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Research Article

Stability of Virus Infection Models with Antibodies and Chronically Infected Cells

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Two virus infection models with antibody immune response and chronically infected cells are proposed and analyzed. Bilinear incidence rate is considered in the first model, while the incidence rate is given by a saturated functional response in the second one. One main feature of these models is that it includes both short-lived infected cells and chronically infected cells. The chronically infected cells produce much smaller amounts of virus than the short-lived infected cells and die at a much slower rate. Our mathematical analysis establishes that the global dynamics of the two models are determined by two threshold parameters R_0 and R_1. By constructing Lyapunov functions and using LaSalle's invariance principle, we have established the global asymptotic stability of all steady states of the models. We have proven that, the uninfected steady state is globally asymptotically stable (GAS) if $R_0 < 1$, the infected steady state without antibody immune response exists and it is GAS if $R_1 < 1 < R_0$, and the infected steady state with antibody immune response exists and it is GAS if $R_1 > 1$. We check our theorems with numerical simulation in the end.

1. Introduction

In recent years, many mathematical models have been proposed to study the dynamics of viral infections such as the human immunodeficiency virus (HIV), the hepatitis C virus (HCV), and the hepatitis B virus (HBV) (see, e.g., [1–17]). Such virus infection models can be very useful in the control of epidemic diseases and provide insights into the dynamics of viral load in vivo. Therefore, mathematical analysis of the virus infection models can play a significant role in the development of a better understanding of diseases and various drug therapy strategies. Most of the mathematical models of viral infection presented in the literature did not differentiate between the short-lived infected cells and chronically infected cells. The chronically infected cells produce much smaller amounts of virus than the short-lived infected cells and die at a much slower rate [18]. The virus dynamics model with chronically infected cells and under the effect of antiviral drug therapy was introduced in [18] as

$$\begin{aligned}
\dot{T} &= \lambda - dT - (1-\varepsilon)\,kTV,\\
\dot{T}^* &= (1-\alpha)(1-\varepsilon)\,kTV - \delta T^*,\\
\dot{C}^* &= \alpha(1-\varepsilon)\,kTV - aC^*,\\
\dot{V} &= N_T\delta T^* + N_C aC^* - cV,
\end{aligned} \tag{1}$$

where T, T^*, C^*, and V are the concentration of the uninfected cells, short-lived infected cells, chronically infected cells, and free virus particles, respectively. The constant λ is the rate at which new uninfected cells are generated and d is the natural death rate constant of uninfected cells. k is the infection rate constant. The fractions $(1-\alpha)$ and α with $0 < \alpha < 1$ are the probabilities that, upon infection, an uninfected cell will become either short-lived infected or chronically infected. δ and a are the death rate constants of the short-lived infected cells and chronically infected cells, respectively. N_T and N_C are the average number of virions produced in the lifetime of the short-lived infected and chronically infected cells, respectively. The chronically infected cells produce much smaller amounts of virus than the short-lived infected cells and die at a much slower rate (i.e., $N_T > N_C$ and $\delta > a$). The free viruses are cleared with rate constant c. The drug efficacy is denoted by ε and $0 \le \varepsilon \le 1$.

It is observed that the basic and global properties of model (1) are not studied in the literature. Moreover, model (1) did not take into consideration the immune response. During viral infections, the host immune system reacts with antigen-specific immune response. The immune system is described as having two "arms": the cellular arm, which depends on T cells to mediate attacks on virally infected or cancerous cells, and the humoral arm, which depends on B cells. The B cell is a type of blood cell which belongs to a group of white blood cells (WBCs) called lymphocytes. WBCs protect the body from infection. The main job of B cells is to fight infection. B cells get activated when an infection occurs and they produce molecules called antibodies that attach to the surface of the infectious agent. These antibodies either kill the infection causing organism or make it prone to attack by other WBCs. They play a major role in the immune system, which guards the body against infection. Virus infection models with antibody immune response have been analyzed by many researchers (see [19–28]). However, in all of these works, the chronically infected cells have been neglected.

In this paper, we propose two virus infection models with antibody immune response and chronically infected cells. In the first model, bilinear incidence rate which is based on the law of mass-action is considered. The second model generalizes the first one where the incidence rate is given by a saturation functional response. The global stability of all equilibria of the models is established using the method of Lyapunov function. We prove that the global dynamics of the models are determined by two threshold parameters R_0 and R_1. If $R_0 \le 1$, then the infection-free equilibrium is globally asymptotically stable (GAS), if $R_1 \le 1 < R_0$, then the infected equilibrium without antibody immune response exists and it is GAS, and if $R_1 > 1$ then the infected equilibrium with antibody immune response exists and it is GAS.

2. Model with Bilinear Incidence Rate

In this section we propose a viral dynamics model with antibody immune response, taking into consideration the chronically infected cells. Based on the mass-action principle, we assume that the incidence rate of infection is bilinear; that is, the infection rate per virus and per uninfected cell is constant:

$$\dot{T} = \lambda - dT - (1-\varepsilon)\,kTV, \tag{2}$$

$$\dot{T}^* = (1-\alpha)(1-\varepsilon)\,kTV - \delta T^*, \tag{3}$$

$$\dot{C}^* = \alpha(1-\varepsilon)\,kTV - aC^*, \tag{4}$$

$$\dot{V} = N_T\delta T^* + N_C aC^* - cV - rVZ, \tag{5}$$

$$\dot{Z} = gVZ - \mu Z, \tag{6}$$

where Z is the concentration of antibody immune cells. The viruses are attacked by the antibodies with rate rVZ. The antibody immune cells are proliferated at rate gVZ and die at rate μZ. All the other variables and parameters of the model have the same meanings as given in (1).

2.1. Positive Invariance. We note that model (2)–(6) are biologically acceptable in the sense that no population goes negative. It is straightforward to check the positive invariance of the nonnegative orthant $\mathbb{R}^5_+$ by model (2)–(6) (see, e.g., [6]). In the following, we show the boundedness of the solution of model (2)–(6).

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

$$\Omega = \left\{(T, T^*, C^*, V, Z) \in \mathbb{R}^4_+ : 0 \le T, T^*, C^* \le L_1,\ 0 \le V \le L_2, 0 \le Z \le L_3\right\} \tag{7}$$

is positively invariant.

Proof. To show the boundedness of the solutions we let $G_1(t) = T(t) + T^*(t) + C^*(t)$; then

$$\begin{aligned}\dot{G}_1(t) &= \lambda - dT(t) - (1-\varepsilon)\,kT(t)V(t) \\ &\quad + (1-\alpha)(1-\varepsilon)\,kT(t)V(t) - \delta T^* \\ &\quad + \alpha(1-\varepsilon)\,kT(t)V(t) - aC^*(t) \\ &\le \lambda - s_1 G_1(t),\end{aligned} \tag{8}$$

where $s_1 = \min\{d, a, \delta\}$. Hence $G_1(t) \le L_1$, if $G_1(0) \le L_1$ where $L_1 = \lambda/s_1$. Since $T(t) > 0$, $T^*(t) \ge 0$, and $C^*(t) \ge 0$, then $0 \le T(t), T^*(t), C^*(t) \le L_1$ if $0 \le T(0) + T^*(0) + C^*(0) \le L_1$. Let $G_2(t) = V(t) + (r/g)Z(t)$; then

$$\begin{aligned}\dot{G}_2(t) &= N_T\delta T^*(t) + N_C aC^*(t) - cV(t) - \frac{r\mu}{g}Z(t) \\ &\le \left(N_T\delta + N_C a\right)L_1 - s_2\left(V(t) + \frac{r}{g}Z(t)\right) \\ &= \left(N_T\delta + N_C a\right)L_1 - s_2 G_2(t),\end{aligned} \tag{9}$$

where $s_2 = \min\{c, \mu\}$. Hence $G_2(t) \le L_2$, if $G_2(0) \le L_2$, where $L_2 = (N_T\delta + N_C a)L_1/s_2$. Since $V(t) \ge 0$ and $Z(t) \ge 0$ then $0 \le V(t) \le L_2$ and $0 \le Z(t) \le L_3$ if $0 \le V(0) + (r/g)Z(0) \le L_2$, where $L_3 = gL_2/r$. □

2.2. Equilibria. System (2)–(6) always admits an infection-free equilibrium $E_0 = (T_0, 0, 0, 0, 0)$, where $T_0 = \lambda/d$. In addition to E_0, the system can have an infected equilibrium without antibody immune response $E_1(T_1, T_1^*, C_1^*, V_1, 0)$ and an infected equilibrium with antibody immune response $E_2(T_2, T_2^*, C_2^*, V_2, Z_2)$ where

$$T_1 = \frac{c}{(1-\varepsilon)\,k\left[(1-\alpha)N_T + \alpha N_C\right]},$$

$$T_1^* = \frac{(1-\alpha)\,\lambda\left\{(1-\varepsilon)\,kT_0\left[(1-\alpha)N_T + \alpha N_C\right] - c\right\}}{\delta(1-\varepsilon)\,kT_0\left[(1-\alpha)N_T + \alpha N_C\right]},$$

$$C_1^* = \frac{\alpha\lambda\left\{(1-\varepsilon)\,kT_0\left[(1-\alpha)N_T + \alpha N_C\right] - c\right\}}{a(1-\varepsilon)\,kT_0\left[(1-\alpha)N_T + \alpha N_C\right]},$$

$$V_1 = \frac{d\left\{(1-\varepsilon)\,kT_0\left[(1-\alpha)N_T + \alpha N_C\right] - c\right\}}{(1-\varepsilon)\,kc},$$

$$T_2 = \frac{\lambda g}{gd + (1-\varepsilon)k\mu}, \qquad T_2^* = \frac{(1-\alpha)(1-\varepsilon)k\lambda\mu}{\delta(dg + (1-\varepsilon)k\mu)},$$
$$C_2^* = \frac{\alpha(1-\varepsilon)k\lambda\mu}{a(dg + (1-\varepsilon)k\mu)}, \qquad V_2 = \frac{\mu}{g},$$
$$Z_2 = \frac{c}{r}\left(\frac{dg(1-\varepsilon)kT_0[(1-\alpha)N_T + \alpha N_C]}{c(dg + (1-\varepsilon)k\mu)} - 1\right). \tag{10}$$

We discuss the local stability of the infection-free equilibrium E_0. At the infection-free equilibrium $E_0(T_0, 0, 0, 0, 0)$, the system has the Jacobian matrix given by

$$J_{E_0} = \begin{bmatrix} -d & 0 & 0 & -(1-\varepsilon)kT_0 & 0 \\ 0 & -\delta & 0 & (1-\alpha)(1-\varepsilon)kT_0 & 0 \\ 0 & 0 & -a & \alpha(1-\varepsilon)kT_0 & 0 \\ 0 & \delta N_T & aN_C & -c & 0 \\ 0 & 0 & 0 & 0 & -\mu \end{bmatrix}. \tag{11}$$

The characteristic equation of the Jacobian matrix evaluated at E_0 is

$$(s+d)(s+\mu)\left(s^3 + a_1 s^2 + a_2 s + a_3\right) = 0, \tag{12}$$

where

$$\begin{aligned} a_1 &= a + c + \delta, \\ a_2 &= ac + a\delta + c\delta - (1-\alpha)(1-\varepsilon)kT_0 N_T \delta \\ &\quad - \alpha(1-\varepsilon)kT_0 N_C a, \\ a_3 &= ac\delta\left(1 - \frac{(1-\varepsilon)kT_0[(1-\alpha)N_T + \alpha N_C]}{c}\right). \end{aligned} \tag{13}$$

We observe that (12) has two negative eigenvalues $s_1 = -d$ and $s_2 = -\mu$. By the Routh-Hurwitz criterion, the remaining three eigenvalues of (12) have negative real parts if $a_1 > 0$, $a_3 > 0$, and $a_1 a_2 - a_3 > 0$. We have $a_1 > 0$ and if $(1-\varepsilon)kT_0[(1-\alpha)N_T + \alpha N_C]/c < 1$, then $a_3 > 0$ and

$$\begin{aligned} a_1 a_2 - a_3 &= a\delta^2 + a^2\delta + 2ac\delta \\ &\quad + a(a+c)[c - \alpha(1-\varepsilon)kT_0 N_C] \\ &\quad + \delta(\delta + c)[c - (1-\alpha)(1-\varepsilon)kT_0 N_T] \\ &> 0. \end{aligned} \tag{14}$$

Now we define the basic reproduction number for system (2)–(6) as

$$R_0 = \frac{(1-\varepsilon)kT_0[(1-\alpha)N_T + \alpha N_C]}{c}. \tag{15}$$

It follows that the equilibria E_1 and E_2 can be written as

$$T_1 = \frac{T_0}{R_0}, \qquad T_1^* = \frac{(1-\alpha)\lambda}{\delta}\frac{(R_0 - 1)}{R_0},$$
$$C_1^* = \frac{\alpha\lambda}{a}\frac{(R_0-1)}{R_0}, \qquad V_1 = \frac{d}{(1-\varepsilon)k}(R_0 - 1),$$
$$T_2 = \frac{\lambda g}{gd + (1-\varepsilon)k\mu}, \qquad T_2^* = \frac{(1-\alpha)(1-\varepsilon)k\lambda\mu}{\delta(dg + (1-\varepsilon)k\mu)},$$
$$C_2^* = \frac{\alpha(1-\varepsilon)k\lambda\mu}{a(dg + (1-\varepsilon)k\mu)}, \qquad V_2 = \frac{\mu}{g},$$
$$Z_2 = \frac{c}{r}\left(\frac{dgR_0}{dg + (1-\varepsilon)k\mu} - 1\right). \tag{16}$$

We note that T_1, T_1^*, C_1^*, and V_1 are positive when $R_0 > 1$ and that $Z_2 > 0$ when $dgR_0/(dg + (1-\varepsilon)k\mu) > 1$. Now we define another threshold parameter R_1 as

$$R_1 = \frac{R_0}{1 + ((1-\varepsilon)k\mu/dg)}. \tag{17}$$

Clearly $R_1 < R_0$.

From (2.2) we have the following statements:

(i) if $R_0 \le 1$, then there exists only positive equilibrium E_0;

(ii) if $R_1 \le 1 < R_0$, then there exist two positive equilibria E_0 and E_1;

(iii) if $R_1 > 1$, then there exist three positive equilibria E_0, E_1, and E_2.

2.3. Global Stability Analysis. In this section, we study the global stability of all the equilibria of system (2)–(6) employing the method of Lyapunov function.

Theorem 2. *For system* (2)–(6)*, if* $R_0 \le 1$*, then* E_0 *is GAS.*

Proof. Define a Lyapunov function U_0 as follows:

$$U_0 = T_0\left(\frac{T}{T_0} - 1 - \ln\left(\frac{T}{T_0}\right)\right) + \eta_1 T^* + \eta_2 C^* + \eta_3 V + \eta_4 Z, \tag{18}$$

where η_i, $i = 1, \ldots, 4$, are positive constants to be determined below. Calculating the derivative of U_0 along the solutions of the system (2)–(6) and applying $\lambda = T_0 d$, we obtain

$$\begin{aligned} \frac{dU_0}{dt} &= \left(1 - \frac{T_0}{T}\right)(\lambda - dT - (1-\varepsilon)kTV) \\ &\quad + \eta_1((1-\alpha)(1-\varepsilon)kTV - \delta T^*) \\ &\quad + \eta_2(\alpha(1-\varepsilon)kTV - aC^*) \\ &\quad + \eta_3(N_T\delta T^* + N_C a C^* - cV - rVZ) \\ &\quad + \eta_4(gVZ - \mu Z). \end{aligned} \tag{19}$$

Let η_i, $i = 1, \ldots, 4$, be chosen such as

$$\begin{aligned} &(1-\alpha)\eta_1 + \alpha\eta_2 = 1, \qquad \eta_1 - N_T\eta_3 = 0, \\ &\eta_2 - N_C\eta_3 = 0, \qquad g\eta_4 - r\eta_3 = 0. \end{aligned} \tag{20}$$

The solution of (20) is given by

$$\eta_1 = \frac{N_T}{(1-\alpha)N_T + \alpha N_C}, \qquad \eta_2 = \frac{N_C}{(1-\alpha)N_T + \alpha N_C},$$
$$\eta_3 = \frac{1}{(1-\alpha)N_T + \alpha N_C}, \qquad \eta_4 = \frac{r}{g[(1-\alpha)N_T + \alpha N_C]}. \tag{21}$$

The values of η_i, $i = 1,\ldots,4$, given by (21) will be used throughout the paper. Then

$$\frac{dU_0}{dt} = \left(1 - \frac{T_0}{T}\right)(\lambda - dT) + (1-\varepsilon)\,kT_0V - \eta_3 cV - \eta_4 \mu Z$$
$$= -d\frac{(T-T_0)^2}{T} + \eta_3 c\,(R_0 - 1)\,V - \eta_4 \mu Z. \tag{22}$$

If $R_0 \le 1$ then $dU_0/dt \le 0$ for all $T, V, Z > 0$. Thus the solutions of system (2)–(6) limit to M, the largest invariant subset of $\{dU_0/dt = 0\}$. Clearly, it follows from (22) that $dU_0/dt = 0$ if and only if $T = T_0$, $V = 0$, and $Z = 0$. Noting that M is invariant, for each element of M we have $V = 0$ and $Z = 0$, and then $\dot{V} = 0$. From (5) we derive that

$$0 = \dot{V} = N_T \delta T^* + N_C a C^*. \tag{23}$$

Since $T^*, C^* \ge 0$, then $T^* = C^* = 0$. Hence $dU_0/dt = 0$ if and only if $T = T_0$, $T^* = 0$, $C^* = 0$, $V = 0$, and $Z = 0$. It follows from LaSalle's invariance principle that the infection-free equilibrium E_0 is GAS when $R_0 \le 1$. □

Theorem 3. *For system* (2)–(6), *if* $R_1 \le 1 < R_0$, *then* E_1 *is GAS.*

Proof. Define the following Lyapunov function:

$$U_1 = T_1\left(\frac{T}{T_1} - 1 - \ln\left(\frac{T}{T_1}\right)\right) + \eta_1 T_1^*\left(\frac{T^*}{T_1^*} - 1 - \ln\left(\frac{T^*}{T_1^*}\right)\right)$$
$$+ \eta_2 C_1^*\left(\frac{C^*}{C_1^*} - 1 - \ln\left(\frac{C^*}{C_1^*}\right)\right)$$
$$+ \eta_3 V_1\left(\frac{V}{V_1} - 1 - \ln\left(\frac{V}{V_1}\right)\right) + \eta_4 Z. \tag{24}$$

The time derivative of U_1 along the trajectories of (2)–(6) is given by

$$\frac{dU_1}{dt} = \left(1 - \frac{T_1}{T}\right)(\lambda - dT - (1-\varepsilon)\,kTV)$$
$$+ \eta_1\left(1 - \frac{T_1^*}{T^*}\right)\left((1-\alpha)(1-\varepsilon)\,kTV - \delta T^*\right)$$
$$+ \eta_2\left(1 - \frac{C_1^*}{C^*}\right)\left(\alpha(1-\varepsilon)\,kTV - aC^*\right)$$
$$+ \eta_3\left(1 - \frac{V_1}{V}\right)\left(N_T\delta T^* + N_C a C^* - cV - rVZ\right)$$
$$+ \eta_4\left(gVZ - \mu Z\right). \tag{25}$$

Applying $\lambda = dT_1 + (1-\varepsilon)kT_1V_1$ we get

$$\frac{dU_1}{dt} = \left(1 - \frac{T_1}{T}\right)(dT_1 - dT) + (1-\varepsilon)\,kT_1V_1\left(1 - \frac{T_1}{T}\right)$$
$$+ (1-\varepsilon)\,kT_1V - \eta_1(1-\alpha)(1-\varepsilon)\,kTV\frac{T_1^*}{T^*} + \eta_1\delta T_1^*$$
$$- \eta_2\alpha(1-\varepsilon)\,kTV\frac{C_1^*}{C^*} + \eta_2 a C_1^* - \delta\eta_1\frac{V_1T^*}{V}$$
$$- a\eta_2\frac{V_1C^*}{V} - c\eta_3 V + c\eta_3 V_1 + r\eta_3 V_1 Z - \mu\eta_4 Z. \tag{26}$$

Using the following equilibrium conditions for E_1,

$$(1-\alpha)(1-\varepsilon)\,kT_1V_1 = \delta T_1^*,$$
$$\alpha(1-\varepsilon)\,kT_1V_1 = aC_1^*, \tag{27}$$
$$cV_1 = N_T\delta T_1^* + N_C a C_1^*,$$

then we have $(1-\varepsilon)kT_1V_1 = \eta_1\delta T_1^* + \eta_2 a C_1^*$ and

$$\frac{dU_1}{dt} = -d\frac{(T-T_1)^2}{T} + \eta_1\delta T_1^*\left(1 - \frac{T_1}{T}\right) + \eta_2 a C_1^*\left(1 - \frac{T_1}{T}\right)$$
$$- \eta_1\delta T_1^*\frac{TVT_1^*}{T_1V_1T^*} + \eta_1\delta T_1^* - \eta_2 a C_1^*\frac{TVC_1^*}{T_1V_1C^*}$$
$$+ \eta_2 a C_1^* - \eta_1\delta T_1^*\frac{V_1T^*}{VT_1^*} - \eta_2 a C_1^*\frac{V_1C^*}{VC_1^*}$$
$$+ \eta_1\delta T_1^* + \eta_2 a C_1^* + r\eta_3\left(V_1 - \frac{\mu}{g}\right)Z$$
$$= -d\frac{(T-T_1)^2}{T} + \eta_1\delta T_1^*\left[3 - \frac{T_1}{T} - \frac{T_1^*TV}{T^*T_1V_1} - \frac{V_1T^*}{VT_1^*}\right]$$
$$+ \eta_2 a C_1^*\left[3 - \frac{T_1}{T} - \frac{C_1^*TV}{C^*T_1V_1} - \frac{C^*V_1}{C_1^*V}\right]$$
$$+ r\eta_3\left(\frac{dg + (1-\varepsilon)\,k\mu}{g(1-\varepsilon)\,k}\right)(R_1 - 1)\,Z. \tag{28}$$

We have that if $R_0 > 1$, then $T_1, T_1^*, C_1^*, V_1 > 0$. Since the arithmetical mean is greater than or equal to the geometrical mean, then if $R_1 \le 1$ then $dU_1/dt \le 0$ for all $T, T^*, C^*, V, Z > 0$. It can be seen that $dU_1/dt = 0$ if and only if $T = T_1$, $T^* = T_1^*$, $C^* = C_1^*$, $V = V_1$, and $Z = 0$. LaSalle's invariance principle implies global stability of E_1. □

Theorem 4. *For system* (2)–(6), *if* $R_0 \le 1$, *then* E_0 *is GAS.*

Proof. We consider a Lyapunov function

$$U_2 = T_2\left(\frac{T}{T_2} - 1 - \ln\left(\frac{T}{T_2}\right)\right) + \eta_1 T_2^*\left(\frac{T^*}{T_2^*} - 1 - \ln\left(\frac{T^*}{T_2^*}\right)\right)$$
$$+ \eta_2 C_2^*\left(\frac{C^*}{C_2^*} - 1 - \ln\left(\frac{C^*}{C_2^*}\right)\right)$$
$$+ \eta_3 V_2\left(\frac{V}{V_2} - 1 - \ln\left(\frac{V}{V_2}\right)\right)$$
$$+ \eta_4 Z_2\left(\frac{Z}{Z_2} - 1 - \ln\left(\frac{Z}{Z_2}\right)\right). \tag{29}$$

Further, function U_2 along the trajectories of system (2)–(6) satisfies

$$\begin{aligned}\frac{dU_2}{dt} &= \left(1-\frac{T_2}{T}\right)(\lambda - dT - (1-\varepsilon)kTV)\\ &\quad + \eta_1\left(1-\frac{T_2^*}{T^*}\right)((1-\alpha)(1-\varepsilon)kTV - \delta T^*)\\ &\quad + \eta_2\left(1-\frac{C_2^*}{C^*}\right)(\alpha(1-\varepsilon)kTV - aC^*)\\ &\quad + \eta_3\left(1-\frac{V_2}{V}\right)(N_T\delta T^* + N_C aC^* - cV - rVZ)\\ &\quad + \eta_4\left(1-\frac{Z_2}{Z}\right)(gVZ - \mu Z).\end{aligned} \tag{30}$$

Using the following equilibrium conditions for E_2,

$$\begin{aligned}\lambda = dT_2 + (1-\varepsilon)kT_2V_2, \qquad (1-\alpha)(1-\varepsilon)kT_2V_2 = \delta T_2^*,\\ \alpha(1-\varepsilon)kT_2V_2 = aC_2^*,\\ cV_2 + rV_2Z_2 = N_T\delta T_2^* + N_C aC_2^*,\end{aligned} \tag{31}$$

we get

$$\begin{aligned}\frac{dU_2}{dt} &= -d\frac{(T-T_2)^2}{T} + (1-\varepsilon)kT_2V_2\left(1-\frac{T_2}{T}\right)\\ &\quad + (1-\varepsilon)kT_2V - \eta_1(1-\alpha)(1-\varepsilon)kTV\frac{T_2^*}{T^*}\\ &\quad + \delta\eta_1 T_2^* - \eta_2\alpha(1-\varepsilon)kTV\frac{C_2^*}{C^*} + a\eta_2 C_2^*\\ &\quad - \delta\eta_1\frac{V_2T^*}{V} - a\eta_2\frac{V_2C^*}{V} - c\eta_3 V + c\eta_3 V_2\\ &\quad + r\eta_4 V_2 Z - r\eta_4 Z_2 V + \mu\eta_4 Z_2 - \mu\eta_4 Z\\ &= -d\frac{(T-T_2)^2}{T} + \eta_1\delta T_2^*\left(1-\frac{T_2}{T}\right)\\ &\quad + \eta_2 aC_2^*\left(1-\frac{T_2}{T}\right) - \eta_1\delta T_2^*\frac{TVT_2^*}{T_2V_2T^*} + \eta_1\delta T_2^*\\ &\quad - \eta_2 aC_2^*\frac{TVC_2^*}{T_2V_2C^*} + \eta_2 aC_2^* - \eta_1\delta T_2^*\frac{V_2T^*}{VT_2^*}\\ &\quad - \eta_2 aC_2^*\frac{V_2C^*}{VC_2^*} + \eta_1\delta T_2^* + \eta_2 aC_2^*\\ &= -d\frac{(T-T_2)^2}{T} + \eta_1\delta T_2^*\left[3 - \frac{T_2}{T} - \frac{T_2^*TV}{T^*T_2V_2} - \frac{V_2T^*}{VT_2^*}\right]\\ &\quad + \eta_2 aC_2^*\left[3 - \frac{T_2}{T} - \frac{C_2^*TV}{C^*T_2V_2} - \frac{C^*V_2}{C_2^*V}\right].\end{aligned} \tag{32}$$

Thus, if $R_1 > 1$, then T_2, T_2^*, C_2^*, V_2 and $Z_2 > 0$. Since the arithmetical mean is greater than or equal to the geometrical mean, then $dU_2/dt \le 0$. It can be seen that $dU_2/dt = 0$ if and only if $T = T_2$, $T^* = T_2^*$, $C^* = C_2^*$, and $V = V_2$. From (5), if $V = V_2$, then $\dot{V} = 0$ and $0 = N_T\delta T_2^* + N_C aC_2^* - cV - rV_2Z = 0$, so $Z = Z_2$ and hence dU_2/dt is equal to zero at E_2. So, the global stability of the equilibrium E_2 follows from LaSalle's invariance principle. □

3. Model with Saturation Incidence Rate

In model (2)–(6), the infection process is characterized by bilinear incidence rate $(1-\varepsilon)kxv$. However, there are a number of reasons why this bilinear incidence can be insufficient to describe infection process in detail (see, e.g., [29–31]). For example, a less than linear response in v could occur when the concentration of viruses becomes higher, where the infectious fraction is high so that exposure is very likely [29]. Experiments reported in [32] strongly suggested that the infection rate of microparasitic infections is an increasing function of the parasite dose and is usually sigmoidal in shape (see, e.g., [33]). In [33], to place the model on more sound biological grounds, Regoes et al. replaced the mass-action infection rate with a dose-dependent infection rates. In this section, the incidence rate is given by a saturation functional response:

$$\dot{T} = \lambda - dT - \frac{(1-\varepsilon)kTV}{1+\beta V}, \tag{33}$$

$$\dot{T}^* = \frac{(1-\alpha)(1-\varepsilon)kTV}{1+\beta V} - \delta T^*, \tag{34}$$

$$\dot{C}^* = \frac{\alpha(1-\varepsilon)kTV}{1+\beta V} - aC^*, \tag{35}$$

$$\dot{V} = N_T\delta T^* + N_C aC^* - cV - rVZ, \tag{36}$$

$$\dot{Z} = gVZ - \mu Z, \tag{37}$$

where $\beta > 0$ is a constant, which represents the saturation infection rate constant.

All the variables and parameters have the same meanings as given in model (2)–(6).

3.1. Equilibria. Similar to the previous section, we can define two threshold parameters R_0 and R_1 for system (33)–(37) as

$$\begin{aligned}R_0 &= \frac{(1-\varepsilon)kT_0[(1-\alpha)N_T + \alpha N_C]}{c},\\ R_1 &= \frac{R_0}{1 + (d\beta\mu + (1-\varepsilon)k\mu/dg)}.\end{aligned} \tag{38}$$

Clearly $R_1 < R_0$. It is clear that system (33)–(37) has an infection-free equilibrium $E_0 = (T_0, 0, 0, 0, 0)$, where $T_0 = \lambda/d$. In addition to E_0, the system can have an

infected equilibrium without antibody immune response $E_1(T_1, T_1^*, C_1^*, V_1, 0)$, where

$$T_1 = \frac{\beta\lambda\left[(1-\alpha)N_T + \alpha N_C\right] + c}{\left((1-\varepsilon)k + d\beta\right)\left[(1-\alpha)N_T + \alpha N_C\right]},$$
$$T_1^* = \frac{(1-\alpha)cd}{\delta\left((1-\varepsilon)k + d\beta\right)\left[(1-\alpha)N_T + \alpha N_C\right]}\left(R_0 - 1\right),$$
$$C_1^* = \frac{\alpha cd}{a\left((1-\varepsilon)k + d\beta\right)\left[(1-\alpha)N_T + \alpha N_C\right]}\left(R_0 - 1\right),$$
$$V_1 = \frac{d}{(1-\varepsilon)k + d\beta}\left(R_0 - 1\right), \tag{39}$$

and infected equilibrium with antibody immune response $E_2(T_2, T_2^*, C_2^*, V_2, Z_2)$, where

$$T_2 = \frac{\lambda\left(g + \beta\mu\right)}{gd + (1-\varepsilon)k\mu + d\beta\mu},$$
$$T_2^* = \frac{(1-\alpha)(1-\varepsilon)k\lambda\mu}{\delta\left(dg + (1-\varepsilon)k\mu + d\beta\mu\right)},$$
$$C_2^* = \frac{\alpha(1-\varepsilon)k\lambda\mu}{a\left(dg + (1-\varepsilon)k\mu + d\beta\mu\right)}, \qquad V_2 = \frac{\mu}{g},$$
$$Z_2 = \frac{c}{r}\left(R_1 - 1\right). \tag{40}$$

It is clear from (39) and (40) that

(i) if $R_0 \le 1$, then there exists only positive equilibrium E_0;

(ii) if $R_1 \le 1 < R_0$, then there exist two positive equilibria E_0 and E_1;

(iii) if $R_1 > 1$, then there exist three positive equilibria E_0, E_1, and E_2.

3.2. Global Stability Analysis. In this section, we study the global stability of all the equilibria of system (33)–(37) employing the method of Lyapunov function and LaSalle's invariance principle.

Theorem 5. *For system* (33)–(37)*, if* $R_0 \le 1$*, then* E_0 *is GAS.*

Proof. Define a Lyapunov function U_0 as follows:

$$U_0 = T_0\left(\frac{T}{T_0} - 1 - \ln\left(\frac{T}{T_0}\right)\right) + \eta_1 T^* + \eta_2 C^* + \eta_3 V + \eta_4 Z. \tag{41}$$

Calculating the derivative of U_0 along the solutions of system (33)–(37) and applying $\lambda = T_0 d$, we obtain

$$\begin{aligned}\frac{dU_0}{dt} &= \left(1 - \frac{T_0}{T}\right)\left(\lambda - dT - \frac{(1-\varepsilon)kTV}{1+\beta V}\right) \\ &\quad + \eta_1\left(\frac{(1-\alpha)(1-\varepsilon)kTV}{1+\beta V} - \delta T^*\right) \\ &\quad + \eta_2\left(\frac{\alpha(1-\varepsilon)kTV}{1+\beta V} - aC^*\right) \\ &\quad + \eta_3\left(N_T\delta T^* + N_C aC^* - cV - rVZ\right) \\ &\quad + \eta_4\left(gVZ - \mu Z\right) \\ &= \left(1 - \frac{T_0}{T}\right)(\lambda - dT) + \frac{(1-\varepsilon)kT_0V}{1+\beta V} \\ &\quad - c\eta_3 V - \mu\eta_4 Z \\ &= -\left[d\frac{(T-T_0)^2}{T} + \eta_3\frac{c\beta R_0 V^2}{(1+\beta V)} + \mu\eta_4 Z\right] \\ &\quad + c\eta_3\left(R_0 - 1\right)V.\end{aligned} \tag{42}$$

Similar to the proof of Theorem 2, one can easily show that E_0 is GAS when $R_0 \le 1$. □

Theorem 6. *For system* (33)–(37)*, if* $R_1 \le 1 < R_0$*, then* E_1 *is GAS.*

Proof. Construct a Lyapunov function as follows:

$$\begin{aligned}U_1 &= T_1\left(\frac{T}{T_1} - 1 - \ln\left(\frac{T}{T_1}\right)\right) \\ &\quad + \eta_1 T_1^*\left(\frac{T^*}{T_1^*} - 1 - \ln\left(\frac{T^*}{T_1^*}\right)\right) \\ &\quad + \eta_2 C_1^*\left(\frac{C^*}{C_1^*} - 1 - \ln\left(\frac{C^*}{C_1^*}\right)\right) \\ &\quad + \eta_3 V_1\left(\frac{V}{V_1} - 1 - \ln\left(\frac{V}{V_1}\right)\right) + \eta_4 Z.\end{aligned} \tag{43}$$

The derivative of U_1 along the trajectories of system (33)–(37) is given by

$$\begin{aligned}\frac{dU_1}{dt} &= \left(1 - \frac{T_1}{T}\right)\left(\lambda - dT - \frac{(1-\varepsilon)kTV}{1+\beta V}\right) \\ &\quad + \eta_1\left(1 - \frac{T_1^*}{T^*}\right)\left(\frac{(1-\alpha)(1-\varepsilon)kTV}{1+\beta V} - \delta T^*\right) \\ &\quad + \eta_2\left(1 - \frac{C_1^*}{C^*}\right)\left(\frac{\alpha(1-\varepsilon)kTV}{1+\beta V} - aC^*\right) \\ &\quad + \eta_3\left(1 - \frac{V_1}{V}\right)\left(N_T\delta T^* + N_C aC^* - cV - rVZ\right) \\ &\quad + \eta_4\left(gVZ - \mu Z\right).\end{aligned} \tag{44}$$

Applying $\lambda = dT_1 + ((1-\varepsilon)kT_1V_1/(1+\beta V_1))$ we get

$$\begin{aligned}\frac{dU_1}{dt} &= \left(1 - \frac{T_1}{T}\right)\left(dT_1 - dT\right) \\ &\quad + \frac{(1-\varepsilon)kT_1V_1}{1+\beta V_1}\left(1 - \frac{T_1}{T}\right) + \frac{(1-\varepsilon)kT_1V}{1+\beta V}\end{aligned}$$

$$
\begin{aligned}
&- \eta_1 (1-\alpha) \frac{(1-\varepsilon) kTV}{1+\beta V} \frac{T_1^*}{T^*} + \eta_1 \delta T_1^* \\
&- \eta_2 \alpha \frac{(1-\varepsilon) kTV}{1+\beta V} \frac{C_1^*}{C^*} + \eta_2 a C_1^* \\
&- \eta_1 \delta \frac{V_1 T^*}{V} - \eta_2 a \frac{V_1 C^*}{V} - c\eta_3 V \\
&+ c\eta_3 V_1 + r\eta_3 V_1 Z - \mu \eta_4 Z.
\end{aligned} \tag{45}
$$

Using the following equilibrium conditions for E_1,

$$
\begin{aligned}
&\frac{(1-\alpha)(1-\varepsilon) kT_1 V_1}{1+\beta V_1} = \delta T_1^*, \\
&\frac{\alpha (1-\varepsilon) kT_1 V_1}{1+\beta V_1} = a C_1^*, \qquad c V_1 = N_T \delta T_1^* + N_C a C_1^*,
\end{aligned} \tag{46}
$$

we get

$$
\begin{aligned}
\frac{dU_1}{dt} &= -d \frac{(T-T_1)^2}{T} + \eta_1 \delta T_1^* \left(1 - \frac{T_1}{T}\right) + \eta_2 a C_1^* \left(1 - \frac{T_1}{T}\right) \\
&+ \frac{(1-\varepsilon) kT_1 V_1}{1+\beta V_1} \left[\frac{V(1+\beta V_1)}{V_1(1+\beta V)} - \frac{V}{V_1}\right] \\
&- \eta_1 \delta T_1^* \frac{TVT_1^*(1+\beta V_1)}{T_1 V_1 T^*(1+\beta V)} + \eta_1 \delta T_1^* \\
&- \eta_2 a C_1^* \frac{TVC_1^*(1+\beta V_1)}{T_1 V_1 C^*(1+\beta V)} + \eta_2 a C_1^* \\
&- \eta_1 \delta T_1^* \frac{V_1 T^*}{V T_1^*} - \eta_2 a C_1^* \frac{V_1 C^*}{V C_1^*} \\
&+ \eta_1 \delta T_1^* + \eta_2 a C_1^* + r\eta_3 \left(V_1 - \frac{\mu}{g}\right) Z \\
&= -d \frac{(T-T_1)^2}{T} \\
&+ \frac{(1-\varepsilon) kT_1 V_1}{1+\beta V_1} \left[-1 + \frac{V(1+\beta V_1)}{V_1(1+\beta V)} - \frac{V}{V_1} + \frac{1+\beta V}{1+\beta V_1}\right] \\
&+ \eta_1 \delta T_1^* \left[4 - \frac{T_1}{T} - \frac{TVT_1^*(1+\beta V_1)}{T_1 V_1 T^*(1+\beta V)} - \frac{V_1 T^*}{V T_1^*} \right. \\
&\qquad \left. - \frac{1+\beta V}{1+\beta V_1}\right] \\
&+ \eta_2 a C_1^* \left[4 - \frac{T_1}{T} - \frac{TVC_1^*(1+\beta V_1)}{T_1 V_1 C^*(1+\beta V)} - \frac{C^* V_1}{C_1^* V} \right. \\
&\qquad \left. - \frac{1+\beta V}{1+\beta V_1}\right] + r\eta_3 \left(V_1 - \frac{\mu}{g}\right) Z
\end{aligned}
$$

$$
\begin{aligned}
&= -d \frac{(T-T_1)^2}{T} \\
&- \frac{(1-\varepsilon) kT_1 V_1}{1+\beta V_1} \left[\frac{\beta (V-V_1)^2}{V_1(1+\beta V)(1+\beta V_1)}\right] \\
&+ \eta_1 \delta T_1^* \left[4 - \frac{T_1}{T} - \frac{TVT_1^*(1+\beta V_1)}{T_1 V_1 T^*(1+\beta V)} - \frac{V_1 T^*}{V T_1^*} \right. \\
&\qquad \left. - \frac{1+\beta V}{1+\beta V_1}\right] \\
&+ \eta_2 a C_1^* \left[4 - \frac{T_1}{T} - \frac{TVC_1^*(1+\beta V_1)}{T_1 V_1 C^*(1+\beta V)} - \frac{C^* V_1}{C_1^* V} \right. \\
&\qquad \left. - \frac{1+\beta V}{1+\beta V_1}\right] \\
&+ r\eta_3 \left(\frac{dg + (1-\varepsilon) k\mu + d\beta\mu}{g(1-\varepsilon) k + dg\beta}\right) (R_1 - 1) Z.
\end{aligned} \tag{47}
$$

We have that if $R_1 \le 1 < R_0$, then $dU_1/dt \le 0$ where equality occurs at E_1. LaSalle's invariance principle implies global stability of E_1. □

Theorem 7. *For system* (33)–(37)*, if* $R_1 > 1$*, then* E_2 *is GAS.*

Proof. We consider a Lyapunov function as follows:

$$
\begin{aligned}
U_2 &= T_2 \left(\frac{T}{T_2} - 1 - \ln\left(\frac{T}{T_2}\right)\right) + \eta_1 T_2^* \left(\frac{T^*}{T_2^*} - 1 - \ln\left(\frac{T^*}{T_2^*}\right)\right) \\
&+ \eta_2 C_2^* \left(\frac{C^*}{C_2^*} - 1 - \ln\left(\frac{C^*}{C_2^*}\right)\right) \\
&+ \eta_3 V_2 \left(\frac{V}{V_2} - 1 - \ln\left(\frac{V}{V_2}\right)\right) \\
&+ \eta_4 Z_2 \left(\frac{Z}{Z_2} - 1 - \ln\left(\frac{Z}{Z_2}\right)\right).
\end{aligned} \tag{48}
$$

Further, function U_2 along the trajectories of system (33)–(37) satisfies

$$
\begin{aligned}
\frac{dU_2}{dt} &= \left(1 - \frac{T_2}{T}\right) \left(\lambda - dT - \frac{(1-\varepsilon) kTV}{1+\beta V}\right) \\
&+ \eta_1 \left(1 - \frac{T_2^*}{T^*}\right) \left(\frac{(1-\alpha)(1-\varepsilon) kTV}{1+\beta V} - \delta T^*\right) \\
&+ \eta_2 \left(1 - \frac{C_2^*}{C^*}\right) \left(\frac{\alpha (1-\varepsilon) kTV}{1+\beta V} - a C^*\right) \\
&+ \eta_3 \left(1 - \frac{V_2}{V}\right) (N_T \delta T^* + N_C a C^* - cV - rVZ) \\
&+ \eta_4 \left(1 - \frac{Z_2}{Z}\right) (gVZ - \mu Z).
\end{aligned} \tag{49}
$$

Using the following equilibrium conditions for E_2,

$$\begin{aligned}
\lambda &= dT_2 + \frac{(1-\varepsilon)\,kT_2V_2}{1+\beta V_2},\\
\delta T_2^* &= \frac{(1-\alpha)\,(1-\varepsilon)\,kT_2V_2}{1+\beta V_2},\\
aC_2^* &= \frac{\alpha\,(1-\varepsilon)\,kT_2V_2}{1+\beta V_2},\\
cV_2 + rV_2Z_2 &= N_T\delta T_2^* + N_C aC_2^*,
\end{aligned} \tag{50}$$

we get

$$\begin{aligned}
\frac{dU_2}{dt} &= -d\frac{(T-T_2)^2}{T} + \frac{(1-\varepsilon)\,kT_2V_2}{1+\beta V_2}\left(1-\frac{T_2}{T}\right)\\
&\quad + \frac{(1-\varepsilon)\,kT_2V}{1+\beta V} - \eta_1(1-\alpha)\frac{(1-\varepsilon)\,kTV}{1+\beta V}\frac{T_2^*}{T^*}\\
&\quad + \eta_1\delta T_2^* - \eta_2\alpha\frac{(1-\varepsilon)\,kTV}{1+\beta V}\frac{C_2^*}{C^*} + \eta_2 aC_2^*\\
&\quad - \eta_1\delta\frac{V_2T^*}{V} - \eta_2 a\frac{V_2C^*}{V} - \eta_3 cV + \eta_3 cV_2\\
&\quad + \eta_3 rV_2Z - \eta_4 gZ_2V + \mu\eta_4 Z_2 - \mu\eta_4 Z\\
&= -d\frac{(T-T_2)^2}{T} + \eta_1\delta T_2^*\left(1-\frac{T_2}{T}\right) + \eta_2 aC_2^*\left(1-\frac{T_2}{T}\right)\\
&\quad + \frac{(1-\varepsilon)\,kT_2V_2}{1+\beta V_2}\left[\frac{V(1+\beta V_2)}{V_2(1+\beta V)} - \frac{V}{V_2}\right]\\
&\quad - \eta_1\delta T_2^*\frac{TVT_2^*(1+\beta V_2)}{T_2V_2T^*(1+\beta V)} + \eta_1\delta T_2^*\\
&\quad - \eta_2 aC_2^*\frac{TVC_2^*(1+\beta V_2)}{T_2V_2C^*(1+\beta V)} + \eta_2 aC_2^*\\
&\quad - \eta_1\delta T_2^*\frac{V_2T^*}{VT_2^*} - \eta_2 aC_2^*\frac{V_2C^*}{VC_2^*} + \eta_1\delta T_2^* + \eta_2 aC_2^*\\
&= -d\frac{(T-T_2)^2}{T}\\
&\quad - \frac{(1-\varepsilon)\,kT_2V_2}{1+\beta V_2}\left[\frac{\beta(V-V_2)^2}{V_2(1+\beta V)(1+\beta V_2)}\right]\\
&\quad + \eta_1\delta T_2^*\left[4 - \frac{T_2}{T} - \frac{TVT_2^*(1+\beta V_2)}{T_2V_2T^*(1+\beta V)} - \frac{V_2T^*}{VT_2^*}\right.\\
&\qquad \left. - \frac{1+\beta V}{1+\beta V_2}\right]\\
&\quad + \eta_2 aC_2^*\left[4 - \frac{T_2}{T} - \frac{TVC_2^*(1+\beta V_2)}{T_2V_2C^*(1+\beta V)} - \frac{C^*V_2}{C_2^*V}\right.\\
&\qquad \left. - \frac{1+\beta V}{1+\beta V_2}\right].
\end{aligned} \tag{51}$$

Similar to the proof of Theorem 4, one can show that E_2 is GAS. □

4. Numerical Simulations

We now use simple numerical simulations to illustrate our theoretical results for the two models. In both models we will fix the following data: $\lambda = 10\,\mathrm{mm}^{-3}\,\mathrm{day}^{-1}$, $d = 0.01\ \mathrm{day}^{-1}$, $k = 0.001\,\mathrm{mm}^3\,\mathrm{day}^{-1}$, $\delta = 0.5\ \mathrm{day}^{-1}$, $\alpha = 0.5$, $a = 0.1\ \mathrm{day}^{-1}$, $c = 3\ \mathrm{day}^{-1}$, $N_T = 10$, $N_C = 5$, $r = 0.01\,\mathrm{mm}^3\,\mathrm{day}^{-1}$, and $\mu = 0.1\ \mathrm{day}^{-1}$. The other parameters will be chosen below. All computations were carried out by MATLAB.

4.1. Model with Bilinear Incidence Rate. In this section, we perform simulation results for model (2)–(6) to check our theoretical results given in Theorems 2–4. We have the following cases.

(i) $R_0 \le 1$. We choose $\varepsilon = 0.63$ and $g = 0.01\,\mathrm{mm}^3\,\mathrm{day}^{-1}$. Using these data we compute $R_0 = 0.92$ and $R_1 = 0.672$. Figures 1, 2, 3, 4, and 5 show that the numerical results are consistent with Theorem 2. We can see that, the concentration of uninfected cells is increased and converges to its normal value $\lambda/d = 1000\,\mathrm{mm}^{-3}$, while the concentrations of short-lived infected cells, chronically infected cells, free viruses, and antibody immune cells are decaying and tend to zero.

(ii) $R_1 \le 1 < R_0$. We take $\varepsilon = 0$ and $g = 0.005\,\mathrm{mm}^3\,\mathrm{day}^{-1}$. In this case, $R_0 = 2.5$ and $R_1 = 0.833$. Figures 1–5 show that the numerical results are consistent with Theorem 3. We can see that the trajectory of the system will tend to the infected equilibrium without antibody immune response $E_1(400, 6, 27.77, 15, 0)$. In this case, the infection becomes chronic but with no persistent antibody immune response.

(iii) $R_1 > 1$. We choose $\varepsilon = 0$ and $g = 0.01\,\mathrm{mm}^3\,\mathrm{day}^{-1}$. Then we compute $R_0 = 2.5$ and $R_1 = 1.25$. From Figures 1–5 we can see that our simulation results are consistent with the theoretical results of Theorem 4. We observe that the trajectory of the system will tend to the infected equilibrium with antibody immune response $E_2(500.04, 5, 23.15, 10, 57.03)$. In this case, the infection becomes chronic but with persistent antibody immune response.

We note that the values of the parameters g, r, and μ have no impact on the value of R_0, since R_0 is independent of those parameters. This fact seems to suggest that antibodies do not play a role in eliminating the viruses. From the definition of R_1, we can see that R_1 can be increased by increasing g or decreasing μ.

Figures 1 and 4 show that the presence of antibody immune response (i.e., $R_1 > 1$) reduces the concentration of free viruses and increases the concentration of uninfected cells. This can be seen by comparing the virus and uninfected cell components in the equilibria E_1 and E_2 under the

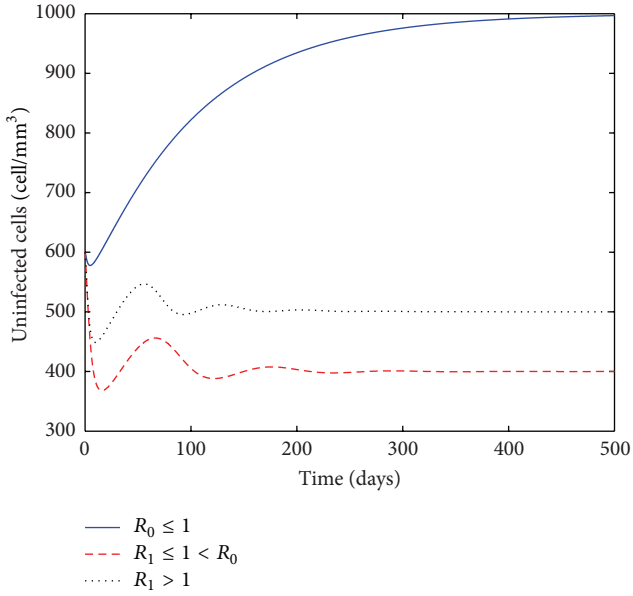

Figure 1: The evolution of uninfected cells for model (2)–(6).

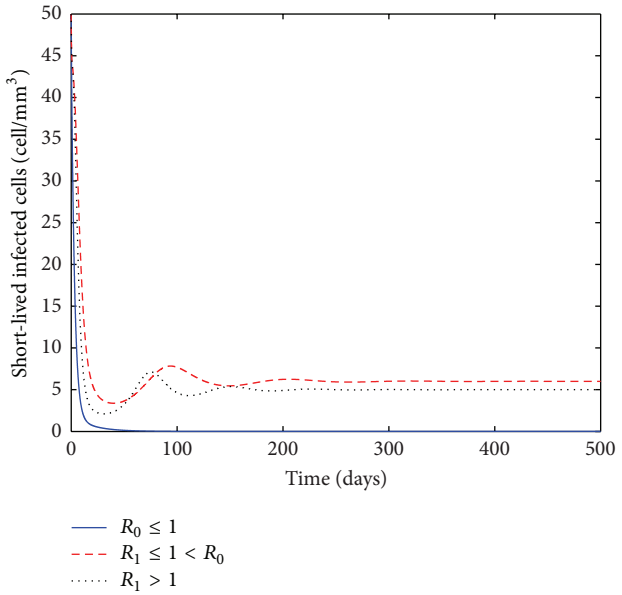

Figure 2: The evolution of short-lived infected cells for model (2)–(6).

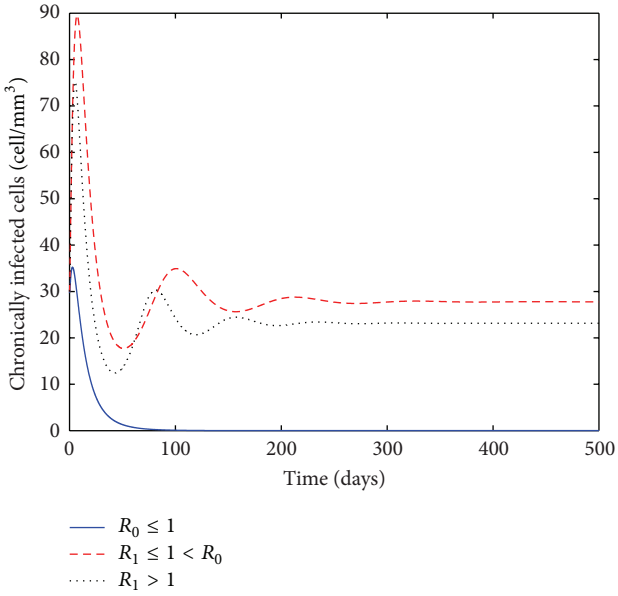

Figure 3: The evolution of chronically infected cells for model (2)–(6).

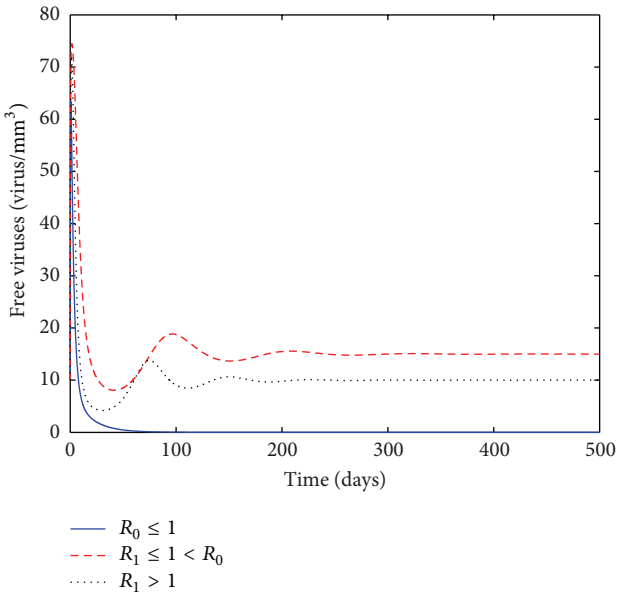

Figure 4: The evolution of free viruses for model (2)–(6).

condition $R_1 > 1$. For model (2)–(6), simple calculation shows that

$$V_1 - V_2 = \left(\frac{dg + (1-\varepsilon) k\mu}{g(1-\varepsilon) k} \right) (R_1 - 1). \tag{52}$$

It follows that if $R_1 > 1$, then $V_2 < V_1$. From (2) and at any equilibrium point $\overline{E}(\overline{T}, \overline{T}^*, \overline{C}^*, \overline{V}, \overline{Z})$ we have

$$\overline{T} = \frac{\lambda}{d + (1-\varepsilon) k\overline{V}}. \tag{53}$$

Clearly, $\overline{T}$ is a decreasing function of $\overline{V}$. This yields that if $R_1 > 1$, then $V_2 < V_1$ and $T_2 > T_1$.

4.2. Model with Saturation Functional Response. In this section, we perform simulation results to check Theorems 5–7. The parameter β is chosen as $\alpha = 0.2\,\text{mm}^3$. We have the following cases.

(i) $R_0 \le 1$. We take $\varepsilon = 0.63$ and $g = 0.01\,\text{mm}^3\,\text{day}^{-1}$. Using these data, we compute $R_0 = 0.92$ and $R_1 = 0.273$. The simulation results of this case are shown in Figures 6, 7, 8, 9, and 10. We can see that the numerical

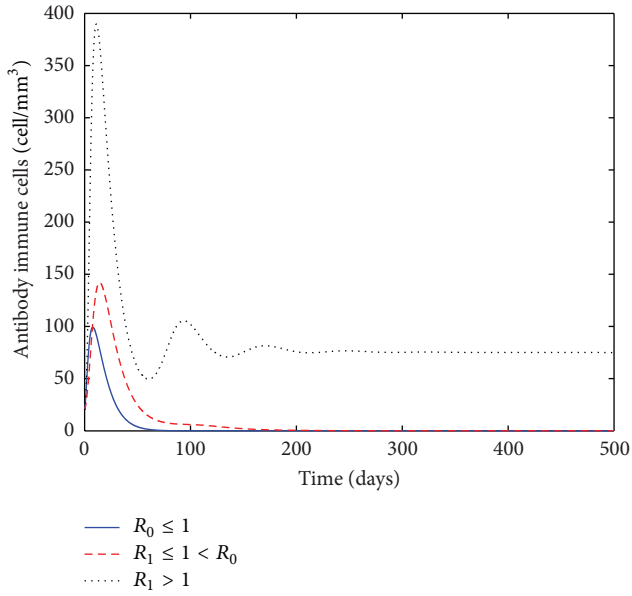

Figure 5: The evolution of antibody immune cells for model (2)–(6).

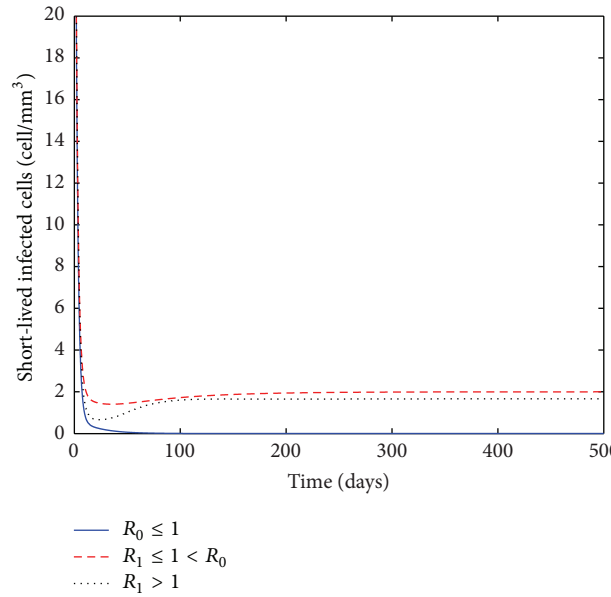

Figure 7: The evolution of short-lived infected cells for model (33)–(37).

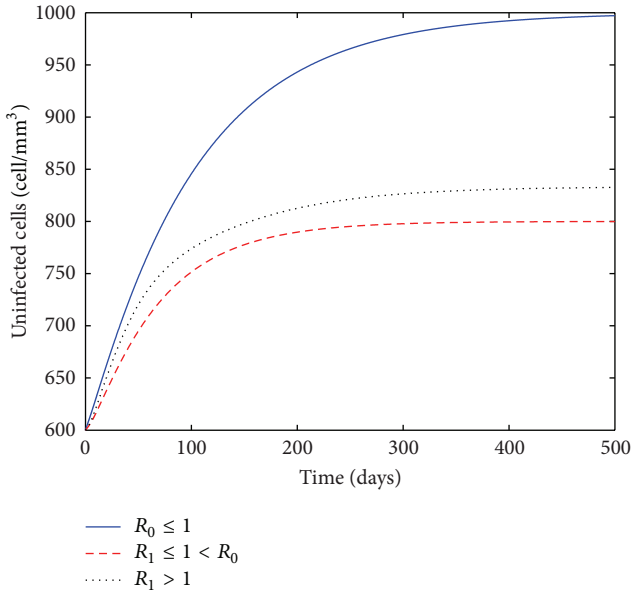

Figure 6: The evolution of uninfected cells for model (33)–(37).

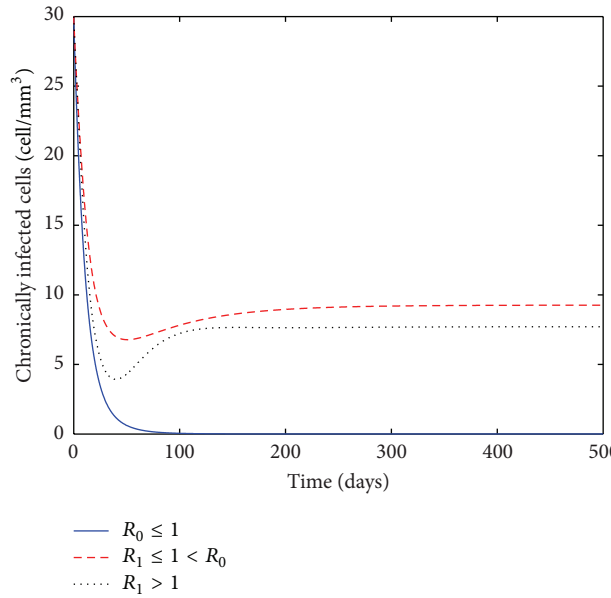

Figure 8: The evolution of chronically infected cells for model (33)–(37).

results are consistent with Theorem 5. It is observed that the viruses will be cleared and the uninfected cells will return to their normal value.

(ii) $R_1 \le 1 < R_0$. To satisfy this condition, we take $\varepsilon = 0$ and $g = 0.005\,\text{mm}^3\,\text{day}^{-1}$. This will give $R_0 = 2.5$ and $R_1 = 0.833$. Figures 6–10 show that the numerical results are consistent with Theorem 6. We see that the infected equilibrium $E_1(800, 2, 9.25, 5, 0)$ is GAS, and the infection becomes chronic but with no persistent antibody immune response.

(iii) $R_1 > 1$. This condition is satisfied by choosing $\varepsilon = 0$ and $g = 0.01\,\text{mm}^3\,\text{day}^{-1}$. This yields $R_0 = 2.5$ and $R_1 = 1.25$. Figures 6–10 demonstrate the global stability of $E_2(832.58, 1.67, 7.71, 3.34, 74.55)$. Then, the infection becomes chronic but with persistent antibody immune response.

From the definition of the parameter R_0, we can see that the value of the saturation infection rate constant β has no impact on the value of R_0. This means that saturation does not play a role in eliminating the virus. From the definition

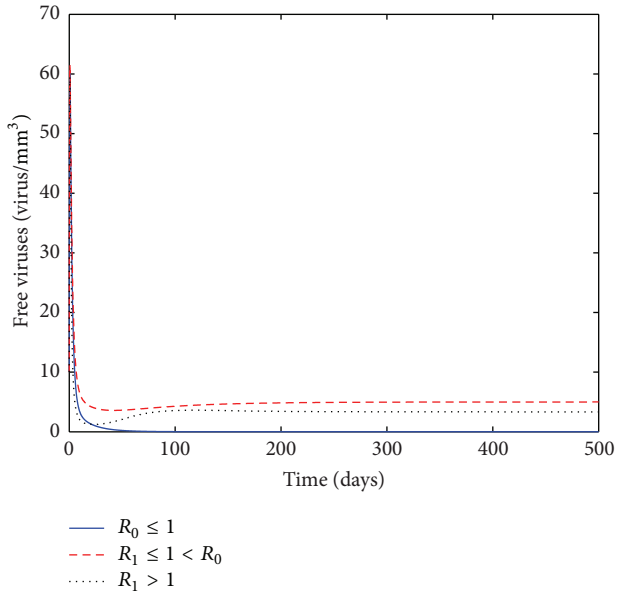

Figure 9: The evolution of free viruses for model (33)–(37).

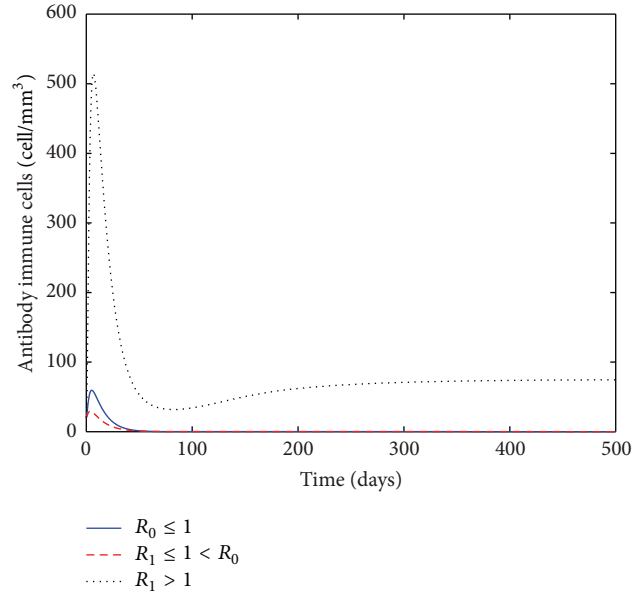

Figure 10: The evolution of antibody immune cells for model (33)–(37).

of R_1, we can see that R_1 can be increased by increasing g or decreasing μ and β.

Figures 6 and 9 show that if $R_1 > 1$ the antibody immune response reduces the concentration of free viruses and increases the concentration of uninfected cells. For model (33)–(37), simple calculation shows that

$$V_1 - V_2 = \left(\frac{dg + (1-\varepsilon) k\mu + d\beta\mu}{g(1-\varepsilon)k + dg\beta} \right) (R_1 - 1). \quad (54)$$

As a result, if $R_1 > 1$, then $V_2 < V_1$. From (33) and at any equilibrium point $\overline{E}(\overline{T}, \overline{T}^*, \overline{C}^*, \overline{V}, \overline{Z})$ we have

$$\overline{T} = \frac{\left(1 + \beta\overline{V}\right)\lambda}{d + (1-\varepsilon)k\overline{V} + d\overline{V}\beta},$$
$$\frac{d\overline{T}}{d\overline{V}} = \frac{-(1-\varepsilon)k\lambda}{\left(d + (1-\varepsilon)k\overline{V} + d\overline{V}\beta\right)^2}. \quad (55)$$

Then, $\overline{T}$ is a decreasing function of $\overline{V}$. It follows that if $R_1 > 1$ then $V_2 < V_1$ and $T_2 > T_1$.

5. Conclusions

In this paper, we have proposed two virus infection models with antibody immune response taking into account the chronically infected cells. In the first model we have assumed that the incidence rate of infection is bilinear while in the second model the incidence rate is given by saturation functional response. We have shown that the dynamics of the models are fully determined by two threshold parameters R_0 and R_1. The parameter R_0 determines whether a chronic infection can be established while R_1 determines whether a persistent antibody response can be established. By constructing Lyapunov function and using LaSalle's invariance principle, we have investigated the global stability of all equilibria of the two models. We have proven that if $R_0 \le 1$ then the infection-free equilibrium E_0 is GAS, and the viruses are cleared. If $R_1 \le 1 < R_0$, then the infected equilibrium without antibody immune response E_1 exists and it is GAS, and the infection becomes chronic but with no persistent antibody immune response. If $R_1 > 1$, then the infected equilibrium with antibody immune response E_2 exists and it is GAS, and the infection is chronic with persistent antibody immune response. Numerical simulations have been performed for the two models. Our simulation results confirm the analytic results given in Theorems 2–7.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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