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GLOBAL ANALYSIS FOR A DELAY-DISTRIBUTED VIRAL INFECTION MODEL WITH ANTIBODIES AND GENERAL NONLINEAR INCIDENCE RATE

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ABSTRACT. In this work, we investigate the global stability analysis of a viral infection model with antibody immune response. The incidence rate is given by a general function of the populations of the uninfected target cells, infected cells and free viruses. The model has been incorporated with two types of intracellular distributed time delays to describe the time required for viral contacting an uninfected cell and releasing new infectious viruses. We have established a set of conditions on the general incidence rate function and determined two threshold parameters R_0 (the basic infection reproduction number) and R_1 (the antibody immune response activation number) which are sufficient to determine the global dynamics of the model. The global asymptotic stability of the equilibria of the model has been proven by using Lyapunov theory and applying LaSalle's invariance principle.

1. INTRODUCTION

In recent past, many mathematicians have been presented and developed mathematical models in order to describe the interaction between the uninfected cells and the viruses such as human immunodeficiency virus (HIV) (see e.g. [1]-[22]), hepatitis B virus (HBV) [23]-[26], hepatitis C virus (HCV) [27]-[29], human T cell leukemia HTLV [30] and dengue virus [31], etc. Mathematical models of viral infection can help for understanding the viral dynamics and developing antiviral drug therapies. The immune system has two main responses to viral infections. The first is based on the Cytotoxic T Lymphocyte (CTL) cells which are responsible to attack and kill the infected cells. The second immune response is based on the antibodies that are produced by the B cells. The function of the antibodies is to attack the viruses [4]. In some infections such as in malaria, the CTL immune response is less effective than the antibody immune response [32]. In the literature, several mathematical models have been appeared to

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consider the antibody immune response into the viral infection models ([33]-[39]). The basic model of viral infection with antibody immune response has been introduced by Murase et. al. [33] and Shifi Wang [39] as:

$$\dot{x}(t) = s - dx(t) - \beta v(t)x(t), \tag{1.1}$$

$$\dot{y}(t) = \beta v(t)x(t) - ay(t), \tag{1.2}$$

$$\dot{v}(t) = ky(t) - bz(t)v(t) - cv(t), \tag{1.3}$$

$$\dot{z}(t) = rz(t)v(t) - \mu z(t), \tag{1.4}$$

where $x(t)$, $y(t)$, $v(t)$ and $z(t)$ denote the populations of uninfected target cells, infected cells, free virus particles and antibody immune cells at time t, respectively. Parameters s, k and r 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 antibody immune cells. Parameters d, a, c and μ are the natural death rate constants of the uninfected cells, infected cells, free virus particles and antibody immune cells, respectively. Parameter β is the infection rate constant and b is the removal rate constant of the virus due to the antibodies. All the parameters given in model (1.1)-(1.4) are positive.

In model (1.1)-(1.4), the intracellular time delays in the viral life cycle is neglected. Actually, there is a delay between the virus contact a target cell and the creation of new infectious viruses. When the time delay is considered, the interaction between the viruses and target cells will be modeled by delay differential equations [11]-[20]. We note that, the incidence rate of infection is based on the mass action principle which can not be completely describe the interaction between the uninfected target cells and viruses. Nevertheless, there are many types of improved incidence rates which are more commonly used due to their benefit for helping us gain the unification theory through passing over the unessential details (see e.g. [40] and [41]). Different forms of the incidence rate have been considered in viral infection models with antibody immune response such as saturated incidence rate, $\frac{\beta xv}{1+\alpha v}$ where $\alpha \geq 0$ [42], [37], Beddington-DeAngelis functional response, $\frac{\beta xv}{1+\gamma x+\alpha v}$, $\alpha, \gamma \geq 0$ [36], and general form, $\psi(x, v)v$ [38]. In [38], a discrete time delay has been incorporated within the model. 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 [25], [24]. In [43]-[46], a viral infection model with general incidence rate $\psi(x, y, v)v$ and discrete time delays has been studied, however the antibody immune response has been neglected.

Our aim in this paper is to investigate the global stability analysis of a viral infection model with antibody immune response taking into consideration two types of distributed time delays. We assume that the incidence rate is given by a general function which satisfies a set of conditions. Two threshold parameters will be derived, the basic infection reproduction number R_0 and the antibody immune response activation number R_1. We will show that, under a set of conditions of the incidence rate function and on the parameters R_0 and R_1, the global stability of equilibria of the model can be established.

2. THE MATHEMATICAL MODEL

In this section, we consider the following viral infection model with general incidence rate taking into consideration the antibody immune response and two types of intracellular distributed delays.

$$\dot{x}(t) = s - dx(t) - \psi(x(t), y(t), v(t))v(t), \tag{2.1}$$

$$\dot{y}(t) = \int_0^{h_1} \rho_1(\tau) e^{-\mu_1 \tau} \psi(x(t-\tau), y(t-\tau), v(t-\tau)) v(t-\tau) d\tau - ay(t), \tag{2.2}$$

$$\dot{v}(t) = Na \int_0^{h_2} \rho_2(\tau) e^{-\mu_2 \tau} y(t-\tau) d\tau - bz(t)v(t) - cv(t), \tag{2.3}$$

$$\dot{z}(t) = rz(t)v(t) - \mu z(t), \tag{2.4}$$

where N is the average number of virus particles generated in the lifetime of the infected cell. We assume that, the virus contacts an uninfected target cell at time $t - \tau$, the cell becomes infected at time t, where τ is linked to a probability distribution $\rho_1(\tau)$ over the time interval $[0, h_1]$ and h_1 is limit superior of this delay period. The term $e^{-\mu_1 \tau}$ represents the probability of surviving the contacted cell during the time delay interval, where μ_1 is the death rate constant of the contacted cells. In addition, we assume that, a cell infected at time $t - \tau$ starts to generate new infectious viruses at time t, where τ is linked to a probability distribution $\rho_2(\tau)$ over the time interval $[0, h_2]$ and h_2 is limit superior of this delay. The term $e^{-\mu_2 \tau}$ denotes the probability of surviving the infected cell during the time delay interval, where μ_2 is a constant. The definitions of all variables and parameters are identical to those given in Section 1. The incidence rate of infection is presented by a general function in the form $\psi(x, y, v)v$, where ψ is continuously differentiable and satisfies the following assumptions:

Assumption A1. $\psi(0, y, v) = 0$ for all $y, v \geq 0$, $\psi(x, y, v) > 0$ for all $x > 0$, $y \geq 0$, $v \geq 0$.

Assumption A2. $\dfrac{\partial \psi(x, y, v)}{\partial x} > 0$ for all $x > 0$, $y \geq 0$ and $v \geq 0$.

Assumption A3. $\dfrac{\partial \psi(x, y, v)}{\partial y} < 0$, $\dfrac{\partial \psi(x, y, v)}{\partial v} < 0$ for all $x, y, v > 0$.

Assumption A4. $\dfrac{\partial \left(\psi(x, y, v)v\right)}{\partial v} > 0$ for all $x > 0$, $y > 0$ and $v > 0$.

Let us assume that the probability distribution functions $\rho_1(\tau)$ and $\rho_2(\tau)$ satisfy $\rho_1(\tau) > 0$ and $\rho_2(\tau) > 0$, and

$$\int_0^{h_1} \rho_1(\tau) d\tau = \int_0^{h_2} \rho_2(\tau) d\tau = 1, \quad \int_0^{h_1} \rho_1(u) e^{\ell u} du < \infty, \quad \int_0^{h_2} \rho_2(u) e^{\ell u} du < \infty,$$

where $\ell > 0$. Let us denote:

$$F = \int_0^{h_1} \rho_1(\tau) e^{-\mu_1 \tau} d\tau, \qquad G = \int_0^{h_2} \rho_2(\tau) e^{-\mu_2 \tau} d\tau.$$

Thus

$$0 < F \leq 1,\ 0 < G \leq 1.$$

Let the initial conditions for system (2.1)-(2.4) be given as:

$$\begin{aligned} &x(\eta) = \zeta_1(\eta),\ y(\eta) = \zeta_2(\eta), v(\eta) = \zeta_3(\eta),\ z(\eta) = \zeta_4(\eta), \\ &\zeta_j(\eta) \geq 0,\ \eta \in [-\omega, 0),\ \ j = 1, ..., 4, \\ &\zeta_j(0) > 0,\ j = 1, ..., 4, \end{aligned} \tag{2.5}$$

where $\omega = \max\{h_1, h_2\}$, $(\zeta_1(\eta), \zeta_2(\eta), \zeta_3(\eta), \zeta_4(\eta)) \in C([-\omega, 0], \mathbb{R}^4_{\geq 0})$. We denote by $C = C([-\omega, 0], \mathbb{R}^4_{\geq 0})$ the Banach space of continuous functions mapping the interval $[-\omega, 0]$ into $\mathbb{R}^4_{\geq 0}$; with norm $\|\zeta\| = \sup_{-\omega \leq \eta \leq 0} |\zeta(\eta)|$ for $\zeta \in C$. We note that the system (2.1)-(2.4) with initial states (2.5) has a unique solution [47].

3. Non-negativity and boundedness of solutions

In this section, we show that the solutions of (2.1)-(2.4) with initial states (2.5) are non-negative and bounded.

Proposition 3.1. *Assume that Assumption A1 is satisfied. Then all solutions of (2.1)-(2.4) with initial conditions (2.5), are non-negative and ultimately bounded.*

Proof. The solution $(x(t), y(t), v(t), z(t))$ of system (2.1)-(2.4) with initial states (2.5) exists and is unique on its maximal interval of existence $[0, \gamma]$ for some $\gamma > 0$ [47]. We see that $x(t) > 0$ for all $t \in [0, \gamma]$. Indeed this follows from equation (2.1) that $\dot{x} \mid_{x=0} = s > 0$, for any $t \in [0, \gamma]$. Now from Eqs. (2.2)-(2.4) we get

$$y(t) = y(0)e^{-at} + \int_0^t e^{-a(t-\eta)} \int_0^{h_1} \rho_1(\tau) e^{-\mu_1 \tau} \psi(x(\eta - \tau), y(\eta - \tau), v(\eta - \tau)) v(\eta - \tau) d\tau d\eta,$$

$$v(t) = v(0)e^{-\int_0^t (c + bz(\xi)) d\xi} + Na \int_0^t e^{-\int_\eta^t (c + bz(\xi)) d\xi} \int_0^{h_2} \rho_2(\tau) e^{-\mu_2 \tau} y(\eta - \tau) d\tau d\eta,$$

$$z(t) = z(0)e^{-\int_0^t (\mu - rv(\xi)) d\xi},$$

which yield $y(t), v(t), z(t) \geq 0$ for all $t \in [0, \omega]$. By a recursive argument, we get that $y(t), v(t), z(t) \geq 0$ for all $t \geq 0$.

Next we prove the ultimate bound of the solutions of system (2.1)-(2.4). From equation (2.1) we get $\dot{x}(t) \leq s - dx(t)$ and thus $\limsup_{t\to\infty} x(t) \leq \frac{s}{d}$. Let $T_1(t) = \int_0^{h_1} \rho_1(\tau)e^{-\mu_1\tau}x(t-\tau)d\tau + y(t)$, then

$$\begin{aligned}
\dot{T_1}(t) &= \int_0^{h_1} \rho_1(\tau)e^{-\mu_1\tau}\left(s - dx(t-\tau) - \psi(x(t-\tau), y(t-\tau), v(t-\tau))v(t-\tau)\right)d\tau \\
&+ \int_0^{h_1} \rho_1(\tau)e^{-\mu_1\tau}\psi(x(t-\tau), y(t-\tau), v(t-\tau))v(t-\tau)d\tau - ay(t) \\
&= s\int_0^{h_1} \rho_1(\tau)e^{-\mu_1\tau}d\tau - d\int_0^{h_1} \rho_1(\tau)e^{-\mu_1\tau}x(t-\tau)d\tau - ay(t) \\
&\leq s\int_0^{h_1} \rho_1(\tau)e^{-\mu_1\tau}d\tau - \sigma_1\left(\int_0^{h_1} \rho_1(\tau)e^{-\mu_1\tau}x(t-\tau)d\tau + y(t)\right) \\
&= s\int_0^{h_1} \rho_1(\tau)e^{-\mu_1\tau}d\tau - \sigma_1 T_1(t) \leq s - \sigma_1 T_1(t),
\end{aligned}$$

where $\sigma_1 = \min\{d, a\}$. Hence $\limsup_{t\to\infty} T_1(t) \leq L_1$, where $L_1 = \dfrac{s}{\sigma_1}$. Since $\int_0^{h_1} \rho_1(\tau)e^{-\mu_1\tau}x(t-\tau)d\tau > 0$ and $y(t) \geq 0$, then $\limsup_{t\to\infty} y(t) \leq L_1$. Moreover, let $T_2(t) = v(t) + \frac{b}{r}z(t)$,

$$\begin{aligned}
\dot{T_2}(t) &= Na\int_0^{h_2} \rho_2(\tau)e^{-\mu_2\tau}y(t-\tau)d\tau - cv(t) - \frac{b\mu}{r}z(t) \\
&\leq NaL_1\int_0^{h_2} \rho_2(\tau)e^{-\mu_2\tau}d\tau - \sigma_2(v(t) + \frac{b}{r}z(t)) \\
&= NaL_1\int_0^{h_2} \rho_2(\tau)e^{-\mu_2\tau}d\tau - \sigma_2 T_2(t) \leq NaL_1 - \sigma_2 T_2(t),
\end{aligned}$$

where $\sigma_2 = \min\{c, \mu\}$. It follows that, $\limsup_{t\to\infty} T_2(t) \leq L_2$, where $L_2 = \dfrac{NaL_1}{\sigma_2}$. Since $v(t)$ and $z(t)$ are non-negative, $\limsup_{t\to\infty} v(t) \leq L_2$ and $\limsup_{t\to\infty} z(t) \leq L_3$, where $L_3 = \frac{r}{b}L_2$. Therefore, all the state variables of the system are ultimately bounded. □

4. THE EQUILIBRIA AND THRESHOLD PARAMETERS

At any equilibrium we have

$$s - dx - \psi(x, y, v)v = 0, \tag{4.1}$$

$$F\psi(x, y, v)v - ay = 0, \tag{4.2}$$

$$NaGy - bzv - cv = 0, \tag{4.3}$$

$$(rv - \mu)\, z = 0. \tag{4.4}$$

From equation (4.4), either $z = 0$ or $z \neq 0$. If $z = 0$, then from Eqs. (4.1)-(4.3) we get

$$y = \frac{F(s - dx)}{a} = \frac{c}{NaG}v, \qquad v = \frac{NFG(s - dx)}{c}. \tag{4.5}$$

Substituting from equation (4.5) into equation (4.2) we get:

$$\left[\psi\left(x, \frac{F(s - dx)}{a}, \frac{NFG(s - dx)}{c}\right) - \frac{c}{NFG}\right] v = 0. \tag{4.6}$$

equation (4.6) has two possible solutions $v = 0$ or $v \neq 0$. If $v = 0$, then from Eqs. (4.1) and (4.2), we get $x = s/d$ and $y = 0$ which leads to the infection-free equilibrium $E_0(x_0, 0, 0, 0)$ where $x_0 = s/d$. If $v \neq 0$, then we have

$$\psi\left(x, \frac{F(s - dx)}{a}, \frac{NFG(s - dx)}{c}\right) - \frac{c}{NFG} = 0.$$

Let

$$\Phi_1(x) = \psi\left(x, \frac{F(s - dx)}{a}, \frac{NFG(s - dx)}{c}\right) - \frac{c}{NFG} = 0,$$

then, we have

$$\Phi_1'(x) = \frac{\partial \psi}{\partial x} - \frac{Fd}{a}\frac{\partial \psi}{\partial y} - \frac{NFGd}{c}\frac{\partial \psi}{\partial v}.$$

Because of Assumptions A2 and A3, we have $\Phi_1'(x) > 0$ which implies that function $\Phi_1(x)$ is strictly increasing function of x. Moreover,

$$\Phi_1(0) = \psi\left(0, \frac{Fs}{a}, \frac{NFGs}{c}\right) - \frac{c}{NFG} = -\frac{c}{NFG} < 0,$$

$$\Phi_1(x_0) = \psi(x_0, 0, 0) - \frac{c}{NFG} = \frac{c}{NFG}\left(\frac{NFG\psi(x_0, 0, 0)}{c} - 1\right).$$

Therefore, if $\dfrac{NFG\psi(x_0, 0, 0)}{c} > 1$, then there exists a unique $x_1 \in (0, x_0)$ such that $\Phi_1(x_1) = 0$. It follows from equation (4.5) that $y_1 = \dfrac{Fd(x_0 - x_1)}{a} > 0$ and $v_1 = \dfrac{NFGd(x_0 - x_1)}{c} > 0$. Therefore, a chronic-infection equilibrium without antibody immune response $E_1(x_1, y_1, v_1, 0)$ exists when $\dfrac{NFG\psi(x_0, 0, 0)}{c} > 1$. Let us define the basic infection reproduction number as:

$$R_0 = \frac{NFG\psi\left(x_0, 0, 0\right)}{c}.$$

The parameter R_0 determines whether a chronic-infection can be established. The other possibility of equation (4.4) is $z \neq 0$ which leads to $v_2 = \dfrac{\mu}{r}$. From equation (4.1) we let

$$\Phi_2(x) = s - dx - \psi(x, \frac{F(s-dx)}{a}, v_2)v_2 = 0.$$

According to Assumptions A2 and A3, we know that Φ_2 is a strictly decreasing function of x. Clearly, $\Phi_2(0) = s > 0$ and $\Phi_2(x_0) = -\psi(x_0, 0, v_2)v_2 < 0$. Thus, there exists a unique $x_2 \in (0, x_0)$ such that $\Phi_2(x_2) = 0$. It follows from Eqs. (4.3) and (4.5) that, $y_2 = \dfrac{Fd\left(x_0 - x_2\right)}{a} > 0$ and

$$z_2 = \frac{NFG\psi(x_2, y_2, v_2)}{b} - \frac{c}{b} = \frac{c}{b}\left(\frac{NFG\psi(x_2, y_2, v_2)}{c} - 1\right).$$

Then, if $\dfrac{NFG\psi(x_2, y_2, v_2)}{c} > 1$ then $z_2 > 0$. Now we define the antibody immune response activation number as:

$$R_1 = \frac{NFG\psi(x_2, y_2, v_2)}{c},$$

which determines whether a persistent antibody immune response can be established. Hence, z_2 can be rewritten as $z_2 = \dfrac{c}{b}(R_1 - 1)$. It follows that, there exists a chronic-infection equilibrium with antibody immune response $E_2(x_2, y_2, v_2, z_2)$ when $R_1 > 1$.

Clearly from Assumptions A2 and A3, we have

$$R_1 = \frac{NFG\psi(x_2, y_2, v_2)}{c} < \frac{NFG\psi(x_0, y_2, v_2)}{c} < \frac{NFG\psi(x_0, 0, 0)}{c} = R_0.$$

5. GLOBAL STABILITY ANALYSIS

In this subsection, we give proofs of the global asymptotic stability of the three equilibria of model (2.1)-(2.4) by using direct Lyapunov method and applying LaSalle's invariance principle. Let us define the function $H : (0, \infty) \to [0, \infty)$ as

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

Theorem 5.1. *Let Assumptions A1-A3 be hold true and $R_0 \leq 1$, then the infection-free equilibrium E_0 is globally asymptotically stable (GAS).*

Proof. We construct a Lyapunov functional as:

$$\begin{aligned} U_0 = NFG \Bigg[& x - x_0 - \int_{x_0}^{x} \frac{\psi(x_0,0,0)}{\psi(\eta,0,0)} d\eta + \frac{1}{F} y \\ & + \frac{1}{F} \int_0^{h_1} \rho_1(\tau) e^{-\mu_1 \tau} \int_0^{\tau} \psi(x(t-\eta), y(t-\eta), v(t-\eta)) v(t-\eta) d\eta d\tau \\ & + \frac{a}{FG} \int_0^{h_2} \rho_2(\tau) e^{-\mu_2 \tau} \int_0^{\tau} y(t-\eta) d\eta d\tau \Bigg] + v + \frac{b}{r} z. \end{aligned} \tag{5.1}$$

We calculate $\frac{dU_0}{dt}$ along the solutions of model (2.1)-(2.4) as:

$$\begin{aligned} \frac{dU_0}{dt} = NFG \Bigg[& \left(1 - \frac{\psi(x_0,0,0)}{\psi(x,0,0)}\right) (s - dx - \psi(x,y,v)\, v) \\ & + \frac{1}{F} \int_0^{h_1} \rho_1(\tau) e^{-\mu_1 \tau} \psi(x(t-\tau), y(t-\tau), v(t-\tau)) v(t-\tau) d\tau - \frac{a}{F} y \\ & + \frac{1}{F} \int_0^{h_1} \rho_1(\tau) e^{-\mu_1 \tau} \left(\psi(x,y,v) v - \psi(x(t-\tau), y(t-\tau), v(t-\tau)) v(t-\tau)\right) d\tau \\ & + \frac{a}{FG} \int_0^{h_2} \rho_2(\tau) e^{-\mu_2 \tau} (y - y(t-\tau)) d\tau \Bigg] + Na \int_0^{h_2} \rho_2(\tau) e^{-\mu_2 \tau} y(t-\tau) d\tau \\ & - bzv - cv + bzv - \frac{b\mu}{r} z \\ = {} & NFGs \left(1 - \frac{x}{x_0}\right) \left(1 - \frac{\psi(x_0,0,0)}{\psi(x,0,0)}\right) + \left(NFG\psi(x,y,v) \frac{\psi(x_0,0,0)}{\psi(x,0,0)} - c\right) v - \frac{b\mu}{r} z \\ = {} & NFGs \left(1 - \frac{x}{x_0}\right) \left(1 - \frac{\psi(x_0,0,0)}{\psi(x,0,0)}\right) + c \left(R_0 \frac{\psi(x,y,v)}{\psi(x,0,0)} - 1\right) v - \frac{b\mu}{r} z. \end{aligned} \tag{5.2}$$

From Assumptions A2-A3 we know that $\psi(x,y,v)$ is a strictly increasing function of x and a strictly decreasing function of y and v. Then, the first term of equation (5.2) is less than or equal zero and

$$\psi(x,y,v) < \psi(x,0,0), \quad x,y,v > 0$$

It follows that

$$\frac{dU_0}{dt} \leq NFGs \left(1 - \frac{x}{x_0}\right) \left(1 - \frac{\psi(x_0,0,0)}{\psi(x,0,0)}\right) + c\,(R_0 - 1)\, v - \frac{b\mu}{r} z. \tag{5.3}$$

Therefore, if $R_0 \leq 1$, then $\frac{dU_0}{dt} \leq 0$ for all $x, y, v, z > 0$. Hence, solutions of system (2.1)-(2.4) with (2.5) limited to M, the largest invariant subset of $\left\{ \frac{dU_0}{dt} = 0 \right\}$ [47]. 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. By the above discussion each element of M satisfies $v(t) = 0$ and $z(t) = 0$. Then, from equation (2.3)

$$\dot{v}(t) = 0 = Na \int_0^{h_2} \rho_2(\tau) e^{-\mu_2 \tau} y(t-\tau) d\tau.$$

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

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

Assumption A5.

$$\left(1 - \frac{\psi(x,y,v)}{\psi(x,y_i,v_i)}\right)\left(\frac{\psi(x,y_i,v_i)}{\psi(x,y,v)} - \frac{v}{v_i}\right) \leq 0, \ i = 1,2 \text{ for all } x, y, v > 0.$$

Theorem 5.2. *Let Assumptions A1-A5 be hold true and $R_1 \leq 1 < R_0$, then the chronic-infection equilibrium without antibody immune response E_1 is GAS.*

Proof. Define

$$\begin{aligned} U_1 = NFG \Bigg[& x - x_1 - \int_{x_1}^{x} \frac{\psi(x_1,y_1,v_1)}{\psi(\eta,y_1,v_1)} d\eta + \frac{1}{F} y_1 H\left(\frac{y}{y_1}\right) \\ & + \frac{\psi(x_1,y_1,v_1)v_1}{F} \int_0^{h_1} \rho_1(\tau) e^{-\mu_1 \tau} \int_0^{\tau} H\left(\frac{\psi\left(x(t-\eta), y(t-\eta), v(t-\eta)\right) v(t-\eta)}{\psi(x_1,y_1,v_1)v_1}\right) d\eta d\tau \\ & + \frac{a y_1}{FG} \int_0^{h_2} \rho_2(\tau) e^{-\mu_2 \tau} \int_0^{\tau} H\left(\frac{y(t-\eta)}{y_1}\right) d\eta d\tau \Bigg] + v_1 H\left(\frac{v}{v_1}\right) + \frac{b}{r} z. \end{aligned} \tag{5.4}$$

Calculating the time derivative of U_1 along the trajectories of system (2.1)-(2.4), we obtain

$$\begin{aligned}
\frac{dU_1}{dt} &= NFG\left[\left(1-\frac{\psi(x_1,y_1,v_1)}{\psi(x,y_1,v_1)}\right)(s-dx-\psi(x,y,v)\,v)\right.\\
&+\frac{1}{F}\left(1-\frac{y_1}{y}\right)\left(\int_0^{h_1}\rho_1(\tau)e^{-\mu_1\tau}\psi(x(t-\tau),y(t-\tau),v(t-\tau))v(t-\tau)d\tau-ay\right)\\
&+\frac{1}{F}\int_0^{h_1}\rho_1(\tau)e^{-\mu_1\tau}\left(\psi(x,y,v)v-\psi(x(t-\tau),y(t-\tau),v(t-\tau))v(t-\tau)\right.\\
&\left.\left.+\psi(x_1,y_1,v_1)v_1\ln\left(\frac{\psi(x(t-\tau),y(t-\tau),v(t-\tau))v(t-\tau)}{\psi(x,y,v)v}\right)\right)d\tau\right.\\
&\left.+\frac{a}{FG}\int_0^{h_2}\rho_2(\tau)e^{-\mu_2\tau}\left(y-y(t-\tau)+y_1\ln\left(\frac{y(t-\tau)}{y}\right)\right)d\tau\right]\\
&+\left(1-\frac{v_1}{v}\right)\left(Na\int_0^{h_2}\rho_2(\tau)e^{-\mu_2\tau}y(t-\tau)d\tau-cv-bvz\right)+bvz-\frac{b\mu}{r}z\\
&=NFG\left[\left(1-\frac{\psi(x_1,y_1,v_1)}{\psi(x,y_1,v_1)}\right)(s-dx)+\frac{\psi(x_1,y_1,v_1)\psi(x,y,v)v}{\psi(x,y_1,v_1)}\right.\\
&-\frac{1}{F}\frac{y_1}{y}\int_0^{h_1}\rho_1(\tau)e^{-\mu_1\tau}\psi(x(t-\tau),y(t-\tau),v(t-\tau))v(t-\tau)d\tau+\frac{a}{F}y_1\\
&+\frac{\psi(x_1,y_1,v_1)v_1}{F}\int_0^{h_1}\rho_1(\tau)e^{-\mu_1\tau}\ln\left(\frac{\psi(x(t-\tau),y(t-\tau),v(t-\tau))v(t-\tau)}{\psi(x,y,v)v}\right)d\tau\\
&\left.+\frac{ay_1}{FG}\int_0^{h_2}\rho_2(\tau)e^{-\mu_2\tau}\ln\left(\frac{y(t-\tau)}{y}\right)d\tau\right]-cv\\
&-\frac{v_1}{v}Na\int_0^{h_2}\rho_2(\tau)e^{-\mu_2\tau}y(t-\tau)d\tau+cv_1+bv_1z-\frac{b\mu}{r}z. \qquad (5.5)
\end{aligned}$$

Using the equilibrium conditions for E_1:

$$s=dx_1+\frac{a}{F}y_1,\quad F\psi(x_1,y_1,v_1)v_1=ay_1,\quad cv_1=NaGy_1,$$

we obtain

$$\begin{aligned}\frac{dU_1}{dt} &= NFG\left[dx_1\left(1-\frac{x}{x_1}\right)\left(1-\frac{\psi(x_1,y_1,v_1)}{\psi(x,y_1,v_1)}\right)+\frac{a}{F}y_1\right.\\ &\quad -\frac{a}{F}y_1\frac{\psi(x_1,y_1,v_1)}{\psi(x,y_1,v_1)}+\frac{a}{F}y_1\frac{\psi(x,y,v)v}{\psi(x,y_1,v_1)v_1}\\ &\quad -\frac{a}{F^2}y_1\int_0^{h_1}\rho_1(\tau)e^{-\mu_1\tau}\frac{y_1\psi(x(t-\tau),y(t-\tau),v(t-\tau))v(t-\tau)}{y\psi(x_1,y_1,v_1)v_1}d\tau+2\frac{a}{F}y_1\\ &\quad +\frac{a}{F^2}y_1\int_0^{h_1}\rho_1(\tau)e^{-\mu_1\tau}\ln\left(\frac{\psi(x(t-\tau),y(t-\tau),v(t-\tau))v(t-\tau)}{\psi(x,y,v)v}\right)d\tau\\ &\quad +\frac{ay_1}{FG}\int_0^{h_2}\rho_2(\tau)e^{-\mu_2\tau}\ln\left(\frac{y(t-\tau)}{y}\right)d\tau\\ &\quad \left.-\frac{ay_1}{FG}\int_0^{h_2}\rho_2(\tau)e^{-\mu_2\tau}\frac{v_1y(t-\tau)}{vy_1}d\tau-\frac{a}{F}y_1\frac{v}{v_1}\right]\\ &\quad +b\left(v_1-\frac{\mu}{r}\right)z. \end{aligned} \tag{5.6}$$

Using the following equalities:

$$\begin{aligned}&\ln\left(\frac{\psi(x(t-\tau),y(t-\tau),v(t-\tau))v(t-\tau)}{\psi(x,y,v)v}\right)\\ &\qquad=\ln\left(\frac{y_1\psi(x(t-\tau),y(t-\tau),v(t-\tau))v(t-\tau)}{y\psi(x_1,y_1,v_1)v_1}\right)\\ &\qquad\quad+\ln\left(\frac{\psi(x_1,y_1,v_1)}{\psi(x,y_1,v_1)}\right)+\ln\left(\frac{\psi(x,y_1,v_1)}{\psi(x,y,v)}\right)+\ln\left(\frac{v_1y}{vy_1}\right),\\ &\ln\left(\frac{y(t-\tau)}{y}\right)=\ln\left(\frac{vy_1}{v_1y}\right)+\ln\left(\frac{v_1y(t-\tau)}{vy_1}\right),\end{aligned}$$

we get

$$\begin{aligned}\frac{dU_1}{dt} &= NFG\left[dx_1\left(1-\frac{x}{x_1}\right)\left(1-\frac{\psi(x_1,y_1,v_1)}{\psi(x,y_1,v_1)}\right)-\frac{ay_1}{F}\left(\frac{\psi(x_1,y_1,v_1)}{\psi(x,y_1,v_1)}-1\right.\right.\\ &\quad\left.-\ln\left(\frac{\psi(x_1,y_1,v_1)}{\psi(x,y_1,v_1)}\right)\right)+\frac{ay_1}{F}\left(\frac{\psi(x,y,v)v}{\psi(x,y_1,v_1)v_1}-\frac{v}{v_1}-1+\frac{\psi(x,y_1,v_1)}{\psi(x,y,v)}\right)\\ &\quad-\frac{ay_1}{F}\left(\frac{\psi(x,y_1,v_1)}{\psi(x,y,v)}-1-\ln\left(\frac{\psi(x,y_1,v_1)}{\psi(x,y,v)}\right)\right)\\ &\quad-\frac{ay_1}{F^2}\int_0^{h_1}\rho_1(\tau)e^{-\mu_1\tau}\left(\frac{y_1\psi(x(t-\tau),y(t-\tau),v(t-\tau))v(t-\tau)}{y\psi(x_1,y_1,v_1)v_1}-1\right.\\ &\quad\left.-\ln\left(\frac{y_1\psi(x(t-\tau),y(t-\tau),v(t-\tau))v(t-\tau)}{y\psi(x_1,y_1,v_1)v_1}\right)\right)d\tau\\ &\quad-\frac{ay_1}{FG}\int_0^{h_2}\rho_2(\tau)e^{-\mu_2\tau}\left(\frac{v_1y(t-\tau)}{vy_1}-1-\ln\left(\frac{v_1y(t-\tau)}{vy_1}\right)\right)d\tau\Bigg]+b\left(v_1-\frac{\mu}{r}\right)z.\end{aligned} \tag{5.7}$$

equation (5.7) can be simplified as:

$$\begin{aligned}\frac{dU_1}{dt} &= NFG\left[dx_1\left(1-\frac{x}{x_1}\right)\left(1-\frac{\psi(x_1,y_1,v_1)}{\psi(x,y_1,v_1)}\right)\right.\\ &\quad+\frac{ay_1}{F}\left(1-\frac{\psi(x,y,v)}{\psi(x,y_1,v_1)}\right)\left(\frac{\psi(x,y_1,v_1)}{\psi(x,y,v)}-\frac{v}{v_1}\right)\\ &\quad-\frac{ay_1}{F}H\left(\frac{\psi(x_1,y_1,v_1)}{\psi(x,y_1,v_1)}\right)-\frac{ay_1}{F}H\left(\frac{\psi(x,y_1,v_1)}{\psi(x,y,v)}\right)\\ &\quad-\frac{ay_1}{F^2}\int_0^{h_1}\rho_1(\tau)e^{-\mu_1\tau}H\left(\frac{y_1\psi(x(t-\tau),y(t-\tau),v(t-\tau))v(t-\tau)}{y\psi(x_1,y_1,v_1)v_1}\right)d\tau\\ &\quad\left.-\frac{ay_1}{FG}\int_0^{h_2}\rho_2(\tau)e^{-\mu_2\tau}H\left(\frac{v_1y(t-\tau)}{vy_1}\right)d\tau\right]+b\left(v_1-\frac{\mu}{r}\right)z.\end{aligned} \tag{5.8}$$

From Assumptions A1 and A5, we get that the first and second terms of equation (5.8) are less than or equal zero. Now we show that if $R_1 \leq 1$ then $v_1 \leq \frac{\mu}{r} = v_2$. Let $R_0 > 1$, then we want to show that

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

From Assumptions A2-A4, for $x_1, x_2, y_1, y_2, v_1, v_2 > 0$, we have

$$(\psi(x_2, y_2, v_2) - \psi(x_1, y_2, v_2))(x_2 - x_1) > 0, \tag{5.9}$$

$$(\psi(x_1,y_1,v_1)-\psi(x_1,y_2,v_1))(y_2-y_1)>0, \tag{5.10}$$

$$(\psi(x_1,y_1,v_1)-\psi(x_1,y_1,v_2))(v_2-v_1)>0, \tag{5.11}$$

$$(\psi(x_2,y_2,v_2)v_2-\psi(x_2,y_2,v_1)v_1)(v_2-v_1)>0. \tag{5.12}$$

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 have

$$\begin{aligned}(s-dx_2)-(s-dx_1)&=\psi(x_2,y_2,v_2)v_2-\psi(x_1,y_1,v_1)v_1\\&=\frac{a}{F}(y_2-y_1).\end{aligned} \tag{5.13}$$

Then

$$sgn\,(x_2-x_1)=sgn\,(y_1-y_2)\,. \tag{5.14}$$

Moreover,

$$\begin{aligned}(s-dx_2)-(s-dx_1)&=\psi(x_2,y_2,v_2)v_2-\psi(x_1,y_1,v_1)v_1\\&=(\psi(x_2,y_2,v_2)v_2-\psi(x_2,y_2,v_1)v_1)+(\psi(x_2,y_2,v_1)v_1\\&-\psi(x_1,y_2,v_1)v_1)+(\psi(x_1,y_2,v_1)v_1-\psi(x_1,y_1,v_1)v_1).\end{aligned}$$

Therefore, from Eqs. (5.9)-(5.14) we get:

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

which leads to contradiction. Thus, $sgn\,(x_2-x_1)=sgn\,(v_1-v_2)$. Using the equilibrium conditions for E_1 we have $\frac{NFG\psi(x_1,y_1,v_1)}{c}=1$, then

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

We get $sgn(R_1-1)=sgn(v_1-v_2)$. Hence, if $R_0>1$, then $x_1,y_1,v_1>0$, and if $R_1\le 1$, then $v_1\le v_2=\frac{\mu}{r}$. It follows from the above discussion that $\frac{dU_1}{dt}\le 0$ for all $x,y,v,z>0$. The solutions of model (2.1)-(2.4) converge to Ω, the largest invariant subset of $\left\{(x,y,v,z):\frac{dU_1}{dt}=0\right\}$[47]. We have $\frac{dU_1}{dt}=0$ iff $x=x_1,v=v_1,z=0$ and $H=0$ i.e.

$$\frac{y_1\psi(x(t-\tau),y(t-\tau),v(t-\tau))v(t-\tau)}{y\psi(x_1,y_1,v_1)v_1}=\frac{v_1y(t-\tau)}{vy_1}=1 \text{ for all } \tau\in[0,\omega]. \tag{5.15}$$

From equation (5.15), if $v=v_1$ then $y=y_1$ and hence $\frac{dU_1}{dt}=0$ at E_1. So Ω contains a unique point, that is E_1. Thus, the global asymptotic stability of the chronic-infection equilibrium without antibody immune response E_1 follows from LaSalle's invariance principle. □

In the following we consider the global asymptotic stability of the chronic-infection equilibrium with antibody immune response E_2.

Theorem 5.3. *Let Assumptions A1-A5 be hold true and $R_1>1$, then E_2 is GAS.*

Proof. We construct a Lyapunov functional in the form:

$$
\begin{aligned}
U_2 = NFG \Bigg[& x - x_2 - \int_{x_2}^{x} \frac{\psi(x_2, y_2, v_2)}{\psi(\eta, y_2, v_2)} d\eta + \frac{1}{F} y_2 H\left(\frac{y}{y_2}\right) \\
& + \frac{\psi(x_2, y_2, v_2) v_2}{F} \int_0^{h_1} \rho_1(\tau) e^{-\mu_1 \tau} \int_0^{\tau} H\left(\frac{\psi\left(x(t-\eta), y(t-\eta), v(t-\eta)\right) v(t-\eta)}{\psi(x_2, y_2, v_2) v_2}\right) d\eta d\tau \\
& + \frac{a y_2}{FG} \int_0^{h_2} \rho_2(\tau) e^{-\mu_2 \tau} \int_0^{\tau} H\left(\frac{y(t-\eta)}{y_2}\right) d\eta d\tau \Bigg] \\
& + v_2 H\left(\frac{v}{v_2}\right) + \frac{b}{r} z_2 H\left(\frac{z}{z_2}\right). \qquad (5.16)
\end{aligned}
$$

Function U_2 satisfies:

$$
\begin{aligned}
\frac{dU_2}{dt} = NFG \Bigg[& \left(1 - \frac{\psi(x_2, y_2, v_2)}{\psi(x, y_2, v_2)}\right) (s - dx - \psi(x, y, v) v) \\
& + \frac{1}{F} \left(1 - \frac{y_2}{y}\right) \left(\int_0^{h_1} \rho_1(\tau) e^{-\mu_1 \tau} \psi(x(t-\tau), y(t-\tau), v(t-\tau)) v(t-\tau) d\tau - a y \right) \\
& + \frac{1}{F} \int_0^{h_1} \rho_1(\tau) e^{-\mu_1 \tau} \left(\psi(x, y, v) v - \psi(x(t-\tau), y(t-\tau), v(t-\tau)) v(t-\tau) \right. \\
& \left. + \psi(x_2, y_2, v_2) v_2 \ln\left(\frac{\psi(x(t-\tau), y(t-\tau), v(t-\tau)) v(t-\tau)}{\psi(x, y, v) v}\right)\right) d\tau \\
& + \frac{a}{FG} \int_0^{h_2} \rho_2(\tau) e^{-\mu_2 \tau} \left(y - y(t-\tau) + y_2 \ln\left(\frac{y(t-\tau)}{y}\right)\right) d\tau \Bigg] \\
& + \left(1 - \frac{v_2}{v}\right) \left(N a \int_0^{h_2} \rho_2(\tau) e^{-\mu_2 \tau} y(t-\tau) d\tau - b z v - c v \right) \\
& + \left(1 - \frac{z_2}{z}\right) \left(b z v - \frac{b \mu}{r} z \right). \qquad (5.17)
\end{aligned}
$$

Collecting terms of equation (5.17) and applying $s = dx_2 + \frac{a}{F}y_2$, we get

$$\begin{aligned}\frac{dU_2}{dt} &= NFG\left[d(x_2-x)\left(1-\frac{\psi(x_2,y_2,v_2)}{\psi(x,y_2,v_2)}\right)+\frac{a}{F}y_2-\frac{a}{F}y_2\frac{\psi(x_2,y_2,v_2)}{\psi(x,y_2,v_2)}\right.\\
&+\psi(x,y,v)v\frac{\psi(x_2,y_2,v_2)}{\psi(x,y_2,v_2)}-\frac{1}{F}\psi(x_2,y_2,v_2)v_2\int_0^{h_1}\left(\rho_1(\tau)e^{-\mu_1\tau}\right.\\
&\left.\left.\frac{y_2\psi(x(t-\tau),y(t-\tau),v(t-\tau))v(t-\tau)}{y\psi(x_2,y_2,v_2)v_2}\right)d\tau+\frac{a}{F}y_2\right.\\
&+\frac{\psi(x_2,y_2,v_2)v_2}{F}\int_0^{h_1}\rho_1(\tau)e^{-\mu_1\tau}\ln\left(\frac{\psi(x(t-\tau),y(t-\tau),v(t-\tau))v(t-\tau)}{\psi(x,y,v)v}\right)d\tau\\
&\left.+\frac{ay_2}{FG}\int_0^{h_2}\rho_2(\tau)e^{-\mu_2\tau}\ln\left(\frac{y(t-\tau)}{y}\right)d\tau-\frac{ay_2}{FG}\int_0^{h_2}\rho_2(\tau)e^{-\mu_2\tau}\frac{v_2y(t-\tau)}{vy_2}d\tau\right]\\
&-cv+cv_2+bv_2z-bvz_2-\frac{b\mu}{r}z+\frac{b\mu}{r}z_2. \qquad (5.18)\end{aligned}$$

By using the equilibrium conditions of E_2

$$F\psi(x_2,y_2,v_2)v_2 = ay_2, \quad cv_2 = NaGy_2 - bv_2z_2, \quad \mu = rv_2,$$

and the following equalities

$$\begin{aligned}cv &= cv_2\frac{v}{v_2} = (NaGy_2 - bv_2z_2)\frac{v}{v_2},\\
\ln\left(\frac{\psi(x(t-\tau),y(t-\tau),v(t-\tau))v(t-\tau)}{\psi(x,y,v)v}\right)&\\
&= \ln\left(\frac{y_2\psi(x(t-\tau),y(t-\tau),v(t-\tau))v(t-\tau)}{y\psi(x_2,y_2,v_2)v_2}\right)\\
&+\ln\left(\frac{\psi(x_2,y_2,v_2)}{\psi(x,y_2,v_2)}\right)+\ln\left(\frac{\psi(x,y_2,v_2)}{\psi(x,y,v)}\right)\\
&+\ln\left(\frac{v_2y}{vy_2}\right),\\
\ln\left(\frac{y(t-\tau)}{y}\right) &= \ln\left(\frac{vy_2}{v_2y}\right)+\ln\left(\frac{v_2y(t-\tau)}{vy_2}\right),\end{aligned}$$

we obtain

$$\begin{aligned}\frac{dU_2}{dt} &= NFG\left[d(x_2-x)\left(1-\frac{\psi(x_2,y_2,v_2)}{\psi(x,y_2,v_2)}\right)+\frac{ay_2}{F}\left(\frac{\psi(x,y,v)v}{\psi(x,y_2,v_2)v_2}\right.\right.\\ &+\frac{\psi(x,y_2,v_2)}{\psi(x,y,v)}-\frac{v}{v_2}-1\Big)-\frac{ay_2}{F}\left(\frac{\psi(x,y_2,v_2)}{\psi(x,y,v)}-1-\ln\left(\frac{\psi(x,y_2,v_2)}{\psi(x,y,v)}\right)\right)\\ &-\frac{ay_2}{F}\left(\frac{\psi(x_2,y_2,v_2)}{\psi(x,y_2,v_2)}-1-\ln\left(\frac{\psi(x_2,y_2,v_2)}{\psi(x,y_2,v_2)}\right)\right)\\ &-\frac{ay_2}{F^2}\int_0^{h_1}\rho_1(\tau)e^{-\mu_1\tau}\left(\frac{y_2\psi(x(t-\tau),y(t-\tau),v(t-\tau))v(t-\tau)}{y\psi(x_2,y_2,v_2)v_2}-1\right.\\ &\left.-\ln\left(\frac{y_2\psi(x(t-\tau),y(t-\tau),v(t-\tau))v(t-\tau)}{y\psi(x_2,y_2,v_2)v_2}\right)\right)d\tau\\ &-\frac{ay_2}{FG}\int_0^{h_2}\rho_2(\tau)e^{-\mu_2\tau}\left(\frac{v_2y(t-\tau)}{vy_2}-1-\ln\left(\frac{v_2y(t-\tau)}{vy_2}\right)\right)d\tau\Bigg]. \end{aligned}\tag{5.19}$$

We can rewrite equation (5.19) as

$$\begin{aligned}\frac{dU_2}{dt} &= NFG\left[dx_2\left(1-\frac{x}{x_2}\right)\left(1-\frac{\psi(x_2,y_2,v_2)}{\psi(x,y_2,v_2)}\right)+\frac{ay_2}{F}\left(1-\frac{\psi(x,y,v)}{\psi(x,y_2,v_2)}\right)\right.\\ &\left(\frac{\psi(x,y_2,v_2)}{\psi(x,y,v)}-\frac{v}{v_2}\right)-\frac{ay_2}{F}H\left(\frac{\psi(x_2,y_2,v_2)}{\psi(x,y_2,v_2)}\right)-\frac{ay_2}{F}H\left(\frac{\psi(x,y_2,v_2)}{\psi(x,y,v)}\right)\\ &-\frac{ay_2}{F^2}\int_0^{h_1}\rho_1(\tau)e^{-\mu_1\tau}H\left(\frac{y_2\psi(x(t-\tau),y(t-\tau),v(t-\tau))v(t-\tau)}{y\psi(x_2,y_2,v_2)v_2}\right)d\tau\\ &\left.-\frac{ay_2}{FG}\int_0^{h_2}\rho_2(\tau)e^{-\mu_2\tau}H\left(\frac{v_2y(t-\tau)}{vy_2}\right)d\tau\right]. \end{aligned}\tag{5.20}$$

We note that from Assumptions A2 and A5, the first and second terms of equation (5.20) are less than or equal zero. Noting that $x,y,v,z>0$, we have that $\frac{dU_2}{dt}\leq 0$. The solutions of model (2.1)-(2.4) converge to Ω, the largest invariant subset of $\left\{(x,y,v,z):\frac{dU_2}{dt}=0\right\}$[47]. We have $\frac{dU_2}{dt}=0$ if and only if $x=x_2, v=v_2$ and $H=0$ i.e.,

$$\frac{y_2\psi(x(t-\tau),y(t-\tau),v(t-\tau))v(t-\tau)}{y\psi(x_2,y_2,v_2)v_2}=\frac{v_2y(t-\tau)}{vy_2}=1 \text{ for all } \tau\in[0,\omega].\tag{5.21}$$

This yields that $y=y_2$ for all $\tau\in[0,\omega]$. Therefore, if $v=v_2$ and $y=y_2$, then from equation (2.3) we have $0=ky_2-bzv_2-cv_2$ which gives $z=z_2$. Therefore, $\frac{dU_2}{dt}=0$ at E_2. The global

asymptotic stability of the chronic-infection equilibrium with antibody immune response E_2 follows from LaSalle's invariance principle. □

6. Conclusion

In this paper, we have proposed a viral infection model with general incidence rate function and antibody immune response. Two types of distributed time delays have been incorporated into the model to describe the time needed for the virus enters the target cell and the emission of new infectious viruses. We have derived a set of conditions on the general functional response and have determined two threshold parameters R_0 and R_1 to prove the existence and the global stability of the model's equilibria. The global asymptotic stability of the three equilibria, infection-free, chronic-infection without antibody immune response and chronic-infection with antibody immune response has been proven by using direct Lyapunov method and LaSalle's invariance principle.

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