mathematics

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Global Stability of Within-Host Virus Dynamics Models with Multitarget Cells

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Received: 26 April 2018; Accepted: 2 July 2018; Published: 10 July 2018

Abstract: In this paper, we study the stability analysis of two within-host virus dynamics models with antibody immune response. We assume that the virus infects n classes of target cells. The second model considers two types of infected cells: (i) latently infected cells; and (ii) actively infected cells that produce the virus particles. For each model, we derive a biological threshold number $\mathcal{R}_0$. Using the method of Lyapunov function, we establish the global stability of the steady states of the models. The theoretical results are confirmed by numerical simulations.

Keywords: global stability; virus infection; target cells; latency; Lyapunov function

1. Introduction

Recently, many mathematicians have proposed several mathematical models to describe the interaction between viruses (such as HIV, HCV, HBV, HTLV and CHIKV) and human target cells (see, e.g., [1–36]). Mathematical models of human viruses can lead to the development of efficient antiviral drugs and to understand the interaction of the viruses with target cells [2]. Studying the stability analysis of the models is also important to understand the behavior of the virus. Immune response plays an important role in controlling the infection of several viruses. Cytotoxic T Lymphocyte (CTL) and antibodies are the two effector responses of the immune system. CTL cells attack and kill the infected cells. The B cell produces antibodies to neutralize the viruses. The antibody immune response is more effective than CTL immune response in some infection processes [37]. The basic virus dynamics model with antibody immune response has been presented in [29,30] as:

$$\dot{S} = \mu - dS - bSV, \tag{1}$$

$$\dot{I} = bSV - \epsilon I, \tag{2}$$

$$\dot{V} = mI - rV - qBV, \tag{3}$$

$$\dot{B} = cBV - \delta B, \tag{4}$$

where S, I, V, and B are the concentrations of uninfected target cells, infected cells, virus particles and B cells, respectively. Parameters d and μ represent the death rate and birth rate constants of the uninfected cells, respectively. The uninfected cells become infected at rate bSV, where b is rate constant of the virus-target incidence. The infected cells and free virus particles die at rates ϵI and rV, respectively. An actively infected cell produces an average number m of virus particles per unit time. The virus particles are attacked by the B cells at rate qVB. The term cBV represents the growth rate of B cells after encountering the virus. The B cells die at rate δB. In 2017, Wang and Liu [36] presented a mathematical model for in host virus infection by considering a constant production rate of the B cells in addition to their proliferation rate. Equation (4) has been modified as:

$$\dot{B} = \eta + cBV - \delta B, \tag{5}$$

where η is the production rate of the B cells.

The model in Equations (1)–(4) assumes that the virus infects only one category of target cells. There are several models for viral infections that have included two categories of target cells (see, e.g., [38–47]). It has been reported in [48] that HIV infects vital cells in the human immune system such as helper T cells (specifically $CD4^+$ T cells), macrophages, and dendritic cells. In the case of CHIKV infection, the CHIKV inoculates into the body via bites from infected mosquitoes and replicates in a variety of cells, such as skeletal muscle satellite cells, fibroblasts, macrophages, monocytes and other skin cells [49–52]. To model the virus dynamics with multiple categories of target cells, Elaiw [53] proposed the following viral infection model:

$$\dot{S}_i = \mu_i - d_i S_i - b_i S_i V, \quad i = 1, ..., n, \tag{6}$$

$$\dot{I}_i = b_i S_i V - \epsilon_i I_i, \quad i = 1, ..., n, \tag{7}$$

$$\dot{V} = \sum_{i=1}^{n} m_i I_i - rV, \tag{8}$$

where n is the number categories of target cells. This model was generalized by Xia et al. [54] by considering general nonlinear rates for viral infection and cell death. In [53,54], the antibody immune response has been neglected. Several mathematical models have been proposed which take the antibody immune response into account (see, e.g., [29–35]). However, these models have included one target cell population. Therefore, our aim in this paper is to introduce two virus infection models to describe the dynamics of the virus with n classes of target cells. The antibody immune response is considered where the population dynamics of the B cells is described by Equation (5). In the second model, we incorporate both latently and actively infected cells. We investigate the nonnegativity and boundedness of the solutions of the models. We establish the existence of the steady states and analyze their global stability. We construct Lyapunov function using the method of Korobeinikov [55].

2. Virus Dynamics Model

We consider a within-host virus dynamics model with n classes of uninfected target cells.

$$\dot{S}_i = \mu_i - d_i S_i - b_i S_i V, \quad i = 1, ..., n, \tag{9}$$

$$\dot{I}_i = b_i S_i V - \epsilon_i I_i, \quad i = 1, ..., n, \tag{10}$$

$$\dot{V} = \sum_{i=1}^{n} m_i I_i - rV - qBV, \tag{11}$$

$$\dot{B} = \eta + cBV - \delta B, \tag{12}$$

where S_i, I_i represent the concentrations of the uninfected target cells and infected cells of class i, respectively.

2.1. Properties of Solutions

To show that the model in Equations (9)–(12) is biologically acceptable in the sense that no population goes negative or infinity, we establish the nonnegativity and boundedness of solutions of the model. Let $\mathbf{S} = (S_1, S_2, ..., S_n)$ and $\mathbf{I} = (I_1, I_2, ..., I_n)$.

Proposition 1. *For the system in Equations (9)–(12), there exists a positively invariant compact set*

$$\Omega = \left\{ (\mathbf{S}, \mathbf{I}, V, B) \in \mathbb{R}^{2n+2}_{\geq 0} : 0 \leq S_i, I_i \leq N_i, i = 1, ..., n. \, 0 \leq V \leq M_1, 0 \leq B \leq M_2 \right\}.$$

Proof. Since

$$\dot{S}_i\big|_{S_i=0} = \mu_i > 0, i = 1, ..., n, \qquad \dot{I}_i\big|_{I_i=0} = b_i S_i V \geq 0 \text{ for all } S_i, V \geq 0, \; i = 1, ..., n,$$
$$\dot{V}\big|_{V=0} = \sum_{i=1}^{n} m_i I_i \geq 0 \text{ for all } I_i \geq 0, \qquad \dot{B}\big|_{B=0} = \eta > 0,$$

then, $\mathbb{R}^{2n+2}_{\geq 0}$ is positively invariant for the system in Equations (9)–(12).

Next, let $T_i(t) = S_i + I_i$, $i = 1, ..., n$, then

$$\dot{T}_i \leq \mu_i - \sigma_i T_i,$$

where $\sigma_i = \min\{d_i, \epsilon_i\}$. Hence, $0 \leq T_i(t) \leq \frac{\mu_i}{\sigma_i}$ for all $t \geq 0$ if $T_i(0) \leq \frac{\mu_i}{\sigma_i}$. It follows that $0 \leq S_i(t), I_i(t) \leq N_i$ for all $t \geq 0$, if $0 \leq S_i(0) + I_i(0) \leq N_i$, where, $N_i = \frac{\mu_i}{\sigma_i}$. Moreover, let $X(t) = V(t) + \frac{q}{c} B(t)$, then

$$\dot{X}(t) = \sum_{i=1}^{n} m_i I_i - rV + \frac{q}{c}\eta - \frac{\delta q}{c} B \leq \sum_{i=1}^{n} m_i N_i + \frac{q}{c}\eta - \rho_1 (V + \frac{q}{c} B) = \sum_{i=1}^{n} m_i N_i + \frac{q}{c}\eta - \rho_1 X(t),$$

where $\rho_1 = \min\{r, \delta\}$. Hence, $X(t) \leq M_1$, where $M_1 = \sum\limits_{i=1}^{n} \frac{m_i N_i + \frac{q}{c}\eta}{\rho_1}$. Since $V(t) \geq 0$ and $B(t) \geq 0$, then $0 \leq V(t) \leq M_1$ and $0 \leq B(t) \leq M_2$ if $0 \leq V(0) + \frac{q}{c} B(0) \leq M_1$, where $M_2 = \frac{cM_1}{q}$. □

2.2. Steady States

In this subsection, we show the existence of the steady states of the model in Equations (9)–(12). The basic reproduction number of the system in Equations (9)–(12) is defined as:

$$\mathcal{R}_0 = \sum_{i=1}^{n} \mathcal{R}_{0i} = \sum_{i=1}^{n} \frac{m_i b_i \mu_i \delta}{d_i \epsilon_i (r\delta + q\eta)}.$$

Lemma 1. *(i) If $\mathcal{R}_0 \leq 1$, then the virus-free steady state Q_0 is the only steady state for the system; and (ii) if $\mathcal{R}_0 > 1$, then the system has a unique endemic steady state Q_1 and $Q_1 \in \mathring{\Omega}$, where $\mathring{\Omega}$ is the interior of Ω.*

Proof. Let the R.H.S of the system in Equations (9)–(12) equal zero; then, we get:

$$S_i = \frac{\mu_i}{d_i + b_i V}, \quad i = 1, ..., n, \tag{13}$$
$$I_i = \frac{b_i S_i V}{\epsilon_i}, \quad i = 1, ..., n, \tag{14}$$
$$\sum_{i=1}^{n} m_i I_i = (r + qB)\, V, \tag{15}$$
$$B = \frac{\eta}{\delta - cV}. \tag{16}$$

Substituting Equations (13), (14) and (16) into Equation (15), we get

$$\begin{aligned}\sum_{i=1}^{n}\frac{m_i b_i \mu_i V}{\epsilon_i\left(d_i+b_i V\right)}-\left(r+qB\right)V&=0,\\ \left(\sum_{i=1}^{n}\frac{m_i b_i \mu_i \delta}{d_i\epsilon_i\left(1+\alpha_i V\right)\left(r\delta+q\eta\right)}-\frac{\left(r+qB\right)\delta}{\left(r\delta+q\eta\right)}\right)V&=0,\\ \left(\sum_{i=1}^{n}\frac{\mathcal{R}_{0i}}{1+\alpha_i V}-\frac{\delta\left(\gamma-rcV\right)}{\gamma\left(\delta-cV\right)}\right)V&=0,\end{aligned}\tag{17}$$

where $\alpha_i = \frac{b_i}{d_i}$ and $\gamma = r\delta + q\eta$. Equation (17) admits $V = 0$ as a solution. Substituting $V = 0$ in Equations (13),(14) and (16), we get the virus-free steady state $Q_0 = (\mathbf{S}^0, \mathbf{I}^0, V^0, B^0)$, where $S_i^0 = \frac{\mu_i}{d_i}$, $I_i^0 = 0$, $V^0 = 0$, and $B^0 = \frac{\eta}{\delta}$. The other possibility of Equation (17) is

$$\sum_{i=1}^{n}\frac{\mathcal{R}_{0i}\gamma\left(\delta-cV\right)}{1+\alpha_i V}-\delta\left(\gamma-rcV\right)=0,\tag{18}$$

where $V \neq \frac{\delta}{c}$.

Let us define a function $F(V)$ as:

$$F(V)=\sum_{i=1}^{n}\frac{\mathcal{R}_{0i}\gamma\left(\delta-cV\right)}{1+\alpha_i V}-\delta\left(\gamma-rcV\right)$$

Then, we get

$$\begin{aligned}F(0)&=\gamma\delta\left(\mathcal{R}_0-1\right),\\ F\left(\frac{\delta}{c}\right)&=-q\delta\eta.\end{aligned}$$

Thus, if $\mathcal{R}_0 > 1$, then $F(0) > 0$, $F\left(\frac{\delta}{c}\right) < 0$ and there exists $V^* \in \left(0, \frac{\delta}{c}\right)$ such that $F(V^*) = 0$. Moreover, from Equations (13), (14) and (16), we obtain $S_i^* > 0, I_i^* > 0$ and $B^* > 0$. Then, $Q_1 = (\mathbf{S}^*, \mathbf{L}^*, \mathbf{I}^*, V^*, B^*)$ exists when $\mathcal{R}_0 > 1$.

Clearly, $Q_0 \in \Omega$. Now, we show that if $\mathcal{R}_0 > 1$, then $Q_1 \in \mathring{\Omega}$. From Equations (13) and (14), we have $d_i S_i^* + \epsilon_i I_i^* = \mu_i$, $i = 1, ..., n$. Since $S_i^* > 0$ and $I_i^* > 0$, then

$$\begin{aligned}d_i S_i^* < \mu_i \Rightarrow S_i^* < \frac{\mu_i}{d_i} \leq N_i,\\ \epsilon_i I_i^* < \mu_i \Rightarrow I_i^* < \frac{\mu_i}{\epsilon_i} \leq N_i.\end{aligned}$$

Moreover, from Equations (15)–(16), we have

$$\begin{aligned}&\sum_{i=1}^{n} m_i I_i^* - rV^* - qV^*B^* + \frac{q}{c}(\eta + cB^*V^* - \delta B^*) = 0,\\ &\Rightarrow rV^* + \frac{\delta q}{c}B^* = \sum_{i=1}^{n} m_i I_i^* + \frac{q}{c}\eta < \sum_{i=1}^{n} m_i N_i + \frac{q}{c}\eta\\ &\Rightarrow V^* < \sum_{i=1}^{n}\frac{m_i N_i + \frac{q}{c}\eta}{r} \leq M_1, \quad B_1 < \frac{c}{q}\sum_{i=1}^{n}\frac{m_i N_i + \frac{q}{c}\eta}{\delta} \leq \frac{cM_1}{q} = M_2.\end{aligned}$$

It follows that $Q_1 \in \mathring{\Omega}$. □

2.3. Global Stability

In the following theorems, we establish the global stability of the two steady states of the system in Equations (9)–(12) by constructing suitable Lyapunov functions. Let us define

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

Clearly, $H(x) \geq 0$ for $x > 0$ and $H(1) = 0$.

Theorem 1. *For the system in Equations (9)–(12), suppose that $\mathcal{R}_0 \leq 1$, then Q_0 is globally asymptotically stable in Ω.*

Theorem 2. *For the system in Equations (9)–(12), suppose that $\mathcal{R}_0 > 1$, then Q_1 is globally asymptotically stable in $\mathring{\Omega}$.*

The proofs of these theorems are given in the Appendix A.

Biologically, when $\mathcal{R}_0 < 1$, then each infected cell will produce less than one infected cell during its life at the beginning of the infection. The virus will be decreased and eliminated from the body. When $\mathcal{R}_0 > 1$, then, at the beginning of the infection, each infected cell will produce more than one infected cell during its life. The viruses will be increased and the infection becomes chronic.

3. Virus Model with Latency

In this section, we study the mathematical model of virus infection with n classes of uninfected target cells, taking into account the latently infected cells (such cells contain the viruses but are not producing it) and the actively infected cells (such cells are producing the viruses).

$$\dot{S}_i = \mu_i - d_i S_i - b_i S_i V, \qquad i = 1, ..., n, \tag{19}$$

$$\dot{L}_i = (1 - p_i) b_i S_i V - (\theta_i + \lambda_i) L_i, \quad i = 1, ..., n, \tag{20}$$

$$\dot{I}_i = p_i b_i S_i V + \lambda_i L_i - \epsilon_i I_i, \qquad i = 1, ..., n, \tag{21}$$

$$\dot{V} = \sum_{i=1}^{n} m_i I_i - rV - qBV, \tag{22}$$

$$\dot{B} = \eta + cBV - \delta B, \tag{23}$$

where L_i and I_i are the concentrations of latently infected and actively infected target cells of class i, respectively. A fraction $(1 - p_i)$ of infected target cells is assumed to be latently infected cells and the remaining p_i becomes actively infected cells, where $0 < p_i < 1$, $i = 1, ..., n$. The latently infected cells are transmitted to actively infected cells at rate $\lambda_i L_i$ and die at rate $\theta_i L_i$.

3.1. Properties of Solutions

In the following, we establish the nonnegativity and boundedness of solutions of the model in Equations (19)–(23). Let $\mathbf{L} = (L_1, L_2, ..., L_n)$.

Proposition 2. *For the system in Equations (19)–(23), there exists a positively invariant compact set*

$$\Omega^L = \left\{ (\mathbf{S}, \mathbf{L}, \mathbf{I}, V, B) \in \mathbb{R}^{3n+2}_{\geq 0} : 0 \leq S_i, L_i, I_i \leq N_i^L,\ i = 1, ..., n.\ 0 \leq V \leq M_1^L, 0 \leq B \leq M_2^L \right\}$$

Proof. Since

$$\begin{aligned}
\dot{S}_i\big|_{S_i=0} &= \mu_i > 0, i = 1, ..., n,\\
\dot{L}_i\big|_{L_i=0} &= (1-p_i)b_iS_iV \geq 0 \text{ for all } S_i, V \geq 0, \ i = 1, ..., n,\\
\dot{I}_i\big|_{I_i=0} &= p_ib_iS_iV + \lambda_iL_i \geq 0 \text{ for all } S_i, L_i, V \geq 0, \ i = 1, ..., n,\\
\dot{V}\big|_{V=0} &= \sum_{i=1}^{n} m_iI_i \geq 0 \text{ for all } I_i \geq 0,\\
\dot{B}\big|_{B=0} &= \eta > 0,
\end{aligned}$$

then, $\mathbb{R}^{3n+2}_{\geq 0}$ is positively invariant for the system in Equations (19)–(23).

We consider $T_i(t) = S_i + L_i + I_i$, $i = 1, ..., n$, then

$$\dot{T}_i(t) \leq \mu_i - \sigma_i^L T_i(t),$$

where $\sigma_i^L = \min\{d_i, \theta_i, \epsilon_i\}$. Hence, $0 \leq T_i(t) \leq \frac{\mu_i}{\sigma_i^L}$ for all $t \geq 0$ if $T_i(0) \leq \frac{\mu_i}{\sigma_i^L}$. It follows that $0 \leq S_i(t), L_i(t), I_i(t) \leq N_i^L$ for all $t \geq 0$, if $0 \leq S_i(0) + L_i(0) + I_i(0) \leq N_i^L$, where $N_i^L = \frac{\mu_i}{\sigma_i^L}$. On the other hand, let $X(t) = V(t) + \frac{q}{c}B(t)$, then

$$\dot{X}(t) = \sum_{i=1}^{n} m_iI_i - rV + \frac{q}{c}\eta - \frac{\delta q}{c}B \leq \sum_{i=1}^{n} m_iN_i + \frac{q}{c}\eta - \rho_2(V + \frac{q}{c}B) = \sum_{i=1}^{n} m_iN_i + \frac{q}{c}\eta - \rho_1X(t).$$

Hence, $X(t) \leq M_1^L$, where $M_1^L = \sum\limits_{i=1}^{n} \frac{m_iN_i + \frac{q}{c}\eta}{\rho_1}$. Since $V(t) \geq 0$ and $B(t) \geq 0$, then $0 \leq V(t) \leq M_1^L$ and $0 \leq B(t) \leq M_2^L$ if $0 \leq V(0) + \frac{q}{c}B(0) \leq M_1^L$, where $M_2^L = \frac{cM_1^L}{q}$. □

3.2. Steady States

In this subsection, we establish the existence of the steady states of the model in Equations (19)–(23). The basic reproduction number of the system in Equations (19)–(23) is defined as:

$$\mathcal{R}_0^L = \sum_{i=1}^{n} \mathcal{R}_{0i}^L = \sum_{i=1}^{n} \frac{m_ib_i\mu_i\delta(\theta_ip_i + \lambda_i)}{d_i\epsilon_i(\theta_i + \lambda_i)(r\delta + q\eta)}.$$

Lemma 2. *(i) If $\mathcal{R}_0^L \leq 1$, then the virus-free steady state Q_0^L is the only steady state for the system; and (ii) if $\mathcal{R}_0^L > 1$, then the system has a unique endemic steady state Q_1^L and $Q_1^L \in \mathring{\Omega}^L$.*

Proof. Let the R.H.S of the system in Equations (19)–(23) equal zero; then, we get:

$$S_i = \frac{\mu_i}{d_i + b_iV}, \quad i = 1, ..., n, \tag{24}$$

$$L_i = \frac{(1-p_i)b_iS_iV}{\theta_i + \lambda_i}, \quad i = 1, ..., n, \tag{25}$$

$$I_i = \frac{b_iS_iV(\theta_ip_i + \lambda_i)}{\epsilon_i(\theta_i + \lambda_i)}, \quad i = 1, ..., n, \tag{26}$$

$$\sum_{i=1}^{n} m_iI_i = (r + qB)\, V, \tag{27}$$

$$B = \frac{\eta}{\delta - cV}. \tag{28}$$

Substituting Equations (24)–(26) and (28) into Equation (27), we get

$$\sum_{i=1}^{n} \frac{m_i b_i \mu_i (\theta_i p_i + \lambda_i) V}{\epsilon_i \left(d_i + b_i V\right) \left(\theta_i + \lambda_i\right)} - (r + qB)\, V = 0,$$
$$\left(\sum_{i=1}^{n} \frac{m_i b_i \mu_i \delta (\theta_i p_i + \lambda_i)}{d_i \epsilon_i \left(1 + \alpha_i V\right) \left(\theta_i + \lambda_i\right) (r\delta + q\eta)} - \frac{(r + qB)\, \delta}{(r\delta + q\eta)} \right) V = 0,$$
$$\left(\sum_{i=1}^{n} \frac{\mathcal{R}_{0i}^{L}}{1 + \alpha_i V} - \frac{\delta\left(\gamma - rcV\right)}{\gamma\left(\delta - cV\right)} \right) V = 0, \tag{29}$$

where $\alpha_i = \frac{b_i}{d_i}$ and $\gamma = r\delta + q\eta$. Equation (29) gives two possible solutions. If $V = 0$, then we get virus-free steady state $Q_0^L = (\mathbf{S}^0, \mathbf{L}^0, \mathbf{I}^0, V^0, B^0) = (\frac{\mu_i}{d_i}, 0, 0, 0, \frac{\eta}{\delta})$. If $V \neq 0$, then Equation (29) becomes

$$\sum_{i=1}^{n} \frac{\mathcal{R}_{0i}^{L} \gamma \left(\delta - cV\right)}{1 + \alpha_i V} - \delta\left(\gamma - rcV\right) = 0. \tag{30}$$

We define a function $G(V)$ as:

$$G(V) = \sum_{i=1}^{n} \frac{\mathcal{R}_{0i}^{L} \gamma \left(\delta - cV\right)}{1 + \alpha_i V} - \delta\left(\gamma - rcV\right).$$

If $\mathcal{R}_0^L > 1$, then

$$G(0) = \gamma\delta\left(\mathcal{R}_0^L - 1\right) > 0,$$
$$G\left(\frac{\delta}{c}\right) = -q\delta\eta < 0.$$

and there exists $V^* \in \left(0, \frac{\delta}{c}\right)$ such that $G(V^*) = 0$. Moreover, from Equations (24)–(26) and (28), we obtain $S_i^* > 0, L_i^* > 0, I_i^* > 0$ and $B^* > 0$.

Similar to the proof of Lemma 1, one can easily show that $Q_0^L \in \Omega^L$ and $Q_1^L \in \mathring{\Omega}^L$. □

3.3. Global Stability

In this section, we use Lyapunov method to prove the global stability of the two steady states of the system in Equations (19)–(23).

Theorem 3. *For the system in Equations (19)–(23), suppose that $\mathcal{R}_0^L \leq 1$, then Q_0^L is globally asymptotically stable in Ω^L.*

Theorem 4. *For the system in Equations (19)–(23), suppose that $\mathcal{R}_0^L > 1$, then Q_1^L is globally asymptotically stable in $\mathring{\Omega}^L$.*

The proofs of these theorems are given in the Appendix A.

4. Numerical Simulations

To illustrate our theoretical results, we perform numerical simulations for the systems in Equations (9)–(12) and Equations (19)–(23). We consider the case $n = 2$.

4.1. Simulations for Virus Dynamics Model

Using the values of the parameters given in Table 1, we show the dynamical behavior of the system states $\mathbf{S}$, $\mathbf{I}$, V and B, to confirm the theoretical results given in Theorems 1–2.

Table 1. The values of the parameters of the model in Equations (9)–(12).

Parameter	Value	Parameter	Value
μ_1	1.826	d_1	0.7979
μ_2	3.198	d_2	0.5
b_1	varied	q	0.5964
c	0.5	r	0.4418
$m_1 = m_2$	2.02	η	1.402
b_2	varied	δ	1.251
$\epsilon_1 = \epsilon_2$	0.4441		

• **Effect of** b_1 and b_2 on the stability of steady states: To show the global stability results, we consider three different initial values as:

IV1: $S_1(0) = 2.0, S_2(0) = 6.0, I_1(0) = 0.3, I_2(0) = 0.4, V(0) = 0.4$ and $B(0) = 2.0$,
IV2: $S_1(0) = 1.7, S_2(0) = 5.5, I_1(0) = 0.7, I_2(0) = 0.7, V(0) = 0.6$ and $B(0) = 4.0$,
IV3: $S_1(0) = 1.4, S_2(0) = 5.0, I_1(0) = 1.1, I_2(0) = 1.0, V(0) = 0.8$ and $B(0) = 6.0$.

We consider two sets of the parameters b_1 and b_2 as follows:

Set (I): We choose $b_1 = 0.005$ and $b_2 = 0.02$. Using these data, we compute $\mathcal{R}_0 = 0.5710 < 1$, then the system has one steady state Q_0. In Figure 1, we can see that the concentrations of the uninfected target cells and B cells return to their normal values $S_1^0 = \frac{\mu_1}{d_1} = 2.2885$, $S_2^0 = \frac{\mu_2}{d_2} = 6.3960$, and $B^0 = \frac{\eta}{\delta} = 1.1207$. On the other hand, the concentrations of infected target cells and virus particles are decaying and approaching zero for all the three initial values IV1–IV3. It means that Q_0 is globally asymptotically stable and the virus will be cleared. This result confirms the result of Theorem 1.

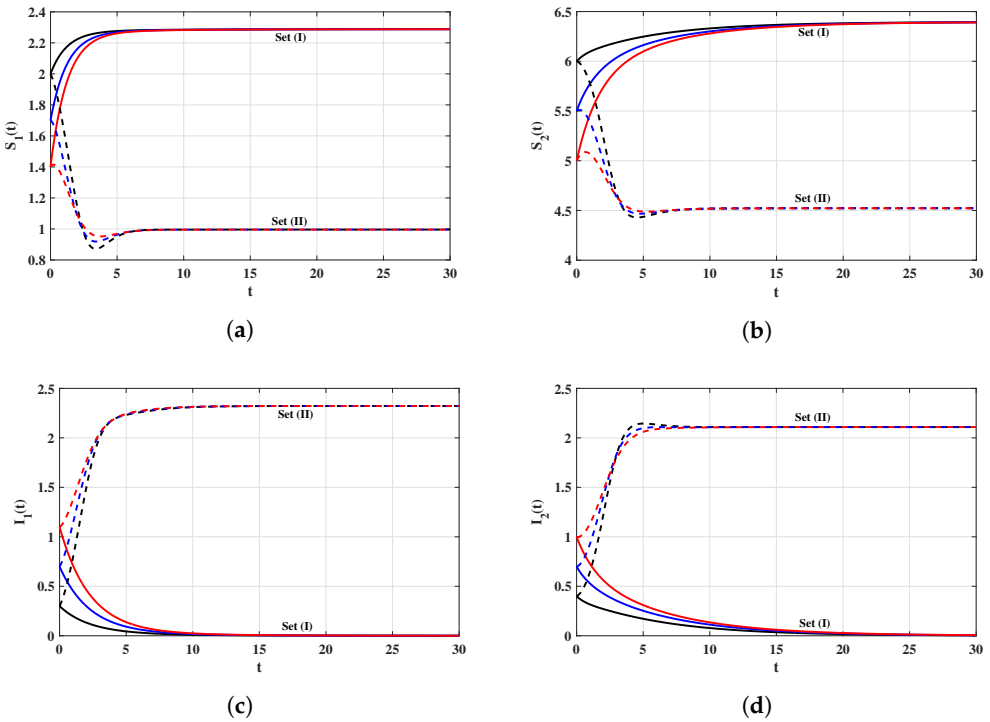
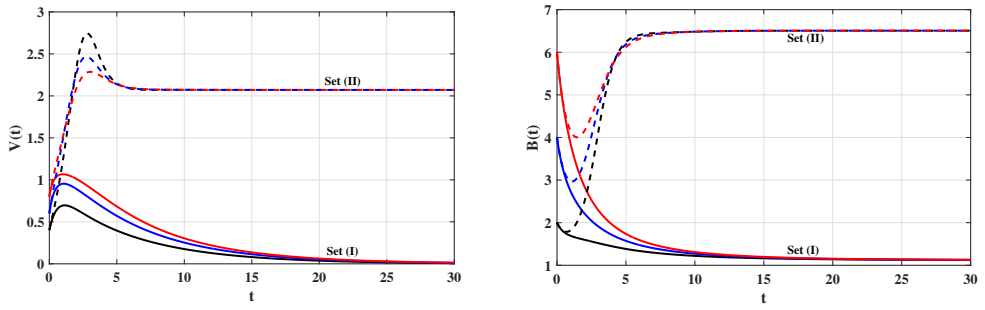


Figure 1. *Cont.*



(**e**) (**f**)

Figure 1. The simulation of trajectories of the system in Equations (9)–(12) with IV1–IV3; (**a**) uninfected target cells type-1; (**b**) uninfected target cells type-2; (**c**) infected target cells type-1; (**d**) infected target cells type-2; (**e**) free virus particles; and (**f**) B cells.

Set (II): We take $b_1 = 0.5$ and $b_2 = 0.1$. Then, we calculate $\mathcal{R}_0 = 7.3086 > 1$. The system has two steady states Q_0 and Q_1. It is clear in Figure 1 that both the numerical results and the theoretical results of Theorem 2 are consistent. It is seen that the solutions of the system converge to the steady state $Q_1 = (0.99595, 4.52267, 2.32229, 2.10913, 2.07104, 6.50639)$ for all the three initial values IV1–IV3.

4.2. Simulations for Virus Model with Latency

In this subsection, we show the numerical results for the system in Equations (19)–(23) with parameters values given in Table 2. The effect of parameters p_i and p_2 on the qualitative behavior of the system is discussed below. We take $p = p_1 = p_2$. The initial values are chosen as: $S_1(0) = 2.25, S_2(0) = 6.0, L_1(0) = 0.1, L_2(0) = 0.05, I_1(0) = 0.1, I_2(0) = 0.5, V(0) = 0.4$ and $B(0) = 1.4$. In Table 3, we have calculated the values of the steady states and $\mathcal{R}_0^L$ for different values of p. It is clearly seen that, as p is increased, $\mathcal{R}_0^L$ is also increased. Let p^{cr} be the value of p, such that

$$\mathcal{R}_0^L = \sum_{i=1}^{2} \frac{m_i b_i \mu_i \delta(\theta_i p^{cr} + \lambda_i)}{d_i \epsilon_i (\theta_i + \lambda_i)(r\delta + q\eta)} = 1.$$

Table 2. The values of the parameters of the model in Equations (19)–(23).

Parameter	Value	Parameter	Value
μ_1	1.826	d_1	0.7979
μ_2	3.198	d_2	0.5
le $b_1 = b_2$	0.04	q	0.5964
c	0.5	r	0.4418
m_1=m_2	2.02	η	1.402
$\lambda_1 = \lambda_2$	0.1	δ	1.251
ϵ_1=ϵ_2	0.4441	$\theta_1 = \theta_2$	0.5
p_1=p_2	varied		

Using the data given in Table 2, we obtain $p^{cr} = 0.643144$. In Figure 2, we can see that, for $p \leq 0.643144$, the trajectory of the system will converge to Q_0^L and, for $p > 0.643144$, the trajectory will converge to Q_1^L. This shows that, the factor $1 - p$ plays the role of a controller which can used to stabilize the system around Q_0^L. Biologically, the factor $1 - p$ plays the role of an antiviral treatment which can be applied to eradicate the virus from the body.

Table 3. The values of steady states, $\mathcal{R}_0^L$ for the model in Equations (19)–(23) with different values of p.

$p = p_1 = p_2$	Steady States	R_0^L
0.1	$Q_0 = (2.26262, 6.28133, 0, 0, 0, 0, 0, 1.23318)$	0.3558
0.2	$Q_0 = (2.26262, 6.28133, 0, 0, 0, 0, 0, 1.23318)$	0.4744
0.3	$Q_0 = (2.26262, 6.28133, 0, 0, 0, 0, 0, 1.23318)$	0.5930
0.4	$Q_0 = (2.26262, 6.28133, 0, 0, 0, 0, 0, 1.23318)$	0.7116
0.5	$Q_0 = (2.26262, 6.28133, 0, 0, 0, 0, 0, 1.23318)$	0.8302
0.6	$Q_0 = (2.26262, 6.28133, 0, 0, 0, 0, 0, 1.23318)$	0.9488
0.643144	$Q_0 = (2.26262, 6.28133, 0, 0, 0, 0, 0, 1.23318)$	1.0000
0.7	$Q_1 = (2.23995, 6.18216, 0.04480, 0.12364, 0.07115, 0.19637, 0.43238, 1.35484)$	1.0674
0.8	$Q_1 = (2.22562, 6.12005, 0.02968, 0.08160, 0.09707, 0.26693, 0.56363, 1.44657)$	1.1860
0.9	$Q_1 = (2.20775, 6.04324, 0.01472, 0.04029, 0.13390, 0.36652, 0.72967, 1.58210)$	1.3046

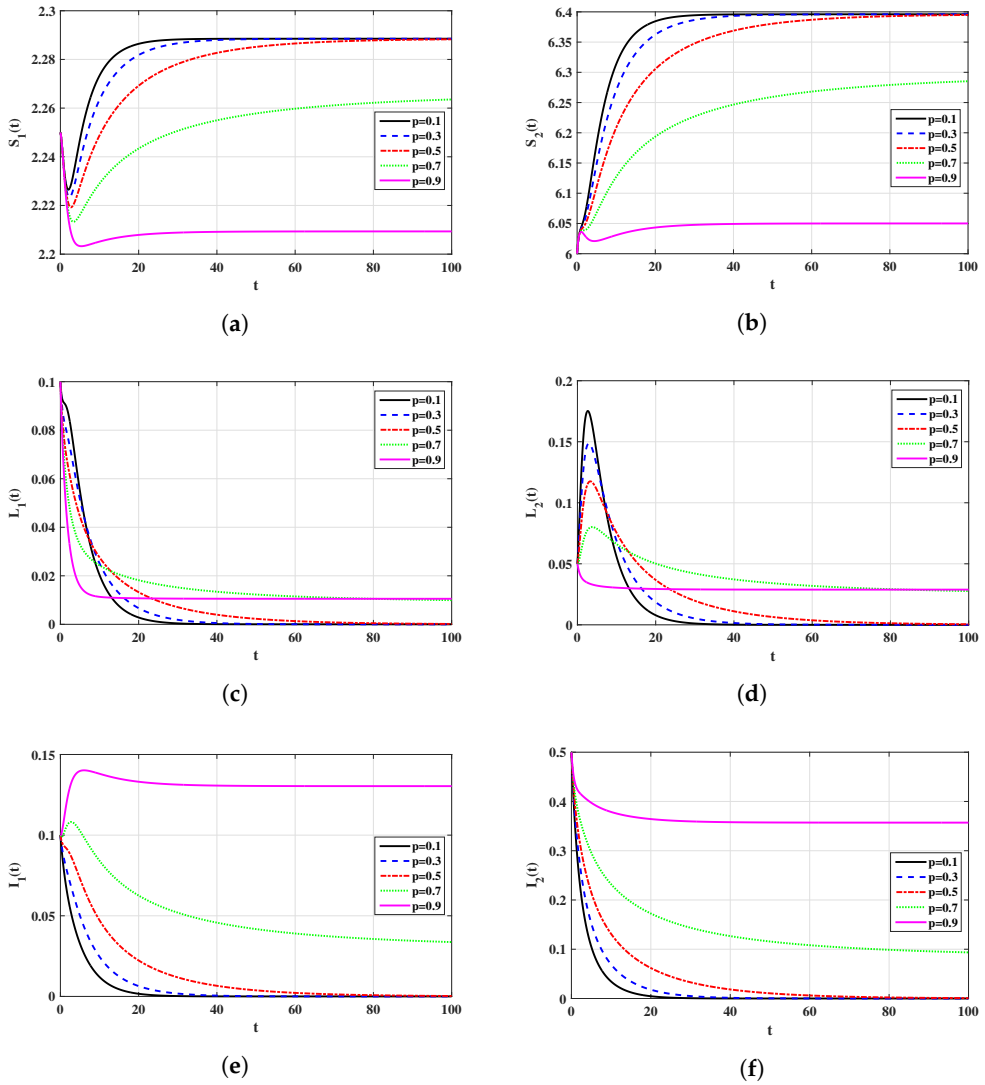
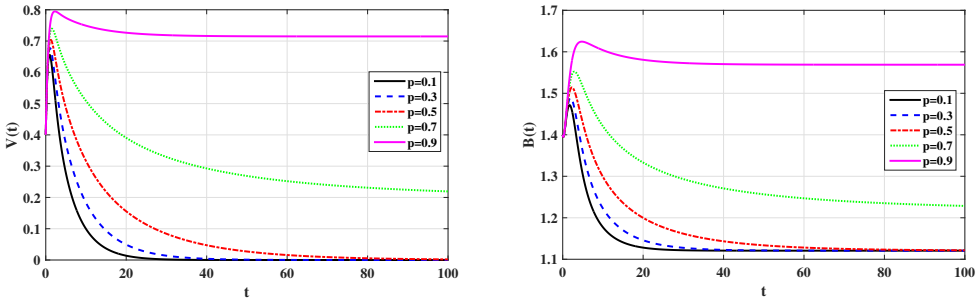


Figure 2. *Cont.*



(**e**) (**f**)

Figure 2. The simulation of trajectories of the system in Equations (19)–(23): (**a**) uninfected target cells type-1; (**b**) uninfected target cells type-2; (**c**) latently infected target cells type-1; (**d**) latently infected target cells type-2; (**e**) actively infected target cells type-1; (**f**) actively infected target cells type-2; (**g**) free virus particles; and (**h**) B cells.

5. Conclusions and Discussion

Most of the existing mathematical models of viral infection study the viral infection and production in one or two classes of target cells.However, HIV and CHIKV can infect three and five types of target cells, respectively. In this paper, we have studied two within-host virus dynamics models with antibody immune response and with n classes of target cells. In the second model, we have considered two types of infected cells, latently infected cells (such cells contain the viruses but are not producing it) and the actively infected cells (such cells are producing the viruses). We have shown that the solutions of each model are nonnegative and bounded, which ensure the well-posedness of the models. For each model, we have derived a biological threshold number $\mathcal{R}_0$ (the basic reproduction number) which fully determines the existence and stability of the two steady states of the model. We have investigated the global stability of the steady states of the model by using Lyapunov method and LaSalle's invariance principle. We have proven that: (i) if $\mathcal{R}_0 \leq 1$ ($\mathcal{R}_0^L \leq 1$), then the virus-free steady state Q_0 (Q_0^L) is globally asymptotically stable and the virus is predicted to be completely cleared from infected individuals; and (ii) if $\mathcal{R}_0 > 1$ ($\mathcal{R}_0^L > 1$), then the endemic steady state Q_1 (Q_1^L) is globally asymptotically stable and a chronic virus infection is attained. We have conducted numerical simulations and have shown that both the theoretical and numerical results are consistent. Our analysis extends some existing results in the literature. For example, the global stability was analyzed for a model with one target cell population [36].

The model in Equations (1)–(4) has three steady states virus-free steady state Q_0^H, endemic steady state without antibody immune response Q_1^H and endemic steady state with antibody immune response Q_2^H. Moreover, the existence and stability of the steady states are determined by two threshold parameters, the basic reproduction number $\mathcal{R}_0^H$ (which determines whether or not the disease will progress) and the antibody immune response activation number $\mathcal{R}_1^H$ (which determines whether a persistent antibody immune response can be established) [30], where

$$\mathcal{R}_0^H = \frac{mb\mu}{d\epsilon r}, \quad \mathcal{R}_1^H = \frac{\mathcal{R}_0^H}{1 + \frac{b\delta}{dc}}.$$

We note that the values of the parameters q, c and δ have no impact on the values of $\mathcal{R}_0^H$. Thus, the model in Equations (1)–(4) implies that the antibody immune response do not play a role in clearing the viruses but can play a significant role in reducing the infection progress.

Our models have two steady states and their existence and stability are determined by one threshold parameter $\mathcal{R}_0$. This is because of considering the production rate of the B cells η. The basic reproduction number of the model in Equations (9)–(12) in the case of $n = 1$ is given by:

$$\mathcal{R}_0 = \frac{m_1 b_1 \mu_1 \delta}{d_1 \epsilon_1 (r\delta + q\eta)}.$$

We can see that $\mathcal{R}_0$ depends on the parameter η. Therefore, if the production rate of the B cells η is increased such that $\mathcal{R}_0 < 1$, then Q_0 is globally asymptotically stable. Thus, the model in Equations (9)–(12) implies that the antibody immune response can clear the virus from body.

In our proposed models, we have only considered one arm of the immune system which is based on the antibodies. CTL cells play a prominent role in achieving the best representation of the dynamics of some types of viruses. The virus dynamics model with n categories of target cells and CTL immune response can be given as:

$$\begin{aligned}
\dot{S}_i &= \mu_i - d_i S_i - b_i S_i V, \qquad i = 1, ..., n,\\
\dot{I}_i &= b_i S_i V - \epsilon_i I_i - \bar{q}_i I_i Z, \qquad i = 1, ..., n,\\
\dot{V} &= \sum_{i=1}^{n} m_i I_i - rV,\\
\dot{Z} &= \bar{\eta} + \sum_{i=1}^{n} \bar{c}_i I_i Z - \bar{\delta} Z.
\end{aligned}$$

In addition to this model, one can formulate a virus dynamics model with n categories of target cells and both antibodies and CTL immune response.

5.1. Effects of Latency on the Virus Dynamics

In this subsection, we show the effect of the presence of latently infected cells on the virus dynamics. Let us incorporate an antiviral treatment with drug efficacy u where $u \in [0, 1)$. The virus dynamics model in Equations (9)–(12) under the effect of treatment is given by:

$$\dot{S}_i = \mu_i - d_i S_i - (1-u) b_i S_i V, \qquad i = 1, ..., n, \tag{31}$$

$$\dot{I}_i = (1-u) b_i S_i V - \epsilon_i I_i, \qquad i = 1, ..., n, \tag{32}$$

$$\dot{V} = \sum_{i=1}^{n} m_i I_i - rV - qBV, \tag{33}$$

$$\dot{B} = \eta + cBV - \delta B. \tag{34}$$

Consequently, the parameter $\mathcal{R}_0$ for the system in Equations (31)–(34) is given by

$$\mathcal{R}_0(u) = (1-u) \sum_{i=1}^{n} \frac{m_i b_i \mu_i \delta}{d_i \epsilon_i (r\delta + q\eta)}.$$

The model in Equations (19)–(23) under the effect of treatment is given by:

$$\dot{S}_i = \mu_i - d_i S_i - (1-u) b_i S_i V, \qquad i = 1, ..., n, \tag{35}$$

$$\dot{L}_i = (1-u)(1-p_i) b_i S_i V - (\theta_i + \lambda_i) L_i, \quad i = 1, ..., n, \tag{36}$$

$$\dot{I}_i = (1-u) p_i b_i S_i V + \lambda_i L_i - \epsilon_i I_i, \qquad i = 1, ..., n, \tag{37}$$

$$\dot{V} = \sum_{i=1}^{n} m_i I_i - rV - qBV, \tag{38}$$

$$\dot{B} = \eta + cBV - \delta B. \tag{39}$$

The parameter $\mathcal{R}_0^L$ for the system in Equations (35)–(39) is given by

$$\mathcal{R}_0^L(u) = (1-u)\sum_{i=1}^{n} \frac{m_i b_i \mu_i \delta(\theta_i p_i + \lambda_i)}{d_i \epsilon_i (\theta_i + \lambda_i)(r\delta + q\eta)}.$$

Since $0 < p_i < 1$, then

$$\mathcal{R}_0^L(u) = (1-u)\sum_{i=1}^{n} \frac{m_i b_i \mu_i \delta(\theta_i p_i + \lambda_i)}{d_i \epsilon_i (\theta_i + \lambda_i)(r\delta + q\eta)} < (1-u)\sum_{i=1}^{n} \frac{m_i b_i \mu_i \delta}{d_i \epsilon_i (r\delta + q\eta)} = \mathcal{R}_0(u).$$

Clearly, the presence of latently infected cells deceases the basic reproduction number of the system. Now we aim to determine the minimum drug efficacy that able to clear the viruses from the body. We determine u_{crit} and u_{crit}^L that make

$$\begin{aligned} \mathcal{R}_0(u) &\leq 1, \quad \text{for all} \quad u_{crit} \leq u < 1, \\ \mathcal{R}_0^L(u) &\leq 1, \quad \text{for all} \quad u_{crit}^L \leq u < 1, \end{aligned}$$

to stabilize the system in Equations (31)–(39) around Q_0 and Q_0^L, respectively. Now, we calculate u_{crit} and u_{crit}^L as:

$$\begin{aligned} u_{crit} &= \max\left\{0, \frac{\mathcal{R}_0(0)-1}{\mathcal{R}_0(0)}\right\}, \\ u_{crit}^L &= \max\left\{0, \frac{\mathcal{R}_0^L(0)-1}{\mathcal{R}_0^L(0)}\right\}. \end{aligned}$$

Clearly, $\mathcal{R}_0^L(0) < \mathcal{R}_0(0)$ and thus $u_{crit}^L < u_{crit}$. Therefore, the drug efficacy necessary to drive the system to the virus-free steady state is actually less for the system in Equations (35)–(39) than that for the system in Equations (31)–(34).

Author Contributions: All authors contributed equally to the writing of this paper. All authors read and approved the final manuscript.

Acknowledgments: This article was funded by the Deanship of Scientific Research (DSR) at King Abdulaziz University, Jeddah. The authors, therefore, acknowledge with thanks DSR for technical and financial support.

Conflicts of Interest: The authors declare te no conflict of interest.

Appendix A

Proof of Theorem A1. Construct a Lyapunov function W_0 as:

$$W_0(\mathbf{S}, \mathbf{I}, V, B) = \sum_{i=1}^{n} y_i \left[S_i^0 H\left(\frac{S_i}{S_i^0}\right) + I_i \right] + V + \frac{q}{c} B^0 H\left(\frac{B}{B^0}\right), \tag{A1}$$

where $y_i = \frac{m_i}{\epsilon_i}$. Note that, $W_0(\mathbf{S}, \mathbf{I}, V, B) > 0$ for all $\mathbf{S}, \mathbf{I}, V, B > 0$ and $W_0(\mathbf{S}^0, 0, 0, B^0) = 0$. Calculating $\frac{dW_0}{dt}$ along the trajectories of Equations (9)–(12) we get

$$\begin{aligned}\frac{dW_0}{dt} &= \sum_{i=1}^{n} y_i \left[\left(1-\frac{S_i^0}{S_i}\right)(\mu_i - d_i S_i - b_i S_i V) + b_i S_i V - \epsilon_i I_i\right] + \sum_{i=1}^{n} m_i I_i - rV - qBV \\ &\quad + \frac{q}{c}\left(1-\frac{B^0}{B}\right)(\eta + cBV - \delta B) \\ &= \sum_{i=1}^{n} y_i d_i \left(1-\frac{S_i^0}{S_i}\right)\left(S_i^0 - S_i\right) + \sum_{i=1}^{n} \frac{m_i b_i S_i^0 V}{\epsilon_i} - rV - qB^0 V + \frac{q}{c}\left(1-\frac{B^0}{B}\right)\left(\delta B^0 - \delta B\right) \\ &= \sum_{i=1}^{n} y_i d_i \left(\frac{S_i - S_i^0}{S_i}\right)\left(S_i^0 - S_i\right) - \frac{q\delta}{c}\frac{(B-B^0)^2}{B} + (r+qB^0)\left(\sum_{i=1}^{n}\frac{m_i b_i \mu_i}{d_i \epsilon_i (r+qB^0)} - 1\right) V \\ &= -\sum_{i=1}^{n} y_i d_i \frac{\left(S_i - S_i^0\right)^2}{S_i} - \frac{q\delta}{c}\frac{(B-B^0)^2}{B} + (r+qB^0)(\mathcal{R}_0 - 1)V.\end{aligned} \tag{A2}$$

If $\mathcal{R}_0 \leq 1$, then $\frac{dW_0}{dt} \leq 0$ for all $\mathbf{S}, \mathbf{I}, V, B > 0$. In addition, $\frac{dW_0}{dt} = 0$ if and only if $S_i = S_i^0$, $B = B^0$, $V = 0$. The solutions of the system in Equations (9)–(12) converge to D, the largest invariant set of $\{(\mathbf{S}, \mathbf{I}, V, B) : \frac{dW_0}{dt} = 0\}$. For any element in D satisfies $V(t) = \dot{V}(t) = 0$. Then, from Equation (11), we have $I_i(t) = 0$. By the LaSalle's invariance principle [56,57], Q_0 is globally asymptotically stable. □

Proof of Theorem A2. Construct a Lyapunov function W_1 as:

$$W_1(\mathbf{S}, \mathbf{I}, V, B) = \sum_{i=1}^{n} y_i \left[S_i^* H\left(\frac{S_i}{S_i^*}\right) + I_i^* H\left(\frac{I_i}{I_i^*}\right)\right] + V^* H\left(\frac{V}{V^*}\right) + \frac{q}{c} B^* H\left(\frac{B}{B^*}\right).$$

We have $W_1(\mathbf{S}, \mathbf{I}, V, B) > 0$ for all $\mathbf{S}, \mathbf{I}, V, B > 0$ and $W_1(\mathbf{S}^*, \mathbf{I}^*, V^*, B^*) = 0$. Calculating $\frac{dW_1}{dt}$ along the trajectories of Equations (9)–(12) we get

$$\begin{aligned}\frac{dW_1}{dt} &= \sum_{i=1}^{n} y_i \left[\left(1-\frac{S_i^*}{S_i}\right)(\mu_i - d_i S_i - b_i S_i V) + \left(1-\frac{I_i^*}{I_i}\right)(b_i S_i V - \epsilon_i I_i)\right] \\ &\quad + \left(1-\frac{V^*}{V}\right)\left(\sum_{i=1}^{n} m_i I_i - rV - qBV\right) + \frac{q}{c}\left(1-\frac{B^*}{B}\right)(\eta + cBV - \delta B) \\ &= \sum_{i=1}^{n} y_i \left[\left(1-\frac{S_i^*}{S_i}\right)(\mu_i - d_i S_i) + b_i S_i^* V - b_i S_i V \frac{I_i^*}{I_i} + \epsilon_i I_i^*\right] \\ &\quad - \sum_{i=1}^{n} m_i I_i \frac{V^*}{V} - rV + rV^* + qBV^* - qB^* V + \frac{q}{c}\left(1-\frac{B^*}{B}\right)(\eta - \delta B).\end{aligned}$$

Applying

$$\mu_i = d_i S_i^* + b_i S_i^* V^*, \ \eta = \delta B^* - cB^* V^*,$$

we obtain

$$\begin{aligned}\frac{dW_1}{dt} &= \sum_{i=1}^{n} y_i \left[\left(1-\frac{S_i^*}{S_i}\right)(d_i S_i^* - d_i S_i) + b_i S_i^* V^*\left(1-\frac{S_i^*}{S_i}\right) + b_i S_i^* V - b_i S_i V \frac{I_i^*}{I_i} + \epsilon_i I_i^*\right] \\ &\quad - \sum_{i=1}^{n} m_i I_i \frac{V^*}{V} - rV + rV^* + qBV^* - qB^* V - qB^* V^* + qB^* V^*\left(\frac{B^*}{B}\right) + \frac{q}{c}\left(1-\frac{B^*}{B}\right)(\delta B^* - \delta B).\end{aligned}$$

Using the endemic steady state conditions

$$\epsilon_i I_i^* = b_i S_i^* V^*, \ \sum_{i=1}^{n} m_i I_i^* = rV^* + qB^* V^*,$$

we get

$$\begin{aligned}\frac{dW_1}{dt} &= \sum_{i=1}^{n} y_i \left[d_i \left(1 - \frac{S_i^*}{S_i}\right)(S_i^* - S_i) + 3\epsilon_i I_i^* - \epsilon_i I_i^* \frac{S_i^*}{S_i} - \epsilon_i I_i^* \frac{S_i V I_i^*}{S_i^* V^* I_i} - \epsilon_i I_i^* \frac{V^* I_i}{V I_i^*} \right] - 2qB^* V^* + qBV^* \\ &+ qB^* V^* \left(\frac{B^*}{B}\right) - \frac{q\delta}{c}\frac{(B-B^*)^2}{B} \\ &= \sum_{i=1}^{n} y_i \left[-d_i \frac{\left(S_i - S_i^*\right)^2}{S_i} + \epsilon_i I_i^* \left(3 - \frac{S_i^*}{S_i} - \frac{S_i V I_i^*}{S_i^* V^* I_i} - \frac{V^* I_i}{V I_i^*}\right) \right] - qB^* V^* \left(2 - \frac{B}{B^*} - \frac{B^*}{B}\right) \\ &- \frac{q\delta}{c}\frac{(B-B^*)^2}{B} \\ &= \sum_{i=1}^{n} y_i \left[-d_i \frac{\left(S_i - S_i^*\right)^2}{S_i} + \epsilon_i I_i^* \left(3 - \frac{S_i^*}{S_i} - \frac{S_i V I_i^*}{S_i^* V^* I_i} - \frac{V^* I_i}{V I_i^*}\right) \right] - \frac{q\eta}{cB^*}\frac{(B-B^*)^2}{B}. \end{aligned} \tag{A3}$$

The relation between the geometrical mean and the arithmetical mean implies that

$$3 \leq \frac{S_i^*}{S_i} + \frac{S_i V I_i^*}{S_i^* V^* I_i} + \frac{V^* I_i}{V I_i^*}.$$

Therefore, if $\mathcal{R}_0 > 1$, then $\mathbf{S}^*, \mathbf{I}^*, V^*, B^* > 0$ and $\frac{dW_1}{dt} \leq 0$ for all $\mathbf{S}, \mathbf{I}, V, B > 0$. The solutions of system limit to D_1, the largest invariant subset of $\left\{ \frac{dW_1}{dt} = 0 \right\}$. We have $\frac{dW_1}{dt} = 0$ if and only if $S_i = S_i^*$, $I_i = I_i^*$, $V = V^*$, and $B = B^*$. It follows from LaSalle's invariance principle that Q_1 is globally asymptotically stable in $\mathring{\Omega}$. □

Proof of Theorem A3. Construct a Lyapunov function W_0^L as:

$$W_0^L(\mathbf{S}, \mathbf{L}, \mathbf{I}, V, B) = \sum_{i=1}^{n} \beta_i \left[S_i^0 H\left(\frac{S_i}{S_i^0}\right) + \frac{\lambda_i}{\theta_i p_i + \lambda_i} L_i + \frac{\theta_i + \lambda_i}{\theta_i p_i + \lambda_i} I_i \right] + V + \frac{q}{c} B^0 H\left(\frac{B}{B^0}\right), \tag{A4}$$

where $\beta_i = \frac{m_i(\theta_i p_i + \lambda_i)}{\epsilon_i(\theta_i + \lambda_i)}$. Calculating $\frac{dW_0^L}{dt}$ along the trajectories of Equations (19)–(23) we get

$$\begin{aligned}\frac{dW_0^L}{dt} &= \sum_{i=1}^{n} \beta_i \left[\left(1 - \frac{S_i^0}{S_i}\right)(\mu_i - d_i S_i - b_i S_i V) + \frac{\lambda_i}{\theta_i p_i + \lambda_i}\left((1-p_i) b_i S_i V - (\theta_i + \lambda_i) L_i\right) \right. \\ &\left. + \frac{\theta_i + \lambda_i}{\theta_i p_i + \lambda_i}\left(p_i b_i S_i V + \lambda_i L_i - \epsilon_i I_i\right) \right] + \sum_{i=1}^{n} m_i I_i - rV - qBV + \frac{q}{c}\left(1 - \frac{B^0}{B}\right)(\eta + cBV - \delta B) \\ &= \sum_{i=1}^{n} \beta_i d_i \left(1 - \frac{S_i^0}{S_i}\right)\left(S_i^0 - S_i\right) + \sum_{i=1}^{n} \frac{m_i b_i S_i^0 (\theta_i p_i + \lambda_i) V}{\epsilon_i(\theta_i + \lambda_i)} - rV - qB^0 V + \frac{q}{c}\left(1 - \frac{B^0}{B}\right)\left(\delta B^0 - \delta B\right) \\ &= \sum_{i=1}^{n} \beta_i d_i \left(\frac{S_i - S_i^0}{S_i}\right)\left(S_i^0 - S_i\right) - \frac{q\delta}{c}\frac{(B-B^0)^2}{B} + (r + qB^0)\left(\sum_{i=1}^{n} \frac{m_i b_i \mu_i (\theta_i p_i + \lambda_i)}{d_i \epsilon_i (\theta_i + \lambda_i)(r + qB^0)} - 1\right) V \\ &= -\sum_{i=1}^{n} \beta_i d_i \frac{\left(S_i - S_i^0\right)^2}{S_i} - \frac{q\delta}{c}\frac{(B-B^0)^2}{B} + (r + qB^0)(\mathcal{R}_0^L - 1) V. \end{aligned} \tag{A5}$$

Therefore if $\mathcal{R}_0^L \leq 1$, then $\frac{dW_0^L}{dt} \leq 0$ for all $\mathbf{S}, \mathbf{L}, \mathbf{I}, V, B > 0$. Moreover, $\frac{dW_0^L}{dt} = 0$ at Q_0^L. By the LaSalle's invariance principle, Q_0^L is globally asymptotically stable. □

Proof of Theorem A4. Construct a Lyapunov function W_1^L as follows:

$$W_1^L = \sum_{i=1}^{n} \beta_i \left[S_i^* H\left(\frac{S_i}{S_i^*}\right) + \frac{\lambda_i}{\theta_i p_i + \lambda_i} L_i^* H\left(\frac{L_i}{L_i^*}\right) + \frac{\theta_i + \lambda_i}{\theta_i p_i + \lambda_i} I_i^* H\left(\frac{I_i}{I_i^*}\right) \right] + V^* H\left(\frac{V}{V^*}\right) + \frac{q}{c} B^* H\left(\frac{B}{B^*}\right).$$

Calculating $\frac{dW_1^L}{dt}$ along the trajectories of Equations (19)–(23) we get

$$\begin{aligned}\frac{dW_1^L}{dt} = \sum_{i=1}^{n}\beta_i \Bigg[\left(1-\frac{S_i^*}{S_i}\right)(\mu_i - d_iS_i - b_iS_iV) + \frac{\lambda_i}{\theta_ip_i+\lambda_i}\left(1-\frac{L_i^*}{L_i}\right)((1-p_i)b_iS_iV - (\theta_i+\lambda_i)L_i)\\ + \frac{\theta_i+\lambda_i}{\theta_ip_i+\lambda_i}\left(1-\frac{I_i^*}{I_i}\right)(p_ib_iS_iV + \lambda_iL_i - \epsilon_iI_i)\Bigg] + \left(1-\frac{V^*}{V}\right)\left(\sum_{i=1}^{n}m_iI_i - rV - qBV\right)\\ + \frac{q}{c}\left(1-\frac{B^*}{B}\right)(\eta + cBV - \delta B).\end{aligned}$$

Applying

$$\mu_i = d_iS_i^* + b_iS_i^*V^*, \quad \eta = \delta B^* - cB^*V^*,$$

we obtain

$$\begin{aligned}\frac{dW_1^L}{dt} = \sum_{i=1}^{n}\beta_i \Bigg[\left(1-\frac{S_i^*}{S_i}\right)(d_iS_i^* - d_iS_i) + b_iS_i^*V^*\left(1-\frac{S_i^*}{S_i}\right) + b_iS_i^*V - \frac{\lambda_i(1-p_i)b_i}{\theta_ip_i+\lambda_i}\frac{S_iVL_i^*}{L_i}\\ + \frac{\lambda_i(\theta_i+\lambda_i)}{\theta_ip_i+\lambda_i}L_i^* - \frac{(\theta_i+\lambda_i)p_ib_i}{\theta_ip_i+\lambda_i}\frac{S_iVI_i^*}{I_i} - \frac{(\theta_i+\lambda_i)\lambda_i}{\theta_ip_i+\lambda_i}\frac{L_iI_i^*}{I_i} + \frac{\theta_i+\lambda_i}{\theta_ip_i+\lambda_i}\epsilon_iI_i^* - \frac{\theta_i+\lambda_i}{\theta_ip_i+\lambda_i}\epsilon_iI_i^*\frac{V^*I_i}{VI_i^*}\Bigg]\\ - rV + rV^* + qBV^* - qB^*V - qB^*V^* + qB^*V^*\left(\frac{B^*}{B}\right) + \frac{q}{c}\left(1-\frac{B^*}{B}\right)(\delta B^* - \delta B).\end{aligned}$$

Using the endemic steady state conditions

$$\begin{aligned}(1-p_i)b_iS_i^*V^* = (\theta_i+\lambda_i)L_i^*, \quad p_ib_iS_i^*V^* = \epsilon_iI_i^* - \lambda_iL_i^*,\\ \sum_{i=1}^{n}m_iI_i^* = rV^* + qB^*V^*,\end{aligned}$$

we get

$$\frac{\theta_i+\lambda_i}{\theta_ip_i+\lambda_i}\epsilon_iI_i^* = b_iS_i^*V^* = \frac{\lambda_i}{\theta_ip_i+\lambda_i}(1-p_i)b_iS_i^*V^* + \frac{\theta_i+\lambda_i}{\theta_ip_i+\lambda_i}p_ib_iS_i^*V^*,$$

and

$$\begin{aligned}\frac{dW_1^L}{dt} = \sum_{i=1}^{n}\beta_i \Bigg[d_i\left(1-\frac{S_i^*}{S_i}\right)(S_i^* - S_i) + b_iS_i^*V^*\left(\frac{\lambda_i}{\theta_ip_i+\lambda_i}(1-p_i) + \frac{\theta_i+\lambda_i}{\theta_ip_i+\lambda_i}p_i\right)\left(1-\frac{S_i^*}{S_i}\right)\\ - \frac{\lambda_i}{\theta_ip_i+\lambda_i}(1-p_i)b_iS_i^*V^*\frac{S_iVL_i^*}{S_i^*V^*L_i} + \frac{\lambda_i}{\theta_ip_i+\lambda_i}(1-p_i)b_iS_i^*V^*\\ - \frac{\theta_i+\lambda_i}{\theta_ip_i+\lambda_i}p_ib_iS_i^*V^*\frac{S_iVI_i^*}{S_i^*V^*I_i} - \frac{\lambda_i}{\theta_ip_i+\lambda_i}(1-p_i)b_iS_i^*V^*\frac{L_iI_i^*}{L_i^*I_i}\\ + \frac{\lambda_i}{\theta_ip_i+\lambda_i}(1-p_i)b_iS_i^*V^* + \frac{\theta_i+\lambda_i}{\theta_ip_i+\lambda_i}p_ib_iS_i^*V^* - \frac{\lambda_i}{\theta_ip_i+\lambda_i}(1-p_i)b_iS_i^*V^*\frac{V^*I_i}{VI_i^*}\\ - \frac{\theta_i+\lambda_i}{\theta_ip_i+\lambda_i}p_ib_iS_i^*V^*\frac{V^*I_i}{VI_i^*} + \frac{\lambda_i}{\theta_ip_i+\lambda_i}(1-p_i)b_iS_i^*V^* + \frac{\theta_i+\lambda_i}{\theta_ip_i+\lambda_i}p_ib_iS_i^*V^*\Bigg]\\ - 2qB^*V^* + qBV^* + qB^*V^*\left(\frac{B^*}{B}\right) - \frac{q\delta}{c}\frac{(B-B^*)^2}{B}.\end{aligned}$$

$$\begin{aligned}\frac{dW_1^L}{dt} &= \sum_{i=1}^{n}\beta_i\left[-d_i\frac{\left(S_i-S_i^*\right)^2}{S_i}+\frac{\lambda_i}{\theta_i p_i+\lambda_i}(1-p_i)b_iS_i^*V^*\left(4-\frac{S_i^*}{S_i}-\frac{S_iVL_i^*}{S_i^*V^*L_i}-\frac{L_iI_i^*}{L_i^*I_i}-\frac{V^*I_i}{VI_i^*}\right)\right.\\ &\left.+\frac{\theta_i+\lambda_i}{\theta_i p_i+\lambda_i}\,p_ib_iS_i^*V^*\left(3-\frac{S_i^*}{S_i}-\frac{S_iVI_i^*}{S_i^*V^*I_i}-\frac{V^*I_i}{VI_i^*}\right)\right]-qB^*V^*\left(2-\frac{B}{B^*}-\frac{B^*}{B}\right)\\ &-\frac{q\delta}{c}\frac{(B-B^*)^2}{B}\\ &=\sum_{i=1}^{n}\beta_i\left[-d_i\frac{\left(S_i-S_i^*\right)^2}{S_i}+\frac{\lambda_i}{\theta_i p_i+\lambda_i}(1-p_i)b_iS_i^*V^*\left(4-\frac{S_i^*}{S_i}-\frac{S_iVL_i^*}{S_i^*V^*L_i}-\frac{L_iI_i^*}{L_i^*I_i}-\frac{V^*I_i}{VI_i^*}\right)\right.\\ &\left.+\frac{\theta_i+\lambda_i}{\theta_i p_i+\lambda_i}\,p_ib_iS_i^*V^*\left(3-\frac{S_i^*}{S_i}-\frac{S_iVI_i^*}{S_i^*V^*I_i}-\frac{V^*I_i}{VI_i^*}\right)\right]-\frac{q\eta}{cB^*}\frac{(B-B^*)^2}{B}.\end{aligned} \tag{A6}$$

Clearly, $\frac{dW_1^L}{dt}\leq 0$ and $\frac{dW_1^L}{dt}=0$ if and only if $S_i=S_i^*$, $L_i=L_i^*$, $I_i=I_i^*$, $V=V^*$ and $B=B^*$. It follows from LaSalle's invariance principle, Q_1^L is globally asymptotically stable in $\mathring{\Omega}^L$. □

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