AIMS Mathematics

http://www.aimspress.com/journal/Math

AIMS Mathematics, 6(1): 114–140.
DOI:10.3934/math.2021009
Received: 09 June 2020
Accepted: 03 September 2020
Published: 30 September 2020

Research article

Stability of general pathogen dynamic models with two types of infectious transmission with immune impairment

B. S. Alofi[1,*] **and S. A. Azoz**[2,*]

[1] Department of Mathematics, Faculty of Science, King Abdulaziz University, P.O. Box 80203, Jeddah 21589, Saudi Arabia

[2] Department of Mathematics, Faculty of Science, Assiut University, Assiut 71516, Egypt

* **Correspondence:** Email: badoora2al3ofi@gmail.com (Alofi), shaimaa.azoz@gmail.com (Azoz); Tel: 00201126975599.

Abstract: In this paper, we investigate the global properties of two general models of pathogen infection with immune deficiency. Both pathogen-to-cell and cell-to-cell transmissions are considered. Latently infected cells are included in the second model. We show that the solutions are nonnegative and bounded. Lyapunov functions are organized to prove the global asymptotic stability for uninfected and infected steady states of the models. Analytical expressions for the basic reproduction number $\mathcal{R}_0$ and the necessary condition under which the uninfected and infected steady states are globally asymptotically stable are established. We prove that if $\mathcal{R}_0 < 1$ then the uninfected steady state is globally asymptotically stable (GAS), and if $\mathcal{R}_0 > 1$ then the infected steady state is GAS. Numerical simulations are performed and used to support the analytical results.

Keywords: pathogen infection; cell-to-cell transmission; immune impairment; global stability
Mathematics Subject Classification: 34D20, 34D23, 37N25, 92B05

1. Introduction

During recent years, there has been a significant effort to develop mathematical models to study epidemic and endemic diseases caused by pathogen attacking such as virus, bacterium, fungus, viroid, and protozoan and studding possible prevention and/or elimination strategies (see e.g. [1–17]). Mathematical analysis and modeling of diseases dynamics has many benefits including (i) its ability to test several conditions and introduce new visions into issues which can not be addressed by clinical or experimental trials, (ii) enhancing diagnosis and treatment strategies in the highest efficiency at the lowest possible cost, and with the minimum of side effects, which increase the hopes of patients, (iii) we can use it to evaluate the values of main parameters which control the process of infection or reduce the

viral load in the body of patients. Certainly, immune response after the pathogen infection is universal and essential for the control or removal of the diseases. In many pathogen infections, cytotoxic T lymphocytes (CTLs) is an essential component of natural immune resistance to pathogen infection and plays an important role in defending the body from pathogens by destroying the infected cells. So, CTLs are assumed to be the principal host immune factor deciding the viral load. The standard pathogen dynamics model with CTL immune response was formulated by Nowak and Bangham [18] as:

$$\dot{S}(t) = \Upsilon - \Phi S(t) - \eta P(t) S(t), \tag{1.1}$$
$$\dot{I}(t) = \eta P(t) S(t) - \Theta I(t) - qI(t)C(t), \tag{1.2}$$
$$\dot{P}(t) = \Omega I(t) - \Sigma P(t), \tag{1.3}$$
$$\dot{C}(t) = \Psi I(t) C(t) - \Lambda C(t), \tag{1.4}$$

$S(t)$, $I(t)$, $P(t)$ and $C(t)$ are, respectively, the concentrations of uninfected cells, infected cells, pathogens and CTLs at time t. The uninfected cells are restored at rate Υ and die at rate ΦS. The uninfected cells are become infected at rate ηPS. The infected cells are killed by CTL at rate qIC and die at rate ΘI. Pathogens proliferate at rate ΩI and die by rate ΣP. CTLs proliferate at rate ΨIC, die by rate ΛC. Accordingly, dynamics of pathogen infections with CTL response has attracted a great deal of attention recently from researchers in related fields [19–28].

Nevertheless, it has been noted that some pathogens can cause impairment in CTL function during the infection. In many papers, pathogenic dynamics models with CTL immune impairment were studied in many papers (see e.g. [29–31]). These papers supposed that the uninfected cells become infected due to pathogen contacts but pathogen can also spread by direct cell-to-cell transmission. Many papers studied two types of pathogen transmissions, cell-to-cell and pathogen-to-cell (see [32–38]). Pathogenic infection models with CTL immune response and two modes of transmission have been developed in [39–43]. However, these papers neglected the effect of immune impairment. Pathogen dynamics model with immune impairment and two types of transmissions can be given as (see [44]):

$$\dot{S}(t) = \Upsilon - \Phi S(t) - \eta_1 P(t) S(t) - \eta_2 I(t) S(t), \tag{1.5}$$
$$\dot{I}(t) = \eta_1 P(t) S(t) + \eta_2 I(t) S(t) - \Theta I(t) - qI(t)C(t), \tag{1.6}$$
$$\dot{P}(t) = \Omega I(t) - \Sigma P(t), \tag{1.7}$$
$$\dot{C}(t) = \Psi I(t) - \Lambda C(t) - \beta I(t) C(t), \tag{1.8}$$

where the terms $\eta_1 PS$ and $\eta_2 SI$ are the incidence rates due to pathogen-to-cell and cell-to-cell mechanisms, respectively. The impairment of the CTL is represented by βIC.

Another barrier to curing the infection in many diseases is the latent reservoirs in human cell types or tissues caused by persistent viruses like human immunodeficiency virus (HIV), hepatitis B and C viruses, several herpesvirus and human T-cell leukemia virus. Viral latency is the tendency of a pathogenic virus to repose latent within the cell, which is referred to as the lysogenic portion of the pathogen life cycle. One form of persistent viral infection is a latent viral infection where latent viruses will incorporate its genetic material into the infected host cell's genetic material. Because it is possible to replicate the pathogen genetic material with the host materials, the virus becomes (invisible) with

respect to the host detection. Latency is the phase in certain pathogens life cycles in which, after initial infection, a proliferation of virus particles ceases. The viral genome, however, isn't completely eradicated. The result of this is that the virus can reactivate and begin producing large amounts of viral progeny without the host becoming reinfected by the new outside pathogen, and stays within the host indefinitely. The latent reservoir can explain antiviral therapies failure to remove the infection (see [6] and [45]). Elaiw et al. [46] studied an HIV dynamics model with latent reservoirs and CTL immune impairment, but they neglected the cell-to-cell transmission. We note that the pathogen-cell and cell-cell incidence rates are given by bilinear forms $\eta_1 PS$ and $\eta_2 SI$. Experimental work [49] showed that the bilinear incidence rate is insufficient to describe the pathogenic infection process in detail. As a result, several pathogen dynamics models with nonlinear incidence were proposed (see e.g. [50, 51]).

The aim of this paper is to propose and analyze pathogen dynamics models with impairment of CTL immunity, which are generalization of several models presented in the literature by including general incidence rates for cell-to-cell and pathogen-to-cell transmissions. The second model is a generalization for the first one by taking into account two groups of infected cells, latently infected cells (remains dormant in the inactive or hidden process) and actively infected cells. We demonstrate that model solutions are non-negative and ultimately finite which ensure the well-posed of the models. Biological threshold parameter $\mathcal{R}_0$ have been derived to determine existence steady states of the models and their stability. Using Lyapunov method and applying LaSalle's invariance principle, we investigate the global stability of the model's steady states. We demonstrate that (i) if $\mathcal{R}_0 < 1$, the uninfected steady state Γ_0 is globally asymptotic stable (GAS) and the epidemic is expected to be removed from the patients, (ii) if $\mathcal{R}_0 > 1$, the infected steady state Γ_1 is GAS and chronic disease is achieved. We conduct numerical simulations to establish that the theoretical and numerical results are compatible.

2. Model with general rate of incidence

In this section, we present a pathogen dynamics model with general pathogen-to-cell and cell-to-cell incidence as follows:

$$\dot{S}(t) = \Upsilon - \Phi S(t) - (h_1(P(t)) + h_2(I(t)))f(S(t)), \tag{2.1}$$

$$\dot{I}(t) = (h_1(P(t)) + h_2(I(t)))f(S(t)) - \Theta I(t) - qI(t)C(t), \tag{2.2}$$

$$\dot{P}(t) = \Omega I(t) - \Sigma P(t), \tag{2.3}$$

$$\dot{C}(t) = \Psi I(t) - \Lambda C(t) - \beta I(t)C(t), \tag{2.4}$$

where $S(t)$, $I(t)$, $P(t)$ and $C(t)$ are respectively the concentrations of uninfected cells, infected cells, pathogens and CTLs at time t. The uninfected cells are restored at rate Υ and die at rate ΦS. The infected cells are killed by CTL at rate qIC and die at rate ΘI. Pathogens proliferate at rate ΩI and die by rate ΣP. CTL cells proliferate at rate ΨI, die by rate ΛC. The impairment of the CTL is represented by βIC where Ψ, Λ and β are constants. The uninfected cells are become infected at rate $(h_1(P) + h_2(I))f(S)$. Functions f, h_1 and h_2 are bounded and continuously differentiable satisfy the following conditions:

(A1) $h_1(z) > 0, h_2(z) > 0$ and $f(z) > 0$ for all $z > 0$ and $h_1(0) = h_2(0) = f(0) = 0$.

(A2) $h_1'(z) > 0, h_2'(z) > 0$ and $f'(z) > 0$ for all $z \geq 0$.

(A3) $\left(\frac{f(S)}{S}\right)' \leq 0, \left(\frac{h_1(P)}{P}\right)' \leq 0$ and $\left(\frac{h_2(I)}{I}\right)' \leq 0$ for all $S > 0, I > 0$ and $P > 0$.

Remark 1. *(i) If $f(S) = S$, $h_1(P) = P$ and $h_2(I) = I$, then model (2.1)-(2.4) will be reduced to the model presented in [47] in the absent of the time delays, (ii) if $f(S) = \frac{S}{1+\alpha S}$, $h_1(P) = P$, $h_2(I) = I$, then model (2.1)-(2.4) will be reduced to the model presented in [48].*

2.1. Basic properties

In this subsection we will discuss the non-negativity and finiteness of model (2.1)-(2.4) solutions:

Lemma 1. *For the model (2.1)-(2.4), a nonnegative invariant compact set exists*

$$\Omega_1 = \left\{(S, I, P, C) \in \mathbb{R}^4_{\geq 0} : 0 \leq S, I \leq n_1, 0 \leq P \leq n_2, 0 \leq C \leq n_3\right\}, \tag{2.5}$$

where $\mathbb{R}_{\geq 0} = \{x \in \mathbb{R} : x \geq 0\}$.

Proof. It is obvious that

$$\begin{aligned}
\dot{S}\big|_{(S=0)} &= \Upsilon > 0, \\
\dot{I}\big|_{(I=0)} &= h_1(P) f(S) \geq 0, \qquad \text{for all } S > 0, P \geq 0, \\
\dot{P}\big|_{(P=0)} &= \Omega I \geq 0, \qquad \text{for all } I \geq 0, \\
\dot{C}\big|_{(C=0)} &= \Psi I \geq 0, \qquad \text{for all } I \geq 0.
\end{aligned}$$

This is an evidence for the positively invariant property of $\mathbb{R}^4_{\geq 0}$ for the system (2.1)-(2.4).
Let $Q = S + I + \frac{\Theta}{2\Omega}P + \frac{\Theta}{4\Psi}C$, then

$$\begin{aligned}
\dot{Q} &= \Upsilon - \Phi S - (h_1(P) + h_2(I)) f(S) \\
&\quad + (h_1(P) + h_2(I)) f(S) - \Theta I - qIC \\
&\quad + \frac{\Theta}{2\Omega}(\Omega I - \Sigma P) + \frac{\Theta}{4\Psi}(\Psi I - \Lambda C - \beta IC) \\
&= \Upsilon - \Phi S - \frac{\Theta}{4} I - \left(q + \frac{\Theta\beta}{4\Psi}\right) IC - \frac{\Theta\Sigma}{2\Omega} P - \frac{\Theta\Lambda}{4\Psi} C \\
&\leq \Upsilon - \Phi S - \frac{\Theta}{4} I - \frac{\Theta\Sigma}{2\Omega} P - \frac{\Theta\Lambda}{4\Psi} C \\
&\leq \Upsilon - \sigma\left(S + I + \frac{\Theta}{2\Omega} P + \frac{\Theta}{4\Psi} C\right) = \Upsilon - \sigma Q,
\end{aligned}$$

where, $\sigma = \min\{\Phi, \frac{\Theta}{4}, \Sigma, \Lambda\}$. Then

$$Q(t) \leq e^{-\sigma t}\left(Q(0) - \frac{\Upsilon}{\sigma}\right) + \frac{\Upsilon}{\sigma}.$$

This yields, $0 \leq Q(t) \leq n_1$ for all $t \geq 0$ if $Q(0) \leq n_1$, where $n_1 = \frac{\Upsilon}{\sigma}$. It follows that $0 \leq S(t), I(t) \leq n_1, 0 \leq P(t) \leq n_2$ and $0 \leq C(t) \leq n_3$ for all $t \geq 0$ if $S(0) + I(0) + \frac{\Theta}{2\Omega}P(0) + \frac{\Theta}{4\Psi}C(0) \leq n_1$, where $n_2 = \frac{2\Omega\Upsilon}{\Theta\sigma}$ and $n_3 = \frac{4\Psi\Upsilon}{\Theta\sigma}$. This prove the boundedness of S, I, P and C. □

The steady state's existence for the system (2.1)-(2.4) will be introduced in the following lemma.

Lemma 2. *Suppose that Assumption A1-A3 are satisfied and there exists a parameter $\mathcal{R}_0 > 0$ such that*
(i) if $\mathcal{R}_0 \leq 1$, then only one steady state Γ_0 exists,
(ii) if $\mathcal{R}_0 > 1$, therefore two steady states Γ_0 and Γ_1 exist.

Proof. To calculate the steady states we let

$$0 = \Upsilon - \Phi S - [h_1(P) + h_2(I)]\, f(S), \tag{2.6}$$
$$0 = [h_1(P) + h_2(I)]\, f(S) - \Theta I - qIC, \tag{2.7}$$
$$0 = \Omega I - \Sigma P, \tag{2.8}$$
$$0 = \Psi I - \Lambda C - \beta IC. \tag{2.9}$$

From Eqs (2.6)-(2.9) we find that the system has uninfected steady state $\Gamma_0 = (S_0, 0, 0, 0)$, where $S_0 = \dfrac{\Upsilon}{\Phi}$ and if $I \neq 0$ we can define another steady state $\Gamma = (S, I, P, C)$ satisfying the following equation

$$0 = \frac{[h_1(P) + h_2(I)]\, f(S)}{I} - \Theta - qC$$

such that

$$P = \frac{\Omega I}{\Sigma}, \tag{2.10}$$

$$C = \frac{\Psi I}{\beta I + \Lambda}, \tag{2.11}$$

and S satisfy the following equation

$$0 = \Upsilon - \Phi S - [h_1(P) + h_2(I)]\, f(S),$$

define a function H on $[0, \infty)$ by

$$H(I) = \frac{[h_1(P) + h_2(I)]\, f(S)}{I} - \Theta - qC$$

Equation (2.10) and the boundedness of h_1 and h_2 imply that $\lim_{I\to\infty} \frac{h_1(p)}{I} = \lim_{I\to\infty} \frac{h_2(I)}{I} = 0$. Since $\lim_{I\to\infty} H(I) = -\Theta - \dfrac{\Psi q}{\beta} < 0$ and $\lim_{I\to 0} H(I) = \left(\frac{\Omega}{\Sigma} h_1'(0) + h_2'(0)\right) f(S_0) - \Theta > 0$. Consequently there exists $I_1 \in (0, \infty)$ and from Eqs (2.10)-(2.11) we have $P_1 = \dfrac{\Omega I_1}{\Sigma} > 0$ and $C_1 = \dfrac{\Psi I_1}{\beta I_1 + \Lambda} > 0$ when $\Theta\left[\left(\frac{\Omega h_1'(0)}{\Theta\Sigma} + \frac{h_2'(0)}{\Theta}\right) f(S_0) - 1\right] > 0$. Thus, we can define the basic infection reproduction number $\mathcal{R}_0$ as:

$$\mathcal{R}_0 = \left(\frac{\Omega h_1'(0)}{\Theta\Sigma} + \frac{h_2'(0)}{\Theta}\right) f(S_0). \tag{2.12}$$

It follow that the infected steady state $\Gamma_1 = (S_1, I_1, P_1, C_1)$ exists if $\mathcal{R}_0 > 1$. □

2.2. Global characteristics

In the following subsection we are going to confirm the global stability of the model (2.1)-(2.4) steady states by creating appropriate Lyapunov functions. Define a function $g : (0, \infty) \to [0, \infty)$ as $g(\upsilon) = \upsilon - 1 - \ln \upsilon$.

Remark 2. *From Assumption (A3) we have* $\frac{h_1(P)}{P} \leq \lim_{P\to 0^+} \frac{h_1(P)}{P} = h_1'(0)$ *and* $\frac{h_2(I)}{I} \leq \lim_{I\to 0^+} \frac{h_2(I)}{I} = h_2'(0)$.

Theorem 1. *For model (2.1)-(2.4), if* $\mathcal{R}_0 < 1$, *then* Γ_0 *is globally asymptotically stable (GAS).*

Proof. Let us define $Y_1(S, I, P, C)$ as:

$$Y_1(S, I, P, C) = S - S_0 - \int_{S_0}^{S} \frac{f(S_0)}{f(\theta)} d\theta + I + \frac{f(S_0)h_1'(0)}{\Sigma} P + \frac{\Theta(1-\mathcal{R}_0)}{\Psi} C.$$

Clearly, $Y_1(S, I, P, C) > 0$ for all $S, I, P, C > 0$ and $Y_1(S_0, 0, 0, 0) = 0$. Calculating $\frac{dY_1}{dt}$ along the system (2.1)-(2.4), we get

$$\begin{aligned}
\frac{dY_1}{dt} &= \left(1 - \frac{f(S_0)}{f(S)}\right)[\Upsilon - \Phi S - (h_1(P) + h_2(I))f(S)] \\
&\quad + (h_1(P) + h_2(I))f(S) - \Theta I - qIC \\
&\quad + \frac{f(S_0)h_1'(0)}{\Sigma}(\Omega I - \Sigma P) + \frac{\Theta(1-\mathcal{R}_0)}{\Psi}(\Psi I - \Lambda C - \beta IC) \\
&= \left(1 - \frac{f(S_0)}{f(S)}\right)(\Upsilon - \Phi S) + f(S_0)h_1(P) + f(S_0)h_2(I) - \Theta\mathcal{R}_0 I \\
&\quad + \frac{f(S_0)h_1'(0)\Omega}{\Sigma} I - f(S_0)h_1'(0)P \\
&\quad - \left(q + \frac{\beta\Theta(1-\mathcal{R}_0)}{\Psi}\right) IC - \frac{\Theta(1-\mathcal{R}_0)\Lambda}{\Psi} C.
\end{aligned}$$

Using $\Upsilon = \Phi S_0$ and from Remark 2 we get

$$\begin{aligned}
\frac{dY_1}{dt} &\leq \Upsilon\left(1 - \frac{f(S_0)}{f(S)}\right)\left(1 - \frac{S}{S_0}\right) + \Theta\left(\frac{f(S_0)h_1'(0)\Omega}{\Sigma\Theta} + \frac{f(S_0)h_2'(0)}{\Theta} - \mathcal{R}_0\right) I \\
&\quad - \left(q + \frac{\beta\Theta(1-\mathcal{R}_0)}{\Psi}\right) IC - \frac{\Theta(1-\mathcal{R}_0)\Lambda}{\Psi} C \\
&= \Upsilon\left(1 - \frac{f(S_0)}{f(S)}\right)\left(1 - \frac{S}{S_0}\right) - \left(q + \frac{\beta\Theta(1-\mathcal{R}_0)}{\Psi}\right) IC - \frac{\Theta(1-\mathcal{R}_0)\Lambda}{\Psi} C.
\end{aligned}$$

From assumption (A2) we have $\left(1 - \frac{f(S_0)}{f(S)}\right)\left(1 - \frac{S}{S_0}\right) \leq 0$. Clearly if $\mathcal{R}_0 < 1$, then $\frac{dY_1}{dt} \leq 0$ for all $S, I, P, C > 0$, moreover $\frac{dY_1}{dt} = 0$ if and only if $S(t) = S_0$ and $C(t) = 0$. Let

$\mathcal{D}_0 = \left\{(S, I, P, C) : \frac{dY_1}{dt} = 0\right\}$ and $\acute{\mathcal{D}}_0$ be the largest invariant subset of $\mathcal{D}_0$, then solutions of the model (2.1)-(2.4) tend to $\acute{\mathcal{D}}_0$. For each element in $\acute{\mathcal{D}}_0$ we have $S(t) = S_0$ and $C(t) = 0$, thus Eq (2.4) yields

$$\dot{C(t)} = 0 = \Psi I(t) - \Lambda C(t) - \beta I(t)C(t),$$

Hence $I(t) = 0$ and from Eq (2.2) we have

$$\dot{I(t)} = 0 = h_1(P(t))f(S_0)$$

then $h_1(P(t)) = 0$, which yields $P(t) = 0$. It follows that $\acute{\mathcal{D}}_0$ contains a single point which is $(S_0, 0, 0, 0)$. LaSalle's invariance principle (LIP) implies that Γ_0 is GAS when $\mathcal{R}_0 < 1$.
Further to study the local stability of Γ_0, we need to calculate the Jacobin matrix at $\Gamma_0 = (S_0, 0, 0, 0)$ as:

$$J = \frac{\partial(\dot{S}, \dot{I}, \dot{P}, \dot{C})}{\partial(S, I, P, C)} \mid_{\Gamma_0} = \begin{pmatrix} -\Phi & -f(S_0)h_2'(0) & -f(S_0)h_1'(0) & 0 \\ 0 & f(S_0)h_2'(0) - \Theta & f(S_0)h_1'(0) & 0 \\ 0 & \Omega & -\Sigma & 0 \\ 0 & \Psi & 0 & -\Lambda \end{pmatrix}.$$

Then the characteristic equation at Γ_0 can be derived from the equation $|J - \lambda I| = 0$, where I here is the identity matrix and λ is the eigenvalues. We obtain

$$(\lambda + \Phi)(\lambda + \Lambda)\left[\lambda^2 + (\Sigma - f(S_0)h_2'(0) + \Theta)\lambda - f(S_0)h_2'(0)\Sigma - f(S_0)h_1'(0)\Omega + \Theta\Sigma\right] = 0. \tag{2.13}$$

This gives two negative eigenvalues $\lambda = -\Phi$ and $\lambda = -\Lambda$. Define a function G_1 on $[0, \infty)$ by

$$G_1(\lambda) = \lambda^2 + (\Sigma - f(S_0)h_2'(0) + \Theta)\lambda - f(S_0)h_2'(0)\Sigma - f(S_0)h_1'(0)\Omega + \Theta\Sigma = 0.$$

We have $G_1(0) = -f(S_0)h_2'(0)\Sigma - f(S_0)h_1'(0)\Omega + \Theta\Sigma = \Theta\Sigma(1 - \mathcal{R}_0) < 0$ when $\mathcal{R}_0 > 1$ and $\lim_{\lambda\to\infty} G_1(\lambda) = \infty$, which means that there exists one eigenvalue $\lambda > 0$ such that $G_1 = 0$ has a positive real root. Hence, Γ_0 is unstable when $\mathcal{R}_0 > 1$.

Remark 3. *From Assumptions (A1)-(A3) we have*

$$\left(\frac{h_1(P)}{P} - \frac{h_1(P_1)}{P_1}\right)(h_1(P) - h_1(P_1)) \leq 0,$$
$$\left(\frac{h_2(I)}{I} - \frac{h_2(I_1)}{I_1}\right)(h_2(I) - h_2(I_1)) \leq 0.$$

Theorem 2. *For the model (2.1)-(2.4),* Γ_1 *is GAS when* $\mathcal{R}_0 > 1$.

Proof. Constructing a function $Y_2(S, I, P, C)$ as:

$$Y_2(S, I, P, C) = S - S_1 - \int_{S_1}^{S} \frac{f(S_1)}{f(\theta)} d\theta + I_1 g\left(\frac{I}{I_1}\right) + \frac{f(S_1)h_1(P_1)}{\Sigma P_1} P_1 g\left(\frac{P}{P_1}\right) + \frac{q}{2(\Psi - \beta C_1)}(C - C_1)^2.$$

Note that $\Psi - hC_1 = \frac{\Lambda C_1}{I_1} > 0$. Clearly $Y_2(S, I, P, C) > 0$ for all $S, I, P, C > 0$ and $Y_2(S_1, I_1, P_1, C_1) = 0$. Moreover

$$\begin{aligned}
\frac{dY_2}{dt} &= \left(1 - \frac{f(S_1)}{f(S)}\right)[\Upsilon - \Phi S - (h_1(P) + h_2(I))f(S)] \\
&+ \left(1 - \frac{I_1}{I}\right)[(h_1(P) + h_2(I))f(S) - \Theta I - qIC] \\
&+ \frac{f(S_1)h_1(P_1)}{\Sigma P_1}\left(1 - \frac{P_1}{P}\right)(\Omega I - \Sigma P) + \frac{q(C - C_1)}{(\Psi - \beta C_1)}(\Psi I - \Lambda C - \beta IC) \\
&= \left(1 - \frac{f(S_1)}{f(S)}\right)(\Upsilon - \Phi S) + (h_1(P) + h_2(I))f(S_1) \\
&- \Theta(I - I_1) - qC(I - I_1) - (h_1(P) + h_2(I))f(S)\frac{I_1}{I} \\
&+ \frac{f(S_1)h_1(P_1)}{\Sigma P_1}\left(\Omega I - \Sigma P - \frac{\Omega P_1 I}{P} + \Sigma P_1\right) \\
&+ \frac{q(C - C_1)}{(\Psi - hC_1)}(\Psi I - \Lambda C - \beta IC). \qquad (2.14)
\end{aligned}$$

Applying the steady state conditions for Γ_1:

$$\begin{aligned}
\Upsilon - \Phi S_1 &= (h_1(P_1) + h_2(I_1))f(S_1) = \Theta I_1 + qI_1C_1, \\
\Omega I_1 &= \Sigma P_1, \\
\Psi I_1 &= \Lambda C_1 + \beta I_1 C_1,
\end{aligned}$$

we get

$$\begin{aligned}
\frac{dY_2}{dt} &= \Phi S_1\left(1 - \frac{f(S_1)}{f(S)}\right)\left(1 - \frac{S}{S_1}\right) + \left(1 - \frac{f(S_1)}{f(S)}\right)(h_1(P_1) + h_2(I_1))f(S_1) \\
&+ (h_1(P) + h_2(I))f(S_1) - \left(\frac{I}{I_1} - 1\right)(h_1(P_1) + h_2(I_1))f(S_1) - (h_1(P) + h_2(I))f(S)\frac{I_1}{I} \\
&+ f(S_1)h_1(P_1)\left(\frac{I}{I_1} - \frac{P}{P_1} - \frac{P_1 I}{PI_1} + 1\right) - q\left(\frac{\Lambda + \beta I}{\Psi - \beta C_1}\right)(C - C_1)^2. \\
&= \Phi S_1\left(1 - \frac{f(S_1)}{f(S)}\right)\left(1 - \frac{S}{S_1}\right) + h_1(P_1)f(S_1)\left(\frac{h_1(P)}{h_1(P_1)} - \frac{P}{P_1} + \frac{Ph_1(P_1)}{P_1h_1(P)} - 1\right) \\
&+ h_1(P_1)f(S_1)\left(4 - \frac{f(S_1)}{f(S)} - \frac{h_1(P)f(S)I_1}{h_1(P_1)f(S_1)I} - \frac{IP_1}{I_1P} - \frac{Ph_1(P_1)}{P_1h_1(P)}\right) \\
&+ h_2(I_1)f(S_1)\left[\left(\frac{h_2(I)}{h_2(I_1)} - \frac{I}{I_1} + \frac{Ih_2(I_1)}{I_1h_2(I)} - 1\right) + \left(3 - \frac{f(S_1)}{f(S)} - \frac{h_2(I)f(S)I_1}{h_2(I_1)f(S_1)I} - \frac{Ih_2(I_1)}{I_1h_2(I)}\right)\right] \\
&- q\left(\frac{\Lambda + \beta I}{\Psi - \beta C_1}\right)(C - C_1)^2. \qquad (2.15)
\end{aligned}$$

Equation (2.15) can be simplified as

$$\frac{dY_2}{dt} = \Phi S_1\left(1 - \frac{f(S_1)}{f(S)}\right)\left(1 - \frac{S}{S_1}\right) + h_1(P_1)f(S_1)\left(\frac{h_1(P)}{h_1(P_1)} - \frac{P}{P_1}\right)\left(1 - \frac{h_1(P_1)}{h_1(P)}\right)$$

$$+ h_1(P_1)f(S_1)\left(4 - \frac{f(S_1)}{f(S)} - \frac{h_1(P)f(S)I_1}{h_1(P_1)f(S_1)I} - \frac{IP_1}{I_1P} - \frac{Ph_1(P_1)}{P_1h_1(P)}\right)$$
$$+ h_2(I_1)f(S_1)\left(3 - \frac{f(S_1)}{f(S)} - \frac{h_2(I)f(S)I_1}{h_2(I_1)f(S_1)I} - \frac{Ih_2(I_1)}{I_1h_2(I)}\right)$$
$$+ h_2(I_1)f(S_1)\left(\frac{h_2(I)}{h_2(I_1)} - \frac{I}{I_1}\right)\left(1 - \frac{h_2(I_1)}{h_2(I)}\right) - q\left(\frac{\Lambda + \beta I}{\Psi - \beta C_1}\right)(C - C_1)^2.$$

Using the geometrical and arithmetical means relationship we obtain

$$4 \leq \frac{f(S_1)}{f(S)} + \frac{h_1(P)f(S)I_1}{h_1(P_1)f(S_1)I} + \frac{IP_1}{I_1P} + \frac{Ph_1(P_1)}{P_1h_1(P)},$$
$$3 \leq \frac{f(S_1)}{f(S)} + \frac{h_2(I)f(S)I_1}{h_2(I_1)f(S_1)I} + \frac{Ih_2(I_1)}{I_1h_2(I)}.$$

Using Remark 3 we get that $\frac{dY_2}{dt} \leq 0$ and $\frac{dY_2}{dt} = 0$ at the point (S_1, I_1, P_1, C_1). Let $\acute{\mathcal{D}}_1$ be the largest invariant subset of the set $\left\{(S, I, P, C) : \frac{dY_2}{dt} = 0\right\}$. Thus, the solutions of model tend to $\acute{\mathcal{D}}_1$. It is clear that $\acute{\mathcal{D}}_1$ contains unique point which is Γ_1. The global asymptotic stability of Γ_1 follows from (LIP). □

3. The model after considering the latent infected cells

Here, we shall present a pathogen dynamic model with general pathogen-to-cell and cell-to-cell transmissions as before with immune impairment but we will consider two groups of infected cells, latently infected and productively infected cells as:

$$\dot{S}(t) = \Upsilon - \Phi S(t) - (h_1(P(t)) + h_2(I(t)))\, f(S), \tag{3.1}$$
$$\dot{L}(t) = (1 - n)\,(h_1(P(t)) + h_2(I(t)))\, f(S(t)) - (d + b)L(t), \tag{3.2}$$
$$\dot{I}(t) = n\,(h_1(P(t)) + h_2(I(t)))\, f(S) - \Theta I + bL - qIC, \tag{3.3}$$
$$\dot{P}(t) = \Omega I(t) - \Sigma P(t), \tag{3.4}$$
$$\dot{C}(t) = \Psi I(t) - \Lambda C(t) - \beta I(t)C(t). \tag{3.5}$$

where, $L(t)$ and $I(t)$ are the concentration of the latently and productively infected cells at time t, respectively. The uninfected cells are become infected at rate $(h_1(P) + h_2(I))f(S)$, where f, h_1 and h_2 are continuously differentiable satisfy Assumptions (A1)-(A3) in section (2), The fractions $(1 - n)$ and n with $0 < n \leq 1$ are the probabilities that upon infection, uninfected cells will become either latently infected or productively infected, b is the average number of latently infected cells become productively infected cells and d is death rate constant of the latently infected cells. All other parameters have the same meaning as system (2.1)-(2.4).

3.1. Basic properties

Now, we will prove the non-negativity and finiteness of the solutions of the model (3.1)-(3.5).

Lemma 3. *For model (3.1)-(3.5) there exists a positively invariant compact set*

$$\Omega_2 = \left\{(S, L, I, P, C) \in \mathbb{R}^5_{\geq 0} : 0 \leq S, L, I \leq n_1, 0 \leq P \leq n_2, 0 \leq C \leq n_3\right\}. \tag{3.6}$$

Proof. We have

$$\begin{aligned}
\dot{S}\big|_{(S=0)} &= \Upsilon > 0, \\
\dot{L}\big|_{(L=0)} &= (1-n)\,(h_1(P)+h_2(I))\,f(S) \geq 0, \qquad \text{for all } S, P, I \geq 0, \\
\dot{I}\big|_{(I=0)} &= nh_1(P)f(S) + bL \geq 0, \qquad \text{for all } S, P, L \geq 0, \\
\dot{P}\big|_{(P=0)} &= \Omega I \geq 0, \qquad \text{for all } I \geq 0, \\
\dot{C}\big|_{(C=0)} &= \Psi I \geq 0, \qquad \text{for all } I \geq 0.
\end{aligned}$$

This shows the positively invariant property of $\mathbb{R}^5_{\geq 0}$ with respect to system (3.1)-(3.5).

Next we will show the finiteness of the solutions for system (3.1)-(3.5),

let $\tilde{Q} = S + L + I + \frac{\Theta}{2\Omega}P + \frac{\Theta}{4\Psi}C$, then

$$\begin{aligned}
\dot{\tilde{Q}} &= \Upsilon - \Phi S - (h_1(P)+h_2(I))\,f(S) \\
&\quad + (1-n)\,(h_1(P)+h_2(I))\,f(S) - (d+b)L \\
&\quad + n\,(h_1(P)+h_2(I))\,f(S) - \Theta I + bL - qIC \\
&\quad + \frac{\Theta}{2\Omega}\,(\Omega I - \Sigma P) + \frac{\Theta}{4\Psi}\,(\Psi I - \Lambda C - \beta IC) \\
&= \Upsilon - \Phi S - dL - \frac{\Theta}{4}I - \left(q + \frac{\Theta\beta}{4\Psi}\right)IC - \frac{\Theta\Sigma}{2\Omega}P - \frac{\Theta\Lambda}{4\Psi}C \\
&\leq \Upsilon - \Phi S - dL - \frac{\Theta}{4}I - \frac{\Theta\Sigma}{2\Omega}P - \frac{\Theta\Lambda}{4\Psi}C \\
&\leq \Upsilon - \tilde{\sigma}\left(S + L + I + \frac{\Theta}{2\Omega}P + \frac{\Theta}{4\Psi}C\right) = \Upsilon - \tilde{\sigma}\tilde{Q},
\end{aligned}$$

where, $\tilde{\sigma} = \min\{\Phi, d, \frac{\Theta}{4}, \Sigma, \Lambda\}$. Then

$$\tilde{Q}(t) \leq e^{-\tilde{\sigma}t}\left(\tilde{Q}(0) - \frac{\Upsilon}{\tilde{\sigma}}\right) + \frac{\Upsilon}{\tilde{\sigma}}.$$

From last equation we conclude that, $0 \leq \tilde{Q}(t) \leq n_1$ for all $t \geq 0$ if $\tilde{Q}(0) \leq n_1$, where $n_1 = \frac{\Upsilon}{\tilde{\sigma}}$. Since $S(t), L(t), I(t), P(t)$ and $C(t)$ are all non-negative, then $0 \leq S(t), L(t), I(t) \leq n_1$, $0 \leq P(t) \leq n_2$ and $C(t) \leq n_3$ for all $t \geq 0$ if $S(0) + L(0) + I(0) + \frac{\Theta}{2\Omega}P(0) + \frac{\Theta}{4\Psi}C(0) \leq n_1$, where $n_2 = \frac{2\Omega\Upsilon}{\Theta\tilde{\sigma}}$ and $n_3 = \frac{4\Psi\Upsilon}{\Theta\tilde{\sigma}}$. Therefore $S(t), L(t), I(t), P(t)$ and $C(t)$ are bounded. □

In the next lemma, we will prove the existence of the steady states for the system (3.1)-(3.5).

Lemma 4. *For the model (3.1)-(3.5), suppose that Assumption (A1)-(A3) are satisfied and there exists a parameter $\mathcal{R}_0 > 0$ such that*

(i) if $\mathcal{R}_0 \leq 1$, then only one steady state Γ_0 exists,

(ii) if $\mathcal{R}_0 > 1$, then two steady states Γ_0 and Γ_1 exist.

Proof. consider (S, L, I, P, C) be any steady state achieve the following equations:

$$0 = \Upsilon - \Phi S - (h_1(P)+h_2(I))\,f(S), \tag{3.7}$$

$$0 = (1-n)\left(h_1(P) + h_2(I)\right) f(S) - (d+b)L, \tag{3.8}$$

$$0 = n\left(h_1(P) + h_2(I)\right) f(S) + bL - \Theta I - qIC \tag{3.9}$$

$$0 = \Omega I - \Sigma P, \tag{3.10}$$

$$0 = \Psi I - \Lambda C - \beta IC. \tag{3.11}$$

From Eqs (3.7)-(3.11), the system has a uninfected steady state $\Gamma_0 = (S_0, 0, 0, 0, 0)$, where $S_0 = \dfrac{\Upsilon}{\Phi}$ and if $I \neq 0$ we can define another steady state $\Gamma = (S, L, I, P, C)$ satisfies the following equation

$$0 = \frac{(h_1(P) + h_2(I))f(S)}{I} - \Theta - \frac{dL}{I} - qC,$$

such that

$$P = \frac{\Omega I}{\Sigma}, \tag{3.12}$$

$$L = \frac{(1-n)(h_1(P) + h_2(I))f(S)}{d+b}, \tag{3.13}$$

$$C = \frac{\Psi I}{\beta I + \Lambda}, \tag{3.14}$$

and S satisfy the equation

$$0 = \Upsilon - \Phi S - (h_1(P) + h_2(I))f(S).$$

Define a function H on $[0, \infty)$ by

$$H(I) = \frac{(nd+b)(h_1(P) + h_2(I))f(S)}{(d+b)I} - \Theta - qC$$

Since $\lim_{I\to\infty} H(I) = -\Theta - \dfrac{\Psi q}{\beta} < 0$ and $\lim_{I\to 0} H(I) = \Theta\left[\left(\frac{nd+b}{\Theta(b+d)}\right)(\frac{\Omega}{\Sigma}h_1'(0) + h_2'(0))f(S_0) - 1\right] > 0$. Consequently there exists $I_1 \in (0, \infty)$ and from Eqs (3.12)-(3.14) we have $P_1 > 0, L_1 > 0$ and $C_1 > 0$ when $\Theta\left[\left(\frac{\Omega h_1'(0)}{\Theta\Sigma} + \frac{h_2'(0)}{\Theta}\right) f(S_0) - 1\right] > 0$. Thus, we can define the basic reproduction number $\mathcal{R}_0$ as:

$$\mathcal{R}_0 = \left(\frac{nd+b}{\Theta(b+d)}\right)\left(\frac{\Omega}{\Sigma}h_1'(0) + h_2'(0)\right) f(S_0). \tag{3.15}$$

It follows that the infected steady state $\Gamma_1 = (S_1, L_1, I_1, P_1, C_1)$ exists if $\mathcal{R}_0 > 1$. □

3.2. Global characteristics

In this subsection, we will show the global stability of the model (3.1)-(3.5) steady states by choosing appropriate Lyapunov functions.

Theorem 3. *For the model (3.1)-(3.5),* Γ_0 *is GAS when* $\mathcal{R}_0 < 1$.

Proof. Let $\mathcal{R}_0 < 1$ and constructing a Lyapunov function $N_1(S, L, I, P, C)$ as:

$$N_1(S, L, I, P, C) = S - S_0 - \int_{S_0}^{S} \frac{f(S_0)}{f(\theta)} d\theta + \frac{b}{nd+b} L + \frac{b+d}{nd+b} I + \frac{f(S_0)h_1'(0)}{\Sigma} P + \frac{\Theta(1-\mathcal{R}_0)}{\Psi} \frac{b+d}{nd+b} C.$$

Clearly, $N_1(S, L, I, P, C) > 0$ for all $S, L, I, P, C > 0$ and $N_1(S_0, 0, 0, 0, 0) = 0$. Calculating $\frac{dN_1}{dt}$ along the system (3.1)-(3.5), we get

$$\begin{aligned}
\frac{dN_1}{dt} &= \left(1 - \frac{f(S_0)}{f(S)}\right)(\Upsilon - \Phi S - (h_1(P) + h_2(I))\, f(S)) \\
&+ \frac{b}{nd+b}\left[(1-n)\,(h_1(P) + h_2(I))\, f(S) - (d+b)L\right] \\
&+ \frac{b+d}{nd+b}\left[n\,(h_1(P) + h_2(I))\, f(S) - \Theta I + bL - qIC\right] \\
&+ \frac{f(S_0)h_1'(0)}{\Sigma}(\Omega I - \Sigma P) + \frac{\Theta(1-\mathcal{R}_0)}{\Psi}\frac{b+d}{nd+b}(\Psi I - \Lambda C - \beta IC) \\
&= \left(1 - \frac{f(S_0)}{f(S)}\right)(\Upsilon - \Phi S) + (h_1(P) + h_2(I))f(S_0) - \mathcal{R}_0 \frac{b+d}{nd+b}\,\Theta I \\
&+ \frac{f(S_0)h_1'(0)}{\Sigma}(\Omega I - \Sigma P) - \frac{b+d}{nd+b}\left(q + \frac{\Theta\beta(1-\mathcal{R}_0)}{\Psi}\right) IC - \frac{b+d}{nd+b}\frac{\Theta\Lambda(1-\mathcal{R}_0)}{\Psi} C.
\end{aligned}$$

From Remark 2 we get

$$\frac{dN_1}{dt} \leq \Upsilon\left(1 - \frac{f(S_0)}{f(S)}\right)\left(1 - \frac{S}{S_0}\right) - \frac{b+d}{nd+b}\left(q + \frac{\Theta\beta(1-\mathcal{R}_0)}{\Psi}\right) IC - \frac{b+d}{nd+b}\frac{\Theta\Lambda(1-\mathcal{R}_0)}{\Psi} C.$$

Since $\mathcal{R}_0 < 1$, then $\frac{dN_1}{dt} \leq 0$ for all $S, L, I, P, C > 0$ and can easily note that $\frac{dN_1}{dt} = 0$ at Γ_0. Applying LIP, we conclude that Γ_0 is GAS.

Furthermore, using the same method that was previously discussed in Theorem 1, the characteristic equation at Γ_0 is given by

$$(\lambda + \Phi)(\lambda + \Lambda)(\lambda^3 + A\lambda^2 + B\lambda + D) = 0, \tag{3.16}$$

where

$$\begin{aligned}
A &= -nf(S_0)h_2'(0) + \Theta + b + \Sigma + d, \\
B &= -nf(S_0)h_2'(0)(\Sigma + d + b) + \Theta(b + d + \Sigma) + \Sigma(d + b), \\
D &= -\left[(nd+b)\,(\Omega h_1'(0) + \Sigma h_2'(0))\right] f(S_0) + \Theta\Sigma(d+b) \\
&= \Theta\Sigma(d+b)\left[1 - \left(\frac{nd+b}{d+b}\right)\left(\frac{\Omega h_1'(0)}{\Theta\Sigma} + \frac{h_2'(0)}{\Theta}\right) f(S_0)\right] \\
&= \Theta\Sigma(d+b)(1 - \mathcal{R}_0).
\end{aligned}$$

This gives $\lambda = -\Phi$ and $\lambda = -\Lambda$. Define a function G_2 on $[0, \infty)$ by

$$G_2(\lambda) = \lambda^3 + A\lambda^2 + B\lambda + D.$$

We have $G_2(0) = \Theta\Sigma(d+b)(1-\mathcal{R}_0) < 0$ when $\mathcal{R}_0 > 1$ and $\lim_{\lambda\to\infty} G_2(\lambda) = \infty$, which means that G_2 has a positive real root. Hence, Γ_0 is unstable for $\mathcal{R}_0 > 1$ and this completes the proof. □

Theorem 4. *For the model (3.1)-(3.5), Γ_1 is GAS when $\mathcal{R}_0 > 1$.*

Proof. Let a Lyapunov function $N_2(S, L, I, P, C)$ be defined as:

$$N_2(S,L,I,P,C) = S - S_1 - \int_{S_1}^{S} \frac{f(S_1)}{f(\theta)}d\theta + \frac{b}{nd+b}L_1 g\left(\frac{L}{L_1}\right) + \frac{b+d}{nd+b}I_1 g\left(\frac{I}{I_1}\right) + \frac{f(S_1)h_1(P_1)}{\Sigma P_1}P_1 g\left(\frac{P}{P_1}\right) + \frac{q}{2(\Psi-\beta C_1)}\frac{b+d}{nd+b}(C-C_1)^2.$$

Clearly, $N_2(S, L, I, P, C) > 0$ for all $S, L, I, P, C > 0$, and $N_2(S_1, L_1, I_1, P_1, C_1) = 0$. Calculating $\frac{dN_2}{dt}$ along the trajectories of (3.1)-(3.5), we get

$$\begin{aligned}
\frac{dN_2}{dt} &= \left(1-\frac{f(S_1)}{f(S)}\right)\left[\Upsilon - \Phi S - (h_1(P)+h_2(I))\,f(S)\right] \\
&+ \frac{b}{nd+b}\left(1-\frac{L_1}{L}\right)\left[(1-n)\,(h_1(P)+h_2(I))\,f(S) - (d+b)L\right] \\
&+ \frac{b+d}{nd+b}\left(1-\frac{I_1}{I}\right)\left[n(h_1(P)+h_2(I))f(S) - \Theta I + bL - qIC\right] \\
&+ \frac{f(S_1)h_1(P_1)}{\Sigma P_1}\left(1-\frac{P_1}{P}\right)(\Omega I - \Sigma P) + \frac{q}{\Psi-\beta C_1}\frac{b+d}{nd+b}(C-C_1)\,(\Psi I - \Lambda C - \beta IC) \\
&= \left(1-\frac{f(S_1)}{f(S)}\right)(\Upsilon - \Phi S) + (h_1(P)+h_2(I))\,f(S_1) \\
&- \frac{b}{nd+b}\left[(1-n)\,(h_1(P)+h_2(I))\,f(S)\frac{L_1}{L} + (d+b)L_1\right] \\
&- \frac{b+d}{nd+b}\left[n\,(h_1(P)+h_2(I))\,f(S)\frac{I_1}{I} + \Theta(I-I_1) + bL\frac{I_1}{I} + qC(I-I_1)\right] \\
&+ f(S_1)h_1(P_1)\left(\frac{\Omega I}{\Sigma P_1} - \frac{P}{P_1} - \frac{\Omega I}{\Sigma P} + 1\right) \\
&+ \frac{q}{\Psi-\beta C_1}\frac{b+d}{nd+b}(C-C_1)\,(\Psi I - \Lambda C - \beta IC)\,. \qquad (3.17)
\end{aligned}$$

Collecting terms of Eq (3.17) and applying the steady state conditions for Γ_1:

$$\begin{aligned}
\Upsilon - \Phi S_1 &= (h_1(P_1)+h_2(I_1))\,f(S_1), \\
(1-n)\,(h_1(P_1)+h_2(I_1))\,f(S_1) &= (d+b)L_1, \\
n\,(h_1(P_1)+h_2(I_1))\,f(S_1) + bL_1 &= \Theta I_1 + qI_1C_1, \\
\Omega I_1 &= \Sigma P_1, \\
\Psi I_1 &= \Lambda C_1 + \beta I_1 C_1,
\end{aligned}$$

and

$$\frac{b+d}{nd+b}(\Theta I_1 + qI_1C_1) = \frac{b+d}{nd+b}\left[n\,(h_1(P_1)+h_2(I_1))\,f(S_1) + bL_1\right]$$

$$
\begin{aligned}
&= \frac{b+d}{nd+b} n\left(h_1(P_1)+h_2(I_1)\right) f(S_1) + \frac{b(1-n)}{nd+b}\left(h_1(P_1)+h_2(I_1)\right) f(S_1) \\
&= \left(h_1(P_1)+h_2(I_1)\right) f(S_1),
\end{aligned}
$$

we get

$$
\begin{aligned}
\frac{dN_2}{dt} &= \Phi S_1\left(1-\frac{f(S_1)}{f(S)}\right)\left(1-\frac{S}{S_1}\right) + \left(1-\frac{f(S_1)}{f(S)}\right)\left(h_1(P_1)+h_2(I_1)\right) f(S_1) + \left(h_1(P)+h_2(I)\right) f(S_1) \\
&\quad - \frac{b(1-n)}{nd+b}\left(h_1(P)+h_2(I)\right) f(S)\frac{L_1}{L} + \frac{b(d+b)}{nd+b}L_1 \\
&\quad - \frac{b+d}{nd+b}\left[n\left(h_1(P)+h_2(I)\right) f(S)\frac{I_1}{I} + \left(n\left(h_1(P_1)+h_2(I_1)\right) f(S_1) + bL_1\right)\left(\frac{I}{I_1}-1\right)\right] \\
&\quad - \frac{b(1-n)}{nd+b}\left(h_1(P_1)+h_2(I_1)\right)\frac{I_1 L}{I L_1} + f(S_1)h_1(P_1)\left(\frac{\Omega I}{\Sigma P_1} - \frac{P}{P_1} - \frac{\Omega I}{\Sigma P} + 1\right) \\
&\quad - \frac{q(\Lambda+hI)}{\Psi-\beta C_1}\frac{b+d}{nd+b}(C-C_1)^2.
\end{aligned}
$$

$$
\begin{aligned}
\frac{dN_2}{dt} &= \Phi S_1\left(1-\frac{f(S_1)}{f(S)}\right)\left(1-\frac{S}{S_1}\right) + h_1(P_1)f(S_1)\left(\frac{h_1(P)}{h_1(P_1)} - \frac{P}{P_1}\right) \\
&\quad + \frac{b(1-n)}{nd+b}h_1(P_1)f(S_1)\left(4 - \frac{f(S_1)}{f(S)} - \frac{L_1 h_1(P) f(S)}{L h_1(P_1) f(S_1)} - \frac{I_1 L}{I L_1} - \frac{I}{I_1} + \frac{I}{I_1} - \frac{P_1 I}{P I_1}\right) \\
&\quad + h_2(I_1)f(S_1)\left(\frac{h_2(I)}{h_2(I_1)} - \frac{I}{I_1}\right) + \frac{b(1-n)}{nd+b}h_2(I_1)f(S_1)\left(3 - \frac{f(S_1)}{f(S)} - \frac{I_1 L}{I L_1} - \frac{L_1 h_2(I) f(S)}{L h_2(I_1) f(S_1)}\right) \\
&\quad + \frac{b+d}{nd+b}nh_1(P_1)f(S_1)\left(3 - \frac{f(S_1)}{f(S)} - \frac{I_1 h_1(P) f(S)}{I h_1(P_1) f(S_1)} - \frac{I}{I_1} + \frac{I}{I_1} - \frac{I P_1}{I_1 P}\right) \\
&\quad + \frac{b+d}{nd+b}nh_2(I_1)f(S_1)\left(2 - \frac{f(S_1)}{f(S)} - \frac{I_1 h_2(I) f(S)}{I h_2(I_1) f(S_1)}\right) \\
&\quad - \frac{q\left(\Lambda+hI\right)}{\Psi-\beta C_1}\frac{b+d}{nd+b}(C-C_1)^2.
\end{aligned}
$$

$$
\begin{aligned}
\frac{dN_2}{dt} &= \Phi S_1\left(1-\frac{f(S_1)}{f(S)}\right)\left(1-\frac{S}{S_1}\right) + h_1(P_1)f(S_1)\left(\frac{h_1(P)}{h_1(P_1)} - \frac{P}{P_1} + \frac{P h_1(P_1)}{P_1 h_1(P)} - 1\right) \\
&\quad + \frac{b(1-n)}{nd+b}h_1(P_1)f(S_1)\left(5 - \frac{f(S_1)}{f(S)} - \frac{L_1 h_1(P) f(S)}{L h_1(P_1) f(S_1)} - \frac{I_1 L}{I L_1} - \frac{P_1 I}{P I_1} - \frac{P h_1(P_1)}{P_1 h_1(P)}\right) \\
&\quad + \frac{b+d}{nd+b}nh_1(P_1)f(S_1)\left(4 - \frac{f(S_1)}{f(S)} - \frac{I P_1}{I_1 P} - \frac{I_1 h_1(P) f(S)}{I h_1(P_1) f(S_1)} - \frac{P h_1(P_1)}{P_1 h_1(P)}\right) \\
&\quad + h_2(I_1)f(S_1)\left(\frac{h_2(I)}{h_2(I_1)} - \frac{I}{I_1} + \frac{I h_2(I_1)}{I_1 h_2(I)} - 1\right) \\
&\quad + \frac{b(1-n)}{nd+b}h_2(I_1)f(S_1)\left(4 - \frac{f(S_1)}{f(S)} - \frac{I_1 L}{I L_1} - \frac{L_1 h_2(I) f(S)}{L h_2(I_1) f(S_1)} - \frac{I h_2(I_1)}{I_1 h_2(I)}\right)
\end{aligned}
$$

$$
\begin{aligned}
&+\frac{b+d}{nd+b}nh_2(I_1)f(S_1)\left(3-\frac{f(S_1)}{f(S)}-\frac{I_1h_2(I)f(S)}{Ih_2(I_1)f(S_1)}-\frac{Ih_2(I_1)}{I_1h_2(I)}\right)\\
&-\frac{q(\Lambda+hI)}{\Psi-\beta C_1}\frac{b+d}{nd+b}(C-C_1)^2\\
&=\Phi S_1\left(1-\frac{f(S_1)}{f(S)}\right)\left(1-\frac{S}{S_1}\right)+h_1(P_1)f(S_1)\left(\frac{h_1(P)}{h_1(P_1)}-\frac{P}{P_1}\right)\left(1-\frac{h_1(P_1)}{h_1(P)}\right)\\
&+\frac{b(1-n)}{nd+b}h_1(P_1)f(S_1)\left(5-\frac{f(S_1)}{f(S)}-\frac{L_1h_1(P)f(S)}{Lh_1(P_1)f(S_1)}-\frac{I_1L}{IL_1}-\frac{P_1I}{PI_1}-\frac{Ph_1(P_1)}{P_1h_1(P)}\right)\\
&+\frac{b+d}{nd+b}nh_1(P_1)f(S_1)\left(4-\frac{f(S_1)}{f(S)}-\frac{IP_1}{I_1P}-\frac{I_1h_1(P)f(S)}{Ih_1(P_1)f(S_1)}-\frac{Ph_1(P_1)}{P_1h_1(P)}\right)\\
&+h_2(I_1)f(S_1)\left(\frac{h_2(I)}{h_2(I_1)}-\frac{I}{I_1}\right)\left(1-\frac{h_2(I_1)}{h_2(I)}\right)\\
&+\frac{b(1-n)}{nd+b}h_2(I_1)f(S_1)\left(4-\frac{f(S_1)}{f(S)}-\frac{I_1L}{IL_1}-\frac{L_1h_2(I)f(S)}{Lh_2(I_1)f(S_1)}-\frac{Ih_2(I_1)}{I_1h_2(I)}\right)\\
&+\frac{b+d}{nd+b}nh_2(I_1)f(S_1)\left(3-\frac{f(S_1)}{f(S)}-\frac{I_1h_2(I)f(S)}{Ih_2(I_1)f(S_1)}-\frac{Ih_2(I_1)}{I_1h_2(I)}\right)\\
&-\frac{q(\Lambda+hI)}{\Psi-\beta C_1}\frac{b+d}{nd+b}(C-C_1)^2. \qquad (3.18)
\end{aligned}
$$

If $\mathcal{R}_0 > 1$, then we have $S_1, L_1, I_1, P_1, C_1 > 0$. The geometrical and arithmetical means relationship implies that

$$
\begin{aligned}
5 &\le \frac{f(S_1)}{f(S)}+\frac{L_1h_1(P)f(S)}{Lh_1(P_1)f(S_1)}+\frac{I_1L}{IL_1}+\frac{P_1I}{PI_1}+\frac{Ph_1(P_1)}{P_1h_1(P)},\\
4 &\le \frac{f(S_1)}{f(S)}+\frac{IP_1}{I_1P}+\frac{I_1h_1(P)f(S)}{Ih_1(P_1)f(S_1)}+\frac{Ph_1(P_1)}{P_1h_1(P)},\\
4 &\le \frac{f(S_1)}{f(S)}+\frac{I_1L}{IL_1}+\frac{L_1h_2(I)f(S)}{Lh_2(I_1)f(S_1)}+\frac{Ih_2(I_1)}{I_1h_2(I)},\\
3 &\le \frac{f(S_1)}{f(S)}+\frac{I_1h_2(I)f(S)}{Ih_2(I_1)f(S_1)}+\frac{Ih_2(I_1)}{I_1h_2(I)}.
\end{aligned}
$$

Thus, $\frac{dN_2}{dt} \le 0$ for all $S, L, I, P, C > 0$ and $\frac{dN_2}{dt} = 0$ when $S = S_1, L = L_1, I = I_1, P = P_1$ and $C = C_1$. Using LIP we conclude that Γ_1 is GAS when $\mathcal{R}_0 > 1$. □

4. Numerical simulations

In this section, we propose two examples and carry out numerical simulations to approve our theoretical results shown in this paper. All of numerical computations are carried out by MATLAB.

4.1. Example of the model (2.1)-(2.4)

To perform numerical simulations and demonstrate the global asymptotic stability of the steady states of models, we choose the following functions $f(S) = \frac{S^r}{1+\alpha_3 S^r}$, $h_1(P) = \frac{\eta_1 P}{1+\alpha_1 P}$ and $h_2(I) = \frac{\eta_2 I}{1+\alpha_2 I}$

where $\eta_1, \eta_1 > 0$, $\alpha_1, \alpha_2 \geq 0$ and $r \leq 1$. We introduce the following model as a special case of the system (2.1)-(2.4)

$$\dot{S} = \Upsilon - \Phi S - \left(\frac{\eta_1 P}{1+\alpha_1 P} + \frac{\eta_2 I}{1+\alpha_2 I}\right)\frac{S^r}{1+\alpha_3 S^r}, \tag{4.1}$$

$$\dot{I} = \left(\frac{\eta_1 P}{1+\alpha_1 P} + \frac{\eta_2 I}{1+\alpha_2 I}\right)\frac{S^r}{1+\alpha_3 S^r} - \Theta I - qIC, \tag{4.2}$$

$$\dot{P} = \Omega I - \Sigma P, \tag{4.3}$$

$$\dot{C} = \Psi I - \Lambda C - \beta IC. \tag{4.4}$$

Now we verify the conditions (A1)-(A3):
(A1) It is clear that $f(S) = \frac{S^r}{1+\alpha_3 S^r} > 0$ as $S > 0$, $h_1(P) = \frac{\eta_1 P}{1+\alpha_1 P} > 0$ as $P > 0$ and $h_2(I) = \frac{\eta_2 I}{1+\alpha_2 I} > 0$ as $I > 0$ where α_1, α_2 and α_3 are a positive constants, also $f(0) = h_1(0) = h_2(0) = 0$.
(A2) $f'(S) = \frac{rS^{r-1}}{(1+\alpha_3 S^r)^2} > 0$ where r is a positive, $h_1'(P) = \frac{\eta_1}{(1+\alpha_1 P)^2} > 0$ and $h_2'(I) = \frac{\eta_2}{(1+\alpha_2 I)^2} > 0$.
(A3) $\left(\frac{f(S)}{S}\right)' = \frac{S^{r-2}[(r-1)-\alpha_3 S^r]}{(1+\alpha_3 S^r)^2} < 0$, $\left(\frac{h_1(P)}{P}\right)' = \frac{-\eta_1\alpha_1}{(1+\alpha_1 P)^2} < 0$ and $\left(\frac{h_2(I)}{I}\right)' = \frac{-\eta_2\alpha_2}{(1+\alpha_2 I)^2} < 0$ for all $S > 0$, $P > 0$ and $I > 0$. The basic reproduction number for the previous functions is $\mathcal{R}_0 = \left(\frac{\Omega\eta_1}{\Theta\Sigma} + \frac{\eta_2}{\Theta}\right)\left(\frac{S_0^r}{1+\alpha_3 S_0^r}\right)$.
We shall carry out numerical simulations for the system (4.1)-(4.4) using the parameters values given in Table 1. We choose three initial conditions as:

IC1: $S(0) = 900, I(0) = 50, P(0) = 100, C(0) = 5.5$,
IC2: $S(0) = 600, I(0) = 30, P(0) = 50, C(0) = 4.5$, and
IC3: $S(0) = 300, I(0) = 20, P(0) = 20, C(0) = 3.5$.

Case (1) To study the effect of η_1 on steady states stability:

We choose $\beta = 0.1$, $\alpha_1 = \alpha_2 = 0$, $\alpha_3 = 0.01$ and η_1 is varied as:

(i) if $\eta_1 = 0.05$, then we compute $\mathcal{R}_0 = 1.7395 > 1$. Lemma 2 states that the system has two steady states Γ_0 and Γ_1. As we can see from Figure 1 that numerical results agree with theoretical results of Theorem 2 and the system solutions converge to the steady state $\Gamma_1 = (124.5669, 45.2466, 82.9521, 4.8919)$ for all IC1-IC3.
(ii) if $\eta_1 = 0.02$ then, $\mathcal{R}_0 = 0.7181 < 1$. From Lemma 2, the system has only one steady state Γ_0. For Figure 1 we note that, uninfected cells concentration is growing up to its original value $S_0 = 1300$, while the concentration of infected cells, pathogens and CTL cells are decreasing and approaching zero for IC1-IC3. It shows that, Γ_0 is GAS and this means that the pathogens are cleaned up, so it supports Theorem 1.

Case(2) Effect of β on the pathogen dynamics:

For this purpose, we let $\eta_1 = 0.05$, $\alpha_3 = 0.01$, and β is varied. Suppose a new set of initial conditions as: IC4: $S(0) = 700, I(0) = 20, P(0) = 35, C(0) = 20$. As it is illustrated in Figure 2 that as β is decreased, the uninfected cells concentrations are increased. While the infected cells concentration and the pathogens are decayed as a result of CTL cells concentration is increased. Also β has not effect on $\mathcal{R}_0$ value, therefore it does not effect the steady states stability properties.

Case (3) Effect of α_3 on the pathogen dynamics:

For this, let $\eta_1 = 0.005$ and α_3 is varied. We suppose the initial conditions

IC5: $S(0) = 600, I(0) = 20, P(0) = 35, C(0) = 4$. From Table 2, we note that $\mathcal{R}_0$ values are increased as α_3 is decreased and we find that: if $\alpha_3 > \alpha_3^c = 0.001464$, then $\mathcal{R}_0 < 1$ and the solutions

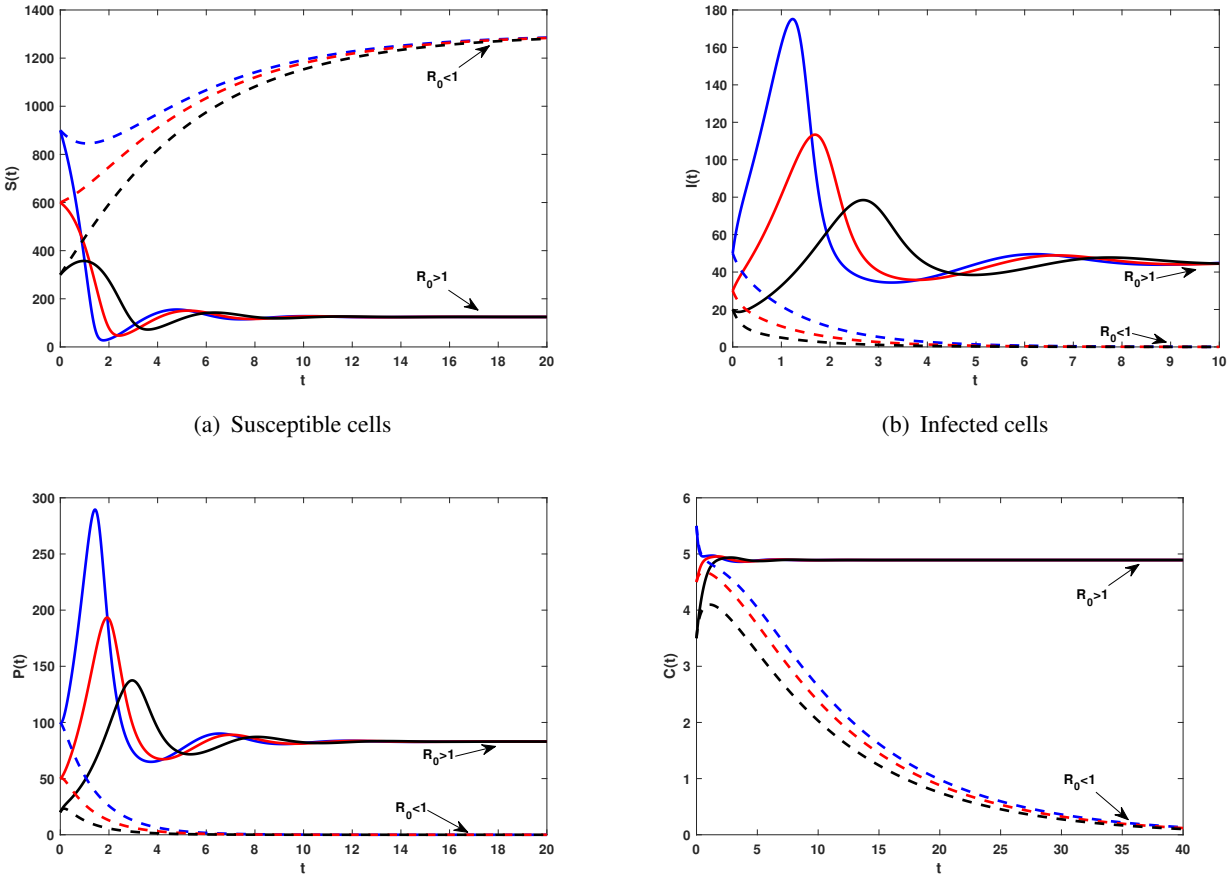
converges to Γ_0, and if $0 < \alpha_3 < 0.001464$, then $\mathcal{R}_0 > 1$ and the system solutions converge to Γ_1. Figures 3 with Theorem 2 have proved the compatibility of numerical and theoretical results.

Table 1. Parameters values of the model (4.1)-(4.4).

Parameter	Value	Parameter	Value	Parameter	Value
Υ	260	η_2	0.002	Σ	3
Φ	0.2	Θ	5	Ψ	0.5
r	1	q	0.04	Λ	2
α_1, α_2	0.01	Ω	5.5	$n, \eta_1, \alpha_3, \beta$	varied

Table 2. Variable α_3 and corresponding steady states and $\mathcal{R}_0$ values for model (4.1)-(4.4).

α_3	Steady state	$\mathcal{R}_0$
0.01	$\Gamma_0 = (1300, 0, 0, 0)$	0.2074
0.001464	$\Gamma_1 = (1297.7, 0.0858, 0.01579, 0.4545)$	1.000
0.0005	$\Gamma_1 = (853.4725, 17.2105, 31.5526, 4.7254)$	1.7596
0	$\Gamma_1 = (656.7340, 24.7780, 45.4263, 4.8060)$	2.9033



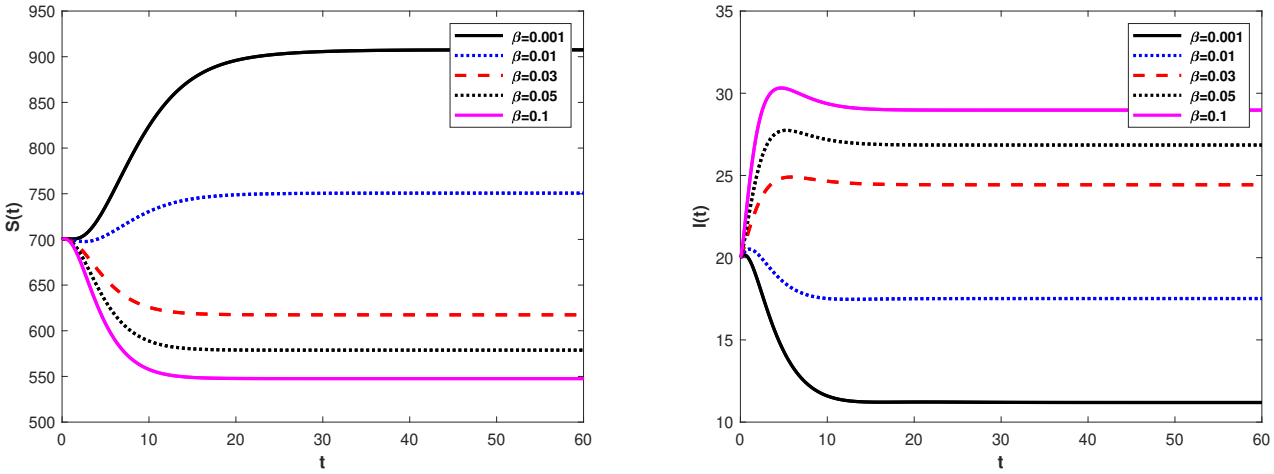
(a) Susceptible cells

(b) Infected cells

(c) Pathogens

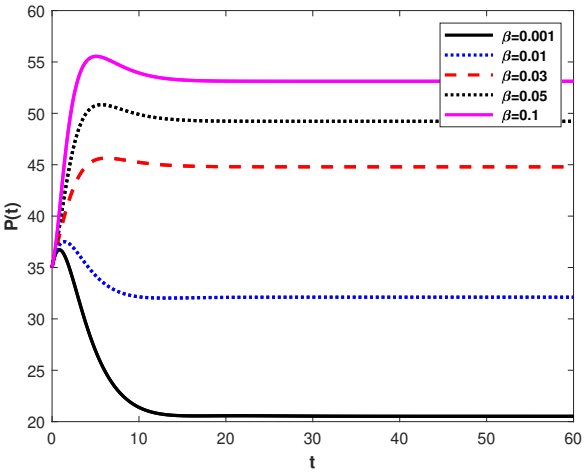
(d) CTL cells

Figure 1. The trajectories simulations of model (4.1)-(4.4) with IC1-IC3.

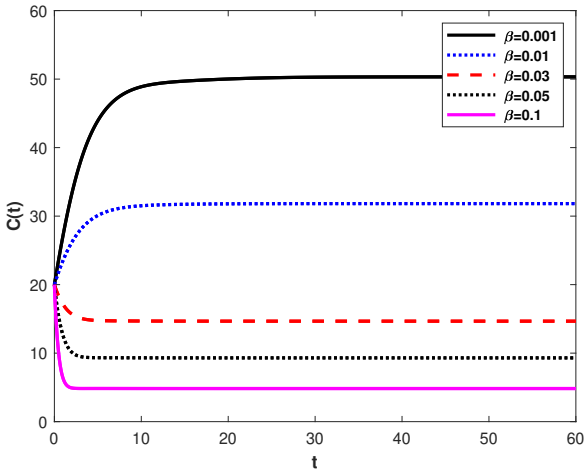


(a) Susceptible cells

(b) Infected cells

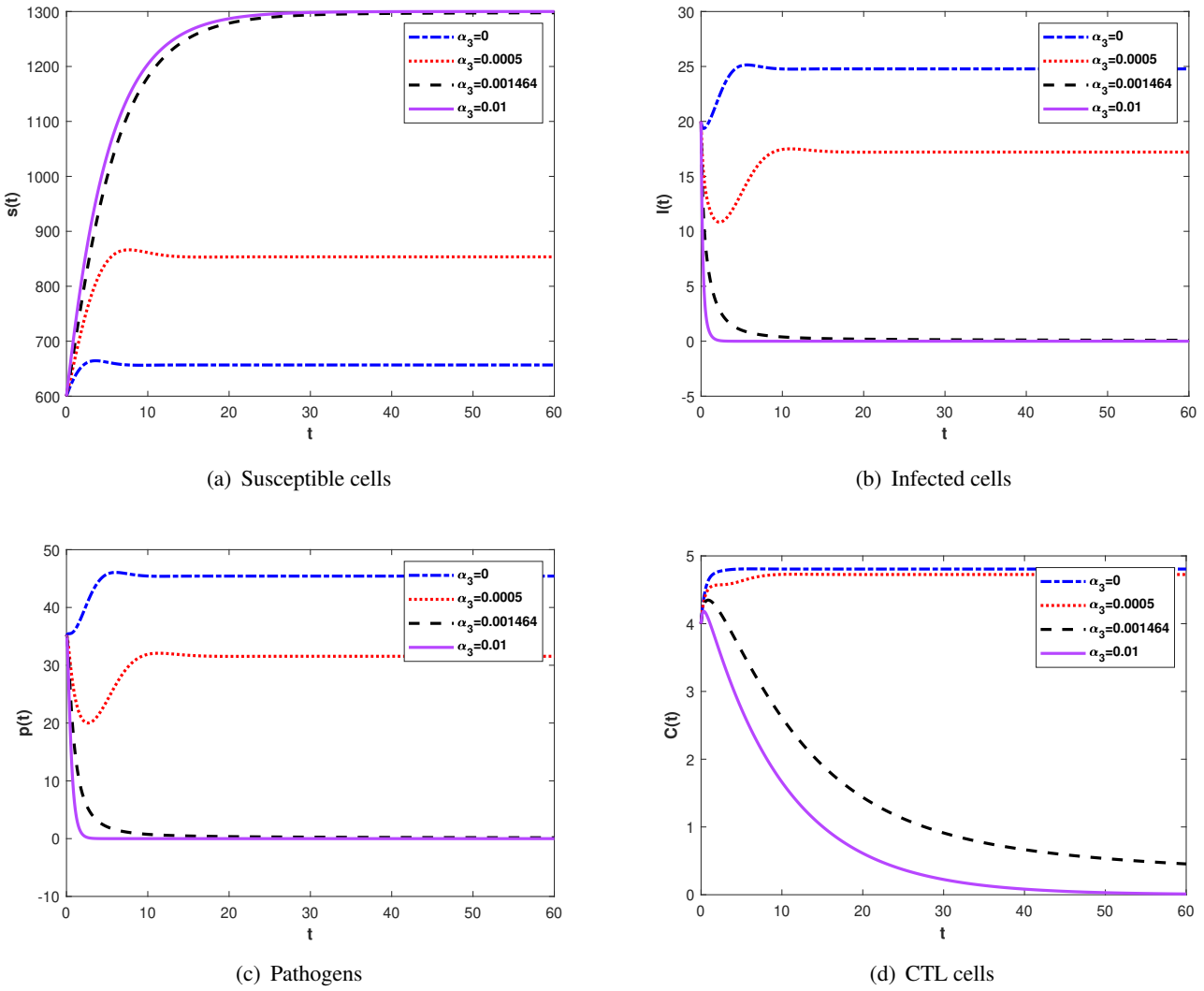


(c) Pathogens



(d) CTL cells

Figure 2. The trajectories simulations of model (4.1)-(4.4) with different values of β.



(a) Susceptible cells

(b) Infected cells

(c) Pathogens

(d) CTL cells

Figure 3. The trajectories simulations of model (4.1)-(4.4) with different values of α_3.

4.2. Example of the model (3.1)-(3.5)

In this subsection, we will implement numerical simulations for a special case of the model (3.1)-(3.5) as

$$\dot{S} = \Upsilon - \Phi S - \left(\frac{\eta_1 P}{1+\alpha_1 P} + \frac{\eta_2 I}{1+\alpha_2 I}\right)\frac{S^r}{1+\alpha_3 S^r}, \tag{4.5}$$

$$\dot{L} = (1-n)\left(\frac{\eta_1 P}{1+\alpha_1 P} + \frac{\eta_2 I}{1+\alpha_2 I}\right)\frac{S^r}{1+\alpha_3 S^r} - (d+b)L, \tag{4.6}$$

$$\dot{I} = n\left(\frac{\eta_1 P}{1+\alpha_1 P} + \frac{\eta_2 I}{1+\alpha_2 I}\right)\frac{S^r}{1+\alpha_3 S^r} - \Theta I - bL - qIC, \tag{4.7}$$

$$\dot{p} = \Omega I - \Sigma P, \tag{4.8}$$

$$\dot{C} = \Psi I - \Lambda C - \beta IC, \tag{4.9}$$

where the parameters values given in Table 3. We suppose that $\alpha_1 = \alpha_2 = \alpha$ with no loss of generality.

We will choose three sets of initial conditions as:

IC1: $S(0) = 900, L(0) = 200, I(0) = 15, P(0) = 30, C(0) = 4.4$,

IC2: $S(0) = 600, L(0) = 150, I(0) = 10, P(0) = 20, C(0) = 3$, and

IC3: $S(0) = 400, L(0) = 75, I(0) = 5, P(0) = 10, C(0) = 2$.

Case (1) Effect of η_1 on steady states stability:

We choose $\alpha = 0.01, \beta = 0.1, n = 0.5, q = 0.04$ and η_1 is varied as:

(i) if $\eta_1 = 0.0005$, then we compute $\mathcal{R}_0 = 0.9682 < 1$. From Lemma 4 we have that the system has only one steady state Γ_0. We observe from Figure 4 that, uninfected cells concentration is rising and tends its free-disease value $S_0 = 1350$, on the other hand we find that the concentrations of latently infected cells, productively infected, pathogens and CTL cells are decreasing and tend to zero for IC1-IC3. This proves that, Γ_0 is GAS, the pathogen will be cleared and this consistent with Theorem 3.

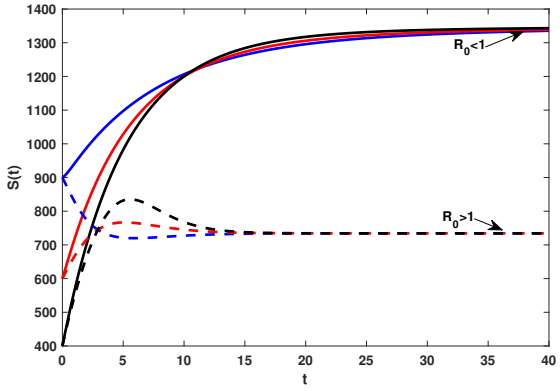
(ii) if $\eta_1 = 0.005$ then, $\mathcal{R}_0 = 2.3182 > 1$. As we discussed before in Lemma 4 that the system has two positive steady states Γ_0 and Γ_1. We note that Figure 4 results are consistent with Theorem 4 results. It is seen that, the solutions of the system converge to the endemic steady state $\Gamma_1 = (734.2778, 205.2407, 14.4357, 26.4654, 4.6761)$ for all IC1-IC3.

Case (2) Effect of saturation on the pathogen dynamics:

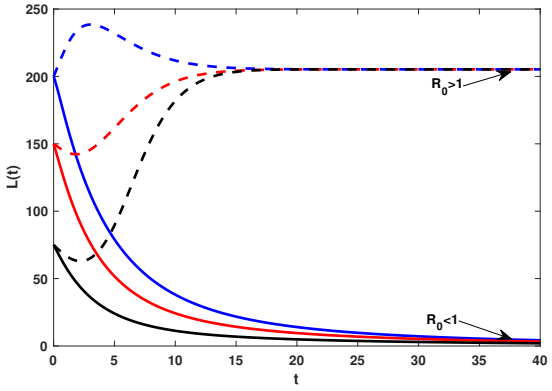
For this purpose, let $\eta_1 = 0.005, \beta = 0.1, n = 0.5$ and α is changed and we will choose the first set of initial conditions. The effect of saturated incidence is incorporated so in Figure 5, we note as α is increased, both pathogen-to-cell and cell-to-cell infection rates are decreased. Accordingly, the susceptible cells concentration is increased, the latently infected cells, productively infected, pathogens and CTL cells are decayed. Also α does not change the value of $\mathcal{R}_0$ and therefore the saturation has no effect on the steady states stability properties.

Table 3. parameters values of system (4.5)-(4.9).

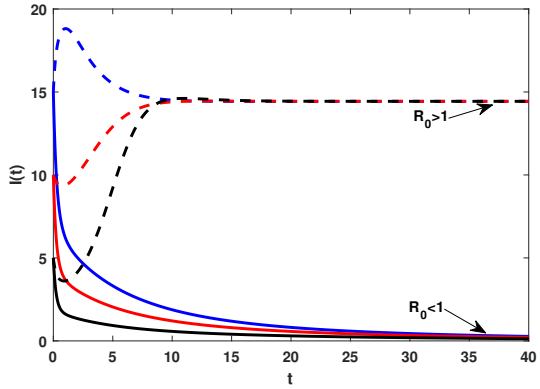
Parameter	Value	Parameter	Value	Parameter	Value
Υ	270	n	varied	Ω	5.5
Φ	0.2	b	0.1	Σ	3
η_1	varied	d	0.2	Ψ	0.5
η_2	0.005	Θ	5.5	Λ	0.1
α_1, α_2	varied	q	0.4	β	varied
α_3	0	r	1		



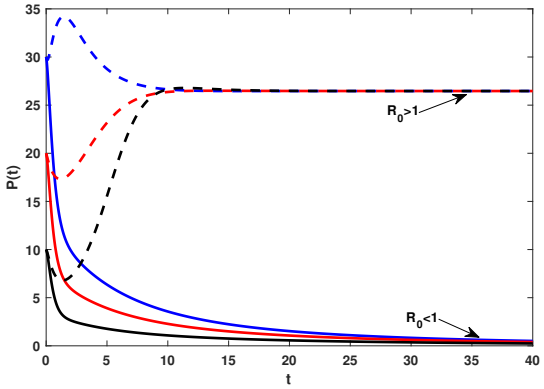
(a) Susceptible cells



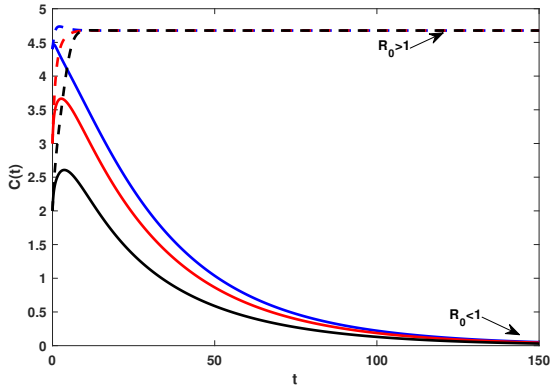
(b) Latently Infected cells



(c) Productively infected cells

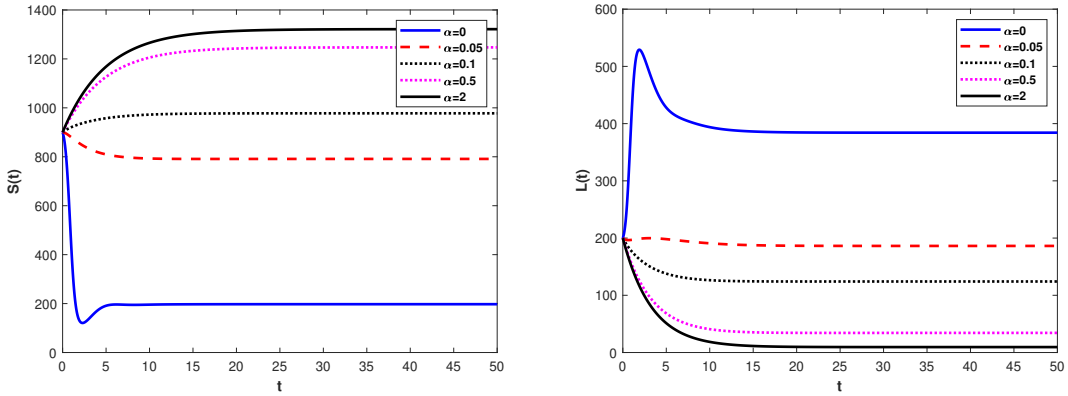


(d) Pathogens



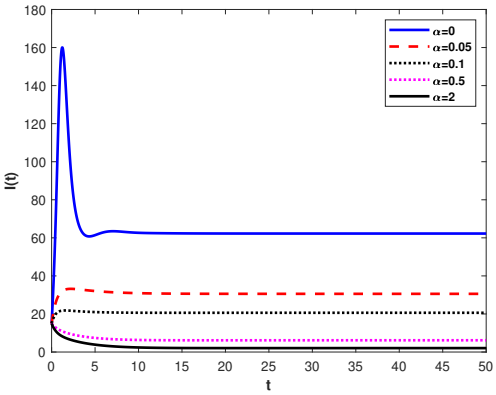
(e) CTL cells

Figure 4. The trajectories simulation of model (4.5)-(4.9) with IC1-IC3.

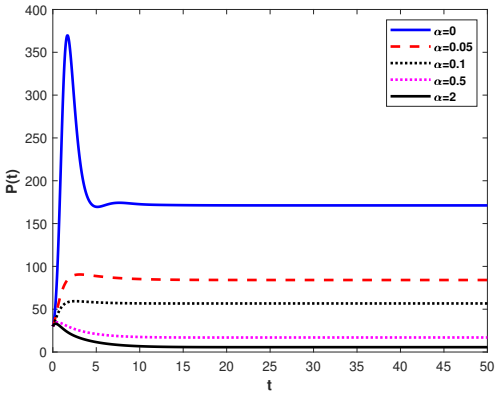


(a) Susceptible cells

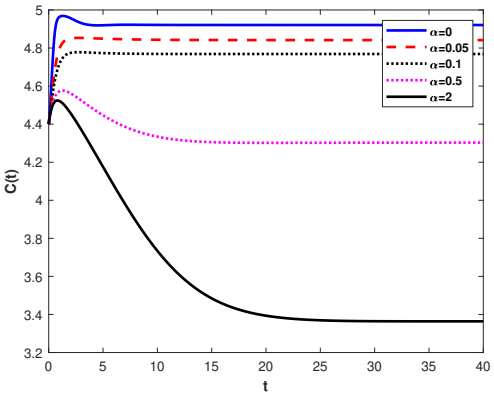
(b) Latently Infected cells



(c) Productively infected cells



(d) Pathogens



(e) CTL cells

Figure 5. The trajectories simulation of model (4.5)-(4.9.) with different value of α

5. Conclusion and discussion

In this paper, we proposed and analyzed two pathogen dynamics models with impairment of CTL immune response and two modes of transmissions, pathogen-to-cell and cell-to-cell. The pathogen-cell and cell-cell incidence rates are represented by general nonlinear functions which generalized several specific forms presented in the literature. In the second model we included the latently infected cells. We proved that the solutions of the model are nonnegative and bounded. We showed that the model has two possible steady states, uninfected steady state Γ_0 and infected steady state Γ_1. We derived the basic infection reproduction number $\mathcal{R}_0$ from the existence of the infected steady state Γ_1. We constructed Lyapunov functions and applied LaSalle's invariance principle to prove the global asymptotic stability of the two steady states. We proved that if $\mathcal{R}_0 < 1$, then Γ_0 is GAS, and if $\mathcal{R}_0 > 1$ then Γ_1 is GAS. The theoretical results were illustrated by numerical simulations. We note that the cell-to-cell transmission has a significant effect on the pathogen dynamics. From model (2.1)-(2.4), the basic infection reproduction number can be written as:

$$\mathcal{R}_0 = \mathcal{R}_0^P + \mathcal{R}_0^C = \frac{\Omega h_1'(0)}{\Theta\Sigma} f(S_0) + \frac{h_2'(0)}{\Theta} f(S_0),$$

where $\mathcal{R}_0^P$ and $\mathcal{R}_0^C$ are the basic infection reproduction numbers due to the pathogen-to-cell and cell-to-cell transmissions, respectively. Since $\mathcal{R}_0 = \mathcal{R}_0^P + \mathcal{R}_0^C > \mathcal{R}_0^P$, therefore, neglecting the cell-to-cell transmission can lead to under-evaluated basic infection reproduction number.

Our proposed pathogenic infection models can be extended and generalized to take into account different biological effects such as stochastic interactions [52], reaction-diffusion [53–56]. Pathogen dynamics model given by fractional-order differential equations can provide better understanding on the dynamical behavior of the pathogen within-host [57]. We mention that our models assume that the pathogen infects one class of target cells. It has been reported in several works that some viruses such as HIV can infect two or more classes of target cells [58]. We leave these extensions for future works.

Conflict of interest

The authors declare that no conflict of interest in this paper.

References

1. M. A. Nowak and R. M. May, *Virus dynamics: Mathematical Principles of Immunology and Virology*, Oxford University, Oxford, 2000.
2. P. K. Roy, A. N. Chatterjee, D. Greenhalgh, et al., Long term dynamics in a mathematical model of HIV-1 infection with delay in different variants of the basic drug therapy model, *Nonlinear Anal-Real*, **14** (2013), 1621–1633.
3. J. Wang, J. Pang and T. Kuniya, A note on global stability for malaria infections model with latencies, *MBE*, **11** (2014), 995–1001.
4. D. S. Callaway and A. S. Perelson, HIV-1 infection and low steady state viral loads, *B. Math. Biol.*, **64** (2002), 29–64.

5. A. M. Elaiw and S. A. Azoz, Global properties of a class of HIV infection models with Beddington-DeAngelis functional response, *Math. Meth. Appl. Sci.*, **36** (2013), 383–394.
6. A. M. Elaiw, Global properties of a class of HIV models, *Nonlinear Anal-Real*, **11** (2010), 2253–2263.
7. M. Y. Li and L. Wang, Backward bifurcation in a mathematical model for HIV infection in vivo with anti-retroviral treatment, *Nonlinear Anal-Real*, **17** (2014), 147–160.
8. K. Wang, A. Fan and A. Torres, Global properties of an improved hepatitis B virus model, *Nonlinear Anal-Real*, **11** (2010), 3131–3138.
9. F. Zhang, J. Li, C. Zheng, et al., Dynamics of an HBV/HCV infection model with intracellular delay and cell proliferation, *Commun. Nonlinear Sci.*, **42** (2017), 464–476.
10. A. M. Elaiw, and N. A. Almuallem, Global dynamics of delay-distributed HIV infection models with differential drug efficacy in cocirculating target cells, *Math. Meth. Appl. Sci.*, **39** (2016), 4–31.
11. A. M. Elaiw, R. M. Abukwaik and E. O. Alzahrani, Global properties of a cell mediated immunity in HIV infection model with two classes of target cells and distributed delays, *Int. J. Biomath.*, **7** (2014), 1450055.
12. S. Zhang and X. Xu, Dynamic analysis and optimal control for a model of hepatitis C with treatment, *Commun. Nonlinear Sci.*, **46** (2017), 14–25.
13. L. Wang, M. Y. Li and D. Kirschner, Mathematical analysis of the global dynamics of a model for HTLV-I infection and ATL progression, *Math. Biosci.*, **179** (2002), 207–217.
14. A. M. Elaiw and E. K. Elnahary, Analysis of general humoral immunity HIV dynamics model with HAART and distributed delays, *Mathematics*, **7** (2019), 157.
15. A. M. Elaiw, S. F. Alshehaiween and A. D. Hobiny, Global properties of a delay-distributed HIV dynamics model including impairment of B-cell functions, *Mathematics*, **7** (2019), 837.
16. A. M. Elaiw, E. K. Elnahary and A. A. Raezah, Effect of cellular reservoirs and delays on the global dynamics of HIV, *Adv. Differ. Equ-NY*, **2018** (2018), 85.
17. A. M. Elaiw, I. A. Hassanien, S. A. Azoz, Global stability of HIV infection models with intracellular delays, *J. Korean Math. Soc.*, **49** (2012), 779–794.
18. M. A. Nowak and C. R. M. Bangham, Population dynamics of immune responses to persistent viruses, *Science*, **272** (1996), 74–79.
19. E. Mondragon and L. Esteva, On CTL Response against Mycobacterium tuberculosis, *SIAM J. Appl. Math.*, **8** (2014), 2383–2389.
20. S. A. Azoz, and A. M. Ibrahim, Effect of cytotoxic T lymphocytes on HIV-1 dynamics, *J. Comput. Anal. Appl.*, **25** (2018), 111–125.
21. M. Y. Li and H. Shu, Global dynamics of a mathematical model for HTLV-I infection of CD4+ T cells with delayed CTL response, *Nonlinear Anal-Real*, **13** (2012), 1080–1092.
22. H. Shu, L. Wang and J. Watmough, Global stability of a nonlinear viral infection model with infinitely distributed intracellular delays and CTL imune responses, *SIAM J. Appl. Math.,* **73** (2013), 1280–1302.

23. D. Huang, X. Zhang, Y. Guo, et al., Analysis of an HIV infection model with treatments and delayed immune response, *Appl. Math. Model.*, **40** (2016), 3081–3089.

24. J. Pang, J.-An Cui. and J. Hui, The importance of immune responses in a model of hepatitis B virus, *Nonlinear Dynam.*, **67** (2012), 723–734.

25. J. Pang and J-An Cui, Analysis of a hepatitis B viral infection model with immune response delay, *Int. J. Biomath.*, **10** (2017), 1750020.

26. Y. Zhao and Z. Xu, Global dynamics for a delyed hepatitis C virus,infection model, *Electron. J. Differ. Eq.*, **2014** (2014), 1–18.

27. J. Wang, C. Qin, Y. Chen, et al., Hopf bifurcation in a CTL-inclusive HIV-1 infection model with two time delays, *MBE*, **16** (2019), 2587–2612.

28. K. Wang, W. Wang and X. Liu, Global Stability in a viral infection model with lytic and nonlytic immune response, *Comput. Math. Appl.*, **51** (2006), 1593–1610.

29. S. Wang, X. Song and Z. Ge, Dynamics analysis of a delayed viral infection model with immune impairment, *Appl. Math. Model.*, **35** (2011), 4877–4885.

30. Z. Hu, J. Zhang, H. Wang, et al., Dynamics analysis of a delayed viral infection model with logistic growth and immune impairment, *Appl. Math. Model.*, **38** (2014), 524–534.

31. A. V. Eric, C. C. Noe, G. A. Gerardo, Analysis of a viral infection model with immune impairment, intracellular delay and general non-linear incidence rate, *Chaos Solitons & Fractals*, **69** (2014), 1–9.

32. R. V. Culshaw, S. Ruan and G. Webb, A mathematical model of cell-to-cell spread of HIV-1 that includes a time delay, *J. Math. Biol.*, **46** (2003), 425–444.

33. J. Wang, J. Lang and X. Zou, Analysis of an age structured HIV infection model with virus-to-cell infection and cell-to-cell transmission, *Nonlinear Anal-Real*, **34** (2017), 75–96.

34. S. S. Chen, C.-Y. Cheng, Y. Takeuchi, Stability analysis in delayed within-host viral dynamics with both viral and cellular infections, *J. Math. Anal. Appl.*, **442** (2016), 642–672.

35. A. M. Elaiw and A. A. Raezah, Stability of general virus dynamics models with both cellular and viral infections and delays, *Math. Meth. Appl. Sci.*, **40** (2017), 5863–5880.

36. X. Lai and X. Zou, Modeling cell-to-cell spread of HIV-1 with logistic target cell growth, *J. Math. Anal. Appl.*, **426** (2015), 563–584.

37. X. Lai and X. Zou, Modelling HIV-1 virus dynamics with both virus-to-cell infection and cell-to-cell transmission, *SIAM J. Appl. Math.*, **74** (2014), 898–917.

38. Y. Yang, L. Zou and S. Ruan, Global dynamics of a delayed within-host viral infection model with both virus-to-cell and cell-to-cell transmissions, *Math. Biosci.*, **270** (2015), 183–191.

39. J. Wang, M. Guo, X. Liu, et al., Threshold dynamics of HIV-1 virus model with cell-to-cell transmission, cell-mediated immune responses and distributed delay, *Appl. Math. Comput.*, **291** (2016), 149–161.

40. A. G. Cervantes-Perez and E. Avila-Vales, Dynamical analysis of multipathways and multidelays of general virus dynamics model, *Int. J. Bifurcat. Chaos*, **29** (2019), 1950031.

41. A. M. Elaiw and N. H. AlShamrani, Stability of a general CTL-mediated immunity HIV infection model with silent infected cell-to-cell spread, *Adv. Differ. Equ-NY*, **2020** (2020), 355.

42. A. M. Elaiw and N. H. AlShamrani, Stability of a general adaptive immunity virus dynamics model with multi-stages of infected cells and two routes of infection, *Math. Meth. Appl. Sci.*, **43** (2020), 1145–1175.

43. A. M. Elaiw and N. H. AlShamrani, Global stability of a delayed adaptive immunity viral infection with two routes of infection and multi-stages of infected cells, *Commun. Nonlinear Sci.*, **86** (2020), 105259.

44. A. M. Elaiw, A. A. Raezah and B. S. Alofi, Stability of pathogen dynamics models with viral and cellular infections and immune impairment, *J. Nonlinear Sci. Appl.*, **11** (2018), 456–468.

45. B. Buonomo and C. Var-De-Le, Global stability for an HIV-1 infection model including an eclipse stage of infected cells, *J. Math. Anal. Appl.*, **385** (2012), 709–720.

46. A. M. Elaiw, A. A. Raezah and S. A. Azoz, Stability of delayed HIV dynamics models with two latent reservoirs and immune impairment, *Adv. Differ. Equ-NY*, **2018** (2018), 414.

47. A. M. Elaiw, A. A. Raezah and B. S. Alofi, Dynamics of delayed pathogen infection models with pathogenic and cellular infections and immune impairment, *AIP Advances*, **8** (2018), 025323.

48. A. M. Elaiw and B. S. Alofi, Stability analysis of immune impairment pathogen dynamics model with two routes of infection and Holling type-II function, *Appl. Math. Sci.*, **12** (2018), 1419–1432.

49. D. Ebert, C. D. Zschokke-Rohringer and H. J. Carius, Does effects and density-dependent regulation of two microparasites of Daphnia magna, *Oecologia*, **122** (2000), 200–209.

50. G. Huang, Y. Takeuchi and W. Ma, Lyapunov functionals for delay differential equations model of viral infections, *SIAM J. Appl. Math.*, **70** (2010), 2693–2708.

51. A. M. Elaiw and N. H. AlShamrani, Global stability of humoral immunity virus dynamics models with nonlinear infection rate and removal, *Nonlinear Anal-Real*, **26** (2015), 161–190.

52. L. Gibelli, A. Elaiw, M. A. Alghamdi, et al., Heterogeneous population dynamics of active particles: Progression, mutations, and selection dynamics, *Mathematical Models and Methods in Applied Sciences*, **27** (2017), 617–640.

53. N. Bellomo and Y. Tao, Stabilization in a chemotaxis model for virus infection, *Discrete and Continuous Dynamical Systems-Series S*, **13** (2020), 105–117.

54. N. Bellomo, K. J. Painter, Y. Tao, et al., Occurrence vs. Absence of taxis-driven instabilities in a May-Nowak model for virus infection, *SIAM J. Appl. Math.*, **79** (2019), 1990–2010.

55. A. M. Elaiw and A. D. AlAgha, Global dynamics of reaction-diffusion oncolytic M1 virotherapy with immune response, *Appl. Math. Comput.*, **367** (2020), 124758.

56. A. M. Elaiw and A. D. AlAgha, Analysis of a delayed and diffusive oncolytic M1 virotherapy model with immune response, *Nonlinear Anal-Real*, **55** (2020), 103116.

57. P. Tamilalagan, S. Karthiga and P. Manivannan, Dynamics of fractional order HIV infection model with antibody and cytotoxic T- lymphocyte immune responses, *J. Comput. Appl. Math.*, **382** (2021), 113064

58. P. Balasubramaniam, M. Prakash and P. Tamilalagan, Stability and Hopf bifurcation analysis of immune response delayed HIV type 1 infection model with two target cells, *Math. Meth. Appl. Sci.*, **38** (2015), 3653–3669.

AIMS Press