Journal of Inequalities and Applications
a SpringerOpen Journal

RESEARCH Open Access

Global dynamics of a delayed latent virus model with both virus-to-cell and cell-to-cell transmissions and humoral immunity

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Abstract

In this paper, the dynamical behaviors for multiple delayed latent virus model with virus-to-cell infection and cell-to-cell transmissions and humoral immunity are investigated. The virus-to-cell and cell-to-cell incidence rates are modeled by general nonlinear functions. The basic reproduction number R_0 and the humoral immune response number R_1 are calculated and proved to be threshold conditions determining the local and global properties of the virus model. The existence of Hopf bifurcation with immune delay as a bifurcation parameter is presented, and the effects of some key parameters on viral dynamics are revealed by numerical simulations.

Keywords: Virus infection model; Cell-to-cell transmission; Latent infection; Stability; Hopf bifurcation

1 Introduction

The role of immune response in controlling within-host dynamics of human viruses such as human immunodeficiency virus (HIV), human T-cell leukemia virus (HTLV), hepatitis C virus (HCV), and hepatitis B virus (HBV) is important. Mathematical modeling and analysis have been essential tools to get a better systematic understanding of within-host viral infection. Nowak et al. [1] designed a mathematical model including uninfected cells, infected cells, and virus to describe HIV-1 infection. Several virus dynamics models have been further constructed and analyzed [2–19]. In different virus infections, immunity system protects us against pathogens. In cell-mediated immune response, activated effector T cells can detect peptide antigens and destroy infected cells. As for humoral immunity, matured B cells migrate from bone marrow to other lymphatic organs, where they begin to generate antibodies to remove the viruses [20]. In some diseases such as malaria, humoral immune response is more powerful than cell-mediated immune response [21]. Murase et al. [22] have extended the basic viral infection model presented in [1] by integrating the basic dynamics of the interaction between uninfected cells, infected cells, viruses, and immune cells.

It is mentioned in [2, 3] that cell-to-cell transmission seems to be a more potent and efficient means of virus propagation than the virus-to-cell transmission. Various models

of viral infection with two ways of transmission have been developed by many researchers [4–11, 16, 17, 19]. A recent review on modeling viral spread can be found in [8]. Li and Wang in [9] dealt with the global dynamics of an HIV infection model which incorporated direct cell-to-cell transmission. Meanwhile, Lai and Zou [10] studied the effect of cell-to-cell transfer of HIV-1 on the virus dynamics. Lin et al. [11] have proposed a delayed viral infection model with humoral immunity and both virus-to-cell and cell-to-cell transmissions, but the latently infected cells has been ignored. Miao et al. [12] have proposed a virus dynamics model with humoral impairment. The model presented in [12] has neglected the latently infected cells and cell-to-cell transmission. In a very recent work, Elaiw et al. [13] have studied the global stability of an HIV infection model with impairment of B-cell functions, but the cell-to-cell transmission has been ignored.

In case of HIV infection, current treatment consisting of several antiretroviral drugs can suppress viral replication to a low level but cannot eradicate the virus. An important reason is that HIV provirus can reside in latently infected cells [14, 15]. Latently infected cells live long, are not affected by antiretroviral drugs or immune responses, but can be activated to produce HIV by relevant antigens [16]. Motivated by the works in [6, 10, 11, 13, 16], in this paper we investigate the effects of combining both virus-to-cell and cell-to-cell transmissions in delayed latent virus infection model with humoral immunity

$$\begin{aligned}
\dot{T}(t) &= s - d_1 T(t) - f_1\big(T(t), V(t)\big) - f_2\big(T(t), I(t)\big),\\
\dot{L}(t) &= \eta e^{-m_1\tau_1}\big\{f_1\big(T(t-\tau_1), V(t-\tau_1)\big) + f_2\big(T(t-\tau_1), I(t-\tau_1)\big)\big\}\\
&\quad - d_2 L(t) - \alpha L(t),\\
\dot{I}(t) &= (1-\eta)e^{-m_1\tau_2}\big\{f_1\big(T(t-\tau_2), V(t-\tau_2)\big) + f_2\big(T(t-\tau_2), I(t-\tau_2)\big)\big\}\\
&\quad + \alpha L(t) - d_3 I(t),\\
\dot{V}(t) &= kI(t) - d_4 V(t) - qV(t)Z(t),\\
\dot{Z}(t) &= cV(t-\tau_3)Z(t-\tau_3) - d_5 Z(t),
\end{aligned} \tag{1}$$

where $T(t)$, $L(t)$, $I(t)$, $V(t)$, and $Z(t)$ denote the concentration of uninfected cells, latently infected cells, productively infected cells, viruses, and B cells at time t. The terms s and d_1T represent the production and death rates of the uninfected cells. The death rates of latently infected cells, productively infected cells, viruses, and B cells are given by d_2L, d_3I, d_4V, and d_5Z, respectively. The viruses are produced at rate kI, and removed by the B cells at rate qVZ. The B cells are proliferated at rate cVZ. Latently infected cells can be activated by their relevant antigens to become productively infected cells at a rate α, The fractions $1-\eta$ and η with $0<\eta<1$ are the probabilities that an uninfected cell will turn into either latently infected cell or productively infected cell. The functions $f_1(T,V)$ and $f_2(T,I)$ are the virus-to-cell and cell-to-cell incidence rates, respectively; τ_1 and τ_2 represent the times between virus particle touches an uninfected cell and the cell becomes latently infected and actively infected cell, respectively; $e^{-m_1\tau_i}$, $i=1,2$, represents the damage of uninfected cells during the interval $[t-\tau_i, t]$. Antigenic stimulation generating antibody response involves a sequence of processes and needs a period of time τ_3.

We need the following assumptions on the function $f_i(T,\theta)$, $i=1,2$:

Define

$$f_{11}(T) = \lim_{V\to 0}\frac{f_1(T,V)}{V} = \frac{\partial f_1(T,0)}{\partial V}, \qquad f_{21}(T) = \lim_{I\to 0}\frac{f_2(T,I)}{I} = \frac{\partial f_2(T,0)}{\partial I}.$$

- (H_1) $f_i(T,\theta)$ is continuously differentiable; $f_i(T,\theta) > 0$ for $T \in (0,\infty), \theta \in (0,\infty)$; $f_i(T,\theta) = 0$ if and only if $T = 0$ or $\theta = 0$.
- (H_2) $\frac{\partial f_i(T,\theta)}{\partial T} > 0$ and $\frac{\partial f_i(T,\theta)}{\partial \theta} > 0$, for all $T > 0$ and $\theta > 0$, $i = 1,2$.
- (H_3) $f_{i1}(T) > 0$ and $f'_{i1}(T) > 0$ for all $T > 0$, $i = 1,2$.
- (H_4) $\frac{f_i(T,\theta)}{\theta}$ is nonincreasing with respect to θ for all $\theta > 0$, $i = 1,2$.

In this paper, the aim is to investigate a virus dynamics model which includes: (i) B-cell functions, (ii) both latently and productively infected cells, (iii) both virus-to-cell and cell-to-cell transmissions, (iv) three time delays, (v) general virus-to-cell and cell-to-cell incidence rates. Our purpose is to investigate the dynamical properties of model (1), expressing the stability of equilibria and the existence of Hopf bifurcation. The reproduction numbers for viral infection and antibody response are calculated. By using Lyapunov functionals and LaSalle's invariance principle, the threshold conditions for the global asymptotic stability of infection-free equilibrium E_0, immune-free equilibrium E_1, and infection equilibrium E_2 with antibody response when the delay $\tau_3 = 0$ are established. By using the linearization method, the instability of equilibria E_0 and E_1, respectively, are also established. Furthermore, by using the numerical simulation method, we will discuss the existence of the Hopf bifurcation and stability switches at equilibrium E_2 when $\tau_3 > 0$.

The organization of our paper is as follows. In Sect. 2, the basic properties of model (1) for the boundedness of solutions, the threshold values and the existence of equilibria are discussed. In Sect. 3, the threshold conditions on the global stability and instability for equilibria E_0, E_1, and E_2 are stated. In Sect. 4, the numerical simulations are presented to further illustrate the dynamical behavior of the model and study the effects of cell-to-cell transmission, viral production rate, death rate of infected cells, and viral removal rate on viral dynamics, respectively. Besides, we perform a sensitivity analysis of reproduction ratios. Finally, we will give a conclusion.

2 Boundedness and equilibrium

Let $\tau = \max\{\tau_1,\tau_2,\tau_3\}$ and $R^5_+ = \{(x_1,x_2,x_3,x_4,x_5) : x_i \geq 0, i = 1,2,3,4,5\}$. By $C([-\tau,0],R^5_+)$ we denote the space of continuous functions mapping interval $[-\tau,0]$ into R^5_+ with norm $\|\phi\| = \sup_{-\tau\leq t\leq 0}\{|\phi(t)|\}$ for any $\phi \in C([-\tau,0],R^5_+)$.

The initial conditions for model (1) are given as follows:

$$\begin{cases} (T(\theta),L(\theta),I(\theta),V(\theta),Z(\theta)) = (\phi_1(\theta),\phi_2(\theta),\phi_3(\theta),\phi_4(\theta),\phi_5(\theta)), \\ \phi_i(\theta) \geq 0, \qquad \theta \in [-\tau,0), \qquad \phi_i(0) > 0 \quad (i = 1,2,3,4,5), \end{cases} \tag{2}$$

where $(\phi_1(\theta),\phi_2(\theta),\phi_3(\theta),\phi_4(\theta),\phi_5(\theta)) \in C([-\tau,0],R^5_+)$. By the fundamental theory of functional differential equations [23, 24], it is easy to see that model (1) admits a unique solution $(T(t),L(t),I(t),V(t),Z(t))$ satisfying the initial conditions (2). We have the following basic result of model (1).

Theorem 2.1 *Let $(T(t),L(t),I(t),V(t),Z(t))$ be the solution of model (1) satisfying initial conditions (2), then $T(t)$, $L(t)$, $I(t)$, $V(t)$, and $Z(t)$ are positive and ultimately bounded.*

Proof We first show that $T(t) > 0$ for all $t > 0$. Assume that there exists a $t_1 > 0$ such that $T(t_1) = 0$, $T(t) > 0$, $t \in [0, t_1)$. Thus, $T'(t_1) \leq 0$. From the first equation of (1), we have $T'(t_1) = s > 0$, which is a contradiction. This implies that $T(t) > 0$ for all $t > 0$. By the last three equations of model (1), we have

$$\begin{aligned}
L(t) &= L(0)e^{-(\alpha+d_2)t} + \int_0^t \eta e^{-m_1\tau_1}\big\{f_1\big(T(\xi-\tau_1), V(\xi-\tau_1)\big) \\
&\quad + f_2\big(T(\xi-\tau_1), I(\xi-\tau_1)\big)\big\}e^{-(\alpha+d_2)(t-\xi)}\,d\xi, \\
I(t) &= I(0)e^{-d_3t} + \int_0^t (1-\eta)e^{-m_1\tau_2}\big\{f_1\big(T(\xi-\tau_2), V(\xi-\tau_2)\big) \\
&\quad + f_2\big(T(\xi-\tau_2), I(\xi-\tau_2)\big) + \alpha L(\xi)\big\}e^{-d_3(t-\xi)}\,d\xi, \\
V(t) &= V(0)e^{-(qZ+d_4)t} + \int_0^t kI(\xi)e^{-(qZ+d_4)(t-\xi)}\,d\xi, \\
Z(t) &= Z(0)e^{-d_5t} + \int_0^t cV(\xi-\tau_3)Z(\xi-\tau_3)e^{-d_5(t-\xi)}\,d\xi,
\end{aligned}$$

which shows that $L(t) > 0$, $I(t) > 0$, $V(t) > 0$, and $Z(t) > 0$ for a small $t > 0$. Now, we prove that $L(t) > 0$, $I(t) > 0$, $V(t) > 0$, and $Z(t) > 0$ for all $t > 0$. Assume that $t_2 > 0$ is the first time such that

$$\min\big\{L(t_2), I(t_2), V(t_2), Z(t_2)\big\} = 0.$$

If $L(t_2) = 0$, $L(t) > 0$ for $t \in [0, t_2)$ and $I(t) > 0$, $V(t) > 0$, $Z(t) > 0$, $t \in [0, t_2]$, then we have $L'(t_2) \leq 0$. On the other hand, from the second equation of (1), we have

$$\dot{L(t_2)} = \eta e^{-m_1\tau_1}\big\{f_1\big(T(t_2-\tau_1), V(t_2-\tau_1)\big) + f_2\big(T(t_2-\tau_1), I(t_2-\tau_1)\big)\big\} > 0.$$

This leads to a contradiction.

If $I(t_2) = 0$, $I(t) > 0$ for $t \in [0, t_2)$ and $L(t) > 0$, $V(t) > 0$, and $Z(t) > 0$, $t \in [0, t_2]$, we also have $\dot{I(t_2)} \leq 0$. However, from the third equation, we have

$$\begin{aligned}
\dot{I(t_2)} &= (1-\eta)e^{-m_1\tau_2}\big\{f_1\big(T(t_2-\tau_2), V(t_2-\tau_2)\big) \\
&\quad + f_2\big(T(t_2-\tau_2), I(t_2-\tau_2)\big) + \alpha L(t_2)\big\} \\
&> 0.
\end{aligned}$$

This also leads to a contradiction.

Similarly, we know that $V(t_2) = 0$ and $Z(t_2) = 0$ are impossible. Thus, $T(t) > 0$, $L(t) > 0$, $I(t) > 0$, $V(t) > 0$, and $Z(t) > 0$ for all $t > 0$.

Next, we prove the boundedness of the solution of model (1) with the initial condition (2). From the positivity of the solution and the first equation of (1), we obtain

$$\dot{T(t)} = s - d_1T(t),$$

which yields

$$\limsup_{t\to\infty} T(t) \leq \frac{s}{d_1}.$$

Let

$$N_1(t) = \eta T(t) + L(t+\tau_1)e^{m_1\tau_2}.$$

Calculating the derivative of $N_1(t)$ along solutions of model (1), we have

$$\begin{aligned}\dot{N}_1(t) &= \eta s - \eta d_1 T(t) - (\alpha + d_2)e^{m_1\tau_1}L(t+\tau_1)\\ &\leq \eta s - \sigma_1 N_1(t),\end{aligned}$$

where $\sigma_1 = \min\{d_1, \alpha + d_2\}$. This yields

$$\limsup_{t\to\infty} N_1(t) \leq \frac{s}{\sigma_1}.$$

Denote

$$N_2(t) = (1-\eta)T(t-\tau_2) + e^{m_1\tau_2}I(t) + \frac{d_3 e^{m_1\tau_2}}{2k}V(t) + \frac{d_3 q e^{m_1\tau_2}}{2ck}Z(t+\tau_3).$$

Calculating the derivative of $N_2(t)$ along solutions of model (1), we have

$$\begin{aligned}\dot{N}_2(t) &= (1-\eta)s - d_1(1-\eta)T(t-\tau_2) + \alpha e^{m_1\tau_2}L(t) - \frac{d_3 e^{m_1\tau_2}}{2}I(t)\\ &\quad - \frac{d_3 d_4 e^{m_1\tau_2}}{2k}V(t) - \frac{d_3 d_5 q e^{m_1\tau_2}}{2ck}Z(t+\tau_3)\\ &\leq a - \sigma_2 N_2(t),\end{aligned}$$

where

$$\sigma_2 = \min\left\{d_1, \frac{d_3}{2}, d_4, d_5\right\},$$

$$a = (1-\eta)s + \frac{\alpha\eta s e^{m_1(\tau_2-\tau_1)}}{\sigma_1}.$$

This implies that $\limsup_{t\to\infty} N_2(t) \leq \frac{a}{\sigma_2}$, and hence, $I(t)$, $V(t)$, and $Z(t)$ are bounded.

Next, we discuss the existence of equilibria of model (1). It always has an infection-free equilibrium $E_0 = (T_0, 0, 0, 0, 0)$, where $T_0 = \frac{s}{d_1}$. Inspired by the method in [25, 26], we consider the infection and viral production, and define matrices $\mathbb{F}$ and $\mathbb{V}$ as

$$\mathbb{F} = \begin{pmatrix} 0 & \eta e^{-m_1\tau_1}\cdot\frac{\partial f_2(\frac{s}{d_1})}{\partial I} & \eta e^{-m_1\tau_1}\cdot\frac{\partial f_1(\frac{s}{d_1})}{\partial V} \\ 0 & (1-\eta)e^{-m_1\tau_2}\cdot\frac{\partial f_2(\frac{s}{d_1})}{\partial I} & (1-\eta)e^{-m_1\tau_2}\cdot\frac{\partial f_1(\frac{s}{d_1})}{\partial V} \\ 0 & 0 & 0 \end{pmatrix}$$

and

$$\mathbb{V} = \begin{pmatrix} \alpha + d_2 & 0 & 0 \\ -\alpha & d_3 & 0 \\ 0 & -k & d_4 \end{pmatrix}.$$

Thus, the basic reproductive number, R_0, can be defined as the spectral radius of the next generation operator $\mathbb{F}\mathbb{V}^{-1}$, where

$$\mathbb{F}\mathbb{V}^{-1} = \begin{pmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ 0 & 0 & 0 \end{pmatrix},$$

where

$$\begin{aligned}
a_{11} &= \eta e^{-m_1\tau_1}\frac{\alpha}{\alpha+d_2}\left(\frac{1}{d_3}\cdot\frac{\partial f_2(\frac{s}{d_1},0)}{\partial I}+\frac{k}{d_3d_4}\cdot\frac{\partial f_1(\frac{s}{d_1},0)}{\partial V}\right),\\
a_{12} &= \eta e^{-m_1\tau_1}\left(\frac{1}{d_3}\cdot\frac{\partial f_2(\frac{s}{d_1},0)}{\partial I}+\frac{k}{d_3d_4}\cdot\frac{\partial f_1(\frac{s}{d_1},0)}{\partial V}\right),\\
a_{13} &= \eta e^{-m_1\tau_1}\frac{\partial f_1(\frac{s}{d_1},0)}{\partial V}\frac{1}{d_4},\\
a_{21} &= (1-\eta)e^{-m_1\tau_2}\frac{\alpha}{\alpha+d_2}\left(\frac{1}{d_3}\cdot\frac{\partial f_2(\frac{s}{d_1},0)}{\partial I}+\frac{k}{d_3d_4}\cdot\frac{\partial f_1(\frac{s}{d_1},0)}{\partial V}\right),\\
a_{22} &= (1-\eta)e^{-m_1\tau_2}\left(\frac{1}{d_3}\cdot\frac{\partial f_2(\frac{s}{d_1},0)}{\partial I}+\frac{k}{d_3d_4}\cdot\frac{\partial f_1(\frac{s}{d_1},0)}{\partial V}\right),\\
a_{23} &= (1-\eta)e^{-m_1\tau_2}\frac{\partial f_1(\frac{s}{d_1},0)}{\partial V}\frac{1}{d_4}.
\end{aligned}$$

Therefore,

$$R_0 = \left(\eta e^{-m_1\tau_1}\frac{\alpha}{\alpha+d_2}+(1-\eta)e^{-m_1\tau_2}\right)\left(\frac{1}{d_3}\cdot\frac{\partial f_2(\frac{s}{d_1},0)}{\partial I}+\frac{k}{d_3d_4}\cdot\frac{\partial f_1(\frac{s}{d_1},0)}{\partial V}\right),$$

which biologically describes the average number of secondary infections produced by one infected cell at the beginning of infection. In the above expression of R_0, divided into parts as $R_0 = R_{01} + R_{02}$, where $R_{01} = (\eta e^{-m_1\tau_1}\frac{\alpha}{\alpha+d_2} + (1-\eta)e^{-m_1\tau_2})\cdot\frac{k}{d_3d_4}\cdot\frac{\partial f_1(\frac{s}{d_1},0)}{\partial V}$ is the basic reproduction number via the virus-to-cell infection and $R_{02} = (\eta e^{-m_1\tau_1}\frac{\alpha}{\alpha+d_2}+(1-\eta)e^{-m_1\tau_2})\cdot\frac{1}{d_3}\cdot\frac{\partial f_2(\frac{s}{d_1},0)}{\partial I}$ is the basic reproduction number via the cell-to-cell transmission, respectively.

To find the equilibria of model (1), we need to solve

$$\begin{aligned}
&s - d_1T(t) - f_1\big(T(t),V(t)\big) - f_2\big(T(t),I(t)\big) = 0,\\
&\eta e^{-m_1\tau_1}\big\{f_1\big(T(t),V(t)\big)+f_2\big(T(t),I(t)\big)\big\} - d_2L(t) - \alpha L(t) = 0,\\
&(1-\eta)e^{-m_1\tau_2}\big\{f_1\big(T(t),V(t)\big)+f_2\big(T(t),I(t)\big)\big\} + \alpha L(t) - d_3I(t) = 0,\\
&kI(t) - d_4V(t) - qV(t)Z(t) = 0,\\
&cV(t)Z(t) - d_5Z(t) = 0.
\end{aligned} \tag{3}$$

When $Z(t) = 0$, the fourth equation of (3) leads to $I = \frac{d_4V}{k}$. From the second and third equations of (3), we obtain $L = \frac{d_3\eta e^{-m_1\tau_1}}{\alpha\eta e^{-m_1\tau_1}+(\alpha+d_2)(1-\eta)e^{-m_1\tau_2}}\cdot\frac{d_4V}{k}$. Solving T from (3), we get

$T = \frac{s}{d_1} - \frac{(\alpha+d_2)d_3d_4V}{d_1k(\alpha\eta e^{-m_1\tau_1}+(\alpha+d_2)(1-\eta)e^{-m_1\tau_2})} \triangleq h(V)$. We get from the second equation that

$$f_1\big(h(V),V\big)+f_2\left(h(V),\frac{d_4V}{k}\right)-\frac{(\alpha+d_2)d_3d_4V}{k(\alpha\eta e^{-m_1\tau_1}+(\alpha+d_2)(1-\eta)e^{-m_1\tau_2})}=0.$$

Define

$$F(V)=f_1\big(h(V),V\big)+f_2\left(h(V),\frac{d_4V}{k}\right)-\frac{(\alpha+d_2)d_3d_4V}{k(\alpha\eta e^{-m_1\tau_1}+(\alpha+d_2)(1-\eta)e^{-m_1\tau_2})},$$

then $F(0)=0$, the positive solution of $h(V)=0$ is given by

$$\bar{V}=\frac{sk(\alpha\eta e^{-m_1\tau_1}+(\alpha+d_2)(1-\eta)e^{-m_1\tau_2})}{(\alpha+d_2)d_3d_4}.$$

We can see that

$$\begin{aligned}F(\bar{V})&=f_1(0,\bar{V})+f_2\left(0,\frac{d_4\bar{V}}{k}\right)-\frac{(\alpha+d_2)d_3d_4\bar{V}}{k(\alpha\eta e^{-m_1\tau_1}+(\alpha+d_2)(1-\eta)e^{-m_1\tau_2})}\\&=-\frac{(\alpha+d_2)d_3d_4\bar{V}}{k(\alpha\eta e^{-m_1\tau_1}+(\alpha+d_2)(1-\eta)e^{-m_1\tau_2})}<0.\end{aligned}$$

Moreover,

$$\begin{aligned}F'(V)=&\frac{\partial f_1(h(V),V)}{\partial T}\cdot h'(V)+\frac{\partial f_1(T,V)}{\partial V}+\frac{\partial f_2(h(V),\frac{d_4V}{k})}{\partial T}\cdot h'(V)\\&+\frac{\partial f_2(T,I)}{\partial I}\cdot\frac{d_4}{k}-\frac{(\alpha+d_2)d_3d_4}{k(\alpha\eta e^{-m_1\tau_1}+(\alpha+d_2)(1-\eta)e^{-m_1\tau_2})}.\end{aligned}$$

Assumption (H_1) implies that $\frac{\partial f_1(T_0,V)}{\partial T}=0$ and $\frac{\partial f_2(T_0,I)}{\partial T}=0$, then

$$\begin{aligned}F'(0)=&\frac{\partial f_1(\frac{s}{d_1},V)}{\partial V}+\frac{\partial f_2(\frac{s}{d_1},I)}{\partial I}\cdot\frac{d_4}{k}-\frac{(\alpha+d_2)d_3d_4}{k(\alpha\eta e^{-m_1\tau_1}+(\alpha+d_2)(1-\eta)e^{-m_1\tau_2})}\\=&\frac{d_3d_4}{k(\frac{\alpha}{\alpha+d_2}\eta e^{-m_1\tau_1}+(1-\eta)e^{-m_1\tau_2})}(R_0-1).\end{aligned}$$

Therefore, if $R_0>1$, then $F'(0)>0$ and $\exists V_1\in(0,\bar{V})$ such that $F(V_1)=0$. Hence, model (1) has a unique immune-free equilibrium $E_1=(T_1,L_1,I_1,V_1,0)$, where

$$\begin{aligned}&T_1=\frac{s}{d_1}-\frac{(\alpha+d_2)d_3d_4V_1}{d_1k(\alpha\eta e^{-m_1\tau_1}+(\alpha+d_2)(1-\eta)e^{-m_1\tau_2})},\\&I_1=\frac{d_4V_1}{k},L_1=\frac{d_3\eta e^{-m_1\tau_1}}{\alpha\eta e^{-m_1\tau_1}+(\alpha+d_2)(1-\eta)e^{-m_1\tau_2}}\cdot\frac{d_4V_1}{k}.\end{aligned}$$

When $Z(t)\neq 0$, the fourth equation of (3) leads to $V=\frac{d_5}{c}$. From the second and third equations of (3), we obtain $L=\frac{d_3\eta e^{-m_1\tau_1}I}{\alpha\eta e^{-m_1\tau_1}+(\alpha+d_2)(1-\eta)e^{-m_1\tau_2}}$. Solving T from (3), we get $T=\frac{s}{d_1}-\frac{(\alpha+d_2)d_3I}{d_1(\alpha\eta e^{-m_1\tau_1}+(\alpha+d_2)(1-\eta)e^{-m_1\tau_2})}\triangleq h(I)$. We get from the second equation that

$$f_1\left(h(I),\frac{d_5}{c}\right)+f_2\big(h(I),I\big)-\frac{(\alpha+d_2)d_3I}{\alpha\eta e^{-m_1\tau_1}+(\alpha+d_2)(1-\eta)e^{-m_1\tau_2}}=0.$$

Define

$$F(I) = f_1\left(h(I), \frac{d_5}{c}\right) + f_2\big(h(I), I\big) - \frac{(\alpha + d_2)d_3 I}{\alpha\eta e^{-m_1\tau_1} + (\alpha + d_2)(1-\eta)e^{-m_1\tau_2}},$$

then $F(0) = f_1(\frac{s}{d_1}, \frac{d_5}{c}) > 0$ and the positive solution of $h(I) = 0$ is given by

$$\bar{I} = \frac{s(\alpha\eta e^{-m_1\tau_1} + (\alpha + d_2)(1-\eta)e^{-m_1\tau_2})}{(\alpha + d_2)d_3}.$$

We can see that

$$\begin{aligned} F(\bar{I}) &= f_1\left(0, \frac{d_5}{c}\right) + f_2(0, \bar{I}) - \frac{(\alpha + d_2)d_3\bar{I}}{\alpha\eta e^{-m_1\tau_1} + (\alpha + d_2)(1-\eta)e^{-m_1\tau_2}} \\ &= -\frac{(\alpha + d_2)d_3\bar{I}}{\alpha\eta e^{-m_1\tau_1} + (\alpha + d_2)(1-\eta)e^{-m_1\tau_2}} < 0. \end{aligned}$$

Moreover,

$$\begin{aligned} F'(I) = {} & \frac{\partial f_1(h(I), \frac{d_5}{c})}{\partial T} \cdot h'(I) + \frac{\partial f_2(h(I), I)}{\partial T} \cdot h'(I) \\ & + \frac{\partial f_2(T, I)}{\partial I} - \frac{(\alpha + d_2)d_3}{\alpha\eta e^{-m_1\tau_1} + (\alpha + d_2)(1-\eta)e^{-m_1\tau_2}}, \end{aligned}$$

then we have

$$\begin{aligned} F'(0) &= \frac{\partial f_2(\frac{s}{d_1}, 0)}{\partial I} - \frac{(\alpha + d_2)d_3d_4}{\alpha\eta e^{-m_1\tau_1} + (\alpha + d_2)(1-\eta)e^{-m_1\tau_2}} \\ &= \frac{(\alpha + d_2)d_3d_4}{\alpha\eta e^{-m_1\tau_1} + (\alpha + d_2)(1-\eta)e^{-m_1\tau_2}}(R_{02} - 1). \end{aligned}$$

Therefore, if $R_{02} > 1$, then $F'(0) > 0$ and $\exists I_2 \in (0, \bar{I})$ such that $F(I_2) = 0$.

Define

$$R_1 = \frac{cV_1}{d_5}.$$

From the fourth equation of (3), we obtain that $Z_2 = \frac{kI_2 - d_4V_2}{qV_2} = \frac{d_4(\frac{kcI_2}{d_4d_5} - 1)}{q} = \frac{d_4(R_1 - 1)}{q}$. Hence, when $R_1 > 1$, model (1) has a unique infection equilibrium $E_2 = (T_2, L_2, I_2, V_2, Z_2)$ with antibody response, where

$$\begin{aligned} T_2 &= \frac{s}{d_1} - \frac{(\alpha + d_2)d_3I_2}{d_1(\alpha\eta e^{-m_1\tau_1} + (\alpha + d_2)(1-\eta)e^{-m_1\tau_2})}, \\ L_2 &= \frac{d_3\eta e^{-m_1\tau_1}I}{\alpha\eta e^{-m_1\tau_1} + (\alpha + d_2)(1-\eta)e^{-m_1\tau_2}}, \quad V_2 = \frac{d_5}{c}. \end{aligned}$$

□

3 Stability analysis

To state the global stability on E_0, we need an additional assumption:

(H_5) The supremum of $\frac{f_{21}(T)}{f_{11}(T)}$ on $(0, T_0]$ is achieved at $T = T_0$.

Theorem 3.1 (*a*) *If* $R_0 \le 1$, *then the infection-free equilibrium* E_0 *is globally asymptotically stable*.

(*b*) *If* $R_0 > 1$, *then the equilibrium* E_0 *is unstable*.

Proof Consider claim (a). Define a Lyapunov functional

$$\begin{aligned} U_1(t) = {} & \left(\frac{\alpha\eta e^{-m_1\tau_1}}{\alpha + d_2} + e^{-m_1\tau_1}(1-\eta)\right)\left(T(t) - \int_{\bar{T}_0}^{T(t)} \lim_{V\to 0}\frac{f_1(T_0,V)}{f_1(\theta,V)}\,\mathrm{d}\theta\right) \\ & + \frac{\alpha}{\alpha + d_2}L(t) + I(t) + \frac{(1-R_{02})d_3V(t)}{k} + \frac{(1-R_{02})d_3q}{ck}Z(t) \\ & + \frac{\alpha\eta e^{-m_1\tau_1}}{\alpha + d_2}\int_{-\tau_1}^{0}\left(f_1\big(T(t+\theta),V(t+\theta)\big) + f_2\big(T(t+\theta),I(t+\theta)\big)\right)\mathrm{d}\theta \\ & + e^{-m_1\tau_2}(1-\eta)\int_{-\tau_1}^{0}\left(f_1\big(T(t+\theta),V(t+\theta)\big)\right. \\ & \left. + f_2\big(T(t+\theta),I(t+\theta)\big)\right)\mathrm{d}\theta + \frac{(1-R_{02})d_3q}{k}\int_{-\tau_1}^{0}V(t+\theta)Z(t+\theta)\,\mathrm{d}\theta. \end{aligned}$$

Calculating the derivative of $U_1(t)$ along positive solution of model (1) and noting that $T_0 = \frac{s}{d_1}$, we obtain

$$\begin{aligned} \frac{dU_1(t)}{dt} = {} & \left(\frac{\alpha\eta e^{-m_1\tau_1}}{\alpha + d_2} + e^{-m_1\tau_1}(1-\eta)\right)\left(1 - \lim_{V\to 0}\frac{f_1(T_0,V)}{f_1(T,V)}\right)(d_1T_0 - d_1T) \\ & + \left(\frac{\alpha\eta e^{-m_1\tau_1}}{\alpha + d_2} + e^{-m_1\tau_1}(1-\eta)\right)\lim_{V\to 0}\frac{f_1(T_0,V)}{f_1(T,V)}\cdot f_1(T,V) \\ & + \left(\frac{\alpha\eta e^{-m_1\tau_1}}{\alpha + d_2} + e^{-m_1\tau_1}(1-\eta)\right)\lim_{V\to 0}\frac{f_1(T_0,V)}{f_1(T,V)}\cdot f_2(T,I) \\ & - \frac{(1-R_{02})d_3d_4}{k}V - R_{02}d_3I - \frac{(1-R_{02})d_3d_5q}{ck}Z, \end{aligned}$$

where

$$\begin{aligned} & \left(\frac{\alpha\eta e^{-m_1\tau_1}}{\alpha + d_2} + e^{-m_1\tau_1}(1-\eta)\right)\lim_{V\to 0}\frac{f_1(T_0,V)}{f_1(T,V)}\cdot f_1(T,V) - \frac{(1-R_{02})d_3d_4}{k}V \\ & \quad = \frac{d_3d_4}{k}(R_0 - 1)V(t) \end{aligned}$$

and

$$\begin{aligned} & \left(\frac{\alpha\eta e^{-m_1\tau_1}}{\alpha + d_2} + e^{-m_1\tau_1}(1-\eta)\right)\lim_{V\to 0}\frac{f_1(T_0,V)}{f_1(T,V)}\cdot f_2(T,I) - R_{02}d_3I \\ & \quad = \left\{\left(\frac{\alpha\eta e^{-m_1\tau_1}}{\alpha + d_2} + e^{-m_1\tau_1}(1-\eta)\right)\cdot\lim_{V\to 0}\frac{f_1(T_0,0)}{f_1(T,0)}\cdot\lim_{I\to 0}\frac{f_2(T,I)}{I}\right. \\ & \qquad \left. - \frac{\partial f_2(T_0,0)}{\partial I}\left(\frac{\alpha\eta e^{-m_1\tau_1}}{\alpha + d_2} + e^{-m_1\tau_1}(1-\eta)\right)\right\}I \\ & \quad < 0. \end{aligned}$$

From Assumption (H_3), we have

$$\left(1-\lim_{V\to 0}\frac{f_1(T_0,V)}{f_1(T,V)}\right)(d_1T_0-d_1T)<0.$$

Moreover, by utilizing Assumptions (H_4)–(H_5), we obtain

$$\frac{f_1(T_0,V)}{f_1(T,V)}\cdot\frac{f_2(T,I)}{I}\le\frac{f_{21}(T)/f_{11}(T)}{f_{21}(T_0)/f_{11}(T_0)}\cdot f_{21}(T_0)\le f_{21}(T_0)\quad\text{for } T\le T_0.$$

Therefore, we obtain

$$\frac{dU_1(t)}{dt}\le\frac{d_3d_4}{k}(R_0-1)V(t)-\frac{(1-R_{02})d_3d_5q}{ck}Z.$$

Note that $\frac{dU_1(t)}{dt}=0$ if and only if $T=T_0$, $L=0$, $V=0$, and $Z=0$. So, the maximal compact invariant set in $\{(T,L,I,V,Z)\in R_+^5:\frac{dU_1(t)}{dt}=0\}$ is the singleton $\{E_0\}$. By the LaSalle's invariance principle [23], E_0 is globally asymptotically stable when $R_0\le 1$.

Next, we consider conclusion (b). The characteristic equation of the linearized system of model (1) at the equilibrium E_0 is

$$(\lambda+d_1)(\lambda+d_5)F(\lambda)=0,$$

where

$$F(\lambda)=\lambda^3+a_1\lambda^2+a_2\lambda+a_3,$$

with

$$\begin{aligned}
a_1&=\alpha+d_2+d_3+d_4-e^{-(\lambda+m_1)\tau_2}(1-\eta)\frac{\partial f_2(T_0,0)}{\partial I},\\
a_2&=e^{-(\lambda+m_1)\tau_2}(1-\eta)\frac{\partial f_2(T_0,0)}{\partial I}(\alpha+d_2+d_4)+d_3d_4+(\alpha+d_2)(d_3+d_4)\\
&\quad-\alpha\eta e^{-(\lambda+m_1)\tau_1}\frac{\partial f_2(T_0,0)}{\partial I}-k(1-\eta)e^{-(\lambda+m_1)\tau_2}\frac{\partial f_1(T_0,0)}{\partial V},\\
a_3&=(\alpha+d_2)\left(d_4\left(-e^{-(\lambda+m_1)\tau_2}(1-\eta)\frac{\partial f_2(T_0,0)}{\partial I}+d_3\right)\right.\\
&\quad\left.-k(1-\eta)e^{-(\lambda+m_1)\tau_2}\frac{\partial f_1(T_0,0)}{\partial V}\right)\\
&\quad+\alpha\left(-d_4\eta e^{-(\lambda+m_1)\tau_1}\frac{\partial f_2(T_0,0)}{\partial I}-k\eta e^{-(\lambda+m_1)\tau_1}\frac{\partial f_1(T_0,0)}{\partial V}\right).
\end{aligned}$$

When $R_0>1$, we have $F(0)=d_3d_4(\alpha+d_2)(1-R_0)<0$ and $\lim_{\lambda\to\infty}F(\lambda)=+\infty$. Hence, there is a $\lambda^*>0$ such that $F(\lambda^*)=0$. Therefore, when $R_0>1$, E_0 is unstable. This completes the proof. □

We establish a set of conditions which are sufficient for the global stability of equilibria for E_1 and E_2. Here, we assume that the functions $f_1(T,V)$ and $f_2(T,I)$ satisfy the following:

(H_6)

$$f_1(T_i,V_i)f_2(T,I)I_i - f_1(T,V_i)f_2(T_i,I_i)I < 0,$$
$$f_1(T,V)V_i - f_1(T,V_i)V < 0, \quad i = 1,2.$$

Theorem 3.2 *Let $R_0 > 1$. (a) If $R_1 \le 1$, then the immune-free equilibrium E_1 is globally asymptotically stable.*

(b) If $R_1 > 1$, then the equilibrium E_1 is unstable.

Proof Letting $H(\xi) = \xi - 1 - \ln\xi$, we have that $H(\xi) \ge 0$ for all $\xi > 0$ and $H(\xi) = 0$ if and only if $\xi = 1$. Consider claim (a). Define a Lyapunov functional

$$\begin{aligned}
U_2(t) = {} & \left(\frac{\alpha\eta e^{-m_1\tau_1}}{\alpha+d_2} + e^{-m_1\tau_2}(1-\eta)\right)\left(T(t) - \int_{\bar{T}_1}^{T(t)} \frac{f_1(T_1,V_1)}{f_1(\theta,V_1)}\,\mathrm{d}\theta\right) \\
& + \frac{\alpha L_1}{\alpha+d_2} H\left(\frac{L}{L_1}\right) + I_1 H\left(\frac{I}{I_1}\right) \\
& + \left(\frac{\alpha\eta e^{-m_1\tau_1}}{\alpha+d_2} + e^{-m_1\tau_2}(1-\eta)\right)\frac{f_1(T_1,V_1)}{d_4 V_1} V_1 H\left(\frac{V}{V_1}\right) \\
& + \left(\frac{\alpha\eta e^{-m_1\tau_1}}{\alpha+d_2} + e^{-m_1\tau_2}(1-\eta)\right)\frac{f_1(T_1,V_1)q}{cd_4 V_1} Z \\
& + \frac{\alpha\eta e^{-m_1\tau_1}}{\alpha+d_2} f_1(T_1,V_1)\int_{-\tau_1}^{0} H\left(\frac{f_1(T(t+\theta),V(t+\theta))}{f_1(T_1,V_1)}\right)\mathrm{d}\theta \\
& + e^{-m_1\tau_2}(1-\eta) f_1(T_1,V_1)\int_{-\tau_2}^{0} H\left(\frac{f_1(T(t+\theta),V(t+\theta))}{f_1(T_1,V_1)}\right)\mathrm{d}\theta \\
& + \frac{\alpha\eta e^{-m_1\tau_1}}{\alpha+d_2} f_2(T_1,I_1)\int_{-\tau_1}^{0} H\left(\frac{f_2(T(t+\theta),I(t+\theta))}{f_2(T_1,I_1)}\right)\mathrm{d}\theta \\
& + e^{-m_1\tau_2}(1-\eta) f_2(T_1,I_1)\int_{-\tau_2}^{0} H\left(\frac{f_2(T(t+\theta),I(t+\theta))}{f_2(T_1,I_1)}\right)\mathrm{d}\theta \\
& + \left(\frac{\alpha\eta e^{-m_1\tau_1}}{\alpha+d_2} + e^{-m_1\tau_2}(1-\eta)\right)\frac{f_1(T_1,V_1)q}{d_4}\int_{-\tau_3}^{0} V(t+\theta)Z(t+\theta)\,\mathrm{d}\theta.
\end{aligned}$$

Calculating the derivative of $U_2(t)$ along positive solution of model (1), it follows that

$$\begin{aligned}
\frac{dU_2(t)}{dt} = {} & \left(\frac{\alpha\eta e^{-m_1\tau_1}}{\alpha+d_2} + e^{-m_1\tau_2}(1-\eta)\right)\left(1 - \frac{f_1(T_1,V_1)}{f_1(T,V_1)}\right)(d_1T_1 - d_1T) \\
& - \left(\frac{\alpha\eta e^{-m_1\tau_1}}{\alpha+d_2} + e^{-m_1\tau_2}(1-\eta)\right)(f_1(T_1,V_1) + f_2(T_1,I_1))H\left(\frac{f_1(T_1,V_1)}{f_1(T,V_1)}\right) \\
& - \frac{\alpha\eta e^{-m_1\tau_1}}{\alpha+d_2} f_1(T_1,V_1)\left(H\left(\frac{L_1 f_1(T(t-\tau_1),V(t-\tau_1))}{L f_1(T_1,V_1)}\right)\right. \\
& \left. + H\left(\frac{I_1 L}{I L_1}\right) + H\left(\frac{I V_1}{I_1 V}\right)\right) \\
& - \frac{\alpha\eta e^{-m_1\tau_1}}{\alpha+d_2} f_2(T_1,I_1)\left(H\left(\frac{L_1 f_2(T(t-\tau_1),I(t-\tau_1))}{L f_2(T_1,I_1)}\right) + H\left(\frac{I_1 L}{I L_1}\right)\right) \\
& - e^{-m_1\tau_2}(1-\eta) f_2(T_1,I_1) H\left(\frac{I_1 f_2(T(t-\tau_2),I(t-\tau_2))}{I f_2(T_1,I_1)}\right)
\end{aligned}$$

$$
\begin{aligned}
&- e^{-m_1\tau_2}(1-\eta)f_1(T_1,V_1)\left(H\left(\frac{I_1 f_1(T(t-\tau_1),V(t-\tau_1))}{If_1(T_1,V_1)}\right)+H\left(\frac{IV_1}{I_1V}\right)\right)\\
&-\left(\frac{\alpha\eta e^{-m_1\tau_1}}{\alpha+d_2}+e^{-m_1\tau_2}(1-\eta)\right)\frac{f_1(T_1,V_1)q}{d_4V_1}(V_2-V_1)Z\\
&+\left(\frac{\alpha\eta e^{-m_1\tau_1}}{\alpha+d_2}+e^{-m_1\tau_2}(1-\eta)\right)\left(\frac{f_1(T_1,V_1)f_2(T,I)}{f_1(T,V_1)}-\frac{f_2(T_1,I_1)I}{I_1}\right)\\
&+\left(\frac{\alpha\eta e^{-m_1\tau_1}}{\alpha+d_2}+e^{-m_1\tau_2}(1-\eta)\right)f_1(T_1,V_1)\left(\frac{f_1(T,V)}{f_1(T,V_1)}-\frac{V}{V_1}\right).
\end{aligned}
$$

From (H_2), (H_4), and (H_6), we have

$$
\begin{aligned}
&\left(1-\frac{f_1(T_1,V_1)}{f_1(T,V_1)}\right)(d_1T_1-d_1T)<0,\frac{f_1(T,V)}{f_1(T,V_1)}-\frac{V}{V_1}<0,\\
&\frac{f_1(T_1,V_1)f_2(T,I)}{f_1(T,V_1)}-\frac{f_2(T_1,I_1)I}{I_1}<0.
\end{aligned}
$$

Hence, $\frac{dU_2(t)}{dt}\le 0$ and $\frac{dU_2(t)}{dt}=0$ if and only if $T(t)=T_1$, $L(t)=L_1$, $I(t)=I_1$, $V(t)=V_1$, and $Z(t)=0$. From the LaSalle's invariance principle [23], we have that E_1 is globally asymptotically stable when $R_0>1$ and $R_1\le 1$.

Next, we consider conclusion (b). The characteristic equation of the linearized system of model (1) at the equilibrium E_1 is

$$h_1(\lambda)h_2(\lambda)=0,$$

where

$$h_1(\lambda)=\lambda+d_5-ce^{-\lambda\tau_3}V_1$$

and

$$
h_2(\lambda)=\begin{vmatrix}
a_{11} & 0 & \frac{\partial f_2(T_1,I_1)}{\partial I} & \frac{\partial f_1(T_1,V_1)}{\partial V}\\
a_{21} & \lambda+\alpha+d_2 & a_{23} & a_{24}\\
a_{31} & -\alpha & a_{33} & a_{34}\\
0 & 0 & -k & \lambda+d_4
\end{vmatrix},
$$

with

$$
\begin{aligned}
&a_{11}=\alpha+d_1+\frac{\partial f_1(T_1,V_1)}{\partial T}+\frac{\partial f_2(T_1,I_1)}{\partial T},\\
&a_{21}=-e^{-(m_1+\lambda)\tau_1}\eta\left(\frac{\partial f_1(T_1,V_1)}{\partial T}+\frac{\partial f_2(T_1,I_1)}{\partial T}\right),\\
&a_{23}=-e^{-(m_1+\lambda)\tau_1}\eta\frac{\partial f_2(T_1,I_1)}{\partial I},\qquad a_{24}=-e^{-(m_1+\lambda)\tau_1}\eta\frac{\partial f_1(T_1,V_1)}{\partial V},\\
&a_{31}=-e^{-(m_1+\lambda)\tau_2}(1-\eta)\left(\frac{\partial f_1(T_1,V_1)}{\partial T}+\frac{\partial f_2(T_1,I_1)}{\partial T}\right),\\
&a_{33}=\lambda-e^{-(m_1+\lambda)\tau_2}(1-\eta)\frac{\partial f_2(T_1,I_1)}{\partial I}+d_3,
\end{aligned}
$$

$$a_{34} = -e^{-(m_1+\lambda)\tau_2}(1-\eta)\frac{\partial f_1(T_1,V_1)}{\partial V}.$$

When $R_1 > 1$, we have $h_1(0) = d_5 - cV_1 < 0$. Since $\lim_{\lambda\to\infty} h_1(\lambda) = +\infty$, there is also a positive root λ^* such that $h_1(\lambda^*) = 0$. Therefore, when $R_1 > 1$, E_1 is unstable. This completes the proof. □

Theorem 3.3 *If $R_1 > 1$ and $\tau_3 = 0$, then the infection equilibrium E_2 with antibody response is globally asymptotically stable.*

Proof Define a Lyapunov functional

$$\begin{aligned}
U_3(t) = {} & \left(\frac{\alpha\eta e^{-m_1\tau_1}}{\alpha+d_2} + e^{-m_1\tau_2}(1-\eta)\right)\left(T(t) - \int_{\bar{T}_2}^{T(t)} \frac{f_1(T_2,V_2)}{f_1(\theta,V_2)}\,\mathrm{d}\theta\right) \\
& + \frac{\alpha L_2}{\alpha+d_2} H\left(\frac{L}{L_2}\right) + I_2 H\left(\frac{I}{I_2}\right) \\
& + \left(\frac{\alpha\eta e^{-m_1\tau_1}}{\alpha+d_2} + e^{-m_1\tau_2}(1-\eta)\right)\frac{f_1(T_2,V_2)}{(d_4+qZ_2)V_2} V_2 H\left(\frac{V}{V_2}\right) \\
& + \left(\frac{\alpha\eta e^{-m_1\tau_1}}{\alpha+d_2} + e^{-m_1\tau_2}(1-\eta)\right)\frac{f_1(T_2,V_2)q}{(d_4+qZ_2)V_2} Z_2 H\left(\frac{Z}{Z_2}\right) \\
& + \frac{\alpha\eta e^{-m_1\tau_1}}{\alpha+d_2} f_1(T_2,V_2)\int_{-\tau_1}^{0} H\left(\frac{f_1(T(t+\theta),V(t+\theta))}{f_1(T_2,V_2)}\right)\mathrm{d}\theta \\
& + e^{-m_1\tau_2}(1-\eta) f_1(T_2,V_2)\int_{-\tau_2}^{0} H\left(\frac{f_1(T(t+\theta),V(t+\theta))}{f_1(T_2,V_2)}\right)\mathrm{d}\theta \\
& + \frac{\alpha\eta e^{-m_1\tau_1}}{\alpha+d_2} f_2(T_2,I_2)\int_{-\tau_1}^{0} H\left(\frac{f_2(T(t+\theta),I(t+\theta))}{f_2(T_2,I_2)}\right)\mathrm{d}\theta \\
& + e^{-m_1\tau_2}(1-\eta) f_2(T_2,I_2)\int_{-\tau_2}^{0} H\left(\frac{f_2(T(t+\theta),I(t+\theta))}{f_2(T_2,I_2)}\right)\mathrm{d}\theta.
\end{aligned}$$

Calculating the derivative of $U_3(t)$ along positive solution of model (1), it follows that

$$\begin{aligned}
\frac{dU_3(t)}{dt} = {} & \left(\frac{\alpha\eta e^{-m_1\tau_1}}{\alpha+d_2} + e^{-m_1\tau_2}(1-\eta)\right)\left(1 - \frac{f_1(T_2,V_2)}{f_1(T,V_2)}\right)(d_1T_2 - d_1T) \\
& - \left(\frac{\alpha\eta e^{-m_1\tau_1}}{\alpha+d_2} + e^{-m_1\tau_2}(1-\eta)\right)(f_1(T_2,V_2) + f_2(T_2,I_2))H\left(\frac{f_1(T_2,V_2)}{f_1(T,V_2)}\right) \\
& - \frac{\alpha\eta e^{-m_1\tau_1}}{\alpha+d_2} f_1(T_2,V_2)\left(H\left(\frac{L_2 f_1(T(t-\tau_1),V(t-\tau_1))}{L f_1(T_2,V_2)}\right)\right. \\
& \left. + H\left(\frac{I_2 L}{I L_2}\right) + H\left(\frac{I V_2}{I_2 V}\right)\right) \\
& - \frac{\alpha\eta e^{-m_1\tau_1}}{\alpha+d_2} f_2(T_2,I_2)\left(H\left(\frac{L_2 f_2(T(t-\tau_1),I(t-\tau_1))}{L f_2(T_2,I_2)}\right) + H\left(\frac{I_2 L}{I L_2}\right)\right) \\
& - e^{-m_1\tau_2}(1-\eta) f_2(T_2,I_2) H\left(\frac{I_2 f_2(T(t-\tau_2),I(t-\tau_2))}{I f_2(T_2,I_2)}\right) \\
& - e^{-m_1\tau_2}(1-\eta) f_1(T_2,V_2)\left(H\left(\frac{I_2 f_1(T(t-\tau_1),V(t-\tau_1))}{I f_1(T_2,V_2)}\right) + H\left(\frac{I V_2}{I_2 V}\right)\right)
\end{aligned}$$

$$+\left(\frac{\alpha\eta e^{-m_1\tau_1}}{\alpha+d_2}+e^{-m_1\tau_2}(1-\eta)\right)\left(\frac{f_1(T_2,V_2)f_2(T,I)}{f_1(T,V_2)}-\frac{f_2(T_2,I_2)I}{I_2}\right)$$
$$+\left(\frac{\alpha\eta e^{-m_1\tau_1}}{\alpha+d_2}+e^{-m_1\tau_2}(1-\eta)\right)f_1(T_2,V_2)\left(\frac{f_1(T,V)}{f_1(T,V_2)}-\frac{V}{V_2}\right).$$

From (H_2), (H_4), and (H_6), we have

$$\left(1-\frac{f_1(T_2,V_2)}{f_1(T,V_2)}\right)(d_1T_2-d_1T)<0,\frac{f_1(T,V)}{f_1(T,V_2)}-\frac{V}{V_2}<0,$$
$$\frac{f_1(T_2,V_2)f_2(T,I)}{f_1(T,V_2)}-\frac{f_2(T_2,I_2)I}{I_2}<0.$$

Hence, $\frac{dU_3(t)}{dt}\leq 0$ and $\frac{dU_3(t)}{dt}=0$ if and only if $T(t)=T_2$, $L(t)=L_2$, $I(t)=I_2$, $V(t)=V_2$, and $Z(t)=Z_2$. From the LaSalle's invariance principle [23], we have that E_2 is globally asymptotically stable when $R_1>1$. This completes the proof. □

4 Numerical simulations

In the above sections, we established the global asymptotic stability of equilibrium E_2 when $\tau_1\geq 0$, $\tau_2\geq 0$, and $\tau_3=0$. However, considering the case $\tau_1\geq 0$, $\tau_2\geq 0$, and $\tau_3\geq 0$, by using the numerical simulation, it is shown that stability switches occur at E_2 as τ_3 increases. In model (1), we have $f_1(T,V)=\frac{\beta_1T(t)V(t)}{1+\alpha_1T(t)+\alpha_2V(t)}$, $f_2(T,I)=\beta_2T(t)I(t)$. Take $s=10$, $d_1=0.01$, $d_2=0.8$, $\beta_1=0.25$, $\beta_2=0.001$, $\alpha_1=0.01$, $\alpha_2=0.01$, $d_3=0.5$, $\alpha=0.01$, $\eta=0.49$, $k=0.4$, $d_4=3$, $q=1$, $c=1.5$, $m_1=0.01$, $m_2=0.01$, $d_5=1$, $\tau_1=2$, and $\tau_2=5$, and choose τ_3 as a free parameter. Computing we obtain $R_0=3.0743>1$, $R_1=1.7440>1$, and $E_2(112,5.2649,8.72,0.6667,2.2321)$.

In the following Figs. 1–4, panels (a), (b), (c), (d), and (e) show the time evolution of $T(t)$, $L(t)$, $I(t)$, $V(t)$, and $Z(t)$.

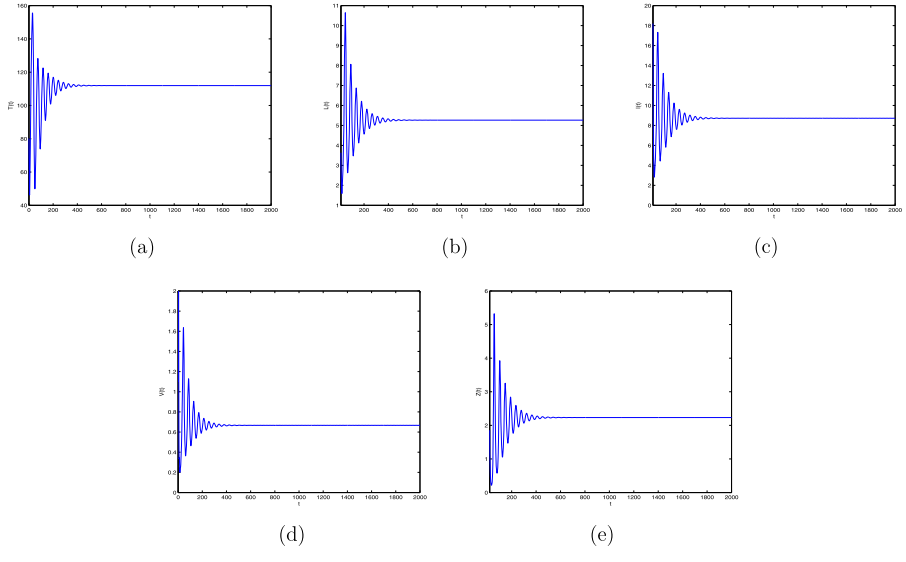

Figure 1 Taking $\tau_3=3$, we have $R_0=3.0743>1$ and $R_1=1.7440>1$, and the infection equilibrium E_2 with antibody response is asymptotically stable

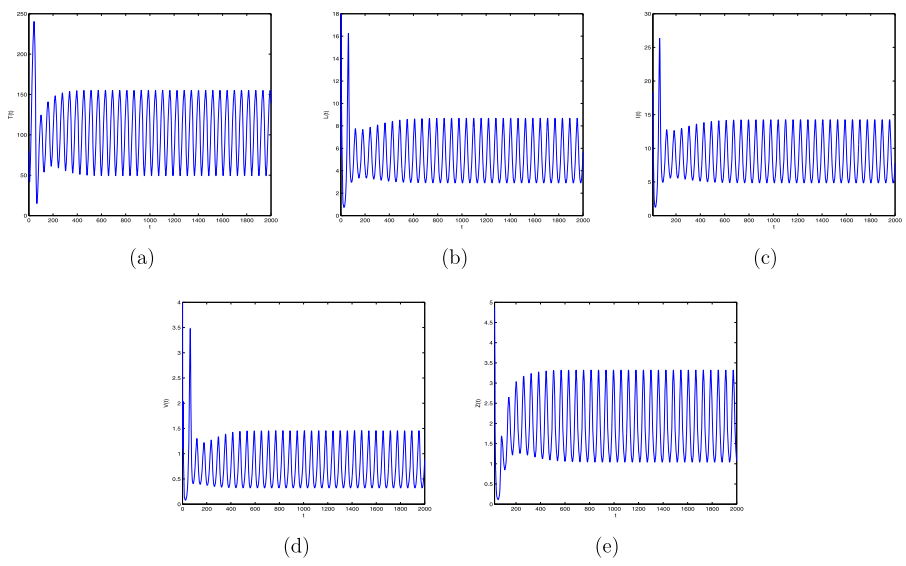

Figure 2 Taking $\tau_3 = 10$, we have $R_0 = 3.0743 > 1$ and $R_1 = 1.7440 > 1$, and the Hopf bifurcation at infection equilibrium E_2 with antibody response occurs

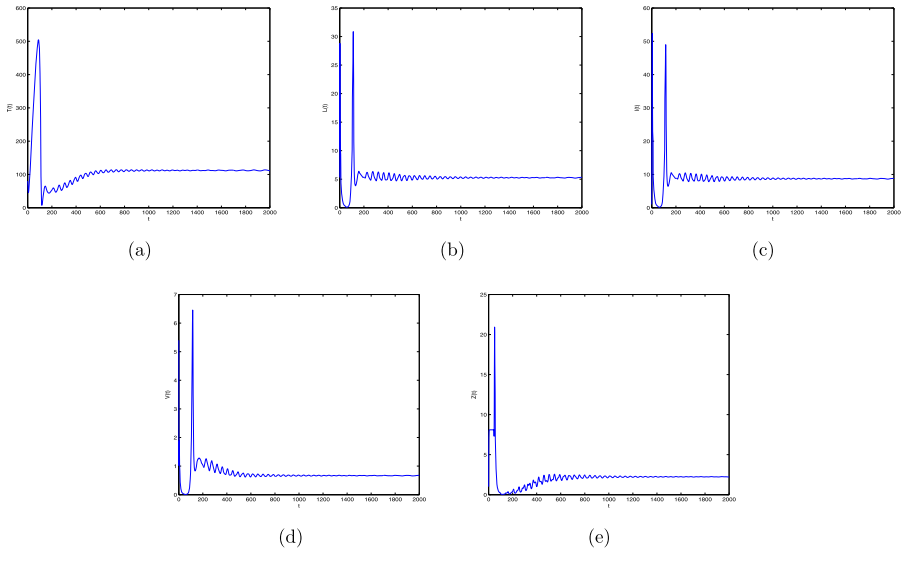

Figure 3 Taking $\tau_3 = 45$, we have $R_0 = 3.0743 > 1$ and $R_1 = 1.7440 > 1$, the infection equilibrium E_2 with antibody response is asymptotically stable

4.1 Effect of cell-to-cell transmission

In order to investigate the effect of cell-to-cell transmission, we carry out some numerical simulations to show the contribution of cell-to-cell transmission during the whole infection. Figure 5 ($\beta_2 = 0$, $\beta_2 = 0.001$, $\beta_2 = 0.0025$, $\beta_2 = 0.005$) shows that latently infected cells, productively infected cells, and virus reach the peak levels quicker and they become larger as β_2 increases. Therefore, cell-to-cell transmission plays an important role in the whole virus infection.

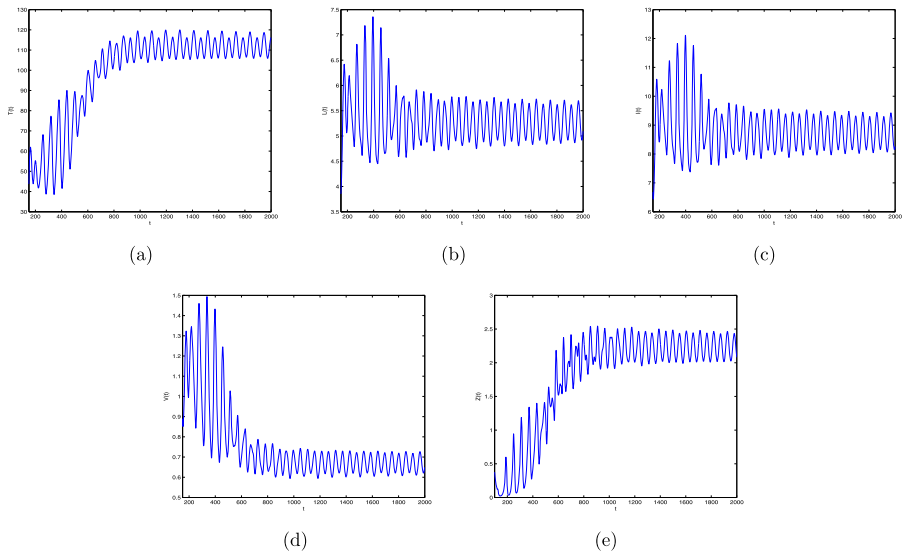

Figure 4 Taking $\tau_3 = 60$, we have $R_0 = 3.0743 > 1$ and $R_1 = 1.7440 > 1$, and the Hopf bifurcation at infection equilibrium E_2 with antibody response occurs

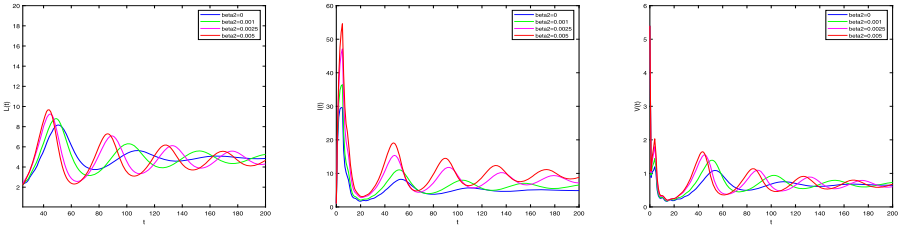

Figure 5 The effect of β_2 on the dynamical behavior of model (1)

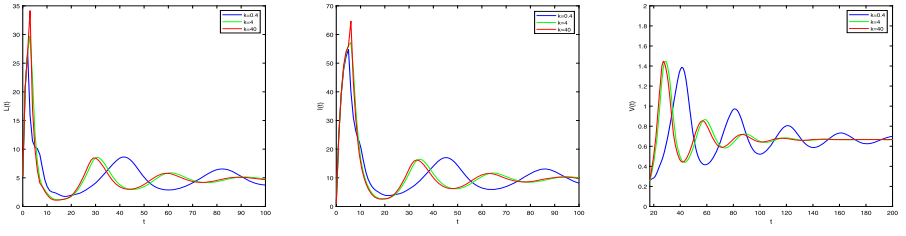

Figure 6 The effect of k on the dynamical behavior of model (1)

4.2 Effect of viral production rate

Viral production rate also has a great influence on the dynamical behavior of the model. We set the viral production rate k as 0.4, 4, and 40. In Fig. 6, we observe that the time to reach the peak levels of latently infected cells, productively infected cells, and virus becomes shorter as k increases, which means that a larger viral production rate contributes to the viral infection. In terms of the prevention and treatment of virus infection, decreasing k contributes to inhibiting virus reproduction.

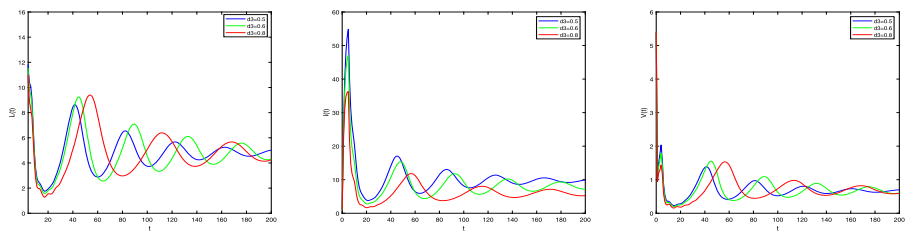

Figure 7 The effect of d_3 on the dynamical behavior of model (1)

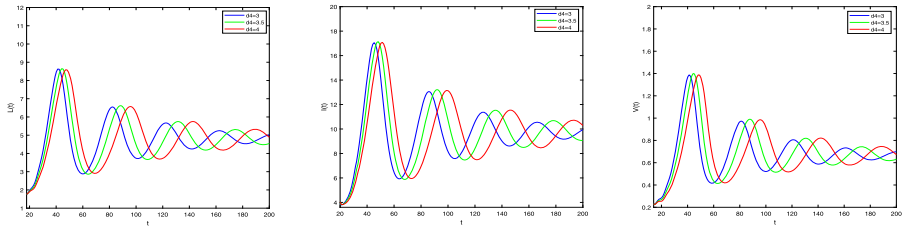

Figure 8 The effect of d_4 on the dynamical behavior of model (1)

4.3 Effect of death rate of infected cells and viral removal rate

Usually, the death rate of infected cells is larger than the death rate of uninfected cells due to the fact that virus infection can kill more host cells. From Fig. 7, we can observe that latently infected cells, productively infected cells, and virus increase more slowly as d_3 increases, which indicates that increasing the death rate of infected cells can slow down the virus infection. Humoral immunity is used to clear virus in our body, so the viral remove rate d_4 has an effect on viral infection as well. Figure 8 implies that as d_4 increases, latently infected cells, productively infected cells, and virus increase more slowly, which has similar results to d_3. Therefore, promoting body's immunity helps increase the mortality of infected cells and viral removal rate.

4.4 Sensitivity analysis

Sensitivity analysis is used to quantify the range of variables in reproduction ratios and to identify the key factors giving rise to reproduction ratios. In [27, 28], Latin hypercube sampling (LHS) is found to be a more efficient statistical sampling technique which has been introduced to the field of disease modeling. In [28], Marino et al. mentioned that partial rank correlation coefficients (PRCCs) provide a measure of the strength of a linear association between the parameters and the reproduction ratios. We perform sensitivity analysis by using the Latin hypercube sampling method to generate 5000 parameter combinations with each parameter. In Fig. 9, we obtain the PRCCs of R_0 and R_1. Specially, we show that β_1, β_2, and k are positively correlative variables with R_0 and R_1, while others are negatively correlated variables.

5 Discussion

In this paper, we developed a delayed latent virus model with both virus-to-cell and cell-to-cell transmissions and humoral immunity. We see that intracellular delay τ_1 and virus replication delay τ_2 do not affect the stability of the equilibria. However, immune response

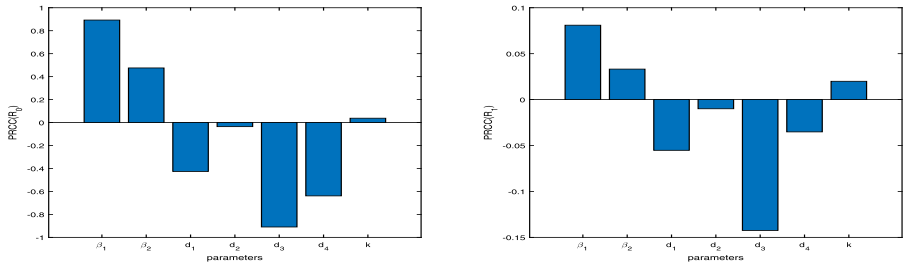

Figure 9 PRCCs of the basic reproduction numbers R_0 and R_1 with respect to some model parameters

delay τ_3 strongly impacts the stability of infection equilibrium with antibody response E_2. Under certain assumptions (H_1)–(H_6), we have shown that, when $R_0 < 1$, E_0 is globally asymptotically stable for any delays $\tau_1 \geq 0$, $\tau_2 \geq 0$, and $\tau_3 \geq 0$, which means that the virus is eradicated. When $R_0 > 1$ and $R_1 \leq 1$, E_1 is globally asymptotically stable for any delays $\tau_1 \geq 0$, $\tau_2 \geq 0$, and $\tau_3 \geq 0$, which means that the antibody response would not be activated and the viral infection vanishes. When $R_1 > 1$ and $\tau_3 = 0$, E_2 is globally asymptotically stable for any delays $\tau_1 \geq 0$ and $\tau_2 \geq 0$, that is, uninfected cells, latently infected cells, productively infected cells, virus and antibodies coexist in vivo.

When $\tau_3 \geq 0$, by numerical simulations, it is shown that the Hopf bifurcation and stability switches occur at E_2 as τ_3 increases. From Figs. 1–4, we see when τ_3 is small enough, E_2 is asymptotically stable and, when τ_3 is increasing, the stability switch occurs at E_2, while, when E_2 is unstable, Hopf bifurcation occurs. Finally, when τ_3 is large enough, E_2 is always unstable. This illustrates that τ_3 plays a negative role in disease prevalence and control. Besides, we can see in Figs. 5–8 the effects of cell-to-cell transmission β_2, viral production rate k, death rate of infected cells d_3, and viral remove rate d_4 on viral dynamics. Figure 9 shows a sensitivity analysis of reproduction ratios, which implies some useful consequences on the prevention and treatment of the viral infection.

It is easy to see that basic reproduction ratios R_0 is the sum of the reproduction ratio determined by virus-to-cell infection R_{01} and cell-to-cell transmission R_{02}. Therefore, neglecting the cell-to-cell transmission will lead to an underevaluated basic reproduction number. Observing all obtained results in this paper, we can directly put forward the following open questions which need to be further studied in the future. First, based on the model in [29, 30], we wonder whether the results obtained in this paper can be extended to control the dynamic process. Second, this model can be extended to incorporate a stochastic perturbation. Meanwhile, model (1) can be extended to describe the HIV dynamics with two classes of target cells and more stages. We leave these problems as possible future works.

Acknowledgements
The authors are grateful to the referees for valuable comments and suggestions that helped them improve this article.

Funding
This work was supported by the National Natural Science Foundation of China (Grant nos. 11901363, 11771373, 12001341, and 12001340), Scientific and Technological Innovation Programs of Higher Education Institutions in Shanxi (Grant no. 2019L0489), the Youth Research Fund for the Shanxi basic research project (Grant no. 2015021025).

Availability of data and materials
Data sharing not applicable to this article as no data sets were generated or analyzed during the current study.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
Each author contributed to every part of the work equally; all authors read and approved the final manuscript.

Publisher's Note

Received: 17 June 2021 Accepted: 31 August 2021 Published online: 22 September 2021

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