Research article

Global dynamics of an age-structured within-host viral infection model with cell-to-cell transmission and general humoral immunity response

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Abstract: In this paper, an age-structured within-host viral infection model with cell-to-cell transmission and general humoral immune response is investigated. We give a rigorous mathematical analysis on some necessary technical materials, including the relative compactness and persistence of the solution semiflow, and existence of a global attractor. By subtle construction and estimates of a Lyapunov functional, we show that the global dynamics is determined by two sharp thresholds, namely, basic reproduction number $\Re_0$ and immune-response reproduction number $\Re_1$. When $\Re_0 < 1$, the virus-free steady state is globally asymptotically stable, which means that the viruses are cleared and immune-response is not active; when $\Re_1 < 1 < \Re_0$, the immune-inactivated infection steady state exists and is globally asymptotically stable; and when $\Re_1 > 1$, which implies that $\Re_0 > 1$, the immune-activated infection steady state exists and is globally asymptotically stable. Numerical simulations are given to support our theoretical results.

Keywords: age structure; viral infection model; immune response; stability; Lyapunov functional

1. Introduction

Since a basic within-host viral infection model introduced by Nowak et al. [1], the dynamics of viral infection such as hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV) infection models have been widely studied by incorporating various biological factors. Consider age as a continuous variable, writing the production rate of viral particles and the death rate of productively infected cells as two continuous functions of age, Nelson et al. [2] studied a HIV

infection model with infection-age, the model is described as follows:

$$
\begin{cases}
\dfrac{dT(t)}{dt} = \Lambda - \mu_1 T(t) - \beta T(t)V(t), \\[2mm]
\left(\dfrac{\partial}{\partial t} + \dfrac{\partial}{\partial a}\right)i(t,a) = -\delta(a)i(t,a), \\[2mm]
\dfrac{dV(t)}{dt} = \displaystyle\int_0^\infty p(a)i(t,a)da - \mu_2 V(t)
\end{cases}
\tag{1.1}
$$

with the boundary and initial condition

$$
\begin{cases}
i(t,0) = \beta T(t)V(t), \\[2mm]
T(0) = T_0 > 0, \quad V(0) = V_0 > 0 \ \text{ and } \ i(0,a) = i_0(a) \in L_+^1(0,\infty),
\end{cases}
\tag{1.2}
$$

where $T(t)$ and $V(t)$ denote the densities of uninfected target cell and free viruses at time t, respectively; $i(t,a)$ denote the density of infected cells at time t with infection-age a. The parameters of model (1.1) are biologically explained in Table 1.

Table 1. Parameters and their biological meaning in model (1.1). All these parameters are assumed to be positive.

Parameter	Interpretation
Λ	Constant recruitment rate;
β	Virus infection rate;
μ_1	Mortality rate of uninfected target cell;
μ_2	Mortality rate of free viruses;
$\delta(a)$	Mortality rate of infected cell with age a;
$p(a)$	Production rate of viral particles.

Nelson et al. analyzed the local stability of the model by evaluating eigenvalues and its related characteristic equation. In [3], Rong et al. extended the model with combination antiretroviral therapy, and analyzed the local stability of the model. Huang et al. [4] have been further investigated the global stability of the model (1.1) with (1.2) by using Lyapunov direct method and LaSalle invariance principle. For some recent works on viral models with age structure, we refer readers to the papers [5–13].

Recently, experimental work [14] shows that direct cell-to-cell transmission also contributes to the viral persistence. In a more recent work [15], the authors reveals that environmental restrictions limit infection by cell-free virions but promote cell-associated HIV-1 transmission. In fact, cell-to-cell transmission could be also found in other viral infection for human and animals. For example, hepatitis C virus [16]; bovine viral diarrhea virus [17]; vaccinia virus [18]. Due to this fact, Lai and Zou [19] formulated a HIV-1 viral model with direct cell-to-cell transmission and studied the global threshold dynamics. Yang et al. [20] studied a cell-to-cell virus model with three distributed delays, they also obtained the global stability of each equilibrium for the model. Wang et al. [21] investigated an age-structured HIV model with virus-to-cell infection and cell-to-cell transmission, the model takes the

following form:

$$
\begin{cases}
\dfrac{dT(t)}{dt} = \Lambda - \mu_1 T(t) - \beta T(t)V(t) - \displaystyle\int_0^\infty k(a)T(t)i(t,a)\mathrm{d}a, \\[2mm]
\left(\dfrac{\partial}{\partial t} + \dfrac{\partial}{\partial a}\right)i(t,a) = -\delta(a)i(t,a), \\[2mm]
\dfrac{dV(t)}{dt} = \displaystyle\int_0^\infty p(a)i(t,a)\mathrm{d}a - \mu_2 V(t),
\end{cases}
\tag{1.3}
$$

with the boundary and initial condition

$$
\begin{cases}
i(t,0) = \beta T(t)V(t) + \displaystyle\int_0^\infty k(a)T(t)i(t,a)\mathrm{d}a, \\[2mm]
T(0) = T_0 > 0, \quad V(0) = V_0 > 0 \ \text{ and } \ i(0,a) = i_0(a) \in L^1_+(0,\infty).
\end{cases}
\tag{1.4}
$$

By constructing suitable Lyapunov functional, Wang et al. were able to complete a global analysis for the model (1.3). In [22], Zhang and Liu studied the Hopf bifurcation of an age-structured HIV model with cell-to-cell transmission and logistic growth.

In viral infection, the host immune system play a critical part on the progress of the infection. The role of the immune system is to fight off pathogenic organisms within the host, for example, cytotoxic T lymphocyte cells (CTLs) attack infected cells, and antibody cells attack viruses (humoral immunity response). In [23], Murase et al. studied an viral infection model with humoral immunity response:

$$
\begin{cases}
\dfrac{dT(t)}{dt} = \Lambda - \mu_1 T(t) - \beta T(t)V(t), \\[2mm]
\dfrac{dI(t)}{dt} = \beta T(t)V(t) - aI(t), \\[2mm]
\dfrac{dV(t)}{dt} = arI(t) - \mu_2 V(t) - kV(t)Z(t), \\[2mm]
\dfrac{dZ(t)}{dt} = hV(t)Z(t) - \mu_3 Z(t),
\end{cases}
\tag{1.5}
$$

where $T(t)$, $I(t)$, $V(t)$ and $Z(t)$ denote the densities of uninfected cells, infected cells, free viruses and humoral immunity response released by B cells, respectively; the viruses are removed at rate kZ by the humoral immunity response; the humoral immunity response are activated in proportion to $hV(t)$ and removed at rate μ_3. The global dynamics of model (1.5) were obtain in [23]. Consider the delay between viral entry into a cell and the maturation delay of the newly produced viruses, Wang et al. [24] studied a virus model with two delays and humoral immunity response. They established the global dynamics based on two threshold parameters, and they found that the three equilibria are globally asymptotically stable under some conditions. For another delay, which is the time that antigenic stimulation needs for generating immunity response, Wang et al. [25] considered another virus model with delay and humoral immunity response, they found that this delay could lead to a Hopf bifurcation at the infected equilibrium with immunity. In [26], Kajiwara et al. proposed a age-structured viral infection model contains humoral immunity response and the effect of absorption of pathogens into uninfected cells, they also proved the global stability of each equilibria. Duan and Yuan [30] considered an infection-age viral model with saturation humoral immune response, the local and global

stability of this model are obtained. Additionally, for the virus model with CTL immune response, we refer readers to the papers [27–29, 31–34] and the reference therein.

Based on the above facts, we propose an age-structured viral infection model with cell-to-cell transmission and general humoral immune response in this paper. Precisely, we study the following model:

$$
\begin{cases}
\dfrac{\mathrm{d}T(t)}{\mathrm{d}t} = \Lambda - \mu_1 T(t) - \beta T(t)V(t) - \displaystyle\int_0^\infty k(a)T(t)i(t,a)\mathrm{d}a, \\[2mm]
\left(\dfrac{\partial}{\partial t} + \dfrac{\partial}{\partial a}\right)i(t,a) = -\delta(a)i(t,a), \\[2mm]
\dfrac{\mathrm{d}V(t)}{\mathrm{d}t} = \displaystyle\int_0^\infty p(a)i(t,a)\mathrm{d}a - \mu_2 V(t) - qV(t)f(Z(t)), \\[2mm]
\dfrac{\mathrm{d}Z(t)}{\mathrm{d}t} = cV(t)f(Z(t)) - \mu_3 Z(t)
\end{cases}
\tag{1.6}
$$

with the boundary and initial condition

$$
\begin{cases}
i(t,0) = \beta T(t)V(t) + \displaystyle\int_0^\infty k(a)T(t)i(t,a)\mathrm{d}a, \\[2mm]
T(0) = T_0 > 0, \quad V(0) = V_0 > 0, \quad Z(0) = Z_0 > 0 \quad \text{and} \quad i(0,a) = i_0(a) \in L_+^1(0,\infty),
\end{cases}
\tag{1.7}
$$

where L_+^1 is the set of integrable functions from $(0,+\infty)$ into $[0,+\infty)$. $T(t)$, $V(t)$ and $Z(t)$ denote the densities of uninfected target cell, free viruses and antibody responses released from B cells at time t, respectively; $i(t,a)$ denotes the density of infected cells at time t with infection-age a; $k(a)$ denote the infection rate of productively infected cells with age a; $qV(t)f(Z(t))$ is the neutralization rate of viruses and $cV(t)f(Z(t))$ is the activation rate of antibody responses. The antibody responses vanish at rate μ_3. Other parameters of model (1.6) have the same biological meaning in the Table 1.

We made the following assumption on parameters and nonlinear function $f : \mathbb{R} \to \mathbb{R}$.

(A1) $k(a)$, $\delta(a)$, $\theta(a)$, $p(a)$, $c(a) \in L_+^\infty(0,\infty)$, with respective essential supremums $\bar{k}$, $\bar{\delta}$, $\bar{\theta}$, $\bar{p}$, $\bar{c}$ and respective essential infimums $\tilde{k}$, $\tilde{\delta}$, $\tilde{\theta}$, $\tilde{p}$, $\tilde{c}$.

(A2) $f(Z) \geqslant 0$ for $Z \geqslant 0$, $f(Z) = 0$ if and only if $Z = 0$; f is Lipschitz continuous on $\mathbb{R}_+$.

(A3) $f(Z)$ is differentiable such that $f'(Z) > 0$ and $f(Z)$ is concave down on $\mathbb{R}_+$.

Here are some examples on function $f(Z)$ satisfies (A2) and (A3):

(i) $f(Z(t)) = Z(t)$ which is the bilinear function (see [23]);

(ii) Saturation immune response function $f(Z(t)) = \frac{Z(t)}{h+Z(t)}$ (see [30]).

The paper is organized as follows. In Section 2, we introduce the existence and uniqueness of the solutions to system (1.6), the steady state and reproduction numbers are also determined in this section; In Section 3, we show that system (1.6) is asymptotically smooth; Section 4 is devoted to proving the local stability of each steady state; uniform persistence and global stability of each steady state is considered in Section 5; We perform a numerical simulation of a special case in Section 6; Section 7 provide some brief discussions.

2. Preliminaries

In this section, we show the existence and uniqueness of the solutions to system (1.6) by a standard method [36] (see also [37, 38]), which is to rewrite system (1.6) as an abstract Cauchy problem.

2.1. Integrated solution

For convenience, we first denote the following notations.

$$\Gamma(a) = e^{-\int_0^a \delta(\tau)d\tau}, \ \ \mathcal{P} = \int_0^\infty p(a)\Gamma(a)da, \ \ \mathcal{K} = \int_0^\infty k(a)\Gamma(a)da.$$

It is easy to see that

$$\Gamma(0) = 1 \ \ \text{and} \ \ \Gamma'(a) = -\delta(a)\Gamma(a).$$

Set the following spaces:

$$\mathcal{X} := \mathbb{R} \times L^1(\mathbb{R}_+, \mathbb{R}) \times \mathbb{R} \times \mathbb{R}, \ \mathcal{X}_+ := \mathbb{R}_+ \times L^1_+(\mathbb{R}_+, \mathbb{R}) \times \mathbb{R}_+ \times \mathbb{R}_+,$$

with the following norm

$$\|\varphi(\cdot), \phi_1, \phi_2, \phi_3\|_\mathcal{X} = \|\varphi\|_{L^1} + |\phi_1| + |\phi_2| + |\phi_3|,$$

Furthermore, define

$$\mathcal{X}_0 := \{0\} \times L^1(\mathbb{R}_+, \mathbb{R}) \times \mathbb{R} \times \mathbb{R} \times \mathbb{R}, \ \mathcal{X}_{0+} := \{0\} \times L^1_+(\mathbb{R}_+, \mathbb{R}) \times \mathbb{R} \times \mathbb{R}_+ \times \mathbb{R}_+,$$

Let $A : \text{Dom}(A) \subset \mathcal{X} \to \mathcal{X}$ be the following linear operator:

$$A \begin{pmatrix} \begin{pmatrix} 0 \\ \varphi \end{pmatrix} \\ \phi_1 \\ \phi_2 \\ \phi_3 \end{pmatrix} = \begin{pmatrix} \begin{pmatrix} -\varphi(0) \\ -\varphi' - \delta\varphi \end{pmatrix} \\ -\mu_1\phi_1 \\ -\mu_2\phi_2 \\ -\mu_3\phi_3 \end{pmatrix} \tag{2.1}$$

with $\text{Dom}(A) = \mathbb{R} \times \{0\} \times W^{1,1}(0, +\infty) \times \mathbb{R} \times \mathbb{R}$. In the following, we apply the method in [36] since $\overline{\text{Dom}(A)} = \mathcal{X}_0$ is not dense in $\mathcal{X}$. Consider the nonlinear map $F : \text{Dom}(A) \to \mathcal{X}$ defined by

$$F \begin{pmatrix} \begin{pmatrix} 0 \\ \varphi \end{pmatrix} \\ \phi_1 \\ \phi_2 \\ \phi_3 \end{pmatrix} = \begin{pmatrix} \begin{pmatrix} \beta\phi_1\phi_2 + \int_0^\infty k(a)\phi_1\varphi(a)da \\ 0 \end{pmatrix} \\ \Lambda - \beta\phi_1\phi_2 - \int_0^\infty k(a)\phi_1\varphi(a)da \\ \int_0^\infty p(a)\varphi(a)da - q\phi_2 f(\phi_3) \\ c\phi_2 f(\phi_3) \end{pmatrix}.$$

One can see that F is Lipschitz continuous on bounded sets. Let

$$u(t) = \left(T(t), \begin{pmatrix} 0 \\ i(t, \cdot) \end{pmatrix}, V(t), Z(t)\right)^{\mathrm{T}},$$

where T represents transposition. Then we can rewrite system (1.6) as the following abstract Cauchy problem:

$$\begin{cases} \dfrac{\mathrm{d}u(t)}{\mathrm{d}t} = Au(t) + F(u(t)), & t \geqslant 0, \\ u(0) = u_0 \in X_{0+}. \end{cases} \tag{2.2}$$

In order to use the method in [36], we need to show that A is a Hille-Yosida operator. Denote $\rho(A)$ be the resolvent set of A. The definition of Hille-Yosida operator is:

Definition 2.1. *(See [36, Definition 2.4.1]) A linear operator $A : Dom(A) \subset X \to X$ on a Banach space $(X, \|\cdot\|)$ (densely defined or not) is called a Hille-Yosida operator if there exist real constants $M \geqslant 1$, and $\omega \in \mathbb{R}$, such that $(\omega, +\infty) \subseteq \rho(A)$, and*

$$\|(\lambda - A)^{-n}\| \leqslant \frac{M}{(\lambda - \omega)^n}, \quad \text{for } n \in \mathbb{N}_+ \text{ and all } \lambda > \omega.$$

Now, we prove the following lemma.

Lemma 2.1. *The operator A defined in (2.1) is a Hille-Yosida operator.*

Proof. Let

$$(\lambda \mathbb{I} - A)^{-1} \begin{pmatrix} \begin{pmatrix} \hat{\varphi}_0 \\ \hat{\varphi}(a) \end{pmatrix} \\ \hat{\phi}_1 \\ \hat{\phi}_2 \\ \hat{\phi}_3 \end{pmatrix} = \begin{pmatrix} \begin{pmatrix} 0 \\ \varphi \end{pmatrix} \\ \phi_1 \\ \phi_2 \\ \phi_3 \end{pmatrix},$$

by some simple calculations, we have

$$\phi_1 = \frac{\hat{\phi}_1}{\lambda + \mu_1}, \quad \phi_2 = \frac{\hat{\phi}_2}{\lambda + \mu_2}, \quad \phi_3 = \frac{\hat{\phi}_3}{\lambda + \mu_3}$$

and

$$\varphi(a) = \hat{\varphi}_0 e^{-\int_0^a (\lambda + \delta(s))\mathrm{d}s} + \int_0^\infty \hat{\varphi}(\tau) e^{-\int_\tau^a (\lambda + \delta(s))\mathrm{d}s} \mathrm{d}\tau.$$

Denote $\zeta = \left(\begin{pmatrix} \hat{\varphi}_0 \\ \hat{\varphi}(a) \end{pmatrix}, \hat{\phi}_1, \hat{\phi}_2, \hat{\phi}_3\right)^{\mathrm{T}}$, then

$$\left\|(\lambda \mathbb{I} - A)^{-1} \zeta\right\|_X = |0| + \int_0^\infty \varphi(a)\mathrm{d}a + |\phi_1| + |\phi_2| + |\phi_3|$$

$$= \int_0^\infty \varphi(a)\mathrm{d}a + \frac{|\hat{\phi}_1|}{|\lambda + \mu_1|} + \frac{|\hat{\phi}_2|}{|\lambda + \mu_2|} + \frac{|\hat{\phi}_3|}{|\lambda + \mu_3|}$$

$$\leqslant \frac{|\hat{\varphi}_0|}{|\lambda + \mu|} + \frac{\|\hat{\varphi}(a)\|_{L_1}}{|\lambda + \mu|} + \frac{|\hat{\phi}_1|}{|\lambda + \mu|} + \frac{|\hat{\phi}_2|}{|\lambda + \mu|} + \frac{|\hat{\phi}_3|}{|\lambda + \mu|}$$

$$= \frac{1}{\lambda + \mu} \|\zeta\|_X .$$

where $\mu = \min\{\mu_1, \mu_2, \mu_3, \tilde{\delta}\}$. By the Definition 2.1, the operator A is a Hille-Yosida operator. This ends the proof. $\qquad\square$

Let $X_0 = \left(T_0, \begin{pmatrix} 0 \\ i_0 \end{pmatrix}, V_0, Z_0 \right)^{\mathrm{T}} \in X_{0+}$, by using [36, Theorem 5.2.7] (see also in [37, 39]), we have the following theorem.

Theorem 2.1. *There exists a uniquely determined semi-flow $\{U(t)\}_{t \geqslant 0}$ on X_{0+} such that for each X_0, there exists a unique continuous map $U \in C([0, +\infty), X_{0+})$ which is an integrated solution of Cauchy problem (2.2), that is*

$$\begin{cases} \displaystyle\int_0^t U(s)X_0 ds \in \mathrm{Dom}(A), \quad \forall t \geqslant 0, \\ \displaystyle U(t)X_0 = X_0 + A \int_0^t U(s)X_0 ds + \int_0^\infty F(U(s)X_0)ds, \quad \forall t \geqslant 0. \end{cases} \tag{2.3}$$

Let

$$\Omega = \left\{ (T, (0, i(\cdot)), V, Z) \in X_{0+} \ \middle| \ T(t) + \int_0^{+\infty} i(t, a) \mathrm{d}a \leqslant \frac{\Lambda}{\mu_0}, \ V(t) + \frac{q}{c} Z(t) \leqslant \frac{\Lambda \bar{p}}{\mu_0 \hat{\mu}} \right\}, \tag{2.4}$$

where $\mu_0 = \min\{\mu_1, \tilde{\delta}\}$ and $\hat{\mu} = \min\{\mu_2, \mu_3\}$. We show that Ω is a positively invariant set under semi-flow $\{U(t)\}_{t \geqslant 0}$.

Theorem 2.2. Ω *is a positively invariant set under semi-flow $\{U(t)\}_{t \geqslant 0}$. Moreover the semi-flow $\{U(t)\}_{t \geqslant 0}$ is point dissipative and Ω attracts all positive solutions of (2.2) in X_{0+}.*

Proof. Integrating the second equation of (1.6) along the characteristic line $t - a = $ constant, yields

$$i(t, a) = \begin{cases} i(t - a, 0)\Gamma(a), \quad t > a > 0, \\ i_0(a - t)\dfrac{\Gamma(a)}{\Gamma(a - t)}, \quad a > t > 0. \end{cases} \tag{2.5}$$

Then

$$\begin{aligned} \int_0^\infty i(t, a)\mathrm{d}a &= \int_0^t i(t - a, 0)\Gamma(a)\mathrm{d}a + \int_t^\infty i_0(a - t)\frac{\Gamma(a)}{\Gamma(a - t)}\mathrm{d}a \\ &= \int_0^t i(\sigma, 0)\Gamma(t - \sigma)\mathrm{d}\sigma + \int_0^\infty i_0(a)\frac{\Gamma(t + a)}{\Gamma(a)}\mathrm{d}a. \end{aligned}$$

Note that $\Gamma(0) = 1$ and $\Gamma'(a) = -\delta(a)\Gamma(a)$, thus

$$\begin{aligned} \frac{\mathrm{d}}{\mathrm{d}t} \int_0^\infty i(t, a)\mathrm{d}a &= \frac{\partial}{\partial t} \int_0^t i(\sigma, 0)\Gamma(t - \sigma)\mathrm{d}\sigma + \frac{\mathrm{d}}{\mathrm{d}t} \int_0^\infty i_0(a)\frac{\Gamma(t + a)}{\Gamma(a)}\mathrm{d}a \\ &= i(t, 0) - \int_0^\infty \delta(a)i(t, a)\mathrm{d}a. \end{aligned}$$

One has that

$$\frac{\mathrm{d}}{\mathrm{d}t}\left(T(t) + \int_0^{+\infty} i(t,a)\mathrm{d}a\right) = \Lambda - \mu_1 T(t) - \int_0^\infty \delta(a)i(t,a)\mathrm{d}a$$

$$\leqslant \Lambda - \mu_0\left(T(t) - \int_0^\infty \delta(a)i(t,a)\mathrm{d}a\right).$$

We have

$$\limsup_{t\to\infty}\left\{T(t) + \int_0^\infty i(t,a)\mathrm{d}a\right\} \leqslant \frac{\Lambda}{\mu_0}, \quad t \geqslant 0.$$

From the third and forth equations of (1.6), it is easy to check

$$\limsup_{t\to\infty}\left(V(t) + \frac{q}{c}Z(t)\right) \leqslant \frac{\Lambda\bar{p}}{\mu_0\hat{\mu}}, \quad t \geqslant 0.$$

Hence

$$\|U(t)X_0\|_{\mathcal{X}_+} \leqslant \Pi,$$

where $\Pi = \frac{\Lambda}{\mu_0}\left(1 + \frac{\bar{p}}{\hat{\mu}} + \frac{c\bar{P}}{q\hat{\mu}}\right)$. Therefore, for any solution of (2.2) satisfying $X_0 \in \Omega$ and $U(t)X_0 \in \Omega$ for all $t \geqslant 0$, Ω is a positively invariant set under semi-flow $\{U(t)\}_{t\geqslant 0}$. Moreover the semi-flow $\{U(t)\}_{t\geqslant 0}$ is point dissipative and Ω attracts all positive solutions of (2.2) in $\mathcal{X}_{0+}$. $\square$

2.2. Steady state

In this subsection, we concern with the existence of steady states for system (1.6). Obviously, the system (1.6) always has a virus-free steady state $E_0 = (T_0, 0, 0, 0) = (\frac{\Lambda}{\mu_1}, 0, 0, 0)$. E^0 is the unique equilibrium if $\mathcal{R}_0 \leqslant 1$, where $\mathcal{R}_0 = \frac{\beta T_0 \mathcal{P}}{\mu_2} + T_0\mathcal{K}$ is the basic reproduction number of system (1.6). If $\mathcal{R}_0 > 1$, there exists an immune-inactivated infection steady state $E_1 = (T_1^*, i_1^*(a), V_1^*, 0)$, which is the same situation in [21], that is,

$$T_1^* = \frac{T_0}{\mathcal{R}_0}, \quad i_1^*(a) = \Lambda\left(1 - \frac{1}{\mathcal{R}_0}\right)\Gamma(a), \quad V_1^* = \frac{1}{\mu_2}\int_0^\infty p(a)i_1^*(a)\mathrm{d}a. \tag{2.6}$$

There also exists another immune-activated infection steady state $E_2 = (T_2^*, i_2^*(a), V_2^*, Z_2^*)$, which is satisfies

$$\begin{cases} \Lambda - \mu_1 T_2^* = i_2^*(0) = \beta T_2^* V_2^* + \int_0^\infty k(a)T_2^* i_2^*(a)\mathrm{d}a, \\[2mm] \dfrac{\mathrm{d}i_2^*(a)}{\mathrm{d}a} = -\delta(a)i_2^*(a), \\[2mm] \displaystyle\int_0^\infty p(a)i_2^*(a)\mathrm{d}a - \varpi(Z_2^*)V_2^* = 0, \\[2mm] cV_2^* f(Z_2^*) - \mu_3 Z_2^* = 0, \end{cases} \tag{2.7}$$

where

$$\varpi(Z_2^*) = \mu_2 + qf(Z_2^*).$$

By some calculations, we have

$$i_2^*(a) = i_2^*(0)\Gamma(a). \tag{2.8}$$

From the third equation of (2.7), yields

$$V_2^* = \frac{\int_0^\infty p(a)i_2^*(a)\mathrm{d}a}{\varpi(Z_2^*)}. \tag{2.9}$$

Substituting (2.8) and (2.9) into the first equation of (2.7) one has that

$$T_2^* = \frac{\varpi(Z_2^*)}{\beta\mathcal{P} + \varpi(Z_2^*)\mathcal{K}} \tag{2.10}$$

and

$$i_2^*(0) = \Lambda - \mu_1 T_2^* = \Lambda - \frac{\varpi(Z_2^*)}{\beta\mathcal{P} + \varpi(Z_2^*)\mathcal{K}}. \tag{2.11}$$

In the following, we show that $Z_2^* > 0$. In fact, combining the last two equations of (2.7) give us

$$\int_0^\infty p(a)\left(\Lambda - \frac{\mu_1\varpi(Z_2^*)}{\beta\mathcal{P} + \varpi(Z_2^*)\mathcal{K}}\right)\Gamma(a)\mathrm{d}a - \frac{\mu_3 Z_2^*\varpi(Z_2^*)}{cf(Z_2^*)} = 0. \tag{2.12}$$

Denote

$$\Phi(Z^*) = \int_0^\infty p(a)\left(\Lambda - \frac{\mu_1\varpi(Z_2^*)}{\beta\mathcal{P} + \varpi(Z_2^*)\mathcal{K}}\right)\Gamma(a)\mathrm{d}a - \frac{\mu_3 Z_2^*\varpi(Z_2^*)}{cf(Z_2^*)}$$

and

$$\mathcal{R}_1 := \frac{\Lambda c\mathcal{P}f'(0)}{\mu_2\mu_3}\left(1 - \frac{1}{\mathcal{R}_0}\right).$$

Then

$$\lim_{Z_2^* \to 0} \Phi(Z_2^*) > 0 \Leftrightarrow \mathcal{R}_1 > 1.$$

It is easy to check $\frac{\mathrm{d}\Phi(Z^*)}{\mathrm{d}Z^*} < 0$ and $\lim_{Z^* \to +\infty} \Phi(Z^*) \to -\infty$. Hence, there is only one positive root for (2.12) if $\mathcal{R}_1 > 1$. By the expressions of $\mathcal{R}_0$ and $\mathcal{R}_1$, we have $\mathcal{R}_1 > 0 \Rightarrow \mathcal{R}_0 > 1$, then there is the following theorem on the existence of steady states.

Theorem 2.3. *For system (1.6), there are two threshold parameters $\mathcal{R}_0$ and $\mathcal{R}_1$ such that*

(i) *if $\mathcal{R}_0 \leq 1$, there exists only one positive steady state E_0;*

(ii) *if $\mathcal{R}_1 < 1 < \mathcal{R}_0$, there exists two positive steady states E_0 and E_1^*;*

(iii) *if $\mathcal{R}_1 > 1$, there exists three positive steady states E_0, E_1^* and E_2^*.*

The following lemma on immune-inactivated infection steady state and immune-activated infection steady state will be used in the proof of global stability.

Lemma 2.2. *The immune-inactivated infection steady state $(T_1^*, i_1^*(a), V_1^*, 0)$ satisfies*

$$\int_0^\infty \left[\frac{\beta T_1^*}{\mu_2}p(a)i_1^*(a)\left(1 - \frac{i_1^*(0)T(t)V(t)}{i(t,0)T_1^*V_1^*}\right) + T_1^*k(a)i_1^*(a)\left(1 - \frac{i_1^*(0)T(t)i(t,a)}{i_1(t,0)T_1^*i_1^*(a)}\right)\right]da = 0, \tag{2.13}$$

and immune-activated infection steady state $(T_2^*, i_2^*(a), V_2^*, Z_2^*)$ satisfies

$$\int_0^\infty \left[\frac{\beta T_2^*}{\mu_2 + qf(Z_2^*)}p(a)i_2^*(a)\left(1 - \frac{i_2^*(0)T(t)V(t)}{i(t,0)T_2^*V_2^*}\right) + T_2^*k(a)i_2^*(a)\left(1 - \frac{i_2^*(0)T(t)i(t,a)}{i_2(t,0)T_2^*i_2^*(a)}\right)\right]da = 0. \tag{2.14}$$

Proof. For the immune-inactivated infection steady state $(T_1^*, i_1^*(a), V_1^*, 0)$, it follows from the third equation of (2.6), we have

$$\int_0^\infty \frac{\beta T_1^*}{\mu_2} p(a) i_1^*(a) \frac{i_1^*(0) T(t) V(t)}{i(t, 0) T_1^* V_1^*} \mathrm{d}a = \frac{\beta i_1^*(0) T(t) V(t)}{i(t, 0) \mu_2 V_1^*} \int_0^\infty p(a) i_1^*(a) \mathrm{d}a$$

$$= \beta T(t) V(t) \frac{i^*(0)}{i(t, 0)}.$$

Recall that $i(t, 0) = \beta T(t) V(t) + \int_0^\infty k(a) T(t) i(t, a) \mathrm{d}a$ in (1.7), hence

$$\int_0^\infty \frac{\beta T_1^*}{\mu} p(a) i_1^*(a) \frac{i_1^*(0) T(t) V(t)}{i(t, 0) T_1^* V_1^*} \mathrm{d}a + \int_0^\infty T_1^* k(a) i_1^*(a) \frac{i_1^*(0) T(t) i(t, a)}{i_i(t, 0) T_1^* i_1^*(a)} \mathrm{d}a$$

$$= \beta T(t) V(t) \frac{i_1^*(0)}{i(t, 0)} + T(t) \int_0^\infty k(a) i(t, a) \mathrm{d}a \frac{i_1^*(0)}{i(t, 0)}$$

$$= i_1^*(0)$$

$$= \beta T_1^* V_1^* + \int_0^\infty k(a) T_1^* i_1^*(a) \mathrm{d}a,$$

Thus, (2.13) holds true. The proof of Eq (2.14) is similar to (2.13), so we omitted it. This ends the proof. □

3. Asymptotically smooth

In this section, we show that the semi-flow $\{U(t)\}_{t \geqslant 0}$ is asymptotically smooth. Since the state space $\mathcal{X}_{0+}$ is the infinite dimensional Banach space, we need the semi-flow $\{U(t)\}_{t \geqslant 0}$ is asymptotically smooth to proof the global stability of each steady states. Rewrite $U := \Phi + \Psi$, where

$$\Phi(t) X_0 := (0, \varpi_1(\cdot, t), 0, 0), \tag{3.1}$$

$$\Psi(t) X_0 := (T(t), \varpi_2(\cdot, t), V(t), Z(t)), \tag{3.2}$$

with

$$\varpi_1(\cdot, t) = \begin{cases} 0, & t > a \geqslant 0, \\ i(t, a), & a \geqslant t \geqslant 0, \end{cases} \quad \text{and} \quad \varpi_2(\cdot, t) = \begin{cases} i(t, a), & t > a \geqslant 0, \\ 0, & a \geqslant t \geqslant 0. \end{cases}$$

We are now in the position to prove the following theorem.

Theorem 3.1. *For any $X_0 \in \Omega$, $\{U(t) X_0 : t \geqslant 0\}$ has compact closure in $\mathcal{X}$ if the following two conditions hold:*

(i) *There exists a function $\Delta : \mathbb{R}_+ \times \mathbb{R}_+ \to \mathbb{R}_+$ such that for any $r > 0$, $\lim_{t \to \infty} \Delta(t, r) = 0$, and if $X_0 \in \Omega$ with $\|X_0\|_\mathcal{X} \leqslant r$, then $\|\Phi(t) X_0\|_\mathcal{X} \leqslant \Delta(t, r)$ for $t \geqslant 0$;*

(ii) *For $t \geqslant 0$, $\Psi(t) X_0$ maps any bounded sets of Ω into sets with compact closure in $\mathcal{X}$.*

Proof. Step I, to show that (i) holds.

Let $\Delta(t, r) := e^{-\tilde{\delta}t}r$, it is obvious that $\lim_{t\to\infty} \Delta(t, r) = 0$. Then for $X_0 \in \Omega$ satisfying $\|X_0\|_{\mathcal{X}} \leqslant r$, we have

$$
\begin{aligned}
\|\Phi(t)X_0\|_{\mathcal{X}} &= |0| + \int_0^\infty |\varpi_1(a, t)\mathrm{d}a| + |0| + |0| \\
&= \int_t^\infty \left| i_0(a - t)\frac{\Gamma(a)}{\Gamma(a - t)} \right| \mathrm{d}a \\
&= \int_0^\infty \left| i_0(s)\frac{\Gamma(s + t)}{\Gamma(s)} \right| \mathrm{d}s \\
&\leqslant e^{-\tilde{\delta}t} \int_0^\infty |i_0(s)|\mathrm{d}s \\
&\leqslant e^{-\tilde{\delta}t}\|X_0\|_{\mathcal{X}} \\
&\leqslant \Delta(t, r), \quad t \geqslant 0.
\end{aligned}
$$

This completes the proof of condition (i).

Step II, to show that (ii) holds.

We just have to show that $\varpi_2(t, a)$ remains in a precompact subset of $L^1_+(0, \infty)$. In order to prove it, we should show the following conditions hold [40, Theorem B.2]:

(a) The supremum of $\int_0^\infty \varpi_2(t, a)\mathrm{d}a$ with respect to $X_0 \in \Omega$ is finite;

(b) $\lim_{u\to\infty} \int_u^\infty \varpi_2(t, a)\mathrm{d}a = 0$ uniformly with respect to $X_0 \in \Omega$;

(c) $\lim_{u\to 0^+} \int_0^\infty (\varpi_2(t, a + u) - \varpi_2(t, a)\mathrm{d}a = 0$ uniformly with respect to $X_0 \in \Omega$;

(d) $\lim_{u\to 0^+} \int_u^\infty \varpi_2(t, a)\mathrm{d}a = 0$ uniformly with respect to $X_0 \in \Omega$.

Conditions (a), (b) and (d) hold since $\varpi_2(t, a) \leqslant \left(\frac{\beta\bar{p}}{\hat{\mu}} + \bar{k}\right)\frac{\Lambda^2}{\mu_0^2}$. Next, we verify condition (c). For sufficiently small $u \in (0, t)$, set $K(t) = \int_0^\infty k(a)i(t, a)\mathrm{d}a$, we have

$$
\begin{aligned}
&\int_0^\infty |\varpi_2(t, a + u) - \varpi_2(t, a)|\mathrm{d}a \\
&= \int_0^{t-u} |(\beta T(t - a - u)V(t - a - u) + K(t - a - u)T(t - a - u))\Gamma(a + u) \\
&\quad - (\beta T(t - a)V(t - a) + K(t - a)T(t - a))\Gamma(a)|\mathrm{d}a \\
&\quad + \int_{t-u}^t |0 - \beta T(t - a)V(t - a) + K(t - a)T(t - a))\Gamma(a)|\mathrm{d}a \\
&\leqslant \int_0^{t-u} (\beta T(t - a - u)V(t - a - u) + K(t - a - u)T(t - a - u))|\Gamma(a + u) - \Gamma(a)|\mathrm{d}a \\
&\quad + \int_0^{t-u} |\beta T(t - a - u)V(t - a - u) - \beta T(t - a)V(t - a)|\Gamma(a)\mathrm{d}a \\
&\quad + \int_0^{t-u} |K(t - a - u)T(t - a - u) - K(t - a)T(t - a)|\Gamma(a)\mathrm{d}a + u\left(\frac{\Lambda}{\mu_0}\right)^2\left(\frac{\beta\bar{p}}{\hat{\mu}} + \tilde{k}\right).
\end{aligned}
$$

Since $\Gamma(a)$ is non-increasing function with respect to a and $0 \leqslant \Gamma(a) \leqslant 1$, we have

$$\int_0^{t-u} |\Gamma(a+u) - \Gamma(a)| \mathrm{d}a = \int_0^{t-u} (\Gamma(a) - \Gamma(a+u)) \, \mathrm{d}a$$
$$= \int_0^{t-u} \Gamma(a)\mathrm{d}a - \int_u^t \Gamma(a)\mathrm{d}a$$
$$\leqslant \int_0^{t-u} \Gamma(a)\mathrm{d}a + \int_{t-u}^u \Gamma(a)\mathrm{d}a \leqslant u.$$

Then

$$\int_0^\infty |\varpi_2(t, a+u) - \varpi_2(t, a)| \mathrm{d}a \leqslant 2u \left(\frac{\Lambda}{\mu_0}\right)^2 \left(\frac{\beta\bar{p}}{\hat{\mu}} + \bar{k}\right) + \Xi,$$

where

$$\Xi = \int_0^{t-u} |\beta T(t-a-u)V(t-a-u) - \beta T(t-a)V(t-a)|\Gamma(a)\mathrm{d}a$$
$$+ \int_0^{t-u} |K(t-a-u)T(t-a-u) - K(t-a)T(t-a)|\Gamma(a)\mathrm{d}a.$$

Thanks to the argument in [41, Proposition 6], $T(\cdot)V(\cdot)$ and $T(\cdot)K(\cdot)$ are Lipschitz on $\mathbb{R}_+$. Let M_1 and M_2 be the Lipschitz coefficients of $T(\cdot)V(\cdot)$ and $T(\cdot)K(\cdot)$ respectively. Then

$$\Xi \leqslant (\beta M_1 + M_2)u \int_0^{t-u} \Gamma(a)\mathrm{d}a \leqslant (\beta M_1 + M_2)u \int_0^{t-u} \Gamma(a)\mathrm{d}a \leqslant \frac{u(\beta M_1 + M_2)}{\tilde{\delta}}.$$

Hence

$$\int_0^\infty |\varpi_2(t, a+u) - \varpi_2(t, a)| \mathrm{d}a \leqslant 2u \left(\frac{\Lambda}{\mu_0}\right)^2 \left(\frac{\beta\bar{p}}{\mu_2} + \bar{k}\right) + \frac{u(\beta M_1 + M_2)}{\tilde{\delta}},$$

which converges to 0 as $u \to 0^+$, the condition (c) holds. Let $\mathcal{Y} \subset \mathcal{X}$ be a bounded closed set and B be a bound for $\mathcal{Y}$, where $B \geqslant A$. It is easy to check M_1 and M_2 are only depend on A, that is M_1 and M_2 are independent on $\mathcal{X}$. Consequently, $\varpi_2(t, a)$ remains in a precompact subset $\mathcal{Y}$ of $L_1^+(0, +\infty)$ and thus

$$\Psi(t, \mathcal{Y}) \subseteq [0, B] \times Y \times [0, B] \times [0, B],$$

which has compact closure in $\mathcal{X}$. The proof is completed. $\qquad\square$

4. Local stability of steady states

In this section, we show the local stability of system (1.6) at each steady states.

4.1. Local stability of virus-free steady state

Theorem 4.1. *If $\mathfrak{R}_0 < 1$, then the virus-free steady state E_0 of system (1.6) is locally asymptotically stable.*

Proof. Denote $\bar{T}_1(t) = T(t) - T_0$, $\bar{i}_1(t,a) = i(t,a)$, $\bar{V}_1(t) = V(t)$ and $\bar{Z}_1(t) = Z(t)$, the linearized equation of (1.6) at E_0 as follows:

$$
\begin{cases}
\dfrac{d\bar{T}_1(t)}{dt} = -\mu_1\bar{T}_1(t) - \beta T_0 \bar{V}_1(t) - \displaystyle\int_0^\infty T_0 k(a)\bar{i}_1(t,a)da, \\[2mm]
\left(\dfrac{\partial}{\partial t} + \dfrac{\partial}{\partial a}\right)\bar{i}_1(t,a) = -\delta(a)\bar{i}_1(t,a), \\[2mm]
\dfrac{d\bar{V}_1(t)}{dt} = \displaystyle\int_0^\infty p(a)\bar{i}_1(t,a)da - \mu_2\bar{V}_1(t), \\[2mm]
\dfrac{d\bar{Z}_1(t)}{dt} = -\mu_3\bar{Z}_1(t), \\[2mm]
\bar{i}_1(t,0) = \beta T_0\bar{V}_1(t) + \displaystyle\int_0^\infty T_0 k(a)\bar{i}_1(t,a)da.
\end{cases}
\tag{4.1}
$$

Let the solution of (4.1) has the following exponential form:

$$
\bar{T}_1(t) = \bar{T}_1 e^{\lambda t}, \quad \bar{V}_1(t) = \bar{V}_1 e^{\lambda t}, \quad \bar{Z}_1(t) = \bar{Z}_1 e^{\lambda t} \text{ and } \bar{i}_1(t,a) = \bar{i}_1(a)e^{\lambda t},
$$

then

$$
\begin{cases}
\lambda\bar{T}_1 = -\mu_1\bar{T}_1 - \beta T_0\bar{V}_1 - \displaystyle\int_0^\infty T_0 k(a)\bar{i}_1(a)da, \\[2mm]
\lambda\bar{i}_1(a) + \dfrac{d\bar{i}_1(a)}{da} = -\delta(a)\bar{i}_1(a), \\[2mm]
\lambda\bar{V}_1 = \displaystyle\int_0^\infty p(a)\bar{i}_1(a)da - \mu_2\bar{V}_1, \\[2mm]
\lambda\bar{Z}_1 = -\mu_3\bar{Z}_1, \\[2mm]
\bar{i}_1(0) = \beta T_0\bar{V}_1 + \displaystyle\int_0^\infty T_0 k(a)\bar{i}_1(a)da.
\end{cases}
\tag{4.2}
$$

Solve the second equation of (4.2) yields

$$
\bar{i}_1(a) = \bar{i}_1(0)e^{-\lambda a}\Gamma(a).
$$

We can write the characteristic equation as following

$$
\begin{vmatrix}
\lambda + \mu_1 & T_0\int_0^\infty k(a)e^{-\lambda a}\Gamma(a)da & \beta T_0 \\
0 & 1 - T_0\int_0^\infty k(a)e^{-\lambda a}\Gamma(a)da & -\beta T_0 \\
0 & -\int_0^\infty p(a)e^{-\lambda a}\Gamma(a)da & \lambda + \mu_2
\end{vmatrix}
$$
$$
= \Delta(\lambda)(\lambda + \mu_1)
$$
$$
= 0,
$$

where

$$
\Delta(\lambda) := \lambda + \mu_2 - \lambda T_0\int_0^\infty k(a)e^{-\lambda a}\Gamma(a)da - \mu_2 T_0\int_0^\infty k(a)e^{-\lambda a}\Gamma(a)da - \beta T_0\int_0^\infty p(a)e^{-\lambda a}\Gamma(a)da.
$$

Since $\lambda = -\mu_1 < 0$, then we only need to consider the root of $\Delta(\lambda) = 0$. By way of contradiction, we assume that it has an eigenvalue λ_0 with $Re(\lambda_0) \geqslant 0$. We have

$$
\begin{aligned}
|\lambda + \mu_2| &= \left| (\lambda + \mu_2)T_0 \int_0^\infty k(a)e^{-\lambda a}\Gamma(a)\mathrm{d}a + \beta T_0 \int_0^\infty p(a)e^{-\lambda a}\Gamma(a)\mathrm{d}a \right| \\
&\leqslant |\lambda + \mu_2| \left| T_0 \int_0^\infty k(a)e^{-\lambda a}\Gamma(a)\mathrm{d}a + \frac{\beta T_0 \int_0^\infty p(a)e^{-\lambda a}\Gamma(a)\mathrm{d}a}{\lambda + \mu_2} \right| \\
&\leqslant |\lambda + \mu_2| \left(T_0 \int_0^\infty k(a)\Gamma(a)\mathrm{d}a + \frac{\beta T_0 \int_0^\infty p(a)\Gamma(a)\mathrm{d}a}{\mu_2} \right).
\end{aligned}
$$

Hence,

$$
T_0 \int_0^\infty k(a)\Gamma(a)\mathrm{d}a + \frac{\beta T_0 \int_0^\infty p(a)\Gamma(a)\mathrm{d}a}{\mu_2} \geqslant 1,
$$

which is impossible because $\mathfrak{R}_0 = \frac{\beta T_0 \mathcal{P}}{\mu_2} + T_0\mathcal{K} < 1$. This completes the proof. $\qquad\square$

4.2. Local stability of immune-inactivated steady state

Theorem 4.2. *If $\mathfrak{R}_1 < 1 < \mathfrak{R}_0$, then the immune-inactivated steady state E_1^* of system (1.6) is locally asymptotically stable.*

Proof. Denote $\bar{T}_2(t) = T(t) - T_1^*$, $\bar{i}_2(t,a) = i(t,a) - i_1^*(a)$, $\bar{V}_1(t) = V(t) - V_1^*$ and $\bar{Z}_2(t) = Z(t)$, the linearized equation of (1.6) at E_1^* as follows:

$$
\begin{cases}
\dfrac{\mathrm{d}\bar{T}_2(t)}{\mathrm{d}t} = -\beta T_1^* \bar{V}_2(t) - \displaystyle\int_0^\infty T_1^* k(a)\bar{i}_2(t,a)\mathrm{d}a - \left(\beta V_1^* + \mu_1 + \int_0^\infty i_1^*(a)k(a)\mathrm{d}a \right)\bar{T}_2(t), \\[3mm]
\left(\dfrac{\partial}{\partial t} + \dfrac{\partial}{\partial a} \right)\bar{i}_2(t,a) = -\delta(a)\bar{i}_1(t,a), \\[3mm]
\dfrac{\mathrm{d}\bar{V}_2(t)}{\mathrm{d}t} = \displaystyle\int_0^\infty p(a)\bar{i}_2(t,a)\mathrm{d}a - \mu_2 \bar{V}_2(t) - qf'(0)V_1^* \bar{Z}_2(t), \\[3mm]
\dfrac{\mathrm{d}\bar{Z}_2(t)}{\mathrm{d}t} = cf'(0)V_1^* \bar{Z}_2(t) - \mu_3 \bar{Z}_2(t), \\[3mm]
\bar{i}_2(t,0) = \beta T_1^* \bar{V}_2(t) + \beta V_1^* \bar{T}_2(t) + \displaystyle\int_0^\infty T_1^* k(a)\bar{i}_2(t,a)\mathrm{d}a + \int_0^\infty i_1^*(a)k(a)\bar{T}_2(t)\mathrm{d}a.
\end{cases}
\tag{4.3}
$$

Let $\bar{T}_2(t) = \bar{T}_2 e^{\lambda t}$, $\bar{V}_2(t) = \bar{V}_2 e^{\lambda t}$, $\bar{Z}_2(t) = \bar{Z}_2 e^{\lambda t}$ and $\bar{i}_2(t,a) = \bar{i}_2(a)e^{\lambda t}$, thus we have the following characteristic equation:

$$
\begin{aligned}
0 = {}& (\lambda - cf'(0)V_1^* + \mu_3)(\lambda + \mu_1)(\lambda + \mu_2)\left(1 - T_1^* \int_0^\infty k(a)e^{-\lambda a}\Gamma(a)\mathrm{d}a \right) \\
&- (\lambda - cf'(0)V_1^* + \mu_3)(\lambda + \mu_1)\beta T_1^* \int_0^\infty p(a)e^{-\lambda a}\Gamma(a)\mathrm{d}a \\
&+ (\lambda - cf'(0)V_1^* + \mu_3)(\lambda + \mu_2)\left(\beta V_1^* + \int_0^\infty k(a)i_1^*(a)\mathrm{d}a \right).
\end{aligned}
$$

Note that $\mathfrak{R}_1 < 1$ and using (2.6), we can obtain that $\mu_3 - cf'(0)V_1^* > 0$, then the characteristic equation is equivalent to

$$
\begin{aligned}
0 =& (\lambda + \mu_1) \left[(\lambda + \mu_2) \left(1 - T_1^* \int_0^\infty k(a)e^{-\lambda a}\Gamma(a)\mathrm{d}a \right) - \beta T_1^* \int_0^\infty p(a)e^{-\lambda a}\Gamma(a)\mathrm{d}a \right] \\
& + (\lambda + \mu_2) \left(\beta V_1^* + \int_0^\infty k(a)i_1^*(a)\mathrm{d}a \right).
\end{aligned}
\tag{4.4}
$$

By way of contradiction, we assume that it has an eigenvalue λ_0 with $Re(\lambda_0) \geqslant 0$. Obviously, $\lambda = -\mu_1$ and $\lambda = -\mu_2$ are not the roots of (4.4) and note that

$$
\begin{aligned}
i_1^*(0) &= T_1^* \int_0^\infty k(a)i_1^*(a)\mathrm{d}a + \frac{\beta T_1^*}{\mu_2} \int_0^\infty p(a)i_1^*(a)\mathrm{d}a \\
&= T_1^* \int_0^\infty k(a)i_1^*(0)\Gamma(a)\mathrm{d}a + \frac{\beta T_1^*}{\mu_2} \int_0^\infty p(a)i_1^*(0)\Gamma(a)\mathrm{d}a.
\end{aligned}
$$

Then we have

$$
\begin{aligned}
& \left| 1 + \frac{\beta V_1^* + \int_0^\infty k(a)i_1^*(a)\mathrm{d}a}{\lambda_0 + \mu_1} \right| \\
=& \left| T_1^* \int_0^\infty k(a)e^{-\lambda_0 a}\Gamma(a)\mathrm{d}a + \frac{1}{\lambda_0 + \mu_2}\beta T_1^* \int_0^\infty p(a)e^{-\lambda_0 a}\Gamma(a)\mathrm{d}a \right| \\
\leqslant& \left| T_1^* \int_0^\infty k(a)\Gamma(a)\mathrm{d}a + \frac{\beta T_1^*}{\mu_2} \int_0^\infty p(a)\Gamma(a)\mathrm{d}a \right| = 1,
\end{aligned}
$$

which is impossible since $V_1^* > 0$ and $i_1^*(a) > 0$. Accordingly, the immune-inactivated steady state E_1^* of system (1.6) is local asymptotically stable if $\mathfrak{R}_1 < 1 < \mathfrak{R}_0$. $\qquad\square$

4.3. Local stability of immune-activated steady state

Theorem 4.3. *If $\mathfrak{R}_1 > 1$, then the immune-activated steady state E_2^* of system (1.6) is locally asymptotically stable.*

Proof. Applying similar method in the proof of the Theorem (4.2), we have the characteristic equation as following:

$$
\begin{aligned}
& (\lambda + \mu_1) \left[(\lambda + \mu_2 + qf(Z_2^*))(\lambda - cV_2^*f'(Z_2^*) + \mu_3) + qcV_2^*f(Z_2^*)f'(Z_2^*) \right] \left(1 - \int_0^\infty T_2^*k(a)e^{-\lambda}\Gamma(a)\mathrm{d}a \right) \\
& + (\lambda + \mu_1)(\lambda - cV_2^*f'(Z_2^*) + \mu_3)\beta T_2^* \int_0^\infty p(a)e^{-\lambda a}\Gamma(a)\mathrm{d}a \\
=& - \left[(\lambda + \mu_2 + qf(Z_2^*))(\lambda - cV_2^*f'(Z_2^*) + \mu_3) + qcV_2^*f(Z_2^*)f'(Z_2^*) \right] \left(\beta V_2^* + \int_0^\infty k(a)i_2^*(a)\mathrm{d}a \right).
\end{aligned}
\tag{4.5}
$$

By way of contradiction, we assume that it has an eigenvalue λ_0 with $Re(\lambda_0) \geqslant 0$. From the concavity of function f in (A2), we have $\mu_3 - cV_2^*f'(Z_2^*) \geqslant 0$ since $\mu_3 Z_2^* - cV_2^*f(Z_2^*) = 0$. Note that $\lambda = -\mu_1$, $\lambda = -(\mu_2 + qf(Z_2^*))$ and $\lambda = cV_2^*f'(Z_2^*) - \mu_3$ are not the roots of (4.5), then we can rewrite (4.5) as

$$
1 + \Xi = \int_0^\infty T_2^*k(a)e^{-\lambda a}\Gamma(a)\mathrm{d}a.
\tag{4.6}
$$

where

$$\Xi = \frac{\left(1 - \int_0^\infty T_2^* k(a) e^{-\lambda a} \Gamma(a) \mathrm{d}a\right) qcV_2^* f(Z_2^*) f'(Z_2^*)}{(\lambda + \mu_2 + qf(Z_2^*))(\lambda - cV_2^* f'(Z_2^*) + \mu_3)} + \frac{\beta T_2^* \int_0^\infty p(a) e^{-\lambda a} \Gamma(a) \mathrm{d}a}{\lambda + \mu_2 + qf(Z_2^*)}$$

$$+ \frac{\beta V_2^* + \int_0^\infty k(a) i_2^*(a) \mathrm{d}a}{\lambda + \mu_1} + \frac{qcV_2^* f(Z_2^*) f'(Z_2^*)\left(\beta V_2^* + \int_0^\infty k(a) i_2^*(a) \mathrm{d}a\right)}{(\lambda + \mu_2 + qf(Z_2^*))(\lambda - cV_2^* f'(Z_2^*) + \mu_3)}.$$

Then

$$|1 + \Xi| = \left|\int_0^\infty T_2^* k(a) e^{-\lambda a} \Gamma(a) \mathrm{d}a\right|$$

$$< \left|\frac{1}{i_2^*(0)}\left(\int_0^\infty i_2^*(0) T_2^* k(a) e^{-\lambda a} \Gamma(a) \mathrm{d}a + \frac{\beta T_2^*}{\mu_2 + qf(Z_2^*)} \int_0^\infty i_2^*(0) p(a) \Gamma(a) \mathrm{d}a\right)\right|$$

$$\leqslant 1,$$

which is contradictory. Here we use the fact:

$$1 - \int_0^\infty T_2^* k(a) e^{-\lambda a} \Gamma(a) \mathrm{d}a = \frac{1}{i_2^*(0)}\left(\beta T_2^* V_2^* + \int_0^\infty T_2^* k(a)\left[1 - e^{-\lambda a}\right] i_2^*(a)\right) > 0.$$

This completes the proof. $\qquad\square$

5. Global stability of steady states

In this section, we discuss the global stability of system (1.6) by using Lyapunov direct method and LaSalle invariance principle. We first give the result on uniform persistence.

Theorem 5.1. *Assume that $\mathfrak{R}_0 > 1$. Then there exists a constant $\zeta > 0$ such that*

$$\liminf_{t \to +\infty} T(t) \geqslant \zeta, \quad \liminf_{t \to +\infty} \|i(\cdot, t)\|_{L^1} \geqslant \zeta, \quad \liminf_{t \to +\infty} V(t) \geqslant \zeta$$

for each $X_0 \in \mathcal{X}$.

The proof of Theorem 5.1 is similar with that in [21, Section 4] or [30], so we omit the details. In the following, we proof the global stability of each steady states.

5.1. Global stability of virus-free steady state

Theorem 5.2. *The virus-free steady state E_0 of system (1.6) is globally asymptotically stable if $\mathfrak{R}_0 < 1$.*

Proof. Let

$$\alpha_1(a) := \int_a^\infty \left(\frac{\beta T^0}{\mu_2} p(\epsilon) + T^0 k(\epsilon)\right) e^{-\int_a^\epsilon \delta(s) \mathrm{d}s} \mathrm{d}\epsilon; \tag{5.1}$$

$$g(x) := x - 1 - \ln x. \tag{5.2}$$

By direct calculations, we have $\alpha_1(0) = \mathfrak{R}_0$ and $\alpha'_1(a) = \delta(a)\alpha(a) - \left(\frac{\beta T^0}{\mu_2}p(a) + T^0 k(a)\right)$. Define the following Lyapunov functional:

$$H(t) = H_1(t) + H_2(t),$$

where

$$H_1(t) = T_0 g\left(\frac{T(t)}{T_0}\right) + \frac{\beta T_0}{\mu_2}V(t) + \frac{q\beta T_0}{c\mu_2}Z(t), \tag{5.3}$$

$$H_2(t) = \int_0^\infty \alpha_1(a)i(t,a)\mathrm{d}a. \tag{5.4}$$

Calculating the derivatives of $H_1(t)$ and $H_2(t)$ along system (1.6), we have

$$\begin{aligned}
\frac{\mathrm{d}H_1(t)}{\mathrm{d}t} &= \left(1 - \frac{T_0}{T(t)}\right)\frac{\mathrm{d}T(t)}{\mathrm{d}t} + \frac{\beta T_0}{\mu_2}\frac{\mathrm{d}V(t)}{\mathrm{d}t} + \frac{q\beta T_0}{c\mu_2}\frac{\mathrm{d}Z(t)}{\mathrm{d}t} \\
&= \mu_1 T_0\left(2 - \frac{T_0}{T(t)} - \frac{T(t)}{T_0}\right) - i(t,0) - \frac{q\beta T_0 \mu_3}{c\mu_2}Z(t) \\
&\quad + \int_0^\infty k(a)T_0 i(t,a)\mathrm{d}a + \frac{\beta T_0}{\mu_2}\int_0^\infty p(a)i(t,a)\mathrm{d}a,
\end{aligned}$$

and

$$\begin{aligned}
\frac{\mathrm{d}H_2(t)}{\mathrm{d}t} &= \int_0^\infty \alpha_1(a)\frac{\partial i(t,a)}{\partial t}\mathrm{d}a \\
&= -\int_0^\infty \alpha_1(a)\frac{\partial i(t,a)}{\partial a}\mathrm{d}a - \int_0^\infty \alpha_1(a)\delta(a)i(t,a)\mathrm{d}a \\
&= \mathfrak{R}_0 i(t,0) - \int_0^\infty \left(\frac{\beta T_0}{\mu_2}p(a) + T_0 k(a)\right)i(t,a)\mathrm{d}a,
\end{aligned}$$

thus

$$\frac{\mathrm{d}H(t)}{\mathrm{d}t} = \mu_1 T_0\left(2 - \frac{T_0}{T(t)} - \frac{T(t)}{T_0}\right) + (\mathfrak{R}_0 - 1)i(t,0) - \frac{q\beta T_0 \mu_3}{c\mu_2}Z(t) \leqslant 0 \tag{5.5}$$

if $\mathfrak{R}_0 < 1$. Note that $\frac{\mathrm{d}H(t)}{\mathrm{d}t}\big|_{(1.6)} = 0$ implies that $T(t) = T_0$, $i(t,0) = 0$ and $Z(t) = 0$, then the largest invariant subset of $\left\{\frac{\mathrm{d}H(t)}{\mathrm{d}t}\big|_{(1.6)} = 0\right\}$ is $\{E_0\}$. Therefore, the virus-free steady state E_0 of system (1.6) is global asymptotically stable if $\mathfrak{R}_0 < 1$ by Lyapunov-LaSalle theorem. This ends the proof. $\qquad\square$

5.2. Global stability of immune-inactivated steady state

Theorem 5.3. *The immune-inactivated steady state $E_1^* = (T_1^*, i_1^*(a), V_1^*, 0)$ of system (1.6) is globally asymptotically stable if $\mathfrak{R}_1 < 1 < \mathfrak{R}_0$.*

Proof. Let

$$\alpha_2(a) := \int_a^\infty \left(\frac{\beta T_1^*}{\mu_2}p(\epsilon) + T_1^* k(\epsilon)\right)e^{-\int_a^\epsilon \delta(s)\mathrm{d}s}\mathrm{d}\epsilon. \tag{5.6}$$

Define the following Lyapunov functional:

$$W(t) := W_1(t) + W_2(t) + W_3(t),$$

where

$$W_1(t) := T_1^* g\left(\frac{T(t)}{T_1^*}\right); \tag{5.7}$$

$$W_2(t) := \int_0^\infty \alpha_2(a) i_1^*(a) g\left(\frac{i(t,a)}{i_1^*(a)}\right) da; \tag{5.8}$$

$$W_3(t) := \frac{\beta T_1^*}{\mu_2} V_1^* g\left(\frac{V(t)}{V_1^*}\right) + \frac{q\beta T_1^*}{c\mu_2} Z(t). \tag{5.9}$$

The derivative of $W_1(t)$ is calculated as follows:

$$
\begin{aligned}
\frac{\mathrm{d}W_1(t)}{\mathrm{d}t} &= \left(1 - \frac{T_1^*}{T(t)}\right)\frac{\mathrm{d}T_1(t)}{\mathrm{d}t} \\
&= \left(1 - \frac{T_1^*}{T(t)}\right)\left(\Lambda - \mu_1 T(t) - \beta T(t)V(t) - \int_0^\infty k(a)T(t)i(t,a)\mathrm{d}a\right) \\
&= \mu_1 T_1^*\left(2 - \frac{T_1^*}{T(t)} - \frac{T(t)}{T_1^*}\right) + (i_1^*(0) - i(t,0))\left(1 - \frac{T_1^*}{T(t)}\right).
\end{aligned}
$$

Note that

$$
\begin{aligned}
&i_1^*(a)\frac{\mathrm{d}}{\mathrm{d}a}\left(\frac{i(t,a)}{i_1^*(a)} - 1 - \ln\frac{i(t,a)}{i_1^*(a)}\right) \\
&= \left(1 - \frac{i_1^*(a)}{i(t,a)}\right)\frac{\partial i(t,a)}{\partial a} + \delta(a)i(t,a)\left(1 - \frac{i_1^*(a)}{i(t,a)}\right),
\end{aligned} \tag{5.10}
$$

which leads to

$$
\begin{aligned}
&\int_0^\infty \alpha_2(a)\left(1 - \frac{i_1^*(a)}{i(t,a)}\right)\frac{\partial i(t,a)}{\partial a}\mathrm{d}a \\
&= \alpha_2(a)i_1^*(a)\left(\frac{i(t,a)}{i_1^*(a)} - 1 - \ln\frac{i(t,a)}{i_1^*(a)}\right)\Bigg|_{a=0}^{a=\infty} + \int_0^\infty \alpha(a)\delta(a)[i_1^*(a) - i(t,a)]\mathrm{d}a \\
&\quad - \int_0^\infty \left(\frac{i(t,a)}{i_1^*(a)} - 1 - \ln\frac{i(t,a)}{i_1^*(a)}\right)\left(\frac{\mathrm{d}\alpha_2(a)}{\mathrm{d}a}i_1^*(a) + \alpha_2(a)\frac{\partial i_1^*(a)}{\partial a}\right)\mathrm{d}a \\
&= \lim_{a\to\infty} \alpha_2(a)i^*(a)g\left(\frac{i(t,a)}{i^*(a)}\right) - \alpha_2(0)i_1^*(0)g\left(\frac{i(t,0)}{i^*(0)}\right) \\
&\quad + \int_0^\infty \alpha_2(a)\delta(a)[i_1^*(a) - i(t,a)]\mathrm{d}a - \int_0^\infty g\left(\frac{i(t,a)}{i^*(a)}\right)\left(\frac{\mathrm{d}\alpha_2(a)}{\mathrm{d}a}i_1^*(a) + \alpha_2(a)\frac{\mathrm{d}i_1^*(a)}{\mathrm{d}a}\right)\mathrm{d}a.
\end{aligned}
$$

By some calculations, we have

$$\alpha_2(0) = 1, \quad \alpha_2'(a) = \delta(a)\alpha_2(a) - \left(\frac{\beta T_1^*}{\mu_2}p(a) + T_1^*k(a)\right),$$

and using the fact that

$$\frac{\mathrm{d}i_1^*(a)}{\mathrm{d}a} = -\delta(a)i_1^*(a).$$

Hence

$$\int_0^\infty \alpha_2(a)\left(1 - \frac{i_1^*(a)}{i(t,a)}\right)\frac{\partial i(t,a)}{\partial a}\mathrm{d}a$$

$$= \lim_{a\to\infty} \alpha_2(a)i^*(a)g\left(\frac{i(t,a)}{i^*(a)}\right) - i_1^*(0)g\left(\frac{i(t,0)}{i^*(0)}\right) + \int_0^\infty \alpha_2(a)\delta(a)[i_1^*(a) - i(t,a))]\mathrm{d}a$$

$$+ \int_0^\infty \left(T_1^* k(a)i^*(a) + \frac{\beta T_1^*}{\mu_2}p(a)i^*(a)\right)g\left(\frac{i(t,a)}{i^*(a)}\right)\mathrm{d}a.$$

Then we have the derivative of $W_2(t)$ as follows:

$$\frac{\mathrm{d}W_2(t)}{\mathrm{d}t} = \int_0^\infty \alpha(a)\left(1 - \frac{i^*(a)}{i(t,a)}\right)\frac{\partial i(t,a)}{\partial t}\mathrm{d}a$$

$$= -\int_0^\infty \alpha(a)\left(1 - \frac{i^*(a)}{i(t,a)}\right)\left(\frac{\partial i(t,a)}{\partial a} + \delta(a)i(t,a)\right)\mathrm{d}a$$

$$= -\lim_{a\to\infty} \alpha(a)i^*(a)g\left(\frac{i(t,a)}{i^*(a)}\right) + i^*(0)g\left(\frac{i(t,0)}{i^*(0)}\right)$$

$$- \int_0^\infty T_1^* k(a)i^*(a)g\left(\frac{i(t,a)}{i^*(a)}\right)\mathrm{d}a - \int_0^\infty \frac{\beta T_1^*}{\mu_2}p(a)i^*(a)g\left(\frac{i(t,a)}{i^*(a)}\right)\mathrm{d}a.$$

For $W_3(t)$, we have

$$\frac{\mathrm{d}W_3(t)}{\mathrm{d}t} = \frac{\beta T_1^*}{\mu_2}\left(1 - \frac{V_1^*}{V(t)}\right)\frac{\mathrm{d}V(t)}{\mathrm{d}t} + \frac{q\beta T_1^*}{c\mu_2}\frac{\mathrm{d}Z(t)}{\mathrm{d}t}$$

$$= \frac{\beta T_1^*}{\mu_2}\int_0^\infty p(a)i(t,a)\mathrm{d}a - \frac{\beta T_1^*}{\mu_2}\mu_2 V(t) - \frac{\beta T_1^*}{\mu_2}\frac{V_1^*}{V(t)}\int_0^\infty p(a)i(t,a)\mathrm{d}a + \frac{\beta T_1^*}{\mu_2}\mu_2 V_1^*$$

$$+ \frac{q\beta T_1^*}{\mu_2}V_1^* f(Z(t)) - \frac{q\beta T_1^*}{c\mu_2}\mu_3 Z(t).$$

Hence,

$$\frac{\mathrm{d}W(t)}{\mathrm{d}t} = \mu_1 T_1^*\left(2 - \frac{T_1^*}{T(t)} - \frac{T(t)}{T_1^*}\right)$$

$$- \beta T_1^* V_1^* \frac{T_1^*}{T(t)} - \int_0^\infty k(a)T_1^* i_1^*(a)\frac{T_1^*}{T(t)}\mathrm{d}a + \int_0^\infty k(a)T_1^* i(t,a)\mathrm{d}a$$

$$- \lim_{a\to\infty} \alpha(a)i_1^*(a)g\left(\frac{i(t,a)}{i_1^*(a)}\right) - i_1^*(0)\ln\frac{i(t,0)}{i_1^*(0)} - \int_0^\infty p(a)i_1^*(a)g\left(\frac{i(t,a)}{i_1^*(a)}\right)\mathrm{d}a$$

$$+ \frac{\beta T_1^*}{\mu_2}\int_0^\infty p(a)i(t,a)\mathrm{d}a - \frac{\beta T_1^*}{\mu_2}\frac{V_1^*}{V(t)}\int_0^\infty p(a)i(t,a)\mathrm{d}a + \frac{\beta T_1^*}{\mu_2}\mu_2 V_1^*$$

$$+ \frac{q\beta T_1^*}{\mu_2}V_1^* f(Z(t)) - \frac{q\beta T_1^*}{c\mu_2}\mu_3 Z(t). \tag{5.11}$$

Recalling that $V_1^* = \int_0^\infty \frac{p(a)}{\mu_2} i_1^*(a)\mathrm{d}a$ and $i_1^*(0) = \beta T_1^* V_1^* + \int_0^\infty k(a)T_1^* i_1^*(a)\mathrm{d}a$. Substituting (2.13) into (5.11), after some calculations and rearranging the equation yield

$$
\begin{aligned}
\frac{\mathrm{d}W(t)}{\mathrm{d}t} =& \mu_1 T_1^* \left(2 - \frac{T_1^*}{T(t)} - \frac{T(t)}{T_1^*}\right) - \lim_{a\to\infty} \alpha(a)i_1^*(a)g\left(\frac{i(t,a)}{i_1^*(a)}\right) \\
&+ \int_0^\infty \frac{\beta T_1^*}{\mu_2} p(a)i_1^*(a)\left(2 - \frac{T_1^*}{T(t)} - \frac{V_1^* i(t,a)}{V(t)i_1^*(a)} - \ln\frac{i(t,0)}{i_1^*(0)} + \ln\frac{i(t,a)}{i_1^*(a)}\right)\mathrm{d}a \\
&+ \int_0^\infty T_1^* k(a)i_1^*(a)\left(1 - \frac{T_1^*}{T(t)} - \ln\frac{i(t,0)}{i_1^*(0)} + \ln\frac{i(t,a)}{i_1^*(a)}\right)\mathrm{d}a \\
&+ \int_0^\infty \frac{\beta T_1^*}{\mu_2} p(a)i_1^*(a)\left(1 - \frac{i_1^*(0)T(t)V(t)}{i(t,0)T_1^* V_1^*}\right)\mathrm{d}a \\
&+ \int_0^\infty T_1^* k(a)i_1^*(a)\left(1 - \frac{i_1^*(0)T(t)i(t,a)}{i(t,0)T_1^* i_1^*(a)}\right)\mathrm{d}a \\
=& \mu_1 T_1^* \left(2 - \frac{T_1^*}{T(t)} - \frac{T(t)}{T_1^*}\right) - \lim_{a\to\infty} \alpha(a)i_1^*(a)g\left(\frac{i(t,a)}{i_1^*(a)}\right) \\
&- \int_0^\infty \frac{\beta T_1^*}{\mu_2} p(a)i^*(a)\left\{g\left(\frac{T_1^*}{T(t)}\right) + g\left(\frac{V_1^* i(t,a)}{V(t)i_1^*(a)}\right) + g\left(\frac{i_1^*(0)T(t)V(t)}{i(t,0)T_1^* V_1^*}\right)\right\}\mathrm{d}a \\
&- \int_0^\infty T_1^* k(a)i_1^*(a)\left\{g\left(\frac{T_1^*}{T(t)}\right) + g\left(\frac{i_1^*(0)T(t)i(t,a)}{i(t,0)T_1^* i_1^*(a)}\right)\right\}\mathrm{d}a \\
&+ \frac{q\beta T_1^*}{\mu_2} V_1^* f(Z(t)) - \frac{q\beta T_1^*}{c\mu_2}\mu_3 Z(t).
\end{aligned}
$$

Note that

$$
\begin{aligned}
\frac{q\beta T_1^*}{\mu_2} V_1^* f(Z(t)) - \frac{q\beta T_1^*}{c\mu_2}\mu_3 Z(t) &\leqslant \frac{q\beta T_1^*}{c\mu_2}\left[\frac{\Lambda c \mathcal{P} f'(0)}{\mu_2 \mu_3}\left(1 - \frac{1}{\mathfrak{R}_0}\right) - 1\right] \\
&= \frac{q\beta T_1^*}{c\mu_2}(\mathfrak{R}_1 - 1).
\end{aligned}
$$

Thus $\frac{\mathrm{d}W(t)}{\mathrm{d}t}|_{(1.6)} \leqslant 0$ when $\mathfrak{R}_1 < 1 < \mathfrak{R}_0$, $\frac{\mathrm{d}W(t)}{\mathrm{d}t} = 0$ if and only if $(T(t), i(t,a), V(t), Z(t)) = (T_1^*, i_1^*(a), V_1^*, 0)$. Applying Lyapunov-LaSalle theorem, the immune-inactivated steady state $E_1^* = (T_1^*, i_1^*(a), V_1^*, 0)$ of system (1.6) is globally asymptotically stable if $\mathfrak{R}_1 < 1 < \mathfrak{R}_0$. □

5.3. Global stability of immune-activated steady state

Theorem 5.4. *The immune-activated steady state $E_2^* = (T_2^*, i_2^*(a), V_2^*, Z_2^*)$ of system (1.6) is globally asymptotically stable if $\mathfrak{R}_1 > 1$.*

Proof. Let

$$
\alpha_3(a) := \int_a^\infty \left(\frac{\beta T_2^*}{\varpi(Z_2^*)} p(\epsilon) + T_2^* k(\epsilon)\right) e^{-\int_a^\epsilon \delta(s)\mathrm{d}s}\mathrm{d}\epsilon. \tag{5.12}
$$

Define the Lyapunov functional as follows

$$
L(t) := L_1(t) + L_2(t) + L_3(t) + L_4(t),
$$

where

$$L_1(t) := T_2^* g\left(\frac{T(t)}{T_2^*}\right);$$

$$L_2(t) := \int_0^\infty \alpha_3(a) i_2^*(a) g\left(\frac{i(t,a)}{i_2^*(a)}\right) da;$$

$$L_3(t) := \frac{\beta T_2^*}{\mu_2} V_2^* g\left(\frac{V(t)}{V_2^*}\right) + \frac{q\beta T_2^*}{c\mu_2}\left(Z(t) - Z_2^* - \int_{Z_2^*}^{Z(t)} \frac{f(Z_2^*)}{f(\tau)} d\tau\right).$$

Using the results in the proof of Theorem (5.3), after some calculations, we have the derivative of $L(t)$ as follows:

$$
\begin{aligned}
\frac{dL(t)}{dt} =& \mu_1 T_2^*\left(2 - \frac{T_2^*}{T(t)} - \frac{T(t)}{T_2^*}\right) - \lim_{a\to\infty} \alpha_3(a) i_2^*(a) g\left(\frac{i(t,a)}{i_2^*(a)}\right) \\
&- \int_0^\infty \frac{\beta T_2^*}{\varpi(Z_2^*)} p(a) i_2^*(a)\left\{g\left(\frac{T_2^*}{T(t)}\right) + g\left(\frac{V_2^* i(t,a)}{V(t) i_2^*(a)}\right) + g\left(\frac{i_2^*(0) T(t) V(t)}{i(t,0) T_2^* V_2^*}\right)\right\} da \\
&- \int_0^\infty T_2^* k(a) i_2^*(a)\left\{g\left(\frac{T_2^*}{T(t)}\right) + g\left(\frac{i_2^*(0) T(t) i(t,a)}{i(t,0) T_2^* i_2^*(a)}\right)\right\} da \\
&+ \frac{q\beta T_2^* V_2^* f(Z_2^*)}{\varpi(Z_2^*)}\left(\frac{Z(t)}{Z_2^*} - \frac{f(Z(t))}{f(Z_2^*)}\right)\left(\frac{f(Z_2^*)}{f(Z(t))} - 1\right).
\end{aligned}
$$

It follows from follows (A2) and (A3) that $\left(\frac{Z(t)}{Z_2^*} - \frac{f(Z(t))}{f(Z_2^*)}\right)\left(\frac{f(Z_2^*)}{f(Z(t))} - 1\right) \leqslant 0$, thus $\frac{dL(t)}{dt}\big|_{(1.6)} \leqslant 0$ and $\frac{dL(t)}{dt} = 0$ if and only if $(T(t), i(t,a), V(t), Z(t)) = (T_2^*, i_2^*(a), V_2^*, Z_2^*)$. Therefore, the immune-activated steady state E_2 of system (1.6) is global asymptotically stable if $\mathfrak{R}_1 > 1$ by Lyapunov-LaSalle theorem. □

6. Special case and numerical simulation

6.1. Example

In this subsection, as special case for the age-infection model (1.6) and (1.7) with general nonlinear immune response $f(Z)$, we introduce the following age-infection model with saturation immune response function, which have been used for modeling HIV infection in [30, 42].

$$
\begin{cases}
\dfrac{dT(t)}{dt} = \Lambda - \mu_1 T(t) - \beta T(t) V(t) - \displaystyle\int_0^\infty k(a) T(t) i(t,a) da, \\[2ex]
\left(\dfrac{\partial}{\partial t} + \dfrac{\partial}{\partial a}\right) i(t,a) = -\delta(a) i(t,a), \\[2ex]
\dfrac{dV(t)}{dt} = \displaystyle\int_0^\infty p(a) i(t,a) da - \mu_2 V(t) - \dfrac{qV(t)Z(t)}{h + Z(t)}, \\[2ex]
\dfrac{dZ(t)}{dt} = \dfrac{cV(t)Z(t)}{h + Z(t)} - \mu_3 Z(t)
\end{cases}
\tag{6.1}
$$

with the boundary and initial condition

$$
\begin{cases}
i(t,0) = \beta T(t) V(t) + \displaystyle\int_0^\infty k(a) T(t) i(t,a) da, \\[2ex]
T(0) = T_0 > 0, \;\; V(0) = V_0 > 0, \;\; Z(0) = Z_0 > 0 \;\; \text{and} \;\; i(0,a) = i_0(a) \in L_+^1(0,\infty).
\end{cases}
\tag{6.2}
$$

The model without cell-to-cell transmission of system (6.1) with (6.2) has been studied in [30]. It is easy to see that $f(Z) = \frac{Z(t)}{h+Z(t)}$ satisfy (A2) and (A3). System (6.1) with (6.2) is a special case of the original system (1.6) and (1.7).

The virus-free equilibrium of system (6.1) with (6.2) is similar to the previous one, $E_{01} = (T_0, 0, 0, 0)$, where $T_0 = \frac{\Lambda}{\mu_1}$. By some calculation, we obtain the basic reproduction number and immune-activated reproduction number of system (6.1) with (6.2) as $\mathfrak{R}_{01} = \frac{\beta T_0 \mathcal{P}}{\mu_2} + T_0 \mathcal{K}$ and $\mathfrak{R}_{11} = \frac{\Lambda c \mathcal{P}}{h \mu_2 \mu_3} \left(1 - \frac{1}{\mathfrak{R}_0} \right)$, respectively. We have the following corollary:

Corollary 6.1. *For system (6.1) with (6.2), there are two threshold parameters $\mathfrak{R}_{01}$ and $\mathfrak{R}_{11}$ with $\mathfrak{R}_{01} > \mathfrak{R}_{11}$ such that*

(i) *If $\mathfrak{R}_{01} < 1$, there exists a virus-free steady state E_{01}, and E_{01} is globally asymptotically stable;*

(ii) *If $\mathfrak{R}_{11} < 1 < \mathfrak{R}_{01}$, there exists a immune-inactivated steady state E_{11} which is globally asymptotically stable;*

(iii) *If $\mathfrak{R}_{11} > 1$, there exists a immune-activated steady state E_{21} which is globally asymptotically stable.*

Table 2. Parameter values for numerical simulations.

Parameter	Value	Unite	Case 1	Case 2	Case 3	Ref.
Λ	$0 \sim 100$	cells ml-day^{-1}	1.2	8	100	[44]
β	$5 \times 10^{-7} \sim 0.5$	ml virion-day^{-1}	0.001	0.001	0.001	[42]
μ_1	$0.007 \sim 0.1$	day^{-1}	0.01	0.01	0.01	[44]
μ_2	$2.4 \sim 3$	day^{-1}	6	6	6	[44]
μ_3	0.3	day^{-1}	0.3	0.3	0.3	[45]
q	0.006	ml cell^{-1} day^{-1}	0.006	0.006	0.006	[45]
c	0.1	ml virion^{-1}day^{-1}	0.1	0.1	0.1	[45]
h	$1 \sim 100$	Saturation constant	10	10	100	Assumed

6.2. Numerical simulation

In this subsection, we perform some numerical simulations to the validity of the theoretical result of this paper. Specifically, we focus on the age-infection model with saturation immune response function (see model (6.1)).

The parameter values will be used in numerical simulation are listed in Table 2. Furthermore, we set the maximum age for the viral production as $a^{\dagger} = 10$ and we set

$$\delta(a) = 0.03 \left(1 + \sin \frac{(a-5)\pi}{10} \right), \quad p(a) = 2.9 \left(1 + \sin \frac{(a-5)\pi}{10} \right)$$

and

$$k(a) = 0.0003 \left(1 + \sin \frac{(a-5)\pi}{10} \right).$$

Thus, the averages of $\delta(a)$, $p(a)$ and $k(a)$ are 0.03, 2.9 and 0.0003, which are the same in [20, 43].

Numerical simulation shows the following three cases:

Case 1: Choose parameter values as in Case 1 of Table 2, then we can calculate the basic reproduction number as $\mathfrak{R}_0 \approx 0.8093 < 1$. Corollary 6.1 asserts that the virus-free steady state of system (6.1) with (6.2) is globally asymptotically stable. From Figure 1, one can observe that the levels of all compartmental individuals tend to stable values, where $T(t)$, $V(t)$, $i(t,a)$ and $Z(t)$ converge to a virus-free steady states $(100,0,0,0)$.
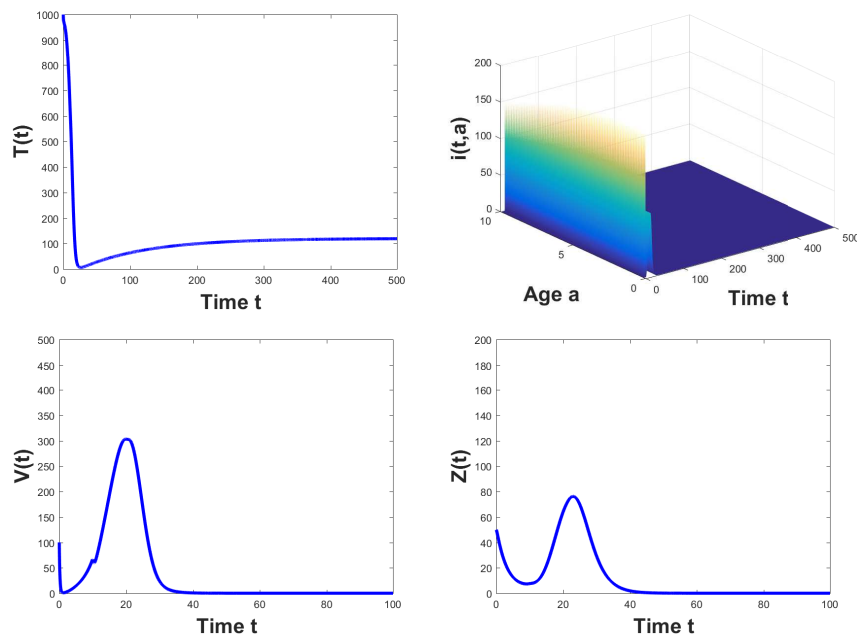
Figure 1. The long time dynamical behaviors of system (6.1) with (6.2) for $\mathfrak{R}_0 = 0.8093 < 1$, that is, the virus-free steady state of system (6.1) with (6.2) is globally asymptotically stable.

Case 2: Choose parameter values as in Case 2 of Table 2. By some computing, we can obtain that $\mathfrak{R}_0 \approx 5.3952 > 1 > \mathfrak{R}_1 \approx 0.9040$. From Corollary 6.1, we derive that immune-inactivated infection steady state is globally asymptotically stable. Numerical simulation illustrates this fact (see Figure 2).

Case 3: Choose parameter values as in Case 3 of Table 2. Similarly, we can obtain that $\mathfrak{R}_0 \approx 29.9893 > 1$ and $\mathfrak{R}_1 \approx 1.3408 > 1$. Numerical simulation shows that the levels of all compartmental individuals tend to stable values (see Figure 3), that is, immune-inactivated infection steady state is globally asymptotically stable.
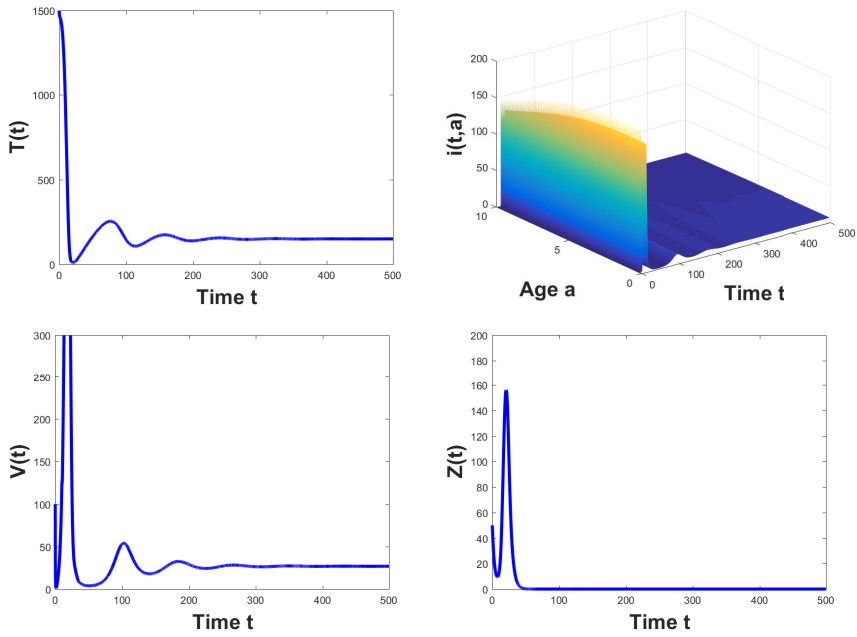
Figure 2. The long time dynamical behaviors of system (6.1) with (6.2) for $\mathfrak{R}_0 \approx 5.3952$ and $\mathfrak{R}_1 \approx 0.9040$, that is, the immune-activated steady state of system (6.1) with (6.2) is globally asymptotically stable.
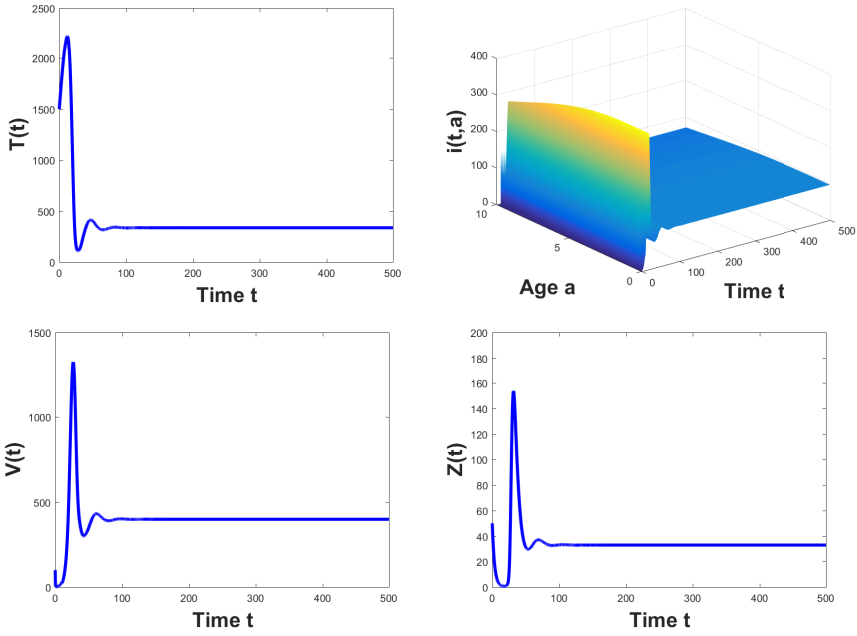

Figure 3. The long time dynamical behaviors of system (6.1) with (6.2) for $\mathfrak{R}_0 \approx 29.9893 > 1$ and $\mathfrak{R}_1 \approx 1.3408 > 1$, that is, the immune-activated steady state of system (6.1) with (6.2) is globally asymptotically stable.

7. Conclusion and discussion

In this paper, we proposed and investigated an age-structured within-host viral infection model with cell-to-cell transmission and general humoral immunity response. We have shown that the global stability of equilibria of model (1.6) are determined by the corresponding basic reproduction numbers $\mathfrak{R}_0$ and the basic immune reproductive number $\mathfrak{R}_1$. That is, when $\mathfrak{R}_0 < 1$, the virus-free steady state is globally asymptotically stable, which means that the viruses are cleared and immune response is not active; when $\mathfrak{R}_1 < 1 < \mathfrak{R}_0$, the immune-inactivated infection steady state exists and is globally asymptotically stable, which means that viral infection becomes chronic and humoral immune response would not be activated; and when $\mathfrak{R}_1 > 1$, the immune-activated infection steady state exists and is globally asymptotically stable, in this case the infection causes a persistent humoral immune response and is chronic.

Now, we show the relevance of model formulations between our age-structured model (1.6) and the standard ODE models. We consider $\delta(a) \equiv \delta$, $k(a) \equiv k$ and $p(a) \equiv p$ in model (1.6). Letting

$$I(t) = \int_0^\infty i(t, a) \mathrm{d}a.$$

Recall that

$$i(t, 0) = \beta T(t)V(t) + kT(t)I(t),$$

then we have

$$\begin{aligned}
\frac{\mathrm{d}I(t)}{\mathrm{d}t} &= \int_0^\infty \frac{\partial i(t, a)}{\partial t} \mathrm{d}a = -\int_0^\infty \left(\frac{\partial i(t, a)}{\partial a} + \delta i(t, a) \right) \mathrm{d}a \\
&= i(t, 0) - \int_0^\infty \delta i(t, a) \mathrm{d}a \\
&= \beta T(t)V(t) + kT(t)I(t) - \delta I(t),
\end{aligned}$$

here we assume that $\lim_{a \to \infty} i(t, a) = 0$, which means that there is no biological individual can live forever. Thus, system (1.6) is equivalent to the following ODE model as

$$\begin{cases}
\dfrac{\mathrm{d}T(t)}{\mathrm{d}t} = \Lambda - \mu_1 T(t) - \beta T(t)V(t) - kT(t)I(t), \\[2mm]
\dfrac{\mathrm{d}I(t)}{\mathrm{d}t} = \beta T(t)V(t) + kT(t)I(t) - \delta I(t), \\[2mm]
\dfrac{\mathrm{d}V(t)}{\mathrm{d}t} = pI(t) - \mu_2 V(t) - qV(t)f(Z(t)), \\[2mm]
\dfrac{\mathrm{d}Z(t)}{\mathrm{d}t} = cV(t)f(Z(t)) - \mu_3 Z(t),
\end{cases} \tag{7.1}$$

which is the model studied by [23] when $f(Z) = Z$ and $k = 0$. In fact, we have not found the above model in any existing literatures, but we think it has the same dynamic behavior with (1.6).

It is necessary to mention it here, in the proof of Lemma 4.1, there may exists zero eigenvalue if $R_0 = 1$, and it may lead to more complex dynamic behavior. For example, Qesmi et al. [46] propose a mathematical model describing the dynamics of hepatitis B or C virus infection with age-structure, and

they found that when $\mathfrak{R}_0 = 1$, the system may undergo a backward bifurcation. In a recent work [22], Zhang and Liu studied an age-structured HIV model with cell-to-cell transmission and logistic growth in uninfected cells. They have shown that there exists Hopf bifurcation of the model by using the Hopf bifurcation theory for semilinear equations with non-dense domain. Introducing logistic growth in uninfected cells to model (1.6), it will be interesting to investigate the existence of a Hopf bifurcation. We leave the above two studies for future consideration.

Acknowledgments

Conflict of interest

All authors declare no conflicts of interest in this paper.

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