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Stability analysis of general viral infection models with humoral immunity

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Abstract

We present two nonlinear viral infection models with humoral immune response and investigate their global stability. The first model describes the interaction of the virus, uninfected cells, infected cells and B cells. This model is an improvement of some existing models by incorporating more general nonlinear functions for: (i) the intrinsic growth rate of uninfected cells; (ii) the incidence rate of infection; (iii) the removal rate of infected cells; (iv) the production, death and neutralize rates of viruses; (v) the activation and removal rate of B cells. In the second model, we introduce an additional population representing the latently infected cells. The latent-to-active conversion rate is also given by a more general nonlinear function. For each model, we derive two threshold parameters and establish a set of conditions on the general functions which are sufficient to determine the global dynamics of the models. By using suitable Lyapunov functions and LaSalle's invariance principle, we prove the global asymptotic stability of all equilibria of the models.

Keywords: Viral infection, global stability, humoral immune response, Lyapunov function.
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1. Introduction

There have been serious attempts from mathematicians and biologists to formulate mathematical models that characterize the interaction between the target cells and viruses with the aim of helping to guide treatment strategies [29]. Mathematical analysis for these models is necessary to obtain an integrated view for the virus dynamics in vivo. Studying the qualitative analysis such as global stability of equilibria for

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these models, will give us a detailed information and enhance our understanding about the virus dynamics. In the literature, several researchers have studied the global stability of mathematical models which describe the dynamics of viruses that infect the human body, such as human immunodeficiency virus (HIV) [31]. [1], [5], [9], [11], [25], [36], [39], [41], hepatitis B virus (HBV) [4], [14], [24], [27], [33], [40], hepatitis C virus (HCV) [38] and human T cell leukemia virus (HTLV) [23].

In reality, the humoral immune response is universal and necessary to eliminate or control the disease after viral infection [2]. Therefore, several mathematical models have been proposed to describe the virus dynamics with humoral immunity [7, 8, 10, 28, 30, 34, 35, 37]. The basic virus dynamics model with humoral immune response has four state variables: x, the population of uninfected target cells; y, the population of productive infected cells; v, the population of free virus particles in the blood; and z, the population of B cells. The model equations are as follow [28]:

$$\dot{x} = s - dx - \beta xv, \tag{1.1}$$

$$\dot{y} = \beta xv - ay, \tag{1.2}$$

$$\dot{v} = ky - cv - qzv, \tag{1.3}$$

$$\dot{z} = rzv - \mu z, \tag{1.4}$$

where s, k and r represent the rate at which new healthy cells are generated from the source within the body, the production rate constant of free viruses from infected cells and the proliferation rate constant of B cells, respectively. Parameters d, a, c and μ are the natural death rate constants of the uninfected target cells, infected cells, free virus particles and B cells, respectively. The parameter β is the infection rate constant and q is the neutralization rate constant of the viruses. All the parameters given in model (1.1)–(1.4) are positive.

In model (1.1)–(1.4), it is assumed that the incidence rate of infection is given by bilinear one which is based on the law of mass action. In reality, bilinear incidence rate is not accurate enough to describe the virus dynamics during the full course of infection (see e.g. [3, 6, 13, 17, 19, 22, 26]). Recently, several works have been done to generalize model (1.1)–(1.4) by choosing general incidence rate in the forms $\psi(x, v)v$ [35] and $\psi(x, v)$ [7]. However, the infection rate does not depend on the infected cells y. In some viral infections such as HBV, the infection rate depends on x, y and v (see e.g. [4, 14, 27]). In [27], the bilinear form has been modified by considering an incidence function of the form $\frac{\beta xv}{x+y}$. In [16], the infection rate is given by $\psi(x, y, v)v$. A more general infection rate in the form $\psi(x, y, v)$ has been considered in [32]. However, in [4, 14, 16, 27, 32], the humoral immune response has been neglected.

The death rates of the four compartments and the production rate of viruses presented in model (1.1)–(1.4) are given by linear functions; moreover, the activation rate of the B cells and the neutralization rate of viruses are given by specific forms. However, all of these rates may be different in different situations and different infections.

In this paper we aim to propose and analyze two general nonlinear viral infection models with humoral immune response which contain most of the above mentioned models as special cases. In the second model, we include the latently infected cells into the model, which is due to the delay between the moment when the virus contacts an uninfected cell and the moment when the infected cell becomes active to produce infectious viruses. For both models we derive two threshold parameters, the basic infection reproduction number and the humoral immune response activation number. We established a set of conditions which are sufficient for the global stability of all equilibria of the models.

The rest of the paper is organized as follows. We propose the models to be studied in Sections 2 and 3. For each model, we study some properties of its solutions, derive two threshold parameters, and investigate the existence and stability of the equilibria. The conclusion of our paper is given in Section 4.

2. Nonlinear humoral immunity viral infection model

In this section, we propose a viral infection model with humoral immune response. The model can be seen as a generalization of several viral infection models by considering general function for: (i) the intrinsic growth rate of uninfected cells; (ii) the incidence rate of infection; (iii) the death rate of infected cells; (iv) the production, death and neutralization rates of viruses; (v) the activation and removal rates of B cells.

$$\dot{x} = n(x) - \psi(x, y, v), \tag{2.1}$$
$$\dot{y} = \psi(x, y, v) - a\varphi_1(y), \tag{2.2}$$
$$\dot{v} = k\varphi_1(y) - c\varphi_2(v) - q\varphi_3(z)\varphi_2(v), \tag{2.3}$$
$$\dot{z} = r\varphi_3(z)\varphi_2(v) - \mu\varphi_3(z), \tag{2.4}$$

where $n(x)$ represents the intrinsic growth rate of uninfected cells accounting for both production and natural mortality; $\psi(x, y, v)$ denotes the incidence rate of infection; $a\varphi_1(y)$ refers to the removal rate of infected cells; $k\varphi_1(y)$ and $c\varphi_2(v)$ denote the production and death rates of free virus particles; $q\varphi_3(z)\varphi_2(v)$ represents the neutralization rate of viruses; $r\varphi_3(z)\varphi_2(v)$ and $\mu\varphi_3(z)$ refer to the activation and removal rates of B cells, respectively. Functions n, ψ, φ_i, $i = 1, 2, 3$ are continuously differentiable and satisfy:

Assumption A1.
(i) there exists x_0 such that $n(x_0) = 0$, $n(x) > 0$ for $x \in [0, x_0)$,
(ii) $n'(x) < 0$ for all $x > 0$,
(iii) there are s, $\bar{s} > 0$ such that $n(x) \le s - \bar{s}x$ for $x \ge 0$.

Assumption A2.
(i) $\psi(x, y, v) > 0$ and $\psi(0, y, v) = \psi(x, y, 0) = 0$ for all $x > 0$, $y \ge 0$, $v > 0$,
(ii) $\dfrac{\partial\psi(x,y,v)}{\partial x} > 0$, $\dfrac{\partial\psi(x,y,v)}{\partial y} < 0$, $\dfrac{\partial\psi(x,y,v)}{\partial v} > 0$ and $\dfrac{\partial\psi(x,0,0)}{\partial v} > 0$ for all $x > 0$, $y \ge 0$, $v > 0$,
(iii) $\dfrac{d}{dx}\left(\dfrac{\partial\psi(x,0,0)}{\partial v}\right) > 0$ for all $x > 0$.

Assumption A3.
(i) $\varphi_j(u) > 0$ for all $u > 0$, $\varphi_j(0) = 0$, $j = 1, 2, 3$,
(ii) $\varphi_j'(u) > 0$, for all $u > 0$, $j = 1, 3$, $\varphi_2'(u) > 0$, for all $u \ge 0$,
(iii) there are $\alpha_j \ge 0$, $j = 1, 2, 3$ such that $\varphi_j(u) \ge \alpha_j u$, for all $u \ge 0$.

Assumption A4.
$\dfrac{\psi(x,y,v)}{\varphi_2(v)}$ is decreasing with respect to v for all $v > 0$.

2.1. Properties of solutions

In this subsection, we study some properties of the solution of the model such as non-negativity and boundedness of solutions.

Proposition 2.1. *Assume that Assumptions* A1–A3 *are satisfied. Then there exist positive numbers* L_i, $i = 1, 2, 3$, *such that the compact set*

$$\Gamma_1 = \left\{(x, y, v, z) \in \mathbb{R}^4_{\ge 0} : 0 \le x, y \le L_1, 0 \le v \le L_2, 0 \le z \le L_3\right\}$$

is positively invariant.

Proof. We have

$$\begin{aligned}
&\dot{x}\mid_{x=0} = n(0) > 0, \\
&\dot{y}\mid_{y=0} = \psi(x, 0, v) \ge 0 \qquad \text{for all } x \ge 0, v \ge 0, \\
&\dot{v}\mid_{v=0} = k\varphi_1(y) \ge 0 \qquad \text{for all } y \ge 0, \\
&\dot{z}\mid_{z=0} = 0.
\end{aligned}$$

Hence, the orthant $\mathbb{R}^4_{\ge 0}$ is positively invariant for system (2.1)–(2.4) [12]. Next, we show that the solutions of the system are bounded. Let $T_1(t) = x(t) + y(t) + \frac{a}{2k}v(t) + \frac{aq}{2rk}z(t)$; then

$$\dot{T}_1(t) = n(x) - \frac{a}{2}\varphi_1(y) - \frac{ac}{2k}\varphi_2(v) - \frac{aq\mu}{2rk}\varphi_3(z) \le s - \bar{s}x - \frac{a}{2}\alpha_1 y - \frac{ac}{2k}\alpha_2 v - \frac{aq\mu}{2rk}\alpha_3 z$$

$$\leq s - \sigma_1 \left(x + y + \frac{a}{2k} v + \frac{aq}{2rk} z \right) = s - \sigma_1 T_1(t),$$

where $\sigma_1 = \min\{\bar{s}, \frac{a}{2}\alpha_1, c\alpha_2, \mu\alpha_3\}$. Then,

$$T_1(t) \leq T_1(0)e^{-\sigma_1 t} + \frac{s}{\sigma_1}\left(1 - e^{-\sigma_1 t}\right) = e^{-\sigma_1 t}\left(T_1(0) - \frac{s}{\sigma_1}\right) + \frac{s}{\sigma_1}.$$

Hence, $0 \leq T_1(t) \leq L_1$ if $T_1(0) \leq L_1$ for $t \geq 0$ where $L_1 = \frac{s}{\sigma_1}$. It follows that $0 \leq x(t), y(t) \leq L_1$, $0 \leq v(t) \leq L_2$ and $0 \leq z(t) \leq L_3$ for all $t \geq 0$ if $x(0) + y(0) + \frac{a}{2k}v(0) + \frac{aq}{2rk}z(0) \leq L_1$, where $L_2 = \dfrac{2kL_1}{a}$ and $L_3 = \dfrac{2rkL_1}{aq}$. Therefore, $x(t)$, $y(t)$, $v(t)$, and $z(t)$ are all bounded. □

2.2. The equilibria and threshold parameters

Lemma 2.2. *Assume that Assumptions* A1–A4 *are satisfied. Then there exist two threshold parameters $R_0 > 0$ and $R_1 > 0$ with $R_1 < R_0$ such that*

(i) if $R_0 \leq 1$, then there exists only one positive equilibrium $E_0 \in \Gamma_1$,

(ii) if $R_1 \leq 1 < R_0$, then there exist only two positive equilibria $E_0 \in \Gamma_1$ and $E_1 \in \Gamma_1$, and

(iii) if $R_1 > 1$, then there exist three positive equilibria $E_0 \in \Gamma_1$, $E_1 \in \Gamma_1$ and $E_2 \in \mathring{\Gamma}_1$, where $\mathring{\Gamma}_1$ is the interior of Γ_1.

Proof. At any equilibrium we have

$$n(x) - \psi(x, y, v) = 0, \tag{2.5}$$
$$\psi(x, y, v) - a\varphi_1(y) = 0, \tag{2.6}$$
$$k\varphi_1(y) - c\varphi_2(v) - q\varphi_2(v)\varphi_3(z) = 0, \tag{2.7}$$
$$(r\varphi_2(v) - \mu)\varphi_3(z) = 0. \tag{2.8}$$

From (2.8), either $\varphi_3(z) = 0$ or $\varphi_3(z) \neq 0$. If $\varphi_3(z) = 0$, then from Assumption A3 we get, $z = 0$ and from (2.5)–(2.7) we have

$$n(x) = \psi(x, y, v) = a\varphi_1(y) = \frac{ac\varphi_2(v)}{k}. \tag{2.9}$$

From (2.9), we have $\varphi_1(y) = \frac{n(x)}{a}$, $\varphi_2(v) = \frac{kn(x)}{ac}$. Since φ_1, φ_2 are continuous and strictly increasing functions with $\varphi_1(0) = \varphi_2(0) = 0$, then φ_1^{-1}, φ_2^{-1} exist and they are also continuous and strictly increasing [21]. Let $\varkappa_1(x) = \varphi_1^{-1}\left(\frac{n(x)}{a}\right)$ and $\varkappa_2(x) = \varphi_2^{-1}\left(\frac{kn(x)}{ac}\right)$; then

$$y = \varkappa_1(x), \ v = \varkappa_2(x). \tag{2.10}$$

Obviously from Assumption A1, $\varkappa_1(x), \varkappa_2(x) > 0$ for $x \in [0, x_0)$ and $\varkappa_1(x_0) = \varkappa_2(x_0) = 0$. Substituting y and v from (2.10) into (2.9), we get

$$\psi\left(x, \varkappa_1(x), \varkappa_2(x)\right) - \frac{ac}{k}\varphi_2(\varkappa_2(x)) = 0. \tag{2.11}$$

We note that, $x = x_0$ is a solution of (2.11). Then, from (2.10) we have $y = v = 0$, and this case leads to the infection-free equilibrium $E_0 = (x_0, 0, 0, 0)$. Let

$$\Phi_1(x) = \psi\left(x, \varkappa_1(x), \varkappa_2(x)\right) - \frac{ac}{k}\varphi_2(\varkappa_2(x)) = 0.$$

Then from Assumptions A1–A3, we have

$$\Phi_1(0) = -\frac{ac}{k}\varphi_2(\varkappa_2(0)) < 0,$$

$$\Phi_1(x_0) = \psi(x_0, 0, 0) - \frac{ac}{k}\varphi_2(0) = 0.$$

Moreover,

$$\Phi_1'(x_0) = \frac{\partial\psi(x_0,0,0)}{\partial x} + \varkappa_1'(x_0)\frac{\partial\psi(x_0,0,0)}{\partial y} + \varkappa_2'(x_0)\frac{\partial\psi(x_0,0,0)}{\partial v} - \frac{ac}{k}\varphi_2'(0)\varkappa_2'(x_0).$$

Assumption A2 implies that $\frac{\partial\psi(x_0,0,0)}{\partial x} = \frac{\partial\psi(x_0,0,0)}{\partial y} = 0$. Also, from Assumption A3, we have $\varphi_2'(0) > 0$, and then

$$\Phi_1'(x_0) = \frac{ac}{k}\varkappa_2'(x_0)\varphi_2'(0)\left(\frac{k}{ac\varphi_2'(0)}\frac{\partial\psi(x_0,0,0)}{\partial v} - 1\right).$$

From (2.10), we get

$$\Phi_1'(x_0) = n'(x_0)\left(\frac{k}{ac\varphi_2'(0)}\frac{\partial\psi(x_0,0,0)}{\partial v} - 1\right).$$

From Assumption A1, we have $n'(x_0) < 0$. Therefore, if $\frac{k}{ac\varphi_2'(0)}\frac{\partial\psi(x_0,0,0)}{\partial v} > 1$. Then $\Phi_1'(x_0) < 0$ and there exists an $x_1 \in (0, x_0)$ such that $\Phi_1(x_1) = 0$. From (2.10), we have $y_1 = \varkappa_1(x_1) > 0$ and $v_1 = \varkappa_2(x_1) > 0$. It follows that a chronic-infection equilibrium without humoral immune response $E_1 = (x_1, y_1, v_1, 0)$ exists when $\frac{k}{ac\varphi_2'(0)}\frac{\partial\psi(x_0,0,0)}{\partial v} > 1$. Let us define

$$R_0 = \frac{k}{ac\varphi_2'(0)}\frac{\partial\psi(x_0,0,0)}{\partial v},$$

which represents the basic infection reproduction number and determines whether a chronic-infection can be established. The other possibility of (2.8) is $v = v_2 = \varphi_2^{-1}\left(\frac{\mu}{r}\right) > 0$. From (2.10) and by letting $v = v_2$ in (2.5), we get

$$\Phi_2(x) = n(x) - \psi(x, \varkappa_1(x), v_2) = 0.$$

Clearly,

$$\Phi_2(0) = n(0) > 0 \text{ and } \Phi_2(x_0) = -\psi(x_0, 0, v_2) < 0.$$

According to Assumptions A1 and A2, $\Phi_2(x)$ is a strictly decreasing function of x. Thus, there exists a unique $x_2 \in (0, x_0)$ such that $\Phi_2(x_2) = 0$. It follows that $y_2 = \varkappa_1(x_2) > 0$ and $z_2 = \varphi_3^{-1}\left(\frac{c}{q}\left(\frac{k\psi(x_2,y_2,v_2)}{ac\varphi_2(v_2)} - 1\right)\right)$. From Assumption A3, we have: if $\frac{k\psi(x_2,y_2,v_2)}{ac\varphi_2(v_2)} > 1$, then $z_2 > 0$. Now we define

$$R_1 = \frac{k\psi(x_2,y_2,v_2)}{ac\varphi_2(v_2)},$$

which represents the humoral immune response activation number and determines whether a persistent humoral immune response can be established. Hence, z_2 can be rewritten as $z_2 = \varphi_3^{-1}\left(\frac{c}{q}(R_1 - 1)\right)$. It follows that there exists a chronic-infection equilibrium with humoral immune response $E_2 = (x_2, y_2, v_2, z_2)$ if $R_1 > 1$.

Now, we show that $E_0, E_1 \in \Gamma_1$ and $E_2 \in \overset{\circ}{\Gamma}_1$. Clearly, $E_0 \in \Gamma_1$. We have $x_1 < x_0$; then from Assumption A1

$$0 = n(x_0) < n(x_1) \leq s - \bar{s}x_1.$$

It follows that

$$0 < x_1 < \frac{s}{\bar{s}} \leq \frac{s}{\sigma_1} = L_1.$$

From (2.5)–(2.6), we get

$$a\alpha_1 y_1 \leq a\varphi_1(y_1) = n(x_1) < n(0) \leq s \Rightarrow 0 < y_1 < \frac{s}{a\alpha_1} < \frac{s}{\frac{a}{2}\alpha_1} \leq L_1.$$

Eq. (2.9) implies that,

$$c\alpha_2 v_1 \leq c\varphi_2(v_1) = k\varphi_1(y_1) = \frac{k}{a}n(x_1) < \frac{k}{a}n(0) \leq \frac{ks}{a} \Rightarrow 0 < v_1 < \frac{ks}{ac\alpha_2} < \frac{2ks}{ac\alpha_2} \leq L_2.$$

Moreover, we have $z_1 = 0$, so $E_1 \in \Gamma_1$. Let $R_1 > 1$; then one can show that $0 < x_2 < L_1$, $0 < y_2 < L_1$. Now we show that $0 < v_2 < L_2$ and $0 < z_2 < L_3$. From (2.7), we have

$$c\varphi_2(v_2) + q\varphi_2(v_2)\varphi_3(z_2) = k\varphi_1(y_2).$$

Then

$$c\varphi_2(v_2) < k\varphi_1(y_2) \Rightarrow c\alpha_2 v_2 < \frac{k}{a}n(x_2) < \frac{ks}{a} \Rightarrow 0 < v_2 < \frac{ks}{ac\alpha_2} < \frac{2ks}{ac\alpha_2} \leq L_2,$$

and

$$q\varphi_2(v_2)\varphi_3(z_2) < k\varphi_1(y_2) \Rightarrow \frac{q\mu}{r}\alpha_3 z_2 < \frac{k}{a}n(x_2) < \frac{ks}{a} \Rightarrow 0 < z_2 < \frac{krs}{aq\mu\alpha_3} < \frac{2krs}{aq\mu\alpha_3} \leq L_3.$$

Then, $E_2 \in \mathring{\Gamma}_1$. Clearly from Assumptions A2 and A4, we obtain

$$\begin{aligned} R_1 &= \frac{k\psi(x_2, y_2, v_2)}{ac\varphi_2(v_2)} < \frac{k\psi(x_2, 0, v_2)}{ac\varphi_2(v_2)} \leq \frac{k}{ac}\lim_{v\to 0^+}\frac{\psi(x_2, 0, v)}{\varphi_2(v)} \\ &= \frac{k}{ac\varphi_2'(0)}\frac{\partial\psi(x_2, 0, 0)}{\partial v} < \frac{k}{ac\varphi_2'(0)}\frac{\partial\psi(x_0, 0, 0)}{\partial v} = R_0. \end{aligned}$$

□

2.3. Global stability analysis

In this subsection, the global asymptotic stability of the three equilibria of model (2.1)–(2.4) will be established by using direct Lyapunov method and applying LaSalle's invariance principle.

Theorem 2.3. *Let Assumptions* A1–A4 *be true and* $R_0 \leq 1$. *Then the infection-free equilibrium* E_0 *is globally asymptotically stable (GAS) in* Γ_1.

Proof. We construct a Lyapunov functional by

$$U_0(x, y, v, z) = x - x_0 - \int_{x_0}^{x}\lim_{v\to 0^+}\frac{\psi(x_0, 0, v)}{\psi(\eta, 0, v)}d\eta + y + \frac{a}{k}v + \frac{aq}{rk}z. \tag{2.12}$$

It is obvious that $U_0(x, y, v, z) > 0$ for all $x, y, v, z > 0$ while $U_0(x, y, v, z)$ reaches its global minimum at E_0. We calculate $\frac{dU_0}{dt}$ along the solutions of model (2.1)–(2.4) as:

$$\begin{aligned} \frac{dU_0}{dt} &= \left(1 - \lim_{v\to 0^+}\frac{\psi(x_0, 0, v)}{\psi(x, 0, v)}\right)(n(x) - \psi(x, y, v)) + \psi(x, y, v) - a\varphi_1(y) \\ &\quad + \frac{a}{k}\left(k\varphi_1(y) - c\varphi_2(v) - q\varphi_2(v)\varphi_3(z)\right) + \frac{aq}{rk}(r\varphi_3(z)\varphi_2(v) - \mu\varphi_3(z)) \\ &= n(x)\left(1 - \lim_{v\to 0^+}\frac{\psi(x_0, 0, v)}{\psi(x, 0, v)}\right) + \psi(x, y, v)\lim_{v\to 0^+}\frac{\psi(x_0, 0, v)}{\psi(x, 0, v)} - \frac{ac}{k}\varphi_2(v) - \frac{aq\mu}{rk}\varphi_3(z). \end{aligned} \tag{2.13}$$

Since $n(x_0) = 0$, we get

$$\begin{aligned}\frac{dU_0}{dt} &= (n(x) - n(x_0))\left(1 - \lim_{v\to 0^+}\frac{\psi(x_0,0,v)}{\psi(x,0,v)}\right)\\ &\quad + \frac{ac}{k}\left(\frac{k}{ac}\frac{\psi(x,y,v)}{\varphi_2(v)}\lim_{v\to 0^+}\frac{\psi(x_0,0,v)}{\psi(x,0,v)} - 1\right)\varphi_2(v) - \frac{aq\mu}{rk}\varphi_3(z).\end{aligned} \tag{2.14}$$

From Assumptions A2 and A4, we have

$$\frac{\psi(x,y,v)}{\varphi_2(v)} < \frac{\psi(x,0,v)}{\varphi_2(v)} \le \lim_{v\to 0^+}\frac{\psi(x,0,v)}{\varphi_2(v)} = \frac{1}{\varphi_2'(0)}\frac{\partial\psi(x,0,0)}{\partial v}.$$

Then,

$$\begin{aligned}\frac{dU_0}{dt} &\le (n(x) - n(x_0))\left(1 - \frac{(\partial\psi(x_0,0,0)/\partial v)}{(\partial\psi(x,0,0)/\partial v)}\right) + \frac{ac}{k}\left(\frac{k}{ac\varphi_2'(0)}\frac{\partial\psi(x_0,0,0)}{\partial v} - 1\right)\varphi_2(v) - \frac{aq\mu}{rk}\varphi_3(z)\\ &= (n(x) - n(x_0))\left(1 - \frac{(\partial\psi(x_0,0,0)/\partial v)}{(\partial\psi(x,0,0)/\partial v)}\right) + \frac{ac}{k}(R_0 - 1)\varphi_2(v) - \frac{aq\mu}{rk}\varphi_3(z).\end{aligned} \tag{2.15}$$

From Assumptions A1 and A2, we have

$$(n(x) - n(x_0))\left(1 - \frac{(\partial\psi(x_0,0,0)/\partial v)}{(\partial\psi(x,0,0)/\partial v)}\right) \le 0.$$

Therefore, if $R_0 \le 1$, then $\frac{dU_0}{dt} \le 0$ for all $x, v, z > 0$. We note that the solutions of system (2.1)–(2.4) are limited by Υ, the largest invariant subset of $\left\{\frac{dU_0}{dt} = 0\right\}$[15]. We see that $\frac{dU_0}{dt} = 0$ if and only if $x(t) = x_0$, $v(t) = 0$, and $z(t) = 0$ for all t. Each element of Υ satisfies $v(t) = 0$ and $z(t) = 0$. Then from (2.3), we have

$$\dot{v}(t) = 0 = k\varphi_1(y(t)).$$

It follows from Assumption A3 that $y(t) = 0$ for all t. Using LaSalle's invariance principle, we derive that E_0 is GAS. □

To prove the global stability of the equilibria E_1 and E_2, we need the following condition on the incidence rate function.

Assumption A5.

$$\left(\frac{\psi(x,y,v)}{\psi(x,y_i,v_i)} - \frac{\varphi_2(v)}{\varphi_2(v_i)}\right)\left(1 - \frac{\psi(x,y_i,v_i)}{\psi(x,y,v)}\right) \le 0, \quad x,y,v > 0,\ i = 1,2.$$

Lemma 2.4. *Suppose that Assumptions* A1–A4 *are satisfied and* $R_0 > 1$*. Then* $x_1, x_2, y_1, y_2, v_1, v_2$ *exist satisfying*

$$sgn(x_2 - x_1) = sgn(v_1 - v_2) = sgn(y_1 - y_2) = sgn(R_1 - 1).$$

Proof. It follows from Assumptions A1 and A2 that

$$(n(x_2) - n(x_1))(x_1 - x_2) > 0, \tag{2.16}$$

$$(\psi(x_2,y_2,v_2) - \psi(x_1,y_2,v_2))(x_2 - x_1) > 0, \tag{2.17}$$

$$(\psi(x_1,y_2,v_2) - \psi(x_1,y_1,v_2))(y_1 - y_2) > 0, \tag{2.18}$$

$$(\psi(x_1,y_1,v_2) - \psi(x_1,y_1,v_1))(v_2 - v_1) > 0. \tag{2.19}$$

First, we claim $sgn(x_2 - x_1) = sgn(v_1 - v_2)$. Suppose this is not true, i.e., $sgn(x_2 - x_1) = sgn(v_2 - v_1)$. Using the conditions of the equilibria E_1 and E_2 we would have

$$n(x_2) - n(x_1) = \psi(x_2, y_2, v_2) - \psi(x_1, y_1, v_1) = a(\varphi_1(y_2) - \varphi_1(y_1)). \tag{2.20}$$

Since φ_1 is an increasing function of y, then from (2.20) we would have, $sgn(x_1 - x_2) = sgn(y_2 - y_1)$. Moreover

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

Therefore, from (2.17)–(2.20) we would get:

$$sgn\,(x_1 - x_2) = sgn\,(x_2 - x_1)\,,$$

which leads to a contradiction. Thus, $sgn\,(x_2 - x_1) = sgn\,(v_1 - v_2)$. Assumption A4 implies that

$$\left(\frac{\psi(x_1, y_1, v_2)}{\varphi_2(v_2)} - \frac{\psi(x_1, y_1, v_1)}{\varphi_2(v_1)}\right)(v_1 - v_2) > 0. \tag{2.21}$$

Using the equilibrium conditions for E_1, we have $\dfrac{k\psi(x_1, y_1, v_1)}{ac\varphi_2(v_1)} = 1$. Then

$$\begin{aligned} R_1 - 1 &= \frac{k\psi(x_2, y_2, v_2)}{ac\varphi_2(v_2)} - \frac{k\psi(x_1, y_1, v_1)}{ac\varphi_2(v_1)} = \frac{k}{ac}\left[\frac{\psi(x_2, y_2, v_2)}{\varphi_2(v_2)} - \frac{\psi(x_1, y_1, v_1)}{\varphi_2(v_1)}\right] \\ &= \frac{k}{ac}\left[\frac{1}{\varphi_2(v_2)}(\psi(x_2, y_2, v_2) - \psi(x_1, y_2, v_2)) + \frac{1}{\varphi_2(v_2)}(\psi(x_1, y_2, v_2) - \psi(x_1, y_1, v_2))\right. \\ &\quad \left. + \left(\frac{\psi(x_1, y_1, v_2)}{\varphi_2(v_2)} - \frac{\psi(x_1, y_1, v_1)}{\varphi_2(v_1)}\right)\right]. \end{aligned}$$

Thus, from (2.18), (2.19), (2.20), and (2.21) we get $sgn(R_1 - 1) = sgn(v_1 - v_2)$. □

Theorem 2.5. *Let Assumptions* A1–A5 *be true and* $R_1 \le 1 < R_0$. *Then the chronic-infection equilibrium without humoral immune response* E_1 *is GAS in* Γ_1.

Proof. Define

$$U_1(x, y, v, z) = x - x_1 - \int_{x_1}^{x} \frac{\psi(x_1, y_1, v_1)}{\psi(\eta, y_1, v_1)} d\eta + y - y_1 - \int_{y_1}^{y} \frac{\varphi_1(y_1)}{\varphi_1(\eta)} d\eta + \frac{a}{k}\left(v - v_1 - \int_{v_1}^{v} \frac{\varphi_2(v_1)}{\varphi_2(\eta)} d\eta\right) + \frac{aq}{rk} z. \tag{2.22}$$

It is seen that $U_1(x, y, v, z) > 0$ for all $x, y, v, z > 0$ while $U_1(x, y, v, z)$ reaches its global minimum at E_1. Calculating the time derivative of U_1 along the trajectories of system (2.1)–(2.4), we obtain

$$\begin{aligned} \frac{dU_1}{dt} &= \left(1 - \frac{\psi(x_1, y_1, v_1)}{\psi(x, y_1, v_1)}\right)(n(x) - \psi(x, y, v)) + \left(1 - \frac{\varphi_1(y_1)}{\varphi_1(y)}\right)(\psi(x, y, v) - a\varphi_1(y)) \\ &\quad + \frac{a}{k}\left(1 - \frac{\varphi_2(v_1)}{\varphi_2(v)}\right)(k\varphi_1(y) - c\varphi_2(v) - q\varphi_2(v)\varphi_3(z)) + \frac{aq}{rk}(r\varphi_2(v)\varphi_3(z) - \mu\varphi_3(z)) \\ &= \left(1 - \frac{\psi(x_1, y_1, v_1)}{\psi(x, y_1, v_1)}\right)n(x) + \psi(x_1, y_1, v_1)\frac{\psi(x, y, v)}{\psi(x, y_1, v_1)} - \frac{\varphi_1(y_1)}{\varphi_1(y)}\psi(x, y, v) \\ &\quad + a\varphi_1(y_1) - \frac{ac}{k}\varphi_2(v) - a\varphi_1(y)\frac{\varphi_2(v_1)}{\varphi_2(v)} + \frac{ac}{k}\varphi_2(v_1) + \frac{aq}{k}\varphi_2(v_1)\varphi_3(z) - \frac{aq\mu}{rk}\varphi_3(z). \end{aligned} \tag{2.23}$$

Using the equilibrium conditions for E_1

$$n(x_1) = \psi(x_1, y_1, v_1) = a\varphi_1(y_1) = \frac{ac}{k}\varphi_2(v_1),$$

we obtain

$$\frac{dU_1}{dt} = (n(x) - n(x_1))\left(1 - \frac{\psi(x_1,y_1,v_1)}{\psi(x,y_1,v_1)}\right) + 3a\varphi_1(y_1) - a\varphi_1(y_1)\frac{\psi(x_1,y_1,v_1)}{\psi(x,y_1,v_1)} + a\varphi_1(y_1)\frac{\psi(x,y,v)}{\psi(x,y_1,v_1)}$$
$$- a\varphi_1(y_1)\frac{\varphi_1(y_1)\psi(x,y,v)}{\varphi_1(y)\psi(x_1,y_1,v_1)} - a\varphi_1(y_1)\frac{\varphi_2(v)}{\varphi_2(v_1)} - a\varphi_1(y_1)\frac{\varphi_2(v_1)\varphi_1(y)}{\varphi_2(v)\varphi_1(y_1)} + \frac{aq}{k}\left(\varphi_2(v_1) - \frac{\mu}{r}\right)\varphi_3(z). \tag{2.24}$$

Collecting terms of (2.24), we get

$$\frac{dU_1}{dt} = (n(x) - n(x_1))\left(1 - \frac{\psi(x_1,y_1,v_1)}{\psi(x,y_1,v_1)}\right) + a\varphi_1(y_1)\left(\frac{\psi(x,y,v)}{\psi(x,y_1,v_1)} - \frac{\varphi_2(v)}{\varphi_2(v_1)} - 1 + \frac{\varphi_2(v)\psi(x,y_1,v_1)}{\varphi_2(v_1)\psi(x,y,v)}\right)$$
$$+ a\varphi_1(y_1)\left[4 - \frac{\psi(x_1,y_1,v_1)}{\psi(x,y_1,v_1)} - \frac{\varphi_1(y_1)\psi(x,y,v)}{\varphi_1(y)\psi(x_1,y_1,v_1)} - \frac{\varphi_2(v_1)\varphi_1(y)}{\varphi_2(v)\varphi_1(y_1)} - \frac{\varphi_2(v)\psi(x,y_1,v_1)}{\varphi_2(v_1)\psi(x,y,v)}\right]$$
$$+ \frac{aq}{k}\left(\varphi_2(v_1) - \varphi_2(v_2)\right)\varphi_3(z). \tag{2.25}$$

This can be simplified as

$$\frac{dU_1}{dt} = (n(x) - n(x_1))\left(1 - \frac{\psi(x_1,y_1,v_1)}{\psi(x,y_1,v_1)}\right) + a\varphi_1(y_1)\left(\frac{\psi(x,y,v)}{\psi(x,y_1,v_1)} - \frac{\varphi_2(v)}{\varphi_2(v_1)}\right)\left(1 - \frac{\psi(x,y_1,v_1)}{\psi(x,y,v)}\right)$$
$$+ a\varphi_1(y_1)\left[4 - \frac{\psi(x_1,y_1,v_1)}{\psi(x,y_1,v_1)} - \frac{\varphi_1(y_1)\psi(x,y,v)}{\varphi_1(y)\psi(x_1,y_1,v_1)} - \frac{\varphi_2(v_1)\varphi_1(y)}{\varphi_2(v)\varphi_1(y_1)} - \frac{\varphi_2(v)\psi(x,y_1,v_1)}{\varphi_2(v_1)\psi(x,y,v)}\right]$$
$$+ \frac{aq}{k}\left(\varphi_2(v_1) - \varphi_2(v_2)\right)\varphi_3(z). \tag{2.26}$$

From Assumptions A1–A5, we get that the first and second terms of (2.26) are less than or equal to zero. Since the geometrical mean is less than or equal to the arithmetical mean, then the third term of (2.26) is also less than or equal to zero. Lemma 2 implies that if $R_1 \leq 1$, then $\varphi_2(v_1) < \varphi_2(v_2)$. It follows that, $\frac{dU_1}{dt} \leq 0$ for all $x, y, v, z > 0$. The solutions of system (2.1)–(2.4) are limited by Ω, the largest invariant subset of $\left\{(x,y,v,z) : \frac{dU_1}{dt} = 0\right\}$[15]. We have $\frac{dU_1}{dt} = 0$ if and only if $x(t) = x_1, y(t) = y_1, v(t) = v_1$ and $z(t) = 0$. So, Ω contains a unique point, that is E_1. Thus, the global asymptotic stability of the chronic-infection equilibrium without humoral immune response E_1 follows from LaSalle's invariance principle. □

Theorem 2.6. *Let Assumptions* A1–A5 *be true and* $R_1 > 1$. *Then the chronic-infection equilibrium with humoral immune response* E_2 *is GAS in* $\overset{\circ}{\Gamma}_1$.

Proof. We construct a Lyapunov functional by

$$U_2(x,y,v,z) = x - x_2 - \int_{x_2}^{x}\frac{\psi(x_2,y_2,v_2)}{\psi(\eta,y_2,v_2)}d\eta + y - y_2 - \int_{y_2}^{y}\frac{\varphi_1(y_2)}{\varphi_1(\eta)}d\eta + \frac{a}{k}\left(v - v_2 - \int_{v_2}^{v}\frac{\varphi_2(v_2)}{\varphi_2(\eta)}d\eta\right)$$
$$+ \frac{aq}{rk}\left(z - z_2 - \int_{z_2}^{z}\frac{\varphi_3(z_2)}{\varphi_3(\eta)}d\eta\right). \tag{2.27}$$

It can be seen that $U_2(x,y,v,z) > 0$ for all $x,y,v,z > 0$ while $U_2(x,y,v,z)$ reaches its global minimum at E_2. The function U_2 satisfies

$$\frac{dU_2}{dt} = \left(1 - \frac{\psi(x_2,y_2,v_2)}{\psi(x,y_2,v_2)}\right)(n(x) - \psi(x,y,v)) + \left(1 - \frac{\varphi_1(y_2)}{\varphi_1(y)}\right)(\psi(x,y,v) - a\varphi_1(y))$$
$$+ \frac{a}{k}\left(1 - \frac{\varphi_2(v_2)}{\varphi_2(v)}\right)(k\varphi_1(y) - c\varphi_2(v) - q\varphi_2(v)\varphi_3(z))$$
$$+ \frac{aq}{rk}\left(1 - \frac{\varphi_3(z_2)}{\varphi_3(z)}\right)(r\varphi_2(v)\varphi_3(z) - \mu\varphi_3(z)). \tag{2.28}$$

Collecting the terms of (2.28) and using $n(x_2) = a\varphi_1(y_2)$, we obtain

$$\begin{aligned}\frac{dU_2}{dt} &= (n(x)-n(x_2))\left(1-\frac{\psi(x_2,y_2,v_2)}{\psi(x,y_2,v_2)}\right)+a\varphi_1(y_2)-a\varphi_1(y_2)\frac{\psi(x_2,y_2,v_2)}{\psi(x,y_2,v_2)}\\ &\quad+\psi(x,y,v)\frac{\psi(x_2,y_2,v_2)}{\psi(x,y_2,v_2)}-\frac{\varphi_1(y_2)\psi(x,y,v)}{\varphi_1(y)}+a\varphi_1(y_2)-\frac{ac}{k}\varphi_2(v)-a\varphi_1(y)\frac{\varphi_2(v_2)}{\varphi_2(v)}\\ &\quad+\frac{ac}{k}\varphi_2(v_2)+\frac{aq}{k}\varphi_2(v_2)\varphi_3(z)-\frac{aq\mu}{rk}\varphi_3(z)-\frac{aq}{k}\varphi_3(z_2)\varphi_2(v)+\frac{aq\mu}{rk}\varphi_3(z_2).\end{aligned}\tag{2.29}$$

By using the equilibrium conditions of E_2

$$\psi(x_2,y_2,v_2)=a\varphi_1(y_2)=\frac{ac}{k}\varphi_2(v_2)+\frac{aq}{k}\varphi_2(v_2)\varphi_3(z_2),\quad \mu=r\varphi_2(v_2),$$

we get

$$\begin{aligned}\frac{dU_2}{dt} &= (n(x)-n(x_2))\left(1-\frac{\psi(x_2,y_2,v_2)}{\psi(x,y_2,v_2)}\right)+a\varphi_1(y_2)-a\varphi_1(y_2)\frac{\psi(x_2,y_2,v_2)}{\psi(x,y_2,v_2)}\\ &\quad+a\varphi_1(y_2)\frac{\psi(x,y,v)}{\psi(x,y_2,v_2)}-a\varphi_1(y_2)\frac{\varphi_1(y_2)\psi(x,y,v)}{\varphi_1(y)\psi(x_2,y_2,v_2)}+a\varphi_1(y_2)\\ &\quad-\left(a\varphi_1(y_2)-\frac{aq}{k}\varphi_2(v_2)\varphi_3(z_2)\right)\frac{\varphi_2(v)}{\varphi_2(v_2)}-a\varphi_1(y_2)\frac{\varphi_2(v_2)\varphi_1(y)}{\varphi_2(v)\varphi_1(y_2)}\\ &\quad+a\varphi_1(y_2)-\frac{aq}{k}\varphi_2(v_2)\varphi_3(z_2)+\frac{aq}{k}\varphi_2(v_2)\varphi_3(z)-\frac{aq}{k}\varphi_2(v_2)\varphi_3(z)\\ &\quad-\frac{aq}{k}\varphi_3(z_2)\varphi_2(v)+\frac{aq}{k}\varphi_2(v_2)\varphi_3(z_2).\end{aligned}\tag{2.30}$$

Collecting the terms of (2.30), we get

$$\begin{aligned}\frac{dU_2}{dt} &= (n(x)-n(x_2))\left(1-\frac{\psi(x_2,y_2,v_2)}{\psi(x,y_2,v_2)}\right)+a\varphi_1(y_2)\left(\frac{\psi(x,y,v)}{\psi(x,y_2,v_2)}-\frac{\varphi_2(v)}{\varphi_2(v_2)}-1+\frac{\varphi_2(v)\psi(x,y_2,v_2)}{\varphi_2(v_2)\psi(x,y,v)}\right)\\ &\quad+a\varphi_1(y_2)\left[4-\frac{\psi(x_2,y_2,v_2)}{\psi(x,y_2,v_2)}-\frac{\varphi_1(y_2)\psi(x,y,v)}{\varphi_1(y)\psi(x_2,y_2,v_2)}-\frac{\varphi_2(v_2)\varphi_1(y)}{\varphi_2(v)\varphi_1(y_2)}-\frac{\varphi_2(v)\psi(x,y_2,v_2)}{\varphi_2(v_2)\psi(x,y,v)}\right].\end{aligned}\tag{2.31}$$

We can rewrite (2.31) as

$$\begin{aligned}\frac{dU_2}{dt} &= (n(x)-n(x_2))\left(1-\frac{\psi(x_2,y_2,v_2)}{\psi(x,y_2,v_2)}\right)+a\varphi_1(y_2)\left(\frac{\psi(x,y,v)}{\psi(x,y_2,v_2)}-\frac{\varphi_2(v)}{\varphi_2(v_2)}\right)\left(1-\frac{\psi(x,y_2,v_2)}{\psi(x,y,v)}\right)\\ &\quad+a\varphi_1(y_2)\left[4-\frac{\psi(x_2,y_2,v_2)}{\psi(x,y_2,v_2)}-\frac{\varphi_1(y_2)\psi(x,y,v)}{\varphi_1(y)\psi(x_2,y_2,v_2)}-\frac{\varphi_2(v_2)\varphi_1(y)}{\varphi_2(v)\varphi_1(y_2)}-\frac{\varphi_2(v)\psi(x,y_2,v_2)}{\varphi_2(v_2)\psi(x,y,v)}\right].\end{aligned}\tag{2.32}$$

We note that from Assumptions A1–A5 and the relationship between the arithmetical and geometrical means, we obtain $\frac{dU_2}{dt}\le 0$ for all $x,y,v,z>0$. The solutions of model (2.1)–(2.4) are limited by Λ, the largest invariant subset of $\left\{(x,y,v,z):\frac{dU_2}{dt}=0\right\}$[15]. We have $\frac{dU_2}{dt}=0$ if and only if $x(t)=x_2, y(t)=y_2$ and $v(t)=v_2$. Therefore, if $v(t)=v_2$ and $y(t)=y_2$, then from (2.3), we have $k\varphi_1(y_2)-c\varphi_2(v_2)-q\varphi_2(v_2)\varphi_3(z(t))=0$, which gives $z(t)=z_2$. Thus, $\frac{dU_2}{dt}=0$ occurs at E_2. The global asymptotic stability of the chronic-infection equilibrium with humoral immune response E_2 follows from LaSalle's invariance principle. □

3. Model with latently infected cells

As pointed out by Krakauer and Nowak [20] that, in case of HIV infection, once in a cell not each virus initiates active virion production. A large proportion of CD4+ cells are latently infected following the integration of pro-viral DNA into the host cell genome. Much of this DNA is not replication competent. Some of this material can remain quiescent for long periods of time before becoming activated [20]. Our goal in this section is to study a viral infection model taking into account both the latently and productively infected cells . Latently infected cells have been considered in the virus dynamics models in several works (see e.g. [1, 11, 18, 20]). However, the humoral immune response was neglected in those papers. Therefore, in this section we propose the following model:

$$\dot{x} = n(x) - \phi(x, w, y, v), \tag{3.1}$$
$$\dot{w} = (1 - p)\phi(x, w, y, v) - (e + \delta)\xi(w), \tag{3.2}$$
$$\dot{y} = p\phi(x, w, y, v) + \delta\xi(w) - a\varphi_1(y), \tag{3.3}$$
$$\dot{v} = k\varphi_1(y) - c\varphi_2(v) - q\varphi_2(v)\varphi_3(z), \tag{3.4}$$
$$\dot{z} = r\varphi_2(v)\varphi_3(z) - \mu\varphi_3(z), \tag{3.5}$$

where w and y represent, respectively, the populations of the latently infected and productively infected cells. Eq. (3.2) describes the population dynamics of the latently infected cells and shows that they die with rate $e\xi(w)$ and they are converted to productively infected cells with rate $\delta\xi(w)$ where e and δ are positive constants. The fractions $(1 - p)$ and p, with $0 < p < 1$, are the probabilities that upon infection, an uninfected cell will become either latently infected or productively infected. The functions n, φ_1, φ_2 and φ_3 are assumed to satisfy Assumptions A1 and A3. All other parameters and variables of model (3.1)–(3.5) have the same biological identifications as those given in Sections 1 and 2. Moreover, the functions ϕ and ξ are continuously differentiable and satisfy

Assumption B1.
(i) $\phi(x, w, y, v) > 0$ and $\phi(0, w, y, v) = \phi(x, w, y, 0) = 0$ for all $x > 0$, $w \geq 0$, $y \geq 0$, $v > 0$,
(ii) $\dfrac{\partial\phi(x, w, y, v)}{\partial x} > 0$, $\dfrac{\partial\phi(x, w, y, v)}{\partial w} < 0$, $\dfrac{\partial\phi(x, w, y, v)}{\partial y} < 0$, $\dfrac{\partial\phi(x, w, y, v)}{\partial v} > 0$ and $\dfrac{\partial\phi(x, 0, 0, 0)}{\partial v} > 0$ for all $x > 0$, $w \geq 0$, $y \geq 0$, $v > 0$ and
(iii) $\dfrac{d}{dx}\left(\dfrac{\partial\phi(x, 0, 0, 0)}{\partial v}\right) > 0$ for all $x > 0$.

Assumption B2.
(i) $\xi(w) > 0$ for $w > 0$, $\xi(0) = 0$,
(ii) $\xi'(w) > 0$ for $w > 0$ and
(iii) there is an $\alpha_4 \geq 0$ such that $\xi(w) \geq \alpha_4 w$ for $w \geq 0$.

Assumption B3.
$\dfrac{\phi(x, w, y, v)}{\varphi_2(v)}$ is decreasing with respect to v for all $v > 0$.

3.1. Properties of solutions

In this subsection, we study some properties of the solutions of the model such as the non-negativity and boundedness.

Proposition 3.1. *Assume that Assumptions* A1, A3, B1 *and* B2 *are satisfied. Then there exist positive numbers* M_i, $i = 1, 2, 3$, *such that the compact set*

$$\Gamma_2 = \left\{(x, w, y, v, z) \in \mathbb{R}^5_{\geq 0} : 0 \leq x, w, y \leq M_1, 0 \leq v \leq M_2, 0 \leq z \leq M_3\right\}$$

is positively invariant.

Proof. Similar to the proof of Proposition 1, one can show that the orthant $\mathbb{R}^5_{\geq 0}$ is positively invariant for system (3.1)–(3.5). To show boundedness of the solutions we let $T_2(t) = x(t) + w(t) + y(t) + \frac{a}{2k}v(t) + \frac{aq}{2rk}z(t)$. Then

$$\begin{aligned}
\dot{T}_2(t) &= n(x) - e\xi(w) - \frac{a}{2}\varphi_1(y) - \frac{ac}{2k}\varphi_2(v) - \frac{aq\mu}{2rk}\varphi_3(z) \\
&\leq s - \bar{s}x - e\alpha_4 w - \frac{a}{2}\alpha_1 y - \frac{ac}{2k}\alpha_2 v - \frac{aq\mu}{2rk}\alpha_3 z \\
&\leq s - \sigma_2 T_2(t),
\end{aligned}$$

where $\sigma_2 = \min\{\bar{s}, e\alpha_4, \frac{a}{2}\alpha_1, c\alpha_2, \mu\alpha_3\}$. It follows that $0 \leq x(t), w(t), y(t) \leq M_1$, $0 \leq v(t) \leq M_2$, and $0 \leq z(t) \leq M_3$ for all $t \geq 0$ if $x(0) + w(0) + y(0) + \frac{a}{2k}v(0) + \frac{aq}{2rk}z(0) \leq M_1$, where $M_1 = \frac{s}{\sigma_2}$, $M_2 = \dfrac{2kM_1}{a}$ and $M_3 = \dfrac{2rkM_1}{aq}$. Therefore, $x(t), w(t), y(t), v(t)$, and $z(t)$ are all bounded. □

3.2. The equilibria and threshold parameters

In this subsection, we calculate the equilibria of model (3.1)–(3.5) and derive two threshold parameters.

Lemma 3.2. *Assume that Assumptions* A1, A3 *and* B1–B3 *are satisfied; then there exist two threshold parameters* $R_0^L > 0$ *and* $R_1^L > 0$ *with* $R_1^L < R_0^L$ *such that*

(i) if $R_0^L \leq 1$*, then there exists only one positive equilibrium* $E_0 \in \Gamma_2$*,*

(ii) if $R_1^L \leq 1 < R_0^L$*, then there exist only two positive equilibria* $E_0 \in \Gamma_2$ *and* $E_1 \in \Gamma_2$*, and*

(iii) if $R_1^L > 1$*, then there exist three positive equilibria* $E_0 \in \Gamma_2$*,* $E_1 \in \Gamma_2$*, and* $E_2 \in \mathring{\Gamma}_2$*.*

Proof. The equilibria of (3.1)–(3.5) satisfy

$$n(x) - \phi(x, w, y, v) = 0, \tag{3.6}$$
$$(1-p)\phi(x, w, y, v) - (e+\delta)\xi(w) = 0, \tag{3.7}$$
$$p\phi(x, w, y, v) + \delta\xi(w) - a\varphi_1(y) = 0, \tag{3.8}$$
$$k\varphi_1(y) - c\varphi_2(v) - q\varphi_2(v)\varphi_3(z) = 0, \tag{3.9}$$
$$(r\varphi_2(v) - \mu)\varphi_3(z) = 0. \tag{3.10}$$

Equation (3.10) has two possible solutions, $\varphi_3(z) = 0$ or $\varphi_2(v) = \mu/r$. Let us consider the case $\varphi_3(z) = 0$. Then from Assumption A3 we get, $z = 0$. From Assumptions A3 and B2, we have that φ_1^{-1} and ξ^{-1} exist and are strictly increasing functions. Let us define

$$f(x) = \xi^{-1}\left(\frac{(1-p)n(x)}{e+\delta}\right), \; g(x) = \varphi_1^{-1}\left(\frac{(ep+\delta)n(x)}{a(e+\delta)}\right), \; \ell(x) = \varphi_2^{-1}\left(\frac{k(ep+\delta)n(x)}{ac(e+\delta)}\right).$$

Equations (3.7)–(3.9) imply that

$$w = f(x), \; y = g(x), \; v = \ell(x). \tag{3.11}$$

Obviously, f, g, and ℓ are strictly decreasing functions with $f(x), g(x), \ell(x) > 0$ for $x \in [0, x_0)$ and $f(x_0) = g(x_0) = \ell(x_0) = 0$. Substituting (3.11) into (3.9), we obtain

$$\frac{k(ep+\delta)\phi(x, f(x), g(x), \ell(x))}{a(e+\delta)} - c\varphi_2(\ell(x)) = 0. \tag{3.12}$$

Equation (3.12) admits a solution $x = x_0$ which gives $w = y = v = 0$ and leads to the infection-free equilibrium $E_0 = (x_0, 0, 0, 0, 0)$. Let

$$\Psi_1(x) = \frac{k(ep+\delta)}{a(e+\delta)}\phi\left(x, f(x), g(x), \ell(x)\right) - c\varphi_2(\ell(x)) = 0.$$

It is clear from Assumptions A1, A3 and B1–B2 that,

$$\Psi_1(0) = -c\varphi_2(\ell(0)) < 0,$$
$$\Psi_1(x_0) = \frac{k(ep+\delta)}{a(e+\delta)}\phi\left(x_0, 0, 0, 0\right) - c\varphi_2(0) = 0.$$

Moreover,

$$\Psi_1'(x_0) = \frac{k(ep+\delta)}{a(e+\delta)}\left[\frac{\partial\phi(x_0,0,0,0)}{\partial x} + f'(x_0)\frac{\partial\phi(x_0,0,0,0)}{\partial w} + g'(x_0)\frac{\partial\phi(x_0,0,0,0)}{\partial y}\right.$$
$$\left. + \ell'(x_0)\frac{\partial\phi(x_0,0,0,0)}{\partial v}\right] - c\varphi_2'(0)\ell'(x_0).$$

We note that $\frac{\partial\phi(x_0,0,0,0)}{\partial x} = \frac{\partial\phi(x_0,0,0,0)}{\partial w} = \frac{\partial\phi(x_0,0,0,0)}{\partial y} = 0$. Then,

$$\Psi_1'(x_0) = c\ell'(x_0)\varphi_2'(0)\left(\frac{k(ep+\delta)}{ac(e+\delta)\varphi_2'(0)}\frac{\partial\phi(x_0,0,0,0)}{\partial v}-1\right)$$
$$= \frac{k(ep+\delta)n'(x_0)}{a(e+\delta)}\left(\frac{k(ep+\delta)}{ac(e+\delta)\varphi_2'(0)}\frac{\partial\phi(x_0,0,0,0)}{\partial v}-1\right).$$

Therefore, from Assumption A1, we have $n'(x_0)<0$ and if

$$\frac{k(ep+\delta)}{ac(e+\delta)\varphi_2'(0)}\frac{\partial\phi(x_0,0,0,0)}{\partial v}>1,$$

then $\Psi_1'(x_0)<0$ and there exists an $x_1\in(0,x_0)$ such that $\Psi_1(x_1)=0$. It follows from (3.11) that $w_1=f(x_1)>0$, $y_1=g(x_1)>0$, and $v_1=\ell(x_1)>0$. It means that a chronic-infection equilibrium without humoral immune response $E_1=(x_1,w_1,y_1,v_1,0)$ exists when $\frac{k(ep+\delta)}{ac(e+\delta)\varphi_2'(0)}\frac{\partial\phi(x_0,0,0,0)}{\partial v}>1$. Let us define R_0^L by

$$R_0^L=\frac{k(ep+\delta)}{ac(e+\delta)\varphi_2'(0)}\frac{\partial\phi(x_0,0,0,0)}{\partial v}.$$

which represents the basic infection reproduction number and determines whether a chronic-infection can be established. The other possibility of (3.10) is $v=v_2=\varphi_2^{-1}\left(\frac{\mu}{r}\right)>0$. Insert the value of v_2 in (3.6) and define

$$\Psi_2(x)=n(x)-\phi(x,f(x),g(x),v_2)=0.$$

Clearly, Ψ_2 is a strictly decreasing function of x, $\Psi_2(0)=n(0)>0$ and $\Psi_2(x_0)=-\phi(x_0,0,0,v_2)<0$. Thus, there exists a unique $x_2\in(0,x_0)$ such that $\Psi_2(x_2)=0$. It follows that

$$w_2=f(x_2)>0,\ y_2=g(x_2)>0,\quad z_2=\varphi_3^{-1}\left(\frac{c}{q}\left(\frac{k(ep+\delta)\phi(x_2,w_2,y_2,v_2)}{ac(e+\delta)\varphi_2(v_2)}-1\right)\right).$$

Clearly, $z_2>0$ when $\frac{k(ep+\delta)\phi(x_2,w_2,y_2,v_2)}{ac(e+\delta)\varphi_2(v_2)}>1$. Now we define R_1^L by

$$R_1^L=\frac{k(ep+\delta)\phi(x_2,w_2,y_2,v_2)}{ac(e+\delta)\varphi_2(v_2)},$$

which represents the humoral immune response activation number and determines whether a persistent humoral immune response can be established. Hence, z_2 can be rewritten as $z_2=\varphi_3^{-1}\left(\frac{c}{q}(R_1^L-1)\right)$. It follows that there exists a chronic-infection equilibrium with humoral immune response $E_2=(x_2,w_2,y_2,v_2,z_2)$ when $R_1^L>1$.

Now we show that $E_0,E_1\in\Gamma_2$ and $E_2\in\mathring{\Gamma}_2$. Clearly, $E_0\in\Gamma_2$. Since $x_1<x_0$, Assumption A1 implies that

$$0=n(x_0)<n(x_1)\le s-\bar{s}x_1.$$

It follows that

$$0<x_1<\frac{s}{\bar{s}}\le\frac{s}{\sigma_2}=M_1.$$

From (3.6)–(3.8), we get

$$\alpha_4 w_1\le\xi(w_1)=\frac{(1-p)n(x_1)}{e+\delta}<\frac{(1-p)n(0)}{(e+\delta)}\le\frac{(1-p)s}{(e+\delta)}.$$

Since $0<p<1$, we have

$$0<w_1<\frac{s}{e\alpha_4}\le M_1.$$

Also,

$$a\alpha_1 y_1 \leq a\varphi_1(y_1) = \frac{(ep+\delta)n(x_1)}{(e+\delta)} < \frac{(ep+\delta)n(0)}{(e+\delta)} \leq \frac{(ep+\delta)s}{(e+\delta)}.$$

Since $0 < p < 1$, we have

$$0 < y_1 < \frac{s}{a\alpha_1} < \frac{s}{\frac{a}{2}\alpha_1} \leq M_1.$$

Equation (3.11) implies that

$$c\alpha_2 v_1 \leq c\varphi_2(v_1) = \frac{k(ep+\delta)n(x_1)}{a(e+\delta)} < \frac{k(ep+\delta)n(0)}{a(e+\delta)} \leq \frac{ks(ep+\delta)}{a(e+\delta)} \leq \frac{ks}{a} \Rightarrow 0 < v_1 < \frac{ks}{ac\alpha_2} < \frac{2ks}{ac\alpha_2} \leq M_2.$$

We have also $z_1 = 0$. Then $E_1 \in \Gamma_2$. Similarly, one can show that $0 < x_2 < M_1$, $0 < w_2 < M_1$, $0 < y_2 < M_1$. Now we show that $0 < v_2 < M_2$ and $0 < z_2 \leq M_3$. From (3.9), if $R_1^L > 1$, then we have

$$c\varphi_2(v_2) + q\varphi_2(v_2)\varphi_3(z_2) = k\varphi_1(y_2).$$

Then

$$c\varphi_2(v_2) \leq k\varphi_1(y_2) \Rightarrow c\alpha_2 v_2 \leq \frac{k}{a}n(x_2) < \frac{ks}{a} \Rightarrow 0 < v_2 < \frac{ks}{ac\alpha_2} < \frac{2ks}{ac\alpha_2} \leq M_2,$$

and

$$q\varphi_2(v_2)\varphi_3(z_2) \leq k\varphi_1(y_2) \Rightarrow \frac{q\mu}{r}\alpha_3 z_2 \leq \frac{k}{a}n(x_2) < \frac{ks}{a} \Rightarrow 0 < z_2 < \frac{krs}{aq\mu\alpha_3} < \frac{2krs}{aq\mu\alpha_3} \leq M_3.$$

Then, $E_2 \in \mathring{\Gamma}_2$. Clearly, from Assumptions B1 and B3, we have

$$\begin{aligned} R_1^L &= \frac{k(ep+\delta)\phi(x_2,w_2,y_2,v_2)}{ac(e+\delta)\varphi_2(v_2)} < \frac{k(ep+\delta)\phi(x_2,0,0,v_2)}{ac(e+\delta)\varphi_2(v_2)} \leq \frac{k(ep+\delta)}{ac(e+\delta)} \lim_{v\to 0^+} \frac{\phi(x_2,0,0,v)}{\varphi_2(v)} \\ &= \frac{k(ep+\delta)}{ac(e+\delta)\varphi_2'(0)} \frac{\partial\phi(x_2,0,0,0)}{\partial v} < \frac{k(ep+\delta)}{ac(e+\delta)\varphi_2'(0)} \frac{\partial\phi(x_0,0,0,0)}{\partial v} = R_0^L. \end{aligned}$$

□

3.3. Global stability analysis

Theorem 3.3. *For system* (3.1)–(3.5)*, let Assumptions* A1, A3 *and* B1–B3 *be true and* $R_0^L \leq 1$*. Then* E_0 *is GAS in* Γ_2.

Proof. Define a Lyapunov functional W_0 by

$$W_0(x,w,y,v,z) = x - x_0 - \int_{x_0}^{x} \lim_{v\to 0^+} \frac{\phi(x_0,0,0,v)}{\phi(\eta,0,0,v)} d\eta + k_1 w + k_2 y + k_3 v + k_4 z. \tag{3.13}$$

where

$$k_1(1-p) + k_2 p = 1, \; k_1(e+\delta) = k_2\delta, \; k_2 a = k_3 k, \; k_3 q = k_4 r. \tag{3.14}$$

The solution of (3.14) is given by

$$k_1 = \frac{\delta}{ep+\delta}, \; k_2 = \frac{e+\delta}{ep+\delta}, \; k_3 = \frac{a(e+\delta)}{k(ep+\delta)}, \; k_4 = \frac{aq(e+\delta)}{kr(ep+\delta)}. \tag{3.15}$$

It is clear that $W_0(x,w,y,v,z) > 0$ for all $x,w,y,v,z > 0$ while $W_0(x,w,y,v,z)$ reaches its global minimum at E_0. The time derivative of W_0 along the trajectories of (3.1)–(3.5) satisfies

$$\begin{aligned}
\frac{dW_0}{dt} &= \left(1-\lim_{v\to 0^+}\frac{\phi(x_0,0,0,v)}{\phi(x,0,0,v)}\right)(n(x)-\phi(x,w,y,v))+k_1\left((1-p)\phi(x,w,y,v)-(e+\delta)\xi(w)\right)\\
&\quad+k_2\left(p\phi(x,w,y,v)+\delta\xi(w)-a\varphi_1(y)\right)+k_3\left(k\varphi_1(y)-c\varphi_2(v)-q\varphi_2(v)\varphi_3(z)\right)\\
&\quad+k_4\left(r\varphi_2(v)\varphi_3(z)-\mu\varphi_3(z)\right)\\
&=(n(x)-n(x_0))\left(1-\lim_{v\to 0^+}\frac{\phi(x_0,0,0,v)}{\phi(x,0,0,v)}\right)+\left(\frac{\phi(x,w,y,v)}{\varphi_2(v)}\lim_{v\to 0^+}\frac{\phi(x_0,0,0,v)}{\phi(x,0,0,v)}-k_3c\right)\varphi_2(v)\\
&\quad-k_4\mu\varphi_3(z)\\
&\le(n(x)-n(x_0))\left(1-\lim_{v\to 0^+}\frac{\phi(x_0,0,0,v)}{\phi(x,0,0,v)}\right)+\left(\frac{\phi(x,0,0,v)}{\varphi_2(v)}\lim_{v\to 0^+}\frac{\phi(x_0,0,0,v)}{\phi(x,0,0,v)}-k_3c\right)\varphi_2(v)\\
&\quad-k_4\mu\varphi_3(z)\\
&\le(n(x)-n(x_0))\left(1-\lim_{v\to 0^+}\frac{\phi(x_0,0,0,v)}{\phi(x,0,0,v)}\right)+\left(\lim_{v\to 0^+}\frac{\phi(x,0,0,v)}{\varphi_2(v)}\lim_{v\to 0^+}\frac{\phi(x_0,0,0,v)}{\phi(x,0,0,v)}-k_3c\right)\varphi_2(v)\\
&\quad-k_4\mu\varphi_3(z)\\
&\le(n(x)-n(x_0))\left(1-\frac{\partial\phi(x_0,0,0,0)/\partial v}{\partial\phi(x,0,0,0)/\partial v}\right)+k_3c\left(\frac{1}{k_3c\varphi_2'(0)}\frac{\partial\phi(x_0,0,0,0)}{\partial v}-1\right)\varphi_2(v)-k_4\mu\varphi_3(z)\\
&=(n(x)-n(x_0))\left(1-\frac{\partial\phi(x_0,0,0,0)/\partial v}{\partial\phi(x,0,0,0)/\partial v}\right)+k_3c(R_0^L-1)\varphi_2(v)-k_4\mu\varphi_3(z).
\end{aligned}\tag{3.16}$$

Similarly to the previous section, one can show that E_0 is GAS. □

The global stability of the equilibria E_1 and E_2 requires the following condition:
Assumption B4.

$$\left(\frac{\phi(x,w,y,v)}{\phi(x,w_i,y_i,v_i)}-\frac{\varphi_2(v)}{\varphi_2(v_i)}\right)\left(1-\frac{\phi(x,w_i,y_i,v_i)}{\phi(x,w,y,v)}\right)\le 0,\quad x,w,y,v>0,\ i=1,2.$$

Lemma 3.4. *Suppose that Assumptions* A1, A3 *and* B1–B3 *are satisfied and* $R_0^L>1$*. Then* $x_1,x_2,w_1,w_2,y_1,y_2,v_1,v_2$ *exist satisfying*

$$sgn(x_2-x_1)=sgn(v_1-v_2)=sgn(w_1-w_2)=sgn(y_1-y_2)=sgn(R_1^L-1).$$

Proof. It follows from Assumptions A1 and B2 that for $x_1,x_2,w_1,w_2,y_1,y_2,v_1,v_2>0$, we have

$$(n(x_2)-n(x_1))(x_1-x_2)>0,\tag{3.17}$$
$$(\phi(x_2,w_2,y_2,v_2)-\phi(x_1,w_2,y_2,v_2))(x_2-x_1)>0,\tag{3.18}$$
$$(\phi(x_1,w_2,y_2,v_2)-\phi(x_1,w_1,y_2,v_2))(w_1-w_2)>0,\tag{3.19}$$
$$(\phi(x_1,w_1,y_2,v_2)-\phi(x_1,w_1,y_1,v_2))(y_1-y_2)>0,\tag{3.20}$$
$$(\phi(x_1,w_1,y_1,v_2)-\phi(x_1,w_1,y_1,v_1))(v_2-v_1)>0.\tag{3.21}$$

First, we claim $sgn(x_2-x_1)=sgn(v_1-v_2)$. Suppose this is not true, i.e., $sgn(x_2-x_1)=sgn(v_2-v_1)$. Using the conditions of the equilibria E_1 and E_2 we would have

$$n(x_2)-n(x_1)=\phi(x_2,w_2,y_2,v_2)-\phi(x_1,w_1,y_1,v_1)=\frac{e+\delta}{1-p}\left(\xi(w_2)-\xi(w_1)\right),\tag{3.22}$$

and

$$n(x_2)-n(x_1)=\phi(x_2,w_2,y_2,v_2)-\phi(x_1,w_1,y_1,v_1)=\frac{a\,(e+\delta)}{ep+\delta}(\varphi_1(y_2)-\varphi_1(y_1)).\tag{3.23}$$

Since ξ and φ_1 are increasing functions of w and y, respectively, then from (3.22) and (3.23) we would have $sgn(x_1 - x_2) = sgn(w_2 - w_1) = sgn(y_2 - y_1)$. Moreover,

$$\begin{aligned} n(x_2) - n(x_1) &= \phi(x_2, w_2, y_2, v_2) - \phi(x_1, w_1, y_1, v_1) \\ &= (\phi(x_2, w_2, y_2, v_2) - \phi(x_1, w_2, y_2, v_2)) + (\phi(x_1, w_2, y_2, v_2) - \phi(x_1, w_1, y_2, v_2)) \\ &\quad + (\phi(x_1, w_1, y_2, v_2) - \phi(x_1, w_1, y_1, v_2)) + (\phi(x_1, w_1, y_1, v_2) - \phi(x_1, w_1, y_1, v_1)). \end{aligned}$$

Therefore, from (3.17)–(3.23) we would get

$$sgn\,(x_1 - x_2) = sgn\,(x_2 - x_1)\,,$$

which leads to a contradiction. Thus, $sgn\,(x_2 - x_1) = sgn\,(v_1 - v_2)$. Assumption B3 implies that

$$\left(\frac{\phi(x_1, w_1, y_1, v_2)}{\varphi_2(v_2)} - \frac{\phi(x_1, w_1, y_1, v_1)}{\varphi_2(v_1)}\right)(v_1 - v_2) > 0. \tag{3.24}$$

Using the equilibrium conditions for E_1 we have $\frac{k(ep+\delta)\phi(x_1,w_1,y_1,v_1)}{ac(e+\delta)\varphi_2(v_1)} = 1$. Then

$$\begin{aligned} R_1^L - 1 &= \frac{k(ep+\delta)\phi(x_2, w_2, y_2, v_2)}{ac(e+\delta)\varphi_2(v_2)} - \frac{k(ep+\delta)\phi(x_1, w_1, y_1, v_1)}{ac(e+\delta)\varphi_2(v_1)} \\ &= \frac{k(ep+\delta)}{ac(e+\delta)}\left[\frac{\phi(x_2, w_2, y_2, v_2)}{\varphi_2(v_2)} - \frac{\phi(x_1, w_1, y_1, v_1)}{\varphi_2(v_1)}\right] \\ &= \frac{k(ep+\delta)}{ac(e+\delta)}\left[\frac{1}{\varphi_2(v_2)}\left(\phi(x_2, w_2, y_2, v_2) - \phi(x_1, w_2, y_2, v_2)\right)\right. \\ &\quad + \frac{1}{\varphi_2(v_2)}\left(\phi(x_1, w_2, y_2, v_2) - \phi(x_1, w_1, y_2, v_2)\right) + \frac{1}{\varphi_2(v_2)}(\phi(x_1, w_1, y_2, v_2) - \phi(x_1, w_1, y_1, v_2)) \\ &\quad \left. + \left(\frac{\phi(x_1, w_1, y_1, v_2)}{\varphi_2(v_2)} - \frac{\phi(x_1, w_1, y_1, v_1)}{\varphi_2(v_1)}\right)\right]. \end{aligned}$$

Thus, from (3.18)–(3.20) and (3.22)–(3.24) we get $sgn(R_1^L - 1) = sgn(v_1 - v_2)$. □

Theorem 3.5. *For system* (3.1)–(3.5)*, let Assumptions* A1, A3 *and* B1–B4 *be satisfied and* $R_1^L \le 1 < R_0^L$. *Then* E_1 *is GAS in* Γ_2.

Proof. We construct the following Lyapunov functional

$$\begin{aligned} W_1(x, w, y, v, z) &= x - x_1 - \int_{x_1}^{x} \frac{\phi(x_1, w_1, y_1, v_1)}{\phi(\eta, w_1, y_1, v_1)} d\eta + k_1\left(w - w_1 - \int_{w_1}^{w} \frac{\xi(w_1)}{\xi(\eta)} d\eta\right) \\ &\quad + k_2\left(y - y_1 - \int_{y_1}^{y} \frac{\varphi_1(y_1)}{\varphi_1(\eta)} d\eta\right) + k_3\left(v - v_1 - \int_{v_1}^{v} \frac{\varphi_2(v_1)}{\varphi_2(\eta)} d\eta\right) + k_4 z, \end{aligned} \tag{3.25}$$

where k_i, $i = 1, 2, 3, 4$, are defined by (3.15). It is obvious that $W_1(x, w, y, v, z) > 0$ for all $x, w, y, v, z > 0$ while $W_1(x, w, y, v, z)$ reaches its global minimum at E_1. The time derivative of W_1 along the trajectories of (3.1)–(3.5) is given by

$$\begin{aligned} \frac{dW_1}{dt} &= \left(1 - \frac{\phi(x_1, w_1, y_1, v_1)}{\phi(x, w_1, y_1, v_1)}\right)(n(x) - \phi(x, w, y, v)) + k_1\left(1 - \frac{\xi(w_1)}{\xi(w)}\right)((1-p)\phi(x, w, y, v) \\ &\quad -(e+\delta)\xi(w)) + k_2\left(1 - \frac{\varphi_1(y_1)}{\varphi_1(y)}\right)(p\phi(x, w, y, v) + \delta\xi(w) - a\varphi_1(y)) \\ &\quad + k_3\left(1 - \frac{\varphi_2(v_1)}{\varphi_2(v)}\right)(k\varphi_1(y) - c\varphi_2(v) - q\varphi_2(v)\varphi_3(z)) + k_4\left(r\varphi_2(v)\varphi_3(z) - \mu\varphi_3(z)\right). \end{aligned} \tag{3.26}$$

Collecting the terms of (3.26) and applying $n(x_1) = \phi(x_1, w_1, y_1, v_1)$, $k\varphi_1(y_1) = c\varphi_2(v_1)$ we get

$$\begin{aligned}\frac{dW_1}{dt} &= (n(x)-n(x_1))\left(1-\frac{\phi(x_1,w_1,y_1,v_1)}{\phi(x,w_1,y_1,v_1)}\right)+\phi(x_1,w_1,y_1,v_1)\left(1-\frac{\phi(x_1,w_1,y_1,v_1)}{\phi(x,w_1,y_1,v_1)}\right)\\
&+\phi(x,w,y,v)\frac{\phi(x_1,w_1,y_1,v_1)}{\phi(x,w_1,y_1,v_1)}+k_1\left(-(1-p)\phi(x,w,y,v)\frac{\xi(w_1)}{\xi(w)}+(e+\delta)\xi(w_1)\right)\\
&+k_2\left(-p\phi(x,w,y,v)\frac{\varphi_1(y_1)}{\varphi_1(y)}-\delta\frac{\varphi_1(y_1)\xi(w)}{\varphi_1(y)}+a\varphi_1(y_1)\right)\\
&+k_3\left(-c\varphi_2(v)-k\frac{\varphi_1(y)\varphi_2(v_1)}{\varphi_2(v)}+k\varphi_1(y_1)+q\varphi_2(v_1)\varphi_3(z)\right)+k_4\left(-\mu\varphi_3(z)\right).\end{aligned} \tag{3.27}$$

Using the equilibrium conditions for E_1, one can easily obtain that

$$k_1(1-p)\phi(x_1,w_1,y_1,v_1)=k_1(e+\delta)\xi(w_1)=k_2\delta\xi(w_1),\ \ k_2a\varphi_1(y_1)=\phi(x_1,w_1,y_1,v_1).$$

Then, we have

$$\begin{aligned}\frac{dW_1}{dt} &= (n(x)-n(x_1))\left(1-\frac{\phi(x_1,w_1,y_1,v_1)}{\phi(x,w_1,y_1,v_1)}\right)+\phi(x_1,w_1,y_1,v_1)\left(1-\frac{\phi(x_1,w_1,y_1,v_1)}{\phi(x,w_1,y_1,v_1)}\right)\\
&+\phi(x_1,w_1,y_1,v_1)\frac{\phi(x,w,y,v)}{\phi(x,w_1,y_1,v_1)}-k_1(1-p)\phi(x_1,w_1,y_1,v_1)\frac{\xi(w_1)\phi(x,w,y,v)}{\xi(w)\phi(x_1,w_1,y_1,v_1)}\\
&+k_1(1-p)\phi(x_1,w_1,y_1,v_1)-k_2p\phi(x_1,w_1,y_1,v_1)\frac{\varphi_1(y_1)\phi(x,w,y,v)}{\varphi_1(y)\phi(x_1,w_1,y_1,v_1)}\\
&-k_2\delta\xi(w_1)\frac{\varphi_1(y_1)\xi(w)}{\varphi_1(y)\xi(w_1)}+\phi(x_1,w_1,y_1,v_1)-k_2a\varphi_1(y_1)\frac{\varphi_2(v)}{\varphi_2(v_1)}-k_2a\varphi_1(y_1)\frac{\varphi_1(y)\varphi_2(v_1)}{\varphi_1(y_1)\varphi_2(v)}\\
&+k_2a\varphi_1(y_1)+\frac{k_2aq}{k}\varphi_2(v_1)\varphi_3(z)-\frac{k_2aq\mu}{rk}\varphi_3(z)\\
&=(n(x)-n(x_1))\left(1-\frac{\phi(x_1,w_1,y_1,v_1)}{\phi(x,w_1,y_1,v_1)}\right)+\left(k_1(1-p)+k_2p\right)\phi(x_1,w_1,y_1,v_1)\left(1-\frac{\phi(x_1,w_1,y_1,v_1)}{\phi(x,w_1,y_1,v_1)}\right)\\
&+\phi(x_1,w_1,y_1,v_1)\left(\frac{\phi(x,w,y,v)}{\phi(x,w_1,y_1,v_1)}-\frac{\varphi_2(v)}{\varphi_2(v_1)}\right)-k_1(1-p)\phi(x_1,w_1,y_1,v_1)\frac{\xi(w_1)\phi(x,w,y,v)}{\xi(w)\phi(x_1,w_1,y_1,v_1)}\\
&+k_1(1-p)\phi(x_1,w_1,y_1,v_1)-k_2p\phi(x_1,w_1,y_1,v_1)\frac{\varphi_1(y_1)\phi(x,w,y,v)}{\varphi_1(y)\phi(x_1,w_1,y_1,v_1)}\\
&-k_1(1-p)\phi(x_1,w_1,y_1,v_1)\frac{\varphi_1(y_1)\xi(w)}{\varphi_1(y)\xi(w_1)}+k_1(1-p)\phi(x_1,w_1,y_1,v_1)+k_2p\phi(x_1,w_1,y_1,v_1)\\
&-k_1(1-p)\phi(x_1,w_1,y_1,v_1)\frac{\varphi_1(y)\varphi_2(v_1)}{\varphi_1(y_1)\varphi_2(v)}-k_2p\phi(x_1,w_1,y_1,v_1)\frac{\varphi_1(y)\varphi_2(v_1)}{\varphi_1(y_1)\varphi_2(v)}\\
&+k_1(1-p)\phi(x_1,w_1,y_1,v_1)+k_2p\phi(x_1,w_1,y_1,v_1)+k_2\frac{aq}{k}\left(\varphi_2(v_1)-\varphi_2(v_2)\right)\varphi_3(z).\end{aligned} \tag{3.28}$$

Collecting the terms of (3.28) we get

$$\begin{aligned}\frac{dW_1}{dt} &= (n(x)-n(x_1))\left(1-\frac{\phi(x_1,w_1,y_1,v_1)}{\phi(x,w_1,y_1,v_1)}\right)\\
&+\phi(x_1,w_1,y_1,v_1)\left(\frac{\phi(x,w,y,v)}{\phi(x,w_1,y_1,v_1)}-\frac{\varphi_2(v)}{\varphi_2(v_1)}\right)\left(1-\frac{\phi(x,w_1,y_1,v_1)}{\phi(x,w,y,v)}\right)\\
&+(1-p)k_1\phi(x_1,w_1,y_1,v_1)\left[5-\frac{\phi(x_1,w_1,y_1,v_1)}{\phi(x,w_1,y_1,v_1)}-\frac{\xi(w_1)\phi(x,w,y,v)}{\xi(w)\phi(x_1,w_1,y_1,v_1)}\right.\\
&\left.-\frac{\varphi_1(y_1)\xi(w)}{\varphi_1(y)\xi(w_1)}-\frac{\varphi_1(y)\varphi_2(v_1)}{\varphi_1(y_1)\varphi_2(v)}-\frac{\varphi_2(v)\phi(x,w_1,y_1,v_1)}{\varphi_2(v_1)\phi(x,w,y,v)}\right]\\
&+pk_2\phi(x_1,w_1,y_1,v_1)\left[4-\frac{\phi(x_1,w_1,y_1,v_1)}{\phi(x,w_1,y_1,v_1)}-\frac{\varphi_1(y_1)\phi(x,w,y,v)}{\varphi_1(y)\phi(x_1,w_1,y_1,v_1)}\right.\end{aligned}$$

$$-\frac{\varphi_1(y)\varphi_2(v_1)}{\varphi_1(y_1)\varphi_2(v)} - \frac{\varphi_2(v)\phi(x,w_1,y_1,v_1)}{\varphi_2(v_1)\phi(x,w,y,v)}\Bigg] + k_2\frac{aq}{k}\left(\varphi_2(v_1)-\varphi_2(v_2)\right)\varphi_3(z). \tag{3.29}$$

Assumptions A1, A3 and B1–B4 imply that the first and second terms of (3.29) are less than or equal to zero. Because the geometrical mean is less than or equal to the arithmetical mean, the third and fourth terms of (3.29) are less than or equal to zero. Lemma 4 implies that if $R_1^L \leq 1$, then $\varphi_2(v_1) \leq \varphi_2(v_2)$. Therefore, if $R_1^L \leq 1$, then $\frac{dW_1}{dt} \leq 0$ for all $x,w,y,v,z > 0$ where the equality occurs at the equilibrium E_1. LaSalle's invariance principle implies the global asymptotic stability of E_1. □

Theorem 3.6. *For system* (3.1)–(3.5)*, let Assumptions* A1, A3 *and* B1–B4 *be satisfied and* $R_1^L > 1$*. Then* E_2 *is GAS in* $\overset{\circ}{\Gamma}_2$.

Proof. We construct the following Lyapunov functional

$$\begin{aligned}W_2(x,w,y,v,z) &= x - x_2 - \int_{x_2}^{x}\frac{\phi(x_2,w_2,y_2,v_2)}{\phi(\eta,w_2,y_2,v_2)}d\eta + k_1\left(w - w_2 - \int_{w_2}^{w}\frac{\xi(w_2)}{\xi(\eta)}d\eta\right)\\ &\quad + k_2\left(y - y_2 - \int_{y_2}^{y}\frac{\varphi_1(y_2)}{\varphi_1(\eta)}d\eta\right) + k_3\left(v - v_2 - \int_{v_2}^{v}\frac{\varphi_2(v_2)}{\varphi_2(\eta)}d\eta\right)\\ &\quad + k_4\left(z - z_2 - \int_{z_2}^{z}\frac{\varphi_3(z_2)}{\varphi_3(\eta)}d\eta\right),\end{aligned} \tag{3.30}$$

where k_i, $i = 1,2,3,4$, are defined by (3.15). It can be seen that $W_2(x,w,y,v,z) > 0$ for all $x,w,y,v,z > 0$ while $W_2(x,w,y,v,z)$ reaches its global minimum at E_2. The time derivative of W_2 along the trajectories of (3.1)–(3.5) is given by

$$\begin{aligned}\frac{dW_2}{dt} &= \left(1 - \frac{\phi(x_2,w_2,y_2,v_2)}{\phi(x,w_2,y_2,v_2)}\right)(n(x) - \phi(x,w,y,v)) + k_1\left(1 - \frac{\xi(w_2)}{\xi(w)}\right)((1-p)\phi(x,w,y,v)\\ &\quad -(e+\delta)\xi(w)) + k_2\left(1 - \frac{\varphi_1(y_2)}{\varphi_1(y)}\right)(p\phi(x,w,y,v) + \delta\xi(w) - a\varphi_1(y))\\ &\quad + k_3\left(1 - \frac{\varphi_2(v_2)}{\varphi_2(v)}\right)(k\varphi_1(y) - c\varphi_2(v) - q\varphi_2(v)\varphi_3(z))\\ &\quad + k_4\left(1 - \frac{\varphi_3(z_2)}{\varphi_3(z)}\right)(r\varphi_2(v)\varphi_3(z) - \mu\varphi_3(z)).\end{aligned} \tag{3.31}$$

Applying $n(x_2) = \phi(x_2,w_2,y_2,v_2)$ and collecting the terms of (3.31) we get

$$\begin{aligned}\frac{dW_2}{dt} &= (n(x) - n(x_2))\left(1 - \frac{\phi(x_2,w_2,y_2,v_2)}{\phi(x,w_2,y_2,v_2)}\right) + \phi(x_2,w_2,y_2,v_2)\left(1 - \frac{\phi(x_2,w_2,y_2,v_2)}{\phi(x,w_2,y_2,v_2)}\right)\\ &\quad + \phi(x,w,y,v)\frac{\phi(x_2,w_2,y_2,v_2)}{\phi(x,w_2,y_2,v_2)} + k_1\left(-(1-p)\phi(x,w,y,v)\frac{\xi(w_2)}{\xi(w)} + (e+\delta)\xi(w_2)\right)\\ &\quad + k_2\left(-p\phi(x,w,y,v)\frac{\varphi_1(y_2)}{\varphi_1(y)} - \delta\frac{\varphi_1(y_2)\xi(w)}{\varphi_1(y)} + a\varphi_1(y_2)\right)\\ &\quad + k_3\left(-c\varphi_2(v) - k\frac{\varphi_1(y)\varphi_2(v_2)}{\varphi_2(v)} + c\varphi_2(v_2) + q\varphi_2(v_2)\varphi_3(z)\right)\\ &\quad + k_4\left(-\mu\varphi_3(z) - r\varphi_3(z_2)\varphi_2(v) + \mu\varphi_3(z_2)\right).\end{aligned} \tag{3.32}$$

Using the equilibrium conditions for E_2, one can easily obtain

$$k_1(1-p)\phi(x_2,w_2,y_2,v_2) = k_1(e+\delta)\xi(w_2) = k_2\delta\xi(w_2),\ \ k_2a\varphi_1(y_2) = \phi(x_2,w_2,y_2,v_2),$$

$$k\varphi_1(y_2) = c\varphi_2(v_2) + q\varphi_2(v_2)\varphi_3(z_2),\ \mu = r\varphi_2(v_2).$$

Then, we get

$$\begin{aligned}
\frac{dW_2}{dt} &= (n(x)-n(x_2))\left(1-\frac{\phi(x_2,w_2,y_2,v_2)}{\phi(x,w_2,y_2,v_2)}\right)+\phi(x_2,w_2,y_2,v_2)\left(1-\frac{\phi(x_2,w_2,y_2,v_2)}{\phi(x,w_2,y_2,v_2)}\right)\\
&\quad+\phi(x_2,w_2,y_2,v_2)\frac{\phi(x,w,y,v)}{\phi(x,w_2,y_2,v_2)}-k_1(1-p)\phi(x_2,w_2,y_2,v_2)\frac{\xi(w_2)\phi(x,w,y,v)}{\xi(w)\phi(x_2,w_2,y_2,v_2)}\\
&\quad+k_1(1-p)\phi(x_2,w_2,y_2,v_2)-k_2p\phi(x_2,w_2,y_2,v_2)\frac{\varphi_1(y_2)\phi(x,w,y,v)}{\varphi_1(y)\phi(x_2,w_2,y_2,v_2)}\\
&\quad-k_2\delta\xi(w_2)\frac{\varphi_1(y_2)\xi(w)}{\varphi_1(y)\xi(w_2)}+\phi(x_2,w_2,y_2,v_2)-\frac{k_2a}{k}c\varphi_2(v_2)\frac{\varphi_2(v)}{\varphi_2(v_2)}\\
&\quad-k_2a\varphi_1(y_2)\frac{\varphi_1(y)\varphi_2(v_2)}{\varphi_1(y_2)\varphi_2(v)}+\frac{k_2a}{k}c\varphi_2(v_2)-\frac{k_2aq}{k}\varphi_2(v_2)\varphi_3(z_2)\frac{\varphi_2(v)}{\varphi_2(v_2)}+\frac{k_2aq}{k}\varphi_2(v_2)\varphi_3(z_2)\\
&=(n(x)-n(x_2))\left(1-\frac{\phi(x_2,w_2,y_2,v_2)}{\phi(x,w_2,y_2,v_2)}\right)+\phi(x_2,w_2,y_2,v_2)\left(3-\frac{\phi(x_2,w_2,y_2,v_2)}{\phi(x,w_2,y_2,v_2)}\right)\\
&\quad+\phi(x_2,w_2,y_2,v_2)\frac{\phi(x,w,y,v)}{\phi(x,w_2,y_2,v_2)}-k_1(1-p)\phi(x_2,w_2,y_2,v_2)\frac{\xi(w_2)\phi(x,w,y,v)}{\xi(w)\phi(x_2,w_2,y_2,v_2)}\\
&\quad+k_1(1-p)\phi(x_2,w_2,y_2,v_2)-k_2p\phi(x_2,w_2,y_2,v_2)\frac{\varphi_1(y_2)\phi(x,w,y,v)}{\varphi_1(y)\phi(x_2,w_2,y_2,v_2)}\\
&\quad-k_1(1-p)\phi(x_2,w_2,y_2,v_2)\frac{\varphi_1(y_2)\xi(w)}{\varphi_1(y)\xi(w_2)}-\phi(x_2,w_2,y_2,v_2)\frac{\varphi_2(v)}{\varphi_2(v_2)}\\
&\quad-\phi(x_2,w_2,y_2,v_2)\frac{\varphi_1(y)\varphi_2(v_2)}{\varphi_1(y_2)\varphi_2(v)}.
\end{aligned}\tag{3.33}$$

Collecting the terms we get

$$\begin{aligned}
\frac{dW_2}{dt} &= (n(x)-n(x_2))\left(1-\frac{\phi(x_2,w_2,y_2,v_2)}{\phi(x,w_2,y_2,v_2)}\right)\\
&\quad+\phi(x_2,w_2,y_2,v_2)\left(\frac{\phi(x,w,y,v)}{\phi(x,w_2,y_2,v_2)}-\frac{\varphi_2(v)}{\varphi_2(v_2)}\right)\left(1-\frac{\phi(x,w_2,y_2,v_2)}{\phi(x,w,y,v)}\right)\\
&\quad+(1-p)k_1\phi(x_2,w_2,y_2,v_2)\left[5-\frac{\phi(x_2,w_2,y_2,v_2)}{\phi(x,w_2,y_2,v_2)}-\frac{\xi(w_2)\phi(x,w,y,v)}{\xi(w)\phi(x_2,w_2,y_2,v_2)}\right.\\
&\quad\left.-\frac{\varphi_1(y_2)\xi(w)}{\varphi_1(y)\xi(w_2)}-\frac{\varphi_1(y)\varphi_2(v_2)}{\varphi_1(y_2)\varphi_2(v)}-\frac{\varphi_2(v)\phi(x,w_2,y_2,v_2)}{\varphi_2(v_2)\phi(x,w,y,v)}\right]\\
&\quad+pk_2\phi(x_2,w_2,y_2,v_2)\left[4-\frac{\phi(x_2,w_2,y_2,v_2)}{\phi(x,w_2,y_2,v_2)}-\frac{\varphi_1(y_2)\phi(x,w,y,v)}{\varphi_1(y)\phi(x_2,w_2,y_2,v_2)}\right.\\
&\quad\left.-\frac{\varphi_1(y)\varphi_2(v_2)}{\varphi_1(y_2)\varphi_2(v)}-\frac{\varphi_2(v)\phi(x,w_2,y_2,v_2)}{\varphi_2(v_2)\phi(x,w,y,v)}\right].
\end{aligned}\tag{3.34}$$

Thus, if $R_1^L > 1$, then x_2, w_2, y_2, v_2 and $z_2 > 0$. From Assumptions A1, A3 and B1–B4, we get that the first and second terms of (3.34) are less than or equal to zero. Since the arithmetical mean is greater than or equal to the geometrical mean, we have $\frac{dW_2}{dt} \leq 0$ for all $x, w, y, v, z > 0$. Similar to the proof of Theorem 3, one can easily show that E_2 is GAS in $\mathring{\Gamma}_2$. □

4. Conclusion

We proposed and analyzed two nonlinear viral infection models with humoral immune response. The first model contains four compartments, the uninfected target cells, productively infected cells, free virus particles and B cells. In the second model, two classes of infected cells were considered, productively infected cells and latently infected cells. We considered more general nonlinear functions for the incidence, production and removal rates. We derived a set of conditions on these general functions and determined the threshold parameters to prove the existence and the global stability of the model's equilibria. The global asymptotic stability of the three equilibria for each model, infection-free, chronic-infection without humoral immune response and chronic-infection with humoral immune response is proven using direct Lyapunov method and LaSalle's invariance principle.

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