DISCRETE AND CONTINUOUS
DYNAMICAL SYSTEMS SERIES B
Volume **19**, Number **10**, December **2014**

doi:10.3934/dcdsb.2014.19.3379

pp. **3379–3396**

THE EFFECT OF IMMUNE RESPONSES IN VIRAL INFECTIONS: A MATHEMATICAL MODEL VIEW

Kaifa Wang[1]

School of Biomedical Engineering
Third Military Medical University
Chongqing, 400038, China

Yu Jin[2]

Department of Mathematics
University of Nebraska-Lincoln
Lincoln, NE 68588, USA

Aijun Fan

Chongqing Academy of Science & Technology
Chongqing, 401123, China

Dedicated to the 60th birthday of Chris Cosner

Abstract. To study the effect of immune response in viral infections, a new mathematical model is proposed and analyzed. It describes the interactions between susceptible host cells, infected host cells, free virus, lytic and nonlytic immune response. Using the LaSalle's invariance principle, we establish conditions for the global stability of equilibria. Uniform persistence is obtained when there is a unique endemic equilibrium. Mathematical analysis and numerical simulations indicate that the basic reproduction number of the virus and immune response reproductive number are sharp threshold parameters to determine outcomes of infection. Lytic and nonlytic antiviral activities play a significant role in the amount of susceptible host cells and immune cells in the endemic steady state. We also present potential applications of the model in clinical practice by introducing antiviral effects of antiviral drugs.

1. **Introduction.** Viral infections, such as hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV) infections, have become a significant public health concern [38]. Mathematical models have been introduced to describe the transmission process of various virus infectious diseases, and they have become useful tools to verify various hypotheses and to determine methods of medical treatments; see e.g., [1, 12, 14, 18, 25, 26, 28, 29, 30], and references therein.

During viral infections, immune stress is one of the main factors on virus dynamics within-host and it affects the process, severity and outcome of the infection. Although the relationship between viral replication, cytopathicity and the immune

2010 *Mathematics Subject Classification.* Primary: 92C60, 92D30; Secondary: 34D23.

Key words and phrases. Viral infection, immune responses, reproductive number, stability, uniform persistence.

[1]Supported by the National Natural Science Fund of China (No. 11271369) and the Natural Science Foundation Project of CQ CSTC (2010BB5020).

[2]Corresponding author (yjin6@unl.edu). Supported by AMS-Simons Travel Grants in USA and a startup fund of University of Nebraska-Lincoln.

response is very complex, the antiviral immune effector mechanisms can be broadly divided into lytic and nonlytic components [37]. The lytic immune function is to kill infected cells, just as the natural killer cells lyse infected cells or cytotoxic T lymphocytes kill infected cells, and hence, it increases the death rate of infected cells. The nonlytic immune function is to inhibit viral replication, through soluble mediators, such as interferon α or interferon β, and hence, it reduces the replication rate of the virus. It has been indicated in [37] that if the viral cytopathicity is low relative to the rate of viral replication, then a combination of lytic and nonlytic effector mechanisms is likely to be required.

Population dynamics of viral infection with immune responses, via mathematical modeling and analysis, has been paid increasing attention in last few decades; see e.g., [14, 19, 22, 23, 24, 26, 31, 35, 37, 39] and references therein. The basic population dynamic model of immune responses to persistent viruses was introduced by Nowak and Bangham in [24], where the model described the dynamics of susceptible host cells, infected host cells, free virus and lytic immune response; see also [14, 19, 22, 23, 26, 39]. Based on the assumption that the turnover of free virus is much faster than that of infected cells, the dynamics of free virus was not explicitly included in models in [31, 35, 37]. Instead, a quasi steady-state assumption was imposed there and it indicated that the amount of free virus was simply proportional to the number of infected cells, and hence, the number of infected host cells was considered as a measure of virus load. In [33], it shows that explicit dynamics of free virus may induce fluctuations while the model without free virus component only admits equilibrium steady states. Therefore, the popular quasi-steady-state assumption may not be reasonable in the sense that explicit dynamics of free virus may affect the dynamical behaviors in host-microparasite systems. Hence, incorporating the free virus population into a mathematical model is rather reasonable and important to better reflect the infection process.

To better understand the effect of immune response in viral infections, we present a new mathematical model to describe dynamical behaviors within-host, including the lytic and nonlytic antiviral activity and the explicit activity of free virus. The theoretical analysis shows that the basic reproduction number of the virus (R_1) and the immune response reproductive number (R_2) are sharp threshold parameters. If $R_1 < 1$, only a virus-free equilibrium (corresponding to no infection) exists and it is globally asymptotically stable. If $R_1 > 1$ and $R_2 < 1$, an immune-free equilibrium (corresponding to immune exhaustion) appears and it is asymptotically stable. If $R_2 > 1$, an endemic equilibrium (corresponding to coexistence of virus and immunity) appears and it is asymptotically stable. Furthermore, global stability of the immune-free equilibrium and the endemic equilibrium is also obtained when the efficacy of nonlytic component is sufficient small, while numerical simulations show that this condition may not be necessary. In addition, we investigate the role of lytic and nonlytic immune effectors in viral infections through numerical simulations, and explore potential applications in clinical practice.

The organization of this paper is as follows. We introduce the model in Section 2. In Section 3, we present dynamic analysis, including the dissipativity of the system, the existence and stability of equilibria, and uniform persistence of the system. Numerical simulations of the model are presented in Section 4 with biological interpretations. Finally, a short discussion completes the paper.

2. **The model.** In order to study population dynamics of immune response to persistent viruses, Nowak and Bangham in [24] proposed the following model of the interaction between susceptible host cells ($x(t)$), infected host cells ($y(t)$), free virus particles ($v(t)$), and immune cells ($z(t)$):

$$\begin{cases} x' = r - d_1 x - \beta x v, \\ y' = \beta x v - d_2 y - pyz, \\ v' = k_1 d_2 y - d_3 v, \\ z' = k_2 yz - d_4 z, \end{cases} \tag{1}$$

where immune cells can kill infected host cells but the nonlytic immune response is not considered (i.e., only the lytic immune response is assumed). Wodarz et al. [37] then introduced a different model for viral infection as follows:

$$\begin{cases} x' = r - d_1 x - \frac{\beta x y}{1+qz}, \\ y' = \frac{\beta x y}{1+qz} - d_2 y - pyz, \\ z' = k_2 y - d_4 z, \end{cases} \tag{2}$$

which took into account the nonlytic immune response (q) in antiviral immune effector mechanisms besides lytic immune response but did not consider free virus explicitly based on the assumption that the turnover of free virus is much faster than that of infected cells.

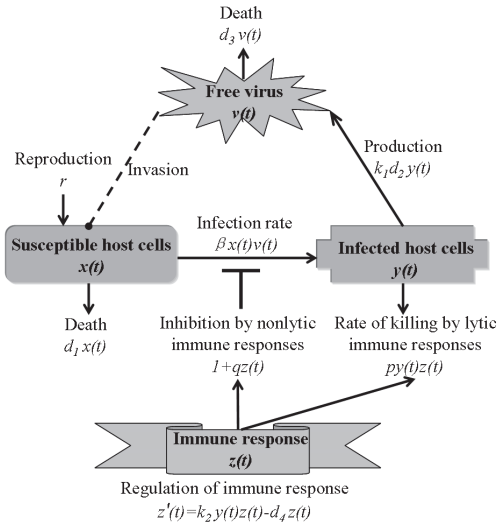

FIGURE 1. The schematic of model (3), a modification of [37, Fig. 1].

Inspired by the work in [24, 37], we consider the following population model (see Figure 1) of viral infection, describing the dynamics of susceptible host cells, infected host cells, free virus, the lytic and nonlytic immune response:

$$\begin{cases} x' = r - d_1 x - \frac{\beta x v}{1+qz}, \\ y' = \frac{\beta x v}{1+qz} - d_2 y - pyz, \\ v' = k_1 d_2 y - d_3 v, \\ z' = k_2 yz - d_4 z, \end{cases} \tag{3}$$

where $x(t)$ is the number of susceptible host cells, $y(t)$ represents infected host cells that can produce free virus particles, $v(t)$ is the number of free virus particles, and $z(t)$ represents immune cells that can inhibit viral infection (nonlytic immune response) and kill infected host cells (lytic immune response). Susceptible cells reproduce at a rate r, die at a rate d_1, and become infected cells by free virus at a rate βv. $1 + qz$ is the inhibition rate of viral infection by the nonlytic antiviral activity with q denoting the strength of the nonlytic immune response. Infected cells die at a rate d_2 and are killed by the lytic antiviral activity of immune response at a rate pz with p denoting the strength of the lytic immune response. k_1 is the burst size, which means the total number of virions produced by an infected cell during its life span. d_3 is the death rate of free virus. Immune cells die at a rate d_4 and are generated at a rate $k_2 y$, which indicates that the production of immune cells is a bilinear form, depending on the contact strength of infected cells and immune cells (see other function forms based on different mechanism assumptions in [5, 6]). Here, all parameters $r, d_1, \beta, q, d_2, p, k_1, d_3, k_2$ and d_4 are nonnegative constants according to their biological significance. The dynamics of free virus is explicitly described but not studied by virtue of infected host cells in model (3). We also consider the antiviral immune effector mechanisms in the viral infection process and assume the nonlytic antiviral activity in model (3) as well as the lytic effector mechanisms of immune responses.

In the study of population dynamics of immune response to persistent viruses *in vivo*, it is important to predict whether the infection disappears, or the immune exhaustion appears, or the virus and the immunity coexist. These phenomena correspond to different asymptotic behaviors of solutions to model (3), i.e., the stability of the equilibria. In the rest of the paper, we first focus on mathematical analysis of global dynamics of (3), and then give biological interpretations of the model and results via numerical simulations.

3. Dynamic analysis.

In this section, we will obtain the dissipativity, derive the basic reproduction number and the immune response reproductive number, and analyze the existence and stability of equilibria and the uniform persistence for model (3).

3.1. Dissipativity.

For biological reason, we consider model (3) in the first octant of $\mathbb{R}^4$. Note that $x'|_{x=0} = r > 0$, $y'|_{y=0} = \beta xv/(1+qz)$, $v'|_{v=0} = k_1 d_2 y$, $z'|_{z=0} = 0$. This implies that $(x(t), y(t), v(t), z(t)) \in \mathbb{R}^4_+$ for all $t > 0$, provided that $(x(0), y(0), v(0), z(0)) \in \mathbb{R}^4_+$.

The following result shows that all solutions of model (3) in $\mathbb{R}^4_+$ are ultimately bounded and that solutions with positive initial value conditions are positive, which indicates that model (3) is biologically well behaved and dissipative.

Theorem 3.1. *For model (3), there exists $M > 0$, such that all solutions in $\mathbb{R}^4_+$ satisfy $x(t) < M, y(t) < M, v(t) < M, z(t) < M$ for all sufficiently large t. Moreover, all solutions with positive initial value conditions*

$$x(0) > 0,\ y(0) > 0,\ v(0) > 0,\ \text{and } z(0) > 0 \tag{4}$$

are positive for $t > 0$ (i.e., $x(t) > 0$, $y(t) > 0$, $v(t) > 0$, and $z(t) > 0$ for all $t > 0$).

Proof. Firstly, we sketch the arguments for ultimate boundedness of solutions of (3) in $\mathbb{R}^4_+$. Let $N_1(t) = x(t) + y(t)$ and $d_5 = \min\{d_1, d_2\}$. Since all components of

a solution of (3) are nonnegative, we have

$$N_1' = r - d_1 x - d_2 y - pyz < r - d_5 N_1.$$

It then follows from the comparison principle and the dynamics of the system $N'(t) = r - d_5 N_1$ that $x(t), y(t) < N_1(t) < 2r/d_5$ for sufficiently large t. Let $N_2(t) = x(t) + y(t) + v(t)/k_1 + pz(t)/k_2$ and $d_6 = \min\{d_1, d_2, d_3, d_4\}$. Then, for large t,

$$N_2' = r + d_5 y - d_1 x - d_5 y - \frac{d_3}{k_1} v - \frac{p d_4}{k_2} z < 3r - d_6 N_2.$$

Therefore, $N_2 < 4r/d_6$ for all large t, and hence, $x(t)$, $y(t)$, $v(t)$ and $z(t)$ are ultimately bounded by positive constant $M = (4r/d_6)\min\{1, k_1, k_2/p\}$.

Now we consider solutions with positive initial value conditions. Note that $z = 0$ is a constant solution of system (3). By the uniqueness and continuity of solutions with respect to initial conditions, for any solution of (3) with initial value conditions (4), we have $z(t) > 0$ for all $t > 0$. Next, we prove that $x(t), y(t)$ and $v(t)$ are positive for all $t > 0$. Suppose that $x(t)$ is not always positive. Let $\tau > 0$ be the first time such that $x(\tau) = 0$. By the first equation of (3) we have $x'(\tau) = r > 0$, which implies $x(t) < 0$ for $t \in (\tau - \epsilon, \tau)$, for sufficiently small $\epsilon > 0$. A contradiction. Thus, $x(t)$ is positive for all $t > 0$. To show that $y(t)$ and $v(t)$ are positive, we first show that they are nonnegative. As $z(t)$ and $x(t)$ are positive, we see from (3) that y' and v have the same sign when $y = 0$, and v' and y have the same sign when $v = 0$. If v reaches 0 for the first time at $t = \tau_1$ while y is still positive (i.e., $y(\tau_1) > 0$), then $v'(\tau_1) > 0$. This contradicts to the fact that $v > 0$ for $t < \tau_1$. We can obtain a similar contradiction if assuming that y reaches 0 for the first time while v is still positive. Therefore, y and v must reach 0 at the same time for the first time, and then remain at 0, which indicates that $y(t)$ and $v(t)$ must be nonnegative. Then by the second and third equations of (3), we have

$$\begin{aligned} y(t) &= \left(y(0) + \int_0^t \tfrac{\beta x(s) v(s)}{1+qz(s)} e^{\int_0^s (d_2 + pz(\theta))d\theta} ds\right) e^{-\int_0^t (d_2 + pz(s))ds} \\ &\geq y(0) e^{-\int_0^t (d_2 + pz(s))ds} > 0, \\ v(t) &= \left(v(0) + \int_0^t k_1 d_2 y(\theta) e^{d_3 \theta} d\theta\right) e^{-d_3 t} \geq v(0) e^{-d_3 t} > 0, \end{aligned}$$

for all $t > 0$. Therefore, any solution of (3) with initial conditions (4) is positive. □

3.2. **Basic reproductive numbers and equilibria.** To obtain equilibria of model (3), we consider the following algebraic system

$$\begin{cases} r - d_1 x - \frac{\beta x v}{1+qz} = 0, \\ \frac{\beta x v}{1+qz} - d_2 y - pyz = 0, \\ k_1 d_2 y - d_3 v = 0, \\ k_2 yz - d_4 z = 0. \end{cases} \tag{5}$$

It is easy to see that (3) always admits a virus-free equilibrium $E_0 = (r/d_1, 0, 0, 0)$, which satisfies (5) and corresponds to the "no infection" state.

3.2.1. *The basic reproduction number and the immune-free equilibrium.* Recall that the basic reproduction number is the mean number of secondary cases which is caused by a typical infected individual in a totally susceptible population during its lifetime in the absence of any control policies [8, 32]. During its mean lifetime of $T = 1/d_2$, an infected cell averagely generates $P(T) = k_1 d_2 T$ virus. A virus has an average lifetime of $1/d_3$, and hence, it can produce a maximum amount of

$I(T) = r\beta/d_1d_3$ infections. Therefore, *the basic reproduction number* of virus for (3) can be defined as

$$R_1 = P(T)I(T) = \frac{k_1 r\beta}{d_1 d_3}. \tag{6}$$

Based on (5), if $R_1 > 1$, suppose that the immune response has not established, i.e., $z = 0$, (3) admits a unique immune-free equilibrium $E_1 = (x_1^*, y_1^*, v_1^*, 0)$, where

$$x_1^* = \frac{d_3}{k_1\beta}, \quad y_1^* = \frac{k_1 r\beta - d_1 d_3}{k_1\beta d_2}, \quad v_1^* = \frac{k_1 r\beta - d_1 d_3}{\beta d_3}, \tag{7}$$

and E_1 corresponds to the "immune exhaustion" state.

3.2.2. *The immune response reproductive number and the endemic equilibrium.* Similarly as we define the basic reproduction number of virus, we derive the immune response reproductive number R_2, which describes the average number of newly immune cells generated from one immune cell during its mean lifetime. Note that the immune-free equilibrium E_1 corresponds to no immune response. In this state, the amount of infected cells is $y_1^* = (k_1 r\beta - d_1 d_3)/k_1\beta d_2$. Suppose that an immune cell is introduced into this state. Then $k_2 y_1^*$ new immune cells will be produced by the initially introduced immune cell during a time unit (see the fourth equation of (3)). Since an immune response has an average lifetime of $1/d_4$, the initially introduced immune cell produces $k_2 y_1^*/d_4$ new immune cells in total during one immune response process, and hence, *the immune response reproductive number* for (3) can be given by

$$R_2 = \frac{k_2 y_1^*}{d_4} = \frac{k_2(k_1 r\beta - d_1 d_3)}{k_1\beta d_2 d_4}. \tag{8}$$

By (5) again, we can obtain that model (3) admits a unique endemic equilibrium $E_2 = (x_2^*, y_2^*, v_2^*, z_2^*)$, whose components are all positive, if $R_2 > 1$. This corresponds to the "virus and immunity coexistence" state. Here

$$\begin{aligned} x_2^* &= \tfrac{k_2 r - d_2 d_4 - p d_4 z_2^*}{k_2 d_1} = \tfrac{y_2^*(1+qz_2^*)(d_2+pz_2^*)}{\beta v_2^*}, \\ y_2^* &= \tfrac{d_4}{k_2}, \\ v_2^* &= \tfrac{k_1 d_2 d_4}{k_2 d_3}, \\ z_2^* &= \tfrac{-K_2 + \sqrt{K_2^2 - 4K_1K_3}}{2K_1}, \end{aligned} \tag{9}$$

where z_2^* is the positive real root of the quadratic equation $K_1 z^2 + K_2 z + K_3 = 0$, in which

$$\begin{aligned} K_1 &= k_2 q p d_1 d_3, \\ K_2 &= k_2 p d_1 d_3 + k_2 q d_1 d_2 d_3 + \beta k_1 p d_2 d_4, \\ K_3 &= d_2(k_2 d_1 d_3 - \beta r k_1 k_2 + \beta k_1 d_2 d_4). \end{aligned}$$

Remark 1. Note that by (6) and (8), we have $R_2 > 1$ implies $R_1 > 1$.

We summarize this subsection by the following theorem.

Theorem 3.2. *For system (3), the virus-free equilibrium $E_0 = (r/d_1, 0, 0, 0)$ always exists; if $R_1 > 1$ and $R_2 < 1$, the immune-free equilibrium E_1 appears; if $R_2 > 1$, a unique endemic equilibrium E_2 appears.*

3.3. **Local stability of equilibria.** In this subsection, we consider the local stability of equilibria of model (3). The Jacobian matrix J of (3) is

$$J = \begin{bmatrix} -d_1 - \frac{\beta v}{1+qz} & 0 & -\frac{\beta x}{1+qz} & \frac{q\beta xv}{(1+qz)^2} \\ \frac{\beta v}{1+qz} & -d_2 - pz & \frac{\beta x}{1+qz} & -py - \frac{q\beta xv}{(1+qz)^2} \\ 0 & k_1 d_2 & -d_3 & 0 \\ 0 & k_2 z & 0 & k_2 y - d_4 \end{bmatrix}. \tag{10}$$

The characteristic equation associated with the Jacobian matrix J at the equilibrium E_0 is

$$H_{E_0}(\lambda) := (\lambda + d_1)(\lambda + d_4)(\lambda^2 + (d_2 + d_3)\lambda + d_2 d_3(1 - R_1)) = 0. \tag{11}$$

Clearly, all eigenvalues of (11) are negative real numbers if $R_1 < 1$ and there is one positive eigenvalue if $R_1 > 1$. Thus, we have the following result.

Theorem 3.3. *For (3), the virus-free equilibrium E_0 is locally asymptotically stable if $R_1 < 1$ and it is unstable if $R_1 > 1$.*

As for the stability of the equilibrium E_1 of (3), we have the following result.

Theorem 3.4. *For (3), the immune-free equilibrium E_1 is locally asymptotically stable if $R_1 > 1$ and $R_2 < 1$, and is unstable if $R_2 > 1$.*

Proof. The characteristic equation associated with the Jacobian matrix J at E_1 is given by

$$H_{E_1}(\lambda) := (\lambda + d_4 - k_2 y_1^*) H_1(\lambda) = 0, \tag{12}$$

where

$$H_1(\lambda) = \lambda^3 + A_1\lambda^2 + A_2\lambda + A_3,$$

and

$$A_1 = d_1 + d_2 + d_3 + \beta v_1^*, \quad A_2 = (d_2 + d_3)(d_1 + \beta v_1^*), \quad A_3 = k_1 d_2 r \beta.$$

By (7), we have

$$k_2 y_1^* - d_4 = \frac{k_2(k_1 r\beta - d_1 d_3) - k_1 d_2 d_4 \beta}{k_1 d_2 \beta} \begin{cases} < 0 & \text{if } R_2 < 1, \\ > 0 & \text{if } R_2 > 1. \end{cases}$$

Furthermore, note that $A_1 > 0, A_3 > 0$ and

$$\Delta_2 = \begin{vmatrix} A_1 & 1 \\ A_3 & A_2 \end{vmatrix} = A_1 A_2 - A_3 = \frac{k_1 r\beta(d_3^3 + (d_2 + d_3)(k_1 r\beta + d_2 d_3))}{d_3^2} > 0.$$

Thus, the theorem follows from the Routh-Hurwitz criterion. □

The stability of the equilibrium E_2 of (3) is given in the following theorem.

Theorem 3.5. *For (3), the endemic equilibrium E_2 is locally asymptotically stable if $R_2 > 1$.*

Proof. Through lengthly algebraic calculations, the characteristic equation associated with the Jacobian matrix J at E_2 can be given by

$$H_{E_2}(\lambda) := \lambda^4 + A_1\lambda^3 + A_2\lambda^2 + A_3\lambda + A_4 = 0, \tag{13}$$

where

$$\begin{aligned} A_1 &= d_2 + d_3 + \tfrac{r}{x_2^*} + pz_2^* > 0, \\ A_2 &= pd_4 z_2^* + \tfrac{r(d_2 + d_3 + pz_2^*)}{x_2^*} + \tfrac{qk_2(r - d_1 x_2^*)z_2^*}{1+qz_2^*} > 0, \\ A_3 &= pd_3 d_4 z_2^* + \tfrac{rpd_4 z_2^*}{x_2^*} + \tfrac{(r - d_1 x_2^*)(k_1 d_2 \beta + qk_2(d_1 + d_3)z_2^*)}{1+qz_2^*} > 0, \\ A_4 &= \tfrac{prd_3 d_4 z_2^*}{x_2^*} + \tfrac{qd_1 d_3 k_2(r - d_1 x_2^*)z_2^*}{1+qz_2^*} > 0. \end{aligned}$$

Here, we used $\beta x_2^* v_2^*/(1+qz_2^*) = r-d_1x_2^* = y_2^*(d_2+pz_2^*), k_2y_2^*-d_4 = 0, d_3(d_2+pz_2^*) = k_1d_2\beta x_2^*/(1+qz_2^*)$ and (9).

Furthermore, with the aid of MATHEMATICA, we obtain

$$\begin{aligned}\Delta_2 &= \begin{vmatrix} A_1 & 1 \\ A_3 & A_2 \end{vmatrix} = A_1A_2 - A_3 \\ &= pd_4z_2^*(d_2+pz_2^*) + \tfrac{r(d_2+d_3+pz_2^*)}{x_2^*}(d_2+d_3+pz_2^*+\tfrac{r}{x_2^*}) \\ &\quad + \tfrac{r-d_1x_2^*}{1+qz_2^*}(\beta k_1d_2 + qk_2z_2^*(d_2+pz_2^*) + \tfrac{qk_2z_2^*(r-d_1z_2^*)}{x_2^*}) > 0\end{aligned}$$

and

$$\begin{aligned}\Delta_3 &= \begin{vmatrix} A_1 & 1 & 0 \\ A_3 & A_2 & A_1 \\ 0 & A_4 & A_3 \end{vmatrix} = A_1A_2A_3 - A_3^2 - A_1^2A_4 = \Delta_2A_3 - A_1^2A_4 \\ &= p^2d_3d_4^2z_2^{*2}(d_2+pz_2^*) + \tfrac{pr^3d_4z_2^*(d_2+pz_2^*)}{x_2^{*3}} + \tfrac{p^2rd_4^2z_2^{*2}(d_2+pz_2^*)}{x_2^*} \\ &\quad + \tfrac{pr^2d_4z_2^*(d_2+pz_2^*)(d_2+d_3+pz_2^*)}{x_2^{*2}} + \tfrac{(r-d_1x_2^*)H(x_2^*,z_2^*)}{x_2^{*2}(1+qz_2^*)^2},\end{aligned}$$

where

$$H(x_2^*,z_2^*) = r\beta d_2^3k_1x_2^*(1+qz_2^*) + d_2^2H_1(x_2^*,z_2^*) + qk_2z_2^*H_2(x_2^*,z_2^*) + d_2H_3(x_2^*,z_2^*)$$

with

$$\begin{aligned}H_1(x_2^*,z_2^*) &= \beta^2k_1^2x_2^{*2}(r-d_1x_2^*) + qk_2x_2^*z_2^*(1+qz_2^*)(d_1r+d_3(r-d_1x_2^*)) \\ &\quad + \beta k_1(r^2 + (qr^2+2prx_2^*+pd_4x_2^{*2}+qk_2x_2^{*2}(r-d_1x_2^*))z_2^* \\ &\quad + pqx_2^*(2r+d_4x_2^*)z_2^{*2} + 2rd_3x_2^*(1+qz_2^*)), \\ H_2(x_2^*,z_2^*) &= d_3^2(r-d_1x_2^*)(1+qz_2^*)(d_3x_2^*+r+2px_2^*z_2^*) \\ &\quad + d_3z_2^*(qk_2x_2^*(r-d_1x_2^*)(r-d_1x_2^*+px_2^*z_2^*) \\ &\quad + pd_4x_2^*(1+qz_2^*)(r-d_1x_2^*+2px_2^*z_2^*) \\ &\quad + p(1+qz_2^*)(r^2+px_2^*z_2^*(r-d_1x_2^*))) \\ &\quad + z_2^*((1+qz_2^*)(prd_1(r+px_2^*z_2^*) + p^2d_4x_2^*z_2^*(r+d_1x_2^*)) \\ &\quad + qd_1x_2^*(r-d_1x_2^*)(k_2(r-d_1x_2^*)+pk_1x_2^*z_2^*)) \\ &\quad + (1+qz_2^*)prd_4(r-d_1x_2^*), \\ H_3(x_2^*,z_2^*) &= d_3^2x_2^*(1+qz_2^*)(\beta rk_1 + 2qk_2z_2^*(r-d_1x_2^*)) + d_3(\beta k_1(r^2(1+qz_2^*) \\ &\quad + z_2^*(2prx_2^*+pd_4x_2^{*2}(r-d_1x_2^*)) + pqx_2^*(2r+d_4x_2^*)z_2^{*2}) \\ &\quad + qk_2z_2^*(r^2(1+qz_2^*) + x_2^*z_2^*(2pd_4x_2^* + (r-d_1x_2^*)(2p+qk_2x_2^*)) \\ &\quad + 2pqx_2^*z_2^{*2}(r-d_1x_2^*+d_4x_2^*))) \\ &\quad + z_2^*(\beta k_1(r+px_2^*z_2^*)(qk_2x_2^*(r-d_1x_2^*) + p(1+qz_2^*)(r+d_4x_2^*)) \\ &\quad + qk_2(qd_1k_2x_2^{*2}z_2^*(r-d_1x_2^*) \\ &\quad + (1+qz_2^*)(r^2d_1 + px_2^*z_2^*(d_1(r+d_4x_2^*) + r(d_1+d_4))))).\end{aligned}$$

Note that $r-d_1x_2^* = y_2^*(d_2+pz_2^*) > 0$. We have $H_1(x_2^*,z_2^*) > 0, H_2(x_2^*,z_2^*) > 0$ and $H_3(x_2^*,z_2^*) > 0$. Thus, $H(x_2^*,z_2^*) > 0$ and $\Delta_3 > 0$. It then follows from the Routh-Hurwitz criterion that all eigenvalues of (13) have negative real parts, and hence, the endemic equilibrium E_2 is locally asymptotically stable once it exists, i.e, when $R_2 > 1$. □

3.4. **Global stability of equilibria.** The objective of this subsection is to investigate the global stability of the equilibria. The global properties of (3) are given by the following theorem.

Theorem 3.6. *For (3), the following results are true.*

(i) If $R_1 < 1$, then the virus-free equilibrium E_0 is globally asymptotically stable;

(ii) If $R_1 > 1, R_2 < 1$ and $q = 0$, then the immune-free equilibrium E_1 is globally asymptotically stable;

(iii) If $R_2 > 1$ and $q = 0$, then the endemic equilibrium E_2 is globally asymptotically stable.

Proof. (i) Define a Lyapunov function,

$$V_1 = x - \frac{r}{d_1} - \frac{r}{d_1}\ln\frac{d_1 x}{r} + y + \frac{v}{k_1} + \frac{pz}{k_2}.$$

Along the trajectories of system (3), we have

$$\begin{aligned} V_1'|_{(3)} &= (1-\tfrac{r}{d_1 x})x' + y' + \tfrac{1}{k_1}v' + \tfrac{p}{k_2}z' \\ &= -\tfrac{d_1}{x}(x-\tfrac{r}{d_1})^2 - \tfrac{d_3(1-R_1+qz)}{k_1(1+qz)}v - \tfrac{pd_4}{k_2}z. \end{aligned} \tag{14}$$

Note that all solutions of system (3) are positive for $t > 0$. All terms of the right hand side of (14) are nonpositive when $R_1 < 1$, which implies that $V_1' \le 0$ and that $V_1' = 0$ if and only if $x = r/d_1, v = 0$ and $z = 0$. Therefore, the maximal invariant set in $\{(x, y, v, z) : V_1' = 0\}$ is the singleton $\{E_0\}$. The globally asymptotical stability of E_0 when $R_1 < 1$ follows from LaSalle's invariance principle [17] and Theorem 3.3.

(ii) Define a Lyapunov function,

$$V_2 = x - x_1^* - x_1^*\ln\frac{x}{x_1^*} + y - y_1^* - y_1^*\ln\frac{y}{y_1^*} + \frac{1}{k_1}(v - v_1^* - v_1^*\ln\frac{v}{v_1^*}) + \frac{pz}{k_2}.$$

Note that $(x+y+v/k_1+pz/k_2)' = r - d_1 x - d_3 v/k_1 - pd_4 z/k_2$. Along the trajectories of system (3), we have

$$\begin{aligned} V_2'|_{(3)} &= (1-\tfrac{x_1^*}{x})x' + (1-\tfrac{y_1^*}{y})y' + \tfrac{1}{k_1}(1-\tfrac{v_1^*}{v})v' + \tfrac{p}{k_2}z' \\ &= d_1 x_1^*(2 - \tfrac{x_1^*}{x} - \tfrac{x}{x_1^*}) + d_2 y_1^*(3 - \tfrac{x_1^*}{x} - \tfrac{y_1^* x v}{x_1^* v_1^* y} - \tfrac{v_1^* y}{y_1^* v}) \\ &\quad + pz(y_1^* - \tfrac{d_4}{k_2}) + \tfrac{qzv(\beta k_1 y_1^* x - d_3 y)}{k_1 y(1+qz)}, \end{aligned} \tag{15}$$

where we use $r = d_1 x_1^* + \beta x_1^* v_1^* = d_1 x_1^* + d_2 y_1^*, \beta = d_2 y_1^*/x_1^* v_1^*, d_3/k_1 = d_2 y_1^*/v_1^*$ and (7).

Since $y_1^* - d_4/k_2 = d_4(R_2 - 1)/k_2$, we have $y_1^* - d_4/k_2 < 0$ if $R_2 < 1$. Furthermore, by the theorem that the arithmetic mean is greater than or equal to the geometric mean, when $q = 0$, $V_2' \le 0$ and $V_2' = 0$ holds only if $x = x_1^*, z = 0$ and $v_1^* y = v y_1^*$ simultaneously. Therefore, the maximal invariant set in $\{(x, y, v, z) : V_2' = 0\}$ is the singleton $\{E_1\}$. Using LaSalle's invariance principle [17] and Theorem 3.4, the immune-free equilibrium E_1 is globally asymptotically stable if $R_1 > 1, R_2 < 1$ and $q = 0$.

(iii) Considering the following Lyapunov function,

$$\begin{aligned} V_3 &= x - x_2^* - x_2^*\ln\tfrac{x}{x_2^*} + y - y_2^* - y_2^*\ln\tfrac{y}{y_2^*} \\ &\quad + (\tfrac{1}{k_1} + \tfrac{pz_2^*}{k_1 d_2})(v - v_2^* - v_2^*\ln\tfrac{v}{v_2^*}) + \tfrac{p}{k_2}(z - z_2^* - z_2^*\ln\tfrac{z}{z_2^*}). \end{aligned}$$

Along the trajectories of system (3), we have

$$\begin{aligned} V_3'|_{(3)} &= (1-\tfrac{x_2^*}{x})x' + (1-\tfrac{y_2^*}{y})y' \\ &\quad + (\tfrac{1}{k_1} + \tfrac{pz_2^*}{k_1 d_2})(1-\tfrac{v_2^*}{v})v' + \tfrac{p}{k_2}(1-\tfrac{z_2^*}{z})z' \\ &= d_1 x_2^*(2 - \tfrac{x}{x_2^*} - \tfrac{x_2^*}{x}) + (d_2 y_2^* + p y_2^* z_2^*)(3 - \tfrac{x_2^*}{x} - \tfrac{v_2^* y}{y_2^* v} - \tfrac{y_2^* x v}{x_2^* v_2^* y}) \\ &\quad - \tfrac{q y_2^* v(d_2 + pz_2^*)(z - z_2^*)(x_2^* y - y_2^* x)}{x_2^* v_2^* y(1+qz)}, \end{aligned} \tag{16}$$

where we use $r = d_1x_2^* + \beta x_2^* v_2^*/(1+qz_2^*) = d_1x_2^* + d_2y_2^* + py_2^*z_2^*, \beta = (d_2+pz_2^*)(1+qz_2^*)y_2^*/x_2^*v_2^*, d_3/k_1 = d_2y_2^*/v_2^*$ and (9). Hence, similar to the above analysis, by LaSalle's invariance principle [17] and Theorem 3.5, the endemic equilibrium E_2 is globally asymptotically stable if $R_2 > 1$ and $q = 0$. This completes the proof. □

Remark 2. Note that q expresses the efficacy of the nonlytic component. Thus, Theorem 3.6 implies that system (3) is globally asymptotically stable if the nonlytic antiviral activity is neglected, i.e., $q = 0$. Furthermore, by (15) and (16) and the continuity of functions involved there, we can conclude that system (3) should maintain its global properties when the nonlytic antiviral activity is sufficient small.

3.5. **Uniform persistence.** In this subsection, we investigate the uniform persistence of (3). We first introduce a preliminary theory. Let X be a complete metric space. Suppose that X^0 is an open set in X, $X_0 \subset X$, $X^0 \cap X_0 = \emptyset$, and $X^0 \cup X_0 = X$. Assume that $T(t)$ is a C_0-semigroup of X satisfying

$$\begin{cases} T(t) : X^0 \to X^0, \\ T(t) : X_0 \to X_0. \end{cases} \tag{17}$$

Let $T_\partial(t) = T(t)|X_0$, and let A_∂ be the global attractor for $T_\partial(t)$. The following result is provided in [11].

Lemma 3.7. *([11, Theorem 4.1]) Suppose that $T(t)$ satisfies (17) and that the following conditions are valid.*

(i) There is a $t_0 \geq 0$ such that $T(t)$ is compact for $t > t_0$.

(ii) $T(t)$ is point dissipative in X.

(iii) $\tilde{A}_\partial = \bigcup_{x \in A_\partial} \omega(x)$ is isolated and has an acyclic covering $\tilde{M}$, where $\tilde{M} = \{M_1, M_2, \ldots, M_n\}$.

(iv) $W^s(M_i) \cap X^0 = \emptyset$, $i = 1, 2, \ldots, n$.

Then $T(t)$ is uniformly persistent in the sense that there is an $\varepsilon > 0$, such that, for any $x \in X^0$, $\liminf_{t\to+\infty} d(T(t)x, X_0) \geq \varepsilon$, where d is the distance of $T(t)x$ from X_0.

By applying Lemma 3.7 to (3), we can obtain the following result for the uniform persistence of (3).

Theorem 3.8. *If $R_2 > 1$, then system (3) is uniformly persistent, in the sense that, there exists $\varepsilon > 0$ (independent of initial conditions), such that, $\liminf_{t\to+\infty} x(t) \geq \varepsilon$, $\liminf_{t\to+\infty} y(t) \geq \varepsilon$, $\liminf_{t\to+\infty} v(t) \geq \varepsilon$ and $\liminf_{t\to+\infty} z(t) \geq \varepsilon$, for all solutions of (3) with initial conditions (4).*

Proof. Let $X = \mathbb{R}^4_+$, $X_0 = U_1 \cup U_2$, where

$$U_1 = \{(x, y, v, z) \in \mathbb{R}^4_+ : z \equiv 0\}, \quad U_2 = \{(x, y, v, z) \in \mathbb{R}^4_+ : y \equiv 0, v \equiv 0\},$$

and let $X^0 = X \setminus X_0$. Basic analysis of (3) implies that X_0 is a positive invariant set for (3). The positive invariance of X^0 follows from Theorem 3.1 and simple analysis of (3) when any initial component is zero. Therefore, (17) is satisfied.

For any initial value condition $\phi_0 = (x_0, y_0, v_0, z_0)$ in $\mathbb{R}^4$, define $T(t)$ for $t \geq 0$ as $T(t)\phi_0 := (x(t), y(t), v(t), z(t))$ for $t \geq 0$, where $(x(t), y(t), v(t), z(t))$ is a solution of (3) with initial condition ϕ_0. Then $\{T(t)\}_{t\geq 0}$ is a C_0 semigroup generated by (3). By Theorem 3.1 we have $T(t)$ is dissipative in X, and hence, conditions (i) and (ii) of Lemma 3.7 are satisfied. Note that system (3) admits two boundary equilibria

$E_0 = (r/d_1, 0, 0, 0)$ and $E_1 = (x_1^*, y_1^*, v_1^*, 0)$. For any solution of (3) with initial condition $(x(0), y(0), v(0), z(0)) \in U_1$, we have $z(t) \equiv 0$ for all $t \geq 0$ and

$$\begin{cases} x' = r - d_1 x - \beta x v, \\ y' = \beta x v - d_2 y, \\ v' = k_1 d_2 y - d_3 v. \end{cases} \tag{18}$$

It then follows from the result in [16] that $(x(t), y(t), v(t)) \to (x_1^*, y_1^*, v_1^*)$ as $t \to +\infty$ if $R_1 > 1$. For any solution of (3) with initial condition $(x(0), y(0), v(0), z(0)) \in U_2$, it is clear that $y(t) \equiv 0$, $v(t) \equiv 0$, $z(t) \to 0$ and $x(t) \to r/d_1$ as $t \to +\infty$. Hence $\{E_0, E_1\}$ contains all ω-limit sets in X_0. By Theorem 3.3 and Theorem 3.4, both E_0 and E_1 are unstable if $R_2 > 1$. Then E_0 and E_1 are isolated, and hence, $\{E_0, E_1\}$ is isolated and acyclic covering and the condition (iii) of Lemma 3.7 is satisfied. Moreover, as $W^s(E_0) \cap X^0 = \emptyset$ and $W^s(E_1) \cap X^0 = \emptyset$, the condition (iv) of Lemma 3.7 is satisfied. Therefore, Lemma 3.7 implies that all solutions of system (3) in X^0 are uniform repellers with respect to X_0, i.e., there is an $\varepsilon_0 > 0$ such that for any solution $\Phi(t) = (x(t), y(t), v(t), z(t))$ of system (3) with initial condition in X^0, we have $\liminf_{t\to+\infty} d(\Phi(t), X_0) \geq \varepsilon_0$, where d is the distance of $\Phi(t)$ from X_0. Thus, there exists an $\varepsilon_1 > 0$ such that

$$\liminf_{t\to+\infty} (y(t) + v(t)) \geq \varepsilon_1, \quad \liminf_{t\to+\infty} z(t) \geq \varepsilon_1$$

for any solution of system (3) with initial condition in X^0.

Furthermore, by using the first equation of (3), Theorem 3.1 and the above result, we have

$$x' = r - d_1 x - \frac{\beta x v}{1 + qz} > r - d_7 x,$$

where $d_7 = d_1 + \beta M/(1 + q\varepsilon_1)$. It then follows from comparison principle and the dynamics of the system $x' = r - d_7 x$ that $x(t) > r/2d_7$ for sufficiently large t, for any solution of (3) with initial value conditions in X^0.

Let $y_\infty = \liminf_{t\to+\infty} y(t)$ and $v_\infty = \liminf_{t\to+\infty} v(t)$. By the fluctuations Lemma [13, Lemma 4.2], there exists a sequence $(\tau_n) \uparrow \infty$ such that $v(\tau_n) \to v_\infty$ and $v'(\tau_n) = 0$. Then by the third equation of (3), we have $0 = k_1 d_2 \lim_{n\to\infty} y(\tau_n) - d_3 v_\infty$. So, $k_1 d_2 y_\infty \leq k_1 d_2 \lim_{n\to\infty} y(\tau_n) = d_3 v_\infty$, and hence, $d_3 v_\infty/(k_1 d_2) + v_\infty \geq y_\infty + v_\infty \geq \varepsilon_1$. Therefore, $v_\infty \geq \varepsilon_1/(1 + d_3/k_1 d_2) = \varepsilon_1 k_1 d_2/(k_1 d_2 + d_3)$.

Similarly as above, there exists a sequence $(\tau_n) \uparrow \infty$ such that $y(\tau_n) \to y_\infty$ and $y'(\tau_n) = 0$. By the second equation of (3), we have

$$0 = \lim_{n\to\infty} \frac{\beta x(\tau_n) v(\tau_n)}{1 + qz(\tau_n)} - d_2 y_\infty - \lim_{n\to\infty} p y_\infty z(\tau_n),$$

and hence,

$$\begin{aligned} y_\infty &\geq \frac{\beta \frac{r}{2d_7} v_\infty}{(1+qM)(d_2+pM)} \geq \frac{\beta \frac{r}{2d_7} \frac{\varepsilon_1 k_1 d_2}{(k_1 d_2 + d_3)}}{(1+qM)(d_2+pM)} \\ &= \frac{\beta r \varepsilon_1 k_1 d_2}{2d_7 (k_1 d_2 + d_3)(1+qM)(d_2+pM)} := \varepsilon_2. \end{aligned}$$

Therefore, taking $\varepsilon = \min\{r/2d_7, \varepsilon_2, \varepsilon_1 k_1 d_2/(k_1 d_2 + d_3), \varepsilon_1\}$, we can conclude that

$$\liminf_{t\to+\infty} x(t) \geq \varepsilon, \quad \liminf_{t\to+\infty} y(t) \geq \varepsilon, \quad \liminf_{t\to+\infty} v(t) \geq \varepsilon, \quad \liminf_{t\to+\infty} z(t) \geq \varepsilon$$

are valid for any solution of system (3) with initial value conditions in X^0. This completes the proof. □

Remark 3. Note that $R_2 > 1$ implies that $R_1 > 1$ and there is a positive proportional relationship between k_1 and R_1. k_1 is the burst size, representing the viral replicative capacity. Thus, our theoretical results (Theorem 3.5 and Theorem 3.6) have implications for supporting the mechanism in [2], i.e., viral replicative capacity is the primary determinant of lymphocytic choriomeningitis virus persistence and immunosuppression.

4. **Numerical simulations.** In this section, we give numerical simulations to investigate the effect of the dynamics between lytic and nonlytic antiviral activity, and explore potential applications in clinical practice. All parameter values are within similar ranges as in [19, 30]. In particular, the parameter values in the whole section are taken in the following parameter set (**P**) unless otherwise notified in the figures.

(**P**) $r = 1.0 \times 10^4$ ml$^{-1} \cdot$ day^{-1}, $\beta = 2.4 \times 10^{-8}$ ml$^{-1} \cdot$ day^{-1}, $d_1 = 0.01$ day^{-1}, $d_2 = 1.0$ day^{-1}, $d_3 = 23$ day^{-1}, $d_4 = 0.035$ day^{-1}, $k_1 = 2000$, $k_2 = 9.0 \times 10^{-6}$ ml $\cdot$ day^{-1}, $p = 0.5$ ml $\cdot$ day^{-1} and $q = 0.5$ ml.

It follows from (6) and (8) that $R_1 = 2.09 > 1$ and $R_2 = 1.34 > 1$ for (3) with parameters in (**P**), and hence, the virus-free equilibrium $E_0 = (1.0 \times 10^6, 0, 0, 0)$ and immune-free equilibrium $E_1 = (4.79 \times 10^5, 5.21 \times 10^3, 4.53 \times 10^5, 0)$ are unstable and the endemic equilibrium $E_2 = (5.74 \times 10^5, 3.89 \times 10^3, 3.38 \times 10^5, 0.19)$ is asymptotically stable in this situation.

4.1. **Effects of the lytic and nonlytic strength on reproductive numbers and equilibria.** By the expressions of the basic reproduction number of virus (6) and the immune response reproductive number (8), we see that the reproductive numbers have no concern with the efficacy of the lytic component (p) and lytic component (q). In addition, (7) indicates that the immune-free equilibrium E_1 is also independent of p and q since the immune response is not established at such state. However, (9) shows that the components of susceptible host cells (x_2^*) and immune cells (z_2^*) in the endemic equilibrium E_2 are apparently related to p and q.

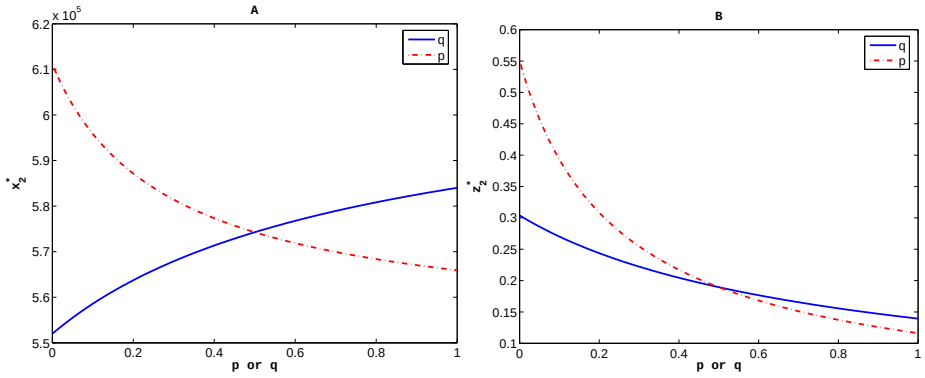

FIGURE 2. The effect of the lytic antiviral activity and the nonlytic antiviral activity on the steady state of susceptible host cells (x_2^*) and immune cells (z_2^*) in the endemic equilibrium E_2.

Figure 2A shows that as p or q increases, the steady state of susceptible host cells (x_2^*) decreases. This implies that larger lytic antiviral activity may induce more

serious outcome during viral infection, whereas large nonlytic antiviral activity may be advantageous to increase the amount of susceptible host cells. These phenomena agree well with the reports that noncytolytic effector mechanisms "cure" infected cells [3, 4, 10, 27, 37]. From Figure 2B, we can find that the steady state of immune cells (z_2^*) follows the same trend along with the increase of p or q, but the shift downward with p is faster than that with q.

4.2. **Effects of the nonlytic strength on the global stability of equilibria.** In Theorem 3.6, we obtain sufficient conditions for global stability of equilibria of (3). Furthermore, by Remark 2, we know that system (3) may maintain its global properties when the nonlytic antiviral activity is sufficient small. But it is unclear whether the immune-free equilibrium and the endemic equilibrium maintain their global stability or not when the nonlytic strength becomes large.

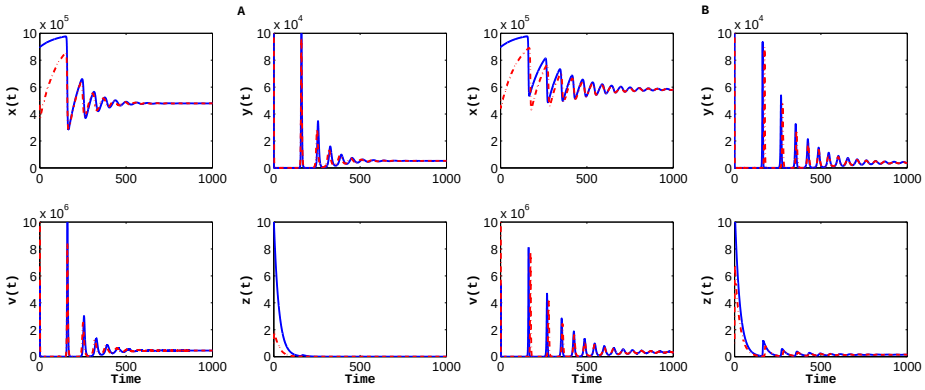

FIGURE 3. Time series of susceptible host cells ($x(t)$), infected host cells ($y(t)$), virus load ($v(t)$) and immune cells ($z(t)$) in host as predicted by the model (3). Here parameters are in (**P**) except $q = 0.9$, $k_2 = 2.0 \times 10^{-6}$ in (A) and $k_2 = 9.0 \times 10^{-6}$ in (B). Note that solid lines correspond to the initial condition $(x(0), y(0), v(0), z(0)) = (9.0 \times 10^5, 1.0 \times 10^5, 100.0, 10.0)$ and the dash-dot lines correspond to the initial condition $(x(0), y(0), v(0), z(0)) = (5.0 \times 10^5, 5.0 \times 10^5, 1.0 \times 10^6, 1.0)$.

When the coefficient of the production rate of immune responses is $k_2 = 2.0 \times 10^{-6}$ ($R_1 = 2.09 > 1$ and $R_2 = 0.30 < 1$), we find that the immune-free equilibrium $E_1 = (4.79 \times 10^5, 5.21 \times 10^3, 4.53 \times 10^5, 0)$ is globally asymptotically stable although the nonlytic strength q is as large as 0.9 (Figure 3A). When $k_2 = 9.0 \times 10^{-6}$ ($R_1 = 2.09 > 1$ and $R_2 = 1.34 > 1$), Figure 3B indicates that the endemic equilibrium $E_2 = (5.83 \times 10^5, 3.89 \times 10^3, 3.38 \times 10^5, 0.15)$ is globally asymptotically stable even if $q = 0.9$. Thus, we conjecture that the global properties of (3) will hold whatever the nonlytic strength is, i.e., the condition $q = 0$ can be removed in Theorem 3.6, but the rigorous mathematical proof remains open.

Note that the components of infected host cells and virus load in equilibrium E_1 are larger than that in E_2, but the amount of immune cells in E_1 is zero. Hence the global stability of the immune-free equilibrium may be chalked up to the high antigen levels, which is supported by the recent experimental results in [21].

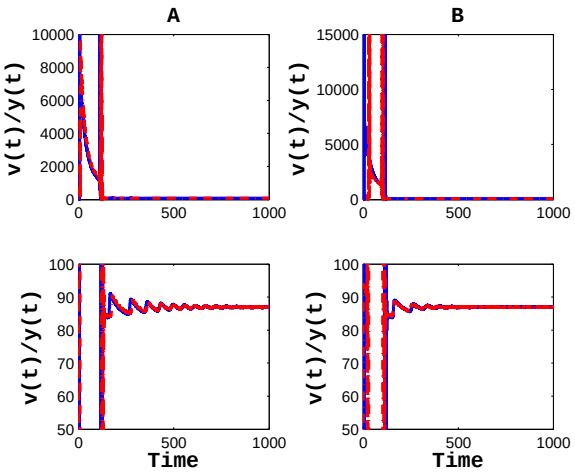

FIGURE 4. Illustration of the proportion of virus load $(v(t))$ and infected cells $(y(t))$ during infection. Here parameters are in $(\mathbf{P})$ except $q = 0.9$, $k_2 = 2.0 \times 10^{-6}$ in (A) and $k_2 = 9.0 \times 10^{-6}$ in (B). Note that solid lines correspond to the initial condition $(x(0), y(0), v(0), z(0)) = (9.0 \times 10^5, 1.0 \times 10^5, 100.0, 10.0)$, the dash-dot lines correspond to the initial condition $(x(0), y(0), v(0), z(0)) = (5.0 \times 10^5, 5.0 \times 10^5, 1.0 \times 10^6, 1.0)$, and the bottom figures are partial enlargement of the top figures.

Furthermore, since parameter k_2 denotes the immune responsiveness and the value of k_2 in Figure 3A is less than that in Figure 3B, we also observe the variation in immune responsiveness, i.e, a weak responder allows a large virus population, whereas a strong responder limits the virus to low levels [24].

Moreover, Figure 4 shows that there might be complex nonlinear relationship between the proportion of virus load $(v(t))$ and infected cells $(y(t))$ before the response steady state is established. Thus, the quasi steady-state assumption, i.e., the amount of free virus is simply proportional to the number of infected cells, might not be suitable, at least in the early phase of infection.

4.3. **Effects of antiviral drug therapy.** Although it is difficult to cure virus infection, such as HIV or HBV infection, drugs can be used in controlling virus and its complications. For example, Lamivudine has been used for treatment of chronic hepatitis B at a lower dose and for treatment of HIV at a higher dose. Usually, antiviral drugs (anti-HIV drugs, for instance) can be classified by mechanism, including non-nucleoside reverse transcriptase inhibitors (NNRTIs), nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors (PIs), entry and fusion inhibitors, and integrase inhibitors [9, 18]. Reverse transcriptase inhibitors (RTIs) block the translation of viral RNA into DNA for incorporation into the host genome, preventing the infection of new cells. In contrast, PIs interfere with essential steps of protein cleavage in new virions, preventing infected cells from producing infectious viral particles [15]. Furthermore, PIs have an effect on immune reconstitution that is independent of their ability to suppress HIV-1 replication [7]. Thus, taking into account the influence of antiviral drugs, we adjust model (3) to the following

model:

$$\begin{cases} x' = r - d_1 x - \frac{\beta(1-\eta)xv}{1+qz}, \\ y' = \frac{\beta(1-\eta)xv}{1+qz} - d_2 y - pyz, \\ v' = k_1(1-\zeta)d_2 y - d_3 v, \\ z' = k_2(1+\xi)yz - d_4 z. \end{cases} \tag{19}$$

Here η and ζ are the restraining strengths and ξ is the impelling strength by antiviral drugs.

Mathematically, (19) can be obtained by replacing β, k_1 and k_2 in (3) with $\beta(1-\eta)$, $k_1(1-\zeta)$ and $k_2(1+\xi)$, respectively. Therefore, by virtue of (6) and (8), we can obtain the basic reproduction number of virus and the immune response reproductive number for (19) as

$$R_1^* = \frac{k_1 r\beta(1-\zeta)(1-\eta)}{d_1 d_3} \tag{20}$$

and

$$R_2^* = \frac{k_2(1+\xi)(k_1 r\beta(1-\zeta)(1-\eta) - d_1 d_3)}{k_1\beta d_2 d_4(1-\zeta)(1-\eta)}, \tag{21}$$

respectively.

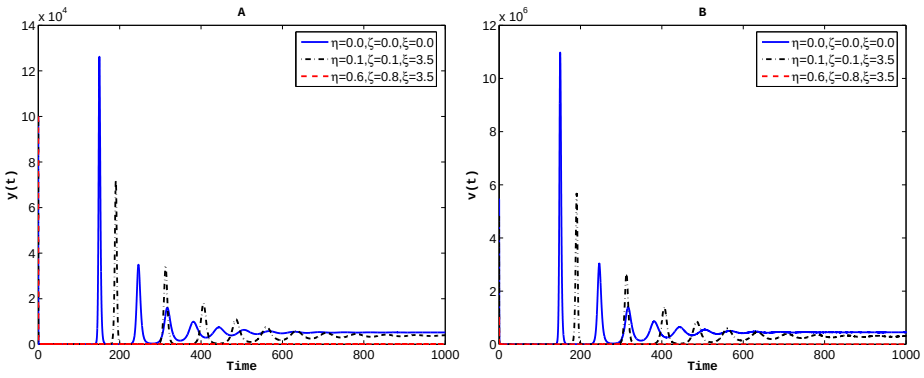

FIGURE 5. Time series of infected host cells ($y(t)$) and virus load ($v(t)$) in host as predicted by the model (19). Here parameters are in (**P**) except $k_2 = 2.0 \times 10^{-6}$ and the initial condition is $(x(0), y(0), v(0), z(0)) = (9.0 \times 10^5, 1.0 \times 10^5, 100.0, 10.0)$.

Clearly, from (20), the restraining strengths of drugs, η and ζ, can reduce the basic reproduction number of virus R_1^*. Conversely, from (21), the impelling strength of drugs, ξ can increase the immune response reproductive number R_2^*. For example, suppose that the immune responsiveness $k_2 = 2.0 \times 10^{-6}$. Then $R_1 = 2.09 > 1, R_2 = 0.30 < 1$ before the drug therapy by (6) and (8). Thus, the immune-free equilibrium $E_1 = (4.79 \times 10^5, 5.21 \times 10^3, 4.53 \times 10^5, 0)$ is globally asymptotically stable. If drug therapy is applied, when $\eta = \zeta = 0.1, \xi = 3.5$, we have $R_1 = 1.69 > 1, R_2 = 1.05 > 1$, and the endemic equilibrium $E_2 = (6.06 \times 10^5, 3.89 \times 10^3, 3.04 \times 10^5, 2.47 \times 10^{-2})$ is globally asymptotically stable. When $\eta = 0.6, \zeta = 0.8, \xi = 3.5$, we have $R_1 = 0.17 < 1$, and the virus-free equilibrium $E_0 = (1.0 \times 10^6, 0, 0, 0)$ is globally asymptotically stable. Comparing the amount of infected host cells (see Figure 5A) and virus load (see Figure 5B) in each

stable equilibrium, we can conclude that higher drugs effect can induce better outcome of the treatment. Although the simulations concentrate on the steady state outcome in Figure 5, the host may die before the dynamics have reached a steady state in some infections because the peak of virus load or infected cells is sufficient high [37]. Note that treatment may induce a significant decrease of the peaks in Figure 5. Hence antiviral drugs therapy has always been capable of gaining some advantage in clinic.

5. **Discussion.** Since the interaction between virus replication and immune responses is a complex dynamical process, mathematical models are helpful in predicting the progression of the infection, and clinical researches combined with mathematical modeling can enhance the progress of understanding viral infections. In this paper, we have developed a phenomenological model of viral infections to describe interactions among susceptible host cells, infected host cells, free virus, and immune cells. The purpose of the paper is to study the global dynamic behavior of model (3), to investigate the role of lytic and nonlytic immune effectors in viral infections, and to explore the potential applications in clinical practice.

Rigorous analysis of stability of equilibria is usually very complicated, especially for models with more than three variables [22]. This paper presents a mathematical study on global dynamics of a model with four variables. We studied existence as well as local and global stability of equilibria, and proved the uniform persistence of the system when there is an endemic equilibrium. The theoretical analysis and numerical experiments show that our model does not exhibit complicated dynamics, such as bifurcation and periodic fluctuation [12, 33, 34, 36], and that global properties of model (3) can be decided by the basic reproduction number of virus and the immune response reproductive number. Although the lytic and nonlytic components do not affect the reproductive numbers, the lytic and nonlytic antiviral activity plays a significant role in the amount of susceptible host cells and immune cells in the endemic steady state, which can be seen from the formula of the endemic steady state E_2 and numerical simulations for the endemic equilibrium in section 4. Therefore, the proposed model (3) has implications for improving our understanding of cytokine-mediated 'cure' of infected cells during viral infections [3, 4, 10, 27, 37]. Moreover, since the reproductive numbers are relevant to the effects of antiviral drugs, (3) also has the potential applications in the investigation of the effects of antiviral drugs in clinical practice.

It's should be noted that we adopted the parameters estimated by [19, 30] in numerical simulations, but these parameters may not directly obtain from experimental data. Thus, similarly to [3, 20, 28, 34], it is significant to combine the model (3) with clinical data during antiviral therapy to obtain the fitted parameters with clinical significance. This will help us to understand the clinical progression of virus infection better and has potential benefits in evaluating different drug therapy regimens. These are left for future work.

Acknowledgments. We would like to thank the anonymous reviewers for their comments that helped improve our paper.

REFERENCES

[1] B. S. Adiwijaya, T. L. Kieffer, J. Henshaw, K. Elsenhauer, H. Kimko, J. J. Alam, R. S. Kauffman and V. Garg, A viral dynamic model for treatment regimens with direct-acting antivirals for chronic hepatitis C infection, *PLoS Comput. Biol.*, **8** (2012), e1002339.

[2] A. Bergthaler, L. Flatz, A. N. Hegazy, S. Johnson, E. Horvath, M. Löhning and D. D. Pinschewer, Viral replicative capacity is the primary determinant of lymphocytic choriomeningitis virus persistence and immunosuppression, *Proc. Natl. Acad. Sci. USA*, **107** (2010), 21641–21646.
[3] S. M. Ciupe, R. M. Ribeiro, P. W. Nelson and A. S. Perelson, Modeling the mechanisms of acute hepatitis B virus infection, *J. Theor. Biol.*, **247** (2007), 23–35.
[4] H. Dahari, E. Shudo, R. M. Ribeiro and A. S. Perelson, Modeling complex decay profiles of hepatitis B virus during antiviral therapy, *Hepatology,* **49** (2009), 32–38.
[5] R. J. De Boer and A. S. Perelson, Towards a general function describing T cell proliferation, *J. Theor. Biol.,* **175** (1995), 567–576.
[6] R. J. De Boer and A. S. Perelson, Target cell limited and immune control models of HIV infection: A comparison, *J. Theor. Biol.,* **190** (1998), 201–214.
[7] S. G. Deeks, Protease inhibitors as immunomodulatory drugs for HIV infection, *Clin. Pharmacol. Ther.,* **82** (2007), 248–250.
[8] O. Diekmann, J. A. P. Heesterbeek and J. A. J. Metz, On the definition and the computation of the basic reproduction ratio R0 in models for infectious diseases in heterogeneous populations, *J. Math. Biol.,* **28** (1990), 365–382.
[9] C. Flexner, HIV drug development: The next 25 years, *Nat. Rev. Drug Discov.,* **6** (2007), 959–966.
[10] L. G. Guidotti, R. Rochford, J. Chung, M. Shapiro, R. Purcell and F. V. Chisari, Viral clearance without destruction of infected cells during acute HBV infection, *Science,* **284** (1999), 825–829.
[11] J. K. Hale and P. Waltman, Persistence in infinite-dimensional systems, *SIAM J. Math. Anal.,* **20** (1989), 388–395.
[12] S. Hews, S. Eikenberry, J. D. Nagy and Y. Kuang, Rich dynamics of a hepatitis B viral infection model with logistic hepatocyte growth, *J. Math. Biol.*, **60** (2010), 573–590.
[13] W. M. Hirsh, H. Hanisch and J. P. Gabriel, Differential equation models of some parasitic infections: Methods for the study of asymptotic behavior, *Commun. Pur. Appl. Math.,* **38** (1985), 733–753.
[14] G. Huang, Y. Takeuchi and A. Korobeinikov, HIV evolution and progression of the infection to AIDS, *J. Theor. Biol.,* **307** (2012), 149–159.
[15] C. A. Janeway, J. P. Travers, M. Walport and M. J. Shlomchik, *Immunobiology 5: The Immune System in Health and Disease*, Garland Publishing, New York, 2001.
[16] A. Korobeinikov, Global properties of basic virus dynamics models, *Bull. Math. Biol.*, **66** (2004), 879–883.
[17] J. P. LaSalle, *The Stability of Dynamical Systems*, in Regional Conference Series in Applied Mathematics, SIAM, Philadelphia, PA, 1976.
[18] Q. Li, F. Lu and K. Wang, Modeling of HIV-1 infection: Insights to the role of monocytes/macrophages, latently infected T4 cells, and HAART regimes, *PLoS ONE,* **7** (2012), e46026.
[19] W. M. Liu, Nonlinear oscillation in models of immune responses to persistent viruses, *Theor. Popul. Biol.,* **52** (1997), 224–230.
[20] H. Miao, X. Xia, A. S. Perelson and H. Wu, On identifiability of nonlinear ODE models and applications in viral dynamics, *SIAM Rev.,* **53** (2011), 3–39.
[21] S. N. Mueller and R. Ahmed, High antigen levels are the cause of T cell exhaustion during chronic viral infection, *Proc. Natl. Acad. Sci. USA,* **106** (2009), 8623–8628.
[22] A. Murase, T. Sasaki and T. Kajiwara, Stability analysis of pathogen-immune interaction dynamics, *J. Math. Biol.,* **51** (2005), 247–267.
[23] Y. Nakata, Global dynamics of a cell mediated immunity in viral infection models with distributed delays, *J. Math. Anal. Appl.,* **375** (2011), 14–27.
[24] M. A. Nowak and C. R. M. Bangham, Population dynamics of immune responses to persistent viruses, *Science,* **272** (1996), 74–79.
[25] M. A. Nowak and R. M. May, *Virus Dynamics*, Oxford University Press, New York, 2000.
[26] J. Pang, J. A. Cui and J. Hui, The importance of immune responses in a model of hepatitis B virus, *Nonlinear Dynam.,* **67** (2012), 723–734.
[27] A. S. Perelson, Modelling viral and immune system dynamics, *Nat. Rev. Immunol.,* **2** (2002), 28–36.
[28] A. S. Perelson and P. W. Nelson, Mathematical analysis of HIV-1 dynamics in vivo, *SIAM Rev.,* **41** (1999), 3–44.

[29] L. Rong, Z. Feng and A. S. Perelson, Mathematical analysis of age-structured HIV-1 dynamics with combination antiretroviral therapy, *SIAM J. Appl. Math.*, **67** (2007), 731–756.
[30] L. Rong and A. S. Perelson, Modeling latently infected cell activation: Viral and latent reservoir persistence, and viral blips in HIV-infected patients on potent therapy, *PLoS Comput. Biol.,* **5** (2009), e1000533, 18pp.
[31] C. Vargas De León and A. Korobeinikov, Global stability of a population dynamics model with inhibition and negative feedback, *Math. Med. Biol.*, **30** (2013), 65–72.
[32] P. van den Driessche and J. Watmough, Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission, *Math. Biosci.,* **180** (2002), 29–48.
[33] K. Wang and Y. Kuang, Fluctuation and extinction dynamics in host-microparasite systems, *Commun. Pur. Appl. Anal.,* **10** (2011), 1537–1548.
[34] K. Wang, W. Tan, Y. Tang and G. Deng, Numerical diagnoses of superinfection in chronic hepatitis B viral dynamics, *Intervirology,* **54** (2011), 349–356.
[35] K. Wang, W. Wang and X. Liu, Global stability in a viral infection model with lytic and nonlytic immune responses, *Comput. Math. Appl.,* **51** (2006), 1593–1610.
[36] K. Wang, W. Wang, H. Pang and X. Liu, Complex dynamic behavior in a viral model with delayed immune response, *Physica D,* **226** (2007), 197–208.
[37] D. Wodarz, J. P. Christensen and A. R. Thomsen, The importance of lytic and nonlytic immune responses in viral infections, *TRENDS Immunol.,* **23** (2002), 194–200.
[38] J. S. Yi, M. A. Cox and A. J. Zajac, T-cell exhaustion: Characteristics, causes and conversion, *Immunology,* **129** (2010), 474–481.
[39] N. Yousfi, K. Hattaf and A. Tridane, Modeling the adaptive immune response in HBV infection, *J. Math. Biol.,* **63** (2011), 933–957.

Received February 2013; revised July 2013.

E-mail address: kfwang001@gmail.com
E-mail address: yjin6@unl.edu
E-mail address: aijun71@163.com