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Stability of delayed virus infection model with a general incidence rate and adaptive immune response

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Abstract

We present the dynamical behaviors of a virus infection model with general infection rate, immune responses and two intracellular delays which describe the interactions of the HIV virus, target cells, CTL cells and antibodies within host. Three factors are incorporated in this model: (1) the intrinsic growth rate of uninfected cells, (2) a nonlinear incidence rate function considering both virus-to-cell infection and cell-to-cell transmission, and (3) a nonlinear productivity and removal function. By the method of Lyapunov functionals and LaSalle's invariance principle, we show that the global dynamics of the model is determined by the reproductive numbers for viral infection R_0, for antibody immune response R_1, for CTL immune response R_2, for CTL immune competition R_3 and for antibody immune competition R_4. The numerical simulations are given to illustrate our theoretical results.

Keywords: General incidence rate; Cellular immunity response; Humoral immunity response; Distributed delay; Basic reproductive numbers; Global stability; Lyapunov functional

MSC 2010 No: 34D20, 34D23, 92B20, 92D30

1. Introduction

In the past few decades, many authors have proposed virus infection models and analysed the dynamics of them. Mathematical models provide powerful tools for understanding the virus infection mechanisms. In the viral infection, the immune system usually defends against the virus. Such as human immunodeficiency virus (HIV) (Jiang and Wang 2014, Sattentau 2011, Samba and Hamad 2014), the hepatitis B virus (HBV) (Min et al. 2008) and the hepatitis C virus (HCV) (Wodarz 2003, Yousfi et al. 2013, Zhao and Xu 2014), the adaptive immune system has cellular

and humoral immunity. The cellular immune response directly kills infected cells by CTL cells. The humoral immune response neutralizes the virus antibodies which are produced by the B cells. Therefore, cellular and humoral immunity are essential in defending infection of the virus. Wodarz (2003) put forword the following model with cellular and humoral immunity:

$$\begin{cases} \frac{\mathrm{d}x(t)}{\mathrm{d}t} = \lambda - dx(t) - \beta x(t)v(t), \\ \frac{\mathrm{d}y(t)}{\mathrm{d}t} = \beta x(t)v(t) - ay(t) - py(t)z(t), \\ \frac{\mathrm{d}v(t)}{\mathrm{d}t} = ky(t) - uv(t) - qv(t)w(t), \\ \frac{\mathrm{d}z(t)}{\mathrm{d}t} = cy(t)z(t) - bz(t), \\ \frac{\mathrm{d}w(t)}{\mathrm{d}t} = rv(t)z(t) - hw(t), \end{cases} \tag{1.1}$$

where, $x(t), y(t), v(t), z(t)$ and $w(t)$ represent the the concentration of susceptible target cells, infected cells, free virus, CTL cells and antibodies at time t, respectively. Parameter β represents the rate for susceptible target cells to be infected by virus. Parameters d, a, u, b and h represent the removal rate of susceptible taeget cells, infected cells, free virus, CTL cells and antibodies , respectively. Parameters p and q denote, respectively, the rate at which infected cells are killed by CTL cells and the neutralization rate of the virus by the antibodies. All parameters are positive constants.

In fact, there is always time delays in real virus infection. So, several researchers introduced time delays and studied the obtained delay differential equations. In many literatures, several mathematical models in Elaiw et al. (2016), Jiang and Wang (2014), Sattentau (2011), Wodarz (2003), Wang et al. (2013), Yousfi et al. (2013) have incorporated cellular or humoral immune response. However, the constant delays are not strictly conforming to biological significance.

Furthermore, some authors studied viral infection with distribution time delays Elaiw and Alshamrani (2015); Elaiw and Alshamrani (2014), Hattaf and Yousfi (2016), Samba and Hamad (2014), Wang et al. (2014). These delays may or may not induce periodic scillations via Hopf bifurcations, this depends on how and in what forms the delays are incorporated Xu et al. (2011), Xu and Shao (2011), Xu and Liao (2014), Xu et al. (2013), Xu (2013). Although there is no intracellular delays, it is known that target-cell dynamic can cause sustained oscilliations Sattentau (2011).

In order to investigate the effect of distributed time delays, Wang et al. (2014) put forward the following virus infection model with two continuous distributed delays and nonlinear incidence rate:

$$\begin{cases} \frac{\mathrm{d}x(t)}{\mathrm{d}t} = \lambda - dx(t) - kx(t)f(v(t)), \\ \frac{\mathrm{d}y(t)}{\mathrm{d}t} = \int_0^\infty f_1(\tau)e^{-m_1\tau}x(t-\tau)f(v(t-\tau)\mathrm{d}\tau - ay(t) - py(t)z(t), \\ \frac{\mathrm{d}v(t)}{\mathrm{d}t} = k\int_0^\infty f_2(\tau)e^{-m_2\tau}y(t-\tau)\mathrm{d}\tau - uv(t) - qv(t)w(t), \\ \frac{\mathrm{d}z(t)}{\mathrm{d}t} = cy(t)z(t) - bz(t), \\ \frac{\mathrm{d}w(t)}{\mathrm{d}t} = rv(t)w(t) - hw(t), \end{cases} \tag{1.2}$$

where, $e^{-m_1\tau}$ denoted as the possibility that susceptible target cells survive from $t-\tau>0$ to t, $e^{-m_2\tau}$ accounted for the possibility that infected cells survive from $t-\tau>0$ to t.
In addition, it was assumed that distribution functions $f_1(\tau)$ and $f_2(\tau)$ satisfied:

$$f_i(\tau)>0\ , \int_0^\infty f_i(\tau)\mathrm{d}\tau=1,$$

and

$$0<\eta_i=\int_0^\infty f_i(\tau)e^{-m_i\tau}\mathrm{d}\tau\leq 1,\ \text{for } i=1,2.$$

$\int_0^\infty f_1(\tau)e^{-m_1\tau}d\tau$ was the probability that target cells contacted by the virus particles at time $t-\tau$ survived τ time units and became infected at time t, $\int_0^\infty f_2(\tau)e^{-m_2\tau}d\tau$ was the probability that a cell infected at time $t-\tau$ started to yield new infectious virus at time t [Wang et al. (2014)].

In recent literatures, it has been shown that infected cells could also infect target cells Sattentau (2011), Sattentau (2010). But the incidence rates of the above models are not related to infected cells y and only related to the susceptible cells x and virus v. Therefore, Elaiw (2010) put forward virus infection model with standard incidence rate $\frac{xv}{x+y}$. Hattaf and Yousfi (2016) proposed virus infection model with general incidence rate $f(x,y,v)v$. Elaiw and Alshamrani (2016) presented virus infection model with $f(x,y,v)$.

Motivated by the work of Elaiw and Alshamrani (2014), Hattaf and Yousfi (2016), Wang et al. (2014), Zhao and Xu (2014), we propose the following viral infection model with two distributed delays, cellular and humoral immunity:

$$\begin{cases}\frac{\mathrm{d}x(t)}{\mathrm{d}t}=n(x(t))-f(x(t),y(t),v(t)),\\ \frac{\mathrm{d}y(t)}{dt}=\int_0^\infty f_1(\tau)e^{-m_1\tau}f(x(t-\tau),y(t-\tau),v(t-\tau))\mathrm{d}\tau-ag_1(y(t))-pg_1(y(t))g_4(z(t)),\\ \frac{\mathrm{d}v(t)}{dt}=k\int_0^\infty f_2(\tau)e^{-m_2\tau}g_1(y(t-\tau))\mathrm{d}\tau-ug_2(v(t))-qg_2(v(t))g_3(w(t)),\\ \frac{\mathrm{d}z(t)}{\mathrm{d}t}=cg_1(y(t))g_4(z(t))-bg_4(z(t)),\\ \frac{\mathrm{d}w(t)}{\mathrm{d}t}=rg_2(v(t))g_3(w(t))-hg_3(w(t)).\end{cases}\tag{1.3}$$

In this model, $n(x(t))$ represents intrinsic growth rate of uninfected cells accounting for both production and natural mortality. We assume that continuously differentiable $n(x)$ satisfies following assumption:

Hypothesis H1.

- $\exists\ x_0^*>0$ such that $n(x_0^*)=0$, $n(x)>0\ ,\forall\ x\in[0,x_0^*)$,
- $n(x)$ is decreasing with respect to x , $x>0$,
- there are s and $\overline{s}>0$ such that $n(x)\leq s-\overline{s}x$ for $x\geq 0$.

In the literature of virus dynamics, there are two main typical forms: one is $n(x(t))=\lambda-dx(t)$ (Elaiw et al. 2016), and the other is $n(x)=\lambda-dx(t)+rx(t)(1-\frac{x}{K})$ (Sattentau 2011), where λ,d,r,K are positive real numbers. In addition, we assume that general incidence rate function $f(x,y,v)$ is continuously differentiable and satisfies following assumption:

Hypothesis H2.

- $f(x,y,v) > 0$ and $f(0,y,v) = f(x,y,0) = 0, \forall\ x > 0,\ y \geq 0,\ v > 0,$
- $\frac{\partial f(x,y,v)}{\partial x} > 0, \frac{\partial f(x,y,v)}{\partial y} < 0, \frac{\partial f(x,y,v)}{\partial v} > 0$ and $\frac{\partial f(x,0,0)}{\partial v} > 0$, $\forall\ x > 0,\ y \geq 0,\ v > 0,$
- $\frac{\mathrm{d}}{\mathrm{d}x}(\frac{\partial f(x,0,0)}{\partial v}) > 0$,$\forall\ x > 0.$

The presented function $f(x,y,v)$ is very extensive, can include many forms, such as: (1) bilinear incidence rate βxv (Elaiw et al. 2016), (2) standard incidence rate $\frac{\beta xv}{x+y}$ (Elaiw 2010, Min et al. 2008), (3) saturated incidence rate $\frac{\beta xv}{1+\alpha_1 v}$ (Song 2007), (4) Holling-type II type $\frac{\beta xv}{1+\alpha_2 x}$ (Lin and Ma 1993), (5) Beddington-DeAngelis type $\frac{\beta xv}{1+\alpha_1 v+\alpha_2 x}$ (Dubey, Dubey and Dubey 2015), (6) Crowley-Martin type $\frac{\beta xv}{1+\alpha_1 v+\alpha_2 x+\alpha_1\alpha_2 xv}$ (Xu 2012, Zhao and Cui 2011), where $\beta, \alpha_1, \alpha_2 > 0$.

It is also assumed that $ag_1(y), ug_2(v), hg_3(w), bg_4(z)$ denote the death rates of the infected target cells, free viruses, antibodies, and CTL cells, respectively. Let $pg_1(y)g_4(z)$ and $cg_1(y)g_4(z)$ be the killing rate of infected cells and the birth rate of the CTL cells, let $qg_2(v)g_3(w)$ and $rg_2(v)g_3(w)$ be the neutralization rate of viruses and activation rate of B cells, respectively. We assume that continuously differentiable function $g_i(u)$, $i = 1,2,3,4$, satisfy following assumption:

Hypothesis H3.

- $g_j(u) > 0$, $\forall\ u > 0, g_j(0) = 0, j = 1,2,3,4,$
- $g_j'(u) > 0$, $\forall\ u > 0, j = 1,2,3,4,\ g_j(u) \geq 0, \forall\ u \geq 0,$
- $\exists\ c_j \geq 0, j = 1,2,3,4,$ such that $g_j(u) > c_j u, \forall\ u \geq 0.$

Hypothesis H4.

- $\frac{f(x,y,v)}{g_2(v)}$ is decreasing with respect to v, $\forall\ v > 0.$

In this study, we will explore the dynamics of virus infection model with two distributed delays, adaptive immune response and nonlinear incidence rate. Our aim is to carry out the global stability of system (1.3). We first derive five threshold parameters, then use the method of Lyapunov functionals, and finally obtain the global stabilities of the equilibria of system (1.3). The global stability only depends on the threshold parameters.

This paper is organized as follows. In the next section, we obtain the basic properties of system (1.3), such as the solution of the non-negative and boundedness. We study the equilibria and threshold parameters of system (1.3) in section 3. In section 4, by the method of Lyapunov functionals, we show that the global stabilities of the five equilibria, In section 5, we present some numerical simulations to illustrate the main theoretical results and some biological significance is discussed in last section.

2. Non-negativity and boundedness of solutions

To study the basic properties of model (1.3), we choose a suitable phase.

Let $R_+^5 = \{(x_1,x_2,x_3,x_4,x_5) : x_i \geq 0, i = 1,2,3,4,5\}$, $\mathcal{C} = C \times C \times C \times C \times C$ and

$$C := \{\phi \in C((-\infty,0],R) : \phi(\theta)e^{\alpha\theta} \text{ is uniformly continuous on} (-\infty,0] \text{ and } \|\phi\| < \infty\},$$

where $\alpha > 0$ is constant and norm is defined by $\|\phi\| = sup_{\theta\leq 0}|\phi(\theta)|e^{\alpha\theta}$ for $\phi \in C$, we assume that the initial conditions for system (1.3) satisfy:

$$\begin{cases} x(\theta) = \phi_1(\theta), y(\theta) = \phi_2(\theta), v(\theta) = \phi_3(\theta), z(\theta) = \phi_4(\theta), \\ w(\theta) = \phi_5(\theta), \theta \in (-\infty, 0], \phi_i(0) > 0, i = 1, 2, 3, 4, 5. \end{cases} \tag{2.1}$$

Note that C is a Banach space of fading memory type. By the fundamental theory of functional differential equation (Kuang 1993), system (1.3) admits a unique solution $(x(t), y(t), v(t), z(t), w(t))^T$ satisfying initial conditions (2.1).

Next, we discuss the non-negativity and boundness of the solution of system (1.3). For convenience, the Hypothesis H1-H4 will be used throughout this paper.

Theorem 2.1.

Let $(x(t), y(t), v(t), z(t), w(t))^T$ be the solution of system (1.3) with initial conditions (2.1), then $(x(t), y(t), v(t), z(t), w(t))^T$ are all non-negative and ultimately uniformly bounded.

Proof:

To show the non-negativity of the solution of system (1.3). We put the system into the matrix from $X'(t) = Y(X(t))$, where

$$X(t) = \Big[x(t), y(t), v(t), z(t), w(t)\Big]^T,\ Y = \Big[Y_1, Y_2, Y_3, Y_4, Y_5\Big]^T,$$

$$Y(X(t)) = \Big[Y_1(X(t)), Y_2(X(t)), Y_3(X(t)), Y_4(X(t)), Y_5(X(t))\Big]^T$$

$$= \begin{bmatrix} n(x(t)) - f(x(t), y(t), v(t)) \\ \int_0^\infty f_1(\tau)e^{-m_1\tau}f(x(t-\tau), y(t-\tau), v(t-\tau))\mathrm{d}\tau - ag_1(y(t)) - pg_1(y(t))g_4(z(t)) \\ k\int_0^\infty f_2(\tau)e^{-m_2\tau}g_1((y(t-\tau))\mathrm{d}\tau - ug_2(v(t)) - qg_2(v(t))g_3(w(t)) \\ cg_1(y(t))g_4(z(t)) - bg_4(z(t)) \\ rg_2(v(t))g_3(w(t)) - hg_3(w(t)) \end{bmatrix}.$$

It is easy to see that function Y satisfies the following conditions:

$$Y_i(X(t))|_{X_i(t)=0,\ X(t)\in R_+^5} \geq 0,\ i = 1, 2, 3, 4, 5,$$

thus implies $(x(t), y(t), v(t), z(t), w(t))^T$ are non-negativity.

Next, we prove that the system are ultimately bounded. From the first equation of system (1.3), we have $\dot{x} \leq n(x) \leq s - \bar{s}x$, implying $\limsup_{t\to\infty} x(t) \leq \frac{s}{\bar{s}}$.

Let

$$F_1(t) = \int_0^\infty f_1(\tau)e^{-m_1\tau}x(t-\tau)\mathrm{d}\tau + y(t) + \frac{p}{c}z(t).$$

Then,

$$\begin{aligned} F_1'(t) &= \int_0^\infty f_1(\tau)e^{-m_1\tau}n(x(t-\tau))\mathrm{d}\tau - ag_1(y) - \frac{p}{c}bg_4(z) \\ &\leq \int_0^\infty f_1(\tau)e^{-m_1\tau}(s - \bar{s}x(t-\tau))\mathrm{d}\tau - ac_1y - bc_4\frac{p}{c}z \end{aligned}$$

$$\leq s\int_0^\infty f_1(\tau)e^{-m_1\tau}\mathrm{d}\tau - \overline{s}\int_0^\infty f_1(\tau)e^{-m_1\tau}x(t-\tau)\mathrm{d}\tau - ac_1y - bc_4\frac{p}{c}z$$
$$= s - \delta_1 F_1(t),$$

where $\delta_1 = min\{\overline{s}, ac_1, \frac{bc_4p}{c}\}$. By standard comparison principle, we have $\limsup_{t\to\infty} F_1(t) \leq \frac{s}{\delta_1}$, and thus, $\limsup_{t\to\infty} y(t) \leq \frac{s}{\delta_1}$ and $\limsup_{t\to\infty} z(t) \leq \frac{s}{\delta_1}$.

Let

$$F_2(t) = v(t) + \frac{q}{r}w(t).$$

Then,

$$F_2'(t) = k\int_0^\infty f_2(\tau)e^{-m_2\tau}g_1(y(t-\tau))\mathrm{d}\tau - ug_2(v(t)) - \frac{q}{r}hg_3(w(t))$$
$$\leq kg_1(\frac{s}{\delta_1})\int_0^\infty f_2(\tau)e^{-m_2\tau}\mathrm{d}\tau - uc_2v(t) - hc_3\frac{q}{r}w(t)$$
$$\leq k\eta_2 g_1(\frac{s}{\delta_1}) - \delta_2 F_2(t).$$

Hence, we have

$$F_2'(t) \leq M_2 - \delta_2 F_2(t),$$

where $M_2 = k\eta_2 g_1(\frac{s}{\delta_1})$, and $\delta_2 = min\{uc_2, \frac{hc_3q}{r}\}$. Similarly, $\limsup_{t\to\infty} F_2(t) \leq \frac{M_2}{\delta_2}$, and thus, $\limsup_{t\to\infty} v(t) \leq \frac{M_2}{\delta_2}$ and $\limsup_{t\to\infty} w(t) \leq \frac{r}{q}\frac{M_2}{\delta_2}$. Therefore, $x(t), y(t), v(t), z(t), w(t)$ are ultimately uniformly bounded. This completes the proof. ∎

We denote

$$\Gamma = \{(x, y, v, z, w) \in C : \|x\| \leq \frac{s}{\overline{s}}, \|y\| \leq \frac{s}{\delta_1}, \|v\| \leq \frac{M_2}{\delta_2}, \|z\| \leq \frac{s}{\delta_1}, \|w\| \leq \frac{rM_2}{q\delta_2}\},$$

where $\|\phi\| = \limsup_{t\to\infty} \phi(t)$.

It can prove that the bounded region Γ is positively invariant with respect to system (1.3).

3. Threshold parameters and equilibria

In the section, we define five threshold parameters, and obtain five possible equilibria which satisfy certain conditions. First, five threshold parameters are given below, which are called the basic reproduction numbers Miaoet al.(2016), Wanget al.(2014), Zhao and Xu(2014), and more basic reproductive number theory can referred literatures Diekmann et al. (1990); Van and Watmough (2002).

$$R_0 = \frac{k\eta_1\eta_2}{aug_2'(0)}\frac{\partial f(x_0^*, 0, 0)}{\partial v},$$

which represents the basic infection reproduction number of system (1.3).

$$R_1 = \frac{k\eta_1\eta_2}{au}\frac{f(x_2^*, y_2^*, v_2^*)}{g_2(v_2^*)},$$

which is called the antibody immune response reproductive number of system (1.3).

$$R_2 = \frac{k\eta_1\eta_2}{au}\frac{f(x_3^*, y_3^*, v_3^*)}{g_2(v_3^*)},$$

which is called the CTL immune response reproductive number of system (1.3).

$$R_3 = \frac{c\eta_1 f(x_4^*, y_4^*, v_4^*)}{ab} \text{ and } R_4 = \frac{k\eta_2 br}{uch},$$

which are called tht CTL immune competitive reproductive number and the antibody immune competitive reproductive number of system (1.3), respectively.

Remark 1.

From Hypothesis H2 and Hypothesis H4, we can get $R_1 < R_0$ and $R_2 < R_0$. Next we will prove them.

$$\begin{aligned} R_1 &= \frac{k\eta_1\eta_2}{au}\frac{f(x_2^*, y_2^*, v_2^*)}{g_2(v_2^*)} \le \frac{k\eta_1\eta_2}{au}\lim_{v\to 0^+}\frac{f(x_2^*, y_2^*, v)}{g_2(v)} \\ &= \frac{k\eta_1\eta_2}{aug_2'(0)}\frac{\partial f(x_2^*, y_2^*, v_2^*)}{\partial v} < \frac{k\eta_1\eta_2}{aug_2'(0)}\frac{\partial f(x_0^*, 0, 0)}{\partial v} = R_0, \end{aligned}$$

and

$$\begin{aligned} R_2 &= \frac{k\eta_1\eta_2}{au}\frac{f(x_3^*, y_3^*, v_3^*)}{g_2(v_3^*)} \le \frac{k\eta_1\eta_2}{au}\lim_{v\to 0^+}\frac{f(x_3^*, y_3^*, v)}{g_2(v)} \\ &= \frac{k\eta_1\eta_2}{aug_2'(0)}\frac{\partial f(x_3^*, y_3^*, v)}{\partial v} < \frac{k\eta_1\eta_2}{aug_2'(0)}\frac{\partial f(x_0^*, 0, 0)}{\partial v} = R_0. \end{aligned}$$

Hence, we have the following theorem:

Theorem 3.1.

System (1.3) exist five threshold parameters R_0, R_1, R_2, R_3, R_4, such that:

(1) If $R_0 \le 1$, then system (1.3) has an infection-free equilibrium $E_0 = (x_0^*,\ 0,\ 0,\ 0,\ 0)$;
(2) If $R_0 > 1$, $R_1 \le 1$ and $R_2 \le 1$, then system (1.3) has an immune-free infection equilibrium $E_1 = (x_1^*,\ y_1^*,\ v_1^*,\ 0,\ 0)$;
(3) If $R_1 > 1$, then system (1.3) has an infection equilibrium $E_2 = (x_2^*,\ y_2^*,\ v_2^*,\ 0,\ w_2^*)$ with only antibody immune responses;
(4) If $R_2 > 1$, then system (1.3) has an infection equilibrium $E_3 = (x_3^*,\ y_3^*,\ v_3^*,\ z_3^*,\ 0)$ with only CTL immune responses;
(5) If $R_3 > 1$ and $R_4 > 1$, then system (1.3) has an infection equilibrium $E_4 = (x_4^*,\ y_4^*,\ v_4^*,\ z_4^*,\ w_4^*)$ with both CTL and antibody immune responses.

Proof:

Let

$$\begin{cases} 0 = n(x) - f(x, y, v), \\ 0 = \eta_1 f(x, y, v) - ag_1(y) - pg_1(y)g_4(z), \\ 0 = k\eta_2 g_1(y) - ug_2(v) - qg_2(v)g_3(w), \\ 0 = cg_1(y)g_4(z) - bg_4(z), \\ 0 = rg_2(v)g_3(w) - hg_3(w). \end{cases} \tag{3.1}$$

(1) It is obvious that system (1.3) has an infection-free equilibrium $E_0 = (x_0^*,\ 0,\ 0,\ 0,\ 0)$;

(2) When $z = 0, w = 0$, the existence of immune-free equilibrium $E_1 = (x_1^*,\ y_1^*,\ v_1^*,\ 0,\ 0)$ is equivalent to the existence of positive solution (x_1^*, y_1^*, v_1^*) of the following equations:

$$n(x) = f(x, y, v) = \frac{a}{\eta_1} g_1(y) = \frac{au}{k\eta_1\eta_2} g_2(v). \tag{3.2}$$

Hypothesis H3 implies g_1^{-1}, g_2^{-1} exists. Therefore,

$$y = g_1^{-1}\left(\frac{\eta_1 n(x)}{a}\right) = \varphi_1(x), v = g_2^{-1}\left(\frac{k\eta_1\eta_2}{au} n(x)\right) = \varphi_2(x). \tag{3.3}$$

Define

$$G_1(x) = f(x, \varphi_1(x), \varphi_2(x)) - \frac{au}{k\eta_1\eta_2} g_2(\varphi_2(x)).$$

Then, from Hypothesis H1-H3, we have

$$G_1(0) = -\frac{au}{k\eta_1\eta_2} g_2(\varphi_2(0)) < 0,$$

$$G_1(x_0^*) = f(x_0, 0, 0) - \frac{au}{k\eta_1\eta_2} g_2(0) = 0.$$

In addition,

$$G_1'(x_0^*) = \frac{\partial f(x_0, 0, 0)}{\partial x} + \varphi_1'(x_0^*)\frac{\partial f(x_0^*, 0, 0)}{\partial y} + \varphi_2'(x_0^*)\frac{\partial f(x_0^*, 0, 0)}{\partial v} - \frac{au}{k\eta_1\eta_2} g_2'(0)\varphi_2'(x_0^*).$$

Hypothesis H2 implies that $\frac{\partial f(x_0^*,0,0)}{\partial x} = \frac{\partial f(x_0^*,0,0)}{\partial y} = 0$. From Hypothesis H3, we know that $g_2'(0) > 0$.

Note that

$$\begin{aligned} G_1'(x_0^*) &= \frac{f(x_0^*, 0, 0)}{\partial x} + \frac{f(x_0^*, 0, 0)}{\partial y}\varphi_1'(x_0^*) + \frac{f(x_0^*, 0, 0)}{\partial v}\varphi_2'(x_0^*) - \frac{au}{k\eta_1\eta_2} g_2'(0)\varphi_2'(x_0^*) \\ &= \frac{au}{k\eta_1\eta_2}\varphi_2'(x_0^*) g_2'(0)\left(\frac{k\eta_1\eta_2}{aug_2'(0)}\frac{\partial f(x_0^*, 0, 0)}{\partial v} - 1\right) = \frac{au}{k\eta_1\eta_2}\varphi_2'(x_0^*) g_2'(0)(R_0 - 1). \end{aligned}$$

Hence, if $R_0 > 1$, then $G_1'(x_0^*) < 0$ and there exists $x_1^* \in (0, x_0^*)$ such that $G_1(x_1^*) = 0$. From (3.3) we have $y_1^* = \varphi_2(x_1^*)$, $v_1^* = \varphi(x_1^*)$. Therefore, E_1 exists if $R_0 > 1$.

(3) When $z = 0,\ w \neq 0$, consider the existence of infection equilibrium $E_2 = (x_2^*,\ y_2^*,\ v_2^*,\ 0,\ w_2^*)$ with only antibody immune response. It is clear that $v_2^* = g_2^{-1}(\frac{h}{r})$. Define

$$G_2(x) = n(x) - f(x, \varphi_1(x), v_2^*).$$

There exists a unique $x_2^* \in (0, x_0^*)$ such that $G_2(x_2^*) = 0$ since $G_2(0) = n(0) > 0$ and $G_2(x_0^*) = n(x_0^*) - f(x_0^*, y_2^*, v_2^*) < 0$. Then, we have $y_2^* = \varphi_1(x_2^*) > 0$.

Solving w_2^* from (3.1), we obtain that

$$w_2^* = g_3^{-1}\left(\frac{k\eta_2 g_1(y_2^*) - ug_2(v_2^*)}{qg_2(v_2^*)}\right) = g_3^{-1}\left(\frac{u}{q}\left(\frac{k\eta_2 g_1(y_2^*)}{ug_2(v_2^*)} - 1\right)\right)$$
$$= g_3^{-1}\left(\frac{u}{q}\left(\frac{k\eta_1\eta_2 f(x_2^*, y_2^*, v_2^*)}{aug_2(v_2^*)} - 1\right)\right) = g_3^{-1}\left(\frac{u(R_1-1)}{q}\right).$$

If $R_1 > 1$, then $w_2^* > 0$. Therefore, E_2 exists and is unique if $R_1 > 1$.

(4) When $z \neq 0,\ w = 0$, we consider the existence of infection equilibrium $E_3 = (x_3^*,\ y_3^*,\ v_3^*,\ z_3^*,\ 0)$ with only CTL immune response. From the third and fourth equations of (3.1), we obtain unique $y_3^* = g_1^{-1}(\frac{b}{c})$ and $v_3^* = g_2^{-1}(\frac{bk\eta_2}{cu})$. Define

$$G_3(x) = n(x) - f(x, y_3^*, v_3^*).$$

By Hypothesis H1 and Hypothesis H2, we have $G_3'(x) = n'(x) - \frac{\partial f(x, y_3^*, v_3^*)}{\partial x} < 0$, since $G_3(0) = n(0) > 0$ and $G_3(x_0^*) = n(x_0^*) - f(x_0^*, y_3^*, v_3^*) < 0$, there exists a unique $x_3^* \in (0, x_0^*)$ such that $G_2(x_3^*) = 0$. Solving the second equation of system (3.1), we have

$$z_3^* = g_4^{-1}\left(\frac{\eta_1 f(x_3^*, y_3^*, v_3^*) - ag_1(y_3^*)}{qg_1(y_3^*)}\right) = g_4^{-1}\left(\frac{a}{p}\left(\frac{\eta_1 f(x_3^*, y_3^*, v_3^*)}{ag_2(y_3^*)} - 1\right)\right)$$
$$= g_4^{-1}\left(\frac{a}{p}\left(\frac{k\eta_1\eta_2 f(x_3^*, y_3^*, v_3^*)}{aug_2(v_3^*)} - 1\right)\right) = g_4^{-1}\left(\frac{a(R_2-1)}{p}\right).$$

If $R_2 > 1$, then $z_3^* > 0$. Therefore, E_3 exists and is unique if $R_2 > 1$.

(5) When $z \neq 0,\ w \neq 0$, consider the existence of infection equilibrium $E_4 = (x_4^*,\ y_4^*,\ v_4^*,\ z_4^*,\ w_4^*)$ with both CTL and antibody immune responses. From the fourth and fifth equation of (3.1), we obtain unique $y_4^* = g_1^{-1}(\frac{b}{c})$ and $v_4^* = g_2^{-1}(\frac{h}{r})$. Define

$$G_4(x) = n(x) - f(x, y_4^*, v_4^*).$$

By Hypothesis H1 and Hypothesis H2, one has $G_4'(x) < 0$, since $G_4(0) = n(0) > 0$ and $G_4(x_0^*) = n(x_0^*) - f(x_0^*, y_4^*, v_4^*) < 0$, there exists a unique $x_4^* \in (0, x_0^*)$ such that $G_4(x_4^*) = 0$. From the second equation of (3.1), we further obtain a unique

$$z_4^* = g_4^{-1}\left(\frac{\eta_1 f(x_4^*, y_4^*, v_4^*) - ag_1(y_4^*)}{pg_1(y_4^*)}\right) = g_4^{-1}\left(\frac{a}{p}\left(\frac{\eta_1 f(x_4^*, y_4^*, v_4^*)}{ag_1(y_4^*)} - 1\right)\right)$$
$$= g_4^{-1}\left(\frac{a}{p}\left(\frac{c\eta_1 f(x_4^*, y_4^*, v_4^*)}{ab} - 1\right)\right) = g_4^{-1}\left(\frac{a(R_3-1)}{p}\right).$$

From the third equation of (3.1), we have

$$w_4^* = g_3^{-1}\left(\frac{k\eta_2 g_1(y_4^*) - ug_2(v_4^*)}{qg_2(v_4^*)}\right) = g_3^{-1}\left(\frac{u}{q}\left(\frac{k\eta_2 g_1(y_4^*)}{ug_2(v_4^*)} - 1\right)\right)$$
$$= g_4^{-1}\left(\frac{u}{q}\left(\frac{k\eta_2 br}{uch} - 1\right)\right) = g_4^{-1}\left(\frac{u(R_4-1)}{q}\right).$$

If $R_3 > 1$ and $R_4 > 1$, then $z_4^* > 0$ and $w_4^* > 0$. Therefore, E_4 exists and is unique if $R_3 > 1$ and $R_4 > 1$. This completes the proof. ∎

4. Threshold parameters and equilibria

In this section, we consider the global asymptotic stabilities of five possible equilibria. For convenience, we define:

$$H(u) = u - 1 - \ln u,\ u \in (0, +\infty).$$

It is easy to see that $H(u) \geq 0$, $u \in (0, +\infty)$ for all $u \in (0, +\infty)$ and $\min\limits_{0<u<\infty} H(u) = H(1) = 0$.

4.1. Stability of Equilibrium E_0

Theorem 4.1.

If $R_0 \leq 1$, then infection-free equilibrium E_0 is globally asymptotically stable.

Proof:

We construct a Lyapunov functional $V_0(t) : \Gamma \to R$ as follows:

$$\begin{aligned} V_0(t) =& x(t) - \int_{x_0^*}^{x(t)} \lim_{v\to 0} \frac{f(x_0^*, 0, v)}{f(\theta, 0, v)} \mathrm{d}\theta + \frac{1}{\eta_1} y(t) + \frac{a}{k\eta_1\eta_2} v(t) + \frac{p}{c\eta_1} z(t) + \frac{aq}{kr\eta_1\eta_2} w(t) \\ &+ \frac{1}{\eta_1} \int_0^\infty f_1(\tau) e^{-m_1\tau} \int_{-\tau}^0 f(x(t+s), y(t+s), v(t+s)) \mathrm{d}s\mathrm{d}\tau \\ &+ \frac{a}{\eta_1\eta_2} \int_0^\infty f_2(\tau) e^{-m_2\tau} \int_{-\tau}^0 g_1(y(t+s)) \mathrm{d}s\mathrm{d}\tau. \end{aligned}$$

Calculating the time derivative of $V_0(t)$ along solutions of system (1.3), we obtain

$$\begin{aligned} \frac{\mathrm{d}V_0(t)}{\mathrm{d}t} =& \left(1 - \lim_{v\to 0} \frac{f(x_0^*, 0, v)}{f(x, 0, v)}\right) (n(x) - f(x, y, v)) \\ &+ \frac{1}{\eta_1} \left(\int_0^\infty f_1(\tau) e^{-m_1\tau} f(x(t-\tau), y(t-\tau), v(t-\tau)) \mathrm{d}\tau - a g_1(y) - p g_1(y) g_4(z) \right) \\ &+ \frac{a}{k\eta_1\eta_2} \left(k \int_0^\infty f_2(\tau) e^{-m_2\tau} g_1(y(t-\tau)) \mathrm{d}\tau - u g_2(v) - q g_2(v) g_3(w) \right) \\ &+ \frac{p}{c\eta_1} (c g_1(y) g_4(z) - b g_4(z)) + \frac{aq}{kr\eta_1\eta_2} (r g_2(v) g_3(w) - h g_3(w)) \\ &+ f(x, y, v) - \frac{1}{\eta_1} \int_0^\infty f_1(\tau) e^{-m_1\tau} f(x(t-\tau), y(t-\tau), v(t-\tau)) \mathrm{d}\tau \\ &+ \frac{a}{\eta_1} g_1(y) - \frac{a}{\eta_1\eta_2} \int_0^\infty f_2(\tau) g_1(y(t-\tau)) \mathrm{d}\tau \\ =& n(x) \left(1 - \lim_{v\to 0} \frac{f(x_0^*, 0, v)}{f(x, 0, v)}\right) + f(x, y, v) \lim_{v\to 0} \frac{f(x_0^*, 0, v)}{f(x, y, v)} \\ &- \frac{au}{k\eta_1\eta_2} g_2(v) - \frac{pb}{c\eta_1} g_4(z) - \frac{aqh}{kr\eta_1\eta_2} g_3(w) \\ =& n(x) \left(1 - \lim_{v\to 0} \frac{f(x_0^*, 0, v)}{f(x, 0, v)}\right) + \frac{au}{k\eta_1\eta_2} g_2(v) \left(\frac{k\eta_1\eta_2}{au} \frac{f(x, 0, v)}{g_2(v)} \lim_{v\to 0} \frac{f(x_0^*, 0, v)}{f(x, y, v)} - 1 \right) \\ &- \frac{pb\eta_1}{c} g_4(z) - \frac{aqh}{kr\eta_1\eta_2} g_3(w). \end{aligned}$$

By Hypothesis H1 and Hypothesis H2, we have

$$(n(x)-n(x_0^*))\left(1-\frac{\partial f(x_0^*,0,0)/\partial v}{\partial f(x,0,0)/\partial v}\right)\leq 0.$$

By Hypothesis H1 and Hypothesis H4, we get

$$\frac{f(x,y,v)}{g_2(v)}<\frac{f(x,0,v)}{g_2(v)}\leq\lim_{v\to 0}\frac{f(x,0,v)}{g_2(v)}=\frac{1}{g_2'(0)}\frac{\partial f(x,0,0)}{\partial v}.$$

Then,

$$\begin{aligned}\frac{\mathrm{d}V_0(t)}{\mathrm{d}t}\leq&(n(x)-n(x_0^*))\left(1-\lim_{v\to 0}\frac{f(x_0^*,0,v)}{f(x,0,v)}\right)+\frac{au}{k\eta_1\eta_2}g_2(v)(R_0-1)\\&-\frac{pb}{c\eta_1}g_4(z)-\frac{aqh}{kr\eta_1\eta_2}g_3(w).\end{aligned}$$

Therefore, if $R_0\leq 1$, then $\frac{\mathrm{d}V_0(t)}{\mathrm{d}t}\leq 0$ for all x, y, v, z, $w>0$, we know that $\frac{\mathrm{d}V_0(t)}{\mathrm{d}t}=0$ if and only if $x(t)=x_0^*$, $v(t)=0$, $z(t)=0$, $y(t)=0$ and $w(t)=0$. It easy to see that the largest invariant set in $\{(x,y,v,z,w)\in\Gamma:\frac{\mathrm{d}V_0(t)}{\mathrm{d}t}=0\}$ is singleton $\{E_0\}$. By LaSalleï¿œï¿œs invariance principle (Kuang 1993), we derive that E_0 is globally asymptotically stable. This completes the proof. ■

To prove the global stability of the equilibria $E1$, $E2$, $E3$ and $E4$, By Hypothesis H2 and Hypothesis H4, we obtain

$$\left(\frac{f(x,y,v)}{f(x,y_i^*,v_i^*)}-1\right)\left(\frac{g_2(v_i^*)}{g_2(v)}-\frac{f(x,y_i^*,v_i^*)}{f(x,y,v)}\right)\leq 0,\ i=1,\ 2,\ 3,\ 4,\ \text{for all } x,\ y,\ v>0.$$

4.2. Stability of Equilibrium E_1

To prove the global stability of equilibrium E_1, we introduce two lemmas.

Lemma 4.2.

If $R_0>1$, let x_2^* and v_2^* satisfy $n(x_2^*)=f(x_2^*,y_2^*,v_2^*)$ and $g_2(v_2^*)=\frac{h}{r}$. Compare with $E_1=(x_1^*,y_1^*,v_1^*,0,0)$, we have $sign(x_2^*-x_1^*)=sign(v_1^*-v_2^*)=sign(R_1-1)$.

Proof:

By monotonicity in Hypothesis H1 and Hypothesis H2, we obtain

$$(n(x_2^*)-n(x_1^*))(x_1^*-x_2^*)>0, \tag{4.1}$$
$$(f(x_2^*,y_2^*,v_2^*)-f(x_1^*,y_2^*,v_2^*))(x_2^*-x_1^*)>0, \tag{4.2}$$
$$(f(x_1^*,y_2^*,v_2^*)-f(x_1^*,y_1^*,v_2^*))(y_1^*-y_2^*)>0, \tag{4.3}$$
$$(f(x_1^*,y_1^*,v_2^*)-f(x_1^*,y_1^*,v_1^*))(v_2^*-v_1^*)>0. \tag{4.4}$$

First, we prove $sign(x_2^* - x_1^*) = sign(v_1^* - v_2^*)$. Suppose $sign(x_2^* - x_1^*) = sign(v_2^* - v_1^*)$. From $n(x_1^*) = f(x_1^*, y_1^*, v_1^*)$, we get

$$n(x_2^*) - n(x_1^*) = f(x_2^*, y_2^*, v_2^*) - f(x_1^*, y_1^*, v_1^*) = a(g_1(y_2^*) - g_1(y_1^*)). \tag{4.5}$$

Hypothesis H3 implies $g_1(y)$ is an increasing function, then $sign(x_1^* - x_2^*) = sign(y_2^* - y_1^*)$.

Note that

$$\begin{aligned} n(x_2^*) - n(x_1^*) =& f(x_2^*, y_2^*, v_2^*) - f(x_1^*, y_1^*, v_1^*) \\ =& (f(x_2^*, y_2^*, v_2^*) - f(x_1^*, y_2^*, v_2^*)) + (f(x_1^*, y_2^*, v_2^*) - f(x_1^*, y_1^*, v_2^*)) \\ &+ (f(x_1^*, y_1^*, v_2^*) - f(x_1^*, y_1^*, v_1^*)). \end{aligned}$$

From $(4.1) - (4.5)$, we have

$$sign(x_1^* - x_2^*) = sign(x_2^* - x_1^*),$$

which is a contradiction. Thus $sign(x_2^* - x_1^*) = sign(v_1^* - v_2^*)$. Hypothesis H4 implies that

$$\left(\frac{f(x_1^*, y_1^*, v_2^*)}{g_2(v_2^*)} - \frac{f(x_1^*, y_1^*, v_1^*)}{g_2(v_1^*)} \right) (v_1^* - v_2^*) > 0. \tag{4.6}$$

Using $\frac{k\eta_1\eta_2}{au} \frac{f(x_1^*, y_1^*, v_1^*)}{g_2(v_1^*)} = 1$, we have

$$\begin{aligned} R_1 - 1 =& \frac{k\eta_1\eta_2}{au} \left[\left(\frac{1}{g_2(v_2)} (f(x_2^*, y_2^*, v_2^*) - f(x_1^*, y_2^*, v_2^*) \right) + \frac{1}{g_2(v_2^*)} ((f(x_1^*, y_2^*, v_2^*) - f(x_1^*, y_1^*, v_2^*)) \right. \\ &+ \left. \left(\frac{f(x_1^*, y_1^*, v_2^*)}{g_2(v_2^*)} - \frac{f(x_1^*, y_1^*, v_1^*)}{g_2(v_1^*)} \right) \right]. \end{aligned}$$

Thus, from (4.3), (4.4), (4.5) and (4.6), we obtain $sign(R_1 - 1) = sign(v_1^* - v_2^*)$. This completes the proof. ∎

Lemma 4.3.

If $R_0 > 1$, let x_3^*, y_3^* and v_3^* satisfy $s(x_3^*) = f(x_3^*, y_3^*, v_3^*)$ and $g_1(y_3^*) = \frac{b}{c}$, $g_2(v_3^*) = \frac{kb\eta_2}{uc}$, then we have $sign(x_3^* - x_1^*) = sign(v_1^* - v_3^*) = sign(y_1^* - y_3^*) = sign(R_2 - 1)$.

Proof:

It is similar to the proof of lemma 4.1. ∎

Theorem 4.4.

If $R_0 > 1, R_1 \leq 1$ and $R_2 \leq 1$, then immune-free equilibrium E_1 is globally asymptotically stable.

Proof:

We define a Lyapunov functional $V_1(t) : \Gamma \to R$ as follows:

$$\begin{aligned}V_1(t) =& x(t) - \int_{x_1^*}^{x(t)} \frac{f(x_1^*, y_1^*, v_1^*)}{f(\theta, y_1^*, v_1^*)} \mathrm{d}\theta + \frac{1}{\eta_1}\left(y(t) - \int_{y_1^*}^{y(t)} \frac{g_1(y_1^*)}{g_1(\theta)}\mathrm{d}\theta\right)\\ &+ \frac{a}{k\eta_1\eta_2}\left(v(t) - \int_{v_1^*}^{v(t)} \frac{g_2(y_1^*)}{g_2(\theta)}\mathrm{d}\theta\right) + \frac{p}{c\eta_1}z(t) + \frac{aq}{rk\eta_1\eta_2}w(t)\\ &+ \frac{f(x_1^*, y_1^*, v_1^*)}{\eta_1}\int_0^\infty f_1(\tau)e^{-m_1\tau}\int_{-\tau}^0 H\left(\frac{f(x(t+s), y(t+s), v(t+s))}{f(x_1^*, y_1^*, v_1^*)}\right)\mathrm{d}s\mathrm{d}\tau\\ &+ \frac{ag_1(y_1^*)}{\eta_1\eta_2}\int_0^\infty f_2(\tau)e^{-m_2\tau}\int_{-\tau}^0 H\left(\frac{g_1(y(t+s))}{g_1(y_1^*)}\right)\mathrm{d}s\mathrm{d}\tau.\end{aligned}$$

Calculating the derivative of $V_1(t)$ along solutions of system (1.3), we have

$$\begin{aligned}\frac{\mathrm{d}V_1(t)}{\mathrm{d}t} =& \left(1 - \frac{f(x_1^*, y_1^*, v_1^*)}{f(x, y_1^*, v_1^*)}\right)(n(x) - f(x, y, v))\\ &+ \frac{1}{\eta_1}\left(1 - \frac{g_1(y_1^*)}{g_1(y)}\right)\left(\int_0^\infty f_1(\tau)e^{-m_1\tau}f(x(t-\tau), y(t-\tau), v(t-\tau))\mathrm{d}\tau\right.\\ &\left.- ag_1(y) - pg_1(y)g_4(z)\right)\\ &+ \frac{a}{k\eta_1\eta_2}\left(1 - \frac{g_2(v_1^*)}{g_2(v)}\right)\left(k\int_0^\infty f_2(\tau)e^{-m_2\tau}g_1(y(t-\tau))\mathrm{d}\tau\right.\\ &\left.- ug_2(v) - qg_2(v)g_3(w)\right)\\ &+ \frac{p}{c\eta_1}(cg_1(y)g_4(z) - bg_4(z)) + \frac{aq}{rk\eta_1\eta_2}(rg_2(v)g_3(w) - hg_3(w))\\ &+ \frac{f(x_1^*, y_1^*, v_1^*)}{\eta_1}\int_0^\infty f_1(\tau)e^{-m_1\tau}\left(\frac{f(x, y, v)}{f(x_1^*, y_1^*, v_1^*)} - \frac{f(x(t-\tau), y(t-\tau), v(t-\tau))}{f(x_1^*, y_1^*, v_1^*)}\right.\\ &\left.+ \ln\frac{f(x(t-\tau), y(t-\tau), v(t-\tau))}{f(x, y, v)}\right)\mathrm{d}\tau\\ &+ \frac{ag_1(y_1^*)}{\eta_1\eta_2}\int_0^\infty f_2(\tau)e^{-m_2\tau}\left(\frac{g_1(y)}{g_1(y_1^*)} - \frac{g_1(y(t-\tau))}{g_1(y_1^*))} + \ln\frac{g_1(y(t-\tau))}{g_1(y_1^*))}\right)\mathrm{d}\tau.\end{aligned}$$

Note that

$$n(x_1^*) = f(x_1^*, y_1^*, v_1^*) = \frac{ag_1(y_1^*)}{\eta_1} = \frac{au}{k\eta_1\eta_2}g_2(v_1^*).$$

We have

$$\begin{aligned}\frac{\mathrm{d}V_1(t)}{\mathrm{d}t} =&(n(x)-n(x_1^*))\left(1-\frac{f(x_1^*,y_1^*,v_1^*)}{f(x,y_1^*,v_1^*)}\right)\\ &+f(x_1^*,y_1^*,v_1^*)\left(-1+\frac{g_2(v)f(x,y_1^*,v_1^*)}{g_2(v_1^*)f(x,y,v)}+\frac{f(x,y,v)}{f(x,y_1^*,v_1^*)}-\frac{g_(v)}{g_2(v_1^*)}\right)\\ &+f(x_1^*,y_1^*,v_1^*)\left(1-\frac{1}{\eta_1}\int_0^\infty f_1(\tau)e^{-m_1\tau}\frac{g_1(y_1^*)f(x(t-\tau),y(t-\tau),v(t-\tau))}{g_1(y)f(x_1^*,y_1^*,v_1^*)}\mathrm{d}\tau\right)\\ &+f(x_1^*,y_1^*,v_1^*)\left(1-\frac{1}{\eta_2}\int_0^\infty f_2(\tau)e^{-m_2\tau}\frac{g_2(v_1^*)g_1(y(t-\tau))}{g_2(v)g_1(y)}\mathrm{d}\tau\right)\\ &+\frac{f(x_1^*,y_1^*,v_1^*)}{\eta_1}\int_0^\infty f_1(\tau)e^{-m_1\tau}\ln\frac{f(x(t-\tau),y(t-\tau),v(t-\tau))}{f(x,y,v)}d\tau\\ &+\frac{f(x_1^*,y_1^*,v_1^*)}{\eta_2}\int_0^\infty f_2(\tau)e^{-m_2\tau}\ln\frac{g_1(y(t-\tau))}{g_1(y)}\mathrm{d}\tau\\ &+\frac{p}{\eta_1}g_4(z)(g_1(y_1^*)-g_1(y_3^*))+\frac{aq}{k\eta_1\eta_2}g_3(w)(g_2(v_1^*)-g_2(v_3^*)).\end{aligned}$$

We obtain

$$\begin{aligned}\frac{\mathrm{d}V_1(t)}{\mathrm{d}t} =&(n(x)-n(x_1^*))\left(1-\frac{f(x_1^*,y_1^*,v_1^*)}{f(x,y_1^*,v_1^*)}\right)\\ &+f(x_1^*,y_1^*,v_1^*)\frac{g_2(v)}{g_2(v_1^*)}\left(\frac{f(x,y,v)}{f(x,y_1^*,v_1^*)}-1\right)\left(\frac{g_2(v_1^*)}{g_2(v)}-\frac{f(x,y_1^*,v_1^*)}{f(x,y,v)}\right)\\ &-f(x_1^*,y_1^*,v_1^*)H\left(\frac{f(x_1^*,y_1^*,v_1^*)}{f(x,y_1^*,v_1^*)}\right)-f(x_1^*,y_1^*,v_1^*)H\left(\frac{g_2(v)f(x,y_1^*,v_1^*))}{g_2(v_1^*)f(x,y,v)}\right)\\ &-\frac{f(x_1^*,y_1^*,v_1^*)}{\eta_1}\int_0^\infty f_1(\tau)e^{-m_1\tau}H\left(\frac{g_1(y_1^*)f(x(t-\tau),y(t-\tau),v(t-\tau))}{g_1(y)f(x_1^*,y_1^*,v_1^*)}\right)\mathrm{d}\tau\\ &-\frac{f(x_1^*,y_1^*,v_1^*)}{\eta_2}\int_0^\infty f_2(\tau)e^{-m_2\tau}H\left(\frac{g_2(v_1^*)g_1(y(t-\tau))}{g_2(v)g_1(y_1^*))}\right)\mathrm{d}\tau\\ &+\frac{p}{\eta_1}g_4(z)(g_1(y_1^*)-g_1(y_3^*))+\frac{aq}{k\eta_1\eta_2}g_3(w)(g_2(v_1^*)-g_2(v_3^*)).\end{aligned}$$

From the Hypothesis H1-H4, we have

$$(n(x)-n(x_1^*))\left(1-\frac{f(x_1^*,y_1^*,v_1^*)}{f(x,y_1^*,v_1^*)}\right)\le 0,$$

and

$$\left(\frac{f(x,y,v)}{f(x,y_1^*,v_1^*)}-1\right)\left(\frac{g_2(v_1^*)}{g_2(v)}-\frac{f(x,y_1^*,v_1^*)}{f(x,y,v)}\right)\le 0.$$

From Lemma 4.1 and 4.2, we get $g_1(y_1^*)\le g_1(y_3^*)$ and $g_2(v_1^*)\le g_2(v_3^*)$ if $R_1\le 1$ and $R_2\le 1$. Thus, we have $\frac{\mathrm{d}V_1(t)}{\mathrm{d}t}\le 0$. Let the largest invariant set $M_1=\{(x(t),y(t),v(t),z(t),w(t))\in\Gamma:\frac{\mathrm{d}V_1(t)}{\mathrm{d}t}=0\}$. Obviously, $\frac{\mathrm{d}V_1(t)}{\mathrm{d}t}=0$ if and only if $x(t)=x_1^*,y(t)=y_1^*,v(t)=v_1^*,z(t)=0$, and $w(t)=0$.

Therefore, the largest invariant set M_1 is singleton $\{E_1\}$. Clearly, the global asymptotic stability of

equilibrium E_1 following from LaSalleï¿œï¿œs invariance principle (Kuang 1993). This completes the proof. ∎

4.3. Stability of Equilibrium E_2

Lemma 4.5.

If $R_1 > 1$ and $R_3 \leq 1$. Let $\overline{E_4} = (\overline{x_4}, \overline{y_4}, \overline{v_4}, \overline{z_4}, \overline{w_4})$ be the solution of equation (3.1) with $\overline{v_4} = g_2^{-1}(\frac{h}{r})$ and $\overline{y_4} = g_1^{-1}(\frac{b}{c})$, then for equilibrium $E_2 = (x_2^*, y_2^*, v_2^*, 0, w_2^*)$, $y_2^* \leq \overline{y_4}$.

Proof:

Since $\overline{y_4} = g_1^{-1}(\frac{b}{c})$, $\overline{v_4} = g_2^{-1}(\frac{h}{r})$, and $\overline{x_4} = x_2^*$. Compared with E_4, we obtain $\overline{x_4} = x_4^*$ and $\overline{v_4} = v_4^*$. When $R_3 \leq 1$,we have $z_4 < 0$. Because equilibrium E_2 and equilibrium $\overline{E_4}$ satisfy the second equations of the system

$$\eta_1 f(x_2^*, y_2^*, v_2^*) = a g_1(y_2^*), \tag{4.7}$$

$$\eta_1 f(\overline{x_4}, \overline{y_4}, \overline{v_4}) = a g_1(\overline{y_4}) + p g_1(\overline{y_4}) g_4(\overline{z_4}), \tag{4.8}$$

it followings that $y_2^* \leq \overline{y_4}$ if $R_1 > 1$ and $R_3 > 1$. This completes the proof. ∎

Theorem 4.6.

If $R_1 > 1$ and $R_3 \leq 1$, then infection equilibrium E_2 with only antibody immune response is globally asymptotically stable.

Proof:

We construct a Lyapunov functional $V_2(t) : \Gamma \to R$ as follows:

$$\begin{aligned} V_2(t) =& x(t) - \int_{x_2^*}^{x(t)} \frac{f(x_2^*, y_2^*, v_2^*)}{f(\theta, y_2^*, v_2^*)} \mathrm{d}\theta + \frac{1}{\eta_1} \left(y(t) - \int_{y_2^*}^{y(t)} \frac{g_1(y_2^*)}{k r g_1(\theta)} \mathrm{d}\theta \right) \\ &+ \frac{a}{k\eta_1\eta_2} \left(v(t) - \int_{v_2^*}^{v(t)} \frac{g_2(v_2^*)}{g_2(\theta)} \mathrm{d}\theta \right) + \frac{p}{c\eta_1} z(t) + \frac{aq}{rk\eta_1\eta_2} \left(w(t) - \int_{w_2^*}^{w(t)} \frac{g_3(w_2^*)}{g_3(\theta)} \mathrm{d}\theta \right) \\ &+ \frac{f(x_2^*, y_2^*, v_2^*)}{\eta_1} \int_0^\infty f_1(\tau) e^{-m_1\tau} \int_{-\tau}^0 H \left(\frac{f(x(t+s), y(t+s), v(t+s))}{f(x_2^*, y_2^*, v_2^*)} \right) \mathrm{d}s\mathrm{d}\tau \\ &+ \frac{f(x_2^*, y_2^*, v_2^*)}{\eta_2} \int_0^\infty f_2(\tau) e^{-m_2\tau} \int_{-\tau}^0 H \left(\frac{g_1(y(t+s))}{g_1(y_2^*)} \right) \mathrm{d}s\mathrm{d}\tau. \end{aligned}$$

Calculating the derivative of $V_2(t)$ along solutions of system (1.3), we have

$$\begin{aligned}\frac{\mathrm{d}V_2(t)}{\mathrm{d}t} =& \left(1-\frac{f(x_2^*,y_2^*,v_2^*)}{f(x,y_2^*,v_2^*)}\right)x'(x)) + \frac{1}{\eta_1}\left(1-\frac{g_1(y_2^*)}{g_1(y)}\right)y'(t)\\ &+\frac{a}{g_2(v_2^*)(k\eta_1\eta_2)}v'(t)+\frac{p}{c\eta_1}z'(t)+\frac{aq}{rk\eta_1\eta_2}\left(1-\frac{g_3(w_2^*)}{g_3(w)}\right)w'(t)\\ &+\frac{f(x_2^*,y_2^*,v_2^*)}{\eta_1}\int_0^\infty f_1(\tau)e^{-m_1\tau}\left(\frac{f(x,y,v)}{f(x_2^*,y_2^*,v_2^*)}\right.\\ &\left.-\frac{f(x(t-\tau),y(t-\tau),v(t-\tau))}{f(x_2^*,y_2^*,v_2^*)}+\ln\frac{f(x(t-\tau),y(t-\tau),v(t-\tau))}{f(x,y,v)}\right)\mathrm{d}\tau\\ &+\frac{f(x_2^*,y_2^*,v_2^*)}{\eta_2}\int_0^\infty f_2(\tau)e^{-m_2\tau}\left(\frac{g_1(y)}{g_1(y_2^*)}-\frac{g_1(y(t-\tau))}{g_1(y_2^*)}+\ln\frac{g_1(y(t-\tau))}{g_1(y)}\right)\mathrm{d}\tau.\end{aligned}$$

Note that

$$n(x_2)=f(x_2^*,y_2^*,v_2^*)=\frac{ag_1(y_2^*)}{\eta_1}=\frac{ak}{u+qg_3(w_2^*)},\ g_2(v_2^*)=\frac{h}{r}.$$

Consequently

$$\begin{aligned}\frac{\mathrm{d}V_2(t)}{\mathrm{d}t} =&(n(x)-n(x_2^*))\left(1-\frac{f(x_2^*,y_2^*,v_2^*)}{f(x,y_2^*,v_2^*)}\right)\\ &+f(x_2^*,y_2^*,v_2^*)\left(-1+\frac{g_2(v)f(x,y_2^*,v_2^*)}{g_2(v_2^*)f(x,y,v)}+\frac{f(x,y,v)}{f(x,y_2^*,v_2^*)}-\frac{g_2(v)}{g_2(v_2^*)}\right)\\ &+f(x_2^*,y_2^*,v_2^*)\left(1-\frac{1}{\eta_1}\int_0^\infty f_1(\tau)e^{-m_1\tau}\frac{g_1(y_2^*)f(x(t-\tau),y(t-\tau),v(t-\tau))}{g_1(y)f(x,y,v)}\mathrm{d}\tau\right)\\ &+f(x_2^*,y_2^*,v_2^*)\left(1-\frac{1}{\eta_2}\int_0^\infty f_2(\tau)e^{-m_2\tau}\frac{g_2(v_2^*)g_1(y(t-\tau))}{g_2(v)g_1(y)}\mathrm{d}\tau\right)\\ &+\frac{f(x_2^*,y_2^*,v_2^*)}{\eta_1}\int_0^\infty f_1(\tau)e^{-m_1\tau}\ln\frac{f(x(t-\tau),y(t-\tau),v(t-\tau))}{f(x,y,v)}\mathrm{d}\tau\\ &+\frac{f(x_2^*,y_2^*,v_2^*)}{\eta_2}\int_0^\infty f_2(\tau)e^{-m_2\tau}\ln\frac{g_1(y(t-\tau))}{g_1(y)}\mathrm{d}\tau\\ &+\frac{p}{\eta_1}g_4(z)(g_1(y_1^*)-g_1(\overline{y_4}))\\ \frac{\mathrm{d}V_2(t)}{\mathrm{d}t} =&(n(x)-n(x_2^*))\left(1-\frac{f(x_2^*,y_2^*,v_2^*)}{f(x,y_2^*,v_2^*)}\right)\\ &+f(x_2^*,y_2^*,v_2^*)\frac{g_2(v)}{g_2(v_2^*)}\left(\frac{f(x,y,v)}{f(x,y_2^*,v_2^*)}-1\right)\left(\frac{g_1(v_2^*)}{g_2(v)}-\frac{f(x,y_2^*,v_2^*)}{f(x,y,v)}\right)\\ &-f(x_2^*,y_2^*,v_2^*)\left[H\left(\frac{f(x_2^*,y_2^*,v_2^*)}{f(x,y_2^*,v_2^*)}\right)-H\left(\frac{g_2(v)f(x,y_2^*,v_2^*)}{g_2(v_2^*)f(x,y,v)}\right)\right]\\ &-\frac{f(x_2^*,y_2^*,v_2^*)}{\eta_1}\int_0^\infty f_1(\tau)e^{-m_1\tau}H\left(\frac{g_1(y_2^*)f(x(t-\tau),y(t-\tau),v(t-\tau))}{g_1(y)f(x_2^*,y_2^*,v_2^*)}\right)\mathrm{d}\tau\\ &-\frac{f(x_2^*,y_2^*,v_2^*)}{\eta_2}\int_0^\infty f_2(\tau)e^{-m_2\tau}H\left(\frac{g_1(y(t-\tau))g_2(v_2^*))}{g_1(y_2^*)g_2(v)}\right)\mathrm{d}\tau\\ &+\frac{p}{\eta_1}g_4(z)(g_1(y_2^*)-g_1(\overline{y_4})).\end{aligned}$$

From the Hypothesis H1-H4, we have

$$(n(x) - n(x_2^*)) \left(1 - \frac{f(x_2^*, y_2^*, v_2^*)}{f(x, y_2^*, v_2^*)}\right) \leq 0,$$

and

$$\left(\frac{f(x, y, v)}{f(x, y_2^*, v_2^*)} - 1\right) \left(\frac{g_2(v_2^*)}{g_2(v)} - \frac{f(x, y_2^*, v_2^*)}{f(x, y, v)}\right) \leq 0,$$

Lemma 4.3 implies $g_1(y_2^*) \leq g_1(\overline{y_4})$, we obtain $\frac{\mathrm{d}V_2(t)}{\mathrm{d}t} = 0$ if and only if $x(t) = x_2^*,\ y(t) = y_2^*,\ v(t) = v_2^*,\ z(t) = 0$ and $w(t) = w_2^*$. Therefore, the largest invariant set in $\{(x, y, v, z, w) \in \Gamma : \frac{\mathrm{d}V_2(t)}{\mathrm{d}t} = 0\}$ is singleton E_2. From LaSalle's invariance principle (Kuang 1993), the equilibrium E_2 of system (1.3) is globally asymptotically stable. This completes the proof. ∎

4.4. Stability of Equilibrium E_3

Lemma 4.7.

If $R_2 > 1$ and $R_4 \leq 1$, Let $\overline{E_4} = (\overline{x_4}, \overline{y_4}, \overline{v_4}, \overline{z_4}, \overline{w_4})$ be the solution of (3.1) with $\overline{v_4} = g_2^{-1}(\frac{h}{r})$ and $\overline{y_4} = g_1^{-1}(\frac{b}{c})$, then infection equilibrium $E_3 = (x_3^*, y_3^*, v_3^*, z_3^*, 0)$, we have $v_3^* \leq \overline{v_4}$.

Proof:

It is similar to the proof of lemma 4.3. ∎

Theorem 4.8.

If $R_2 > 1$ and $R_4 \leq 1$, then infection equilibrium E_3 with only CTL immune response is globally asymptotically stable.

Proof:

Define $V_3(t) : \Gamma \to R$ as follows:

$$\begin{aligned}
V_3(t) =& x(t) - \int_{x_3^*}^{x(t)} \frac{f(x_3^*, y_3^*, v_3^*)}{f(\theta, y_3^*, v_3^*)} d\theta + \frac{1}{\eta_1} \left(y(t) - \int_{y_3^*}^{y(t)} \frac{g_1(y_3^*)}{g_1(\theta)} \mathrm{d}\theta\right) \\
&+ \frac{a + pg_4(z_3^*)}{k\eta_1\eta_2} \left(v(t) - \int_{v_3^*}^{v(t)} \frac{g_2(v_3^*)}{g_2(\theta)} \mathrm{d}\theta\right) \\
&+ \frac{p}{c\eta_1} \left(z(t) - \int_{z_3^*}^{z(t)} \frac{g_4(z_3^*)}{g_4(\theta)} \mathrm{d}\theta\right) + \frac{a + pg_4(z_3^*)}{k\eta_1\eta_2} w(t) \\
&+ \frac{f(x_3^*, y_3^*, v_3^*)}{\eta_1} \int_0^\infty f_1(\tau) e^{-m_1\tau} \int_{-\tau}^0 H\left(\frac{f(x(t+s), y(t+s), v(t+s))}{f(x_3^*, y_3^* v_3^*)}\right) \mathrm{d}s\mathrm{d}\tau \\
&+ \frac{a + pg_4(z_3^*)}{k\eta_1\eta_2} \int_0^\infty f_2(\tau) e^{-m_2\tau} \int_{-\tau}^0 H\left(\frac{g_1(y(t+s))}{g_1(y_3^*)}\right) \mathrm{d}s\mathrm{d}\tau.
\end{aligned}$$

Calculating the derivative of $V_3(t)$ along solutions of system (1.3), we have

$$\begin{aligned}\frac{\mathrm{d}V_3(t)}{\mathrm{d}t} =& \left(1-\frac{f(x_3^*,y_3^*,v_3^*)}{f(x,y_3^*,v_3^*)}\right)x'(t)+\frac{1}{\eta_1}\left(1-\frac{g_1(y_3^*)}{g_1(y)}\right)y'(t)\\ &+\frac{a+pg_4(z_3^*)}{k\eta_1\eta_2}\left(1-\frac{g_2(v_3^*)}{g_2(v)}\right)v'(t)+\frac{p}{c\eta_1}z'(t)+\frac{a+pg_4(z_3^*)}{rk\eta_1\eta_2}w'(t)\\ &+\frac{f(x_3^*,y_3^*,v_3^*)}{\eta_1}\int_0^\infty f_1(\tau)e^{-m_1\tau}\left(\frac{f(x,y,v)}{f(x_3^*,y_3^*,v_3^*)}\right.\\ &\left.-\frac{f(x(t-\tau),y(t-\tau),v(t-\tau))}{f(x_3^*,y_3^*,v_3^*)}+\ln\frac{f(x(t-\tau),y(t-\tau),v(t-\tau))}{f(x,y,v)}\right)\mathrm{d}\tau\\ &+\frac{a+pg_4(z_3^*)}{\eta_1\eta_2}\int_0^\infty f_2(\tau)e^{-m_2\tau}\left(\frac{g_1(y)}{g_1(y_3^*)}-\frac{g_1(y(t-\tau))}{g_1(y_3^*)}+\ln\frac{g_1(y(t-\tau))}{g_1(y)}\right)\mathrm{d}\tau.\end{aligned}$$

Note that

$$n(x_3^*)=f(x_3^*,y_3^*,v_3^*)=\frac{(a+pg_4(z_3^*))g_1(y_3^*)}{\eta_1}=\frac{u(a+pg_4(z_3^*))g_2(v_3^*)}{k\eta_1\eta_2},\ g_1(y_3^*)=\frac{b}{c}.$$

Consequently

$$\begin{aligned}\frac{\mathrm{d}V_3(t)}{\mathrm{d}t} =&(n(x)-n(x_3^*))\left(1-\frac{f(x_3^*,y_3^*,v_3^*)}{f(x,y_3^*,v_3^*)}\right)\\ &+f(x_3^*,y_3^*,v_3^*)\left(-1+\frac{g_2(v)f(x,y_3^*,v_3^*)}{g_2(v_3^*)f(x,y,v)}+\frac{f(x,y,v)}{f(x,y_3^*,v_3^*)}-\frac{g_2(v)}{g_2(v_3^*)}\right)\\ &+f(x_3^*,y_3^*,v_3^*)\left(1-\int_0^\infty f_1(\tau)e^{-m_1\tau}\frac{g_1(y_3^*)f(x(t-\tau),y(t-\tau),v(t-\tau))}{g_1(y)f(x_3^*,y_3^*,v_3^*)}\mathrm{d}\tau\right)\\ &+f(x_3^*,y_3^*,v_3^*)\left(1-\frac{g_2(v)}{g_2(v_3^*)}-\frac{1}{\eta_2}\int_0^\infty f_2(\tau)e^{-m_2\tau}\ln\frac{g_1(y(t-\tau))g_2(v_3^*)}{g_1(y_3^*))g_2(v)}\mathrm{d}\tau\right)\\ &+\frac{f(x_3^*,y_3^*,v_3^*)}{\eta_1}\int_0^\infty f_1(\tau)e^{-m_1\tau}\ln\frac{f(x(t-\tau),y(t-\tau),v(t-\tau))}{f(x,y,v)}d\tau\\ &+\frac{f(x_3^*,y_3^*,v_3^*)}{\eta_1\eta_2}\int_0^\infty f_2(\tau)e^{-m_2\tau}\ln\frac{g_1(y(t-\tau))}{g_1(y_3^*)}\mathrm{d}\tau\\ &+\frac{(a+pg_4(z_3^*))q}{k\eta_1\eta_2}g_3(w)(g_2(v_3^*)-g_2(\overline{v_4}))\\ =&(n(x)-n(x_3^*))\left(1-\frac{f(x_3^*,y_3^*,v_3^*)}{f(x,y_3^*,v_3^*)}\right)\\ &+f(x_3^*,y_3^*,v_3^*)\frac{g_2(v)}{g_2(v_3^*)}\left(\frac{f(x,y,v)}{f(x,y_3^*,v_3^*)}-1\right)\left(\frac{g_2(v_3^*)}{g_2(v)}-\frac{f(x,y_3^*,v_3^*)}{f(x,y,v)}\right)\\ &-f(x_3^*,y_3^*,v_3^*)\left[H\left(\frac{f(x_3^*,y_3^*,v_3^*)}{f(x,y_3^*,v_3^*)}\right)-H\left(\frac{g_2(v)f(x,y_3^*,v_3^*))}{g_2(v_3^*)f(x,y,v)}\right)\right]\\ &-\frac{f(x_3^*,y_3^*,v_3^*)}{\eta_1}\int_0^\infty f_1(\tau)e^{-m_1\tau}H\left(\frac{g_1(y_3^*)f(x(t-\tau),y(t-\tau),v(t-\tau))}{g_1(y)f(x,y,v)}\right)\mathrm{d}\tau\\ &-\frac{f(x_3^*,y_3^*,v_3^*)}{\eta_2}\int_0^\infty f_2(\tau)e^{-m_2\tau}H\left(\frac{g_2(v_3^*)g_1(y(t-\tau))}{g_2(v)g_1(y_1^*))}\right)\mathrm{d}\tau\\ &+\frac{(a+pg_4(z_3^*))q}{k\eta_1\eta_2}g_3(w)(g_2(v_3^*)-g_2(\overline{v_4})).\end{aligned}$$

From the Hypothesis H1-H4, we have

$$(n(x) - n(x_3^*)) \left(1 - \frac{f(x_3^*, y_3^*, v_3^*)}{f(x, y_3^*, v_3^*)}\right) \leq 0,$$

and

$$\left(\frac{f(x, y, v)}{f(x, y_3^*, v_3^*)} - 1\right) \left(\frac{g_2(v_3^*)}{g_2(v)} - \frac{f(x, y_3^*, v_3^*)}{f(x, y, v)}\right) \leq 0.$$

Lemma 4.4 implies $v_3^* \leq \overline{v_4}$, Clearly, $\frac{\mathrm{d}V_3(t)}{\mathrm{d}t} \leq 0$. Let $M_3 = \{(x, y, v, z, w) \in \Gamma : \frac{\mathrm{d}V_3(t)}{\mathrm{d}t} = 0\}$. It can be varified $\frac{\mathrm{d}V_3(t)}{\mathrm{d}t} = 0$ if and only if $x(t) = x_3^*, y(t) = y_3^*, v(t) = v_3^*, z(t) = z_3^*$, and $w(t) = 0$. Thus, the largest invariant set in M_3 is singleton $\{E_3\}$. From LaSalleï¿œï¿œs invariance principle (Kuang 1993), then equilibrium E_3 of system (1.3) is globally asymptotically stable.
This completes the proof. ∎

4.5. Stability of Equilibrium E_4

Theorem 4.9.

If $R_3 > 1$ and $R_4 > 1$, then infection equilibrium E_4 with both CTL and antibody immune response is globally asymptotically stable.

Proof:

We construct a Lyapunov functional $V_4(t) : \Gamma \to R$ as follows:

$$\begin{aligned}
V_4(t) =& x(t) - \int_{x_4^*}^{x(t)} \frac{f(x_4^*, y_4^*, v_4^*)}{f(\theta, y_4^*, v_4^*)} \mathrm{d}\theta + \frac{1}{\eta_1} \left(y(t) - \int_{y_4^*}^{y(t)} \frac{g_1(y_4^*)}{g_1(\theta)} \mathrm{d}\theta\right) \\
&+ \frac{a + pg_4(z_4^*)}{k\eta_1\eta_2} \left(v(t) - \int_{v_4^*}^{v(t)} \frac{g_2(v_4^*)}{g_2(\theta)} \mathrm{d}\theta\right) + \frac{p}{c\eta_1} \left(z(t) - \int_{z_4^*}^{z(t)} \frac{g_4(z_4^*)}{g_4(\theta)}) \mathrm{d}\theta\right) \\
&+ \frac{(a + pg_4(z_4^*))q}{rk\eta_1\eta_2} \left(w(t) + \int_{w_4^*}^{w(t)} \frac{g_3(w_4^*)}{g_3(\theta)} \mathrm{d}\theta\right) \\
&+ \frac{f(x_4^*, y_4^*, v_4^*)}{\eta_1} \int_0^\infty f_1(\tau) e^{-m_1\tau} \int_{-\tau}^0 H\left(\frac{f(x(t+s), y(t+s), v(t+s))}{f(x_4^*, y_4^*, v_4^*)}\right) \mathrm{d}s\mathrm{d}\tau \\
&+ \frac{(a + pg_4(z_4^*))g_1(y_4)}{\eta_1\eta_2} \int_0^\infty f_2(\tau) e^{-m_2\tau} \int_{-\tau}^0 H\left(\frac{g_1(y(t+s))}{g_1(y_4^*)}\right) \mathrm{d}s\mathrm{d}\tau.
\end{aligned}$$

Take advantage of the above similar method, we obtain

$$\begin{aligned}\frac{\mathrm{d}V_4(t)}{\mathrm{d}t} =&(n(x)-n(x_4^*))\left(1-\frac{f(x_4^*,y_4^*,v_4^*)}{f(x,y_4^*,v_4^*)}\right)\\ &+f(x_4^*,y_4^*,v_4^*)\frac{g_2(v)}{g_2(v_4^*)}\left(\frac{f(x,y,v)}{f(x,y_4^*,v_4^*)}-1\right)\left(\frac{g_2(v_4^*)}{g_2(v)}-\frac{f(x,y_4^*,v_4^*)}{f(x,y,v)}\right)\\ &-f(x_4^*,y_4^*,v_4^*)H\left(\frac{f(x_4^*,y_4^*,v_4^*)}{f(x,y_4^*,v_4^*)}\right)-f(x_4^*,y_4^*,v_4^*)H\left(\frac{g_2(v)f(x,y_4^*,v_4^*)}{g_2(v_4^*)f(x,y,v)}\right)\\ &-\frac{f(x_4^*,y_4^*,v_4^*)}{\eta_1}\int_0^\infty f_1(\tau)e^{-m_1\tau}H\left(\frac{g_1(y_4^*)f(x(t-\tau),y(t-\tau),v(t-\tau))}{g_1(y)f(x_4^*,y_4^*,v_4^*)}\right)\mathrm{d}\tau\\ &-\frac{f(x_4^*,y_4^*,v_4^*)}{\eta_2}\int_0^\infty f_2(\tau)e^{-m_2\tau}H\left(\frac{g_2(v_4^*)g_1(y(t-\tau))}{g_2(v)g_1(y_4^*))}\right)\mathrm{d}\tau.\end{aligned}$$

From the Hypothesis H1-H4, we have

$$(n(x)-n(x_4^*))\left(1-\frac{f(x_4^*,y_4^*,v_4^*)}{f(x,y_4^*,v_4^*)}\right)\le 0,$$

and

$$\left(\frac{f(x,y,v)}{f(x,y_4^*,v_4^*)}-1\right)\left(\frac{g_2(v_4^*)}{g_2(v)}-\frac{f(x,y_4^*,v_4^*)}{f(x,y,v)}\right)\le 0.$$

Thus, we have $\frac{\mathrm{d}V_4(t)}{\mathrm{d}t}\le 0$, and we can certify that $\frac{\mathrm{d}V_4(t)}{\mathrm{d}t}=0$ if and only if $x(t)=x_4^*, y(t)=y_4^*, v(t)=v_4^*, z(t)=z_4^*$, and $w(t)=w_4^*$. Obviously, the largest invariant set in $\{(x,y,v,z,w)\in\Gamma : \frac{\mathrm{d}V_4(t)}{\mathrm{d}t}=0\}$ is singleton $\{E_4\}$. Thus, the global asymptotic stability of equilibrium E_4 following from LaSalleï¿œï¿œs invariance principle (Kuang 1993). This completes the proof. ∎

5. Numerical simulations

To verify the main analytic results, we choose $n(x(t))=\lambda-dx(t)$ and $f(x(t),y(t),v(t))=\frac{\beta x(t)v(t)}{x(t)+y(t)}$ (Kuang 1993), $g_1(y(t))=y(t)$, $g_2(v(t))=v(t)$, $g_3(w(t))=w(t)$, $g_4(z(t))=z(t)$ and $f_i(\tau)=r_ie^{-r_i\tau}$, $i=1,2$, (Elaiw and Alshamrani 2015).
Then, system (1.3) can be transformed into:

$$\begin{cases}\frac{\mathrm{d}x(t)}{\mathrm{d}t}=\lambda-dx(t)-\frac{\beta x(t)v(t)}{x(t)+y(t)},\\ \frac{\mathrm{d}y(t)}{dt}=r_1\int_0^\infty e^{-(r_1+m_1)\tau}\frac{\beta x(t-\tau)v(t-\tau)}{x(t-\tau)+y(t-\tau)}\mathrm{d}\tau-ay(t)-py(t)z(t),\\ \frac{\mathrm{d}v(t)}{\mathrm{d}t}=kr_2\int_0^\infty e^{-(r_2+m_2)\tau}y(t-\tau)\mathrm{d}\tau-uv(t)-qv(t)w(t),\\ \frac{\mathrm{d}z(t)}{\mathrm{d}t}=cy(t)z(t)-bz(t),\\ \frac{\mathrm{d}w(t)}{\mathrm{d}t}=rv(t)w(t)-hw(t).\end{cases}\tag{5.1}$$

Parameters, their symbols, meanings, default values, and units are showed in Table 1.

Table 1. Parameters, their symbols, meanings and default values are use in model (5.1)

Parameter	Meaning	Range	Unit
λ	Source rate of uninfected cells	[4.33×10^5, 5.85×10^5]	cell ml^{-1} day^{-1}
d	Death rate of uninfected cells	0.039	day^{-1}
β	Average of infection	[2.5×10^{-4}, 0.5]	cell virion^{-1} day^{-1}
r_1	A parameter of $f_1(\tau) = r_1 e^{-r_1\tau}$	0.1	day
r_2	A parameter of $f_2(\tau) = r_2 e^{-r_2\tau}$	0.1	day
m_1	$e^{-m_1\tau}$ denotes the survive rate of infected cells by virus	[0.01, 3]	day
m_2	$e^{-m_2\tau}$ denotes the survive rate of infected cells	[0.011, 3]	day
a	Death rate of infected cells	0.0693	day^{-1}
p	Clearance rate of infection	0.00064	ml cell^{-1} day^{-1}
k	The rate of production the virus	[2, 1250]	virion cell^{-1} day^{-1}
u	Clearance rate of virus	[0.3466, 2.4]	day^{-1}
q	Clearance rate of antibodies	0.5	ml cell^{-1} day^{-1}
c	Activation rate of antibodies	varied	ml cell^{-1} day^{-1}
b	Death rate of antibodies	0.1	day^{-1}
r	Activation rate of CTL cells	varied	ml virion^{-1} day^{-1}
h	Death rate of CTL cells	0.5	day^{-1}

The infection-free equilibrium, the immune-free equilibrium, the infection equilibrium with only antibody immune responses, the infection equilibrium with only CTL immune responses, and the infection equilibrium with both CTL and antibody immune responses of system (5.1) are also denoted by $E_0 = (x_0^*,\ 0,\ 0,\ 0,\ 0)$, $E_1 = (x_1^*,\ y_1^*,\ v_1^*,\ 0,\ 0)$, $E_2 = (x_2^*,\ y_2^*,\ v_2^*,\ 0,\ w_2^*)$, $E_3 = (x_3^*,\ y_3^*,\ v_3^*,\ z_3^*,\ 0)$, and $E_4 = (x_4^*,\ y_4^*,\ v_4^*,\ z_4^*,\ w_4^*)$, respectively.
More concretely, for system (5.1),

$$\begin{cases} x_0^* = \dfrac{\lambda}{d},\ x_1^* = \dfrac{\lambda r_1 - a(r_1+m_1)M^*}{dr_1},\ y_1^* = M^*, v_1^* = \dfrac{kr_2M^*}{u(r_2+m_2)}, \\ x_2^* = \dfrac{\lambda r_1 - a(r_1+m_1)N^*}{dr_1},\ y_2^* = N^*,\ v_2^* = \dfrac{h}{r},\ w_2^* = \dfrac{krr_2N^* - uh(r_2+m_2)}{qh(r_2+m_2)}, \\ x_3^* = P^*,\ y_3^* = \dfrac{b}{c},\ v_3^* = \dfrac{kr_2b}{uc(r_2+m_2)}, \\ z_3^* = \dfrac{c\beta kr_1r_2bP^* - abu(r_1+m_1)(r_2+m_2)(cP^*+b)}{pbu(r_1+m_1)(r_2+m_2)(cP^*+b)}, \\ x_4^* = Q^*,\ y_4^* = \dfrac{b}{c},\ v_4^* = \dfrac{h}{r},\ z_4^* = \dfrac{r_1\beta hc^2Q^* - abr(r_1+m_1)(cQ^*+b)}{pbr(r_1+m_1)(cQ^*+b)}, \\ w_4^* = \dfrac{bkrr_2 - uhc(r_2+m_2)}{cqh(r_2+m_2)}, \end{cases}$$

where;

$$\begin{cases} M^* = \dfrac{\lambda r_1^2 r_2 \beta k - \lambda r_1 u a (r_1+m_1)(r_2+m_2)}{a[\beta k r_1^2 r_2 + \beta k r_1 r_2 m_1 - u a (r_1+m_1)^2 (r_2+m_2) + u d r_1 (r_1+m_1)(r_2+m_2)]}, \\ N^* = \dfrac{r_1(r_1\beta\lambda - a r_1 \beta - a\beta m_1 - a\lambda r_1 - a\lambda m_1)}{a(r_1+m_1)[1-a(r_1+m_1)]}, \\ P^* = \dfrac{\sqrt{\frac{\lambda b}{dc} + dbu(r_2+m_2) + \beta k r_2 b - \lambda c u (r_2+m_2)} - u(r_2+m_2)(db+\lambda c) - \beta k r_2 b}{2dcu(r_2+m_2)}. \end{cases}$$

and

$$Q^* = \frac{\sqrt{4\lambda bcdr^2} + \lambda cr - bdr - c\beta h}{2cdr}.$$

Furthermore, we can obtain $R_0,\ R_1,\ R_2,\ R_3$, and R_4 of system (5.1), respectively:

$$R_0 = \frac{k r_1 r_2 \beta}{a u ((r_1+m_1)(r_2+m_2))},$$

$$R_1 = \frac{k r_1 r_2 \beta}{u((r_1+m_1)(r_2+m_2))} \cdot \frac{x_2^*}{x_2^* + y_2^*},$$

$$R_2 = \frac{k r_1 r_2 \beta}{a u ((r_1+m_1)(r_2+m_2))} \cdot \frac{x_3^*}{x_3^* + y_3^*},$$

$$R_3 = \frac{c\beta r_1}{ab(r_1+m_1)} \cdot \frac{x_4^* v_4^*}{x_4^* + y_4^*},$$

and

$$R_4 = \frac{kbrr_2}{uch(r_2+m_2)}.$$

Next step we introduce two new variables:

$$T(t) = \int_0^\infty e^{-(r_1+m_1)\tau} \frac{\beta x(t-\tau) v(t-\tau)}{x(t-\tau)+y(t-\tau)} \mathrm{d}\tau,$$

and

$$U(t) = \int_0^\infty e^{-(r_2+m_2)\tau} y(t-\tau) \mathrm{d}\tau.$$

It is easy to see that variables $x(t)$, $T(t)$, $y(t)$, $U(t)$, $v(t)$, $z(t)$, and $w(t)$ satisfy the following ODEs without time delays:

$$\begin{cases} \frac{\mathrm{d}x(t)}{\mathrm{d}t} = \lambda - dx(t) - \frac{\beta x(t)v(t)}{x(t)+y(t)}, \\ \frac{\mathrm{d}T(t)}{\mathrm{d}t} = \frac{\beta x(t)v(t)}{x(t)+y(t)} - (r_1+m_1)T(t), \\ \frac{\mathrm{d}y(t)}{\mathrm{d}t} = r_1T(t) - ay(t) - py(t)z(t), \\ \frac{\mathrm{d}U(t)}{\mathrm{d}t} = y(t) - (r_2+m_2)U(t), \\ \frac{\mathrm{d}v(t)}{\mathrm{d}t} = kr_2U(t) - uv(t) - qv(t)w(t), \\ \frac{\mathrm{d}z(t)}{\mathrm{d}t} = cy(t)z(t) - bz(t), \\ \frac{\mathrm{d}w(t)}{\mathrm{d}t} = rv(t)w(t) - hw(t). \end{cases} \tag{5.2}$$

The initial values for system (5.2) are $x(0) = I_1$, $y(0) = I_2$, $v(0) = I_3$, $z(0) = I_4$, $w(0) = I_5$, $T(0) = I_6 = \frac{\beta}{r_1+m_1} \cdot \frac{I_1I_3}{I_1+I_2}$, $U(0) = I_7 = \frac{I_2}{r_2+m_2}$. The asymptotic behaviors of the variables x, y, v, z, and w in the system (5.1) are obtained by selecting the appropriate parameters and simulating the asymptotic behaviors of the corresponding variables x, y, v, z, and w in the auxiliary system (5.2). We simulate the results of Theorem 4.1, Theorem 4.4, Theorem 4.6, Theorem 4.8, and Theorem 4.9. For each result, we give different parameter values and three sets of initial values. Five figures are obtained. Each picture has a real line, a dotted line and a point line, and they are the results of the simulation corresponding to the different initial values.

The values of ten parameters remain unchanged in all of the five figures, and they are shown in Table 2. The other six changing parameters are illustrated below each corresponding picture. The

Table 2. Simulation parameters

Parameter	Value	Unit
λ	50400	cell ml^{-1} day^{-1}
d	0.039	day^{-1}
r_1	0.1	day
r_2	0.1	day
a	0.0693	day^{-1}
p	0.00064	ml cell^{-1} day^{-1}
u	0.67	day^{-1}
q	0.5	ml cell^{-1} day^{-1}
b	0.1	day^{-1}
h	0.5	day^{-1}

three sets of initial conditions are exhibited in Table 3 and Table 4.

Table 3. Three sets of different initial values

Initial Value	I_1	I_2	I_3	I_4	I_5
IV1, IIV1, IIIV1, IVV1, VV1	700	1	6	20	30
IV2, IIV2, IIIV2, IVV2, VV2	400	3	7	30	40
IV3, IIV3, IIIV3, IVV3, VV3	60	6	9	40	50
Unit	cell ml^{-1}	cell ml^{-1} day^{-2}	cell ml^{-1}	cell ml^{-1} day^{-1}	virion ml^{-1}

Table 4. Three sets of different initial values

Initial Value	I_6	I_7
IV1	0.0545	0.3266
IV2	0.0632	0.9677
IV3	0.0744	1.9355
IIV1	0.4639	0.3226
IIV2	0.8066	0.9677
IIV3	0.6333	1.9355
IIIV1	19.6082	9.0909
IIIV2	34.1074	27.2727
IIIV3	26.7766	54.5455
IVV1	0.6958	0.3266
IVV2	1.2100	0.9677
IVV3	0.9499	1.9355
VV1	2.5055	0.9091
VV2	4.3584	2.7273
VV3	3.4216	5.4545
Unit	cell ml^{-1}	cell ml^{-1}

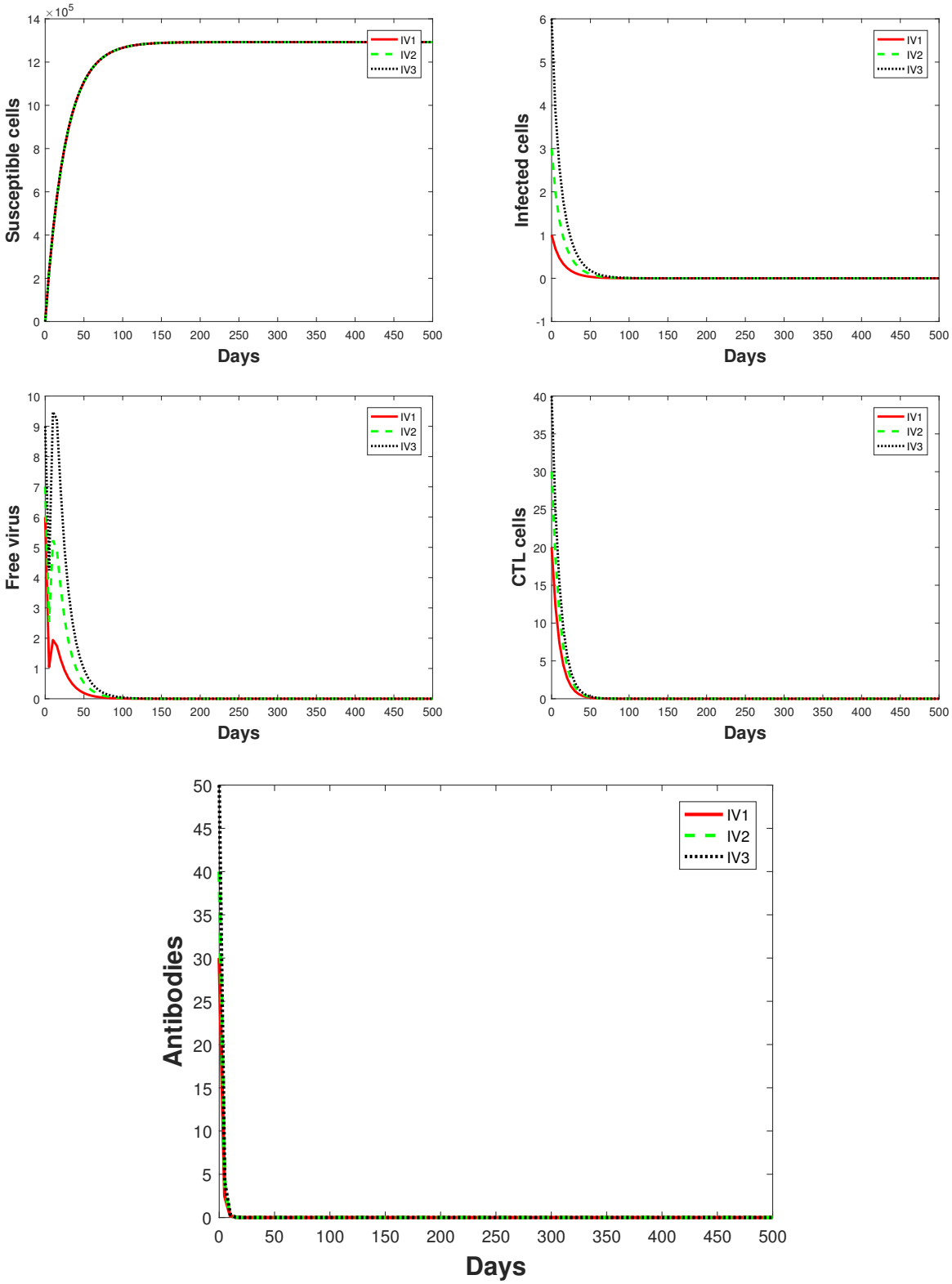

Figure 1. The behavior of the infection dynamics of system (5.1) for $\beta = 0.01$ cell virion^{-1} day^{-1}, $k = 100$ virion cell^{-1} day^{-1}, $c = 10^{-3}$ ml cell^{-1} day^{-1}, $r = 4.4 \times 10^{-4}$ ml virion^{-1} day^{-1}, $m_1 = 1$ day, $m_2 = 3$ day. For the parameters used in this case, the threshold value $R_0 = 0.0632 < 1$, and the infection-free equilibrium E_0 is globally asymptotically stable.

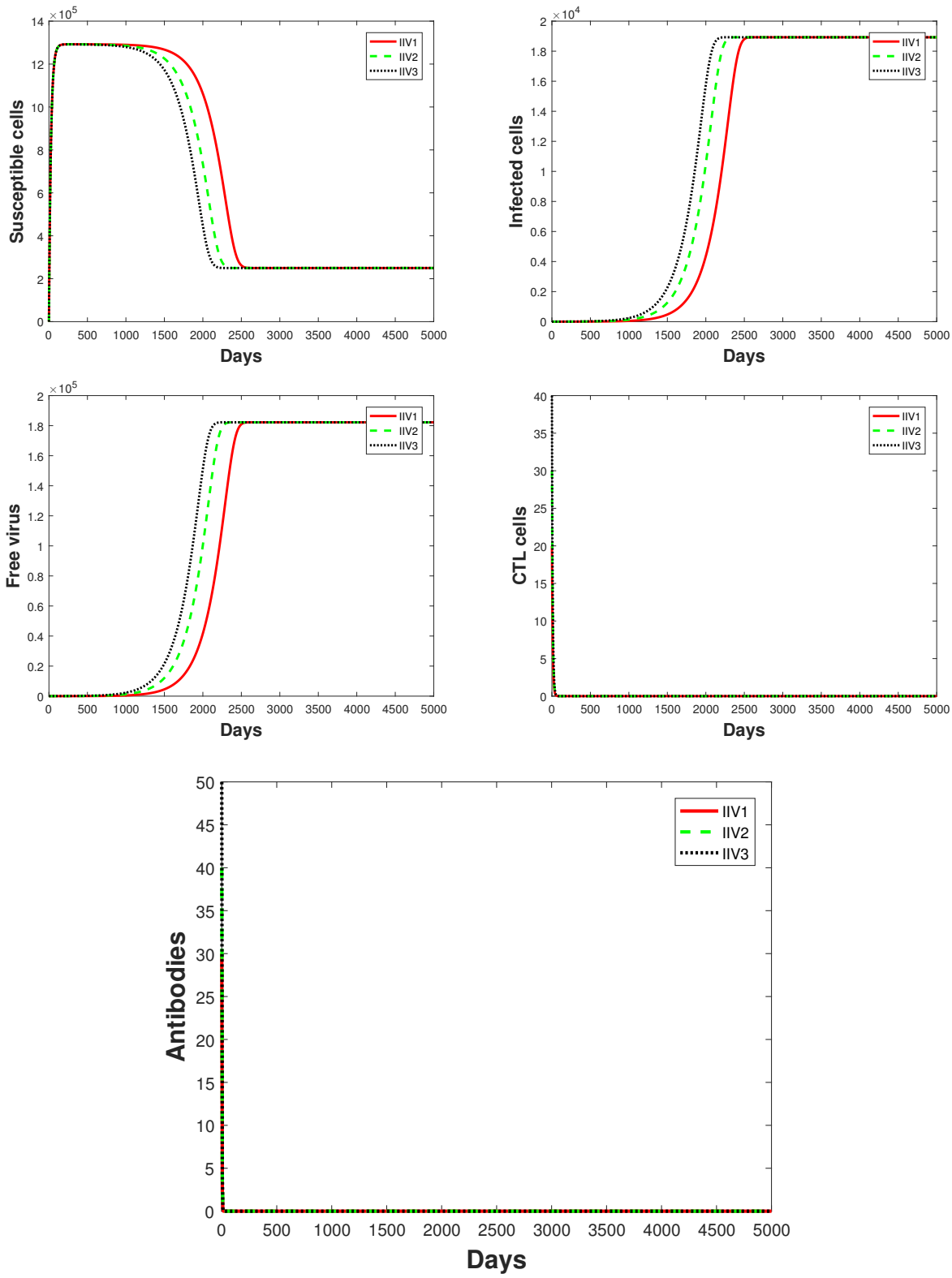

Figure 2. The behavior of the infection dynamics of system (5.1) for $\beta = 0.24$ cell virion^{-1} day^{-1}, $k = 200$ virion cell^{-1} day^{-1}, $c = 10^{-10}$ ml cell^{-1} day^{-1}, $r = 4.4 \times 10^{-7}$ ml virion^{-1} day^{-1}, $m_1 = 3$ day, $m_2 = 3$ day. For the parameters used in this case, the threshold values $R_0 = 1.0757 > 1$, $R_1 = 0.6571 < 1$, and $R_2 = 0.9989 < 1$, then the immune-free infection equilibrium E_1 is globally asymptotically stable.

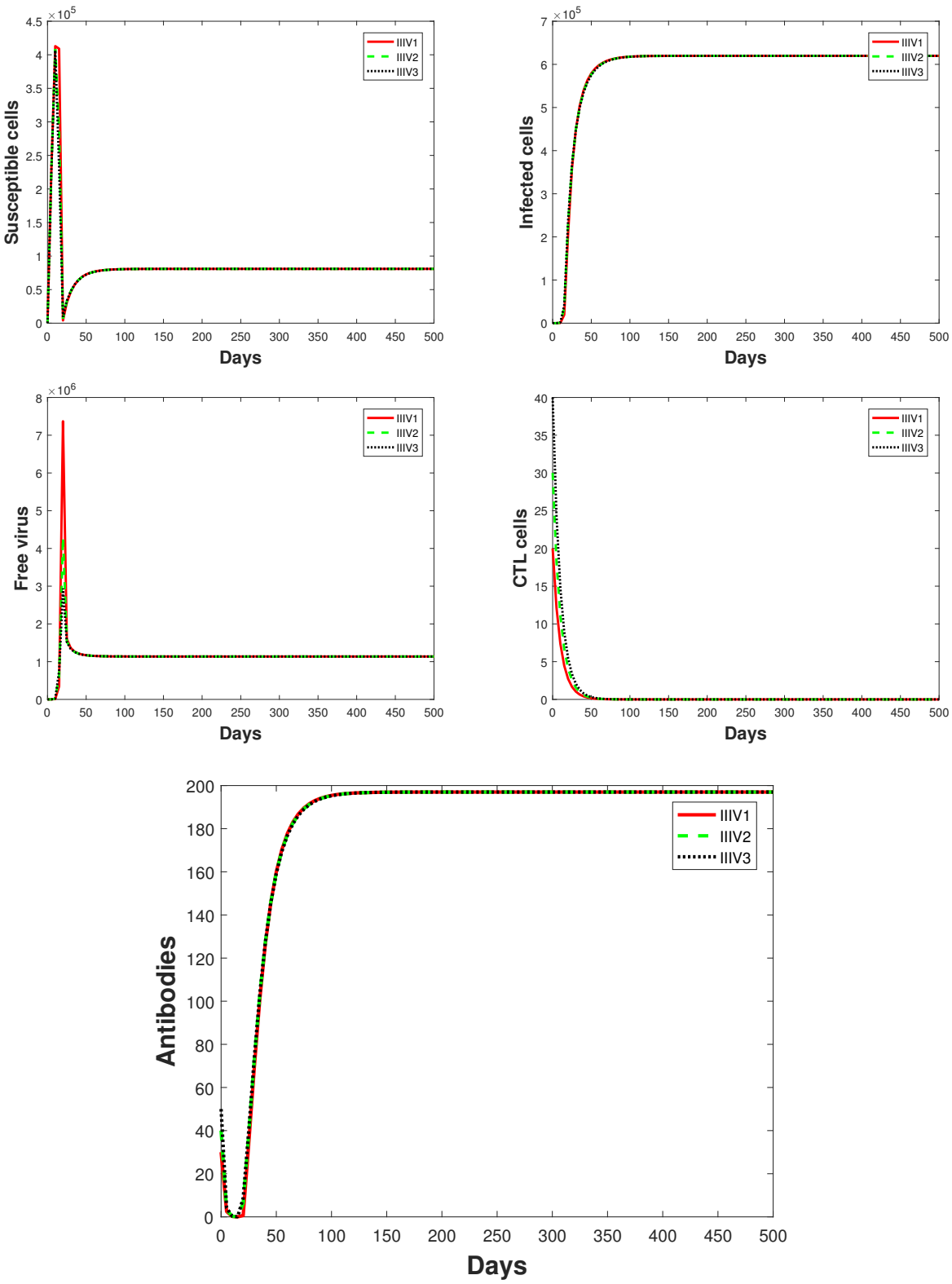

Figure 3. The behavior of the infection dynamics of system (5.1) for $\beta = 0.36$ cell virion^{-1} day^{-1}, $k = 200$ virion cell^{-1} day^{-1}, $c = 10^{-8}$ ml cell^{-1} day^{-1}, $r = 4.4 \times 10^{-7}$ ml virion^{-1} day^{-1}, $m_1 = 0.01$ day, $m_2 = 0.01$ day. For the parameters used in this case, the threshold values $R_1 = 17836.1183 > 1$, and $R_3 = 0.0328 < 1$, then the infection equilibrium E_2 with only antibody immune response is globally asymptotically stable.

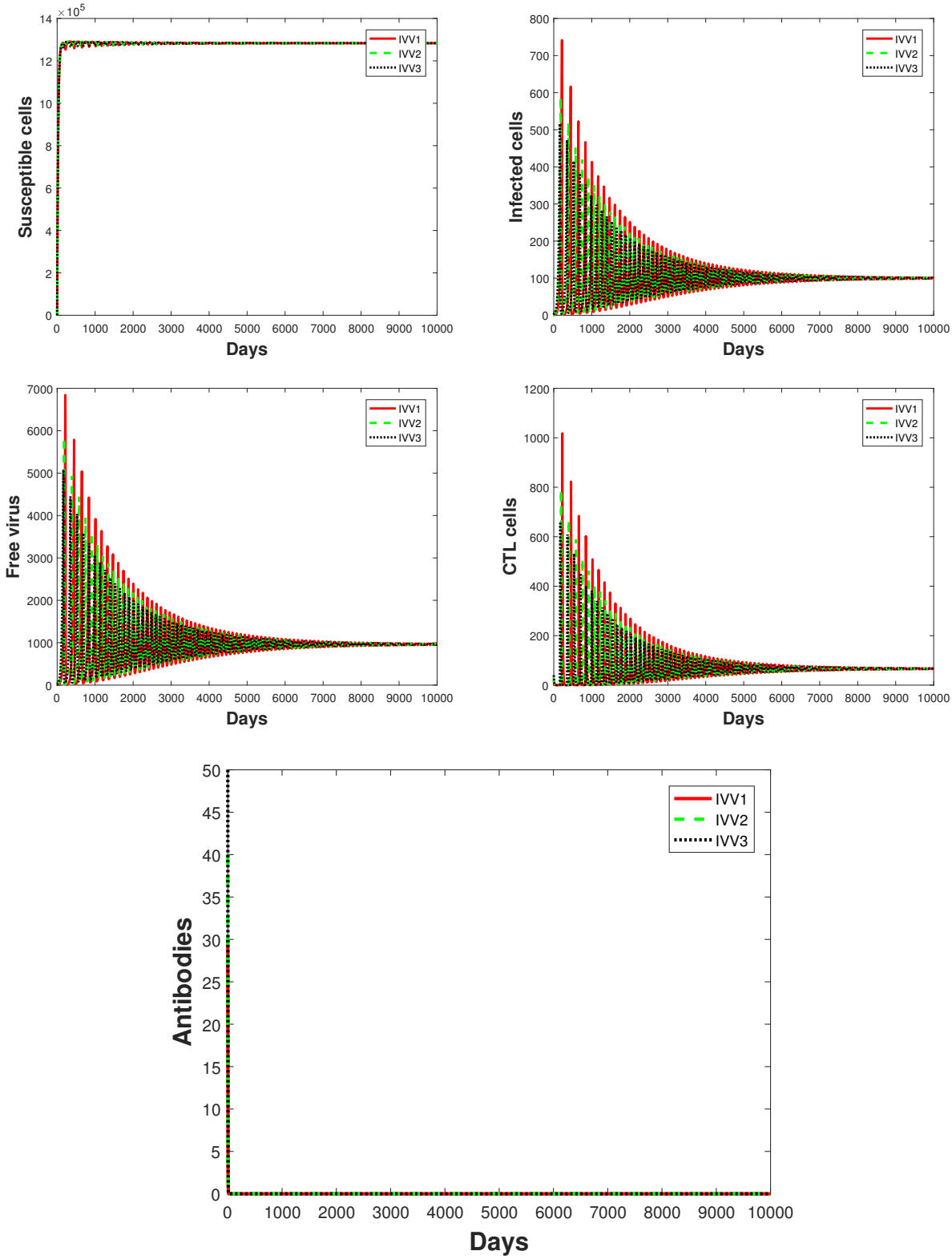

Figure 4. The behavior of the infection dynamics of system (5.1) for $\beta = 0.36$ cell virion^{-1} day^{-1}, $k = 200$ virion cell^{-1} day^{-1}, $c = 10^{-3}$ ml cell^{-1} day^{-1}, $r = 4.4 \times 10^{-7}$ ml virion^{-1} day^{-1}, $m_1 = 3$ day, $m_2 = 3$ day. For the parameters used in this case, the threshold values $R_2 = 1.6134 > 1$, and $R_4 = 8.4738 \times 10^{-4} < 1$, then the infection equilibrium E_3 with only CTL immune response is globally asymptotically stable.

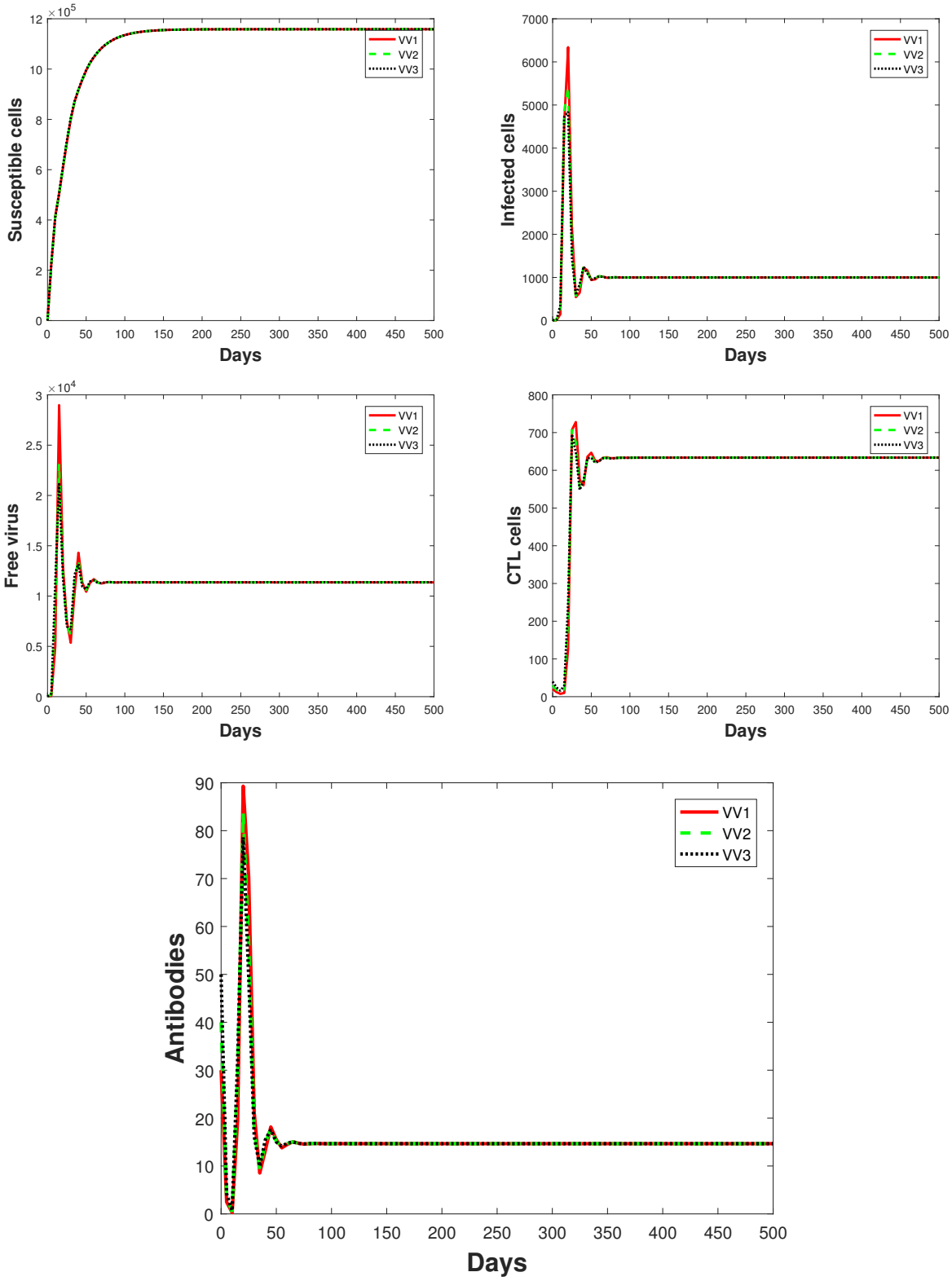

Figure 5. The behavior of the infection dynamics of system (5.1) for $\beta = 0.46$ cell virion^{-1} day^{-1}, $k = 1000$ virion cell^{-1} day^{-1}, $c = 10^{-4}$ ml cell^{-1} day^{-1}, $r = 4.4 \times 10^{-5}$ ml virion^{-1} day^{-1}, $m_1 = 1$ day, $m_2 = 1$ day. For the parameters used in this case, the threshold values $R_3 = 6.8513 > 1$, and $R_4 = 11.9403 > 1$, then the infection equilibrium E_4 with both CTL and antibody immune response is globally asymptotically stable.

6. Conclusion

In this research, we propose an virus model, which describes the dynamics among susceptible target cells, infected target cells, virus, antibodies and CTL cells. The virus infection model with two distributed delays, general target-cell dynamics, nonlinear infection rate and adaptive immunity. And our model contains many models of the literatures as special cases.

It proves that system (1.3) has five possible equilibria: infection-free equilibrium E_0, immune-free equilibrium E_1, infection equilibrium E_2 with only CTL immune response, infection equilibrium E_3 with only antibody immune response, infection equilibrium E_4 with CTL and antibody immune responses. Meanwhile, we have derived five critical threshold parameters: the reproductive numbers for viral infection R_0, for CTL immune response R_1, for antibody immune response R_2, for CTL immune competition R_3 and for antibody immune competition R_4. From insection 5, we know that the stabilities of the five equilibria depend on the according threshold parameters. More concretely, (i) when $R_0 \leq 1$, then infection-free equilibrium E_0 is globally asymptotically stable. (ii) The immune-free equilibrium E_1 is globally asymptotically stable if $R_0 > 1, R_1 \leq 1$ and $R_2 \leq 1$. (iii) when $R_1 > 1$ and $R_3 \leq 1$, then infection equilibrium E_2 with only CTL immune response is is globally asymptotically stable. (iv) The infection equilibrium E_3 with only antibody immune response is globally asymptotically stable if $R_2 > 1$ and $R_4 \leq 1$. (v) when $R_3 \leq 1$ and $R_4 \leq 1$, then infection equilibrium E_4 with both CTL and antibody immune response is globally asymptotically stable.

Furthermore, it is more reasonable to introduce antibody and CTL response distributed delays to the model. In this way, the model studied will have four distributed delays and it is more difficult to investigate the dynamics of the model such as asymptotic behaviors of the equilibria. Due to the introduction of immune delay, the model may cause periodic oscillations via Hopf bifurations. Some work can be referred to the literatures Xu and Liao (2013), Xu and Li (2013).We leave it for the further work.

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