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# GLOBAL THRESHOLD DYNAMICS IN HUMORAL IMMUNITY VIRAL INFECTION MODELS INCLUDING AN ECLIPSE STAGE OF INFECTED CELLS

A. M. ELAIW[1,2]

[1]DEPARTMENT OF MATHEMATICS, FACULTY OF SCIENCE, KING ABDULAZIZ UNIVERSITY, P.O. BOX 80203, JEDDAH 21589, SAUDI ARABIA

[2]DEPARTMENT OF MATHEMATICS, FACULTY OF SCIENCE, AL-AZHAR UNIVERSITY, (ASSIUT BRANCH), ASSIUT, EGYPT

*E-mail address*: a_m_elaiw@yahoo.com

ABSTRACT. In this paper, we propose and analyze three viral infection models with humoral immunity including an eclipse stage of infected cells. The incidence rate of infection is represented by bilinear incidence and saturated incidence in the first and second models, respectively, while it is given by a more general function in the third one. The neutralization rate of viruses is giv0en by bilinear form in the first two models, while it is given by a general function in the third one. For each model, we have derived two threshold parameters, the basic infection reproduction number which determines whether or not a chronic-infection can be established without humoral immunity and the humoral immune response activation number which determines whether or not a chronic-infection can be established with humoral immunity. By constructing suitable Lyapunov functions we have proven the global asymptotic stability of all equilibria of the models. For the third model, we have established a set of conditions on the threshold parameters and on the general functions which are sufficient for the global stability of the equilibria of the model. We have performed some numerical simulations for the third model with specific forms of the incidence and neutralization rates and have shown that the numerical results are consistent with the theoretical results.

## 1. INTRODUCTION

During the last decades, several dangerous viruses have been appeared which attack the human body and some of them causes death. These prompt many researchers to study mathematical modeling and model analysis of the interaction between the host cells and viruses such as human immunodeficiency virus (HIV) (see e.g. [1]-[12]), hepatitis B virus (HBV) [13]-[15], hepatitis C virus (HCV) [16]-[18], human T cell leukemia virus (HTLV) [19] and dengue virus [20], etc. There are many benefits from mathematical models of viral infection including: (i) they provide important quantitative insights into viral dynamics in vivo, (ii) they can improve

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diagnosis and treatment strategies which raise hopes of patients infected with viruses, (iii) they can be used to estimate key parameter values that control the infection process.

The basic viral infection model which was proposed by Nowak and Bangham [2] is a three dimensional ODEs and contains three variables $x$, $y$ and $v$ representing the concentrations of the uninfected target cells, infected cells and free virus particles, respectively. To provide more accurate modelling for the viral infection, the effect of immune response has to be considered. The immune system has two main responses to viral infections, the cell mediated immunity and humoral immunity. The cell mediated immunity is based on the Cytotoxic T Lymphocyte (CTL) cells which are responsible to attack and kill the infected cells. The humoral immunity is based on the antibodies that are produced by the B cells. The function of the antibodies is to attack the viruses [1]. In some infections such as in malaria, the cell mediated immunity is less effective than the humoral immunity [21]. In the literature, several mathematical models have been appeared to consider the humoral immune response into the viral infection models (see e.g. [22]-[28]). The basic model of viral infection with humoral immune response is given by [22], [28]:

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

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

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

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

where $z$ denotes the concentration of the B cells. Parameters $\lambda$, $k$ and $g$ represent, respectively, the rate at which new healthy cells are generated from the source within the body, the generation rate constant of free viruses produced from the infected cells and the proliferation rate constant of B cells. Parameters $d$, $a$, $c$ and $\mu$ are the natural death rate constants of the uninfected cells, infected cells, free virus particles and B cells, respectively. Parameter $\beta$ is the infection rate constant and $r$ is the neutralization rate constant of viruses. All the parameters given in model (1.1)-(1.4) are positive.

Model (1.1)-(1.4), does not take into consideration an eclipse stage of infected cells (such cells are called latently infected cells which contain the viruses but not producing it) which is due to the delay between the moment of infection and the moment when the infected cell becomes active to produce new infectious viruses. Latently infected cells have been incorporated into viral infection models in [3] and [29]. The global stability of viral infection models with latently infected cells has been studied in several works (see e.g. [9], [30] and [31]). However, in [9], [30] and [31], the humoral immune response has been neglected.

Our objective in this paper is to propose a class of viral infection models with humoral immune response taking into consideration both latently and actively infected cells and investigate their basic and global properties. The incidence rate of infection is represented by bilinear infection rate and saturation functional response in the first and second model, respectively, while it is given by a general function in the third one. The neutralization rate of viruses is given by bilinear form in the first two models, while it is given by a general function in the third one. Using Lyapunov functions, we show that the global dynamics of the first two models

are determined by two threshold parameters, the basic infection reproduction number and the humoral immune response activation number. For the third model, we derive two threshold parameters and show that, under a set of conditions on these parameters and on the general functions, all the equilibria of the model are globally asymptotically stable (GAS).

## 2. Model with bilinear incidence rate

In this section, we propose a viral infection model with humoral immune response, taking into account the latently infected and actively infected cells.

$$\dot{x} = \lambda - dx - \beta xv, \tag{2.1}$$

$$\dot{w} = (1-\alpha)\beta xv - (e+b)w, \tag{2.2}$$

$$\dot{y} = \alpha\beta xv + bw - ay, \tag{2.3}$$

$$\dot{v} = ky - cv - rvz, \tag{2.4}$$

$$\dot{z} = gvz - \mu z, \tag{2.5}$$

where $w$ and $y$ are the concentrations of latently and actively infected cells, respectively. Eq. (2.2) describes the dynamics of the latently infected cells and shows that they are converted to actively infected cells with rate constant $b$. The parameters $e$ and $a$ are the death rate constants of the latently and actively infected cells, respectively. The fractions $(1-\alpha)$ and $\alpha$ with $0 < \alpha < 1$ are the probabilities that upon infection, an uninfected cell will become either latently infected or actively infected. The other variables and parameters of the model have the same definitions as given in Section 1.

Model (2.1)-(2.5) may describe the dynamics of several viruses such as HIV, HBV and HCV. In case of HIV, $x$ will represent the concentration of the uninfected CD4$^+$ T cells, while in case of HBV or HCV it represents the hepatocyte cells.

### 2.1. Positive invariance.

We note that, model (2.1)-(2.5) is biologically acceptable in the sense that no population goes negative. It is straightforward to check the positive invariance of the non-negative orthant $\mathbb{R}^5_{\geq 0}$ by model (2.1)-(2.5) (see e.g. [11] and [29]). In the following, we show the boundedness of the solutions of model (2.1)-(2.5).

**Proposition 1.** There exist positive numbers $L_i$, $i = 1, 2, 3$ such that the compact set

$$\Omega = \left\{(x, w, y, v, z) \in \mathbb{R}^5_{\geq 0} : 0 \leq x, w, y \leq L_1,\ 0 \leq v \leq L_2,\ 0 \leq z \leq L_3\right\}$$

is positively invariant.

**Proof**. Let $X_1(t) = x(t) + w(t) + y(t)$, then

$$\dot{X}_1 = \lambda - dx - ew - ay \leq \lambda - s_1 X_1,$$

where $s_1 = \min\{d, a, e\}$. Hence $X_1(t) \leq L_1$, if $X_1(0) \leq L_1$, where $L_1 = \dfrac{\lambda}{s_1}$. Since $x(t) > 0$, $w(t) \geq 0$ and $y(t) \geq 0$, then $0 \leq x(t), w(t), y(t) \leq L_1$ if $0 \leq x(0) + w(0) + y(0) \leq L_1$.

On the other hand, let $X_2(t) = v(t) + \frac{r}{g}z(t)$, then

$$\dot{X}_2 = ky - cv - \frac{r\mu}{g}z \leq kL_1 - s_2\left(v + \frac{r}{g}z\right) = kL_1 - s_2X_2,$$

where $s_2 = \min\{c, \mu\}$. Hence $X_2(t) \leq L_2$, if $X_2(0) \leq L_2$, where $L_2 = \dfrac{kL_1}{s_2}$. Since $v(t) \geq 0$ and $z(t) \geq 0$, then $0 \leq v(t) \leq L_2$ and $0 \leq z(t) \leq L_3$ if $0 \leq v(0) + \frac{r}{g}z(0) \leq L_2$, where $L_3 = \frac{gL_2}{r}$. □

2.2. **Equilibria and biological thresholds.** Now we calculate the equilibria of the model and derive two threshold parameters.

**Lemma 1**. For system (2.1)-(2.5) there exist two threshold parameters $R_0^B > 0$ and $R_1^B > 0$ with $R_1^B < R_0^B$ such that

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

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

(iii) if $R_1^B > 1$, then there exist three positive equilibria $E_0 \in \Omega$, $E_1 \in \Omega$ and $E_2 \in \overset{\circ}{\Omega}$, where $\overset{\circ}{\Omega}$ is the interior of $\Omega$.

**Proof**. Let the right-hand sides of Eqs. (2.1)-(2.5) equal to zero, then we get that system (2.1)-(2.5) can admit three equilibria:

(i) Infection-free equilibrium $E_0 = (x_0, 0, 0, 0, 0)$, where $x_0 = \dfrac{\lambda}{d}$, which represents the state where the viruses are absent.

(ii) Chronic-infection equilibrium without humoral immune response $E_1 = (x_1, w_1, y_1, v_1, 0)$, where

$$x_1 = \frac{ac(e+b)}{k\beta(e\alpha+b)}, \qquad w_1 = \frac{(1-\alpha)adc}{k\beta(e\alpha+b)}\left(\frac{k\beta\lambda(e\alpha+b)}{adc(e+b)} - 1\right),$$
$$y_1 = \frac{cd}{k\beta}\left(\frac{k\beta\lambda(e\alpha+b)}{adc(e+b)} - 1\right), \quad v_1 = \frac{d}{\beta}\left(\frac{k\beta\lambda(e\alpha+b)}{adc(e+b)} - 1\right).$$

Therefore, if $\frac{k\beta\lambda(e\alpha+b)}{adc(e+b)} > 1$, then $w_1, y_1, v_1 > 0$. Let us define

$$R_0^B = \frac{k\beta\lambda(e\alpha+b)}{adc(e+b)},$$

which represents the basic infection reproduction number and determines whether or not a chronic-infection can be established without humoral immune response.

In terms of $R_0^B$, we can write the components of $E_1$ as:

$$x_1 = \frac{x_0}{R_0^B}, \qquad w_1 = \frac{(1-\alpha)adc}{k\beta(e\alpha+b)}(R_0^B - 1), \;\; y_1 = \frac{cd}{k\beta}(R_0^B - 1), \qquad v_1 = \frac{d}{\beta}(R_0^B - 1).$$

Thus, if $R_0^B > 1$, then $E_1$ exists and the infection becomes chronic without humoral immunity.

(iii) Chronic-infection equilibrium with humoral immune response $E_2 = (x_2, w_2, y_2, v_2, z_2)$, where

$$x_2 = \frac{\lambda g}{gd + \beta\mu}, \quad w_2 = \frac{(1-\alpha)\beta\lambda\mu}{(e+b)(dg+\beta\mu)}, \quad y_2 = \frac{(e\alpha+b)\beta\lambda\mu}{a(e+b)(dg+\beta\mu)},$$
$$v_2 = \frac{\mu}{g}, \quad z_2 = \frac{c}{r}\left(\frac{gk\beta\lambda(e\alpha+b)}{ac(e+b)(dg+\beta\mu)} - 1\right).$$

Hence, $z_2 > 0$ when $\frac{gk\beta\lambda(e\alpha+b)}{ac(e+b)(dg+\beta\mu)} > 1$. Let us define the parameter $R_1^B$ as

$$R_1^B = \frac{gk\beta\lambda(e\alpha+b)}{ac(e+b)(dg+\beta\mu)} = \frac{R_0^B}{1+\dfrac{\beta\mu}{dg}},$$

which represents the humoral immune response activation number and determines whether or not a persistent humoral immune response can be established. Then we can write $z_2 = \frac{c}{r}(R_1^B - 1)$. It follows that, if $R_1^B > 1$, then $E_2$ exists. In this case, the infection becomes chronic with humoral immunity. Clearly, $R_1^B < R_0^B$.

Now we show that $E_0 \in \Omega$, $E_1 \in \Omega$ and $E_2 \in \overset{\circ}{\Omega}$. Clearly $E_0 \in \Omega$. From the equilibrium conditions of $E_1$ we have

$$dx_1 + \frac{(e+b)w_1}{1-\alpha} = \lambda, \;\; dx_1 + \frac{a(e+b)}{e\alpha+b}y_1 = \lambda, \;\; cv_1 = ky_1,$$

then

$$0 < x_1 < \frac{\lambda}{d} \le L_1,$$
$$0 < w_1 < \frac{(1-\alpha)\lambda}{e+b} < \frac{\lambda}{e} \le L_1,$$
$$0 < y_1 < \frac{(e\alpha+b)\lambda}{a(e+b)} < \frac{\lambda}{a} \le L_1,$$
$$0 < v_1 = \frac{k}{c}y_1 < \frac{k}{c}L_1 \le \frac{kL_1}{s_2} = L_2,$$

Moreover, $z_1 = 0$ and then, $E_1 \in \Omega$.

Similarly, one can show that $0 < x_2, w_2, y_2 < L_1$. Now we show that, if $R_1^B > 1$, then $0 < v_2 < L_2$ and $0 < z_2 < L_3$. From the steady state condition of $E_2$, we have

$$cv_2 + rv_2z_2 = ky_2,$$

and then

$$cv_2 < ky_2 \Rightarrow 0 < v_2 < \frac{k}{c}L_1 \le L_2,$$
$$rv_2z_2 < ky_2 \Rightarrow 0 < z_2 < \frac{gky_2}{r\mu} \le \frac{gk}{rs_2}L_1 = L_3.$$

It follows that, $E_2 \in \overset{\circ}{\Omega}$. $\square$

2.3. **Global stability.** In this subsection, we prove the global stability of all equilibria of system (2.1)-(2.5) employing the method of Lyapunov function and applying LaSalle's invariance principle. Denote

$$H(s) = s - 1 - \ln s.$$

Then, $H(s) \geq 0$ for $s > 0$ and $H(s) = 0$ if and only if $s = 1$.

**Theorem 1.** For system (2.1)-(2.5) if $R_0^B \leq 1$, then $E_0$ is GAS in $\Omega$.
**Proof.** Define a Lyapunov function $W_0^B$ as follows:

$$W_0^B(x,w,y,v,z) = x_0 H\left(\frac{x}{x_0}\right) + \frac{b}{e\alpha+b}w + \frac{e+b}{e\alpha+b}y + \frac{a(e+b)}{k(e\alpha+b)}v + \frac{ar(e+b)}{kg(e\alpha+b)}z. \quad (2.6)$$

Note that, $W_0^B(x,w,y,v,z) > 0$ for all $x,w,y,v,z > 0$, while $W_0^B(x,w,y,v,z)$ reaches its global minimum at $E_0$. The time derivative of $W_0^B$ along the trajectories of (2.1)-(2.5) is given by:

$$\begin{aligned}
\frac{dW_0^B}{dt} &= \left(1 - \frac{x_0}{x}\right)(\lambda - dx - \beta xv) + \frac{b}{e\alpha+b}\left((1-\alpha)\beta xv - (e+b)w\right) \\
&\quad + \frac{e+b}{e\alpha+b}(\alpha\beta xv + bw - ay) + \frac{a(e+b)}{k(e\alpha+b)}(ky - cv - rvz) + \frac{ar(e+b)}{kg(e\alpha+b)}(gvz - \mu z) \\
&= -d\frac{(x-x_0)^2}{x} + \beta x_0 v - \frac{ac(e+b)}{k(e\alpha+b)}v - \frac{ar\mu(e+b)}{kg(e\alpha+b)}z \\
&= -d\frac{(x-x_0)^2}{x} + \frac{ac(e+b)}{k(e\alpha+b)}(R_0^B - 1)v - \frac{ar\mu(e+b)}{kg(e\alpha+b)}z. \quad (2.7)
\end{aligned}$$

If $R_0^B \leq 1$ then $\frac{dW_0^B}{dt} \leq 0$ for all $x,v,z > 0$. Thus, the solutions of system (2.1)-(2.5) converge to $\Gamma$, the largest invariant subset of $\left\{\frac{dW_0^B}{dt} = 0\right\}$ [32]. Clearly, it follows from Eq. (2.7) that $\frac{dW_0^B}{dt} = 0$ if and only if $x(t) = x_0$, $v(t) = 0$ and $z(t) = 0$. The set $\Gamma$ is invariant and for any element belongs to $\Gamma$ satisfies $v(t) = 0$ and $z(t) = 0$, then $\dot{v}(t) = 0$. We can see from Eq. (2.4) that, $0 = \dot{v}(t) = ky(t)$, and thus $y(t) = 0$. Moreover, from Eq. (2.3) we get $w(t) = 0$. Hence $\frac{dW_0^B}{dt} = 0$ if and only if $x(t) = x_0$, $w(t) = 0$, $y(t) = 0$, $v(t) = 0$ and $z(t) = 0$. From LaSalle's invariance principle, $E_0$ is GAS. $\square$

**Theorem 2.** For system (2.1)-(2.5) if $R_1^B \leq 1 < R_0^B$, then $E_1$ is GAS in $\Omega$.

**Proof.** We construct the following Lyapunov function

$$W_1^B(x,w,y,v,z) = x_1 H\left(\frac{x}{x_1}\right) + \frac{b}{e\alpha+b} w_1 H\left(\frac{w}{w_1}\right) + \frac{e+b}{e\alpha+b} y_1 H\left(\frac{y}{y_1}\right) + \frac{a(e+b)}{k(e\alpha+b)} v_1 H\left(\frac{v}{v_1}\right) + \frac{ar(e+b)}{kg(e\alpha+b)} z.$$

We have $W_1^B(x,w,y,v,z) > 0$ for all $x,w,y,v,z > 0$ and $W_1^B(x_1,w_1,y_1,v_1,0) = 0$. Calculating $\frac{dW_1^B}{dt}$ along the trajectories of (2.1)-(2.5) we get

$$\begin{aligned}\frac{dW_1^B}{dt} &= \left(1-\frac{x_1}{x}\right)(\lambda - dx - \beta xv) + \frac{b}{e\alpha+b}\left(1-\frac{w_1}{w}\right)((1-\alpha)\beta xv - (e+b)w) \\ &+ \frac{e+b}{e\alpha+b}\left(1-\frac{y_1}{y}\right)(\alpha\beta xv + bw - ay) + \frac{a(e+b)}{k(e\alpha+b)}\left(1-\frac{v_1}{v}\right)(ky - cv - rvz) \\ &+ \frac{ar(e+b)}{kg(e\alpha+b)}(gvz - \mu z). \end{aligned} \tag{2.8}$$

Applying $\lambda = dx_1 + \beta x_1 v_1$ and collecting terms of Eq. (2.8) we obtain

$$\begin{aligned}\frac{dW_1^B}{dt} &= -d\frac{(x-x_1)^2}{x} + \beta x_1 v_1\left(1-\frac{x_1}{x}\right) + \beta x_1 v - \frac{b(1-\alpha)}{e\alpha+b}\beta xv\frac{w_1}{w} \\ &+ \frac{b(e+b)}{e\alpha+b}w_1 - \frac{(e+b)\alpha}{e\alpha+b}\beta xv\frac{y_1}{y} - \frac{(e+b)b}{e\alpha+b}\frac{y_1 w}{y} + \frac{e+b}{e\alpha+b}ay_1 - \frac{ac(e+b)}{k(e\alpha+b)}v \\ &- \frac{a(e+b)}{(e\alpha+b)}\frac{yv_1}{v} + \frac{ac(e+b)}{k(e\alpha+b)}v_1 + \frac{ar(e+b)}{k(e\alpha+b)}v_1 z - \frac{ar\mu(e+b)}{kg(e\alpha+b)}z.\end{aligned}$$

Using the equilibrium conditions for $E_1$:

$$(1-\alpha)\beta x_1 v_1 = (e+b)w_1,\ \alpha\beta x_1 v_1 + bw_1 = ay_1,\ cv_1 = ky_1,$$

we get

$$\frac{e+b}{e\alpha+b}ay_1 = \frac{ac(e+b)}{k(e\alpha+b)}v_1 = \beta x_1 v_1 = \frac{b(1-\alpha)}{e\alpha+b}\beta x_1 v_1 + \frac{(e+b)\alpha}{e\alpha+b}\beta x_1 v_1$$

and

$$\begin{aligned}\frac{dW_1^B}{dt} &= -d\frac{(x-x_1)^2}{x} + \frac{b(1-\alpha)}{e\alpha+b}\beta x_1 v_1\left(1-\frac{x_1}{x}\right) + \frac{(e+b)\alpha}{e\alpha+b}\beta x_1 v_1\left(1-\frac{x_1}{x}\right) \\ &- \frac{b(1-\alpha)}{e\alpha+b}\beta x_1 v_1\frac{w_1 xv}{w x_1 v_1} + \frac{b(1-\alpha)}{e\alpha+b}\beta x_1 v_1 \\ &- \frac{(e+b)\alpha}{e\alpha+b}\beta x_1 v_1\frac{y_1 xv}{y x_1 v_1} - \frac{b(1-\alpha)}{e\alpha+b}\beta x_1 v_1\frac{y_1 w}{y w_1} + \frac{b(1-\alpha)}{e\alpha+b}\beta x_1 v_1 \\ &+ \frac{(e+b)\alpha}{e\alpha+b}\beta x_1 v_1 - \frac{b(1-\alpha)}{e\alpha+b}\beta x_1 v_1\frac{yv_1}{y_1 v} - \frac{(e+b)\alpha}{e\alpha+b}\beta x_1 v_1\frac{yv_1}{y_1 v}\end{aligned}$$

$$
\begin{aligned}
&+\frac{b(1-\alpha)}{e\alpha+b}\beta x_1v_1+\frac{(e+b)\alpha}{e\alpha+b}\beta x_1v_1+\frac{ar(e+b)}{k(e\alpha+b)}\left(v_1-\frac{\mu}{g}\right)z\\
&=-d\frac{(x-x_1)^2}{x}+\frac{b(1-\alpha)}{e\alpha+b}\beta x_1v_1\left[4-\frac{x_1}{x}-\frac{w_1xv}{wx_1v_1}-\frac{yv_1}{y_1v}-\frac{y_1w}{yw_1}\right]\\
&+\frac{(e+b)\alpha}{e\alpha+b}\beta x_1v_1\left[3-\frac{x_1}{x}-\frac{yv_1}{y_1v}-\frac{y_1xv}{yx_1v_1}\right]+\frac{ar(e+b)}{k(e\alpha+b)}\left(v_1-\frac{\mu}{g}\right)z\\
&=-d\frac{(x-x_1)^2}{x}+\frac{b(1-\alpha)}{e\alpha+b}\beta x_1v_1\left[4-\frac{x_1}{x}-\frac{w_1xv}{wx_1v_1}-\frac{yv_1}{y_1v}-\frac{y_1w}{yw_1}\right]\\
&+\frac{(e+b)\alpha}{e\alpha+b}\beta x_1v_1\left[3-\frac{x_1}{x}-\frac{yv_1}{y_1v}-\frac{y_1xv}{yx_1v_1}\right]+\frac{adr(e+b)}{k\beta(e\alpha+b)}\left(1+\frac{\beta\mu}{dg}\right)(R_1^B-1)z.
\end{aligned}
$$

We have $x_1, w_1, y_1, v_1 > 0$ when $R_0^B > 1$. Since the geometrical mean is less than or equal to the arithmetical mean, then

$$
\begin{aligned}
3 &\leq \frac{x_1}{x}+\frac{yv_1}{y_1v}+\frac{y_1xv}{yx_1v_1},\\
4 &\leq \frac{x_1}{x}+\frac{w_1xv}{wx_1v_1}+\frac{yv_1}{y_1v}+\frac{y_1w}{yw_1}.
\end{aligned}
$$

It follows that, if $R_1^B \leq 1$ then $\frac{dW_1^B}{dt} \leq 0$ for all $x, w, y, v, z > 0$. Thus, the solutions of system (2.1)-(2.5) limit to the largest invariant subset of $\left\{\frac{dW_1^B}{dt}=0\right\}$ [32]. It can be seen that, $\frac{dW_1^B}{dt}=0$ if and only if $x(t)=x_1$, $w(t)=w_1$, $y(t)=y_1$, $v(t)=v_1$ and $z(t)=0$. Applying LaSalle's invariance principle we obtain that, $E_1$ is GAS. □

**Theorem 3.** For system (2.1)-(2.5) if $R_1^B > 1$, then $E_2$ is GAS in $\overset{\circ}{\Omega}$.

**Proof.** Consider the following Lyapunov function

$$
\begin{aligned}
W_2^B(x,w,y,v,z) = x_2H\left(\frac{x}{x_2}\right)+\frac{b}{e\alpha+b}w_2H\left(\frac{w}{w_2}\right)+\frac{e+b}{e\alpha+b}y_2H\left(\frac{y}{y_2}\right)\\
+\frac{a(e+b)}{k(e\alpha+b)}v_2H\left(\frac{v}{v_2}\right)+\frac{ar(e+b)}{kg(e\alpha+b)}z_2H\left(\frac{z}{z_2}\right).
\end{aligned}
$$

We note that, $W_2^B(x,w,y,v,z) > 0$ for all $x, w, y, v, z > 0$, while $W_2^B(x,w,y,v,z)$ reaches its global minimum at $E_2$. Calculating the time derivative of $W_2^B$ along the trajectories of

(2.1)-(2.5) we get

$$\begin{aligned}\frac{dW_2^B}{dt} &= \left(1-\frac{x_2}{x}\right)(\lambda - dx - \beta xv) + \frac{b}{e\alpha+b}\left(1-\frac{w_2}{w}\right)((1-\alpha)\beta xv - (e+b)w)\\ &+ \frac{e+b}{e\alpha+b}\left(1-\frac{y_2}{y}\right)(\alpha\beta xv + bw - ay) + \frac{a(e+b)}{k(e\alpha+b)}\left(1-\frac{v_2}{v}\right)(ky - cv - rvz)\\ &+ \frac{ar(e+b)}{kg(e\alpha+b)}\left(1-\frac{z_2}{z}\right)(gvz - \mu z). \end{aligned} \tag{2.9}$$

Applying $\lambda = dx_2 + \beta x_2 v_2$, then Eq. (2.9) becomes:

$$\begin{aligned}\frac{dW_2^B}{dt} &= -d\frac{(x-x_2)^2}{x} + \beta x_2 v_2\left(1-\frac{x_2}{x}\right) + \beta x_2 v - \frac{b(1-\alpha)}{e\alpha+b}\beta xv\frac{w_2}{w} + \frac{b(e+b)}{e\alpha+b}w_2\\ &- \frac{(e+b)\alpha}{e\alpha+b}\beta xv\frac{y_2}{y} - \frac{(e+b)b}{e\alpha+b}\frac{y_2 w}{y} + \frac{e+b}{e\alpha+b}ay_2 - \frac{ac(e+b)}{k(e\alpha+b)}v - \frac{a(e+b)}{(e\alpha+b)}\frac{yv_2}{v}\\ &+ \frac{ac(e+b)}{k(e\alpha+b)}v_2 + \frac{ar(e+b)}{k(e\alpha+b)}v_2 z - \frac{ar(e+b)}{k(e\alpha+b)}z_2 v - \frac{ar\mu(e+b)}{kg(e\alpha+b)}z + \frac{ar\mu(e+b)}{kg(e\alpha+b)}z_2.\end{aligned}$$

Using the equilibrium conditions for $E_2$

$$(1-\alpha)\beta x_2 v_2 = (e+b)w_2,\ \ \alpha\beta x_2 v_2 + bw_2 = ay_2, \quad cv_2 + rv_2 z_2 = ky_2,$$

we obtain

$$\begin{aligned}\frac{e+b}{e\alpha+b}ay_2 &= \beta x_2 v_2 = \frac{b(1-\alpha)}{e\alpha+b}\beta x_2 v_2 + \frac{(e+b)\alpha}{e\alpha+b}\beta x_2 v_2,\\ \frac{ac(e+b)}{k(e\alpha+b)}v_2 &= \beta x_2 v_2 - \frac{ar(e+b)}{k(e\alpha+b)}v_2 z_2,\end{aligned}$$

and

$$\begin{aligned}\frac{dW_2^B}{dt} &= -d\frac{(x-x_2)^2}{x} + \frac{b(1-\alpha)}{e\alpha+b}\beta x_2 v_2\left(1-\frac{x_2}{x}\right) + \frac{(e+b)\alpha}{e\alpha+b}\beta x_2 v_2\left(1-\frac{x_2}{x}\right)\\ &- \frac{b(1-\alpha)}{e\alpha+b}\beta x_2 v_2\frac{w_2 xv}{wx_2 v_2} + \frac{b(1-\alpha)}{e\alpha+b}\beta x_2 v_2\\ &- \frac{(e+b)\alpha}{e\alpha+b}\beta x_2 v_2\frac{y_2 xv}{yx_2 v_2} - \frac{b(1-\alpha)}{e\alpha+b}\beta x_2 v_2\frac{y_2 w}{yw_2} + \frac{b(1-\alpha)}{e\alpha+b}\beta x_2 v_2 + \frac{(e+b)\alpha}{e\alpha+b}\beta x_2 v_2\\ &- \frac{b(1-\alpha)}{e\alpha+b}\beta x_2 v_2\frac{yv_2}{y_2 v} - \frac{(e+b)\alpha}{e\alpha+b}\beta x_2 v_2\frac{yv_2}{y_2 v} + \frac{b(1-\alpha)}{e\alpha+b}\beta x_2 v_2 + \frac{(e+b)\alpha}{e\alpha+b}\beta x_2 v_2\\ &= -d\frac{(x-x_2)^2}{x} + \frac{b(1-\alpha)}{e\alpha+b}\beta x_2 v_2\left[4 - \frac{x_2}{x} - \frac{w_2 xv}{wx_2 v_2} - \frac{yv_2}{y_2 v} - \frac{y_2 w}{yw_2}\right]\\ &+ \frac{(e+b)\alpha}{e\alpha+b}\beta x_2 v_2\left[3 - \frac{x_2}{x} - \frac{yv_2}{y_2 v} - \frac{y_2 xv}{yx_2 v_2}\right].\end{aligned}$$

Thus, if $R_1^B > 1$, then $x_2, w_2, y_2, v_2, z_2 > 0$. Using the relation between arithmetical and geometrical means, we get $\frac{dW_2^B}{dt} \leq 0$. Clearly, $\frac{dW_2^B}{dt} = 0$ if and only if $x(t) = x_2$, $w(t) = w_2$, $y(t) = y_2$ and $v(t) = v_2$. If $v(t) = v_2$, then $\dot{v}(t) = 0$ and from Eq. (2.4) we have $0 = ky_2 - cv_2 - rv_2z(t)$, which gives $z(t) = z_2$. Therefore, $\frac{dW_2^B}{dt}$ equal to zero at $E_2$. The global stability of $E_2$ follows from LaSalle's invariance principle. □

**Remark 1**. The parameter $R_0^B$ is the standard basic infection reproduction number in the literature of viral infection models. It measures the average number of newly infected cells produced from any one infected cell at the infection-free equilibrium [1]. Thus, $R_0^B$ is the threshold parameter that determines whether or not a chronic-infection can be established without humoral immune response. If $R_0^B \leq 1$, then the viruses will be cleared from the body. Therefore, using effective antiviral drug therapy can control and prevent the infection by making $R_0^B \leq 1$. In case of $R_0^B > 1$, the infection becomes chronic. The parameter $R_1^B$ represents the humoral immune response activation number and determines whether or not a persistent humoral immune response can be established. When $R_1^B \leq 1 < R_0^B$, the infection always becomes chronic, but no humoral immune response can be established. When $R_1^B > 1$, the infection always becomes chronic with humoral immune response.

## 3. Model with saturation functional response

In model (2.1)-(2.5), we have assumed that, the incidence rate between the uninfected target cells and viruses is given by bilinear, i.e., the infection rate per virus and per uninfected cell is constant. However, this bilinear incidence rate may not completely describe the interaction process between the viruses and uninfected target cells [33], [34]. In some cases, the saturated incidence is more reasonable than the bilinear one (see [24], [35] and [36]). In this section, we modify model (2.1)-(2.5) by assuming that the incidence rate is given by saturation functional response.

$$\dot{x} = \lambda - dx - \frac{\beta xv}{1 + \eta v}, \tag{3.1}$$

$$\dot{w} = \frac{(1-\alpha)\beta xv}{1 + \eta v} - (e + b)w, \tag{3.2}$$

$$\dot{y} = \frac{\alpha\beta xv}{1 + \eta v} + bw - ay, \tag{3.3}$$

$$\dot{v} = ky - cv - rvz, \tag{3.4}$$

$$\dot{z} = gvz - \mu z, \tag{3.5}$$

where $\eta > 0$ is the saturation constant, and all the variables and parameters of the model have the same meanings as given previously.

We note that the compact set $\Omega$ defined in Section 2 is also positively invariant with respect to system (3.1)-(3.5).

**Lemma 2**. For system (3.1)-(3.5) there exist two threshold parameters $R_0^S > 0$ and $R_1^S > 0$ with $R_1^S < R_0^S$ such that

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

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

(iii) if $R_1^S > 1$, then there exist three positive equilibria $E_0 \in \Omega$, $E_1 \in \Omega$ and $E_2 \in \overset{\circ}{\Omega}$.

**Proof**. Similar to the proof of Lemma 1, one can show that system (3.1)-(3.5) admits three equilibria: infection-free equilibrium $E_0 = (x_0, 0, 0, 0, 0)$, where $x_0 = \lambda/d$; chronic-infection equilibrium without humoral immune response $E_1 = (x_1, w_1, y_1, v_1, 0)$; chronic-infection equilibrium with humoral immune response $E_2 = (x_2, w_2, y_2, v_2, z_2)$ where,

$$x_1 = \frac{\lambda(1+\eta v_1)}{d(1+\eta v_1)+\beta v_1},\ w_1 = \frac{(1-\alpha)\lambda\beta v_1}{(e+b)\left[d(1+\eta v_1)+\beta v_1\right]},\ y_1 = \frac{cv_1}{k},\ v_1 = \frac{d\left(R_0^S-1\right)}{\eta d+\beta}$$
$$x_2 = \frac{\lambda(1+\eta v_2)}{d(1+\eta v_2)+\beta v_2},\ w_2 = \frac{(1-\alpha)\lambda\beta v_2}{(e+b)\left[d(1+\eta v_2)+\beta v_2\right]},\ y_2 = \frac{\lambda\beta(e\alpha+b)v_2}{a(e+b)\left[d(1+\eta v_2)+\beta v_2\right]},$$
$$v_2 = \frac{\mu}{g},\ \ z_2 = \frac{c}{r}(R_1^S-1),$$

and

$$R_0^S = \frac{k\beta\lambda(e\alpha+b)}{adc(e+b)} \quad \text{and} \quad R_1^S = \frac{R_0^S}{1+\dfrac{d\eta\mu+\beta\mu}{dg}}$$

are the basic infection reproduction number and the humoral immune response activation number, respectively. It is clear that $R_1^S < R_0^S$. It is seen that, $E_0$ is usually exists, $E_1$ exists when $R_0^S > 1$, and $E_2$ exists when $R_1^S > 1$. Moreover, it can be easily show that, $E_0, E_1 \in \Omega$ and $E_2 \in \overset{\circ}{\Omega}$. $\square$

3.1. **Global stability.** In this subsection, we are concerned with the global stability of the three equilibria of system (3.1)-(3.5). The strategy of the proofs is based on constructing suitable Lyapunov functions and applying LaSalle's invariance principle.

**Theorem 4.** For system (3.1)-(3.5) if $R_0^S \leq 1$, then $E_0$ is GAS in $\Omega$.

**Proof.** Define a Lyapunov function $W_0^S$ as follows:

$$W_0^S(x,w,y,v,z) = x_0 H\left(\frac{x}{x_0}\right) + \frac{b}{e\alpha+b}w + \frac{e+b}{e\alpha+b}y + \frac{a(e+b)}{k(e\alpha+b)}v + \frac{ar(e+b)}{kg(e\alpha+b)}z. \quad (3.6)$$

Function $W_0^S$ satisfies

$$\begin{aligned}\frac{dW_0^S}{dt} &= \left(1-\frac{x_0}{x}\right)\left(\lambda - dx - \frac{\beta x v}{1+\eta v}\right) + \frac{b}{e\alpha+b}\left(\frac{(1-\alpha)\beta x v}{1+\eta v} - (e+b)w\right)\\ &+ \frac{e+b}{e\alpha+b}\left(\frac{\alpha\beta x v}{1+\eta v} + bw - ay\right) + \frac{a(e+b)}{k(e\alpha+b)}\left(ky - cv - rvz\right)\\ &+ \frac{ar(e+b)}{kg(e\alpha+b)}\left(gvz - \mu z\right)\\ &= -d\frac{(x-x_0)^2}{x} + \frac{\beta x_0 v}{1+\eta v} - \frac{ac(e+b)}{k(e\alpha+b)}v - \frac{ar\mu(e+b)}{kg(e\alpha+b)}z\\ &= -d\frac{(x-x_0)^2}{x} + \frac{ac(e+b)}{k(e\alpha+b)}(R_0^S-1)v - \frac{\eta ac(e+b)R_0^S v^2}{k(e\alpha+b)(1+\eta v)} - \frac{ar\mu(e+b)}{kg(e\alpha+b)}z.\end{aligned} \tag{3.7}$$

Clearly if $R_0^S \le 1$, then $\frac{dW_0^S}{dt} \le 0$ for all $x, v, z > 0$. Similar to the previous section, one can easily show that, $\frac{dW_0^S}{dt} = 0$ at $E_0$. Applying LaSalle's invariance principle, we obtain that $E_0$ is GAS. □

**Theorem 5.** For system (3.1)-(3.5) if $R_1^S \le 1 < R_0^S$, then $E_1$ is GAS in $\Omega$.
**Proof.** We consider the following Lyapunov function

$$\begin{aligned}W_1^S(x,w,y,v,z) &= x_1 H\left(\frac{x}{x_1}\right) + \frac{b}{e\alpha+b}w_1 H\left(\frac{w}{w_1}\right) + \frac{e+b}{e\alpha+b}y_1 H\left(\frac{y}{y_1}\right)\\ &+ \frac{a(e+b)}{k(e\alpha+b)}v_1 H\left(\frac{v}{v_1}\right) + \frac{ar(e+b)}{kg(e\alpha+b)}z.\end{aligned}$$

Calculating $\frac{dW_1^S}{dt}$ along the solutions of system (3.1)-(3.5), we get

$$\begin{aligned}\frac{dW_1^S}{dt} &= \left(1-\frac{x_1}{x}\right)\left(\lambda - dx - \frac{\beta x v}{1+\eta v}\right) + \frac{b}{e\alpha+b}\left(1-\frac{w_1}{w}\right)\left(\frac{(1-\alpha)\beta x v}{1+\eta v} - (e+b)w\right)\\ &+ \frac{e+b}{e\alpha+b}\left(1-\frac{y_1}{y}\right)\left(\frac{\alpha\beta x v}{1+\eta v} + bw - ay\right) + \frac{a(e+b)}{k(e\alpha+b)}\left(1-\frac{v_1}{v}\right)\left(ky - cv - rvz\right)\\ &+ \frac{ar(e+b)}{kg(e\alpha+b)}\left(gvz - \mu z\right).\end{aligned}$$

Applying the condition $\lambda = dx_1 + \frac{\beta x_1 v_1}{1+\eta v_1}$ we get

$$\begin{aligned}\frac{dW_1^S}{dt} &= \left(1-\frac{x_1}{x}\right)(dx_1 - dx) + \frac{\beta x_1 v_1}{1+\eta v_1}\left(1-\frac{x_1}{x}\right) + \frac{\beta x_1 v}{1+\eta v} - \frac{b(1-\alpha)}{e\alpha+b}\frac{\beta x v}{1+\eta v}\frac{w_1}{w} \\ &+ \frac{b(e+b)}{e\alpha+b}w_1 - \frac{(e+b)\alpha}{e\alpha+b}\frac{\beta x v}{1+\eta v}\frac{y_1}{y} - \frac{(e+b)b}{e\alpha+b}\frac{y_1 w}{y} + \frac{e+b}{e\alpha+b}ay_1 - \frac{ac(e+b)}{k(e\alpha+b)}v \\ &- \frac{a(e+b)}{(e\alpha+b)}\frac{yv_1}{v} + \frac{ac(e+b)}{k(e\alpha+b)}v_1 + \frac{ar(e+b)}{k(e\alpha+b)}v_1 z - \frac{ar\mu(e+b)}{kg(e\alpha+b)}z.\end{aligned}$$

Using the following equilibrium conditions for $E_1$

$$\frac{(1-\alpha)\beta x_1 v_1}{1+\eta v_1} = (e+b)w_1, \quad \frac{\alpha\beta x_1 v_1}{1+\eta v_1} + bw_1 = ay_1, \quad cv_1 = ky_1,$$

we obtain

$$\frac{e+b}{e\alpha+b}ay_1 = \frac{ac(e+b)}{k(e\alpha+b)}v_1 = \frac{\beta x_1 v_1}{1+\eta v_1} = \frac{b(1-\alpha)}{e\alpha+b}\frac{\beta x_1 v_1}{1+\eta v_1} + \frac{(e+b)\alpha}{e\alpha+b}\frac{\beta x_1 v_1}{1+\eta v_1},$$

and

$$\begin{aligned}\frac{dW_1^S}{dt} &= -d\frac{(x-x_1)^2}{x} + \frac{b(1-\alpha)}{e\alpha+b}\frac{\beta x_1 v_1}{1+\eta v_1}\left(1-\frac{x_1}{x}\right) + \frac{(e+b)\alpha}{e\alpha+b}\frac{\beta x_1 v_1}{1+\eta v_1}\left(1-\frac{x_1}{x}\right) \\ &+ \frac{\beta x_1 v_1}{1+\eta v_1}\left(\frac{v(1+\eta v_1)}{v_1(1+\eta v)} - \frac{v}{v_1}\right) - \frac{b(1-\alpha)}{e\alpha+b}\frac{\beta x_1 v_1}{1+\eta v_1}\frac{w_1 x v(1+\eta v_1)}{w x_1 v_1(1+\eta v)} \\ &+ \frac{b(1-\alpha)}{e\alpha+b}\frac{\beta x_1 v_1}{1+\eta v_1} - \frac{(e+b)\alpha}{e\alpha+b}\frac{\beta x_1 v_1}{1+\eta v_1}\frac{y_1 x v(1+\eta v_1)}{y x_1 v_1(1+\eta v)} - \frac{b(1-\alpha)}{e\alpha+b}\frac{\beta x_1 v_1}{1+\eta v_1}\frac{y_1 w}{y w_1} \\ &+ \frac{b(1-\alpha)}{e\alpha+b}\frac{\beta x_1 v_1}{1+\eta v_1} + \frac{(e+b)\alpha}{e\alpha+b}\frac{\beta x_1 v_1}{1+\eta v_1} - \frac{b(1-\alpha)}{e\alpha+b}\frac{\beta x_1 v_1}{1+\eta v_1}\frac{yv_1}{y_1 v} \\ &- \frac{(e+b)\alpha}{e\alpha+b}\frac{\beta x_1 v_1}{1+\eta v_1}\frac{yv_1}{y_1 v} + \frac{b(1-\alpha)}{e\alpha+b}\frac{\beta x_1 v_1}{1+\eta v_1} \\ &+ \frac{(e+b)\alpha}{e\alpha+b}\frac{\beta x_1 v_1}{1+\eta v_1} + \frac{ar(e+b)}{k(e\alpha+b)}\left(v_1 - \frac{\mu}{g}\right)z \\ &= -d\frac{(x-x_1)^2}{x} + \frac{\beta x_1 v_1}{1+\eta v_1}\left(-1 + \frac{v(1+\eta v_1)}{v_1(1+\eta v)} - \frac{v}{v_1} + \frac{1+\eta v}{1+\eta v_1}\right) \\ &+ \frac{b(1-\alpha)}{e\alpha+b}\frac{\beta x_1 v_1}{1+\eta v_1}\left[5 - \frac{x_1}{x} - \frac{w_1 x v(1+\eta v_1)}{w x_1 v_1(1+\eta v)} - \frac{y_1 w}{y w_1} - \frac{yv_1}{y_1 v} - \frac{1+\eta v}{1+\eta v_1}\right] \\ &+ \frac{(e+b)\alpha}{e\alpha+b}\frac{\beta x_1 v_1}{1+\eta v_1}\left[4 - \frac{x_1}{x} - \frac{y_1 x v(1+\eta v_1)}{y x_1 v_1(1+\eta v)} - \frac{yv_1}{y_1 v} - \frac{1+\eta v}{1+\eta v_1}\right] \\ &+ \frac{ar(e+b)}{k(e\alpha+b)}\left(v_1 - \frac{\mu}{g}\right)z.\end{aligned}$$

We have

$$-1+\frac{v(1+\eta v_1)}{v_1(1+\eta v)}-\frac{v}{v_1}+\frac{1+\eta v}{1+\eta v_1}=-\frac{\eta(v-v_1)^2}{v_1(1+\eta v_1)(1+\eta v)},$$
$$v_1-\frac{\mu}{g}=\frac{dg+\mu d\eta+\beta\mu}{dg\eta+g\beta}(R_1^S-1).$$

Then, $\frac{dW_1^S}{dt}$ can be written as:

$$\begin{aligned}\frac{dW_1^S}{dt}&=-d\frac{(x-x_1)^2}{x}-\frac{\eta\beta x_1(v-v_1)^2}{(1+\eta v)(1+\eta v_1)^2}\\&+\frac{b(1-\alpha)}{e\alpha+b}\frac{\beta x_1v_1}{1+\eta v_1}\left[5-\frac{x_1}{x}-\frac{w_1xv(1+\eta v_1)}{wx_1v_1(1+\eta v)}-\frac{y_1w}{yw_1}-\frac{yv_1}{y_1v}-\frac{1+\eta v}{1+\eta v_1}\right]\\&+\frac{(e+b)\alpha}{e\alpha+b}\frac{\beta x_1v_1}{1+\eta v_1}\left[4-\frac{x_1}{x}-\frac{y_1xv(1+\eta v_1)}{yx_1v_1(1+\eta v)}-\frac{yv_1}{y_1v}-\frac{1+\eta v}{1+\eta v_1}\right]\\&+\frac{ar(e+b)}{k(e\alpha+b)}\left(\frac{dg+\mu d\eta+\beta\mu}{dg\eta+g\beta}\right)(R_1^S-1)z.\end{aligned}\tag{3.8}$$

We have $x_1,w_1,y_1,v_1>0$ when $R_0^S>1$. Since the geometrical mean is less than or equal to the arithmetical mean, then the third and fourth terms of Eq. (3.8) are less than or equal to zero. Hence, if $R_1^S\le 1$, then $\frac{dW_1^S}{dt}\le 0$ for all $x,w,y,v,z>0$ and $\frac{dW_1^S}{dt}=0$ at $E_1$. LaSalle's invariance principle implies the global stability of $E_1$. □

**Theorem 6.** For system (3.1)-(3.5) if $R_1^S>1$, then $E_2$ is GAS in $\overset{\circ}{\Omega}$.
**Proof.** Define

$$\begin{aligned}W_2^S(x,w,y,v,z)&=x_2H\left(\frac{x}{x_2}\right)+\frac{b}{e\alpha+b}w_2H\left(\frac{w}{w_2}\right)+\frac{e+b}{e\alpha+b}y_2H\left(\frac{y}{y_2}\right)\\&+\frac{a(e+b)}{k(e\alpha+b)}v_2H\left(\frac{v}{v_2}\right)+\frac{ar(e+b)}{kg(e\alpha+b)}z_2H\left(\frac{z}{z_2}\right).\end{aligned}$$

The time derivative of $W_2^S$ along the trajectories of system (3.1)-(3.5) is given by

$$\begin{aligned}\frac{dW_2^S}{dt}&=\left(1-\frac{x_2}{x}\right)\left(\lambda-dx-\frac{\beta xv}{1+\eta v}\right)+\frac{b}{e\alpha+b}\left(1-\frac{w_2}{w}\right)\left(\frac{(1-\alpha)\beta xv}{1+\eta v}-(e+b)w\right)\\&+\frac{e+b}{e\alpha+b}\left(1-\frac{y_2}{y}\right)\left(\frac{\alpha\beta xv}{1+\eta v}+bw-ay\right)+\frac{a(e+b)}{k(e\alpha+b)}\left(1-\frac{v_2}{v}\right)(ky-cv-rvz)\\&+\frac{ar(e+b)}{kg(e\alpha+b)}\left(1-\frac{z_2}{z}\right)(gvz-\mu z).\end{aligned}$$

Applying $\lambda = dx_2 + \frac{\beta x_2 v_2}{1+\eta v_2}$ we get

$$\begin{aligned}\frac{dW_2^S}{dt} &= \left(1-\frac{x_2}{x}\right)(dx_2 - dx) + \frac{\beta x_2 v_2}{1+\eta v_2}\left(1-\frac{x_2}{x}\right) + \frac{\beta x_2 v}{1+\eta v} - \frac{b(1-\alpha)}{e\alpha+b}\frac{\beta x v}{1+\eta v}\frac{w_2}{w} \\ &+ \frac{b(e+b)}{e\alpha+b}w_2 - \frac{(e+b)\alpha}{e\alpha+b}\frac{\beta x v}{1+\eta v}\frac{y_2}{y} - \frac{(e+b)b}{e\alpha+b}\frac{y_2 w}{y} + \frac{e+b}{e\alpha+b}a y_2 \\ &- \frac{ac(e+b)}{k(e\alpha+b)}v - \frac{a(e+b)}{(e\alpha+b)}\frac{y v_2}{v} + \frac{ac(e+b)}{k(e\alpha+b)}v_2 + \frac{ar(e+b)}{k(e\alpha+b)}v_2 z \\ &- \frac{ar\mu(e+b)}{kg(e\alpha+b)}z - \frac{ar(e+b)}{k(e\alpha+b)}z_2 v + \frac{ar\mu(e+b)}{kg(e\alpha+b)}z_2.\end{aligned}$$

Using the other equilibrium conditions for $E_2$:

$$\frac{(1-\alpha)\beta x_2 v_2}{1+\eta v_2} = (e+b)w_2, \qquad \frac{\alpha\beta x_2 v_2}{1+\eta v_2} + bw_2 = ay_2, \qquad cv_2 + rv_2 z_2 = ky_2,$$

we obtain

$$\begin{aligned}\frac{e+b}{e\alpha+b}a y_2 &= \frac{\beta x_2 v_2}{1+\eta v_2} = \frac{b(1-\alpha)}{e\alpha+b}\frac{\beta x_2 v_2}{1+\eta v_2} + \frac{(e+b)\alpha}{e\alpha+b}\frac{\beta x_2 v_2}{1+\eta v_2}, \\ \frac{ac(e+b)}{k(e\alpha+b)}v_2 &= \frac{\beta x_2 v_2}{1+\eta v_2} - \frac{ar(e+b)}{k(e\alpha+b)}v_2 z_2,\end{aligned}$$

and thus,

$$\begin{aligned}\frac{dW_2^S}{dt} &= -d\frac{(x-x_2)^2}{x} + \frac{b(1-\alpha)}{e\alpha+b}\frac{\beta x_2 v_2}{1+\eta v_2}\left(1-\frac{x_2}{x}\right) + \frac{(e+b)\alpha}{e\alpha+b}\frac{\beta x_2 v_2}{1+\eta v_2}\left(1-\frac{x_2}{x}\right) \\ &+ \frac{\beta x_2 v_2}{1+\eta v_2}\left(\frac{v(1+\eta v_2)}{v_2(1+\eta v)} - \frac{v}{v_2}\right) - \frac{b(1-\alpha)}{e\alpha+b}\frac{\beta x_2 v_2}{1+\eta v_2}\frac{w_2 x v(1+\eta v_2)}{w x_2 v_2(1+\eta v)} \\ &+ \frac{b(1-\alpha)}{e\alpha+b}\frac{\beta x_2 v_2}{1+\eta v_2} - \frac{(e+b)\alpha}{e\alpha+b}\frac{\beta x_2 v_2}{1+\eta v_2}\frac{y_2 x v(1+\eta v_2)}{y x_2 v_2(1+\eta v)} \\ &- \frac{b(1-\alpha)}{e\alpha+b}\frac{\beta x_2 v_2}{1+\eta v_2}\frac{y_2 w}{y w_2} + \frac{b(1-\alpha)}{e\alpha+b}\frac{\beta x_2 v_2}{1+\eta v_2} + \frac{(e+b)\alpha}{e\alpha+b}\frac{\beta x_2 v_2}{1+\eta v_2} \\ &- \frac{b(1-\alpha)}{e\alpha+b}\frac{\beta x_2 v_2}{1+\eta v_2}\frac{y v_2}{y_2 v} - \frac{(e+b)\alpha}{e\alpha+b}\frac{\beta x_2 v_2}{1+\eta v_2}\frac{y v_2}{y_2 v} \\ &+ \frac{b(1-\alpha)}{e\alpha+b}\frac{\beta x_2 v_2}{1+\eta v_2} + \frac{(e+b)\alpha}{e\alpha+b}\frac{\beta x_2 v_2}{1+\eta v_2} \\ &= -d\frac{(x-x_2)^2}{x} - \frac{\eta\beta x_2 (v-v_2)^2}{(1+\eta v)(1+\eta v_2)^2} \\ &+ \frac{b(1-\alpha)}{e\alpha+b}\frac{\beta x_2 v_2}{1+\eta v_2}\left[5 - \frac{x_2}{x} - \frac{w_2 x v(1+\eta v_2)}{w x_2 v_2(1+\eta v)} - \frac{y v_2}{y_2 v} - \frac{y_2 w}{y w_2} - \frac{1+\eta v}{1+\eta v_2}\right]\end{aligned}$$

$$+\frac{(e+b)\alpha}{e\alpha+b}\frac{\beta x_2 v_2}{1+\eta v_2}\left[4-\frac{x_2}{x}-\frac{yv_2}{y_2v}-\frac{y_2xv(1+\eta v_2)}{yx_2v_2(1+\eta v)}-\frac{1+\eta v}{1+\eta v_2}\right].$$

If follows that, if $R_1^S>1$, then $x_2, w_2, y_2, v_2, z_2>0$. Similar to the proof of Theorem 3, one can show that $E_2$ is GAS. □

## 4. Model with general incidence and neutralization rates

In this section, we propose a viral infection model with latently infected cells and humoral immune response. We assume that the contacts between the viruses and uninfected target cells are given by an incidence function $f(x,v)$. This form of incidence rate is general to encompass several forms of commonly used incidence rates such as bilinear incidence $\beta xv$ [22], [28], saturated incidence $\frac{\beta xv}{1+\eta v}$ [25] and nonlinear incidence in the form $f(x,v)v$ [27]. In [34] and [37], the viral infection models with general incidence rate $f(x,v)$ have been studied, but without taking the humoral immune response into consideration. Further, we assume that the neutralization rate of viruses and the activation rate of B cells are given by $rvh(z)$ and $gvh(z)$, respectively, where $h(z)$ is a general nonlinear function. These forms can be seen as a generalization of the widely used bilinear forms $qzv$ and $rzv$ that appear in several papers (see e.g. [22]-[28]). Furthermore, we assume that the removal rate of the B cells is given by a general function $\mu h(z)$ which generalizes the linear removal rate $\mu z$ presented in [22]-[28]. Based on the above considerations, we propose the following model:

$$\dot{x}=\lambda-dx-f(x,v), \tag{4.1}$$
$$\dot{w}=(1-\alpha)f(x,v)-(e+b)w, \tag{4.2}$$
$$\dot{y}=\alpha f(x,v)+bw-ay, \tag{4.3}$$
$$\dot{v}=ky-cv-rvh(z), \tag{4.4}$$
$$\dot{z}=gvh(z)-\mu h(z), \tag{4.5}$$

Functions $f$ and $h$ are continuously differentiable and satisfy the following assumptions:

**Assumption A1.** (i) $f(x,v)>0$ and $f(0,v)=f(x,0)=0$ for all $x>0, v>0$,
(ii) $\frac{\partial f(x,v)}{\partial x}>0$, $\frac{\partial f(x,v)}{\partial v}>0$ and $\frac{\partial f(x,0)}{\partial v}>0$ for all $x>0, v>0$.
**Assumption A2.** (i) $f(x,v)\le v\frac{\partial f(x,0)}{\partial v}, \quad x,v>0$,
(ii) $\dfrac{d}{dx}\left(\dfrac{\partial f(x,0)}{\partial v}\right)>0$ for all $x>0$.
**Assumption A3**. (i) $h(z)>0$ for all $z>0$, $h(0)=0$,
(ii) $h'(z)>0$ for all $z>0$,
(iii) $h(z)\ge\xi z$ for all $z\ge0, \xi>0$.

### 4.1. Positive invariance.

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

$$\Omega_1=\left\{(x,w,y,v,z)\in\mathbb{R}^5_{\ge0}: 0\le x,w,y\le M_1,\ 0\le v\le M_2,\ 0\le z\le M_3\right\}$$

is positively invariant.

**Proof**. We have

$$\dot{x} \mid_{x=0} = \lambda > 0, \tag{4.6}$$

$$\dot{w} \mid_{w=0} = (1-\alpha) f(x,v) \geq 0 \text{ for all } x, v \geq 0, \tag{4.7}$$

$$\dot{y} \mid_{y=0} = \alpha f(x,v) + bw \geq 0 \text{ for all } x, w, v \geq 0, \tag{4.8}$$

$$\dot{v} \mid_{v=0} = ky \geq 0 \qquad \text{for all } y \geq 0, \tag{4.9}$$

$$\dot{z} \mid_{z=0} = 0. \tag{4.10}$$

Hence, the orthant $\mathbb{R}^5_{\geq 0}$ is positively invariant for system (4.1)-(4.5).

Similar to the proof of Proposition 1, one can show that, $0 \leq x(t)$, $w(t)$, $y(t) \leq M_1$ if $0 \leq x(0) + w(0) + y(0) \leq M_1$, where $M_1 = L_1$. Let $Y(t) = v(t) + \frac{r}{g} z(t)$, then

$$\dot{Y} = ky - cv - \frac{r\mu}{g} h(z) \leq ky - cv - \frac{r\mu}{g} \xi z \leq kM_1 - s_3 \left( v + \frac{r}{g} z \right) = kM_1 - s_3 Y,$$

where $s_3 = \min\{c, \xi\mu\}$. Hence $Y(t) \leq M_2$, if $Y(0) \leq M_2$, where $M_2 = \dfrac{kM_1}{s_3}$. Since $v(t) \geq 0$ and $z(t) \geq 0$, then $0 \leq v(t) \leq M_2$ and $0 \leq z(t) \leq M_3$ if $0 \leq v(0) + \frac{r}{g} z(0) \leq M_2$, where $M_3 = \frac{gM_2}{r}$. □

4.2. **Equilibria and biological thresholds.** In this subsection, we calculate the equilibria of model (4.1)-(4.5) and derive two threshold parameters.

**Lemma 3.** For system (4.1)-(4.5), assume that Assumptions A1-A3 are satisfied, then there exist two threshold parameters $R_0^G > 0$ and $R_1^G > 0$ with $R_1^G < R_0^G$ such that

(i) if $R_0^G \leq 1$, then there exists only one positive equilibrium $E_0 \in \Omega_1$,

(ii) if $R_1^G \leq 1 < R_0^G$, then there exist only two positive equilibria $E_0 \in \Omega_1$ and $E_1 \in \Omega_1$, and

(iii) if $R_1^G > 1$, then there exist three positive equilibria $E_0 \in \Omega_1$, $E_1 \in \Omega_1$ and $E_2 \in \overset{\circ}{\Omega}_1$.

**Proof.** Let $E(x, w, y, v, z)$ be any equilibrium of system (4.1)-(4.5) satisfying the following equations:

$$\lambda - dx - f(x,v) = 0, \tag{4.11}$$

$$(1-\alpha) f(x,v) - (e+b) w = 0, \tag{4.12}$$

$$\alpha f(x,v) + bw - ay = 0, \tag{4.13}$$

$$ky - cv - rvh(z) = 0, \tag{4.14}$$

$$(gv - \mu) h(z) = 0. \tag{4.15}$$

Since $h(0) = 0$, then Eq. (4.15) has two possible solutions, $z = 0$ or $v = \mu/g$. If $z = 0$, then from Eqs. (4.12) and (4.13) we obtain $w$ and $y$ as:

$$w = \frac{(1-\alpha)f(x,v)}{e+b}, \quad y = \frac{(e\alpha+b)f(x,v)}{a(e+b)}. \tag{4.16}$$

Substituting Eq. (4.16) into Eq. (4.14), we obtain

$$\frac{k(e\alpha+b)f(x,v)}{a(e+b)} - cv = 0. \tag{4.17}$$

Using Assumption A1, we have $v = 0$ is one of the solutions of Eq. (4.17). This yields $w = y = 0$ and $x = x_0$ which leads to the infection-free equilibrium $E_0 = (x_0, 0, 0, 0, 0)$, where $x_0 = \lambda/d$. If $v \neq 0$, then from Eqs. (4.11) and (4.17) we obtain

$$v = \frac{k(e\alpha+b)f(x,v)}{ac(e+b)} = \frac{k(e\alpha+b)(\lambda - dx)}{ac(e+b)}, \tag{4.18}$$

$$\Rightarrow x = x_0 - \frac{ac(e+b)}{dk(e\alpha+b)}v. \tag{4.19}$$

Then, Eq. (4.17) becomes

$$\frac{k(e\alpha+b)}{a(e+b)} f\left(x_0 - \frac{ac(e+b)}{dk(e\alpha+b)}v, v\right) - cv = 0.$$

Let us define a function $\Psi_1$ as:

$$\Psi_1(v) = \frac{k(e\alpha+b)}{a(e+b)} f\left(x_0 - \frac{ac(e+b)}{dk(e\alpha+b)}v, v\right) - cv = 0.$$

It is clear from Assumption 1 that, $\Psi_1(0) = 0$, and when $v = \overline{v} = \frac{x_0 dk(e\alpha+b)}{ac(e+b)} > 0$, then

$$\Psi_1(\overline{v}) = \frac{k(e\alpha+b)}{a(e+b)} f(0, \overline{v}) - c\overline{v} = -c\overline{v} < 0.$$

Since $\Psi_1(v)$ is continuous for all $v \geq 0$, then we have

$$\Psi_1'(0) = \frac{k(e\alpha+b)}{a(e+b)} \left[ -\frac{ac(e+b)}{dk(e\alpha+b)} \frac{\partial f(x_0,0)}{\partial x} + \frac{\partial f(x_0,0)}{\partial v} \right] - c.$$

From Assumption A1 we have $\frac{\partial f(x_0,0)}{\partial x} = 0$, then

$$\Psi_1'(0) = \frac{k(e\alpha+b)}{a(e+b)} \frac{\partial f(x_0,0)}{\partial v} - c = c\left( \frac{k(e\alpha+b)}{ac(e+b)} \frac{\partial f(x_0,0)}{\partial v} - 1 \right).$$

Therefore, if $\Psi_1'(0) > 0$ i.e.,

$$\frac{k(e\alpha+b)}{ac(e+b)} \frac{\partial f(x_0,0)}{\partial v} > 1,$$

then there exist a $v_1 \in (0, \overline{v})$ such that $\Psi_1(v_1) = 0$. From Eq. (4.14) we obtain $y_1 = \frac{c}{k} v_1 > 0$. Let $v = v_1$ in Eq. (4.11) and define a function $\Psi_2$ as:

$$\Psi_2(x) = \lambda - dx - f(x, v_1) = 0.$$

Using Assumption A1 we have $\Psi_2(0) = \lambda > 0$ and $\Psi_2(x_0) = -f(x_0, v_1) < 0$. Since $f$ is a strictly increasing function of $x$, then $\Psi_2$ is a strictly decreasing function of $x$, and there exists a unique $x_1 \in (0, x_0)$ such that $\Psi_2(x_1) = 0$. It follows that, $w_1 = \frac{(1-\alpha)f(x_1,v_1)}{e+b} > 0$. It means that, a chronic-infection equilibrium without humoral immune response $E_1 = (x_1, w_1, y_1, v_1, 0)$ exists when $\frac{k(e\alpha+b)}{ac(e+b)}\frac{\partial f(x_0,0)}{\partial v} > 1$. Now we are ready to define the basic infection reproduction number as:

$$R_0^G = \frac{k(e\alpha + b)}{ac(e + b)}\frac{\partial f(x_0, 0)}{\partial v}.$$

The other possibility of Eq. (4.15) is $v_2 = \dfrac{\mu}{g}$. Substituting $v = v_2$ in Eq. (4.11) and defining a function $\Psi_3$ as:

$$\Psi_3(x) = \lambda - dx - f(x, v_2) = 0.$$

According to Assumption A1, $\Psi_3$ is a strictly decreasing function of $x$. Clearly, $\Psi_3(0) = \lambda > 0$ and $\Psi_3(x_0) = -f(x_0, v_2) < 0$. Thus, there exists a unique $x_2 \in (0, x_0)$ such that $\Psi_3(x_2) = 0$. It follows from Eqs. (4.12)-(4.14) that,

$$w_2 = \frac{(1 - \alpha)f(x_2, v_2)}{e + b},\ y_2 = \frac{(e\alpha + b)f(x_2, v_2)}{a(e + b)}, \quad h(z_2) = \frac{c}{r}\left[\frac{k(e\alpha + b)f(x_2, v_2)}{ac(e + b)v_2} - 1\right].$$

Clearly, $w_2, y_2 > 0$. Since $h$ is continuous and strictly increasing function with $h(0) = 0$, then $h^{-1}$ exists and it is also continuous and strictly increasing [38]. Thus, if $\frac{k(e\alpha+b)f(x_2,v_2)}{ac(e+b)v_2} > 1$, then $z_2 = h^{-1}\left(\frac{c}{r}\left(\frac{k(e\alpha+b)f(x_2,v_2)}{ac(e+b)v_2} - 1\right)\right) > 0$. We define the humoral immune response activation number as:

$$R_1^G = \frac{k(e\alpha + b)f(x_2, v_2)}{ac(e + b)v_2}.$$

Hence, $z_2$ can be rewritten as $z_2 = h^{-1}\left(\frac{c}{r}(R_1^G - 1)\right)$. 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 $R_1^G > 1$.

Assumptions A1 and A2 imply that

$$R_1^G = \frac{k(e\alpha + b)f(x_2, v_2)}{ac(e + b)v_2} \leq \frac{k(e\alpha + b)}{ac(e + b)}\frac{\partial f(x_2, 0)}{\partial v} < \frac{k(e\alpha + b)}{ac(e + b)}\frac{\partial f(x_0, 0)}{\partial v} = R_0^G.$$

Similar to the proof of Lemma 1, one can show that $E_0 \in \Omega_1$, $E_1 \in \Omega_1$ and $0 < x_2, w_2, y_2 < M_1$. Now we show that if $R_1^G > 1$, then $0 < v_2 < M_2$ and $0 < z_2 < M_3$. From the equilibrium conditions of $E_2$, we have

$$cv_2 + rv_2h(z_2) = ky_2.$$

Then

$$cv_2 < ky_2 \Rightarrow 0 < v_2 < \frac{k}{c}M_1 \leq M_2,$$

$$rv_2\xi z_2 \leq rv_2h(z_2) < ky_2 \Rightarrow 0 < z_2 < \frac{gky_2}{r\mu\xi} \leq \frac{gk}{rs_3}M_1 = M_3.$$

It follows that, $E_2 \in \overset{\circ}{\Omega}_1$. $\square$

4.3. **Global stability analysis.** In this subsection, we establish the global stability of the three equilibria of system (4.1)-(4.5) employing the direct Lyapunov method and LaSalle's invariance principle. To do so we need the following condition:

**Assumption A4.**

$$\left(\frac{f(x,v)}{f(x,v_i)}-\frac{v}{v_i}\right)\left(1-\frac{f(x,v_i)}{f(x,v)}\right)\leq 0, \quad x,v>0,\ i=1,2.$$

**Theorem 7.** For system (4.1)-(4.5), assume that Assumptions A1-A3 hold and that $R_0^G \leq 1$, then $E_0$ is GAS in $\Omega_1$.

**Proof.** Define a Lyapunov functional $W_0^G$ as follows:

$$W_0^G(x,w,y,v,z) = x - x_0 - \int_{x_0}^{x} \lim_{v\to 0^+} \frac{f(x_0,v)}{f(\theta,v)} d\theta + \frac{b}{e\alpha+b}w + \frac{e+b}{e\alpha+b}y + \frac{a(e+b)}{k(e\alpha+b)}v + \frac{ar(e+b)}{kg(e\alpha+b)}z.$$

We note that, $W_0^G(x,w,y,v,z) > 0$ for $x,w,y,v,z > 0$ and $W_0^G(x_0,0,0,0,0) = 0$. Calculating $\frac{dW_0^G}{dt}$ along the trajectories of (4.1)-(4.5) we obtain

$$\begin{aligned}
\frac{dW_0^G}{dt} &= \left(1-\lim_{v\to 0^+}\frac{f(x_0,v)}{f(x,v)}\right)(\lambda - dx - f(x,v)) + \frac{b}{e\alpha+b}\left((1-\alpha)f(x,v) - (e+b)w\right) \\
&+ \frac{e+b}{e\alpha+b}\left(\alpha f(x,v) + bw - ay\right) + \frac{a(e+b)}{k(e\alpha+b)}\left(ky - cv - rvh(z)\right) \\
&+ \frac{ar(e+b)}{kg(e\alpha+b)}\left(gvh(z) - \mu h(z)\right) \\
&= \lambda\left(1-\frac{\partial f(x_0,0)/\partial v}{\partial f(x,0)/\partial v}\right)\left(1-\frac{x}{x_0}\right) + f(x,v)\frac{\partial f(x_0,0)/\partial v}{\partial f(x,0)/\partial v} \\
&- \frac{ac(e+b)}{k(e\alpha+b)}v - \frac{ar\mu(e+b)}{kg(e\alpha+b)}h(z) \\
&\leq \lambda\left(1-\frac{\partial f(x_0,0)/\partial v}{\partial f(x,0)/\partial v}\right)\left(1-\frac{x}{x_0}\right) + v\frac{\partial f(x_0,0)}{\partial v} - \frac{ac(e+b)}{k(e\alpha+b)}v - \frac{ar\mu(e+b)}{kg(e\alpha+b)}h(z) \\
&= \lambda\left(1-\frac{\partial f(x_0,0)/\partial v}{\partial f(x,0)/\partial v}\right)\left(1-\frac{x}{x_0}\right) + \frac{ac(e+b)}{k(e\alpha+b)}\left(\frac{k(e\alpha+b)}{ac(e+b)}\frac{\partial f(x_0,0)}{\partial v} - 1\right)v \\
&- \frac{ar\mu(e+b)}{kg(e\alpha+b)}h(z)
\end{aligned}$$

$$= \lambda \left(1 - \frac{\partial f(x_0,0)/\partial v}{\partial f(x,0)/\partial v}\right)\left(1 - \frac{x}{x_0}\right) + \frac{ac(e+b)}{k(e\alpha+b)}(R_0^G - 1)v - \frac{ar\mu(e+b)}{kg(e\alpha+b)}h(z). \quad (4.20)$$

Based on Assumption A2, the first term of Eq. (4.20) is less than or equal to zero. Therefore, if $R_0^G \leq 1$, then $\frac{dW_0^G}{dt} \leq 0$ for all $x, v, z > 0$. Similar to the Section 2, one can show that $E_0$ is GAS. □

**Lemma 4.** Suppose that Assumptions A1-A4 are satisfied and $R_0^G > 1$. Then $x_1, x_2, v_1, v_2$ exist satisfying

$$sgn(x_2 - x_1) = sgn(v_1 - v_2) = sgn(R_1^G - 1).$$

**Proof**. From Assumptions A1 and A2, for $x_1, x_2, v_1, v_2 > 0$, we have

$$(f(x_2, v_1) - f(x_1, v_1))(x_2 - x_1) > 0, \quad (4.21)$$

$$(f(x_i, v_2) - f(x_i, v_1))(v_2 - v_1) > 0, \ \ i = 1, 2. \quad (4.22)$$

Using Assumption A4 with $i = 1$, $x = x_1$ and $v = v_2$, we get

$$(f(x_1, v_2)v_1 - f(x_1, v_1)v_2)(f(x_1, v_2) - f(x_1, v_1)) \leq 0.$$

It follows from inequality (4.22) that

$$((f(x_1, v_2)v_1 - f(x_1, v_1)v_2))(v_1 - v_2) > 0. \quad (4.23)$$

Suppose that, $sgn(x_2 - x_1) = sgn(v_2 - v_1)$. Using the conditions of the equilibria $E_1$ and $E_2$ we have

$$\begin{aligned}(\lambda - dx_2) - (\lambda - dx_1) &= f(x_2, v_2) - f(x_1, v_1) \\ &= f(x_2, v_2) - f(x_2, v_1) + f(x_2, v_1) - f(x_1, v_1),\end{aligned}$$

and from inequalities (4.21) and (4.22) we get:

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

which leads to a contradiction. Thus, $sgn(x_2 - x_1) = sgn(v_1 - v_2)$. Using the equilibrium conditions for $E_1$ we have $\frac{k(e\alpha+b)}{ac(e+b)}\frac{f(x_1,v_1)}{v_1} = 1$, then

$$\begin{aligned}R_1^G - 1 &= \frac{k(e\alpha+b)}{ac(e+b)}\left(\frac{f(x_2,v_2)}{v_2} - \frac{f(x_1,v_1)}{v_1}\right) \\ &= \frac{k(e\alpha+b)}{ac(e+b)}\left(\frac{1}{v_2}(f(x_2,v_2) - f(x_1,v_2)) + \frac{1}{v_1v_2}(f(x_1,v_2)v_1 - f(x_1,v_1)v_2)\right).\end{aligned}$$

From inequalities (4.21) and (4.23) we get $sgn\left(R_1^G - 1\right) = sgn(v_1 - v_2)$. □

**Theorem 8.** For system (4.1)-(4.5), assume that Assumptions A1-A4 hold and that $R_1^G \leq 1 < R_0^G$, then $E_1$ is GAS in $\Omega_1$.

**Proof.** We construct the following Lyapunov functional

$$W_1^G(x,w,y,v,z) = x - x_1 - \int_{x_1}^{x} \frac{f(x_1,v_1)}{f(\theta,v_1)}d\theta + \frac{b}{e\alpha+b}w_1 H\left(\frac{w}{w_1}\right) + \frac{e+b}{e\alpha+b}y_1 H\left(\frac{y}{y_1}\right) + \frac{a(e+b)}{k(e\alpha+b)}v_1 H\left(\frac{v}{v_1}\right) + \frac{ar(e+b)}{kg(e\alpha+b)}z.$$

Function $W_1^G(x,w,y,v,z) > 0$ for $x,w,y,v,z > 0$, $W_1^G(x_1,w_1,y_1,v_1,0) = 0$ and its time derivative along the trajectories of (4.1)-(4.5) is given by

$$\begin{aligned}\frac{dW_1^G}{dt} &= \left(1 - \frac{f(x_1,v_1)}{f(x,v_1)}\right)(\lambda - dx - f(x,v)) \\ &+ \frac{b}{e\alpha+b}\left(1 - \frac{w_1}{w}\right)((1-\alpha)f(x,v) - (e+b)w) \\ &+ \frac{e+b}{e\alpha+b}\left(1 - \frac{y_1}{y}\right)(\alpha f(x,v) + bw - ay) \\ &+ \frac{a(e+b)}{k(e\alpha+b)}\left(1 - \frac{v_1}{v}\right)(ky - cv - rvh(z)) \\ &+ \frac{ar(e+b)}{kg(e\alpha+b)}(gvh(z) - \mu h(z)). \end{aligned} \tag{4.24}$$

Applying $\lambda = dx_1 + f(x_1,v_1)$ and collecting terms of Eq. (4.24) we get

$$\begin{aligned}\frac{dW_1^G}{dt} &= \left(1 - \frac{f(x_1,v_1)}{f(x,v_1)}\right)(dx_1 - dx) + f(x_1,v_1)\left(1 - \frac{f(x_1,v_1)}{f(x,v_1)}\right) \\ &+ f(x,v)\frac{f(x_1,v_1)}{f(x,v_1)} - \frac{b(1-\alpha)}{e\alpha+b}f(x,v)\frac{w_1}{w} + \frac{b(e+b)}{e\alpha+b}w_1 - \frac{(e+b)\alpha}{e\alpha+b}f(x,v)\frac{y_1}{y} \\ &- \frac{(e+b)b}{e\alpha+b}\frac{y_1 w}{y} + \frac{e+b}{e\alpha+b}ay_1 - \frac{ac(e+b)}{k(e\alpha+b)}v - \frac{a(e+b)}{(e\alpha+b)}\frac{yv_1}{v} + \frac{ac(e+b)}{k(e\alpha+b)}v_1 \\ &+ \frac{ar(e+b)}{k(e\alpha+b)}v_1 h(z) - \frac{ar\mu(e+b)}{kg(e\alpha+b)}h(z).\end{aligned}$$

Using the equilibrium conditions for $E_1$:

$$(1-\alpha)f(x_1,v_1) = (e+b)w_1, \quad \alpha f(x_1,v_1) + bw_1 = ay_1, \quad cv_1 = ky_1,$$

we obtain

$$\frac{e+b}{e\alpha+b}ay_1 = \frac{ac(e+b)}{k(e\alpha+b)}v_1 = f(x_1,v_1) = \frac{b(1-\alpha)}{e\alpha+b}f(x_1,v_1) + \frac{(e+b)\alpha}{e\alpha+b}f(x_1,v_1),$$

and thus

$$\begin{aligned}
\frac{dW_1^G}{dt} &= dx_1\left(1-\frac{f(x_1,v_1)}{f(x,v_1)}\right)\left(1-\frac{x}{x_1}\right)+\frac{b(1-\alpha)}{e\alpha+b}f(x_1,v_1)\left(1-\frac{f(x_1,v_1)}{f(x,v_1)}\right)\\
&+\frac{(e+b)\alpha}{e\alpha+b}f(x_1,v_1)\left(1-\frac{f(x_1,v_1)}{f(x,v_1)}\right)+f(x_1,v_1)\left(\frac{f(x,v)}{f(x,v_1)}-\frac{v}{v_1}\right)\\
&-\frac{b(1-\alpha)}{e\alpha+b}f(x_1,v_1)\frac{w_1f(x,v)}{wf(x_1,v_1)}+\frac{b(1-\alpha)}{e\alpha+b}f(x_1,v_1)-\frac{(e+b)\alpha}{e\alpha+b}f(x_1,v_1)\frac{y_1f(x,v)}{yf(x_1,v_1)}\\
&-\frac{b(1-\alpha)}{e\alpha+b}f(x_1,v_1)\frac{y_1w}{yw_1}+\frac{b(1-\alpha)}{e\alpha+b}f(x_1,v_1)+\frac{(e+b)\alpha}{e\alpha+b}f(x_1,v_1)\\
&-\frac{b(1-\alpha)}{e\alpha+b}f(x_1,v_1)\frac{yv_1}{y_1v}-\frac{(e+b)\alpha}{e\alpha+b}f(x_1,v_1)\frac{yv_1}{y_1v}+\frac{b(1-\alpha)}{e\alpha+b}f(x_1,v_1)\\
&+\frac{(e+b)\alpha}{e\alpha+b}f(x_1,v_1)+\frac{ar(e+b)}{k(e\alpha+b)}\left(v_1-\frac{\mu}{g}\right)h(z)\\
&=dx_1\left(1-\frac{f(x_1,v_1)}{f(x,v_1)}\right)\left(1-\frac{x}{x_1}\right)+f(x_1,v_1)\left(\frac{f(x,v)}{f(x,v_1)}-\frac{v}{v_1}-1+\frac{vf(x,v_1)}{v_1f(x,v)}\right)\\
&+\frac{b(1-\alpha)}{(e\alpha+b)}f(x_1,v_1)\left[5-\frac{f(x_1,v_1)}{f(x,v_1)}-\frac{w_1f(x,v)}{wf(x_1,v_1)}-\frac{y_1w}{yw_1}-\frac{yv_1}{y_1v}-\frac{vf(x,v_1)}{v_1f(x,v)}\right]\\
&+\frac{(e+b)\alpha}{(e\alpha+b)}f(x_1,v_1)\left[4-\frac{f(x_1,v_1)}{f(x,v_1)}-\frac{y_1f(x,v)}{yf(x_1,v_1)}-\frac{yv_1}{y_1v}-\frac{vf(x,v_1)}{v_1f(x,v)}\right]\\
&+\frac{ar(e+b)}{k(e\alpha+b)}\left(v_1-\frac{\mu}{g}\right)h(z). \qquad (4.25)
\end{aligned}$$

Eq. (4.25) can be written as

$$\begin{aligned}
\frac{dW_1^G}{dt} &= dx_1\left(1-\frac{f(x_1,v_1)}{f(x,v_1)}\right)\left(1-\frac{x}{x_1}\right)+f(x_1,v_1)\left(\frac{f(x,v)}{f(x,v_1)}-\frac{v}{v_1}\right)\left(1-\frac{f(x,v_1)}{f(x,v)}\right)\\
&+\frac{b(1-\alpha)}{(e\alpha+b)}f(x_1,v_1)\left[5-\frac{f(x_1,v_1)}{f(x,v_1)}-\frac{w_1f(x,v)}{wf(x_1,v_1)}-\frac{y_1w}{yw_1}-\frac{yv_1}{y_1v}-\frac{vf(x,v_1)}{v_1f(x,v)}\right]\\
&+\frac{(e+b)\alpha}{(e\alpha+b)}f(x_1,v_1)\left[4-\frac{f(x_1,v_1)}{f(x,v_1)}-\frac{y_1f(x,v)}{yf(x_1,v_1)}-\frac{yv_1}{y_1v}-\frac{vf(x,v_1)}{v_1f(x,v)}\right]\\
&+\frac{ar(e+b)}{k(e\alpha+b)}\left(v_1-v_2\right)h(z). \qquad (4.26)
\end{aligned}$$

From Assumptions A1 and A4, we get that the first and second terms of Eq. (4.26) 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 Eq. (4.26) are less than or equal to zero. Lemma 4 implies that, if $R_1^G \leq 1$, then $v_1 \leq v_2$. Therefore, if $R_1^G \leq 1$, then $\frac{dW_1^G}{dt} \leq 0$ for all $x, w, y, v, z > 0$, where the equality occurs at the equilibrium $E_1$. LaSalle's invariance principle implies the global

stability of $E_1$. □

**Theorem 9.** For system (4.1)-(4.5), suppose that Assumptions A1-A4 are satisfied and $R_1^G > 1$, then $E_2$ is GAS in $\overset{\circ}{\Omega}_1$.

**Proof.** We construct the following Lyapunov functional

$$W_2^G(x,w,y,v,z) = x - x_2 - \int_{x_2}^{x} \frac{f(x_2,v_2)}{f(\theta,v_2)}d\theta + \frac{b}{e\alpha+b}w_2 H\left(\frac{w}{w_2}\right) + \frac{e+b}{e\alpha+b}y_2 H\left(\frac{y}{y_2}\right)$$
$$+ \frac{a(e+b)}{k(e\alpha+b)}v_2 H\left(\frac{v}{v_2}\right) + \frac{ar(e+b)}{kg(e\alpha+b)}\left(z - z_2 - \int_{z_2}^{z}\frac{h(z_2)}{h(\theta)}d\theta\right).$$

Function $W_2^G(x,w,y,v,z) > 0$ for $x,w,y,v,z > 0$ and $W_2^G(x_2,w_2,y_2,v_2,z_2) = 0$. We calculate the time derivative of $W_2^G$ along the trajectories of (4.1)-(4.5) as:

$$\begin{aligned}\frac{dW_2^G}{dt} &= \left(1 - \frac{f(x_2,v_2)}{f(x,v_2)}\right)(\lambda - dx - f(x,v))\\ &+ \frac{b}{e\alpha+b}\left(1-\frac{w_2}{w}\right)((1-\alpha)f(x,v) - (e+b)w)\\ &+ \frac{e+b}{e\alpha+b}\left(1-\frac{y_2}{y}\right)(\alpha f(x,v) + bw - ay)\\ &+ \frac{a(e+b)}{k(e\alpha+b)}\left(1-\frac{v_2}{v}\right)(ky - cv - rvh(z))\\ &+ \frac{ar(e+b)}{kg(e\alpha+b)}\left(1-\frac{h(z_2)}{h(z)}\right)(gvh(z) - \mu h(z)).\end{aligned} \tag{4.27}$$

Applying $\lambda = dx_2 + f(x_2,v_2)$ and collecting terms of Eq. (4.27) we get

$$\begin{aligned}\frac{dW_2^G}{dt} &= \left(1 - \frac{f(x_2,v_2)}{f(x,v_2)}\right)(dx_2 - dx) + f(x_2,v_2)\left(1 - \frac{f(x_2,v_2)}{f(x,v_2)}\right)\\ &+ f(x,v)\frac{f(x_2,v_2)}{f(x,v_2)} - \frac{b(1-\alpha)}{e\alpha+b}f(x,v)\frac{w_2}{w} + \frac{b(e+b)}{e\alpha+b}w_2\\ &- \frac{(e+b)\alpha}{e\alpha+b}f(x,v)\frac{y_2}{y} - \frac{(e+b)b}{e\alpha+b}\frac{y_2 w}{y} + \frac{e+b}{e\alpha+b}ay_2\\ &- \frac{ac(e+b)}{k(e\alpha+b)}v - \frac{a(e+b)}{(e\alpha+b)}\frac{yv_2}{v} + \frac{ac(e+b)}{k(e\alpha+b)}v_2 + \frac{ar(e+b)}{k(e\alpha+b)}v_2 h(z)\\ &- \frac{ar\mu(e+b)}{kg(e\alpha+b)}h(z) - \frac{ar(e+b)}{k(e\alpha+b)}h(z_2)v + \frac{ar\mu(e+b)}{kg(e\alpha+b)}h(z_2).\end{aligned}$$

Using the equilibrium conditions for $E_2$

$$(1-\alpha)f(x_2,v_2) = (e+b)w_2,\ \ \alpha f(x_2,v_2) + bw_2 = ay_2,\ \ ky_2 = cv_2 + rv_2h(z_2),\ \ \mu = gv_2,$$

we obtain

$$\frac{e+b}{e\alpha+b}ay_2 = f(x_2,v_2) = \frac{b(1-\alpha)}{e\alpha+b}f(x_2,v_2) + \frac{(e+b)\alpha}{e\alpha+b}f(x_2,v_2),$$
$$\frac{ac(e+b)}{k(e\alpha+b)}v_2 = f(x_2,v_2) - \frac{ar(e+b)}{k(e\alpha+b)}v_2h(z_2),$$

and then

$$\begin{aligned}
\frac{dW_2^G}{dt} &= dx_2\left(1-\frac{f(x_2,v_2)}{f(x,v_2)}\right)\left(1-\frac{x}{x_2}\right) + \frac{b(1-\alpha)}{e\alpha+b}f(x_2,v_2)\left(1-\frac{f(x_2,v_2)}{f(x,v_2)}\right)\\
&+ \frac{(e+b)\alpha}{e\alpha+b}f(x_2,v_2)\left(1-\frac{f(x_2,v_2)}{f(x,v_2)}\right) + f(x_2,v_2)\left(\frac{f(x,v)}{f(x,v_2)}-\frac{v}{v_2}\right)\\
&- \frac{b(1-\alpha)}{e\alpha+b}f(x_2,v_2)\frac{w_2f(x,v)}{wf(x_2,v_2)} + \frac{b(1-\alpha)}{e\alpha+b}f(x_2,v_2)\\
&- \frac{(e+b)\alpha}{e\alpha+b}f(x_2,v_2)\frac{y_2f(x,v)}{yf(x_2,v_2)} - \frac{b(1-\alpha)}{e\alpha+b}f(x_2,v_2)\frac{y_2w}{yw_2}\\
&+ \frac{b(1-\alpha)}{e\alpha+b}f(x_2,v_2) + \frac{(e+b)\alpha}{e\alpha+b}f(x_2,v_2) - \frac{b(1-\alpha)}{e\alpha+b}f(x_2,v_2)\frac{yv_2}{y_2v}\\
&- \frac{(e+b)\alpha}{e\alpha+b}f(x_2,v_2)\frac{yv_2}{y_2v} + \frac{b(1-\alpha)}{e\alpha+b}f(x_2,v_2) + \frac{(e+b)\alpha}{e\alpha+b}f(x_2,v_2)\\
&= dx_2\left(1-\frac{f(x_2,v_2)}{f(x,v_2)}\right)\left(1-\frac{x}{x_2}\right) + f(x_2,v_2)\left(\frac{f(x,v)}{f(x,v_2)}-\frac{v}{v_2}\right)\left(1-\frac{f(x,v_2)}{f(x,v)}\right)\\
&+ \frac{b(1-\alpha)f(x_2,v_2)}{(e\alpha+b)}\left[5-\frac{f(x_2,v_2)}{f(x,v_2)}-\frac{w_2f(x,v)}{wf(x_2,v_2)}-\frac{y_2w}{yw_2}-\frac{yv_2}{y_2v}-\frac{vf(x,v_2)}{v_2f(x,v)}\right]\\
&+ \frac{(e+b)\alpha f(x_2,v_2)}{(e\alpha+b)}\left[4-\frac{f(x_2,v_2)}{f(x,v_2)}-\frac{y_2f(x,v)}{yf(x_2,v_2)}-\frac{yv_2}{y_2v}-\frac{vf(x,v_2)}{v_2f(x,v)}\right]. \qquad (4.28)
\end{aligned}$$

Thus, if $R_1^G > 1$, then $x_2, w_2, y_2, v_2, z_2 > 0$. From Assumptions A1 and A4, we get that, the first and second terms of Eq. (4.28) are less than or equal to zero. Since the arithmetical mean is greater than or equal to the geometrical mean, then $\frac{dW_2^G}{dt} \leq 0$, where the equality occurs at $E_2$. LaSalle's invariance principle implies the global stability of $E_2$. □

**Remark 2.** By using Lyapunov direct method, we have established a set of conditions on $f(x,v)$ and $h(z)$ ensuring the global asymptotic stability of the equilibria of model (4.1)-(4.5). There are several forms of the incidence rate which satisfy Assumptions A1, A2 and A4 including, bilinear incidence $\beta xv$, saturated incidence $\frac{\beta xv}{1+\eta v}$, Holling type II functional response $\frac{\beta xv}{1+\gamma x}$, Hill-type incidence $\frac{\beta x^m v}{\gamma^m+x^m}$, Beddington-DeAngelis functional response $\frac{\beta xv}{1+\gamma x+\eta v}$, Crowley-Martin functional response $\frac{\beta xv}{(1+\gamma x)(1+\eta v)}$, where $\beta, \gamma, \eta, m > 0$. Examples of function $h(z)$ which satisfy Assumption A3 include $h(z) = \xi_1 z$ and $h(z) = \xi_1 z + \xi_2 z^2$, where $\xi_1, \xi_2 > 0$.

## 5. Numerical Simulations

In this section, we will perform some numerical simulations to confirm our theoretical results. Let us consider the following model:

$$\dot{x} = \lambda - dx - \frac{\beta x^m v}{(\eta_1 + x^{m_1})(\eta_2 + v^{n_1})}, \tag{5.1}$$

$$\dot{w} = \frac{(1-\alpha)\beta x^m v}{(\eta_1 + x^{m_1})(\eta_2 + v^{n_1})} - (e+b)w, \tag{5.2}$$

$$\dot{y} = \frac{\alpha\beta x^m v}{(\eta_1 + x^{m_1})(\eta_2 + v^{n_1})} + bw - ay, \tag{5.3}$$

$$\dot{v} = ky - cv - rvz, \tag{5.4}$$

$$\dot{z} = gvz - \mu z, \tag{5.5}$$

where $\beta, \eta_1, \eta_2, m_1, n_1, m > 0$. Assume that $0 < m_1 \leq m$, $0 < n_1 \leq 1$.

Before performing numerical simulations we have to verify Assumptions A1-A4. We have

$$f(x,v) = \frac{\beta x^m v}{(\eta_1 + x^{m_1})(\eta_2 + v^{n_1})}, \qquad h(z) = z. \tag{5.6}$$

Obviously, $f(x,v) > 0$, $f(0,v) = f(x,0) = 0$ for all $x, v > 0$. Moreover,

$$\frac{\partial f(x,v)}{\partial x} = \frac{\beta\left[\eta_1 m + (m-m_1)x^{m_1}\right]x^{m-1}v}{(\eta_1 + x^{m_1})^2(\eta_2 + v^{n_1})},$$
$$\frac{\partial f(x,v)}{\partial v} = \frac{\beta\left[\eta_2 + (1-n_1)v^{n_1}\right]x^m}{(\eta_1 + x^{m_1})(\eta_2 + v^{n_1})^2},$$
$$\frac{\partial f(x,0)}{\partial v} = \frac{\beta x^m}{\eta_2(\eta_1 + x^{m_1})}.$$

Since, $0 < m_1 \leq m$, $0 < n_1 \leq 1$, then $\frac{\partial f(x,v)}{\partial x} > 0$, $\frac{\partial fx,v)}{\partial v} > 0$ and $\frac{\partial f(x,0)}{\partial v} > 0$ for all $x, v > 0$. Therefore, Assumption A1 is satisfied. We have

$$f(x,v) = \beta\left(\frac{x^m}{\eta_1 + x^{m_1}}\right)\left(\frac{v}{\eta_2 + v^{n_1}}\right) \leq \beta\left(\frac{x^m}{\eta_1 + x^{m_1}}\right)\left(\frac{v}{\eta_2}\right) = v\frac{\partial f(x,0)}{\partial v},$$

then, Assumption A2(i) is satisfied. Also,

$$\frac{d}{dx}\left(\frac{\partial f(x,0)}{\partial v}\right) = \frac{\beta\left[\eta_1 m x^{m-1} + (m-m_1)x^{m+m_1-1}\right]}{\eta_2\left(\eta_1 + x^{m_1}\right)^2} > 0, \text{ for all } x > 0.$$

It follows that, Assumption A2(ii) is satisfied. Moreover,

$$\left(\frac{f(x,v)}{f(x,v_i)} - \frac{v}{v_i}\right)\left(1 - \frac{f(x,v_i)}{f(x,v)}\right) = \frac{1}{(\eta_2 + v^{n_1})(\eta_2 + v_i^{n_1})}\left[\frac{\eta_2}{v_i}(v^{n_1} - v_i^{n_1})(v_i - v)\right.$$
$$\left. + v v_i^{2n_1-1}\left(\left(\frac{v}{v_i}\right)^{n_1} - 1\right)\left(\left(\frac{v}{v_i}\right)^{n_1-1} - 1\right)\right].$$

Since, $0 < n_1 \leq 1$, then we have

$$(v^{n_1} - v_i^{n_1})(v_i - v) \leq 0,$$
$$\left(\left(\frac{v}{v_i}\right)^{n_1} - 1\right)\left(\left(\frac{v}{v_i}\right)^{n_1 - 1} - 1\right) \leq 0.$$

Thus, Assumption A4 is satisfied.

Clearly, function $h(z) = z$ satisfies Assumption A3. Thus the global stability results demonstrated in Theorems 7-9 are valid for model (5.1)-(5.5).

For model (5.1)-(5.5), the parameters $R_0^G$ and $R_1^G$ are given by

$$R_0^G = \frac{k(e\alpha + b)}{ac(e+b)}\frac{\partial f(x_0, 0)}{\partial v} = \frac{k\beta(e\alpha + b)x_0^m}{\eta_2 ac(e+b)(\eta_1 + x_0^{m_1})},$$
$$R_1^G = \frac{k(e\alpha + b)f(x_2, v_2)}{ac(e+b)v_2} = \frac{k\beta(e\alpha + b)x_2^m}{ac(e+b)\,(\eta_1 + x_2^{m_1})\,(\eta_2 + v_2^{n_1})}.$$

Now, we show some numerical results for model (5.1)-(5.5). In Table 1, we provide the values of some parameters of model (5.1)-(5.5). The effect of the other parameters, $\beta$ and $g$ on the dynamical behavior of the system will be discussed below in detail. All computations are carried out by MATLAB.

TABLE 1. The values of the parameters of model (5.1)-(5.5).

| Parameter | Value | Parameter | Value | Parameter | Value |
|---|---|---|---|---|---|
| $\lambda$ | 10 | $b$ | 0.2 | $\eta_2$ | 100 |
| $d$ | 0.01 | $a$ | 0.1 | $n_1$ | 0.5 |
| $e$ | 0.02 | $c$ | 3 | $m$ | 2 |
| $m_1$ | 1 | $k$ | 1 | $\beta$ | Varied |
| $\alpha$ | 0.5 | $r$ | 0.5 | $g$ | Varied |
| $\eta_1$ | 1 | $\mu$ | 0.07 | | |

Now we investigate the theoretical results involved in Theorems 7-9. The evolution of the dynamics of model (5.1)-(5.5) was observed over a time interval $[0, 1200]$. We have chosen three different initial conditions:

**IC1**: $x(0) = 500, w(0) = 12, y(0) = 50, v(0) = 18$ and $z(0) = 0.2$,

**IC2**: $x(0) = 650, w(0) = 4, y(0) = 10, v(0) = 4$ and $z(0) = 0.6$,

**IC3**: $x(0) = 800, w(0) = 8, y(0) = 30, v(0) = 9$ and $z(0) = 0.4$.

We use three sets of the parameters $\beta$ and $g$ to get the following three cases.

**Case (I)**: In this case we choose $\beta = 0.01$ and $g = 0.001$. For this set of parameters, the values of $R_0^G$ and $R_1^G$ are given by $R_0^G = 0.318 < 1$ and $R_1^G = 0.114 < 1$. Figures 1-5 show that, the states of the system eventually approach the infection-free equilibrium $E_0 = (1000, 0, 0, 0, 0)$ for the three initial conditions IC1-IC3. This supports the results of Theorem 7 that the infection-free equilibrium $E_0$ is GAS. In this case, the virus particles will be cleared from the body.

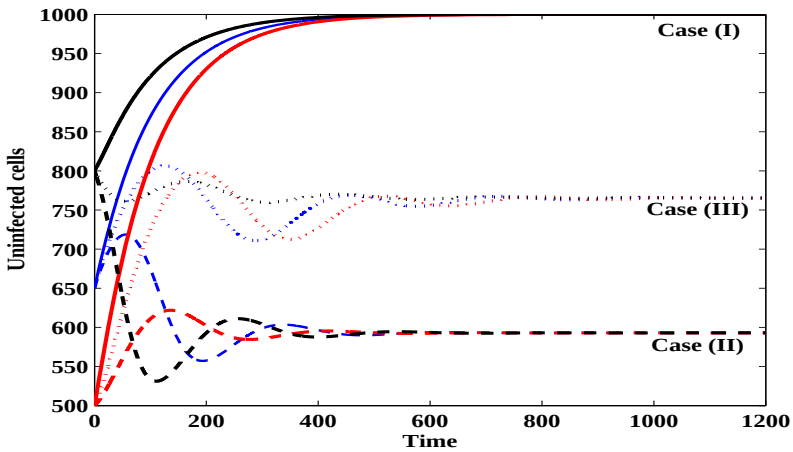


FIGURE 1. The evolution of uninfected target cells for model (5.1)-(5.5).

**Case (II)**: By taking $\beta = 0.055$ and $g = 0.001$. With such choice we get, $R_1^G = 0.226 < 1 < R_0^G = 1.748$. Consequently, based on Lemma 3 and Theorem 8, the system has two equilibria $E_0$ and $E_1$, and $E_1$ is GAS. Figures 1-5 show that the numerical simulations confirm our theoretical result given in Theorem 8. It can be observed that, the states of the system eventually converge to the chronic-infection equilibrium without humoral immune response $E_1 = (592.991, 9.250, 38.851, 12.950, 0)$ for the three initial conditions IC1-IC3. In such case, the infection becomes chronic but with no persistent humoral immune response.

**Case (III)**: We choose, $\beta = 0.045$ and $g = 0.01$. Then, we calculate $R_0^G = 1.43 > 1$ and $R_1^G = 1.023 > 1$. This means that, the system has three equilibria $E_0$, $E_1$ and $E_2$ based on Lemma 3. Moreover, from Theorem 9, $E_2$ is GAS. From Figures 1-5, we can see that, our simulation results are consistent with the theoretical results of Theorem 9. We observe that, the states of the system converge the chronic-infection equilibrium with humoral immune response $E_2 = (765.415, 5.332, 22.392, 7, 0.398)$ for the three initial conditions IC1-IC3. In this case, the infection becomes chronic but with persistent humoral immune response. Figures 1-4 demonstrate that, when $R_1^G > 1$, the humoral immune response is activated and it reduces the concentrations of actively infected cells, latently infected cells and free virus particles and increases the concentration of uninfected cells.

## 6. CONCLUSION AND DISCUSSION

In this paper, we have proposed and analyzed three viral infection models with humoral immune response. The models are five dimensional ODEs that describe the interaction between the uninfected target cells, latently infected cells, actively infected cells, free virus particles and B cells. The incidence rate has been represented by bilinear infection rate and saturation functional response in the first and second models, respectively, while it has been given by a more

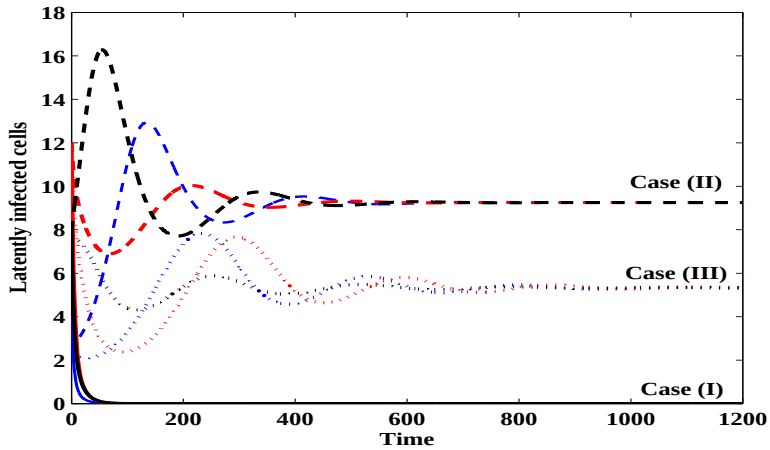


FIGURE 2. The evolution of latently infected cells for model (5.1)-(5.5).

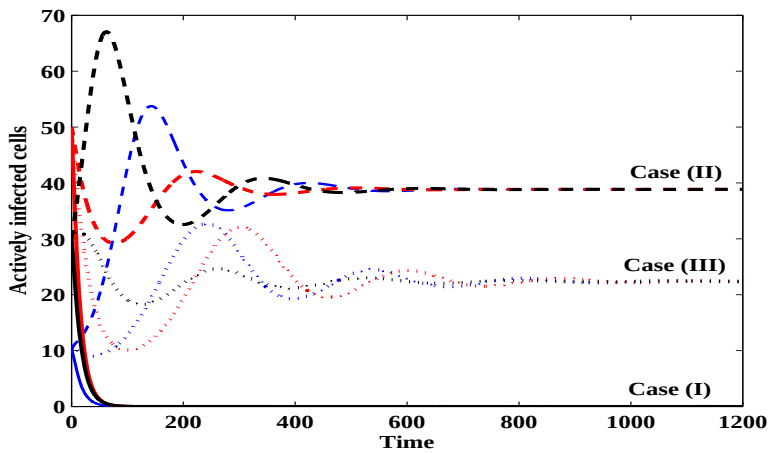


FIGURE 3. The evolution of actively infected cells for model (5.1)-(5.5).

general function in the third one. The neutralization rate of viruses has been given by bilinear form in the first two models, while it is given by a general function in the third one. For each model, we have derived two threshold parameters, the basic infection reproduction number and the humoral immune response activation number. The global stability of the models has been established using Lyapunov method and applying LaSalle's invariance principle. In case of the third model, sufficient conditions have been established which guarantee the global stability of all equilibria of the models. Numerical simulations have been performed for the third model

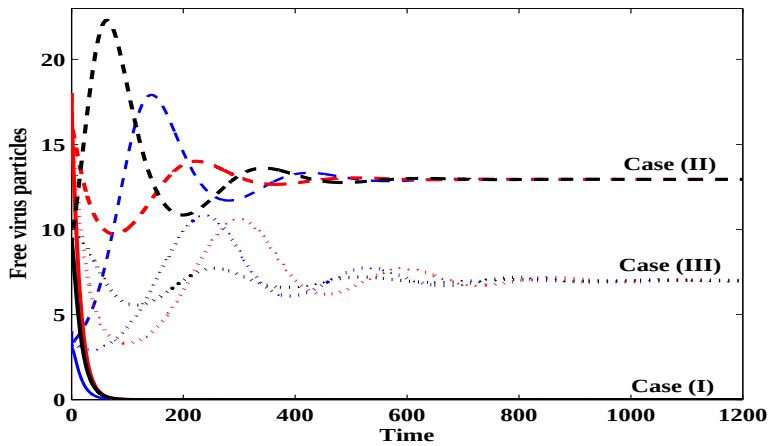


FIGURE 4. The evolution of free virus particles for model (5.1)-(5.5).

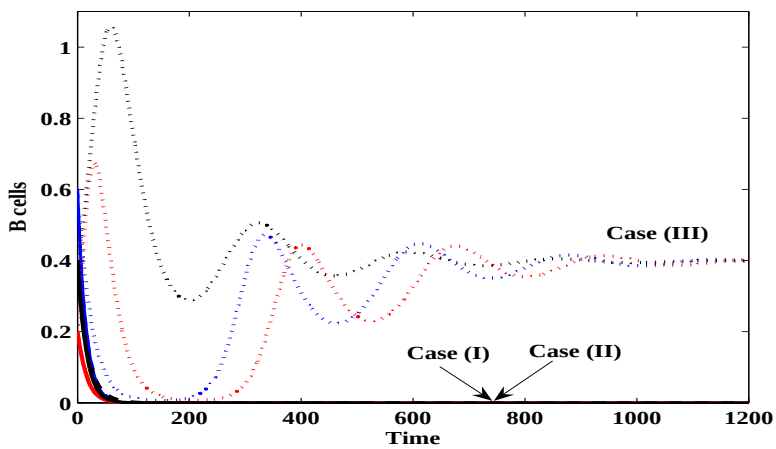


FIGURE 5. The evolution of B cells for model (5.1)-(5.5).

with a special forms of the functions $f(x, v)$ and $h(z)$. We have shown that both numerical and theoretical results are consistent.

6.1. **Effects of latently infected cells on the dynamics and controls of viral infection.** In this subsection, we show the effect of the presence of latently infected cells on the dynamics and controls of the viral infection. Let us consider two models, the first with latently infected cells and the second without latently infected cells. In both model we incorporate two types of antiviral drugs, reverse transcriptase inhibitors (RTIs) which prevent the virus from infecting

the target cells and protease inhibitors (PIs) which prevent the infected cells from producing new infectious viruses. The inclusion of RTIs and PIs allow us to determine the range of drug efficacies that distinguish between the dynamical behaviors of the two models. Model with latently infected cells is given by:

$$\dot{x} = \lambda - dx - \frac{(1-u_{RT})\beta x^m v}{(\eta_1 + x^{m_1})(\eta_2 + v^{n_1})}, \tag{6.1}$$

$$\dot{w} = \frac{(1-u_{RT})(1-\alpha)\beta x^m v}{(\eta_1 + x^{m_1})(\eta_2 + v^{n_1})} - (e+b)w, \tag{6.2}$$

$$\dot{y} = \frac{(1-u_{RT})\alpha\beta x^m v}{(\eta_1 + x^{m_1})(\eta_2 + v^{n_1})} + bw - ay, \tag{6.3}$$

$$\dot{v} = (1-u_{PI})ky - cv - rvz, \tag{6.4}$$

$$\dot{z} = gvz - \mu z, \tag{6.5}$$

where $u_{RT}, u_{PI} \in [0,1)$ are the drug efficacies of RTIs and PIs. Let us define $u = u_{RT} + u_{PI} - u_{RT}u_{PI}$, then $(1-u) = (1-u_{RT})(1-u_{PI})$. Consequently, the parameters $R_0^G$ and $R_1^G$ are given by

$$R_0^G(u) = \frac{(1-u)k\beta(e\alpha+b)x_0^m}{\eta_2 ac(e+b)(\eta_1 + x_0^{m_1})},$$

$$R_1^G(u) = \frac{(1-u)k\beta(e\alpha+b)x_2^m}{ac(e+b)(\eta_1 + x_2^{m_1})(\eta_2 + v_2^{n_1})}.$$

The model without latently infected cells is given by:

$$\dot{x}_i = \lambda - dx - \frac{(1-u_{RT})\beta x^m v}{(\eta_1 + x^{m_1})(\eta_2 + v^{n_1})}, \tag{6.6}$$

$$\dot{y} = \frac{(1-u_{RT})\beta x^m v}{(\eta_1 + x^{m_1})(\eta_2 + v^{n_1})} - ay, \tag{6.7}$$

$$\dot{v} = (1-u_{PI})ky - cv - rvz, \tag{6.8}$$

$$\dot{z} = gvz - \mu z, \tag{6.9}$$

The two threshold parameters for system (6.6)-(6.9) are given by

$$\widetilde{R}_0^G(u) = \frac{(1-u)k\beta x_0^m}{\eta_2 ac(\eta_1 + x_0^{m_1})},$$

$$\widetilde{R}_1^G(u) = \frac{(1-u)k\beta x_2^m}{ac(\eta_1 + x_2^{m_1})(\eta_2 + v_2^{n_1})}.$$

It is clear that

$$R_0^G(u) = \frac{(1-u)k\beta(e\alpha+b)x_0^m}{\eta_2 ac(e+b)(\eta_1 + x_0^{m_1})} < \frac{(1-u)k\beta x_0^m}{\eta_2 ac(\eta_1 + x_0^{m_1})} = \widetilde{R}_0^G(u),$$

$$R_1^G(u) = \frac{(1-u)k\beta(e\alpha+b)x_2^m}{ac(e+b)(\eta_1 + x_2^{m_1})(\eta_2 + v_2^{n_1})} < \frac{(1-u)k\beta x_2^m}{ac(\eta_1 + x_2^{m_1})(\eta_2 + v_2^{n_1})} = \widetilde{R}_1^G(u).$$

It means that, the presence of latently infected cells deceases the two threshold parameters of the system. We note that, the values of the parameters $g$, $r$ and $\mu$ have no impact on the values of $\widetilde{R}_0^G(u)$ and $R_0^G(u)$. This fact seems to suggest that, humoral immune response do not play a role in clearing the viruses but can play a significant role in reducing the infection progress. Since the goal is to clear the viruses from the body, then we have to determine the drug efficacies that make $R_0^G(u) \leq 1$ and $\widetilde{R}_0^G(u) \leq 1$ for systems (6.1)-(6.5) and (6.6)-(6.9), respectively. Now, we calculate the critical drug efficacy (i.e, the efficacy needed in order to stabilize the system around the infection-free equilibrium). For system (6.1)-(6.5), $E_0$ is GAS when $R_0^G(u) \leq 1$ i.e.,

$$u_1^{crit} \leq u < 1,$$
$$u_1^{crit} = \max\left\{0, \frac{R_0^G(0) - 1}{R_0^G(0)}\right\},$$

For system (6.6)-(6.9), $E_0$ is GAS when $\widetilde{R}_0^G(u) \leq 1$ i.e.,

$$u_2^{crit} \leq u < 1,$$
$$u_2^{crit} = \max\left\{0, \frac{\widetilde{R}_0^G(0) - 1}{\widetilde{R}_0^G(0)}\right\}.$$

Clearly, $R_0^G(0) < \widetilde{R}_0^G(0)$ and thus $u_1^{crit} < u_2^{crit}$. Therefore, the drug efficacy necessary to drive the system to the infection-free equilibrium is actually less for system (6.1)-(6.5) than that for system (6.6)-(6.9).

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## REFERENCES

[1] M. A. Nowak and R. M. May, "Virus dynamics: Mathematical Principles of Immunology and Virology," Oxford Uni., Oxford, 2000.

[2] M. A. Nowak and C. R. M. Bangham, *Population dynamics of immune responses to persistent viruses*, Science, **272** (1996), 74-79.

[3] A. S. Perelson and P. W. Nelson, *Mathematical analysis of HIV-1 dynamics in vivo*, SIAM Rev., **41** (1999), 3-44.

[4] L. Wang and M. Y. Li, *Mathematical analysis of the global dynamics of a model for HIV infection of CD4$^+$ T cells*, Math. Biosc., **200(1)** (2006), 44-57.

[5] Y. Zhao, D. T. Dimitrov, H. Liu and Y. Kuang, *Mathematical insights in evaluating state dependent effectiveness of HIV prevention interventions*, Bull. Math. Biol., **75** (2013), 649-675.

[6] D. S. Callaway and A. S. Perelson, *HIV-1 infection and low steady state viral loads*, Bull. Math. Biol., **64** (2002), 29-64.

[7] P. K. Roy, A. N. Chatterjee, D. Greenhalgh and Q. J. A. Khan, *Long term dynamics in a mathematical model of HIV-1 infection with delay in different variants of the basic drug therapy model*, Nonlinear Anal. Real World Appl., **14** ( 2013), 1621-1633.

[8] A. M. Elaiw, I. A. Hassanien and S. A. Azoz, *Global stability of HIV infection models with intracellular delays*, J. Korean Math. Soc., **49** (2012), 779-794.

[9] A. M. Elaiw and S. A. Azoz, *Global properties of a class of HIV infection models with Beddington-DeAngelis functional response*, Math. Methods Appl. Sci., **36** (2013), 383-394.

[10] A. M. Elaiw, *Global properties of a class of virus infection models with multitarget cells*, Nonlinear Dynam., **69** (2012), 423-435.

[11] A. M. Elaiw and X. Xia, *HIV dynamics: Analysis and robust multirate MPC-based treatment schedules*, J. Math. Anal. Appl., **356** (2009), 285-301.

[12] A. M. Elaiw, *Global properties of a class of HIV models,* Nonlinear Anal. Real World Appl., **11** (2010), 2253–2263.

[13] S. Eikenberry, S. Hews, J. D. Nagy and Y. Kuang, *The dynamics of a delay model of HBV infection with logistic hepatocyte growth*, Math. Biosc. Eng., **6** (2009), 283-299.

[14] S. A. Gourley, Y. Kuang and J. D. Nagy, *Dynamics of a delay differential equation model of hepatitis B virus infection,* J. Biol. Dyn., **2** (2008), 140-153.

[15] J. Li, K. Wang and Y. Yang, *Dynamical behaviors of an HBV infection model with logistic hepatocyte growth*, Math. Comput. Modelling, **54** (2011), 704-711.

[16] R. Qesmi, J. Wu, J. Wu and J. M. Heffernan, *Influence of backward bifurcation in a model of hepatitis B and C viruses*, Math. Biosci., **224** (2010), 118–125.

[17] R. Qesmi, S. ElSaadany, J. M. Heffernan and J. Wu, *A hepatitis B and C virus model with age since infection that exhibit backward bifurcation*, SIAM J. Appl. Math., **71** (4) (2011), 1509-1530.

[18] A. U. Neumann, N. P. Lam, H. Dahari, D. R. Gretch, T. E. Wiley, T. J, Layden and A. S. Perelson, *Hepatitis C viral dynamics in vivo and the antiviral efficacy of interferon-alpha therapy*, Science, **282** (1998), 103-107.

[19] M. Y. Li and H. Shu, *Global dynamics of a mathematical model for HTLV-I infection of CD4+ T cells with delayed CTL response*, Nonlinear Anal. Real World Appl., **13** (2012), 1080-1092.

[20] P. Tanvi, G. Gujarati and G. Ambika, *Virus antibody dynamics in primary and secondary dengue infections*, J. Math. Biol., **69** (2014), 1773-1800.

[21] J. A. Deans and S. Cohen, *Immunology of malaria*, Ann. Rev. Microbiol. **37** (1983), 25-49.

[22] A. Murase, T. Sasaki and T. Kajiwara, *Stability analysis of pathogen-immune interaction dynamics*, J. Math. Biol., **51** (2005), 247-267.

[23] A. M. Elaiw and N. H. AlShameani, *Global analysis for a delay-distributed viral infection model with antibodies and general nonlinear incidence rate*, J. Korean Soc. Ind. Appl. Math., **18(4)** (2014), 317-335.

[24] M. A. Obaid and A. M. Elaiw, *Stability of virus infection models with antibodies and chronically infected cells*, Abstr. Appl. Anal, 2014, Article ID 650371**.**

[25] A. M. Elaiw, A. Alhejelan and M. A. Alghamdi, *Global dynamics of virus infection model with antibody immune response and distributed delays*, Discrete Dyn. Nat. Soc., **2013** (2013), Article ID 781407.

[26] T. Wang, Z. Hu and F. Liao, *Stability and Hopf bifurcation for a virus infection model with delayed humoral immunity response*, J. Math. Anal. Appl., **411** (2014) 63-74.

[27] T. Wang, Z. Hu, F. Liao and W. Ma, *Global stability analysis for delayed virus infection model with general incidence rate and humoral immunity,* Math. Comput. Simulation, **89** (2013), 13-22.

[28] S. Wang and D. Zou, *Global stability of in host viral models with humoral immunity and intracellular delays*, J. Appl. Math. Mod., **36** (2012), 1313-1322.

[29] A. S. Perelson, D. Kirschner and R. De Boer, *Dynamics of HIV infection of $CD4^+$ T cells*, Math. Biosci., **114(1)** (1993), 81-125.

[30] A. Korobeinikov, *Global properties of basic virus dynamics models*, Bull. Math. Biol. **66** (2004), 879-883

[31] B. Buonomo and C. Vargas-De-Le, *Global stability for an HIV-1 infection model including an eclipse stage of infected cells*, J. Math. Anal. Appl. **385** (2012), 709-720.

[32] J. K. Hale and S. Verduyn Lunel, "Introduction to functional differential equations," Springer-Verlag, New York, 1993.
[33] X. Song, A. U. Neumann, *Global stability and periodic solution of the viral dynamics*, J. Math. Anal. Appl., **329** (2007), 281-297.
[34] A. Korobeinikov, *Global properties of infectious disease models with nonlinear incidence,* Bull. Math. Biol., **69** (2007), 1871-1886.
[35] R. R. Regoes, D. Ebert, S. Bonhoeffer, *Dose-dependent infection rates of parasites produce the Allee effect in epidemiology*, Proc. R. Soc. Lond. Ser. B, **269** (2002), 271-279.
[36] R. Xu, *Global stability of an HIV-1 infection model with saturation infection and intracellular delay*, J. Math. Anal. Appl., **375** (2011), 75–81.
[37] G. Huang, Y. Takeuchi and W. Ma, *Lyapunov functionals for delay differential equations model of viral infection*, SIAM J. Appl. Math., **70** (2010), 2693-2708.
[38] R. Larson and B. H. Edwards, "Calculus of a single variable," Cengage Learning, Inc., USA, (2010).