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*Research article*

# Spatial dynamics of a viral infection model with nonlinear incidence rate

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**Abstract:** This work investigates the dynamics of a diffusive viral infection model that incorporates a nonlinear incidence and follicular dendritic cells (FDCs). First, the well-posedness is established. Then, We show that the basic reproduction number serves as a critical threshold for global stabilities: the infection-free steady state is globally asymptotically stable when the basic reproduction number is less than one, while the model exhibits a uniform persistence when the basic reproduction number is greater than one. Under the condition that the basic reproduction number equals to one, the infection-free steady state is shown to be globally asymptotically stable given certain additional assumptions. Furthermore, the global stability of the infected steady state is established for the homogeneous case. We find that ignoring the spatial heterogeneity in the infection capacity of viruses and infected cells may lead to an underestimation of the transmission risk. Although the spatial heterogeneity of a FDC does not affect the basic reproduction number, neglecting the infection originating from a FDC may lead to an underestimation of the infection risk.

**Keywords:** spatial heterogeneity; nonlinear incidence; basic reproduction number; global asymptotic stability; uniform persistence

## 1. Introduction

Due to the challenges in frequently collecting patient samples and the potential inaccuracies of viral detection techniques, testing specific hypotheses using clinical and statistical data presents considerable difficulties. These limitations underscore the crucial role of mathematical models in elucidating some infectious or noninfectious disease dynamics. The significance of mathematical models lies in offering essential qualitative and theoretical support for the design of effective control strategies [1–3]. Particularly, a foundation model of viral infections dynamics was proposed by Perelson et al. [1] and Bonhoeffer et al. [2] in the context of HIV infections. Subsequently, motivated by model proposed in [1, 2], numerous studies were established that included a

foundational work by Korobeinikov [4], who proved the model's global stability by introducing the classical Lyapunov function form $\varphi(u) = 1 + \ln u - u$ $(u > 0)$ to establish global stability in within-host viral infection models, which has been adopted for a stability analysis of equilibrium in diverse mathematical models.

As an effective treatment drug, antiretroviral therapy (ART) has achieved substantial success in suppressing the viral replication to a low level. However, its inability to completely eradicate HIV and the persistent risk of viral infection rebound remain major challenges in current research. A reliable and plausible explanation is the existence of viral reservoirs, which pose a significant obstacle to viral eradication. Although latency in $CD4^+$ T cells is one well-documented source of persistent virus [5], follicular dendritic cells (FDCs) also constitute an important reservoir [6]. Studies indicate that FDCs reside in secondary lymphoid organs, particularly within germinal centers, where they bind HIV–antibody complexes. They are capable of retaining up to $10^{11}$ copies of HIV in untreated patients [7]. Consequently, FDCs trap and preserve viruses in their native state for extended periods—often months. Experiments show that a FDC-trapped virus remains infectious for at least 25 days in vitro, whereas a free virus loses infectivity within days. This suggests that HIV bound to FDCs can survive long-term even without active replication, indicating that FDCs stabilize and protect HIV, thereby maintaining a reservoir of infectious virus even under highly active antiretroviral therapy [8–13]. To the best of our knowledge, only a few number of models that incorporate FDCs have been developed [14–17]. For instance, Callaway and Perelson [16] proposed a simple model featuring a new compartment for FDCs (denoted as $W$) to explore the impact of FDCs on the steady state of the viral load. Note that no dynamic analysis of the model in [16] has been conducted. Inspired by this model, Geng and Xu [17] proposed a delayed model that incorporated both immune response and FDCs to analyze the corresponding global dynamics. It is noteworthy that none of the aforementioned dynamic models that involved FDCs accounted for the infectivity of FDC-bound virus. However, literatures have pointed out that HIV particles bound to FDCs remain infectious and can transmit the virus to uninfected cells [6, 8]. Therefore, incorporating the infectivity of FDC–virus complexes is essential for a more comprehensive understanding of viral dynamics.

Additionally, notice that only virus-to-cell infection is considered in the classical model in [16]. Literatures show that uninfected cells can also be infected by inflammatory cytokines [18–21]. In addition, recent studies revealed that large numbers of virions can be transferred to uninfected cells [22]. Experiments have found that viral particles can be directly transmitted to uninfected cells through virological synapses [23]. Thus, the direct cell-to-cell infection can affect the mechanism of HIV transmission in vivo. Consequently, extensive literatures to understand the dynamics of cell-to-cell infections of HIV have been proposed and some of these literatures are listed [24–35]. Beyond cell-to-cell infection, researchers have integrated additional critical factors, including the following: time delay [24–26, 30], spatial heterogeneity [27, 28], age-structure [31–33], stochastic noise [29], immune response [34, 35], and so on.

Recent evidence indicates that spatial heterogeneity plays a crucial role in the within-host viral infection dynamics [36]. It has been pointed out that spatial heterogeneity can enhance the transmission risk in epidemic models [37], while the mobility of infected cells and virions may reduce this risk [38]. In [28], the authors proposed a spatially heterogeneous within-host HIV infection model under Neumann boundary conditions to examine the effects of cellular and viral mobility, as well as the spatial heterogeneity on viral propagation. Shu et al. [39] investigated a general

within-host model that incorporates spatial heterogeneity and multiple infection modes; they analyzed the global dynamics of steady states by constructing an appropriate Lyapunov functional. More recently, Li and Zhao [40] proposed a delayed, nonlocal, reaction–diffusion viral infection model that featured general nonlinear incidence rates for both virus-to-cell and cell-to-cell transmission modes. They defined the basic reproduction number, which serves as a key threshold governing the global dynamics, and established the global attractivity of the infection steady state through the construction of a suitable Lyapunov functional. However, FDCs infection has not been incorporated into the model and investigated. Therefore, it is reasonable and beneficial to integrate spatial heterogeneity and FDCs into dynamical models of HIV infections.

This paper develops an HIV infection model with three infection modes and spatial heterogeneity. The model is an extension of the model introduced by Callaway and Perelson [16]. We investigate the global dynamics of the model in terms of the basic reproduction number $R_0$, which is derived to determine whether the infection will die out or persist. We show that a chronic infection will be established if $R_0 > 1$ and will be eradicated if $R_0 < 1$. Additionally, the critical case $R_0 = 1$ is analyzed. Moreover, by constructing an appropriate Lyapunov functional, the global stability of the positive steady state is demonstrated for the homogeneous case. Numerical simulations of the model are performed to explain the influence of spatial heterogeneity on the dynamics of the model.

## 2. Model formulation

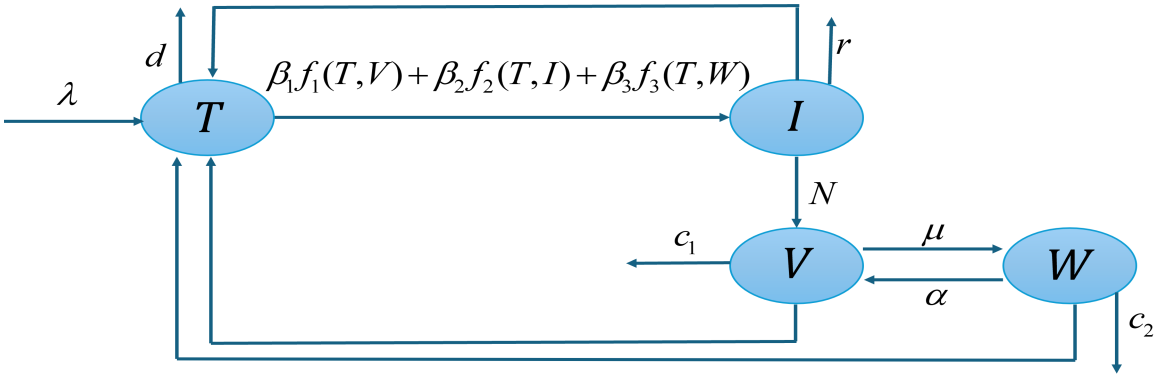


**Figure 1.** Schematic diagram of the model.

Motivated by [16], this paper presents and analyzes a diffusive model that incorporates FDCs and cellular infections. The model consists of four state variables: uninfected cells ($T$), productively infected cells ($I$), infectious virus ($V$), and FDC-virus complexes ($W$). The dynamics of each variable are described as follows.

Uninfected cells ($T$): Production rate $\lambda$, lost due to natural death at rate $dT$, and become infected through contact with infected cells, infectious virus, and FDC-virus complexes at rates $\beta_2 f_2(T, I)$, $\beta_1 f_1(T, V)$, and $\beta_3 f_3(T, W)$, respectively.

Infected cells ($I$): Generated from new infections at the total rate $\beta_2 f_2(T, I)+\beta_1 f_1(T, V)+\beta_3 f_3(T, W)$ and die at rate $rI$.

Infectious virus ($V$): Produced by infected cells at rate $NI$, cleared naturally at rate $c_1V$, removed through binding to FDCs at rate $\mu V$, and replenished by dissociation from FDC-virus complexes at rate $\alpha W$.

FDC-virus complexes ($W$): Formed by binding free virus to FDCs at rate $\mu V$, cleared at rate $c_2W$, and lose virus through dissociation at rate $\alpha W$.

The corresponding model diagram is shown in Figure 1, and the model takes the following form:

$$\begin{cases} \dfrac{\partial T(t,x)}{\partial t} = \nabla\cdot(d_1(x)\nabla T) + \lambda(x) - d(x)T - \beta_1(x)f_1(T,V) - \beta_2(x)f_2(T,I) \\ \qquad\qquad - \beta_3(x)f_3(T,W), x\in\Omega, t>0, \\ \dfrac{\partial I(t,x)}{\partial t} = \nabla\cdot(d_2(x)\nabla I) + \beta_1(x)f_1(T,V) + \beta_2(x)f_2(T,I) + \beta_3(x)f_3(T,W) \\ \qquad\qquad - r(x)I, x\in\Omega, t>0, \\ \dfrac{\partial V(t,x)}{\partial t} = \nabla\cdot(d_3(x)\nabla V) + N(x)I - (c_1(x)+\mu(x))V + \alpha(x)W, x\in\Omega, t>0, \\ \dfrac{\partial W(t,x)}{\partial t} = \nabla\cdot(d_4(x)\nabla W) + \mu(x)V - (c_2(x)+\alpha(x))W, x\in\Omega, t>0, \\ \dfrac{\partial T(t,x)}{\partial \nu} = \dfrac{\partial I(t,x)}{\partial \nu} = \dfrac{\partial V(t,x)}{\partial \nu} = \dfrac{\partial W(t,x)}{\partial \nu} = 0, x\in\partial\Omega, t>0, \end{cases} \tag{2.1}$$

with the following initial condition:

$$T(0,x) = T_0(x), I(0,x) = I_0(x), V(0,x) = V_0(x), W(0,x) = W_0(x), \quad \text{for} \quad x\in\Omega, \tag{2.2}$$

where $\Omega$ is a spatial domain, and $\nu$ is the outward normal vector to $\partial\Omega$. Here, $T(t,x)$, $I(t,x)$, $V(t,x)$, and $W(t,x)$ represent the concentrations of the uninfected cells, productively infected cells, infectious free virus, and virus bound to the FDC, at time $t$ and location $x$, respectively. Here, we assume that all the location-dependent parameters are continuous and strictly positive defined on $\bar{\Omega}$. Details of the parameter information are listed in Table 1. We make the following assumptions for the incidence functions $f_1(T,V)$, $f_2(T,I)$ and $f_3(T,W)$:

**(A1)** $f_1(0,V) = f_1(T,0) = 0$, $f_1(T,V) > 0$, $f_1(T,V) \le TV$, $f_2(0,I) = f_2(T,0) = 0$, $f_2(T,I) > 0$, $f_2(T,I) \le TI$, $f_3(0,W) = f_3(T,0) = 0$, $f_3(T,W) > 0$, $f_3(T,W) \le TW$, for $T,V,I,W \ge 0$.

**(A2)** $\dfrac{\partial f_1(T,V)}{\partial T} > 0$, $\dfrac{\partial f_1(T,V)}{\partial V} > 0$, $\dfrac{\partial^2 f_1(T,V)}{\partial^2 V} \le 0$, $\dfrac{\partial f_2(T,I)}{\partial T} > 0$, $\dfrac{\partial f_2(T,I)}{\partial I} > 0$, $\dfrac{\partial^2 f_2(T,I)}{\partial^2 I} \le 0$, $\dfrac{\partial f_3(T,W)}{\partial T} > 0$, $\dfrac{\partial f_3(T,W)}{\partial W} > 0$, $\dfrac{\partial^2 f_3(T,W)}{\partial^2 W} \le 0$.

The remainder of this paper is structured as follows: in Section 2, we establish the well-posedness and definition of $\mathcal{R}_0$ to Model (2.1); In Section 3, we present the global dynamical behaviors of Model (2.1). In Section 4, the global dynamics of Model (2.1) are investigated when all parameters are constants in Section 4; additionally, we show some simulations in Section 5; a brief conclusions can be found in the last section.

**Table 1.** Parameter descriptions in Model (2.1).

| Parameter | Description (position $x$) | Units |
|---|---|---|
| $\lambda(x)$ | Recruitment rate of uninfected cells | $\text{ml}^{-1}\ \text{day}^{-1}$ |
| $d(x)$ | Death rate of uninfected cells | $\text{day}^{-1}$ |
| $r(x)$ | Death rate of infected cells | $\text{day}^{-1}$ |
| $c_1(x)$ | Death rate of virions | $\text{day}^{-1}$ |
| $c_2(x)$ | Death rate of FDCs | $\text{day}^{-1}$ |
| $\mu(x)$ | Virus binding rate of FDCs | $\text{day}^{-1}$ |
| $\alpha(x)$ | Virus dissociates rate from FDCs | $\text{day}^{-1}$ |
| $N(x)$ | Virus production rate | virions/(cell day) |
| $\beta_1(x)$ | Virus-to-cell infection rate | $\text{ml day}^{-1}$ |
| $\beta_2(x)$ | Cell-to-cell infection rate | $\text{ml day}^{-1}$ |
| $\beta_3(x)$ | FDCs associated virus infection rate | $\text{ml day}^{-1}$ |
| $d_1(x)$ | Diffusion rate of uninfected cells | $\text{nm}^2\ \text{day}^{-1}$ |
| $d_2(x)$ | Diffusion rate of infected cells | $\text{nm}^2\ \text{day}^{-1}$ |
| $d_3(x)$ | Diffusion rate of virions | $\text{nm}^2\ \text{day}^{-1}$ |
| $d_4(x)$ | Diffusion rate of FDCs associated virus | $\text{nm}^2\ \text{day}^{-1}$ |

## 3. Well-posedness

In this section, we present some preliminary results including the existence of a global attractor, the compactness and point dissipative of the solution semiflow, and the definition of the basic reproduction number.

Let $\mathbb{X} := C(\bar{\Omega}, \mathbb{R}^4)$ denote the Banach space equipped with the supremum norm

$$\|\psi\|_{\mathbb{X}} = \max\{\sup_{x\in\bar{\Omega}}|\psi_1(\cdot)|, \sup_{x\in\bar{\Omega}}|\psi_2(\cdot)|, \sup_{x\in\bar{\Omega}}|\psi_3(\cdot)|, \sup_{x\in\bar{\Omega}}|\psi_4(\cdot)|\}, \psi = (\psi_1, \psi_2, \psi_3, \psi_4) \in \mathbb{X},$$

and $(\mathbb{X}, \mathbb{X}_+)$ is a ordered Banach space with $\mathbb{X}_+ := C(\bar{\Omega}, \mathbb{R}^4_+)$. Let $\bar{\varphi} = \max_{x\in\bar{\Omega}}\{\varphi(x)\}$, $\underline{\varphi} = \min_{x\in\bar{\Omega}}\{\varphi(x)\}$, $f_x(x, y) = \frac{\partial f(x,y)}{\partial x}$, and $f_y(x, y) = \frac{\partial f(x,y)}{\partial y}$. Let $\rho_1(x) = d(x)$, $\rho_2(x) = r(x)$, $\rho_3(x) = c_1(x) + \mu(x)$, and $\rho_4(x) = c_2(x) + \alpha(x)$, and denote the $C_0$ semigroups associated with $\nabla \cdot (d_i(x)\nabla) - \rho_i(x)$ by $\mathbb{T}_i(t) : C(\bar{\Omega}, \mathbb{R}) \to C(\bar{\Omega}, \mathbb{R})$, $(i = 1, 2, 3, 4)$, that is,

$$(\mathbb{T}_i(t)\psi)(x) = \int_\Omega \Gamma_i(t, x, y)\psi(y)dy, \quad t > 0, \psi \in C(\bar{\Omega}, \mathbb{R}),$$

where $\Gamma_i(t, x, y)$ is the Green function associated with $\nabla \cdot (d_i(x)\nabla) - \rho_i(\cdot)$ subjects to the Neumann boundary condition. Then, $\mathbb{T}_i(t)$ is compact and strongly positive for $t > 0$ [41]. Thus, there exists an $M > 0$ such that $\|\mathbb{T}_i(t)\| \le Me^{\omega_i t}$ for each $t \ge 0$, where $\omega_i < 0$ is the principle eigenvalue of $\nabla \cdot (d_i(x)\nabla) - \rho_i(\cdot)$.

Define $\mathbb{F} = (\mathbb{F}_1, \mathbb{F}_2, \mathbb{F}_3, \mathbb{F}_4)^{\mathrm{T}} : \mathbb{X}_+ \to \mathbb{X}$ by the following:

$$\begin{aligned}
\mathbb{F}_1(\psi)(x) =& \lambda(x) - \beta_1(x)f_1(\psi_1(x), \psi_3(x)) - \beta_2(x)f_2(\psi_1(x), \psi_2(x)) - \beta_3(x)f_3(\psi_1(x), \psi_4(x)),\\
\mathbb{F}_2(\psi)(x) =& \beta_1(x)f_1(\psi_1(x), \psi_3(x)) + \beta_2(x)f_2(\psi_1(x), \psi_2(x)) + \beta_3(x)f_3(\psi_1(x), \psi_4(x)),
\end{aligned}$$

$$\mathbb{F}_3(\psi)(x) = N(x)\psi_2(x) + \alpha(x)\psi_4(x),$$
$$\mathbb{F}_3(\psi)(x) = \mu(x)\psi_3(x),$$

where $\psi(x) = (\psi_1(x), \psi_2(x), \psi_3(x), \psi_4(x))^{\mathrm{T}} \in \mathbb{X}$. Then, Model (2.1) can be written as the following form:

$$u(t,x) = (\mathbb{T}(t)\psi)(x) + \int_0^t \mathbb{T}(t-s)\mathbb{F}(u(t,s))ds,$$

where $u(t,x) = (T(t,x), I(t,x), V(t,x), W(t,x))^{\mathrm{T}}$, and $\mathbb{T}(t) = diag(\mathbb{T}_1(t), \mathbb{T}_2(t), \mathbb{T}_3(t), \mathbb{T}_4(t))$. Then, it follows from the standard result in [42] that the following lemma can be immediately obtained for Model (2.1) with Condition (2.2).

**Lemma 3.1.** *For any $\psi \in \mathbb{X}_+$, Model* (2.1) *with Condition* (2.2) *admits a unique non-continuable mild solution $u(t,\cdot,\psi) = (T(t,\cdot,\psi), T(t,\cdot,\psi), V(t,\cdot,\psi), W(t,\cdot,\psi),) \in \mathbb{X}_+$ for $t \in [0, \tau_\infty)$, where $\tau_\infty \le \infty$. Moreover, the solution is classical.*

*Proof.* For any $\psi \in \mathbb{X}_+$ and $h > 0$, we have the following

$$\psi + \mathbb{F}(\psi) = \begin{pmatrix} \psi_1 + h[\lambda(x) - (\beta_1(x)f_1(\psi_1(x),\psi_3(x)) + \beta_2(x)f_2(\psi_1(x),\psi_2(x)) + \beta_3(x)f_3(\psi_1(x),\psi_4(x)))] \\ \psi_2 + h[\beta_1(x)f_1(\psi_1(x),\psi_3(x)) + \beta_2(x)f_2(\psi_1(x),\psi_2(x)) + \beta_3(x)f_3(\psi_1(x),\psi_4(x))] \\ \psi_3 + h(N(x)\psi_2 + \alpha(x)\psi_4) \\ \psi_4 + h\mu(x)\psi_3 \end{pmatrix}$$
$$\ge \begin{pmatrix} [1 - h(\bar{\beta}_1\psi_3 + \bar{\beta}_2\psi_2 + \bar{\beta}_3\psi_4)]\psi_1 \\ \psi_2 \\ \psi_3 \\ \psi_4 \end{pmatrix}.$$

Such an inequality indicates that $\psi + h\mathbb{F}(\psi) \in \mathbb{X}_+$ provided that $h$ is sufficiently small. Therefore, we have the following

$$\lim_{h\to 0^+} \frac{1}{h} dist(\psi + h\mathbb{F}(\psi), \mathbb{X}_+) = 0.$$

Hence, the claim follows from [42]. This completes the proof.

Consequently, we can obtain the following results for the well-posedness of the solution and the existence of the global attractor of Model (2.1).

**Theorem 3.1.** *For each $\psi \in \mathbb{X}_+$, Model* (2.1) *with the inital Condition* (2.2) *admits a unique solution $u(t,x,\psi) \in \mathbb{X}_+$ on $[0,+\infty)$ with $u_0 = \psi$, and the solution semiflow $\Phi(t) = u(t,\cdot,\psi) : \mathbb{X}_+ \to \mathbb{X}_+$ has a global compact attractor.*

*Proof.* According to Lemma 3.1, suppose $\tau_\infty < +\infty$; then, Theorem 2 in [42] implies that $\|u(t,\cdot,\psi)\|_{\mathbb{X}} \to \infty$ as $t \to \infty$. Then, the first equation of Model (2.1) indicates that

$$\frac{\partial T}{\partial t} \le \nabla \cdot (d_1(x)\nabla T) + \bar{\lambda} - \underline{d}T, \quad 0 \le t < \tau_\infty, \quad x \in \Omega. \tag{3.1}$$

By applying the comparison principle together with Lemma 2 in [43], we obtain a constant $M_1 > 0$ such that $T(t, x) \le M_1$ for every $t \in [0, \tau_\infty)$, $x \in \bar{\Omega}$. Thus, we obtain the following:

$$\begin{cases} \dfrac{\partial I(t,x)}{\partial t} \le \nabla \cdot (d_2(x)\nabla I) + \bar{\beta}_1 f_{1V}(M_1, 0)V + \bar{\beta}_2 f_{2I}(M_1, 0)I + \bar{\beta}_3 f_{3W}(M_1, 0)W \\ \qquad\qquad - \underline{r} I, x \in \Omega, t > 0, \\ \dfrac{\partial V(t,x)}{\partial t} \le \nabla \cdot (d_3(x)\nabla V) + \bar{N} I - (\underline{c}_1 + \underline{\mu})V + \bar{\alpha} W, x \in \Omega, t > 0, \\ \dfrac{\partial W(t,x)}{\partial t} \le \nabla \cdot (d_4(x)\nabla W) + \bar{\mu} V - (\underline{c}_2 + \underline{\alpha})W, x \in \Omega, t > 0. \end{cases} \tag{3.2}$$

Consider the following system:

$$\begin{cases} \dfrac{\partial u_1(t,x)}{\partial t} = \nabla \cdot (d_2(x)\nabla u_1) + \bar{\beta}_1 f_{1V}(M_1, 0)u_2 + \bar{\beta}_2 f_{2I}(M_1, 0)u_1 \\ \qquad\qquad + \bar{\beta}_3 f_{3W}(M_1, 0)u_3 - \underline{r} u_1, x \in \Omega, t > 0, \\ \dfrac{\partial u_2(t,x)}{\partial t} = \nabla \cdot (d_3(x)\nabla u_2) + \bar{N} u_1 - (\underline{c}_1 + \underline{\mu})u_2 + \bar{\alpha} u_3, x \in \Omega, t > 0, \\ \dfrac{\partial u_3(t,x)}{\partial t} = \nabla \cdot (d_4(x)\nabla u_3) + \bar{\mu} u_2 - (\underline{c}_2 + \underline{\alpha})u_3, x \in \Omega, t > 0. \end{cases} \tag{3.3}$$

The standard Krein-Rutman theorem [44] indicates that Model (3.3) admits a principle eigenvalue $\lambda_0$ which corresponds to a strongly positive eigenfunction $\phi = (\phi_1, \phi_2, \phi_3)$; hence, Model (3.3) has a solution $\sigma e^{\lambda_0 t}\phi(x)$, $t \ge 0$, where $\sigma > 0$ is a constant that satisfies $(I(0, x), V(0, x), W(0, x)) \le (u_1(0, x), u_2(0, x), u_3(0, x)) = \sigma\phi$ for $x \in \bar{\Omega}$. Then, the comparison principle implies that

$$(I(t, x), V(t, x), W(t, x)) \le \sigma e^{\lambda_0 t}\phi(x), \quad t \in [0, \tau_\infty), \quad x \in \bar{\omega}.$$

This indicates that $I(t, x) \le M_2, V(t, x) \le M_2, W(t, x) \le M_2$, $t \in [0, \tau_\infty)$, and $x \in \bar{\Omega}$ for some constant $M_2 > 0$. This leads to a contradiction. Thereby, the global existence holds.

Next, we establish the point dissipativity of the solution semiflow. Denote $\pi_n$ as the eigenvalue of $\nabla \cdot (d_2(x)\nabla) - r(x)$, with the eigenfunction of $\phi_n(s)$ satisfying $\pi_1 > \pi_2 \ge \pi_3 \ge \cdots \ge \pi_n \ge \cdots$. It follows from [45] that $\Gamma_2(t, x, y) = \sum\limits_{n\ge1} e^{\pi_n t}\phi_n(x)\phi_n(y)$. Since $\phi_n(x)$ is uniformly bounded, then there exists a constant $\xi > 0$ such that $\Gamma_2(t, x, y) \le \xi \sum\limits_{n\ge1} e^{\pi_n t}$, for $t > 0$. Assume that $\tau_i$ is the eigenvalue of $\nabla \cdot (d_2(x)\nabla) - \underline{r}$ subjects to the Neumann boundary condition and satisfy $\tau_1 = -\underline{r} > \tau_2 \ge \tau_3 \ge \cdots \ge \tau_n \ge \cdots$. Then, it follows from [46] that $\tau_i \ge \pi_i$ $(i \in \mathbb{N}_+)$. Moreover, there exists a $\xi^* > 0$ such that

$$\Gamma_2(t, x, y) \le \xi \sum_{n\ge1} e^{\pi_n t} \le \xi^* e^{\pi_1 t} = \xi^* e^{-\underline{r}t}, \forall t > 0.$$

According to the comparison principle [43], then there exists a $t_0 > 0$ and $M_3 > 0$ such that $T(t, x) \le M_3$, $t \ge t_0, x \in \bar{\Omega}$. Now, let $G_1(t) = \int_\Omega (T(t, x) + I(t, x))dx$; then,

$$\frac{dG_1}{dt} \le \int_\Omega \lambda(x)dx - \min_{x\in\bar{\Omega}}\{d(x), r(x)\}G_1.$$

Thus, $T + I \le M_4$, $t \ge t_1$ for some $M_4 > 0$. Define $G_2(t) = \int_\Omega (V(t,x) + W(t,x))dx$; then,

$$\frac{dG_2}{dt} = \int_\Omega (N(x)I - c_1(x)V - c_2(x)W)dx \le M_4 \int_\Omega N(x)dx - \min_{x\in\bar{\Omega}}\{c_1(x), c_2(x)\}G_2.$$

Thus, there exists a $M_5 > 0$ such that $G_2 = V + W \le M_5$ for $t \ge t_2$.

Let $t_3 = \min\{t_0, t_1, t_2\}$ for any $t \ge t_3$; then, we get the following:

$$\begin{aligned}
I(t,x) &= \mathbb{T}_2(t)I(t_3,x) + \int_{t_3}^{t} \mathbb{T}_2(t-\tau)[\beta_1(x)f_1(T(\tau,x),V(\tau,x)) \\
&\quad + \beta_2(x)f_2(T(\tau,x),I(\tau,x)) + \beta_3(x)f_3(T(\tau,x),W(\tau,x))]d\tau \\
&\le Me^{\omega_2(t-t_3)}\|I(t_3,x)\| + \int_{t_3}^{t}\int_\Omega \Gamma_2(t-\tau,x,y)[\beta_1(y)f_1(T(\tau,y),V(\tau,y)) \\
&\quad + \beta_2(y)f_2(T(\tau,y),I(\tau,y)) + \beta_3(y)f_3(T(\tau,y),W(\tau,y))]dyd\tau \\
&\le Me^{\omega_2(t-t_3)}\|I(t_3,x)\| + \int_{t_3}^{t}\int_\Omega \xi^* e^{-\underline{r}(t-\tau)}[\bar{\beta}_1 f_{1V}(M_3,0)V(\tau,y) \\
&\quad + \bar{\beta}_2 f_{2I}(M_3,0)I(\tau,y) + \bar{\beta}_3 f_{3W}(M_3,0)W(\tau,y)]dyd\tau \\
&\le Me^{\omega_2(t-t_3)}\|I(t_3,x)\| + \xi^*[\bar{\beta}_1 f_{1V}(M_3,0)M_5 + \bar{\beta}_2 f_{2I}(M_3,0)M_4 \\
&\quad + \bar{\beta}_3 f_{3W}(M_3,0)M_5]\int_{t_3}^{t} e^{-\underline{r}(t-\tau)}d\tau \\
&\le Me^{\omega_2(t-t_3)}\|I(t_3,x)\| + \xi^*[\bar{\beta}_1 f_{1V}(M_3,0)M_5 + \bar{\beta}_2 f_{2I}(M_3,0)M_4 \\
&\quad + \bar{\beta}_3 f_{3W}(M_3,0)M_5]\frac{1-e^{\underline{r}(t-t_3)}}{\underline{r}} \\
&\le Me^{\omega_2(t-t_3)}\|I(t_3,x)\| + \frac{\xi^*}{\underline{r}}[\bar{\beta}_1 f_{1V}(M_3,0)M_5 + \bar{\beta}_2 f_{2I}(M_3,0)M_4 \\
&\quad + \bar{\beta}_3 f_{3W}(M_3,0)M_5].
\end{aligned}$$

Thus, $\limsup_{t\to\infty}\|I(t,x)\| \le \frac{\xi^*}{\underline{r}}[\bar{\beta}_1 f_{1V}(M_3,0)M_5 + \bar{\beta}_2 f_{2I}(M_3,0)M_4 + \bar{\beta}_3 f_{3W}(M_3,0)M_5]$. By the similarly arguments, we can obtain that $\limsup_{t\to\infty}\|V(t,x)\| \le M_6$, $\limsup_{t\to\infty}\|W(t,x)\| \le M_7$ for some constants $M_6 > 0$, $M_7 > 0$, which implies that the point dissipation of Model (2.1) holds. Consequently, according to [47], the solution semifolw $\Phi(t)$ is compact for $t > 0$. Thus, $\Phi(t)$ has a global compact attractor [48]. This completes the proof.

Next, we will define the critical threshold $\mathcal{R}_0$ of Model (2.1) and prove that it serves as a sharp threshold to determine whether the viral infection persists or dies out. According to [43], Model (2.1) has a unique infection-free steady state $E_0(x) = (T_0^*(x), 0, 0, 0)$, where $T_0^*(x)$ satisfies the following equation:

$$\frac{\partial z}{\partial t} = \nabla\cdot(d_1(x)\nabla z) + \lambda(x) - d(x)z. \tag{3.4}$$

Linearizing Model (2.1) at $E_0(x)$, we obtain the following equations:

$$\begin{cases} \dfrac{\partial I(t,x)}{\partial t} = \nabla\cdot(d_2(x)\nabla I) + \beta_1(x)f_{1V}(T_0^*,0)V + \beta_2(x)f_{2I}(T_0^*,0)I \\ \qquad\qquad + \beta_3(x)f_{3W}(T_0^*,0)W - r(x)I, x\in\Omega, t>0, \\ \dfrac{\partial V(t,x)}{\partial t} = \nabla\cdot(d_3(x)\nabla V) + N(x)I - (c_1(x)+\mu(x))V + \alpha(x)W, x\in\Omega, t>0, \\ \dfrac{\partial W(t,x)}{\partial t} = \nabla\cdot(d_4(x)\nabla W) + \mu(x)V - (c_2(x)+\alpha(x))W, x\in\Omega, t>0, \\ \dfrac{\partial I(t,x)}{\partial \nu} = \dfrac{\partial V(t,x)}{\partial \nu} = \dfrac{\partial W(t,x)}{\partial \nu}, t>0, x\in\partial\Omega. \end{cases} \tag{3.5}$$

Let $(I(t,x), V(t,x), W(t,x))^{\mathrm{T}} = e^{\lambda_0 t}(\phi_2,\phi_3,\phi_4)^{\mathrm{T}}$; then, it follows from Model (3.5) that

$$\begin{cases} \lambda_0\phi_2 = \nabla\cdot(d_2(x)\nabla\phi_2) + \beta_1(x)f_{1V}(T_0^*,0)\phi_3 + \beta_2(x)f_{2I}(T_0^*,0)\phi_2 \\ \qquad\qquad + \beta_3(x)f_{3W}(T_0^*,0)\phi_4 - r(x)\phi_2, x\in\Omega, t>0, \\ \lambda_0\phi_3 = \nabla\cdot(d_3(x)\nabla\phi_3) + N(x)\phi_2 - (c_1(x)+\mu(x))\phi_3 + \alpha(x)\phi_4, x\in\Omega, t>0, \\ \lambda_0\phi_4 = \nabla\cdot(d_4(x)\nabla\phi_4) + \mu(x)\phi_3 - (c_2(x)+\alpha(x))\phi_4, x\in\Omega, t>0, \\ \dfrac{\partial\phi_2(t,x)}{\partial \nu} = \dfrac{\partial\phi_3(t,x)}{\partial \nu} = \dfrac{\partial\phi_4(t,x)}{\partial \nu}, t>0, x\in\partial\Omega. \end{cases} \tag{3.6}$$

It follows from [41] that eigenvalue problem (3.6) admits a principal eigenvalue $\lambda_0(T_0^*(x))$ that corresponds to a strictly positive eigenfunction. Applying the method proposed by Wang and Zhao [49], we will define $R_0$ for Model (2.1). We only consider the following infected compartments: $I$, $V$, and $W$. Denote $v = (I,V,W)^{\mathrm{T}} =: (v_2,v_3,v_4)^{\mathrm{T}}$; then, we have

$$\frac{\partial v}{\partial t} = \Delta\cdot(D(x)\Delta v) + \mathcal{F}(x,v) - \mathcal{V}(x,v),$$

where $D(x) = diag\{d_2(x), d_3(x), d_4(x)\}$ and

$$\mathcal{F}(x,v) = \begin{pmatrix} \mathcal{F}_2(x,v) \\ \mathcal{F}_3(x,v) \\ \mathcal{F}_4(x,v) \end{pmatrix}, \mathcal{V}(x,v) = \begin{pmatrix} r(x)I \\ -N(x)I + (c_1(x)+\mu(x))V - \alpha(x)W \\ -\mu(x)V + (c_2(x)+\alpha(x)) \end{pmatrix},$$

with $\mathcal{F}_2(x,v) = \beta_2(x)f_2(T,I) + \beta_1(x)f_1(T,V) + \beta_3(x)f_3(T,W)$, $\mathcal{F}_3(x,v) = \mathcal{F}_4(x,v) = 0$. Then, we can define the newly infection matrix

$$F(x) = \begin{pmatrix} \beta_2(x)f_{2I}(T_0^*(x),0) & \beta_1(x)f_{1V}(T_0^*(x),0) & \beta_3(x)f_{3W}(T_0^*(x),0) \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix},$$

where the entry $F_{ij}(x) = \dfrac{\partial\mathcal{F}_i}{\partial v_j}(E_0(x))(i,j=2,3,4)$.

Let $\Phi(t) : C(\bar{\Omega}, \mathbb{R}^3) \to C(\bar{\Omega}, \mathbb{R}^3)$ be the $C_0$-semigroup generated by the following system:

$$\begin{cases} \dfrac{\partial v_2(t,x)}{\partial t} = \nabla \cdot (d_2(x)\nabla v_2) - r(x)v_2, x \in \Omega, t > 0, \\ \dfrac{\partial v_3(t,x)}{\partial t} = \nabla \cdot (d_3(x)\nabla v_3) + N(x)v_2 - (c_1(x) + \mu(x))v_3 + \alpha(x)v_4, x \in \Omega, t > 0, \\ \dfrac{\partial v_4(t,x)}{\partial t} = \nabla \cdot (d_4(x)\nabla v_4) + \mu(x)v_3 - (c_2(x) + \alpha(x))v_4, x \in \Omega, t > 0, \\ \dfrac{\partial v_2(t,x)}{\partial \nu} = \dfrac{\partial v_3(t,x)}{\partial \nu} = \dfrac{\partial v_4(t,x)}{\partial \nu}, t > 0, x \in \partial\Omega. \end{cases}$$

Assume that the distribution of the initial infection is $\psi = (\psi_2, \psi_3, \psi_4)$; then, $\Phi(t)\psi$ represents the distribution of those infective numbers as time evolves. Thus, the distribution of the total new infective number is as follows:

$$\mathcal{L}(\psi)(x) = \int_0^\infty F(x)\Phi(t)\psi dt.$$

Then, the basic reproduction number can be defined as follows:

$$\mathcal{R}_0 = \rho(\mathcal{L}),$$

where $\rho(L)$ is the spectral radius. Consequently, the following result holds followed by [49].

**Lemma 3.2.** *$\mathcal{R}_0 - 1$ has the same sign as $\lambda_0(T_0^*(x))$, and the infection-free steady state $E_0(x)$ is asymptotically stable for $\mathcal{R}_0 < 1$.*

*Proof.* According to the idea of [49], we define the following transition matrix:

$$V(x) = \begin{pmatrix} r(x) & 0 & 0 \\ -N(x) & c_1(x) + \mu(x) & -\alpha(x) \\ 0 & -\mu(x) & c_2(x) + \alpha(x) \end{pmatrix};$$

then, System (3.5) can be written as follows:

$$\frac{\partial v}{\partial t} = \nabla \cdot (D(x)\nabla v) + F(x)v - V(x)v. \tag{3.7}$$

Let $B = \nabla \cdot (D(x)\nabla) - V(x)$, $A = B + F(x)$, and $s(A)$ be the spectral bound of $A$. It follows from Theorem 3.1 in [49] that $R_0 - 1$ and $s(A)$ have the same sign. In view of (3.7), $A$ generates a positive $C_0$-semigroup; thus, $A$ is resolvent positive and compact. In addition, from the eigenvalue problem (3.6), we have that $\lambda_0(T_0^*(x))$ is the principal eigenvalue of $A$; therefore, $s(A) = \lambda_0(T_0^*(x))$. Consequently, $R_0 - 1$ has the same sign as $\lambda_0(T_0^*(x))$. This complete the first part of Lemma 3.2.

Next, we show that $E_0(x)$ is asymptotically stable. Denote $v_1 = T$; then, linearizing Model (2.1) at $E_0(x)$ yields that

$$\begin{cases} \dfrac{\partial v}{\partial t} = \nabla \cdot (D(x)\nabla v) + (F(x) - V(x))v, \\ \dfrac{\partial v_1}{\partial t} = \nabla \cdot (d_1(x)\nabla v_1) - J(x)v + M_0(x)v_1, \end{cases} \tag{3.8}$$

where $J(x) = (-\beta_2(x)f_{2I}(T_0^*(x),0), -\beta_1(x)f_{1V}(T_0^*(x),0), -\beta_3(x)f_{3W}(T_0^*(x),0))$ and $M_0(x) = -(d(x) + \beta_2(x)f_{2T}(T_0^*(x),0) + \beta_1(x)f_{1T}(T_0^*(x),0) + \beta_3(x)f_{3T}(T_0^*(x),0))$.

Denote the solution semigroup of (3.7) as $Q(t)$, and let $\omega(Q(t))$ be the exponential growth bound of $Q(t)$. Then $B + F$, is the generator of $Q(t)$. In the case where $R_0 < 1$, we have $s(B + F) < 0$. Thus, Theorem 3.14 [50] implies that $\omega(Q) = s(B + F) < 0$. Denote $\Psi(t)$ as the solution semigroup of System (3.8), and $\omega(\Psi)$ is the exponential growth bound of $\Psi(t)$. Because the first equation of (3.8) is independent to the second one, it follows from [49] that $\omega(\Psi) < 0$. Thus, $E_0(x)$ is locally asymptotic stable [51].

## 4. Stability and persistence

In this section, we will establish the global stability of an infection-free steady state and the persistence of Model (2.1). According to the above argument, we first show that the infection-free steady state is globally stable.

**Theorem 4.1.** *If $\mathcal{R}_0 < 1$, then the infection-free steady state $E_0(x)$ is globally asymptotically stable.*

*Proof.* According to Lemma 3.2, there exists a $\varepsilon > 0$ such that $\lambda_0^\varepsilon(T_0^*) = \lambda_0(T_0^* + \varepsilon) < 0$, where $\lambda_0^\varepsilon(T_0^*)$ is the principal eigenvalue of system

$$\begin{cases} \lambda_0^\varepsilon(T_0^*)\phi_2 = \nabla\cdot(d_2(x)\nabla\phi_2) + \beta_1(x)f_{1V}(T_0^*+\varepsilon,0)\phi_3 + \beta_2(x)f_{2I}(T_0^*+\varepsilon,0)\phi_2 \\ \qquad\qquad + \beta_3(x)f_{3W}(T_0^*+\varepsilon,0)\phi_4 - r(x)\phi_2, x\in\Omega, t>0, \\ \lambda_0^\varepsilon(T_0^*)\phi_3 = \nabla\cdot(d_3(x)\nabla\phi_3) + N(x)\phi_2 - (c_1(x)+\mu(x))\phi_3 + \alpha(x)\phi_4, x\in\Omega, t>0, \\ \lambda_0^\varepsilon(T_0^*)\phi_4 = \nabla\cdot(d_4(x)\nabla\phi_4) + \mu(x)\phi_3 - (c_2(x)+\alpha(x))\phi_4, x\in\Omega, t>0, \\ \dfrac{\partial\phi_2(t,x)}{\partial\nu} = \dfrac{\partial\phi_3(t,x)}{\partial\nu} = \dfrac{\partial\phi_4(t,x)}{\partial\nu}, t>0, x\in\partial\Omega. \end{cases}$$

From the first equation of Model (2.1), we obtain that

$$\frac{\partial T}{\partial t} \le \nabla\cdot(d_1(x)\nabla T) + \lambda(x) - d(x)T;$$

then, the comparison principle indicates that there exists a $t^* > 0$ such that $T(t,x) \le T_0^*(x) + \varepsilon$ for all $t > t^*$ and $x \in \Omega$. Thus, it follows that

$$\begin{cases} \dfrac{\partial I(t,x)}{\partial t} \le \nabla\cdot(d_2(x)\nabla I) + \beta_1(x)f_{1V}(T_0^*+\varepsilon,0)V + \beta_2(x)f_{2I}(T_0^*+\varepsilon,0)I \\ \qquad\qquad + \beta_3(x)f_{3W}(T_0^*+\varepsilon,0)W - r(x)I, x\in\Omega, t\ge t^*, \\ \dfrac{\partial V(t,x)}{\partial t} \le \nabla\cdot(d_3(x)\nabla V) + N(x)I - (c_1(x)+\mu(x))V + \alpha(x)W, x\in\Omega, t\ge t^*, \\ \dfrac{\partial W(t,x)}{\partial t} \le \nabla\cdot(d_4(x)\nabla W) + \mu(x)V - (c_2(x)+\alpha(x))W, x\in\Omega, t\ge t^*, \\ \dfrac{\partial I(t,x)}{\partial\nu} = \dfrac{\partial V(t,x)}{\partial\nu} = \dfrac{\partial W(t,x)}{\partial\nu}, t\ge t^*, x\in\partial\Omega. \end{cases}$$

Let $\phi^\varepsilon(x) = (\phi_I^\varepsilon(x), \phi_V^\varepsilon(x), \phi_W^\varepsilon(x))$ be the eigenfunction that corresponds to $\lambda_0^\varepsilon(T_0^*) < 0$. Assume that $(I(t^*,x), V(t^*,x), W(t^*,x)) \le \xi_*(\phi_I^\varepsilon(x), \phi_V^\varepsilon(x), \phi_W^\varepsilon(x))$ for some $\xi_* > 0$. The comparison principle

implies that

$$(I(t,x),V(t,x),W(t,x)) \le \xi_*(\phi_I^\varepsilon(x),\phi_V^\varepsilon(x),\phi_W^\varepsilon(x))e^{\lambda_0^\varepsilon(T_0^*)(t-t_*)}, \forall t \ge t^*.$$

Consequently, we have $\lim_{t\to\infty}(I(t,x),V(t,x),W(t,x)) = (0,0,0)$. Thereby, the equation of $T(t,x)$ is asymptotic to (3.4). According to Lemma 2.2 in [43] and Corollary 4.3 in [52], that $\lim_{t\to\infty} T(t,x) = T_0^*(x)$. Hence, the global asymptotic stability of $E_0(x)$ holds. This completes the proof.

**Lemma 4.1.** *Suppose $u(t,x,\phi)$ is the solution with $u_0 = \phi \in \mathbb{X}_+$. If there exists some $t_0 > 0$ such that $I(t_0,\cdot,\phi) \not\equiv 0$, $V(t_0,\cdot,\phi) \not\equiv 0$, and $W(t_0,\cdot,\phi) \not\equiv 0$, then $I(t,x,\phi) > 0$, $V(t,x,\phi) > 0$, and $W(t,x,\phi) > 0$ for $t > t_0$. Furthermore, for any $\phi \in \mathbb{X}_+$, there exists some $\eta_* > 0$ such that $\lim_{t\to\infty} T(t,x,\phi) \ge \eta_*$.*

*Proof.* The idea of the proof is similar to that of [43, 53]. According to Lemma 3.1 and Model (2.1),

$$\begin{cases} \nabla\cdot(d_2(x)\nabla I) - \dfrac{\partial I}{\partial t} - r(x)I \le 0, \quad t > 0, x \in \Omega, \\ \dfrac{\partial I}{\partial \nu} = 0, \quad t > 0, x \in \partial\Omega, \end{cases}$$

and

$$\begin{cases} \nabla\cdot(d_3(x)\nabla V) - \dfrac{\partial V}{\partial t} - (c_1(x)+\mu(x))V \le 0, \quad t > 0, x \in \Omega, \\ \dfrac{\partial V}{\partial \nu} = 0, \quad t > 0, x \in \partial\Omega, \end{cases}$$

and

$$\begin{cases} \nabla\cdot(d_4(x)\nabla I) - \dfrac{\partial W}{\partial t} - (c_2(x)+\alpha(x))W \le 0, \quad t > 0, x \in \Omega, \\ \dfrac{\partial W}{\partial \nu} = 0, \quad t > 0, x \in \partial\Omega. \end{cases}$$

Thus, the strong maximum principle and Hopf boundary lemma in [54] indicates that $I(t,x,\phi) > 0$, $V(t,x,\phi) > 0$, and $W(t,x,\phi) > 0$. Moreover, the proof of Theorem 3.1 implies that there exists a $M_8 > 0$ and $t_4 > 0$ such that $I(t,x)$, $V(t,x)$, and $W(t,x) \le M_8$ for $t \ge t_4$. From Model (2.1), we have the following:

$$\begin{cases} \dfrac{\partial T}{\partial t} \ge \nabla\cdot(d_1(x)\nabla T) + \lambda(x) - (d(x) + (\beta_1(x)+\beta_2(x)+\beta_3(x))M_8)T, t \ge t_4, x \in \Omega, \\ \dfrac{\partial T}{\partial \nu} = 0, t \ge t_4, x \in \partial\Omega. \end{cases}$$

Then, Lemma 2 in [43] implies that the system

$$\begin{cases} \dfrac{\partial z}{\partial t} = \nabla\cdot(d_1(x)\nabla z) + \lambda(x) - (d(x) + (\beta_1(x)+\beta_2(x)+\beta_3(x))M_8)z, t \ge t_4, x \in \Omega, \\ \dfrac{\partial z}{\partial \nu} = 0, t \ge t_4, x \in \partial\Omega, \end{cases}$$

admits a unique positive steady state $z_*(x)$ and it is globally asymptotically stable. Thus, according to the standard parabolic comparison that, $\lim_{t\infty} T(t,x,\phi) \ge z_*(x)$. This completes the proof.

**Theorem 4.2.** *For any initial value $\phi \in \mathbb{X}$, assume $u(t,x,\phi) = (T(t,x), I(t,x), V(t,x), W(t,x))$ is a solution of Model* (2.1) *on* $[0,+\infty)$. *If $\mathcal{R}_0 > 1$, then there exists a constant $\rho > 0$ such that*

$$\liminf_{t\to\infty}(T(t,x), I(t,x), V(t,x), W(t,x)) \geq (\rho,\rho,\rho,\rho),$$

*for any $\phi \in \mathbb{X}_+$ with $\phi_2 \not\equiv 0$, $\phi_3 \not\equiv 0$, and $\phi_4 \not\equiv 0$. Moreover, there eixsts at least one positive steady state for Model* (2.1).

*Proof.* Let $\mathcal{X}_0 = \{(\phi_1,\phi_2,\phi_3,\phi_4) \in \mathbb{X}_+ : \phi_2 \not\equiv 0, \phi_3 \not\equiv 0, \phi_4 \not\equiv 0\}$. Obviously, $\partial\mathcal{X}_0 = \{\phi_2(\cdot) \equiv 0$ or $\phi_3(\cdot) \equiv 0$ or $\phi_4(\cdot) \equiv 0\}$. For any $\phi \in \mathcal{X}_0$, it follows from Lemma 4.1 that $I(t,x,\phi) > 0$, $V(t,x,\phi) > 0$,a and $W(t,x,\phi) > 0$, that is, $\Phi(t)\mathcal{X}_0 \subseteq \mathcal{X}_0$. Moreover, denote $M_\partial = \{\phi \in \partial\mathcal{X}_0 : \Phi(t)\phi \in \partial\mathcal{X}_0, \forall t \geq 0\}$, and $\omega(\phi)$ is the omega limit set of orbit $\gamma^+(\phi) := \{\Phi(t)\phi : \forall t \geq 0\}$.

Claim 1. $\omega(\phi) = \{(T_0^*(x), 0, 0, 0)\}$, $\forall \phi \in M_\partial$.

Since, $\phi \in M_\partial$, then we have $\Phi(t)\phi \in \partial\mathcal{X}_0$. Hence, $I(t,x,\phi) \equiv 0$ or $V(t,x,\phi) \equiv 0$ or $W(t,x,\phi) \equiv 0$. If $W(t,x,\phi) \equiv 0$, then the last equation of Model (2.1) indicates that $V(t,x,\phi) \equiv 0$. Moreover, the third equation of Model (2.1) implies that $I(t,x,\phi) \equiv 0$. Consequently, $T(t,x,\phi)$ is asymptotic to Eq (3.4). Thus, $\lim_{t\to\infty} T(t,x,\phi) = T_0^*(x)$ uniformly for $x \in \bar{\Omega}$. If $W(t,x,\phi) \not\equiv 0$ for some $\hat{t} > 0$ and $x \in \bar{\Omega}$, then by Lemma 4.1, we have $W(t,x,\phi) > 0$ for $t \geq \hat{t}$ and $x \in \bar{\Omega}$. Thus, $I(t,x,\phi) \equiv 0$ or $V(t,x,\phi) \equiv 0$. For the case when $V(t,x,\phi) \equiv 0$, it follows from the last two equations of Model (2.1) that $W(t,x,\phi) \equiv 0$ and $I(t,x,\phi) \equiv 0$. Furthermore, we have that $T(t,x,\phi)$ is asymptotic to Eq (3.4), which also yields that $\lim_{t\to\infty} T(t,x,\phi) = T_0^*(x)$ uniformly for $x \in \bar{\Omega}$. If $V(t,x,\phi) \not\equiv 0$ for some $\check{t} > 0$, then $V(t,x,\phi) > 0$ for $t \geq \check{t}$; thus, $I(t,x,\phi) \equiv 0$. However, Model (2.1) indicates that $V(t,x,\phi) \equiv W(t,x,\phi) \equiv 0$. Consequently, Model (2.1) implies that $T(t,x,\phi)$ is asymptotic to Eq (3.4); additionally, it holds that $\lim_{t\to\infty} T(t,x,\phi) = T_0^*(x)$ uniformly for $x \in \bar{\Omega}$. Thus, $\omega(\phi) = \{(T_0^*(x), 0, 0, 0)\}$, $\forall \phi \in M_\partial$. Thus, the claim holds.

It follows from $\mathcal{R}_0 > 1$ and Lemma 3.2 that $\lambda_0 > 0$. By continuity, there exists a sufficient small $\epsilon > 0$ such that $\lambda_0^\epsilon = \lambda_0(T_0^*(x) - \epsilon) > 0$, where $\lambda_0^\epsilon$ is the principal eigenvalue of the following equations:

$$\begin{cases} \lambda_0^\epsilon\phi_2 = \nabla\cdot(d_2(x)\nabla\phi_2) + \beta_1(x)f_{1V}(T_0^* - \epsilon, 0)\phi_3 + \beta_2(x)f_{2I}(T_0^* - \epsilon, 0)\phi_2 \\ \qquad\qquad + \beta_3(x)f_{3W}(T_0^* - \epsilon, 0)\phi_4 - r(x)\phi_2, x \in \Omega, t > 0, \\ \lambda_0^\epsilon\phi_3 = \nabla\cdot(d_3(x)\nabla\phi_3) + N(x)\phi_2 - (c_1(x) + \mu(x))\phi_3 + \alpha(x)\phi_4, x \in \Omega, t > 0, \\ \lambda_0^\epsilon\phi_4 = \nabla\cdot(d_4(x)\nabla\phi_4) + \mu(x)\phi_3 - (c_2(x) + \alpha(x))\phi_4, x \in \Omega, t > 0, \\ \dfrac{\partial\phi_2(t,x)}{\partial\nu} = \dfrac{\partial\phi_3(t,x)}{\partial\nu} = \dfrac{\partial\phi_4(t,x)}{\partial\nu}, t > 0, x \in \partial\Omega. \end{cases}$$

Claim 2. $\{(T_0^*(x), 0, 0, 0)\}$ is a uniformly weak repeller in the sense that $\limsup_{t\to\infty} \|\Phi(t)\phi - (T_0^*(x), 0, 0, 0)\| \geq \epsilon$, $\forall \psi \in \mathcal{X}_0$.

Suppose the claim is not true (i.e., there exists a $\tilde{\phi} \in \mathcal{X}_0$ such that $\limsup_{t\to\infty} \|\Phi(t)\phi - (T_0^*(x), 0, 0, 0)\| < \epsilon$). Thus, there exists a $t^{**} > 0$ such that for $t \geq t^{**}$, $T(t,x,\tilde{\phi}) > T_0^*(x) - \epsilon$, $0 < I(t,x,\tilde{\phi}) < \epsilon$,

$0 < V(t, x, \tilde{\phi}) < \epsilon$, and $0 < W(t, x, \tilde{\phi}) < \epsilon$. From Model (2.1), we have the following:

$$\begin{cases} \dfrac{\partial I(t,x)}{\partial t} \geq \nabla \cdot (d_2(x)\nabla I) + \beta_1(x) f_{1V}(T_0^* - \epsilon, \epsilon)V + \beta_2(x) f_{2I}(T_0^* - \epsilon, \epsilon)I \\ \qquad\qquad + \beta_3(x) f_{3W}(T_0^* - \epsilon, \epsilon)W - r(x)I, x \in \Omega, t \geq t^{**}, \\ \dfrac{\partial V(t,x)}{\partial t} \geq \nabla \cdot (d_3(x)\nabla V) + N(x)I - (c_1(x) + \mu(x))V + \alpha(x)W, x \in \Omega, t \geq t^{**}, \\ \dfrac{\partial W(t,x)}{\partial t} \geq \nabla \cdot (d_4(x)\nabla W) + \mu(x)V - (c_2(x) + \alpha(x))W, x \in \Omega, t \geq t^{**}, \\ \dfrac{\partial I(t,x)}{\partial \nu} = \dfrac{\partial V(t,x)}{\partial \nu} = \dfrac{\partial W(t,x)}{\partial \nu}, t \geq t^{**}, x \in \partial\Omega. \end{cases}$$

Let $(\hat{\phi}_2, \hat{\phi}_3, \hat{\phi}_4)$ be the eigenfunction associated with the principal eigenvalue $\lambda_0^{\xi} > 0$. Suppose $(I(t^{**}, x, \tilde{\phi}),\ V(t^{**}, x, \tilde{\phi}), W(t^{**}, x, \tilde{\phi})) \geq \zeta^*(\hat{\phi}_2, \hat{\phi}_3, \hat{\phi}_4)$ for some $\zeta^* > 0$. Then, by the comparison principle, we have

$$(I(t, x, \tilde{\phi}), V(t, x, \tilde{\phi}), W(t, x, \tilde{\phi})) \geq \zeta^*(\hat{\phi}_2, \hat{\phi}_3, \hat{\phi}_4)e^{\lambda_0^{\xi}(t-t^{**})}, \forall t \geq t^{**},$$

which implies that $\lim_{t\to\infty} I(t, x) = \infty$, $\lim_{t\to\infty} V(t, x) = \infty$, and $\lim_{t\to\infty} W(t, x) = \infty$. This becomes a contradiction.

Define a function $p : \mathbb{X}_+ \to [0, \infty)$ by the following:

$$p(\phi) = \min\{\min_{x\in\bar{\Omega}} \phi_2(0, x), \min_{x\in\bar{\Omega}} \phi_3(0, x), \min_{x\in\bar{\Omega}} \phi_4(0, x)\}, \phi \in \mathbb{X}_+.$$

Then, we have $p^{-1}(0, +\infty) \subseteq \mathcal{X}_0$, and it holds that if either $p(\phi) > 0$ or $p(\phi) = 0$ and $\phi \in \mathcal{X}_0$, then $p(\Phi(t)\phi) > 0$. This indicates that $p$ is a generalized distance function for $\Phi(t) : \mathbb{X}_+ \to \mathbb{X}_+$ [55]. Moreover, according to the above discussion that any forward orbit of $\Phi(t)$ in $\mathcal{M}_\partial$ converges to $\{(T_0^*(x), 0, 0, 0)\}$, then $\{(T_0^*(x), 0, 0, 0)\}$ is isolated in $\mathbb{X}_+$ and $W^s(T_0^*(x), 0, 0, 0) \cap \mathcal{X}_0 = \emptyset$, where $W^s(T_0^*(x), 0, 0, 0)$ is the stable set of $\{(T_0^*(x), 0, 0, 0)\}$. Thus, there is no cycle in $\mathcal{M}_\partial$ from $\{(T_0^*(x), 0, 0, 0)\}$ to $\{(T_0^*(x), 0, 0, 0)\}$. Recall that Theorem 3.1 indicates that the semiflow $\Phi(t) : \mathbb{X}_+ \to \mathbb{X}_+$ has a global compact attractor in $\mathbb{X}_+$; then, according to [55], there exists a $\delta > 0$ such that $\min\{p(\phi) : \phi \in \omega(\phi)\} > \delta$ for any $\phi \in \mathcal{X}_0$, which indicates that $\liminf_{t\to\infty} I(t, x, \phi) \geq \delta$, $\liminf_{t\to\infty} V(t, x, \phi) \geq \delta$, $\liminf_{t\to\infty} W(t, x, \phi) \geq \delta$, Then by Lemma 4.1, we have $\liminf_{t\to\infty} T(t, x, \phi) \geq \rho$, $\liminf_{t\to\infty} I(t, x, \phi) \geq \rho$, $\liminf_{t\to\infty} V(t, x, \phi) \geq \rho$, and $\liminf_{t\to\infty} W(t, x, \phi) \geq \rho$, where $\rho = \min\{\eta_*, \delta\}$.

Moreover, Lemma 4.1 and [56] imply that $\Phi(t)$ has at least one steady state in $\mathcal{X}_0$, and it is a positive steady state of Model (2.1). Assume $(\phi_1, \phi_2, \phi_3, \phi_4)$ is a steady state in $\mathcal{X}_0$; then, $\phi_2 \not\equiv 0$, $\phi_3 \not\equiv 0$, and $\phi_4 \not\equiv 0$. Thus, $\phi_2 > 0$, $\phi_3 > 0$ and $\phi_4 > 0$. Moreover, the maximum principle and Hopf boundary lemma in [54] indicates that $\phi_1 > 0$ or $\phi_1 \equiv 0$. Suppose $\phi_1 \equiv 0$; then, the second equation of Model (2.1) and the maximum principle and Hopf boundary lemma in [54] imply that $\phi_2 \equiv 0$, which is a contradiction. Thus, the steady state $(\phi_1, \phi_2, \phi_3, \phi_4)$ is positive.

Next, according to the idea in [57, 58], we show the global stability of $E_0(x)$ in the critical case of $\mathcal{R}_0 = 1$ for a certain condition.

**Theorem 4.3.** *Assume $\mathcal{R}_0 = 1$, $d_1(x) = d_1$ is a constant function and $f_{1V}(T, 0)$, $f_{2I}(T, 0)$, and $f_{3W}(T, 0)$ are Lipschitz continuous; then, the infection-free steady state $E_0(x)$ is globally asymptotically stable.*

*Proof.* First, we show the local stability of $(T_0^*(x), 0, 0, 0)$. Assume $\hat{\varepsilon} > 0$ and set $u_0 = (T_0, I_0, V_0, W_0)$ with $\|u_0 - (T_0^*(x), 0, 0, 0)\| \leq \sigma$ for a small $\sigma > 0$. Let

$$U(t,x) = \frac{T(t,x)}{T_0^*(x)} - 1 \text{ and } \chi(t) = \max_{x\bar{\Omega}}\{U(t,x), 0\}.$$

Recall that $d_1\Delta T_0^*(x) + \lambda(x) - d(x)T_0^*(x) = 0$; then, we have

$$U_t - d_1\Delta U - 2d\frac{\nabla T_0^*(x)\nabla U}{T_0^*(x)} + \frac{\lambda(x)}{T_0^*(x)}U = -\frac{h(t,x)}{T_0^*(x)},$$

where

$$h(t,x) = \beta_1(x)f_1(T(t,x), V(t,x)) + \beta_2(x)f_2(T(t,x), I(t,x)) + \beta_3(x)f_3(T(t,x), W(t,x)).$$

Assume $\tilde{\Gamma}_1(t)$ is the positive semigroup associate to the operator $d_1\Delta + 2d_1\frac{\nabla T_0^*(x)\nabla}{T_0^*(x)} - \frac{\lambda(x)}{T_0^*(x)}$. Then, it follows from [59] that $\|\tilde{\Gamma}_1\| \leq L_1e^{-qt}$ for some $L_1 > 0, q > 0$. Thereby, we can rewrite $U(t,x)$ as follows:

$$U(t,x) = \tilde{\Gamma}_1(t)U(0,x) - \int_0^t \tilde{\Gamma}_1(t-s)\frac{h(s,x)}{S_0^*(x)}ds, \tag{4.1}$$

where $U(0,x) = \frac{T(0,x)}{T_0^*(x)} - 1$.

Then, we have the following:

$$\chi(t) \leq \max_{x\in\bar{\Omega}}\{\tilde{\Gamma}_1(t)U(0,x), 0\} \leq \|\tilde{\Gamma}_1(t)U(0,x)\| \leq \frac{\sigma L_1e^{-qt}}{T_{min}},$$

where $T_{min} = \min_{x\in\bar{\Omega}}\{T_0^*(x)\}$. Moreover, assume $\tilde{\Gamma}_2(t)$ is the semigroup of the following system:

$$\begin{cases} \dfrac{\partial I(t,x)}{\partial t} = \nabla\cdot(d_2(x)\nabla I) + \beta_1(x)f_{1V}(T_0^*, 0)V + \beta_2(x)f_{2I}(T_0^*, 0)I \\ \qquad\qquad + \beta_3(x)f_{3W}(T_0^*, 0)W - r(x)I, x \in \Omega, t > 0, \\ \dfrac{\partial V(t,x)}{\partial t} = \nabla\cdot(d_3(x)\nabla V) + N(x)I - (c_1(x) + \mu(x))V + \alpha(x)W, x \in \Omega, t > 0, \\ \dfrac{\partial W(t,x)}{\partial t} = \nabla\cdot(d_4(x)\nabla W) + \mu(x)V - (c_2(x) + \alpha(x))W, x \in \Omega, t > 0, \\ \dfrac{\partial I(t,x)}{\partial \nu} = \dfrac{\partial V(t,x)}{\partial \nu} = \dfrac{\partial W(t,x)}{\partial \nu}, t > 0, x \in \partial\Omega. \end{cases} \tag{4.2}$$

Let

$$\begin{aligned}\Theta(t,x) = {} & \beta_1(x)f(T(t,x), V(t,x)) - \beta_1(x)f_{1V}(T_0^*(x), 0)V(t,x) \\ & + \beta_2(x)f(T(t,x), I(t,x)) - \beta_2(x)f_{2I}(T_0^*(x), 0)I(t,x) \\ & + \beta_3(x)f(T(t,x), W(t,x)) - \beta_3(x)f_{3W}(T_0^*(x), 0)W(t,x).\end{aligned}$$

Then, we have the following:

$$\begin{aligned}\Theta(t,x) \le & \beta_1(x)(f_{1V}(T(t,x),0) - f_{1V}(T_0^*(x),0))V(t,x)\\ & + \beta_2(x)(f_{2I}(T(t,x),0) - f_{2I}(T_0^*(x),0))I(t,x)\\ & + \beta_3(x)(f_{3W}(T(t,x),0) - f_{3W}(T_0^*(x),0))W(t,x)\\ \le & \beta_1(x)Q_1|T(t,x) - T_0^*(x)|V(t,x) + \beta_2(x)Q_2|T(t,x) - T_0^*(x)|I(t,x)\\ & + \beta_3(x)Q_3|T(t,x) - T_0^*(x)|W(t,x)\\ \le & \beta Q|T(t,x) - T_0^*(x)|(V(t,x) + I(t,x) + W(t,x)) \triangleq \tilde{\Theta}(t,x),\end{aligned}$$

where $Q_i (i = 1, 2, 3)$ are the Lipschitz constants for $f_{1V}$, $f_{3I}$, and $f_{3W}$, respectively, $\beta = \max_{x\in\bar{\Omega}}\{\beta_1(x), \beta_2(x), \beta_3(x)\}$, and $Q = \max\{Q_1, Q_2, Q_3\}$.

By [60], it holds that $\|\tilde{\Gamma}_2\| \le \tilde{L}_1$ for $t \ge 0$ and some constant $\tilde{L}_1 > 0$; then, we have the following:

$$\begin{aligned}\begin{pmatrix} I(t,x)\\ V(t,x)\\ W(t,x)\end{pmatrix} &= \tilde{\Gamma}_2(t)\begin{pmatrix} I(0,x)\\ V(0,x)\\ W(0,x)\end{pmatrix} + \int_0^t \tilde{\Gamma}_2(t-s)\begin{pmatrix}\Theta(s,x)\\ 0\\ 0\end{pmatrix}ds\\ &\le \tilde{\Gamma}_2(t)\begin{pmatrix} I_1(0,x)\\ I_2(0,x)\\ R(0,x)\end{pmatrix} + \int_0^t \tilde{\Gamma}_2(t-s)\begin{pmatrix}\tilde{\Theta}(s,x)\\ 0\\ 0\end{pmatrix}ds.\end{aligned}$$

Thus, we obtain the following:

$$\begin{aligned}&\max\{\|I(t,x)\|, \|V(t,x)\|, \|W(t,x)\|\}\\ &\le \tilde{L}_1\sigma + \tilde{L}_1\beta Q\|T_0^*(x)\|\frac{L_1\sigma}{T_{min}}\int_0^t e^{-qs}(\|I(s,x)\| + \|V(s,x)\| + \|W(s,x)\|)ds\\ &= \tilde{L}_1\sigma + \tilde{L}_2\sigma\int_0^t e^{-qs}(\|I(s,x)\| + \|V(s,x)\| + \|W(s,x)\|)ds,\end{aligned}$$

where $\tilde{L}_2 = \frac{\tilde{L}_1 L_1\beta Q\|T_0^*(x)\|}{T_{min}}$. Consequently, we get the following:

$$\|I(t,x)\| + \|V(t,x)\| + \|W(t,x)\| \le 3\tilde{L}_1\sigma + 3\tilde{L}_2\sigma\int_0^t e^{-qs}(\|I(t,x)\| + \|V(t,x)\| + \|W(t,x)\|)ds.$$

By Gronwall's inequality, it holds that

$$\|I(t,x)\| + \|V(t,x)\| + \|W(t,x)\| \le 3\tilde{L}_1\sigma e^{\frac{3\tilde{L}_2\sigma}{q}}.$$

Therefore, from the first equation of Model (2.1), we can obtain that

$$\frac{\partial T(t,x)}{\partial t} \ge d_1\Delta T(t,x) + \lambda(x) - \Theta_1(x)T(t,x),$$

where $\Theta_1(x) = d(x) + 3\tilde{L}_1\sigma e^{\frac{3\sigma\tilde{L}_2}{q}}(\beta_1(x) + \beta_2(x) + \beta_3(x))$.

Let $\hat{u}(t,x)$ be the solution of the following system:

$$\begin{cases} \dfrac{\partial \hat{u}(t,x)}{\partial t} = d_1 \Delta \hat{u}(t,x) + \lambda(x) - \Theta_1(x)\hat{u}(t,x), t > 0, x \in \Omega, \\ \dfrac{\partial \hat{u}}{\partial \nu} = 0, t > 0, x \in \partial\Omega, \\ \hat{u}(0,x) = T_0(x), x \in \Omega. \end{cases} \tag{4.3}$$

By the comparison principle, we have $T(t,x) > \hat{u}(t,x)$ for $t \geq 0$, $x \in \bar{\Omega}$. Let $T_\sigma$ be the positive steady state of (4.3) and $\hat{T}(t,x) = \hat{u}(t,x) - T_\sigma(x)$; then, $\hat{T}(t,x)$ satisfies the following:

$$\begin{cases} \dfrac{\partial \hat{T}(t,x)}{\partial t} = d_1 \Delta \hat{T}(t,x) - \Theta_1(x)\hat{T}(t,x), t > 0, x \in \Omega, \\ \dfrac{\partial \hat{T}}{\partial \nu} = 0, t > 0, x \in \partial\Omega, \\ \hat{T}(0,x) = \hat{u}(0,x) - T_\sigma(x) = T_0(x) - T_\sigma(x), x \in \Omega, \end{cases}$$

which yields that

$$\hat{T}(t,x) = \mathbb{T}_1(t)\hat{T}(0,x) - 3\tilde{L}_1\sigma e^{\frac{3\sigma\tilde{L}_2}{q}} \int_0^t \mathbb{T}_1(t-s)(\beta_1(x) + \beta_2(x) + \beta_3(x))\hat{T}(s,x)ds.$$

Then, we have the following:

$$\hat{T}(t,x) \leq Me^{\omega_1 t}\|T_0(x) - T_\sigma(x)\| + \tilde{L}_3 \int_0^t e^{\omega_1(t-s)}\|\hat{T}(s,x)\|ds,$$

where $\tilde{L}_3 = 3M\tilde{L}_1\sigma e^{\frac{3\sigma\tilde{L}_2}{q}}(\|\beta_1(x)\| + \|\beta_2(x) + \beta_3(x)\|)$.

By Gronwall's inequality, we have the following:

$$\hat{T}(t,x) = \|\hat{u}(t,x) - T_\sigma(x)\| \leq M\|T_0(x) - T_\sigma(x)\|e^{\tilde{L}_3 t + \omega_1 t}.$$

Choosing a sufficiently small $\sigma > 0$ such that $\tilde{L}_3 < -\frac{\omega_1}{2}$, we can obtain the following:

$$\|\hat{u}(t,x) - T_\sigma(x)\| \leq M\|T_0(x) - T_\sigma(x)\|e^{\frac{\omega_1 t}{2}}. \tag{4.4}$$

It follows from (4.4) that

$$\begin{aligned} T(t,x) - T_0^*(x) \geq \hat{u}(t,x) - T_0^*(x) &= \hat{u}(t,x) - T_\sigma(x) + T_\sigma(x) - T_0^*(x) \\ &\geq -M\|T_0^*(x) - T_\sigma(x)\|e^{\frac{\omega_1 t}{2}} + T_\sigma(x) - T_0^*(x) \\ &\geq -M(\|T_0(x) - T_0^*(x)\| + \|T_0^*(x) - T_\sigma(x)\|) - \|T_\sigma(x) - T_0^*(x)\| \\ &\geq -M\sigma - (M+1)\|T_\sigma(x) - T_0^*(x)\|. \end{aligned}$$

Since $\chi(t) \leq \frac{L_1\sigma e^{-qt}}{T_{\min}}$, then we have $T(t,x) - T_0^*(x) \leq \|T_0^*(x)\|\frac{L_1\sigma}{T_{\min}}$; hence,

$$\|T(t,x) - T_0^*(x)\| \leq \max\left\{\|T_0^*(x)\|\frac{L_1\sigma}{T_{min}}, M\sigma + (M+1)\|T_\sigma(x) - T_0^*(x)\|\right\}.$$

Since $\lim_{\sigma\to 0} T_\sigma(x) = T_0^*(x)$, then for a sufficiently small $\sigma$, we have

$$\|T(t,x) - T_0^*(x)\|, \|I(t,x)\|, \|V(t,x)\|, \|W(t,x)\| \le \hat{\varepsilon}, \forall t > 0,$$

which indicates that $(T_0^*(x), 0, 0, 0)$ is locally asymptotically stable.

Next, we prove that $(T_0^*(x), 0, 0, 0)$ is globally attractive. From Theorem 3.1, we have that $\Phi_t$ adimits a global attractor $\mathcal{A}_0$. Denote

$$\mathbb{M} = \{(T, I, V, W) \in \mathbb{X}_+ : I = V = W = 0\}.$$

Claim 1. $u_0 = (T_0, I_0, V_0, W_0) \in \mathcal{M}_0$, with the omega limit set $\omega(u_0) \subset \mathbb{M}$.

Motivated by the works [53, 57, 58], we define

$$c(t, u_0) := \inf\{\tilde{c} \in \mathbb{R} : I(t,\cdot) \le \tilde{c}\phi_2, V(t,\cdot) \le \tilde{c}\phi_3, W(t,\cdot) \le \tilde{c}\phi_4\},$$

and thus, $c(t, u_0) > 0$ for $t > 0$. We claim that $c(t, u_0)$ is strictly decreasing. In order to show the claim, fix $t_0 > 0$ and let $\tilde{I}(t,\cdot) = c(t_0, u_0)\phi_2$, $\tilde{V}(t,\cdot) = c(t_0, u_0)\phi_3$, and $\tilde{W}(t,\cdot) = c(t_0, u_0)\phi_4$ for $t \ge t_0$. Due to $T(t,x) \le T_0^*(x)$ and hypothesis (A1), we have the following:

$$\begin{cases} \dfrac{\partial \tilde{I}(t,x)}{\partial t} > \nabla\cdot(d_2(x)\nabla\tilde{I}) + \beta_1(x)T\tilde{V} + \beta_2(x)T\tilde{I} + \beta_3(x)T\tilde{W} - r(x)\tilde{I}, x \in \Omega, t > 0, \\ \dfrac{\partial \tilde{V}(t,x)}{\partial t} = \nabla\cdot(d_3(x)\nabla\tilde{V}) + N(x)\tilde{I} - (c_1(x) + \mu(x))\tilde{V} + \alpha(x)\tilde{W}, x \in \Omega, t > 0, \\ \dfrac{\partial \tilde{W}(t,x)}{\partial t} = \nabla\cdot(d_4(x)\nabla\tilde{W}) + \mu(x)\tilde{V} - (c_2(x) + \alpha(x))\tilde{W}, x \in \Omega, t > 0, \\ \dfrac{\partial \tilde{I}(t,x)}{\partial \nu} = \dfrac{\partial \tilde{V}(t,x)}{\partial \nu} = \dfrac{\partial \tilde{W}(t,x)}{\partial \nu} = 0, x \in \partial\Omega, t > 0, \\ (\tilde{I}(t,\cdot), \tilde{V}(t,\cdot), \tilde{W}(t,\cdot)) \ge (I(t_0,x), V(t_0,x), W(t_0,x)), x \in \Omega. \end{cases} \tag{4.5}$$

Since System (4.5) is cooperative, then by the comparison principle, we have $c(t_0, u_0)\phi_2 = \tilde{I}(t,x) > I(t,x)$, $c(t_0, u_0)\phi_3 = \tilde{V}(t,x) > V(t,x)$ and $c(t_0, u_0)\phi_4 = \tilde{W}(t,x) > W(t,x)$ for $t \ge t_0$, $x \in \bar{\Omega}$. Since $t_0 > 0$ is arbitrary, then $c(t, u_0)$ is strictly decreasing.

Denote $c_* = \lim_{t\to\infty} c(t, u_0)$, and $v = (v_1, v_2, v_3, v_4) \in \omega(u_0)$; then, $\Phi(t_k)u_0 \to v$ for some sequence $\{t_k\}$ with $t_k \to \infty$. Since,

$$\lim_{t_k\to\infty} \Phi(t + t_k)u_0 = \Phi(t) \lim_{t_k\to\infty} \Phi(t_k)u_0 = \Phi(t)v,$$

this indicates that $c(t, v) = c_*$ for $t \ge 0$. If $v_2 \ne 0$ or $v_3 \ne 0$ or $v_4 \ne 0$, then a similar analysis procedure to the above shows that $c(t, v)$ is strictly decreasing, which leads to a contradiction and thus $v_2 = v_3 = v_4 = 0$. Then, it holds that $(I(t,x), V(t,x), W(t,x)) \to (0, 0, 0)$. Consequently, from the first equation of Model (2.1) we can obtain that $T(t,x) \to T_0^*(x)$ as $t \to \infty$.

Claim 2. $\mathcal{A}_0 = \{(T_0^*(x), 0, 0, 0)\}$.

It follows from the discussions above that $\{(T_0^*(x), 0, 0, 0)\}$ is globally attractive in $\mathbb{M}$, and $\{(T_0^*(x), 0, 0, 0)\}$ is the unique compact invariant subset in $\mathbb{M}$. Therefore, $\omega(u_0) = \{(T_0^*(x), 0, 0, 0)\}$, because the omega limit set $\omega(u_0)$ is compact invariant and $\omega(u_0) \subset \mathbb{M}$ for $u_0 \in \mathcal{A}_0$. Recall that the global attractor $\mathcal{A}_0$ is compact invariant; then, Lemma 3.11 in [58] indicates that $\mathcal{A}_0 = \{(T_0^*(x), 0, 0, 0)\}$. Consequently, global attractivity combined with local asymptotic stability immediately implies the global asymptotic stability of $\{(T_0^*(x), 0, 0, 0)\}$. This completes the proof.

**Remark 4.1.** *Here, we assume $d_1(x)$ to be constant. This assumption serves two purposes: first, it ensures the feasibility of scaling the variable $T$; and second, it guarantees that the defined semigroup $\tilde{\Gamma}_1$ possesses the desired decay property. If $d_1(x)$ were non-constant, then the scaling of $T$ would become more complicated, and the associated semigroup might lack a sufficient decay; thus, the current proof method may fail. Consequently, understanding how the stability of the infection-free steady state changes when $d_1(x)$ is spatially varying remains a challenging open problem that deserves a further in-depth investigation.*

## 5. Spatially homogeneous case

In this section, we study a spatially homogeneous case of Model (2.1) under a certain assumption that all the parameters are constants, that is,

$$\begin{cases} \frac{\partial T(t,x)}{\partial t} = d_1\Delta T + \lambda - dT - \beta_1 f_1(T,V) - \beta_2 f_2(T,I) - \beta_3 f_3(T,W), x \in \Omega, t > 0, \\ \frac{\partial I(t,x)}{\partial t} = d_2\Delta I + \beta_1 f_1(T,V) + \beta_2 f_2(T,I) + \beta_3 f_3(T,W) - rI, x \in \Omega, t > 0, \\ \frac{\partial V(t,x)}{\partial t} = d_3\Delta V + NI - (c_1+\mu)V + \alpha W, x \in \Omega, t > 0, \\ \frac{\partial W(t,x)}{\partial t} = d_4\Delta W + \mu V - (c_2+\alpha)W, x \in \Omega, t > 0, \\ \frac{\partial T(t,x)}{\partial \nu} = \frac{\partial I(t,x)}{\partial \nu} = \frac{\partial V(t,x)}{\partial \nu} = \frac{\partial W(t,x)}{\partial \nu} = 0, x \in \partial\Omega, t > 0, \end{cases} \tag{5.1}$$

with the initial Condition (2.2). It is obvious that Model (5.1) admits an infection-free equilibrium $E_0 = (T^0, 0, 0, 0)$ with $T^0 = \frac{\lambda}{d}$. Applying the result of [49], we have the following:

$$\mathcal{R}_0 = \frac{\beta_1 f_{1V}(T^0,0) + \beta_2 m f_{2I}(T^0,0) + \beta_3 \frac{\mu}{\alpha+c_2} f_{3W}(T^0,0)}{rm},$$

where $m = \frac{(\mu+c_1)(\alpha+c_2)-\mu\alpha}{N(\alpha+c_2)}$. Biologically, $R_0$ represents the average number of secondary infections. The first term is the average number of secondary infections caused by a virus, which corresponds to virus-to-cell infection mode ($\beta_1$). The second term is the average number of secondary infections due to infected cells, which corresponds to the cell-to-cell infection scheme ($\beta_2$). The third term is the average number of secondary infections caused by FDCs, which corresponds to the FDCs infection mode ($\beta_3$). It follows from the expression of $R_0$ that ignoring the FDCs infection may underestimate the infection risk, which indicates that developing effective drugs to decrease the infection due to FDCs is a benefit to control the infection.

It claims that Model (5.1) admits a unique positive infection steady state $E_* = (T_*, I_*, V_*, W_*)$ that satisfies the following:

$$\begin{cases} \lambda = dT_* + \beta_1 f_1(T_*,V_*) + \beta_2 f_2(T_*,I_*) + \beta_3 f_3(T_*,W_*), \\ \beta_1 f_1(T_*,V_*) + \beta_2 f_2(T_*,I_*) + \beta_3 f_3(T_*,W_*) = rI_*, \\ NI_* + \alpha W_* = (c_1+\mu)V_*, \\ \mu V_* = (c_2+\alpha)W_*. \end{cases} \tag{5.2}$$

Then, we have the following:

$$\begin{aligned} &T_* = \frac{\lambda - rmV_*}{d}, I_* = mV_*, W_* = \frac{\mu V_*}{c_2 + \alpha}, \\ &rmV_* = \beta_1 f_1(T_*, V_*) + \beta_2 f_2(T_*, I_*) + \beta_3 f_3(T_*, W_*). \end{aligned} \tag{5.3}$$

In order to have $T_* > 0, V_* > 0$ at steady state, we must have $V_* \in (0, \tilde{V})$ with $\tilde{V} = \frac{\lambda}{rm}$.

Define

$$G(V) = \beta_1 f_1\left(\frac{\lambda - rmV}{d}, V\right) + \beta_2 f_2\left(\frac{\lambda - rmV}{d}, mV\right) + \beta_3 f_3\left(\frac{\lambda - rmV}{d}, \frac{\mu V}{c_2 + \alpha}\right) - rmV.$$

For all $V > 0$, it is easy to show that $G(0) = 0$ and $G(\tilde{V}) = -\lambda < 0$, which indicates that there exists a $V_* \in (0, \tilde{V})$. For $\mathcal{R}_0 > 1$, we have the following:

$$G'(0) = \beta_1 f_{1V}(T_0, 0) + \beta_2 m f_{2I}(T_0, 0) + \frac{\mu\beta_3}{c_2 + \alpha} f_{3W}(T_0, 0) - rm = rm(\mathcal{R}_0 - 1) > 0.$$

Moreover, by (A1), (A2), and (5.3), the derivatives of $G'(V_*)$ yields the following:

$$\begin{aligned} G'(V_*) = &- \frac{rm}{d}\left(\beta_1 f_{1T}(T_*, V_*) + \beta_2 f_{2T}(T_*, V_*) + \beta_3 f_{3T}(T_*, V_*)\right) \\ &+ \beta_1\left(f_{1V}(T_*, V_*) - \frac{f(T_*, V_*)}{V_*}\right) + \left(\beta_2 m f_{2I}(T_*, I_*) - \frac{f_2(T_*, I_*)}{I_*}\right) \\ &+ \frac{\mu\beta_3}{c_2 + \alpha}\left(f_{3W}(T_*, W_*) - \frac{f_3(T_*, W_*)}{W_*}\right) < 0, \end{aligned}$$

which indicates that $G(V)$ is strictly decreasing at each of its zeros. Thus, $E_*$ is the unique positive steady state of Model (5.1).

**(A3)** $\left(\frac{f_1(T,V)T_*}{f_1(T_*,V_*)T} - \frac{V}{V_*}\right)\left(1 - \frac{f_1(T_*,V_*)T}{f_1(T,V)T_*}\right) \le 0$, $\left(\frac{f_2(T,I)T_*}{f_2(T_*,I_*)T} - \frac{V}{V_*}\right)\left(1 - \frac{f_2(T_*,I_*)T}{f_2(T,I)T_*}\right) \le 0$, $\left(\frac{f_3(T,W)T_*}{f_3(T_*,W_*)T} - \frac{V}{V_*}\right)\left(1 - \frac{f_3(T_*,W_*)T}{f_3(T,W)T_*}\right) \le 0$ for all $T, I, V, W > 0$.

**Theorem 5.1.** *If $\mathcal{R}_0 > 1$ and (A3) holds, then the unique positive steady state $E_*$ of Model* (5.1) *is globally attractive.*

*Proof.* Define a Lyapunov functional as follows:

$$\begin{aligned} H(t) = \int_\Omega \Bigg( &T - T_* - T_* \ln\frac{T}{T_*} + I - I_* - I_* \ln\frac{I}{I_*} + \frac{r}{N}\left(V - V_* - V_* \ln\frac{V}{V_*}\right) \\ &+ \frac{\alpha r}{N(c_2 + \alpha)}\left(W - W_* - W_* \ln\frac{W}{W_*}\right)\Bigg) dx. \end{aligned}$$

By calculating the derivative of $H(t)$ and applying (5.2), we can obtain the following:

$$
\begin{aligned}
H'(t) = \int_\Omega \Big\{ & \Big(1 - \frac{T_*}{T}\Big) d_1 \Delta T + \Big(1 - \frac{I_*}{I}\Big) d_2 \Delta I + \frac{r}{N}\Big(1 - \frac{V_*}{V}\Big) d_3 \Delta V \\
& + \frac{r\alpha}{N(c_2+\alpha)}\Big(1 - \frac{W}{W_*}\Big) d_4 \Delta W \Big\} dx + \int_\Omega \Big\{ dT_* \Big(1 - \frac{T_*}{T}\Big)\Big(1 - \frac{T}{T_*}\Big) \\
& + \beta_1 f_1(T_*, V_*)\Big[3 - \frac{T_*}{T} - \frac{IV_*}{I_*V} - \frac{f_1(T,V)I_*}{f_1(T_*,V_*)I} + \frac{f_1(T,V)T_*}{f_1(T_*,V_*)T} - \frac{V}{V_*}\Big] \\
& + \beta_2 f_2(T_*, I_*)\Big[3 - \frac{T_*}{T} - \frac{IV_*}{I_*V} - \frac{f_2(T,I)I_*}{f_2(T_*,I_*)I} + \frac{f_2(T,I)T_*}{f_2(T_*,I_*)T} - \frac{V}{V_*}\Big] \\
& + \beta_3 f_3(T_*, W_*)\Big[3 - \frac{T_*}{T} - \frac{IV_*}{I_*V} - \frac{f_3(T,W)I_*}{f_3(T_*,W_*)I} + \frac{f_3(T,W)T_*}{f_3(T_*,W_*)T} - \frac{V}{V_*}\Big] \\
& + \frac{r\alpha W_*}{N}\Big(2 - \frac{V_*W}{VW_*} - \frac{VW_*}{V_*W}\Big)\Big\} dx.
\end{aligned}
$$

Recall that

$$
\begin{aligned}
&\int_\Omega \Delta T dx = \int_\Omega \Delta I dx = \int_\Omega \Delta V dx = \int_\Omega \Delta W dx = 0, \int_\Omega \frac{1}{T}\Delta T dx = \int_\Omega \frac{1}{T^2}\|\nabla T\|^2, \\
&\int_\Omega \frac{1}{I}\Delta I dx = \int_\Omega \frac{1}{I^2}\|\nabla I\|^2, \int_\Omega \frac{1}{V}\Delta V dx = \int_\Omega \frac{1}{V^2}\|\nabla V\|^2, \int_\Omega \frac{1}{W}\Delta W dx = \int_\Omega \frac{1}{W^2}\|\nabla W\|^2.
\end{aligned}
$$

Then, we have the following:

$$
\begin{aligned}
H'(t) = & -\int_\Omega \Big\{ \frac{d_1 T_*}{T^2}\|\nabla T\|^2 + \frac{d_2 I_*}{I^2}\|\nabla I\|^2 + \frac{d_3 r V_*}{NV^2}\|\nabla V\|^2 + \frac{d_4 r\alpha W_*}{N(c_2+\alpha)W^2}\|\nabla W\|^2 \Big\} dx \\
& + \int_\Omega \Big\{ dT_*\Big(1 - \frac{T_*}{T}\Big)\Big(1 - \frac{T}{T_*}\Big) + \beta_1 f_1(T_*, V_*)\Big[\varphi\Big(\frac{T_*}{T}\Big) + \varphi\Big(\frac{IV_*}{I_*V}\Big) \\
& + \varphi\Big(\frac{f_1(T,V)I_*}{f_1(T_*,V_*)I}\Big) + \varphi\Big(\frac{f_1(T_*,V_*)TV}{f_1(T,V)T_*V_*}\Big) + \Big(\frac{f_1(T,V)T_*}{f_1(T_*,V_*)T} - \frac{V}{V_*}\Big)\Big(1 - \frac{f_1(T_*,V_*)T}{f_1(T,V)T_*}\Big)\Big] \\
& + \beta_2 f_2(T_*, I_*)\Big[\varphi\Big(\frac{T_*}{T}\Big) + \varphi\Big(\frac{IV_*}{I_*V}\Big) + \varphi\Big(\frac{f_2(T,I)I_*}{f_2(T_*,I_*)I}\Big) + \varphi\Big(\frac{f_2(T_*,I_*)TV}{f_2(T,I)T_*V_*}\Big) \\
& + \Big(\frac{f_2(T,I)T_*}{f_2(T_*,I_*)T} - \frac{V}{V_*}\Big)\Big(1 - \frac{f_2(T_*,I_*)T}{f_2(T,I)T_*}\Big)\Big] + \beta_3 f_3(T_*, W_*)\Big[\varphi\Big(\frac{T_*}{T}\Big) + \varphi\Big(\frac{IV_*}{I_*V}\Big) \\
& + \varphi\Big(\frac{f_3(T,W)I_*}{f_3(T_*,W_*)I}\Big) + \varphi\Big(\frac{f_3(T_*,W_*)TV}{f_3(T,W)T_*V_*}\Big) + \Big(\frac{f_3(T,W)T_*}{f_3(T_*,W_*)T} - \frac{V}{V_*}\Big) \\
& \times \Big(1 - \frac{f_3(T_*,W_*)T}{f_3(T,W)T_*}\Big)\Big] + \frac{r\alpha W_*}{N}\Big(2 - \frac{V_*W}{VW_*} - \frac{VW_*}{V_*W}\Big)\Big\} dx,
\end{aligned}
$$

where $\varphi(\theta) = 1 + \ln\theta - \theta \geq 0$ for $\theta > 0$, with the global maximum $\varphi(1) = 0$. Then, it follows that $H'(t) \leq 0$, and the largest invariant subset $\{(T, I, V, W) : H'(t) = 0\}$ is just the singleton $E_*$. Thus, the positive steady state $E_*$ is globally attractive.

## 6. Numerical simulations

In this section, we perform some numerical analyses to illustrate the results obtained in preceding section. To this end, we select two parameter sets which correspond to $\mathcal{R}_0 < 1$ (when the infection-free steady state is globally asymptotically stable) and $\mathcal{R}_0 > 1$ ( when the infection is persistent and there exists a positive steady state). Moreover, for simplicity, we consider Model (2.1) with the nonlinear incidence functions $f_1(T,V) = \frac{TV}{1+\alpha_1(x)V}$, $f_2(T,I) = \frac{TI}{1+\alpha_2(x)I}$, and $f_3(T,W) = \frac{TW}{1+\alpha_3(x)W}$. Assume $\Omega = [0,10]$. Some of the following parameter values are from [28] and the others are assumed to satisfy the threshold conditions.

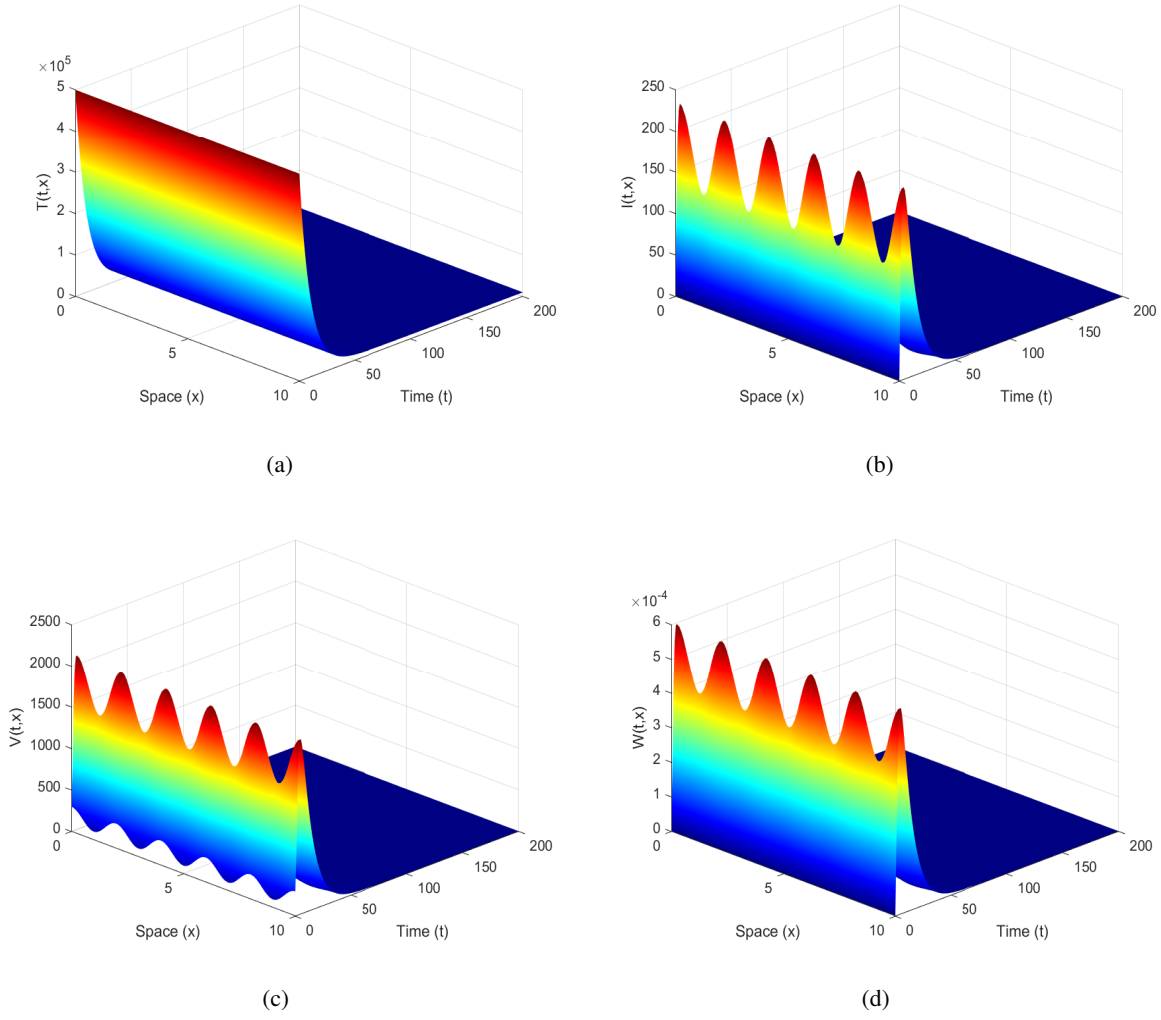


**Figure 2.** When $\mathcal{R}_0 \approx 0.1197 < 1$, then $E_0(x)$ is globally asymptotically stable.

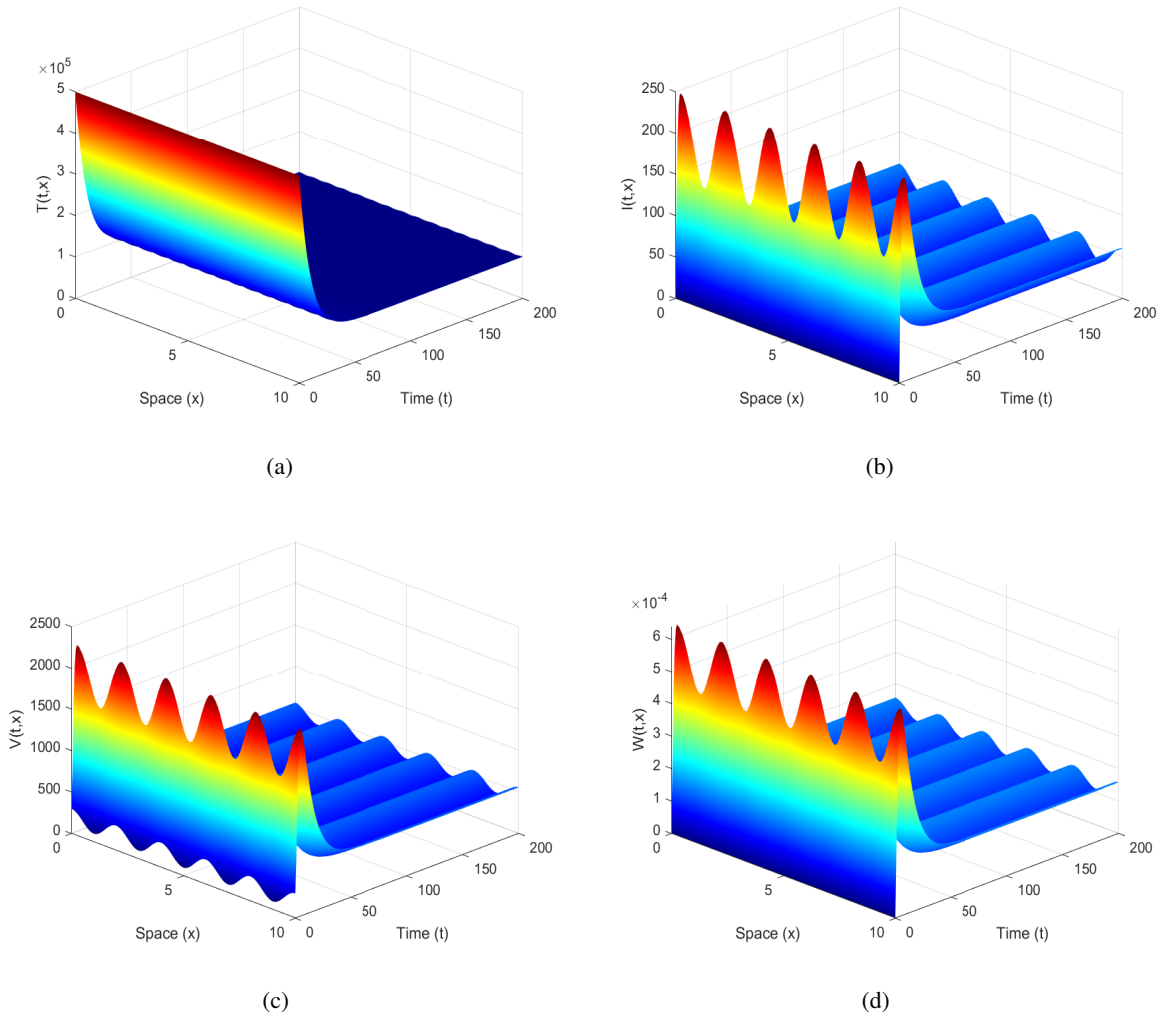


**Figure 3.** When $\mathcal{R}_0 \approx 1.1972 > 1$, then the infection is persistent and there exists a positive infection steady state.

Let $\beta_1(x) = 3.6 \times 10^{-6}(1 + 0.5\cos(\pi x))$, $\beta_2(x) = 1.35 \times 10^{-5}(1 + 0.5\cos(\pi x))$, $\beta_3(x) = 7.5 \times 10^{-6}(1 + 0.5\cos(\pi x))$, $N(x) = 30$, $\lambda(x) = 1000 \times (1 + 0.9\cos(3\pi x))$, $d(x) = 0.01$, $r(x) = 0.5$, $c_1(x) = 3$, $c_2 = 3$, $d_1(x) = 0.09648$, $d_2(x) = 0.05$, $d_3(x) = 0.17$, $d_4(x) = 0.01$, $\mu(x) = 1.5 \times 10^{-5}$, $\alpha(x) = 50$, $\alpha_1(x) = 0.05$, $\alpha_2(x) = 0.06$, $\alpha_3(x) = 0.04$, $V_0(x) = 200(1+0.5\cos(\pi x))$, $T_0(x) = 5\times 10^5$, $I_0(x) = 0$, and $W_0(x) = 0$, for $x \in [0, 10]$. For this case, we have $\mathcal{R}_0 \approx 0.1197 < 1$. It follows from Theorem 4.1 that $E_0(x)$ is globally asymptotically stable, which implies that the infection will eventually die out. Figure 2 validates the above analysis.

Next, let $\lambda = 10{,}000 \times (1 + 0.9\cos(3\pi x))$ and keep other parameters the same as Figure 2. In this case, we have $\mathcal{R}_0 \approx 1.1972 > 1$. According to Theorem 4.2, Model (2.1) is persistent, as shown in Figure 3. The infection persists indefinity, indicating long-term coexistence between the virus and host immune cells, which hinders the viral clearance.

As we known, the infection risk of HIV increases as $\mathcal{R}_0$ increases. Hence, we pay attention to the

influence of spatial heterogeneity on $\mathcal{R}_0$ to show how spatial heterogeneity affects the transmission risk. Let $\beta_1(x) = 3.6 \times 10^{-6}(1 + k_1 \cos(m_1\pi x))$, $\beta_2(x) = 1.35 \times 10^{-5}(1 + k_2 \cos(m_2\pi x))$, and $\beta_3(x) = 7.5 \times 10^{-6}(1 + k_3 \cos(m_3\pi x))$, and keep the other parameter values the same as Figure 2. It follows from Figure 4(a),(b) that $\mathcal{R}_0$ increases as the heterogeneity parameters $k_1$ (for free virus) and $k_2$ (for infected cells) increase, which indicates that the infection risk is underestimated when averaging the infection ability of infected cells and free virus, respectively. Besides, Figure 4(a),(b) also shows that $\mathcal{R}_0$ is decreasing with respect to $m_1$ and $m_2$, respectively. This implies that the fragmentation of the space is detrimental to free viruses and infected cells. However, the spatial heterogeneity of FDCs has no impact on the transmission risk, as shown in Figure 4(c). Therefore, the spatial heterogeneity poses challenges to the treatment and control of HIV infections. These findings underscore the need for more effective antiviral strategies tailored to heterogeneous physiological environments.

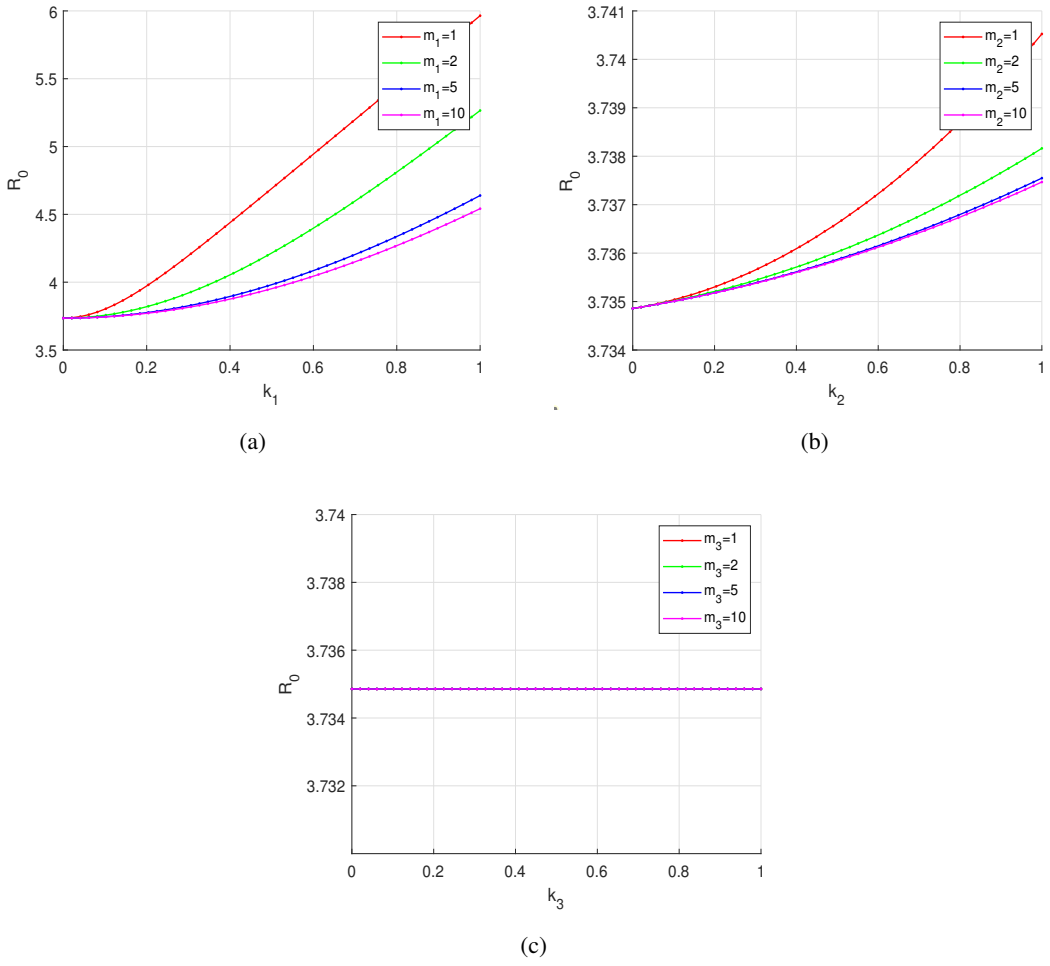


**Figure 4.** Impact of the heterogeneous parameters on $\mathcal{R}_0$. (a) $\beta_1(x) = 3.6 \times 10^{-6}(1 + k_1 \cos(m_1\pi x))$, $\beta_2(x) = 1.35 \times 10^{-5}$, and $\beta_3(x) = 7.5 \times 10^{-6}$. (b) $\beta_1(x) = 3.6 \times 10^{-6}$, $\beta_2(x) = 1.35 \times 10^{-5}(1 + k_2 \cos(m_2\pi x))$, and $\beta_3(x) = 7.5 \times 10^{-6}$. (c) $\beta_1(x) = 3.6 \times 10^{-6}$, $\beta_2(x) = 1.35 \times 10^{-5}$, and $\beta_3(x) = 7.5 \times 10^{-6}(1 + k_3 \cos(m_3\pi x))$. Other parameter values the same as Figure 3.

## 7. Discussion and conclusions

This paper investigated a within-host viral infection model that incorporated spatial heterogeneity and multiple transmission routes to investigate the threshold dynamics in a heterogeneous space. First, we proved the solutions are well-posed and defined $\mathcal{R}_0$, which serves as a sharp threshold to determine the infection extinction or persistence. Specifically, when $\mathcal{R}_0 < 1$, $E_0(x)$ is globally asymptotically stable, which implies that the infection will eventually die out. In contrast, when $\mathcal{R}_0 > 1$, the infection persists indefinity, which indicates a long-term coexistence between the virus and host immune cells and hinders viral clearance. Notably, we established the global stability of the infection-free steady state for the critical case $\mathcal{R}_0 = 1$ by virtue of Gronwall's inequality, the comparison theorem, and semigroup properties. A numerical analysis was conducted to validate the theoretical findings.

Although heterogeneity is inherent in vivo, its precise impact on infection dynamics is difficult to analytically assess. Our simulations revealed that $\mathcal{R}_0$ increases with the heterogeneity intensities of free virus and infected cells, thus suggesting that the ignoring spatial variation in their infectivity leads to an underestimation of the transmission risk. Thus, spatial heterogeneity complicates the viral control and poses additional challenges for the infection clearance. These findings underscore the need for more effective antiviral strategies tailored to heterogeneous physiological environments.

We would like to point out that a time delay was not been considered in Model (2.1). An interesting question is how a time delay influences the dynamic behavior of the corresponding model, and this extension is left for future work.

## Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

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## Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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