\int_0^\infty c(\tau)y(t,\tau)d\tau - d_4z(t)\Big)\\
&= \frac{1}{\epsilon N}(z(t)-z^*)\Big(\int_0^\infty c(\tau)(y(t,\tau)-y^*(\tau))d\tau - d_4(z(t)-z^*)\Big)\\
&= \frac{1}{N}\int_0^\infty p(\tau)\alpha(\tau)(y(t,\tau)-y^*(\tau))(z(t)-z^*)d\tau - d_4\frac{1}{\epsilon N}(z(t)-z^*)^2.
\end{aligned}
$$

By (3.3), it follows that

$$
\frac{1}{N}\int_0^\infty k(\tau)y^*(\tau)d\tau = \beta x^*v^*.
$$

In addition,

$$
\ln\frac{x(t)v(t)}{x^*v^*} + \ln\frac{y^*(\tau)}{y(t,\tau)} = \ln\frac{x(t)}{x^*} + \ln\frac{v(t)y^*(\tau)}{v^*y(t,\tau)}
$$

holds. Subsequently,

$$
\begin{aligned}
\frac{dH(t)}{dt} &= -\frac{d_1}{x(t)}(x(t)-x^*)^2 - \beta x^*v^*g\Big(\frac{x^*}{x(t)}\Big)\\
&\quad -\frac{1}{N}\int_0^\infty k(\tau)y^*(\tau)g\Big(\frac{v^*y(t,\tau)}{v(t)y^*(\tau)}\Big)d\tau - d_4\frac{1}{\epsilon N}(z(t)-z^*)^2 \le 0,
\end{aligned}
$$

the equality holds if and only if

$$
x(t) = x^*,\ \ z(t) = z^*,\ \ \frac{v^*y(t,\tau)}{v(t)y^*(\tau)} = 1. \tag{6.12}
$$

$x(t) = x^*$ implies that $\frac{dx(t)}{dt} = 0$. Hence,

$$
\begin{aligned}
0 &= b - d_1x^* - \beta x^*v(t)\\
&= \beta x^*(v^* - v(t)).
\end{aligned}
$$

Since $x^* \neq 0$, it is obvious to obtain $v(t) = v^*$. Thus, $y(t, \tau) = y^*(\tau)$. Therefore, the largest invariant set that (6.12) holds includes only the infection steady state. This completes the proof. □

7 Numerical Simulations

In this section, we perform some numerical simulations to illustrate the theoretical results obtained above. It was shown that the solutions of system (1.1) tend to the infection-free steady state when the basic reproduction number $\mathcal{R}_0 < 1$ and tend to the infection steady state when $\mathcal{R}_0 > 1$. The stability of the steady states are also confirmed by numerical simulations. In addition, simulation results of the age-structured model and the non-age-structured model are compared.

First of all, we fix the values of some parameters based on the estimated values from the references about hepatitis B virus (HBV) [22,25,27] as follows: $b = 252666$, $d_1 = 0.00379$, $\beta = 0.00018$, $d_3 = 0.67$, $d_4 = 0.05$. We compare two different cases in Figs. 1, 2 and 3.

Case 1: We consider the model in a constant environment. This indicates that the values for the death rate of infected cells, the rate that CTL kill infected cells, the rate that infected cells produce new virus and the CTL proliferate rate are all constants: $d_2(\tau) = 0.01$, $p(\tau) = 0.01$, $k(\tau) = 0.001$ and $c(\tau) = 0.001$.

Case 2: The parameters $d_2(\tau)$, $p(\tau)$, $k(\tau)$ and $c(\tau)$ are infection-age dependent with the following forms:

$$d_2(\tau) = \begin{cases} 0.11 + 0.1\cos\frac{\pi\tau}{50}, & \tau \leq 100, \\ 0.21, & \tau > 100. \end{cases} \tag{7.1}$$

$$p_2(\tau) = \begin{cases} 0.11 + 0.1\cos\frac{\pi\tau}{50}, & \tau \leq 100, \\ 0.21, & \tau > 100. \end{cases} \tag{7.2}$$

$$k(\tau) = \begin{cases} 0.001 + 0.01\sin\frac{\pi\tau}{100}, & \tau \leq 100, \\ 0, & \tau > 100. \end{cases} \tag{7.3}$$

$$c(\tau) = \begin{cases} 0.001 + 0.01\sin\frac{\pi\tau}{100}, & \tau \leq 100, \\ 0, & \tau > 100. \end{cases} \tag{7.4}$$

It is noticed that the number of infected cells in Fig. 1a is larger than that in Fig. 1b, and it approaches the steady state faster. Similar conclusion can be observed in Fig. 2, which shows the number of infected cells at different ages. It implies that the number of infected cells reduces as the infection-age increases. The viral load in Fig. 3a is larger than that in Fig. 3b at the same time. That means that the infection-age would significantly affect the viral load in the host.

In Fig. 4, we perform the numerical simulations to show the global stability of steady states. Figure 4a illustrates the global stability of the infection-free steady state when $\mathcal{R}_0 = 0.8646 < 1$. Meanwhile, Fig. 4b presents the global stability of the infection steady state when $\mathcal{R}_0 = 162.8189 > 1$.

We are more interested in the stability of infection-free steady state when the virus infection dynamics are concerned. In Theorems 4.1 and 4.2, we obtained that the infection-free steady state is global stability when $\mathcal{R}_0 < 1$ and unstable when $\mathcal{R}_0 > 1$. Figure 5a depicts the age distribution of infected cells when $\mathcal{R}_0 = 0.8646 < 1$, and Fig. 5b depicts the viral load when $\mathcal{R}_0 < 1$.

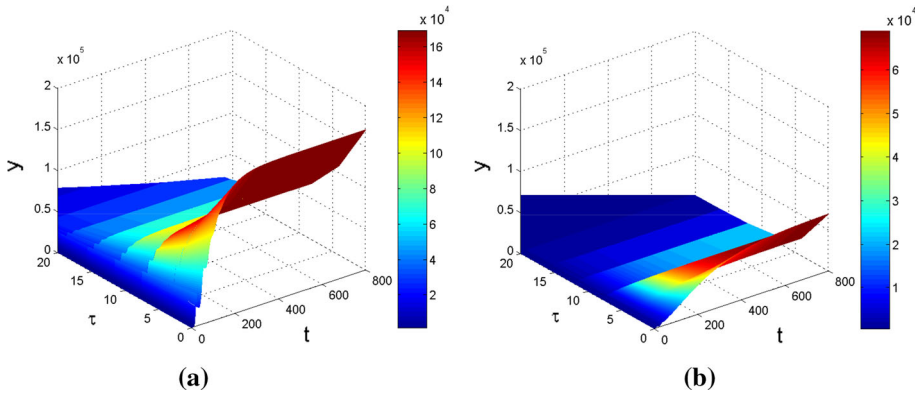

Fig. 1 **a** The age distribution of infected cells in Case 1; **b** the age distribution of infected cells in Case 2

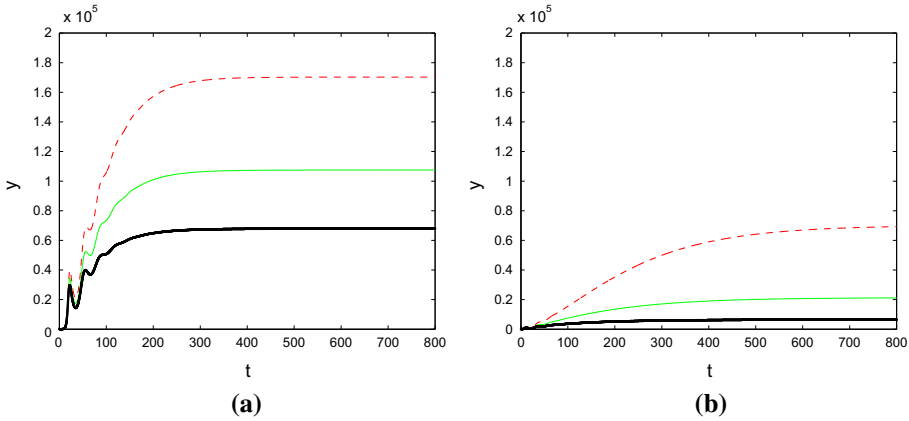

Fig. 2 **a** Time series of infected cells in Case 1; **b** time series of infected cells in Case 2. Red dotted lines represent the number of the new infected cells, that is the infected sells with 0 age. The thin green lines and thick black lines represent older infected cells, respectively (Color figure online)

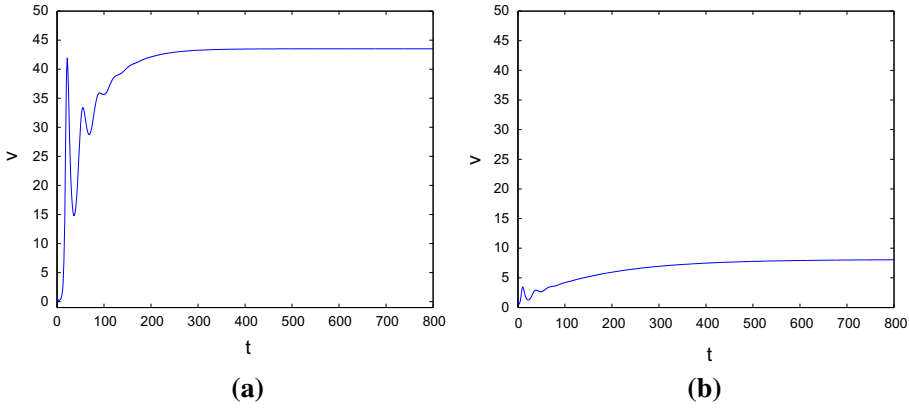

Fig. 3 **a** Viral load as time changes in Case 1; **b** viral load as time changes in Case 2

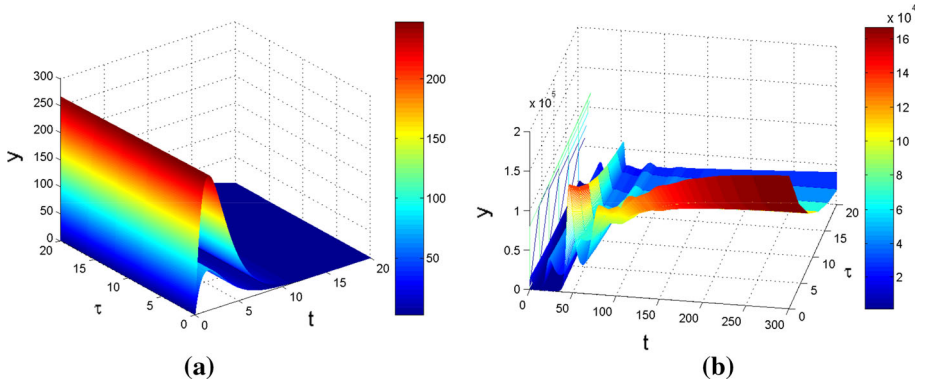

Fig. 4 **a** The global stability of the infection-free steady state when $\mathcal{R}_0 = 0.8646 < 1$; **b** the global stability of the infection steady state when $\mathcal{R}_0 = 162.8189 > 1$

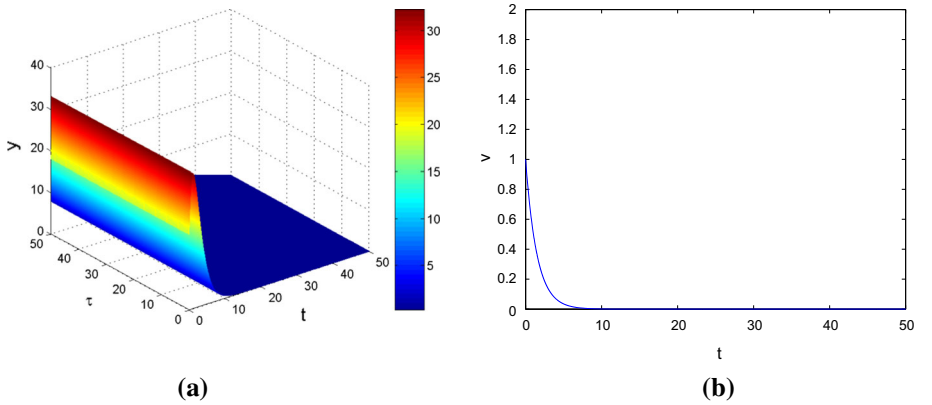

Fig. 5 **a** The age distribution of infected cells when $\mathcal{R}_0 = 0.8646 < 1$; **b** viral load when $\mathcal{R}_0 = 0.8646 < 1$

8 Discussion

The interaction between pathogens and the immune system is a very broad and diverse topic [36]. The CTL response against viral infections has been investigated intensively through mathematical models and numerical approaches.

In this paper, we have considered an infection-age dependent model of viral infections with immune system. The basic reproduction number $\mathcal{R}_0$ and the threshold for the existence of the steady states are obtained. Local stability of the steady states was established by linearizing the system. Furthermore, we obtained global stability of the infection-free steady state by investigating a renewal integral equation under the assumption $\mathcal{R}_0 < 1$. Meanwhile, sufficient conditions for the global stability of the infection steady state were obtained by constructing a Liapunov functional.

The age distribution of the infected cells and the viral load in a constant environment and an infection-age dependent environment were compared by numerical simulations. The simulation results show that although the incorporation of infection-age may not change the dynamics of the model, the distribution of the infected cells and the viral load have a lot of varieties. The number of infected cells would decrease with age, and the viral load would

also decrease as $d_2(\tau)$, $p(\tau)$, $k(\tau)$ and $c(\tau)$ depend on infection-age. Therefore, it is more realistic to incorporate the age of infection in the virus dynamics for better understanding of the interactions between viruses and the immune system.

Many results about immune system dynamics were obtained to understand the importance of CTL responses (we refer to [36–39]). In these studies, the CTL response can be described under various assumptions. Some of researchers assumed that the rate of CTL expansion saturates as the number of CTL grows to relatively high numbers [39]. Some assumed that the rate of CTL expansion is simply proportional to the amount of antigen, but not to the number of CTL [37]. Moreover, modeling lytic and nonlytic CTL responses ([37]) or modeling competition between CTL and antibody responses ([38]) is also important and interesting. It remains challenging to study age-structured models between the viruses and the immune system when the above assumptions are taken into consideration.

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