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Research article

Global dynamics of a delayed diffusive virus infection model with cell-mediated immunity and cell-to-cell transmission

Chunyang Qin[1], **Yuming Chen**[2] **and Xia Wang**[1,3,*]

[1] School of Mathematics and Statistics, Xinyang Normal University, Xinyang 464000, China

[2] Department of Mathematics, Wilfrid Laurier University, Waterloo N2L 3C5, Canada

[3] College of Mathematics and Information Science, Henan Normal University, Xinxiang 453000, China

* **Correspondence:** Email: xywangxia@163.com.

Abstract: In this paper, we propose and analyze a delayed diffusive viral dynamic model incorporating cell-mediated immunity and both cell-free and cell-to-cell transmission. After discussing the well-posedness, we provide some preliminary results on solutions. Then we study the existence and uniqueness of homogeneous steady states, which turned out to be completely determined by the basic reproduction number of infection R_0 and the basic reproduction number of immunity R_1. Note that when R_1 is defined, it is necessary that $R_0 > 1$. The main result is a threefold dynamics. Roughly speaking, when $R_0 < 1$ the infection-free steady state is globally asymptotically stable; when $R_1 \leq 1 < R_0$ the immunity-free infected steady state is globally asymptotically stable; when $R_1 > 1$ the infected-immune steady state is globally asymptotically stable. The approaches are linearization technique and the Lyapunov functional method. The theoretical results are also illustrated with numerical simulations.

Keywords: cell-mediated immunity; cell-to-cell transmission; spatial heterogeneity; delay; global stability

1. Introduction

Viral dynamics is a field of applied mathematics which employs mathematical models to describe the changes over time of infected cells and the viral load. Nowak et al. [1] and Nowak and May [2]

proposed the following basic viral dynamic model,

$$\begin{cases} \dfrac{\mathrm{d}u(t)}{\mathrm{d}t} = s - du(t) - \beta u(t)v(t), \\ \dfrac{\mathrm{d}w(t)}{\mathrm{d}t} = \beta u(t)v(t) - \delta w(t), \\ \dfrac{\mathrm{d}v(t)}{\mathrm{d}t} = N\delta w(t) - cv(t), \end{cases} \tag{1.1}$$

where $u(t)$, $w(t)$, and $v(t)$ are the numbers of uninfected cells, productively infected cells, and virus particles at time t, respectively. See the references for the biological meanings of the parameters. This basic model has been modified to study different viral infections, which include hepatitis C virus (HCV) [3, 4], human immunodeficiency virus (HIV) [5–8], human T-cell leukemia virus (HTLV) [9–11], and so on.

During the process of viral infection, specific immune response plays an important role. Specific immune response includes cell-mediated immunity (which depends on cytotoxic T lymphocytes response (CTLs)) and humoral immunity (which depends on antibody response). Since the work of Nowak and Bangham [12], much has been done on mathematical models on immune response against infected cells [13–16].

Nowadays, time delays have been taken into account in order to better understand viral dynamics. Usually, distributed time delays [17–19] and discrete time delays [20–22] have been incorporated into viral dynamic models. In particular, based on (1.1), Zhu and Zou [20] proposed the following viral dynamic model with time delay and CTL immune response,

$$\begin{cases} \dfrac{\mathrm{d}u(t)}{\mathrm{d}t} = s - du(t) - \beta u(t)v(t), \\ \dfrac{\mathrm{d}w(t)}{\mathrm{d}t} = \beta e^{-m\hat{\tau}} u(t-\hat{\tau})v(t-\hat{\tau}) - \delta w(t) - pw(t)z(t), \\ \dfrac{\mathrm{d}v(t)}{\mathrm{d}t} = N\delta w(t) - cv(t), \\ \dfrac{\mathrm{d}z(t)}{\mathrm{d}t} = qw(t)z(t) - bz(t), \end{cases} \tag{1.2}$$

where $z(t)$ denotes the density of immune effectors at time t. Here the delay $\hat{\tau}$ represents the time from a virus entering a target cell to the production of new free virus particles. We refer to [20] for the meanings of the other parameters.

Note that both models (1.1) and (1.2) and most existing ones are described by ordinary differential equations. The cells and free virus particles are assumed to be uniform in location. In other words, the effect of spatial heterogeneity is ignored. For example, the lymphoid tissues are among the primary sites of HIV infection and replication. The lymphoid tissues consist of many lymph nodes with different sizes. The different tissue architecture and composition and biophysical parameters can influence the spread and replication of the virus [23]. To understand the viral pathogenesis better, it is necessary to consider the spatial aspects of the tissues. In [24], Wang and Wang proposed the

following mathematical model of HBV infection with spatial dependence,

$$\begin{cases} \dfrac{\partial u(x,t)}{\partial t} = s - du(x,t) - \beta u(x,t)v(x,t), \\ \dfrac{\partial w(x,t)}{\partial t} = \beta u(x,t)v(x,t) - \delta w(x,t), \\ \dfrac{\partial v(x,t)}{\partial t} = D\Delta v(x,t) + N\delta w(x,t) - cv(x,t), \end{cases} \tag{1.3}$$

where $u(x,t)$, $w(x,t)$, and $v(x,t)$ are the densities of uninfected cells, productively infected cells, and free virus particles at spatial position x and time t, respectively. D is the diffusion coefficient and Δ is the Laplace operator. Using the geometric singular perturbation method, they studied the existence of traveling waves. Since then a lot of works have followed in this direction (see, for example, [25–29]).

In (1.1), (1.2), and (1.3), only the cell-free transmission (newly released free virus particles infect uninfected cells [2]) is considered. Recent experimental studies [30, 31] prove that a healthy cell can be infected when it comes with close contact of an infected cell (cell-to-cell transmission [32, 33]). Sigal et al. [34] found that the cell-to-cell spread of HIV can still permit ongoing replication even with an antiretroviral therapy. Consequently, viral dynamic models incorporating both transmission modes have been formulated and studied (to name a few, see [35–39]). We should mention that the incidences in these works are bilinear. Incidence is the number of new infections per unit of time. It depends on the infectivity of viruses and behavior of cells. Thus it is reasonable to be nonlinear in general. For example, the saturated incidence rate $\frac{\beta uv}{1+\alpha v}$ is used in [40] and the Beddington-DeAngelis incidence function is used in [41]. In a recent work, Sun and Wang [42] also used a general incidence $f(u,v)$ in a diffusive viral dynamic model.

Based on the above discussion, in this paper, we propose and study the following delayed diffusive viral dynamic model with cell-mediated immunity, cell-to-cell transmission, and general incidences,

$$\begin{cases} \dfrac{\partial u(x,t)}{\partial t} = s - du(x,t) - f(u(x,t),v(x,t)) - g(u(x,t),w(x,t)), \\ \dfrac{\partial w(x,t)}{\partial t} = e^{-m\tau} f(u(x,t-\tau),v(x,t-\tau)) + e^{-m\tau} g(u(x,t-\tau),w(x,t-\tau)) \\ \qquad\qquad -\delta w(x,t) - pw(x,t)z(x,t), \\ \dfrac{\partial v(x,t)}{\partial t} = D_1\Delta v(x,t) + N\delta w(x,t) - cv(x,t),\ x\in\Omega,\ t>0, \\ \dfrac{\partial z(x,t)}{\partial t} = D_2\Delta z(x,t) + qw(x,t)z(x,t) - bz(x,t),\ x\in\Omega,\ t>0, \end{cases} \tag{1.4}$$

where $z(x,t)$ denotes the densities of immune effectors at spatial position x and time t. Ω is a general open bounded domain in $\mathbb{R}^n$ with smooth boundary $\partial\Omega$. We consider model (1.4) with the homogeneous Neumann boundary conditions

$$\frac{\partial v}{\partial \vec{n}} = 0,\ \frac{\partial z}{\partial \vec{n}} = 0,\ x\in\partial\Omega,\ t>0, \tag{1.5}$$

where $\frac{\partial}{\partial \vec{n}}$ denotes the outward normal derivative on $\partial\Omega$. We also assume the initial conditions

$$\begin{aligned} &u(x,\theta) = \phi_1(x,\theta) \geq 0,\ w(x,\theta) = \phi_2(x,\theta) \geq 0, \\ &v(x,\theta) = \phi_3(x,\theta) \geq 0,\ z(x,\theta) = \phi_4(x,\theta) \geq 0,\ (x,\theta)\in\overline{\Omega}\times[-\tau,0], \end{aligned} \tag{1.6}$$

where ϕ_i's ($i = 1, 2, 3, 4$) are bounded and uniformly continuous functions on $\overline{\Omega} \times [-\tau, 0]$.

In (1.4), intracellular delays for both transmission modes are assumed to be the same. In general, the intracellular delay in the cell-to-cell transmission is less than that in the cell-free infection [30, 39]. However, the difference is not large enough. As for some existing studies (for example, [35, 38]), for simplicity of presentation, we make the above assumption on the delays.

In (1.4), the incidences due to the cell-free transmission and the cell-to-cell transmission are given by the nonlinear functions $f(u, v)$ and $g(u, w)$, respectively. As in [26], we always make the following assumption on them in the sequel.

(A1) The nonlinear incidence functions f and g satisfy the following properties.

(i) $f(u, v) \geq 0$ and $g(u, w) \geq 0$ for $u \geq 0$, $v \geq 0$, and $w \geq 0$, and the equalities hold if and only if $uv = 0$ and $uw = 0$;
(ii) There exists $\eta_1 > 0$ and $\eta_2 > 0$ such that $f(u, v) \leq \eta_1 u$ and $g(u, w) \leq \eta_2 u$ for $u \geq 0$, $v \geq 0$, and $w \geq 0$;
(iii) $\frac{\partial f(u,v)}{\partial u}$ and $\frac{\partial g(u,w)}{\partial u}$ are continuous with $\frac{\partial f(u,v)}{\partial u} > 0$ and $\frac{\partial g(u,w)}{\partial u} > 0$ for $u \geq 0$, $v > 0$, and $w > 0$;
(iv) $\frac{\partial f(u,v)}{\partial v}$ and $\frac{\partial g(u,w)}{\partial w}$ are continuous with $\frac{\partial f(u,v)}{\partial v} \geq 0$ and $\frac{\partial g(u,w)}{\partial w} \geq 0$ for $u \geq 0$, $v \geq 0$, and $w \geq 0$;
(v) $v\frac{\partial f(u,v)}{\partial v} - f(u, v) \leq 0$ and $w\frac{\partial g(u,w)}{\partial w} - g(u, w) \leq 0$ for $u \geq 0$, $v \geq 0$, and $w \geq 0$.

Note that, by Assumption (A1), for any $u > 0$,

$$\frac{\partial(\frac{f(u,v)}{v})}{\partial v} = \frac{\frac{\partial f(u,v)}{\partial v}v - f(u, v)}{v^2} < 0,$$

which implies that $\frac{f(u,v)}{v}$ is decreasing on $(0, \infty)$. In particular, for any $u > 0$ and $v > 0$,

$$\frac{f(u, v)}{v} \leq \lim_{v\to 0^+} \frac{f(u, v)}{v} = \frac{\partial f(u, 0)}{\partial v}.$$

An analog also holds for g. Thus we have

$$f(u, v) \leq \frac{\partial f(u, 0)}{\partial v}v \text{ and } g(u, w) \leq \frac{\partial g(u, 0)}{\partial w}w \text{ for } u \geq 0, v \geq 0, \text{ and } w \geq 0. \tag{1.7}$$

The rest of the paper is organized as follows. In section 2, we consider the existence, uniqueness, positivity, and boundedness of solutions to system (1.4)–(1.6). Then we study the existence of homogeneous steady states in section 3, which depend on the basic reproduction number of infection and the basic reproduction number of immunity. The main part is section 4, where we discuss the local and global dynamics of system (1.4)–(1.6) by analyzing the characteristic equations and constructing suitable Lyapunov functionals. These results are supported with numerical simulations in section 5. The paper ends with a brief conclusion.

2. Well-posedness

Let $\mathbf{X} := C(\overline{\Omega}, \mathbb{R}^4)$ be the Banach space equipped with the supremum norm $\|\cdot\|_{\mathbf{X}}$. For $\tau \geq 0$, define $C = C([-\tau, 0], \mathbf{X})$, which is a Banach space equipped with the norm $\|\phi\| = \max_{\theta\in[-\tau,0]} \|\phi(\theta)\|_{\mathbf{X}}$. If $\sigma > 0$ and $U : [-\tau, \sigma) \to \mathbf{X}$, then for $t \in [0, \sigma)$, $U_t \in C$ is defined by $U_t(\theta) = U(t + \theta)$ for $\theta \in [-\tau, 0]$. Denote

$\mathbf{X}^+ = C(\overline{\Omega}, \mathbb{R}^4_+)$ and $C^+ = C([-\tau, 0], \mathbf{X}^+)$. Then both $(\mathbf{X}, \mathbf{X}^+)$ and (C, C^+) are strongly ordered spaces. According to Corollary 4 in [43] , we have the following result on the well-posedness. The arguments are standard and hence are omitted here. Interested readers can refer to, for example, a recent paper by Gao and Wang [44].

Theorem 2.1. *For each $\phi = (\phi_1, \phi_2, \phi_3, \phi_4) \in C^+$, system (1.4)–(1.6) has a unique solution $U(\cdot, t, \phi) = (u(\cdot, t, \phi), w(\cdot, t, \phi), v(\cdot, t, \phi), z(\cdot, t, \phi))$ on $[0, \infty)$ with $U_0(\cdot, \phi) = \phi$. Moreover, $U_t(\cdot, \phi) \in C^+$ for $t \geq 0$ and $U(\cdot, t, \phi)$ is a classical solution.*

Let $\Phi(t) : C^+ \to C^+$ be the solution semiflow associated with (1.4)–(1.6), that is, $\Phi(t, \phi) = U_t(\cdot, \phi)$, where $U(\cdot, t, \phi)$ is the solution of (1.4)–(1.6) with the initial condition $\phi \in C^+$.

The following result gives some properties of solutions.

Lemma 2.2. *For $\phi \in C^+$, the following statements hold for the solution $U(\cdot, t, \phi)$ of (1.4)–(1.6).*

(i) $\limsup_{t\to\infty} u(x, t, \phi) \leq \frac{s}{d}$, $\limsup_{t\to\infty} w(x, t, \phi) \leq \frac{e^{-m\tau}(\eta_1+\eta_2)s}{d\delta}$, $\limsup_{t\to\infty} v(x, t, \phi) \leq \frac{Ne^{-m\tau}(\eta_1+\eta_2)s}{dc}$, *and* $\limsup_{t\to\infty} z(x, t, \phi) \leq \frac{e^{-m\tau}(\eta_1+\eta_2)s}{d\min\{\delta,b\}}$ *uniformly for all $x \in \Omega$.*

(ii) $u(\cdot, t, \phi) > 0$ *for $t > 0$ and* $\liminf_{t\to\infty} u(x, t, \phi) \geq \frac{s}{d+\eta_1+\eta_2}$ *uniformly for all $x \in \Omega$.*

(iii) *If $w(\cdot, t_0, \phi) \not\equiv 0$ or $v(\cdot, t_0, \phi) \not\equiv 0$ for some $t_0 \geq 0$, then $w(x, t, \phi) > 0$ and $v(x, t, \phi) > 0$ for all $x \in \Omega$ and $t > t_0 + \tau$.*

(iv) *If $z(\cdot, t_0, \phi) \not\equiv 0$ for some $t_0 \geq 0$, then $z(x, t, \phi) > 0$ for all $x \in \Omega$ and $t > t_0$.*

Proof. For simplicity of notation, in the proof here we omit ϕ from the expressions of the solution.

(i) First, we have

$$\frac{\partial u(x,t)}{\partial t} \leq s - du(x, t),$$

which implies that $\limsup_{t\to\infty} u(x, t) \leq \frac{s}{d}$ uniformly for all $x \in \Omega$. Next, by Assumption (A1) and the second equation in (1.4), we have

$$\frac{\partial w(x,t)}{\partial t} \leq e^{-m\tau}(\eta_1 + \eta_2)u(x, t) - \delta w(x, t).$$

Then $\limsup_{t\to\infty} w(x, t) \leq \frac{e^{-m\tau}(\eta_1+\eta_2)s}{d\delta}$ uniformly for $x \in \Omega$ follows easily from this and $\limsup_{t\to\infty} u(x, t) \leq \frac{s}{d}$ uniformly for $x \in \Omega$. Similarly, adding the second and fourth equations of (1.4) yields

$$\frac{\partial(w(x,t) + z(x,t))}{\partial t} \leq e^{-m\tau}(\eta_1 + \eta_2)u(x, t) - \min\{\delta, b\}(w(x, t) + z(x, t)).$$

It follows that $\limsup_{t\to\infty}(w(x, t) + z(x, t)) \leq \frac{e^{-m\tau}(\eta_1+\eta_2)s}{d\min\{\delta,b\}}$ uniformly for $x \in \Omega$ and hence $\limsup_{t\to\infty} z(x, t) \leq \frac{e^{-m\tau}(\eta_1+\eta_2)s}{d\min\{\delta,b\}}$ uniformly for $x \in \Omega$. Now, $\limsup_{t\to\infty} w(x, t) \leq \frac{e^{-m\tau}(\eta_1+\eta_2)s}{d\delta}$ uniformly for $x \in \Omega$ together with the third equation of (1.4) (Lemma 1 in [45]), and comparison theorem, gives $\limsup_{t\to\infty} v(x, t) \leq \frac{Ne^{-m\tau}(\eta_1+\eta_2)s}{dc}$ uniformly for $x \in \Omega$.

(ii) Noting that $\frac{\partial u(x,t)}{\partial t} \geq s - (d + \eta_1 + \eta_2)u(x, t)$, one can easily get

$$u(x, t) \geq e^{-(d+\eta_1+\eta_2)t}u(x, 0) + \frac{s}{d + \eta_1 + \eta_2} - \frac{e^{-(d+\eta_1+\eta_2)t}s}{d + \eta_1 + \eta_2}$$

for $x \in \Omega$ and $t \geq 0$. Then (ii) follows immediately.

(iii) Note that the operator $D_1\Delta - c\mathrm{Id}$ generates a positive semigroup on $C(\overline{\Omega}, \mathbb{R})$, where Id is the identity operator. Thus if $w(\cdot, t_0) \not\equiv 0$, then from the third equation of (1.4), we see that $v(\cdot, t) \not\equiv 0$ for $t > t_0$. Without loss of generality, we assume that $v(\cdot, t_0) \not\equiv 0$. We first show that $v(\cdot, t) > 0$ for $t > t_0$. By Theorem 2.1, $v(x, t)$ satisfies

$$\begin{cases} \frac{\partial v(x,t)}{\partial t} \geq D_1\Delta v(x,t) - cv(x,t), & t > t_0,\ x \in \Omega, \\ \frac{\partial v(x,t)}{\partial \vec{n}} = 0, & t > t_0,\ x \in \partial\Omega. \end{cases}$$

Let $\bar{v}(x, t)$ be the solution of

$$\begin{cases} \frac{\partial \bar{v}(x,t)}{\partial t} = D_1\Delta \bar{v}(x,t) - c\bar{v}(x,t), & t > t_0,\ x \in \Omega, \\ \frac{\partial \bar{v}(x,t)}{\partial \vec{n}} = 0, & t > t_0,\ x \in \partial\Omega, \\ \bar{v}(x, t_0) = v(x, t_0),\ x \in \overline{\Omega}. \end{cases}$$

Then $\bar{v}(x, t) > 0$ for $x \in \Omega$ and $t > t_0$. In fact, suppose, by contradiction, there exist $x_0 \in \Omega$ and $\hat{t} > t_0$ such that $\bar{v}(x_0, \hat{t}) = 0$. Then, according to the strong maximum principle [46], $\bar{v}(x, t) \equiv 0$ for each $t \geq t_0$, contradicting with $\bar{v}(\cdot, t_0) \not\equiv 0$. Applying the comparison theorem, we know that $v(x, t) \geq \bar{v}(x, t) > 0$ for $t > t_0$ and $x \in \Omega$. We now prove that $w(x, t) > 0$ for $x \in \Omega$ and $t > t_0 + \tau$. Otherwise, there exist $\bar{x} \in \Omega$ and $\bar{t} > t_0 + \tau$ such that $w(\bar{x}, \bar{t}) = 0$. As $w(x, t) \geq 0$, we have $\frac{\partial w(\bar{x},\bar{t})}{\partial t} = 0$. This is impossible since

$$\frac{\partial w(\bar{x}, \bar{t})}{\partial t} = e^{-m\tau} f(u(\bar{x}, \bar{t} - \tau), v(\bar{x}, \bar{t} - \tau)) + e^{-m\tau} g(u(\bar{x}, \bar{t} - \tau), w(\bar{x}, \bar{t} - \tau)) > 0$$

by Assumption (A1) (ii) due to $u(\bar{x}, \bar{t} - \tau) > 0$ and $v(\bar{x}, \bar{t} - \tau) > 0$. This proves statement (iii).

(iv) The proof is similar to that of (iii) on $v(x, t) > 0$ for $x \in \Omega$ and $t > t_0$ and hence we omit it here. This completes the proof. □

Lemma 2.2 tells us that Φ is point dissipative. Then it follows from Theorem 2.1.8 in [47] that $\Phi(t)$ is compact for all $t > \tau$. This, together with Theorem 3.4.8 in [48], gives the following result.

Theorem 2.3. *The semiflow Φ has a global compact attractor $\mathcal{A}$ in C^+. Moreover, $u(x, t, \phi) \leq \frac{s}{d}$ for all $x \in \overline{\Omega}$, $t \geq 0$, and $\phi \in \mathcal{A}$.*

3. Steady states and basic reproduction numbers

System (1.4) with (1.5) always has a unique infection-free steady state $P_0 = (u_0, 0, 0, 0)$, where $u_0 = s/d$. Applying the result of Wang and Zhao (Theorem 3.4 in [49]), we can obtain the expression of the basic reproduction number of infection, R_0, which is given by

$$R_0 = \frac{Ne^{-m\tau}}{c} \cdot \frac{\partial f(\frac{s}{d}, 0)}{\partial v} + \frac{e^{-m\tau}}{\delta} \cdot \frac{\partial g(\frac{s}{d}, 0)}{\partial w}.$$

Denote

$$R_{01} = \frac{Ne^{-m\tau}}{c} \cdot \frac{\partial f(\frac{s}{d}, 0)}{\partial v} \quad \text{and} \quad R_{02} = \frac{e^{-m\tau}}{\delta} \cdot \frac{\partial g(\frac{s}{d}, 0)}{\partial w}.$$

Then R_{01} is the number of secondly infected cells through the cell-free transmission and it is referred to as the basic reproduction number from the cell-free transmission; while R_{02} is the number of secondly infected cells through the cell-to-cell transmission and it is referred to as the basic reproduction number from the cell-to-cell transmission [38].

In the following, we discuss the existence of homogeneous steady states for (1.4) (the stability results in section 4 indicate that they are the only possible steady states). Clearly, a homogeneous steady state $P = (u, w, v, z)$ satisfies

$$s - du - f(u, v) - g(u, w) = 0, \tag{3.1a}$$

$$f(u, v)e^{-m\tau} + g(u, w)e^{-m\tau} - \delta w - pwz = 0, \tag{3.1b}$$

$$N\delta w - cv = 0, \tag{3.1c}$$

$$qwz - bz = 0. \tag{3.1d}$$

It follows from (3.1d) that $z = 0$ (which corresponds to the immunity-free infected steady states) or $w = \frac{b}{q}$ (which, when $z \neq 0$, corresponds to the infected-immune steady states).

We firstly consider the case where $z = 0$. It follows from (3.1c) that $v = \frac{N\delta w}{c}$. Multiplying both sides of (3.1b) by $e^{m\tau}$ and then adding up the resultant and (3.1a) to get $u = \frac{s-\delta we^{m\tau}}{d}$. It is necessary that $w \in (0, \frac{s}{\delta e^{m\tau}})$. Substituting $u = \frac{s-\delta we^{m\tau}}{d}$ and $v = \frac{N\delta w}{c}$ into (3.1a), we see that w is a positive zero of H_1, where

$$H_1(w) = f\left(\frac{s - \delta we^{m\tau}}{d}, \frac{N\delta w}{c}\right) + g\left(\frac{s - \delta we^{m\tau}}{d}, w\right) - \delta we^{m\tau}. \tag{3.2}$$

According to Assumption (A1), we have $H_1(0) = 0$, $H_1(\frac{s}{\delta e^{m\tau}}) - s < 0$, and

$$H_1'(0) = \delta e^{m\tau}\left(\frac{Ne^{-m\tau}}{c} \cdot \frac{\partial f(\frac{s}{d}, 0)}{\partial v} + \frac{e^{-m\tau}}{\delta} \cdot \frac{\partial g(\frac{s}{d}, 0)}{\partial w}\right) - \delta e^{m\tau} = \delta e^{m\tau}(R_0 - 1).$$

If $R_0 > 1$, then $H_1'(0) > 0$. This, together with $H_1(0) = 0$, implies that $H_1(w)$ is positive for all sufficiently small $w > 0$. By the Intermediate Value Theorem, H_1 has at least one zero in $(0, \frac{s}{\delta e^{m\tau}})$ and hence (1.4) has at least one immunity-free infected steady state. In fact, there is only one such steady state by the claim that $H_1'(w_1) < 0$ for any immunity-free infected steady state, which is proved as follows. Note that $\delta e^{m\tau} = \frac{f(u_1,v_1)}{w_1} + \frac{g(u_1,w_1)}{w_1}$ and $w_1 = \frac{cv_1}{N\delta}$. By Assumption (A1),

$$\begin{aligned}
H_1'(w_1) &= -\frac{\delta e^{m\tau}}{d}\frac{\partial f(u_1, v_1)}{\partial u} + \frac{N\delta}{c}\frac{\partial f(u_1, v_1)}{\partial v} - \frac{\delta e^{m\tau}}{d}\frac{\partial g(u_1, w_1)}{\partial u} \\
&\quad + \frac{\partial g(u_1, w_1)}{\partial w} - \frac{N\delta}{cv_1}f(u_1, v_1) - \frac{1}{w_1}g(u_1, w_1) \\
&= -\frac{\delta e^{m\tau}}{d}\frac{\partial f(u_1, v_1)}{\partial u} - \frac{\delta e^{m\tau}}{d}\frac{\partial g(u_1, w_1)}{\partial u} + \frac{N\delta}{cv_1}\left(v_1\frac{\partial f(u_1, v_1)}{\partial v} - f(u_1, v_1)\right) \\
&\quad + \frac{1}{w_1}\left(w_1\frac{\partial g(u_1, w_1)}{\partial w} - g(u_1, w_1)\right) \\
&< 0.
\end{aligned}$$

This proves the claim. Next, we assume that $R_0 < 1$. Then $H_1'(0) = \delta e^{m\tau}(R_0 - 1) < 0$, which combined with $H_1(0) = 0$ implies that $H_1(w) < 0$ for $w > 0$ sufficiently small. Using the above

claim, we can easily see that there is no immunity-free infected steady state when $R_0 < 1$. Moreover, $H_1(w) < 0$ for $w \in (0, \frac{s}{\delta e^{m\tau}}]$. Finally, we assume that $R_0 = 1$. We use contradictive arguments to show that there is no immunity-free infected steady state in this case. Otherwise, assume that $H_1(w)$ has a positive zero say w^*. Then from the above claim $H_1(w) > 0$ for $w < w^*$ and closely enough to w^*. Note that $H_1(w)$ depends continuously on the parameters and $H_1(w) < 0$ for $w \in (0, \frac{s}{\delta e^{m\tau}}]$ when $R_0 < 1$. Fix $w \in (0, w^*)$. Choose a sequence of parameters such that the basic reproduction number $R_0 < 1$ and tends to 1. Then $H_1(w)$ tends to $H_1(w^*) > 0$, a contradiction to the fact that the limit is less than or equal to 0. This proves that there is no immunity-free infected steady state when $R_0 = 1$.

Now we study the case where $w = \frac{b}{q}$. This, together with (3.1c), yields $v = \frac{N\delta b}{cq}$. As before, add up (3.1a) and (3.1b) multiplied by $e^{m\tau}$ to get $z = \frac{s-du-\delta e^{m\tau}w}{pe^{m\tau}w}$, which necessarily requires $u \in (0, \frac{s}{d} - \frac{\delta b}{dq}e^{m\tau})$. Substituting $w = \frac{b}{q}$ and $z = \frac{s-du-\delta e^{m\tau}w}{pe^{m\tau}w}$ into (3.1a), we see that u is a positive zero of H_2, where

$$H_2(u) = f\left(u, \frac{N\delta b}{cq}\right) + g\left(u, \frac{b}{q}\right) - s + du. \tag{3.3}$$

With Assumption (A1), we have $H_2(0) = -s < 0$ and

$$H_2'(u) = \frac{\partial f(u, \frac{N\delta b}{cq})}{\partial u} + \frac{\partial g(u, \frac{b}{q})}{\partial u} + d > 0.$$

Therefore, in order for model (1.4) to have an infected-immune steady state (if exists there is a unique one), it is necessary and sufficient that $H_2(\frac{s}{d} - \frac{\delta b}{dq}e^{m\tau}) = H_1(\frac{b}{q}) > 0$. Recall that when $R_0 \leq 1$, $H_1(w) < 0$ for $w \in (0, \frac{s}{\delta e^{m\tau}}]$; while when $R_0 > 1$, $H_1(w) > 0$ for $w \in (0, w_1)$ and $H_1(w) < 0$ for $w \in (w_1, \frac{s}{\delta e^{m\tau}})$. It follows that $H_1(\frac{b}{q}) > 0$ if and only if $R_0 > 1$ and $\frac{b}{q} < w_1$. Denote,

$$R_1 = \frac{qw_1}{b}.$$

As q is the average number of immune effectors produced from contacting with a productively infected cell and $\frac{1}{b}$ is the average life of an immune effector, it follows that R_1 is the total number of immune effectors produced at the immunity-free infected steady state. Thus R_1 is called the basic reproduction number of immunity.

Summarizing the above discussion, we have obtained the following result on the existence of homogeneous steady states.

Theorem 3.1. *For model* (1.4) *with* (1.5)*, the following statements on the existence of homogeneous steady states are true.*

(i) *If $R_0 \leq 1$, then there is only the infection-free steady state P_0.*

(ii) *If $R_1 \leq 1 < R_0$, then besides P_0, there is also a unique immunity-free infected steady state $P_1 = (u_1, w_1, v_1, 0)$, where w_1 is the only positive zero of H_1 defined by* (3.2)*, $u_1 = \frac{s-\delta w_1 e^{m\tau}}{d}$ and $v_1 = \frac{N\delta w_1}{c}$.*

(iii) *If $R_1 > 1$ (it is necessary that $R_0 > 1$), then in addition to P_0 and P_1, there is also a unique infected-immune steady state $P_2 = (u_2, w_2, v_2, z_2)$, where u_2 is the only positive zero of H_2 defined by* (3.3)*, $w_2 = \frac{b}{q}$, $v_2 = \frac{N\delta b}{cq}$, and $z_2 = \frac{s-du_2-\delta w_2 e^{m\tau}}{pw_2 e^{m\tau}}$.*

4. Stability analysis

In the main part of this paper, we establish the stability of each steady state obtained in Theorem 3.1. Let $P^* = (u^*, w^*, v^*, z^*)$ be an arbitrary homogeneous steady state. The linearization of (1.4) at P^* is

$$\frac{\partial Q}{\partial t} = \mathbb{L}\Delta Q + AQ + BQ_\tau, \tag{4.1}$$

where

$$\begin{aligned}
\mathbb{L} &= \mathrm{diag}(0, 0, D_1, D_2),\\
Q &= (u(x,t), w(x,t), v(x,t), z(x,t)),\\
Q_\tau &= (u_\tau, w_\tau, v_\tau, z_\tau) = \big(u(x,t-\tau), w(x,t-\tau), v(x,t-\tau), z(x,t-\tau)\big),\\
A &= \begin{pmatrix} -d - \frac{\partial f(u^*,v^*)}{\partial u} - \frac{\partial g(u^*,w^*)}{\partial u} & -\frac{\partial g(u^*,w^*)}{\partial w} & -\frac{\partial f(u^*,v^*)}{\partial v} & 0\\ 0 & -\delta - pz^* & 0 & -pw^*\\ 0 & N\delta & -c & 0\\ 0 & qz^* & 0 & qw^* - b \end{pmatrix},\\
B &= \begin{pmatrix} 0 & 0 & 0 & 0\\ \left(\frac{\partial f(u^*,v^*)}{\partial u} + \frac{\partial g(u^*,w^*)}{\partial u}\right)e^{-m\tau} & \frac{\partial g(u^*,w^*)}{\partial w}e^{-m\tau} & \frac{\partial f(u^*,v^*)}{\partial v}e^{-m\tau} & 0\\ 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0 \end{pmatrix}.
\end{aligned}$$

Denote $0 = \mu_0 < \mu_1 < \mu_2 < \cdots < \mu_n < \cdots$ to be all the eigenvalues of the operator $-\Delta$ on Ω with the homogeneous Neumann boundary condition. Then P^* is locally asymptotically stable if, for any $i \in \mathbb{N} = \{0, 1, 2, \dots\}$, every solution of the characteristic equation

$$|\lambda E + \mu_i \mathbb{L} - A - Be^{-\lambda\tau}| = 0 \tag{4.2}$$

has a negative real part and P^* is unstable if there exists $i_0 \in \mathbb{N}$ such that (4.2) has a solution with a positive real part.

4.1. Stability of the infection-free steady state P_0

We first study the local stability of P_0.

Proposition 4.1. *The infection-free steady state P_0 of* (1.4) *is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.*

Proof. By (4.2), the characteristic equation at P_0 is

$$(\lambda + b + \mu_i D_2)(\lambda + d)\left[(\lambda + c + \mu_i D_1)\left(\lambda + \delta - \frac{\partial g(\frac{s}{d}, 0)}{\partial w}e^{-(\lambda+m)\tau}\right) - N\delta\frac{\partial f(\frac{s}{d}, 0)}{\partial v}e^{-(\lambda+m)\tau}\right] = 0.$$

Obviously, the stability of P_0 is determined by

$$(\lambda + c + \mu_i D_1)\left(\lambda + \delta - \frac{\partial g(\frac{s}{d}, 0)}{\partial w}e^{-m\tau}e^{-\lambda\tau}\right) - N\delta\frac{\partial f(\frac{s}{d}, 0)}{\partial v}e^{-m\tau}e^{-\lambda\tau} = 0. \tag{4.3}$$

Firstly, suppose that $R_0 < 1$. We claim that all roots of (4.3) have negative real parts. Otherwise, there exists $i_0 \in \mathbb{N}$ such that (4.3) has a root λ_0 with $\mathrm{Re}(\lambda_0) \geq 0$. Then

$$1 = \frac{1}{\lambda_0+\delta}\frac{\partial g(\frac{s}{d},0)}{\partial w}e^{-m\tau}e^{-\lambda_0\tau} + \frac{N\delta}{(\lambda_0+\delta)(\lambda_0+c+\mu_{i_0}D_1)}\frac{\partial f(\frac{s}{d},0)}{\partial v}e^{-m\tau}e^{-\lambda_0\tau}.$$

It follows that

$$\begin{aligned}
1 &= \left|\frac{1}{\lambda_0+\delta}\frac{\partial g(\frac{s}{d},0)}{\partial w}e^{-m\tau}e^{-\lambda_0\tau} + \frac{N\delta}{(\lambda_0+\delta)(\lambda_0+c+\mu_{i_0}D_1)}\frac{\partial f(\frac{s}{d},0)}{\partial v}e^{-m\tau}e^{-\lambda_0\tau}\right| \\
&\leq \left|\frac{1}{\lambda_0+\delta}\frac{\partial g(\frac{s}{d},0)}{\partial w}e^{-m\tau}e^{-\lambda_0\tau}\right| + \left|\frac{N\delta}{(\lambda_0+\delta)(\lambda_0+c+\mu_{i_0}D_1)}\frac{\partial f(\frac{s}{d},0)}{\partial v}e^{-m\tau}e^{-\lambda_0\tau}\right| \\
&\leq \frac{1}{\delta}\frac{\partial g(\frac{s}{d},0)}{\partial w}e^{-m\tau} + \frac{N}{c+\mu_{i_0}D_1}\frac{\partial f(\frac{s}{d},0)}{\partial v}e^{-m\tau} \\
&\leq \frac{1}{\delta}\frac{\partial g(\frac{s}{d},0)}{\partial w}e^{-m\tau} + \frac{N}{c}\frac{\partial f(\frac{s}{d},0)}{\partial v}e^{-m\tau} \\
&= R_0,
\end{aligned}$$

a contradiction to $R_0 < 1$. This proves the claim and hence P_0 is locally asymptotically stable when $R_0 < 1$.

Secondly, assume $R_0 > 1$. For $i \in \mathbb{N}$, denote

$$F(\lambda, i) = (\lambda + c + \mu_i D_1)\left(\lambda + \delta - \frac{\partial g(\frac{s}{d},0)}{\partial w}e^{-m\tau}e^{-\lambda\tau}\right) - N\delta\frac{\partial f(\frac{s}{d},0)}{\partial v}e^{-m\tau}e^{-\lambda\tau}.$$

Recall that $\mu_0 = 0$. We have

$$F(0,0) = c\delta(1-R_0) < 0$$

and

$$F(\lambda,0) = \lambda^2 + (c+\delta)\lambda + c\delta - \left(c\delta R_0 + \frac{\partial g(\frac{s}{d},0)}{\partial w}e^{m\tau}\right)e^{-\lambda\tau} \to \infty \text{ as } \lambda \to \infty.$$

By the Intermediate Value Theorem, $F(\lambda, 0)$ has a positive zero and hence (4.3) has at least one positive zero for $i = 0$. This means that P_0 is unstable when $R_0 > 1$. □

In fact, P_0 is globally stable if it is locally stable.

Theorem 4.2. *If $R_0 \leq 1$, then the infection-free steady state P_0 of (1.4) is globally attractive. In particular, P_0 is globally asymptotically stable when $R_0 < 1$.*

Proof. It suffices to show that P_0 is globally attractive in $\mathcal{A}$. For this purpose, we consider the Lyapunov functional

$$\begin{aligned}
W(t) &= \int_\Omega \left(e^{m\tau}w(x,t) + \frac{1}{N}e^{m\tau}v(x,t) + \frac{p}{q}e^{m\tau}z(x,t)\right)\mathrm{d}x \\
&\quad + \int_\Omega \left(\int_{t-\tau}^{t} f(u(x,\theta),v(x,\theta))\mathrm{d}\theta + \int_{t-\tau}^{\infty} g(u(x,\theta),w(x,\theta))\mathrm{d}\theta\right)\mathrm{d}x.
\end{aligned}$$

Calculating the time derivative of $W(t)$ along solutions of model (1.4), we have

$$\frac{\mathrm{d}W(t)}{\mathrm{d}t} = \int_\Omega \left(f(u(x,t),v(x,t)) - \frac{c}{N}e^{m\tau}v(x,t) - \frac{pb}{q}e^{m\tau}z(x,t) \right) \mathrm{d}x + \frac{1}{N}e^{m\tau}\int_\Omega D_1 \Delta v(x,t)\mathrm{d}x.$$

It follows from the homogeneous Neumann boundary condition (1.5) and the Divergence Theorem that

$$\int_\Omega \Delta v(x,t)\mathrm{d}x = \int_{\partial\Omega} \frac{\partial v(x,t)}{\partial \vec{n}}\mathrm{d}x = 0.$$

Moreover, by Theorem 2.3, $u(x,t) \le \frac{s}{d}$ for $x \in \Omega$ and $t \ge 0$. With the help of (1.7), for $v(x,t) > 0$, we have

$$\begin{aligned} f(u(x,t),v(x,t)) - \frac{c}{N}e^{m\tau}v(x,t) &= \frac{c}{N}e^{m\tau}v(x,t)\left(\frac{N}{c}e^{-m\tau}\frac{f(u(x,t),v(x,t))}{v(x,t)} - 1 \right) \\ &\le \frac{c}{N}e^{m\tau}v(x,t)\left(\frac{N}{c}e^{-m\tau}\frac{f(\frac{s}{d},v(x,t))}{v(x,t)} - 1 \right) \\ &\le \frac{c}{N}e^{m\tau}v(x,t)\left(\frac{N}{c}e^{-m\tau}\frac{\partial f(\frac{s}{d},0)}{\partial v} - 1 \right) \\ &\le \frac{c}{N}e^{m\tau}v(x,t)\left(R_0 - 1\right). \end{aligned}$$

The above inequality holds automatically for $v(x,t) = 0$ and also observe that the inequality is strict for $u(x,t) < \frac{s}{d}$ and $v(x,t) > 0$. Therefore,

$$\frac{\mathrm{d}W(t)}{\mathrm{d}t} \le \int_\Omega \left(\frac{c}{N}e^{m\tau}v(x,t)\left(R_0 - 1\right) - \frac{pb}{q}e^{m\tau}z(x,t) \right)\mathrm{d}x \le 0.$$

Moreover, $\frac{\mathrm{d}W(t)}{\mathrm{d}t} = 0$ if and only if $v(x,t) = 0$ and $z(x,t) = 0$. In fact, if $v(x_0,t_0) \neq 0$, then there exists a neighborhood $N_{(x_0,t_0)}$ of (x_0,t_0) such that $v(x,t) \neq 0$ for $(x,t) \in N_{(x_0,t_0)}$. Then by the observation, $u(x,t) = \frac{s}{d}$ for $(x,t) \in N_{(x_0,t_0)}$. This, together with the first equation of (1.4) and Assumption (A1), implies that $v(x,t) = 0$ for $(x,t) \in N_{(x_0,t_0)}$, a contradiction. Then it is easy to see that the largest invariant subset of $\frac{\mathrm{d}W(t)}{\mathrm{d}t} = 0$ is $\{P_0\}$. By LaSalle's Invariance Principle (see Theorem 5.3.1 in [50] or Theorem 3.4.7 in [51]), the infection-free steady state P_0 is globally attractive. In particular, this together with Proposition 4.1, tells us that P_0 is globally asymptotically stable when $R_0 < 1$. □

4.2. Stability of the immunity-free infected steady state P_1

Next we consider the stability of the immunity-free infected steady state P_1. For convenience of notations, denote

$$\begin{aligned} &f_1 = f(u_1,v_1), \quad && g_1 = g(u_1,w_1), \quad && f_{1u} = \tfrac{\partial f(u_1,v_1)}{\partial u}, \\ &f_{1v} = \tfrac{\partial f(u_1,v_1)}{\partial v}, && g_{1u} = \tfrac{\partial g(u_1,w_1)}{\partial u}, && g_{1w} = \tfrac{\partial g(u_1,w_1)}{\partial w}. \end{aligned}$$

Theorem 4.3. *Suppose $R_0 > 1$. Then the immunity-free infected steady state P_1 of* (1.4) *is locally asymptotically stable if $R_1 < 1$ and unstable if $R_1 > 1$.*

Proof. From (4.2), we know that the characteristic equation at P_1 is given by

$$(\lambda - qw_1 + b + \mu_i D_2)\rho_i(\lambda) = 0,\ i \in \mathbb{N},$$

where

$$\rho_i(\lambda) = (\lambda + d + f_{1u} + g_{1u})(\lambda + \delta)(\lambda + c + \mu_i D_1) - [(\lambda + d)(\lambda + c + \mu_i D_1)g_{1w} + (\lambda + d)N\delta f_{1v}]e^{-(\lambda+m)\tau}.$$

Clearly, the eigenvalue $\lambda = b(R_1 - 1) - \mu_i D_2 < 0$ for $i \in \mathbb{N}$ when $R_1 < 1$ but when $R_1 > 1$, with $i = 0$, we have a positive eigenvalue $\lambda = b(R_1 - 1)$. Thus P_1 is unstable if $R_1 > 1$. Now, we assume that $R_1 < 1$. Then the stability of P_1 is determined by the roots of $\rho_i(\lambda) = 0$, which is equivalent to

$$1 = \frac{\lambda + d}{\lambda + d + f_{1u} + g_{1u}} \left(\frac{g_{1w}}{\lambda + \delta} e^{-(\lambda+m)\tau} + \frac{N\delta f_{1v}}{(\lambda + \delta)(\lambda + c + \mu_i D_1)} e^{-(\lambda+m)\tau} \right). \tag{4.4}$$

We claim that all solutions of (4.4) have negative real parts. Otherwise, suppose that there exists $i_1 \in \mathbb{N}$ such that (4.4) has a solution λ_1 with $\mathrm{Re}(\lambda_1) \geq 0$. Then

$$\begin{aligned} 1 &= \left| \frac{\lambda_1 + d}{\lambda_1 + d + f_{1u} + g_{1u}} \left(\frac{g_{1w}}{\lambda_1 + \delta} e^{-m\tau} e^{-\lambda_1\tau} + \frac{N\delta f_{1v}}{(\lambda_1 + \delta)(\lambda_1 + c + \mu_{i_1} D_1)} e^{-m\tau} e^{-\lambda_1\tau} \right) \right| \\ &< \left| \frac{g_{1w}}{\lambda_1 + \delta} e^{-m\tau} e^{-\lambda_1\tau} \right| + \left| \frac{N\delta f_{1v}}{(\lambda_1 + \delta)(\lambda_1 + c + \mu_{i_1} D_1)} e^{-m\tau} e^{-\lambda_1\tau} \right| \\ &< \frac{g_{1w}}{\delta} e^{-m\tau} + \frac{N f_{1v}}{c} e^{-m\tau}. \end{aligned} \tag{4.5}$$

However, from the steady state Eqs (3.1b) and (3.1c), we have

$$\frac{g(u_1, w_1)}{\delta w_1} e^{-m\tau} + \frac{N f(u_1, v_1)}{c v_1} e^{-m\tau} = 1.$$

This and Assumption (A1) (v) together give us

$$\frac{g_{1w}}{\delta} e^{-m\tau} + \frac{N f_{1v}}{c} e^{-m\tau} \leq \frac{g(u_1, w_1)}{\delta w_1} e^{-m\tau} + \frac{N f(u_1, v_1)}{c v_1} e^{-m\tau} = 1,$$

which is a contradiction with (4.5). This proves the claim and hence P_1 is locally asymptotically stable when $R_1 < 1 < R_0$. □

Before studying the global stability of P_1, we establish the persistence of infection.

From the linearized system at P_0 (see (4.1)), we have the following cooperative system for (w, v),

$$\begin{cases} \frac{\partial w(x,t)}{\partial t} &= e^{-m\tau} \frac{\partial f(u_0,0)}{\partial v} v(x, t - \tau) + e^{-m\tau} \frac{\partial g(u_0,0)}{\partial w} w(x, t - \tau) - \delta w(x, t), \\ \frac{\partial v(x,t)}{\partial t} &= D_1 \Delta v(x, t) + N\delta w(x, t) - c v(x, t). \end{cases} \tag{4.6}$$

With similar arguments as those for Lemma 3 and Lemma 4 in Lou and Zhao [45], we can obtain the following results.

Lemma 4.4. *There exists a principal eigenvalue $\bar{\lambda}(u_0, \tau) \triangleq \bar{\lambda}(P_0, \tau)$ of (4.6) associated with a strongly positive eigenvector. Moreover, $\bar{\lambda}(u_0, \tau)$ has the same sign as $\lambda(u_0) \triangleq \bar{\lambda}(u_0, 0)$.*

Lemma 4.5. *$R_0 - 1$ and $\lambda(u_0)$ have the same sign.*

Theorem 4.6. *Suppose $R_1 \le 1 < R_0$. Then the infection is persistent, that is, there exists $\varepsilon > 0$ such that*

$$\liminf_{t\to\infty} u(x,t,\phi) \ge \varepsilon, \quad \liminf_{t\to\infty} w(x,t,\phi) \ge \varepsilon, \quad \liminf_{t\to\infty} v(x,t,\phi) \ge \varepsilon$$

uniformly for all $x \in \overline{\Omega}$, where $\phi \in \mathcal{W}_1 := \{\phi \in C^+ : w(\cdot,0) \not\equiv 0$ and $v(\cdot,0) \not\equiv 0\}$.

Proof. Define

$$\partial\mathcal{W}_1 := C^+ \setminus \mathcal{W}_1 = \{\phi \in C^+ : w(\cdot,0) \equiv 0 \text{ or } v(\cdot,0) \equiv 0\}.$$

By Lemma 2.2 and the second equation of (1.4), we know that $\Phi(t)\mathcal{W}_1 \subseteq \mathcal{W}_1$ for all $t \ge 0$. Denote

$$\mathcal{M}_\partial := \{\phi \in \partial\mathcal{W}_1 : \Phi(t)\phi \in \partial\mathcal{W}_1 \text{ for } t \ge 0\}.$$

Claim 1. $\omega(\phi) = \{(u_0,0,0,0)\}$ for $\phi \in \mathcal{M}_\partial$, where $\omega(\phi)$ is the omega limit set of the orbit $O^+(\phi) := \{\Phi(t)\phi : t \ge 0\}$.

Since $\phi \in \mathcal{M}_\partial$, for all $t \ge 0$, either $w(x,t,\phi) \equiv 0$ or $v(x,t,\phi) \equiv 0$. If $w(x,t,\phi) \equiv 0$ for all $t \ge 0$, then $\lim_{t\to\infty} v(x,t,\phi) = 0$ uniformly for $x \in \overline{\Omega}$ from the third equation of (1.4). Now, suppose that $w(x,t_1,\phi) \not\equiv 0$ for some $t_1 \ge 0$. Then by Lemma 2.2, $w(x,t,\phi) > 0$ for all $t \ge t_1 + \tau$ and $x \in \Omega$. Thus $v(x,t,\phi) \equiv 0$ for all $t \ge t_1 + \tau$. This, combined with the third equation of (1.4), implies that $w(x,t,\phi) \equiv 0$ for $x \in \overline{\Omega}$ and $t \ge t_1 + \tau$. Then, in either case, $\lim_{t\to\infty} v(x,t,\phi) = \lim_{t\to\infty} w(x,t,\phi) = 0$ uniformly for $x \in \overline{\Omega}$. Thus u is asymptotic to

$$\frac{\partial u(x,t)}{\partial t} = s - du(x,t).$$

By Corollary 4.3 in [52], we get $\lim_{t\to\infty} u(x,t,\phi) = u_0$ uniformly for $x \in \overline{\Omega}$. The above discussion tells us that $w(x,t,\phi) \equiv 0$ for all t large enough. Then we can easily see from the fourth equation of (1.4) that $\lim_{t\to\infty} z(x,t,\phi) = 0$ uniformly for $x \in \overline{\Omega}$. This proves $\omega(\phi) = \{(u_0,0,0,0)\}$.

Since $R_1 \le 1 < R_0$, by Lemma 4.4 and Lemma 4.5, there exists a sufficiently small $\varepsilon_0 > 0$ such that the following linear system

$$\begin{cases} \frac{\partial w(x,t)}{\partial t} &= e^{-m\tau}\left(\frac{\partial f(u_0,0)}{\partial v} - \varepsilon_0\right) v(x,t-\tau) + e^{-m\tau}\left(\frac{\partial g(u_0,0)}{\partial w} - \varepsilon_0\right) w(x,t-\tau) - (\delta + p\varepsilon_0) w(x,t), \\ \frac{\partial v(x,t)}{\partial t} &= D_1 \Delta v(x,t) + N\delta w(x,t) - cv(x,t) \end{cases}$$

has a positive principal eigenvalue $\bar{\lambda}(u_0 - \varepsilon_0)$ with positive eigenfunction $(w_{\varepsilon_0}, v_{\varepsilon_0})$. By the continuity in Assumption (A1), there exists $\delta_0 \in (0, \varepsilon_0]$ such that

$$\frac{\partial f(u,v)}{\partial v} \ge \frac{\partial f(u_0,0)}{\partial v} - \varepsilon_0 \quad \text{and} \quad \frac{\partial g(u,w)}{\partial w} \ge \frac{\partial g(u_0,0)}{\partial w} - \varepsilon_0$$

for all $u_0 - \delta_0 \le u \le u_0 + \delta_0$, $0 \le v \le \delta_0$, and $0 \le w \le \delta_0$.

Claim 2. $\{(u_0,0,0,0)\}$ is a uniform weak repeller for $\mathcal{W}_1$ in the sense that

$$\limsup_{t\to\infty} \|\Phi(t)\phi - (u_0,0,0,0)\| \ge \delta_0 \text{ for } \phi \in \mathcal{W}_1.$$

Suppose, by contradiction, there exists $\phi_1^* \in \mathcal{W}_1$ such that $\limsup_{t\to\infty} \|\Phi(t)\phi_1^* - (u_0,0,0,0)\| < \delta_0$. Then there exists $t_2 > 0$ such that $u(x,t,\phi_1^*) > u_0 - \delta_0 \ge u_0 - \varepsilon_0$, $w(x,t,\phi_1^*) \le \delta_0$, and $v(x,t,\phi_1^*) \le \delta_0$ for $t \ge t_2$

and $x \in \overline{\Omega}$. It follows from Assumption (A1) and the choice of δ_0 that w and v satisfy

$$\begin{cases} \frac{\partial w(x,t)}{\partial t} \geq e^{-m\tau}\left(\frac{\partial f(u_0,0)}{\partial v} - \varepsilon_0\right) v(x,t-\tau) + e^{-m\tau}\left(\frac{\partial g(u_0,0)}{\partial w} - \varepsilon_0\right) w(x,t-\tau) - (\delta + p\varepsilon_0) w(x,t), \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad t \geq t_2,\ x \in \Omega, \\ \frac{\partial v(x,t)}{\partial t} = D_1 \Delta v(x,t) + N\delta w(x,t) - cv(x,t), \quad t \geq t_2,\ x \in \Omega, \\ \frac{\partial v(x,t)}{\partial \vec{n}} = 0, \quad t \geq t_2, \quad x \in \partial\Omega. \end{cases} \tag{4.7}$$

Due to $w(x,t,\phi_1^*) > 0$ and $v(x,t,\phi_1^*) > 0$ for $t > 0$ and $x \in \Omega$, there exists $\kappa_1 > 0$ such that $(w(x,t_2+\theta,\phi_1^*), v(x,t_2+\theta,\phi_1^*)) \geq \kappa_1 e^{\bar{\lambda}(u_0-\varepsilon_0)(t_2+\theta)}(w_{\varepsilon_0}(x), v_{\varepsilon_0}(x))$ for all $x \in \Omega$ and $\theta \in [-\tau, 0]$. Then it follows from the comparison principle that $w(x,t,\phi_1^*) \geq \kappa_1 e^{\bar{\lambda}(u_0-\varepsilon_0)t} w_{\varepsilon_0}(x)$ and $v(x,t,\phi_1^*) \geq \kappa_1 e^{\bar{\lambda}(u_0-\varepsilon_0)t} v_{\varepsilon_0}(x)$ for all $x \in \Omega$ and $t \geq t_2$, a contradiction to the fact that both $w(x,t,\phi_1^*)$ and $v(x,t,\phi_1^*)$ are bounded. This proves Claim 2.

Define a continuous function $\mathcal{P}_1 : C^+ \to [0,\infty)$ by

$$\mathcal{P}_1(\phi) := \min\left\{\min_{x\in\overline{\Omega}} \phi_2(x,0),\ \min_{x\in\overline{\Omega}} \phi_3(x,0)\right\} \text{ for all } \phi \in C^+.$$

Clearly, $\mathcal{P}_1^{-1}(0,\infty) \subset \mathcal{W}_1$, and $\mathcal{P}_1$ has the property that if $\mathcal{P}_1(\phi) = 0$ and $\phi \in \mathcal{W}_1$ or $\mathcal{P}_1(\phi) > 0$, then $\mathcal{P}_1(\Phi(t)\phi) > 0$ for all $t > 0$. Hence, $\mathcal{P}_1$ is a generalized distance function for the semiflow $\Phi(t)$ [53]. According to the above discussions, we obtain that any forward orbit of $\Phi(t)$ in $\mathcal{M}_\partial$ converges to $(u_0,0,0,0)$, which is isolated in C^+ and $\mathcal{W}^s(u_0,0,0,0) \cap \mathcal{W}_1 = \emptyset$, where $\mathcal{W}^s(u_0,0,0,0)$ is the stable manifold of $(u_0,0,0,0)$. Moreover, there is no cycle in $\partial\mathcal{W}_1$ from $(u_0,0,0,0)$ to $(u_0,0,0,0)$. Applying Theorem 3 in [53], we know that there exists an $\bar{\varepsilon} > 0$ such that $\min\{\mathcal{P}_1(\phi)\} > \bar{\varepsilon}$ for any $\phi \in \mathcal{W}_1$. It follows that

$$\liminf_{t\to\infty} w(x,t) \geq \bar{\varepsilon} \text{ and } \liminf_{t\to\infty} v(x,t) \geq \bar{\varepsilon} \text{ uniformly for all } x \in \overline{\Omega}.$$

This combined with Lemma 2.2 finishes the proof with $\varepsilon = \min\{\bar{\varepsilon}, \frac{s}{d+\eta_1+\eta_2}\}$. □

In order to study the global stability of P_1, define $G : (0,\infty) \ni x \to x - 1 - \ln x$. Obviously, $G(x) > 0$ for $x \in (0,\infty)$ and G attains its global minimum only at $x = 1$. We also need the following assumption.

(A2) The nonlinear incidence functions $f(u,v)$ and $g(u,w)$ satisfy the following conditions.

(i) For any $u > 0$,

$$\begin{cases} \frac{v}{v_1} \leq \frac{u_1 f(u,v)}{u f(u_1,v_1)} < 1 & \text{if } 0 < v < v_1, \\ 1 \leq \frac{u_1 f(u,v)}{u f(u_1,v_1)} < \frac{v}{v_1} & \text{if } v_1 < v. \end{cases}$$

(ii) For any $u > 0$,

$$\begin{cases} \frac{w}{w_1} \leq \frac{u_1 g(u,w)}{u g(u_1,w_1)} < 1 & \text{if } 0 < w < w_1, \\ 1 \leq \frac{u_1 g(u,w)}{u g(u_1,w_1)} < \frac{w}{w_1} & \text{if } w_1 < w. \end{cases}$$

Theorem 4.7. *Suppose that $R_1 \leq 1 < R_0$ and Assumption (A2) are satisfied. Then the immunity-free infected steady state P_1 is globally attractive in*

$$C_1^+ = \{\phi \in C^+ | \text{there exists } t_3 \in \mathbb{R}^+ \text{ such that } w(\cdot,t_3,\phi) \not\equiv 0 \text{ or } v(\cdot,t_3,\phi) \not\equiv 0\}.$$

In particular, it is globally asymptotically stable in C_1^+ if further $R_1 < 1$.

Proof. According to Lemma 2.2 and Theorem 4.6, we know that there exists $\varepsilon > 0$ such that $\liminf_{t\to\infty} u(x,t,\phi) \geq \varepsilon$, $\liminf_{t\to\infty} w(x,t,\phi) \geq \varepsilon$, and $\liminf_{t\to\infty} v(x,t,\phi) \geq \varepsilon$ for $\phi \in C_1^+$. Without loss of generality, we define a Lyapunov functional

$$L(t) = \int_\Omega L(x,t)\mathrm{d}x,$$

where

$$\begin{aligned} L(x,t) &= u_1 G\left(\frac{u(x,t)}{u_1}\right) + e^{m\tau} w_1 G\left(\frac{w(x,t)}{w_1}\right) + \frac{f(u_1,v_1)}{cv_1} v_1 G\left(\frac{v(x,t)}{v_1}\right) + \frac{p}{q} e^{m\tau} z(x,t) \\ &\quad + f(u_1,v_1)\int_{t-\tau}^{t} G\left(\frac{f(u(x,\theta),v(x,\theta))}{f(u_1,v_1)}\right)\mathrm{d}\theta + g(u_1,w_1)\int_{t-\tau}^{t} G\left(\frac{g(u(x,\theta),w(x,\theta))}{g(u_1,w_1)}\right)\mathrm{d}\theta. \end{aligned}$$

Calculating the time derivative of $L(x,t)$ along solutions of (1.4) yields

$$\begin{aligned} \frac{\partial L(x,t)}{\partial t} &= \left(1 - \frac{u_1}{u(x,t)}\right)[s - du(x,t) - f(u,v) - g(u,w)] + \frac{p}{q} e^{m\tau}[qw(x,t)z(x,t) - bz(x,t)] \\ &\quad + e^{m\tau}\left(1 - \frac{w_1}{w(x,t)}\right)[e^{-m\tau} f(u_\tau,v_\tau) + e^{-m\tau} g(u_\tau,w_\tau) - \delta w(x,t) - pw(x,t)z(x,t)] \\ &\quad + \frac{f(u_1,v_1)}{cv_1}\left(1 - \frac{v_1}{v(x,t)}\right)[D_1\Delta v(x,t) + N\delta w(x,t) - cv(x,t)] + \frac{p}{q} e^{m\tau} D_2 \Delta z(x,t) \\ &\quad + f(u,v) - f(u_\tau,v_\tau) + f(u_1,v_1)\ln\frac{f(u_\tau,v_\tau)}{f(u,v)} \\ &\quad + g(u,w) - g(u_\tau,w_\tau) + g(u_1,w_1)\ln\frac{g(u_\tau,w_\tau)}{g(u,w)}. \end{aligned}$$

With

$$s = du_1 + f(u_1,v_1) + g(u_1,w_1),\ \delta = \frac{e^{-m\tau} f(u_1,v_1) + e^{-m\tau} g(u_1,w_1)}{w_1},\ c = \frac{N\delta w_1}{v_1},$$

we have

$$\begin{aligned} &\frac{\partial L(x,t)}{\partial t} \\ &= du_1\left(2 - \frac{u_1}{u(x,t)} - \frac{u(x,t)}{u_1}\right) + \frac{p}{q} e^{m\tau}(R_1 - 1)z(x,t) \\ &\quad + \frac{f(u_1,v_1)}{cv_1}\left(1 - \frac{v_1}{v(x,t)}\right) D_1\Delta v(x,t) + \frac{p}{q} e^{m\tau} D_2\Delta z(x,t) - f(u_1,v_1)\frac{w(x,t)v_1}{v(x,t)w_1} \\ &\quad + f(u_1,v_1)\left[3 - \frac{u_1}{u(x,t)} - \frac{f(u_\tau,v_\tau)w_1}{f(u_1,v_1)w(x,t)} + \frac{f(u,v)u_1}{f(u_1,v_1)u(x,t)} - \frac{v(x,t)}{v_1} + \ln\frac{f(u_\tau,v_\tau)}{f(u,v)}\right] \\ &\quad + g(u_1,w_1)\left[2 - \frac{u_1}{u(x,t)} - \frac{g(u_\tau,w_\tau)w_1}{g(u_1,w_1)w(x,t)} + \frac{g(u,w)u_1}{g(u_1,w_1)u(x,t)} - \frac{w(x,t)}{w_1} + \ln\frac{g(u_\tau,w_\tau)}{g(u,w)}\right] \\ &= du_1\left(2 - \frac{u_1}{u(x,t)} - \frac{u(x,t)}{u_1}\right) + \frac{p}{q} e^{m\tau}(R_1 - 1)z(x,t) \end{aligned}$$

$$+\frac{f(u_1,v_1)}{cv_1}\left(1-\frac{v_1}{v(x,t)}\right)D_1\Delta v(x,t)+\frac{p}{q}e^{m\tau}D_2\Delta z(x,t)-f(u_1,v_1)G\left(\frac{w(x,t)v_1}{v(x,t)w_1}\right)$$
$$+f(u_1,v_1)\left[G\left(\frac{f(u,v)u_1}{f(u_1,v_1)u(x,t)}\right)-G\left(\frac{v(x,t)}{v_1}\right)-G\left(\frac{u_1}{u(x,t)}\right)-G\left(\frac{f(u_\tau,v_\tau)w_1}{f(u_1,v_1)w(x,t)}\right)\right]$$
$$+g(u_1,w_1)\left[G\left(\frac{g(u,w)u_1}{g(u_1,w_1)u(x,t)}\right)-G\left(\frac{w(x,t)}{w_1}\right)-G\left(\frac{u_1}{u(x,t)}\right)-G\left(\frac{g(u_\tau,w_\tau)w_1}{g(u_1,w_1)w(x,t)}\right)\right].$$

Clearly,

$$\int_\Omega du_1\left(2-\frac{u(x,t)}{u_1}-\frac{u_1}{u(x,t)}\right)\mathrm{d}x\le 0$$

and

$$\int_\Omega\left(\frac{pb}{q}e^{m\tau}(R_1-1)z(x,t)\right)\mathrm{d}x\le 0 \text{ since } R_1\le 1.$$

Using the Divergence Theorem and the homogeneous Neumann boundary conditions of (1.5), we have

$$\int_\Omega\Delta v(x,t)\mathrm{d}x=\int_{\partial\Omega}\frac{\partial v(x,t)}{\partial\vec{n}}\mathrm{d}x=0,\quad \int_\Omega\Delta z(x,t)\mathrm{d}x=\int_{\partial\Omega}\frac{\partial z(x,t)}{\partial\vec{n}}\mathrm{d}x=0,$$

and

$$\begin{aligned}0&=\int_{\partial\Omega}\frac{1}{v(x,t)}\nabla v(x,t)\cdot\vec{n}\,\mathrm{d}x\\&=\int_\Omega\nabla\left(\frac{1}{v(x,t)}\nabla v(x,t)\right)\mathrm{d}x\\&=\int_\Omega\left(\frac{1}{v(x,t)}\Delta v(x,t)-\frac{1}{v^2(x,t)}\|\nabla v(x,t)\|^2\right)\mathrm{d}x.\end{aligned}$$

The latter gives

$$\int_\Omega\frac{1}{v(x,t)}\Delta v(x,t)\mathrm{d}x=\int_\Omega\frac{1}{v^2(x,t)}\|\nabla v(x,t)\|^2\mathrm{d}x\ge 0$$

and hence

$$\int_\Omega\frac{f(u_1,v_1)}{cv_1}\left(1-\frac{v_1}{v(x,t)}\right)D_1\Delta v(x,t)\mathrm{d}x\le 0.$$

To summarize, we have obtained

$$\begin{aligned}\frac{\mathrm{d}L(t)}{\mathrm{d}t}\le\ & f(u_1,v_1)\int_\Omega\left[G\left(\frac{f(u,v)u_1}{f(u_1,v_1)u(x,t)}\right)-G\left(\frac{v(x,t)}{v_1}\right)\right]\mathrm{d}x\\&+g(u_1,w_1)\int_\Omega\left[G\left(\frac{g(u,w)u_1}{g(u_1,w_1)u(x,t)}\right)-G\left(\frac{w(x,t)}{w_1}\right)\right]\mathrm{d}x\\&-g(u_1,w_1)\int_\Omega\left[G\left(\frac{u_1}{u(x,t)}\right)+G\left(\frac{g(u_\tau,w_\tau)w_1}{g(u_1,w_1)w(x,t)}\right)\right]\mathrm{d}x\\&-f(u_1,v_1)\int_\Omega\left[G\left(\frac{u_1}{u(x,t)}\right)+G\left(\frac{f(u_\tau,v_\tau)w_1}{f(u_1,v_1)w(x,t)}\right)+G\left(\frac{w(x,t)v_1}{v(x,t)w_1}\right)\right]\mathrm{d}x.\end{aligned}$$

Note that the monotonicity of $G(x)$ on each side of $x = 1$ and Assumption (A2) give us

$$G\left(\frac{f(u,v)u_1}{f(u_1,v_1)u(x,t)}\right) \le G\left(\frac{v(x,t)}{v_1}\right) \quad \text{and} \quad G\left(\frac{g(u,w)u_1}{g(u_1,w_1)u(x,t)}\right) \le G\left(\frac{w(x,t)}{w_1}\right).$$

Thus

$$\begin{aligned}\frac{\mathrm{d}L(t)}{\mathrm{d}t} &\le -g(u_1,w_1)\int_\Omega \left[G\left(\frac{u_1}{u(x,t)}\right) + G\left(\frac{g(u_\tau,w_\tau)w_1}{g(u_1,w_1)w(x,t)}\right)\right]\mathrm{d}x \\ &\quad -f(u_1,v_1)\int_\Omega \left[G\left(\frac{u_1}{u(x,t)}\right) + G\left(\frac{f(u_\tau,v_\tau)w_1}{f(u_1,v_1)w(x,t)}\right) + G\left(\frac{w(x,t)v_1}{v(x,t)w_1}\right)\right]\mathrm{d}x \\ &\le 0.\end{aligned}$$

Moreover, $\frac{\mathrm{d}L(t)}{\mathrm{d}t} = 0$ if and only if $u(x,t) = u_1$, $w(x,t) = w_1$, $v(x,t) = v_1$, and $z(x,t) = 0$. Then the largest invariant subset of $\frac{\mathrm{d}L(t)}{\mathrm{d}t} = 0$ is $\{P_1\}$. By LaSalle's Invariance Principle (see Theorem 5.3.1 in [50] or Theorem 3.4.7 in [51]), the immunity-free infected steady state P_1 is globally attractive in C_1^+ when $R_1 \le 1 < R_0$. This, together with Theorem 4.3, implies that P_1 is globally asymptotically stable in C_1^+ if further $R_1 < 1$. □

4.3. The stability of the infected-immune steady state P_2

For convenience of notations, denote

$$\begin{aligned} &f_2 = f(u_2,v_2), \quad && g_2 = g(u_2,w_2), \quad && f_{2u} = \tfrac{\partial f(u_2,v_2)}{\partial u}, \\ &f_{2v} = \tfrac{\partial f(u_2,v_2)}{\partial v}, && g_{2u} = \tfrac{\partial g(u_2,w_2)}{\partial u}, && g_{2w} = \tfrac{\partial g(u_2,w_2)}{\partial w}. \end{aligned}$$

Theorem 4.8. *If $R_1 > 1$, then the infected-immune steady state P_2 is locally asymptotically stable.*

Proof. According to (4.2), the characteristic equation at P_2 is

$$\begin{aligned} 0 =&(\lambda + d + f_{2u} + g_{2u})(\lambda + c + \mu_i D_1)(\lambda + b - qw_2 + \mu_i D_2)(\lambda + \delta + pz_2) \\ &+ qw_2 pz_2(\lambda + c + \mu_i D_1)(\lambda + d + f_{2u} + g_{2u}) \\ &- (\lambda + d)(\lambda + c + \mu_i D_1)(\lambda + b - qw_2 + \mu_i D_2)g_{2w}e^{-(\lambda+m)\tau} \\ &- (\lambda + d)(\lambda + b - qw_2 + \mu_i D_2)N\delta f_{2v}e^{-(\lambda+m)\tau}. \end{aligned} \tag{4.8}$$

We claim that all roots of (4.8) have negative real parts. Otherwise, suppose for some $i_2 \in \mathbb{N}$, it has a root λ_2 with $\mathrm{Re}(\lambda_2) \ge 0$. Since $w_2 = \frac{b}{q}$, we have

$$1 = \frac{(\lambda_2 + \mu_{i_2} D_2)(\lambda_2 + d)}{(\lambda_2 + d + f_{2u} + g_{2u})[(\lambda_2 + \mu_{i_2} D_2)(\lambda_2 + \delta + pz_2) + pbz_2]}\left(g_{2w}e^{-(\lambda_2+m)\tau} + \frac{N\delta f_{2v}e^{-(\lambda_2+m)\tau}}{\lambda_2 + c + \mu_{i_2} D_1}\right),$$

which implies

$$1 < \left|\frac{\lambda_2 + \mu_{i_2} D_2}{(\lambda_2 + \mu_{i_2} D_2)(\lambda_2 + \delta + pz_2) + pbz_2}\right| \times \left(g_{2w}e^{-m\tau} + \frac{N\delta f_{2v}e^{-m\tau}}{c}\right).$$

With similar arguments as those in the proof of Theorem 4.3, we can obtain

$$g_{2w}e^{-m\tau} + \frac{N\delta f_{2v}e^{-m\tau}}{c} \le \delta + pz_2.$$

Thus we have arrived at

$$1 < \left| \frac{\lambda_2 + \mu_{i_2} D_2}{(\lambda_2 + \mu_{i_2} D_2)(\lambda_2 + \delta + pz_2) + pbz_2} \right| \times (\delta + pz_2),$$

which is impossible as one can check that $|(\lambda_2 + \mu_{i_2} D_2)(\lambda_2 + \delta + pz_2) + pbz_2| > |(\lambda_2 + \mu_{i_2} D_2)(\delta + pz_2)|$.

This completes the proof. □

To establish the global stability of P_2, we need the persistence of immunity.

From the linearized system at P_1 (see (4.1)), we have the following cooperative system for (w, v, z),

$$\begin{cases} \frac{\partial w(x,t)}{\partial t} &= e^{-m\tau} \frac{\partial f(u_1, v_1)}{\partial v} v(x, t-\tau) + e^{-m\tau} \frac{\partial g(u_1, w_1)}{\partial w} w(x, t-\tau) - (\delta + pz_1) w(x,t) - pw_1 z(x,t), \\ \frac{\partial v(x,t)}{\partial t} &= D_1 \Delta v(x,t) + N\delta w(x,t) - cv(x,t), \\ \frac{\partial z(x,t)}{\partial t} &= D_2 \Delta z(x,t) + qz_1 w(x,t) + (qw_1 - b) z(x,t). \end{cases} \tag{4.9}$$

With similar arguments as those for Lemma 3 and Lemma 4 in Lou and Zhao [45], we can obtain the following results.

Lemma 4.9. *There exists a principal eigenvalue $\hat{\lambda}(P_1, \tau)$ of (4.9) associated with a strongly positive eigenvector. Moreover, $\hat{\lambda}(P_1, \tau)$ has the same sign as $\hat{\lambda}(P_1, 0)$.*

Lemma 4.10. *$R_1 - 1$ and $\hat{\lambda}(P_1, 0)$ have the same sign.*

Theorem 4.11. *Suppose that $R_1 > 1$ (it is necessary that $R_0 > 1$) and (A2) holds. Then the immunity is persistent, that is, there exists $\epsilon > 0$ such that*

$$\liminf_{t\to\infty} u(x,t,\phi) \geq \epsilon, \quad \liminf_{t\to\infty} w(x,t,\phi) \geq \epsilon, \quad \liminf_{t\to\infty} v(x,t,\phi) \geq \epsilon, \quad \liminf_{t\to\infty} z(x,t,\phi) \geq \epsilon$$

uniformly for all $x \in \overline{\Omega}$, where $\phi \in \mathcal{W}_2 := \{\phi \in C^+ : w(\cdot, 0) \not\equiv 0,\ v(\cdot, 0) \not\equiv 0,\ \text{and } z(\cdot, 0) \not\equiv 0\}$.

Proof. The proof is quite similar to that of Theorem 4.6. Denote

$$\partial\mathcal{W}_2 := C^+ \setminus \mathcal{W}_2 = \{\phi \in C^+ : w(\cdot, 0) \equiv 0, \text{ or } v(\cdot, 0) \equiv 0, \text{ or } z(\cdot, 0) \equiv 0\}.$$

Set $M_0 = \{P_0\}$ and $M_1 = \{P_1\}$.

According to Lemma 2.2, we know that $w(x,t,\phi) > 0$, $v(x,t,\phi) > 0$, and $z(x,t,\phi) > 0$ for all $t > 0$ and $x \in \Omega$, $\phi \in \mathcal{W}_2$, which implies that $\Phi(t)\mathcal{W}_2 \subseteq \mathcal{W}_2$ for all $t \geq 0$. Define

$$\mathcal{M}^*_\partial := \{\phi \in \partial\mathcal{W}_2 : \Phi(t)\phi \in \partial\mathcal{W}_2 \text{ for } t \geq 0\}.$$

Claim 3. Let $\phi \in \mathcal{M}^*_\partial$. Then $\omega(\phi) = M_0$ or M_1.

Sine $\phi \in \mathcal{M}^*_\partial$, for any $t \geq 0$, we have either $w(x,t,\phi) \equiv 0$, or $v(x,t,\phi) \equiv 0$, or $z(x,t,\phi) \equiv 0$. If $z(x, t_4, \phi) \not\equiv 0$ for some $t_4 \geq 0$, then by Lemma 2.2, $z(x,t,\phi) > 0$ for $t > t_4$ and $x \in \Omega$. Then either $w(x,t,\phi) \equiv 0$ or $v(x,t,\phi) \equiv 0$ for each $t > t_4$. By the proof of Claim 1, we know that $\omega(\phi) = M_0$. Now, suppose that $z(x,t,\phi) \equiv 0$ for all $t \geq 0$. If for each $t \geq 0$, either $w(x,t,\phi) \equiv 0$ or $v(x,t,\phi) \equiv 0$, then by Claim 1, $\omega(\phi) = M_0$. If there exists $\tilde{t} \geq 0$ such that $w(x,\tilde{t},\phi) \not\equiv 0$ and $v(x,\tilde{t},\phi) \not\equiv 0$. Then by Theorem 4.6, there exists $\xi > 0$ such that

$$\liminf_{t\to\infty} w(x,t,\phi) \geq \xi \text{ and } \liminf_{t\to\infty} v(x,t,\phi) \geq \xi \text{ uniformly in } \overline{\Omega}.$$

Now consider the reduced system of (1.4) with $z = 0$. Modifying the Lyapunov functional $L(t)$ in the proof of Theorem 4.7 by ignoring the term $\frac{p}{q} e^{m\tau} z(x,t)$ in $L(x,t)$, we can show that the solution of the reduced system converges to (u_1, w_1, v_1) and hence $\omega(\phi) = M_1$. This proves Claim 3.

Claim 4. Both M_0 and M_1 are uniform weak repellers for $\mathcal{W}_2$. Since $\mathcal{W}_2 \subset \mathcal{W}_1$, by Claim 2, M_0 is a uniform repeller for $\mathcal{W}_2$. The proof of M_1 being a uniform repeller of $\mathcal{W}_2$ is similar as that of Claim 2 by using Lemma 4.9 and Lemma 4.10. Therefore, we omit the detail here.

Define a continuous function $\mathcal{P}_2 : C^+ \to [0, \infty)$ by

$$\mathcal{P}_2(\phi) := \min\left\{\min_{x\in\overline{\Omega}} \phi_2(x,0),\ \min_{x\in\overline{\Omega}} \phi_3(x,0),\ \min_{x\in\overline{\Omega}} \phi_4(x,0)\right\} \text{ for } \phi \in C^+.$$

It is easy to see that $\mathcal{P}_2^{-1}(0,\infty) \subset \mathcal{W}_2$, and $\mathcal{P}_2$ has the property that if $\mathcal{P}_2(\phi) = 0$ and $\phi \in \mathcal{W}_2$ or $\mathcal{P}_2(\phi) > 0$, then $\mathcal{P}_2(\Phi(t)\phi) > 0$ for all $t > 0$. Thus $\mathcal{P}_2$ is a generalized distance function for the semiflow $\Phi(t)$. As M_0 and M_1 are repellers, we know that both M_0 and M_1 are isolated, and $\mathcal{W}^s(M_i)\cap\mathcal{W}_2 = \emptyset$ for $i = 0$ and 1. Moreover, no subset of $\{M_0, M_1\}$ forms a cycle in $\partial\mathcal{W}_2$. By Smith and Zhao [53, Theorem 3], there exists a $\bar{\epsilon} > 0$ such that $\min\{\mathcal{P}_2(\phi)\} > \bar{\epsilon}$ for any $\phi \in \mathcal{W}_2$. Then as for Theorem 4.6, with $\varepsilon = \min\{\bar{\epsilon}, \frac{s}{d+\eta_1+\eta_2}\}$ finishes the proof. □

As for the global stability of P_2, we make the following assumption to establish the global stability of P_2.

(A3) The nonlinear incidence functions $f(u, v)$ and $g(u, w)$ satisfy the following conditions.

(i) For any $u > 0$,

$$\begin{cases} \frac{v}{v_2} \le \frac{u_2 f(u,v)}{u f(u_2,v_2)} < 1 & \text{if } 0 < v < v_2, \\ 1 \le \frac{u_2 f(u,v)}{u f(u_2,v_2)} < \frac{v}{v_2} & \text{if } v_2 < v. \end{cases}$$

(ii) For any $u > 0$,

$$\begin{cases} \frac{w}{w_2} \le \frac{u_2 g(u,w)}{u g(u_2,w_2)} < 1 & \text{if } 0 < w < w_2, \\ 1 \le \frac{u_2 g(u,w)}{u g(u_2,w_2)} < \frac{w}{w_2} & \text{if } w_2 < w. \end{cases}$$

Theorem 4.12. *Suppose that $R_1 > 1$ and Assumptions (A2) and (A3) are satisfied. Then the infected-immune steady state P_2 is globally asymptotically stable in*

$$C_2^+ = \left\{\phi \in C^+ \;\middle|\; \begin{array}{l} \text{there exists } t_5 \in \mathbb{R}^+ \text{ such that either } w(\cdot, t_5, \phi) \not\equiv 0 \text{ or } v(\cdot, t_5, \phi) \not\equiv 0, \\ \text{there exists } t_6 \in \mathbb{R}^+ \text{ such that } z(\cdot, t_6, \phi) \not\equiv 0 \end{array}\right\}.$$

Proof. It follows from Lemma 2.2 and Theorem 4.11 that there exists an $\varepsilon > 0$ such that

$$\liminf_{t\to\infty} u(x,t,\phi) \ge \varepsilon,\ \liminf_{t\to\infty} w(x,t,\phi) \ge \varepsilon,\ \liminf_{t\to\infty} v(x,t,\phi) \ge \varepsilon,\ \liminf_{t\to\infty} z(x,t,\phi) \ge \varepsilon$$

unfiormly in $\overline{\Omega}$ and $\phi \in C_2^+$. Without loss of generality, we define a Lyapunov functional

$$I(t) = \int_\Omega I(x,t)\mathrm{d}x,$$

where

$$I(x,t) = u_2 G\left(\frac{u(x,t)}{u_2}\right) + e^{m\tau} w_2 G\left(\frac{w(x,t)}{w_2}\right) + \frac{f(u_2,v_2)}{cv_2} v_2 G\left(\frac{v(x,t)}{v_2}\right) + \frac{p}{q} e^{m\tau} z_2 G\left(\frac{z(x,t)}{z_2}\right)$$

$$+f(u_2,v_2)\int_{t-\tau}^{t} G\left(\frac{f(u(x,\theta),v(x,\theta))}{f(u_2,v_2)}\right)\mathrm{d}\theta + g(u_2,w_2)\int_{t-\tau}^{t} G\left(\frac{g(u(x,\theta),w(x,\theta))}{g(u_2,w_2)}\right)\mathrm{d}\theta.$$

Calculate the time derivative of $I(x,t)$ along the solutions of (1.4) to get

$$\begin{aligned}
\frac{\partial I(x,t)}{\partial t} &= \left(1-\frac{u_2}{u(x,t)}\right)[s-du(x,t)-f(u,v)-g(u,w)]\\
&+\frac{p}{q}e^{m\tau}\left(1-\frac{z_2}{z(x,t)}\right)[qw(x,t)z(x,t)-bz(x,t)]\\
&+e^{m\tau}\left(1-\frac{w_2}{w(x,t)}\right)[e^{-m\tau}f(u_\tau,v_\tau)+e^{-m\tau}g(u_\tau,w_\tau)-\delta w(x,t)-pw(x,t)z(x,t)]\\
&+\frac{f(u_2,v_2)}{cv_2}\left(1-\frac{v_2}{v(x,t)}\right)[D_1\Delta v(x,t)+N\delta w(x,t)-cv(x,t)]\\
&+\frac{p}{q}e^{m\tau}\left(1-\frac{z_2}{z(x,t)}\right)D_2\Delta z(x,t)+f(u,v)-f(u_\tau,v_\tau)+f(u_2,v_2)\ln\frac{f(u_\tau,v_\tau)}{f(u,v)}\\
&+g(u,w)-g(u_\tau,w_\tau)+g(u_2,w_2)\ln\frac{g(u_\tau,w_\tau)}{g(u,w)}.
\end{aligned}$$

With the following relations,

$$\begin{aligned}
s &= du_2+f(u_2,v_2)+g(u_2,w_2),\\
\delta &= \frac{e^{-m\tau}f(u_2,v_2)+e^{-m\tau}g(u_2,w_2)-pw_2z_2}{w_2},\\
c &= \frac{N\delta w_2}{v_2},\\
w_2 &= \frac{b}{q},
\end{aligned}$$

we get

$$\begin{aligned}
\frac{\partial I(x,t)}{\partial t} &= du_2\left(2-\frac{u_2}{u(x,t)}-\frac{u(x,t)}{u_2}\right)+\frac{f(u_2,v_2)}{cv_2}\left(1-\frac{v_2}{v(x,t)}\right)D_1\Delta v(x,t)\\
&+\frac{p}{q}e^{m\tau}\left(1-\frac{z_2}{z(x,t)}\right)D_2\Delta z(x,t)-f(u_2,v_2)\frac{w(x,t)v_2}{v(x,t)w_2}\\
&+f(u_2,v_2)\left[3-\frac{u_2}{u(x,t)}-\frac{f(u_\tau,v_\tau)w_2}{f(u_2,v_2)w(x,t)}+\frac{f(u,v)u_2}{f(u_2,v_2)u(x,t)}-\frac{v(x,t)}{v_2}+\ln\frac{f(u_\tau,v_\tau)}{f(u,v)}\right]\\
&+g(u_2,w_2)\left[2-\frac{u_2}{u(x,t)}-\frac{g(u_\tau,w_\tau)w_2}{g(u_2,w_2)w(x,t)}+\frac{g(u,w)u_2}{g(u_2,w_2)u(x,t)}-\frac{w(x,t)}{w_2}+\ln\frac{g(u_\tau,w_\tau)}{g(u,w)}\right].
\end{aligned}$$

Then

$$\begin{aligned}
\frac{\mathrm{d}I(t)}{\mathrm{d}t} &= \int_\Omega du_2\left(2-\frac{u_2}{u(x,t)}-\frac{u(x,t)}{u_2}\right)\mathrm{d}x+\int_\Omega\frac{f(u_2,v_2)}{cv_2}\left(1-\frac{v_2}{v(x,t)}\right)D_1\Delta v(x,t)\mathrm{d}x\\
&+\int_\Omega\frac{p}{q}e^{m\tau}\left(1-\frac{z_2}{z(x,t)}\right)D_2\Delta z(x,t)\mathrm{d}x-f(u_2,v_2)\int_\Omega G\left(\frac{w(x,t)v_2}{v(x,t)w_2}\right)\mathrm{d}x
\end{aligned}$$

$$+f(u_2,v_2)\int_\Omega\left[G\left(\frac{f(u,v)u_2}{f(u_2,v_2)u(x,t)}\right)-G\left(\frac{v(x,t)}{v_2}\right)-G\left(\frac{u_2}{u(x,t)}\right)-G\left(\frac{f(u_\tau,v_\tau)w_2}{f(u_2,v_2)w(x,t)}\right)\right]\mathrm{d}x$$
$$+g(u_2,w_2)\int_\Omega\left[G\left(\frac{g(u,w)u_2}{g(u_2,w_2)u(x,t)}\right)-G\left(\frac{w(x,t)}{w_2}\right)-G\left(\frac{u_2}{u(x,t)}\right)-G\left(\frac{g(u_\tau,w_\tau)w_2}{g(u_2,w_2)w(x,t)}\right)\right]\mathrm{d}x.$$

Similarly as in the proof of Theorem 4.7, we can show

$$\begin{aligned}\int_\Omega du_2\left(2-\frac{u(x,t)}{u_2}-\frac{u_2}{u(x,t)}\right)\mathrm{d}x &\le 0,\\ \int_\Omega\frac{f(u_2,v_2)}{cv_2}\left(1-\frac{v_2}{v(x,t)}\right)D_1\Delta v(x,t)\mathrm{d}x &\le 0,\\ \int_\Omega\frac{p}{q}e^{m\tau}\left(1-\frac{z_2}{z(x,t)}\right)D_2\Delta z(x,t)\mathrm{d}x &\le 0,\\ G\left(\frac{f(u,v)u_2}{f(u_2,v_2)u(x,t)}\right) &\le G\left(\frac{v(x,t)}{v_2}\right),\\ G\left(\frac{g(u,w)u_2}{g(u_2,w_2)u(x,t)}\right) &\le G\left(\frac{w(x,t)}{w_2}\right).\end{aligned}$$

Therefore, we have $\frac{\mathrm{d}I(t)}{\mathrm{d}t}\le 0$. Moreover, $\frac{\mathrm{d}I(t)}{\mathrm{d}t}=0$ if and only if $u(x,t)=u_2$, $w(x,t)=w_2$, $v(x,t)=v_2$, $z(x,t)=z_2$. Then the largest invariant subset of $\frac{\mathrm{d}I(t)}{\mathrm{d}t}=0$ is $\{P_2\}$. By LaSalle's Invariance Principle (see Theorem 5.3.1 in [50] or Theorem 3.4.7 in [51]), the infected-immune steady state P_2 is globally attractive in C_2^+. This, together with Theorem 4.8, implies the global asymptotic stability of P_2 in C_2^+. □

5. Numerical simulations

In this section, we perform some numerical simulations to illustrate the results obtained in section 4. Let $f(u,v)=\frac{\beta_1 uv}{1+\alpha_1 v}$ and $g(u,w)=\frac{\beta_2 uw}{1+\alpha_2 w}$. One can easily verify that f and g satisfy (A1)–(A3). Then the model (1.4) becomes

$$\begin{cases}\dfrac{\partial u(x,t)}{\partial t}=s-du(x,t)-\dfrac{\beta_1 u(x,t)v(x,t)}{1+\alpha_1 v(x,t)}-\dfrac{\beta_2 u(x,t)w(x,t)}{1+\alpha_2 w(x,t)},\ x\in\Omega,\ t>0,\\ \dfrac{\partial w(x,t)}{\partial t}=e^{-m\tau}\left(\dfrac{\beta_1 u(x,t-\tau)v(x,t-\tau)}{1+\alpha_1 v(x,t-\tau)}+\dfrac{\beta_2 u(x,t-\tau)w(x,t-\tau)}{1+\alpha_2 w(x,t-\tau)}\right)\\ \qquad\qquad -\delta w(x,t)-pw(x,t)z(x,t),\ x\in\Omega,\ t>0,\\ \dfrac{\partial v(x,t)}{\partial t}=D_1\Delta v(x,t)+N\delta w(x,t)-cv(x,t),\ x\in\Omega,\ t>0,\\ \dfrac{\partial z(x,t)}{\partial t}=D_2\Delta z(x,t)+qw(x,t)z(x,t)-bz(x,t),\ x\in\Omega,\ t>0,\end{cases}\tag{5.1}$$

subject to the homogeneous Neumann boundary conditions

$$\frac{\partial v}{\partial\vec{n}}=0,\ \frac{\partial z}{\partial\vec{n}}=0,\ x\in\partial\Omega,\ t>0.$$

For (5.1), the basic reproduction number of infection is given by

$$R_0=\frac{N\beta_1 s}{cd}e^{-m\tau}+\frac{\beta_2 s}{\delta d}e^{-m\tau}$$

and the basic reproduction number of immunity is given by

$$R_1 = \frac{qw_1}{b} = \frac{q\left(B_2 + \sqrt{B_2^2 - 4B_1B_3}\right)}{2bB_1},$$

where

$$\begin{aligned}
&B_1 = N\delta^2 e^{m\tau}(\beta_1\alpha_2 + \beta_2\alpha_1 + \alpha_1\alpha_2 d) > 0,\\
&B_2 = \delta d e^{m\tau}(N\delta\alpha_1 + c\alpha_2) - N\delta\beta_1\alpha_2 s + N\delta^2\beta_1 e^{m\tau} - N\delta\beta_2\alpha_1 s + \delta e^{m\tau}\beta_2 c,\\
&B_3 = -dc\delta e^{m\tau}(R_0 - 1) < 0 \text{ since } R_0 > 1.
\end{aligned}$$

For simulations, we take $\alpha_1 = 0.01$, $\alpha_2 = 0.01$, $D_1 = 0.0017$, $D_2 = 0.0001$, and the values of the other parameters are summarized in Table 1. Moreover, $\Omega = [0, 4]$ and the initial condition used is

$$\begin{aligned}
&u(x,\theta) = 23 + 0.2\cos\tfrac{\pi x}{2}, \qquad &&w(x,\theta) = 0.7 + 0.2\cos\tfrac{\pi x}{2},\\
&v(x,\theta) = 3 + 0.2\cos\tfrac{\pi x}{2}, \qquad &&z(x,\theta) = 2 + 0.2\cos\tfrac{\pi x}{2}
\end{aligned}$$

for $x \in [0, 4]$ and $\theta \in [-0.5, 0]$.

Table 1. Parameter values for simulation.

Parameters	Ranges	value	Units	References
s	$0 \sim 10$	10	cells $\text{ml}^{-1}\text{day}^{-1}$	[54]
d	$0.0001 \sim 0.2$	0.01	day^{-1}	[22]
β_1	$4.6 \times 10^{-8} \sim 0.5$	variable	$\text{ml}^{-1}\text{day}^{-1}$	[55]
β_2	$1 \times 10^{-5} \sim 0.7$	2.4×10^{-5}	$\text{ml}^{-1}\text{day}^{-1}$	[39]
m	$\alpha \in [d, \delta]$	0.05	day^{-1}	[55]
τ	$0 \sim 1.5$	0.5	days	[55]
δ	$0.00019 \sim 1.4$	1	day^{-1}	[22]
p	$0.0001 \sim 4.048$	0.024	$\text{ml}^{-1}\text{day}^{-1}$	[22, 55]
N	$6.25 \sim 23599.9$	2000	viron cells^{-1}	[22]
c	$2 \sim 36$	23	day^{-1}	[22, 39]
q	$0.0051 \sim 3.912$	0.15	day^{-1}	[22]
b	$0.004 \sim 8.087$	0.5	day^{-1}	[22, 39]

Firstly, we take $\beta_1 = 1 \times 10^{-5}$. Then $R_0 = 0.8715 < 1$. By Theorem 4.2, the infection-free steady state $P_0 = (1000, 0, 0, 0)$ is globally asymptotically stable (see Figure1).

Next, we choose $\beta_1 = 2.4 \times 10^{-5}$. Then $R_0 = 2.0588 > 1$ and $R_1 = 0.2989 < 1$. From Theorem 4.7, the immunity-free infected steady state $P_1 = (897.8483, 0.9963, 86.6344, 0)$ is globally asymptotically stable (see Figure2).

Finally, with $\beta_1 = 8.4 \times 10^{-5}$, we get $R_0 = 7.1474 > 1$ and $R_1 = 1.1594 > 1$. By Theorem 4.12, the infected-immune steady state $P_2 = (609.8631, 3.3333, 289.8550, 5.8964)$ is globally asymptotically stable (see Figure 3).

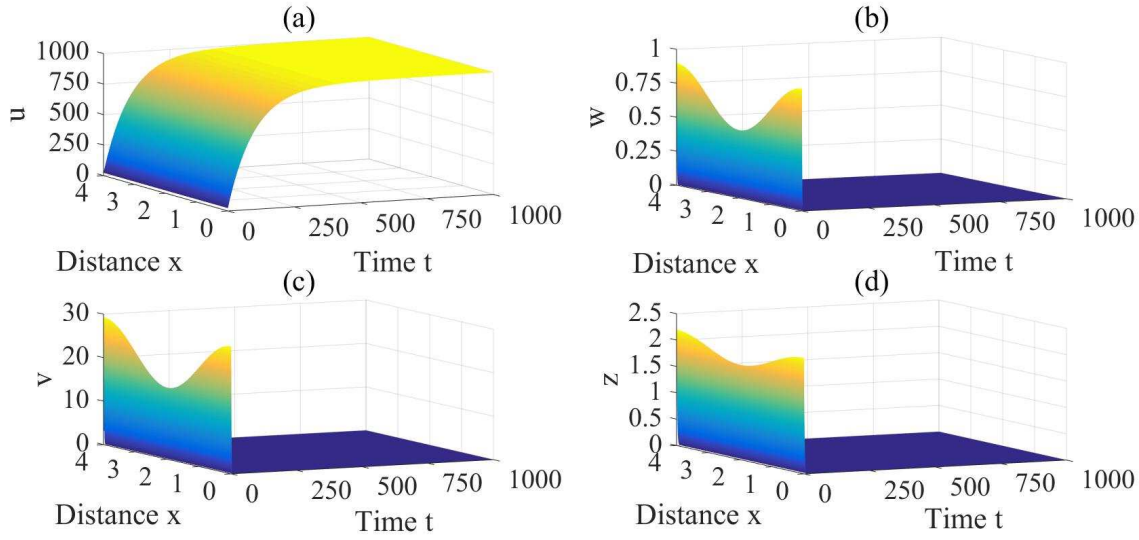

Figure 1. When $R_0 < 1$, the infection-free steady state P_0 is globally asymptotically stable. Parameter values are given in the text.

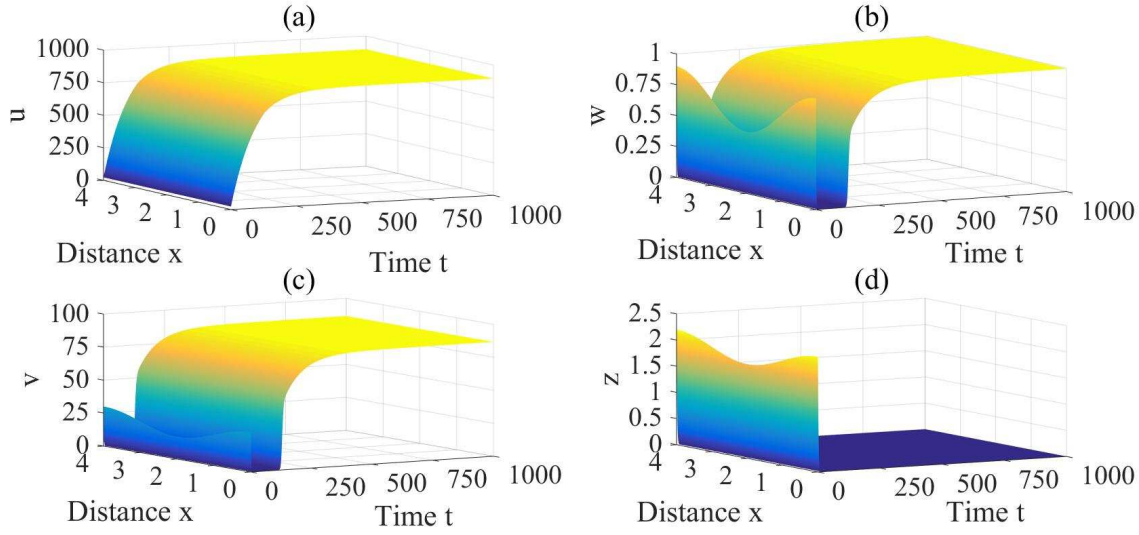

Figure 2. When $R_0 = 2.0588 > 1$ and $R_1 = 0.2989 < 1$, the immunity-free infected steady state P_1 is globally asymptotically stable. See the text for the parameter values.

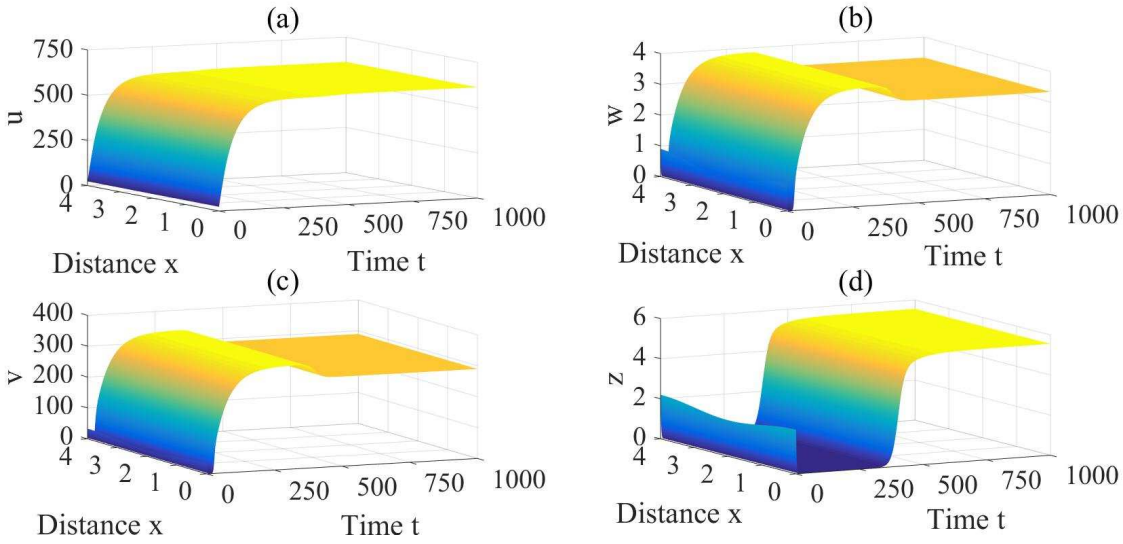

Figure 3. When $R_1 > 1$, the infected-immune steady state P_2 is globally asymptotically stable. See the text for the parameter values.

6. Conclusions

In this paper, we have proposed and studied a reaction-diffusion virus infection model by incorporating time delays, general incidence functions, and cell-to-cell transmission.

We have proved that the global dynamics of system (1.4)–(1.6) is determined by the basic reproduction number of infection R_0 and the basic reproduction number of immunity R_1. By analyzing the characteristic equations and constructing Lyapunov functionals, we have obtained the following conclusions: if $R_0 < 1$, then the infected-free steady state P_0 is globally asymptotically stable; if $R_1 \leq 1 < R_0$, then the immunity-free infected steady state P_1 is globally asymptotically stable under additional Assumption (A2); if $R_1 > 1$, then the infected-immune steady state P_2 is globally asymptotically stable under additional Assumptions (A2) and (A3). We mention that most commonly used incidences satisfy (A1)–(A3). Some examples are the Holling type II incidence $f(u, v) = \frac{\beta uv}{1+\alpha v}$ [40], Beddington-DeAnglis incidence [41], and $f(u, v) = ku \ln(1 + \frac{\beta v}{k})$ [56].

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Conflict of interests

The authors declare that there is no conflict of interest.

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