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STABILITY OF DELAY-DISTRIBUTED HIV INFECTION MODELS WITH MULTIPLE VIRAL PRODUCER CELLS

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ABSTRACT. We investigate a class of HIV infection models with two kinds of target cells: $CD4^+$ T cells and macrophages. We incorporate three distributed time delays into the models. Moreover, we consider the effect of humoral immunity on the dynamical behavior of the HIV. The viruses are produced from four types of infected cells: short-lived infected $CD4^+$T cells, long-lived chronically infected $CD4^+$T cells, short-lived infected macrophages and long-lived chronically infected macrophages. The drug efficacy is assumed to be different for the two types of target cells. The HIV-target incidence rate is given by bilinear and saturation functional response while, for the third model, both HIV-target incidence rate and neutralization rate of viruses are given by nonlinear general functions. We show that the solutions of the proposed models are nonnegative and ultimately bounded. We derive two threshold parameters which fully determine the positivity and stability of the three steady states of the models. Using Lyapunov functionals, we established the global stability of the steady states of the models. The theoretical results are confirmed by numerical simulations.

1. INTRODUCTION

Mathematical modeling and analysis of within-host human immunodeficiency virus (HIV) dynamics have become one of the hot topics during the last decades [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22]. These works can help researchers for better understanding the HIV dynamical behavior and providing new suggestions for clinical treatment. Most of the mathematical models presented in the literature suppose that HIV infects just the $CD4^+$T cells [7, 8, 9, 19, 20, 21, 22], while others suppose that there exist another target cells are called macrophages that HIV infects it in addition to $CD4^+$T cells [12, 13, 14, 15, 18]. For more accurate mathematical models for the HIV dynamics, the model should included both

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CD4$^+$ T cells and macrophages. In [3], an HIV mathematical model has been presented by considering two types of infected cells, short-lived infected cells y_i and long-lived chronically infected cells u_i as:

$$\dot{s}_1 = \rho_1 - \beta_1 s_1 - (1-\varepsilon)\lambda_1 s_1 p, \tag{1.1}$$
$$\dot{s}_2 = \rho_2 - \beta_2 s_2 - (1-f\varepsilon)\lambda_2 s_2 p, \tag{1.2}$$
$$\dot{y}_1 = (1-q)(1-\varepsilon)\lambda_1 s_1 p - \pi y_1, \tag{1.3}$$
$$\dot{y}_2 = (1-q)(1-f\varepsilon)\lambda_2 s_2 p - \pi y_2, \tag{1.4}$$
$$\dot{u}_1 = q(1-\varepsilon)\lambda_1 s_1 p - a u_1, \tag{1.5}$$
$$\dot{u}_2 = q(1-f\varepsilon)\lambda_2 s_2 p - a u_2, \tag{1.6}$$
$$\dot{p} = N\pi(y_1+y_2) + Ma(u_1+u_2) - cp, \tag{1.7}$$

where $i = 1, 2$, are denote, respectively, CD4$^+$T cells and the macrophages. The variables s_i and p represent the concentrations of uninfected cells and free HIV particles, respectively. ρ_i, β_i and λ_i represent the creation rate, the death rate and the infection rate of the uninfected cells, respectively. Parameters π and a are the death rate constants of the two types of infected cells, and c is the death rate of HIV. The model incorporates reverse transcriptase inhibitor (RTI) with efficacy ε for the CD4$^+$ T cells and $f\varepsilon$ for the macrophages where $\varepsilon \in [0, 1]$ and $f \in (0, 1)$. The uninfected target cells become short-lived infected and long-lived chronically infected cells with fractions $(1 - q)$ and q, respectively, where $q \in (0, 1)$. The parameters N and M are the average number of HIV particles generated in the lifetime of the short-lived and long-lived infected cells, respectively.

The immune response and time delays were neglected in system (1.1)-(1.7) while that assumption is unrealistic where there exists a time lag between the virus contacting the uninfected cells and the time of generating new infectious viruses. Herz et al. [4] presented a first HIV mathematical model with intracellular time delay. Several HIV models with delays have been presented and investigated [6, 7, 8, 9, 10, 11, 12, 15, 18, 19, 20, 22].

The aim of this paper is to propose HIV infection models which improve model (1.1)-(1.7) by taking into account humoral immunity and distributed delays. We consider two types of target cells, CD4$^+$T cells and macrophages. We derive two threshold parameters and present some mild sufficient conditions for the positivity and global stability of the steady states of the models.

2. HIV DYNAMICS MODEL WITH BILINEAR INCIDENCE RATE

We formulate an HIV dynamics model with bilinear incidence rate taking into account both humoral immunity and distributed delays,

$$\dot{s}_i(t) = \rho_i - \beta_i s_i(t) - \lambda_i s_i(t)p(t), \qquad i = 1, 2, \tag{2.1}$$
$$\dot{y}_i(t) = (1-q_i)\lambda_i \int_0^{l_i} f_i(\tau)e^{-m_i\tau} s_i(t-\tau)p(t-\tau)d\tau - \pi_i y_i(t), \quad i = 1, 2, \tag{2.2}$$

$$\dot{u}_i(t) = q_i\lambda_i \int_0^{l_i} f_i(\tau)e^{-m_i\tau} s_i(t-\tau)p(t-\tau)d\tau - \omega_i u_i(t), \qquad i = 1,2, \tag{2.3}$$

$$\dot{p}(t) = \sum_{i=1}^{2} \left(N_i\pi_i \int_0^{e_i} g_i(\tau)e^{-n_i\tau} y_i(t-\tau)d\tau + M_i\omega_i \int_0^{\vartheta_i} h_i(\tau)e^{-r_i\tau} u_i(t-\tau)d\tau \right)$$
$$- cp(t) - bp(t)z(t), \tag{2.4}$$

$$\dot{z}(t) = \nu p(t)z(t) - \mu z(t), \tag{2.5}$$

where z represents the concentration of the B cells. Parameters b, ν and μ represent, respectively, the removal rate constant of the virus due to the humoral immunity, the proliferation rate constant of B cells and the natural death rate constant of B cells. We suppose that, the virus contacts an uninfected target cell at time $t-\tau$, the cell becomes infected at time t, where τ is a random variable taken from a probability distribution function $f_i(\tau)$ over the time interval $[0, l_i]$ and l_i is limit superior of this delay period. The factors $e^{-m_i\tau}, e^{-n_i\tau}$ and $e^{-r_i\tau}$ account for the loss of target cells, short-lived infected cells and long-lived chronically infected cells during these delay periods, respectively, where m_i, n_i and r_i are constants. All the variables and other parameters of the model have the same meanings as given in model (1.1)-(1.7), where $\lambda_1 = (1-\varepsilon)\overline{\lambda}_1$, $\lambda_2 = (1-f\varepsilon)\overline{\lambda}_2$.

The probability distribution functions $f_i(\tau)$, $g_i(\tau)$ and $h_i(\tau)$ are assumed to satisfy $f_i(\tau) > 0$, $g_i(\tau) > 0$, $h_i(\tau) > 0$ where $i = 1,2$ and

$$\int_0^{l_i} f_i(\tau)d\tau = \int_0^{e_i} g_i(\tau)d\tau = \int_0^{\vartheta_i} h_i(\tau)d\tau = 1, \quad i = 1,2,$$
$$\int_0^{l_i} f_i(\theta)e^{w\theta}d\theta < \infty, \quad \int_0^{e_i} g_i(\theta)e^{w\theta}d\theta < \infty, \quad \int_0^{\vartheta_i} h_i(\theta)e^{w\theta}d\theta < \infty, \quad i = 1,2,$$

where w is a positive constant. Let $\Theta_i(\tau) = f_i(\tau)e^{-m_i\tau}$, $\Lambda_i(\tau) = g_i(\tau)e^{-n_i\tau}$, $\Delta_i(\tau) = h_i(\tau)e^{-r_i\tau}$ and

$$F_i = \int_0^{l_i} \Theta_i(\tau)d\tau, \quad G_i = \int_0^{e_i} \Lambda_i(\tau)d\tau, \quad C_i = \int_0^{\vartheta_i} \Delta_i(\tau)d\tau, \quad i = 1,2,$$

then $0 < F_i, G_i, C_i \leq 1, \quad i = 1,2.$

2.1. **Preliminaries.** Let $\varrho = \max\{l_1, l_2, e_1, e_2, \vartheta_1, \vartheta_2\}$ and C is the Banach space of continuous functions mapping the interval $[-\varrho, 0]$ into $\mathbb{R}^8_{\geq 0}$. For the model (2.1)-(2.5) we consider initial conditions

$$\begin{aligned} &s_1(\theta) = \varphi_1(\theta),\ s_2(\theta) = \varphi_2(\theta),\ y_1(\theta) = \varphi_3(\theta),\ y_2(\theta) = \varphi_4(\theta),\\ &u_1(\theta) = \varphi_5(\theta), u_2(\theta) = \varphi_6(\theta), p(\theta) = \varphi_7(\theta),\ z(\theta) = \varphi_8(\theta)\\ &\varphi_j(\theta) \geq 0,\ \theta \in [-\varrho, 0),\ \varphi_j(0) > 0,\ j = 1,2,...,8, \end{aligned} \tag{2.6}$$

where $(\varphi_1(\theta), \varphi_2(\theta), ..., \varphi_8(\theta)) \in C([-\varrho, 0], \mathbb{R}^8_{\geq 0})$. Then, the uniqueness of the solution for $t > 0$ is guaranteed [32]

Lemma 1. *The solutions of system (2.1)-(2.5) satisfying the initial conditions (2.6) are non-negative and ultimately bounded for* $t \in [0, \infty)$.

Proof. Let us write system (2.1)-(2.5) in matrix form $\dot{Q}(t) = J(Q(t))$, where $Q = (s_1, s_2, y_1, y_2, u_1, u_2, p, z)^T$, $J = (J_1, J_2, ..., J_8)^T$ and

$$J(Q(t)) = \begin{pmatrix} J_1(Q(t)) \\ J_2(Q(t)) \\ \cdot \\ \cdot \\ \cdot \\ J_8(Q(t)) \end{pmatrix},$$

$$J = \begin{pmatrix} \rho_1 - \beta_1 s_1(t) - \lambda_1 s_1(t)p(t) \\ \rho_2 - \beta_2 s_2(t) - \lambda_2 s_2(t)p(t) \\ (1-q_1)\lambda_1 \int_0^{l_1} f_1(\tau)e^{-m_1\tau}s_1(t-\tau)p(t-\tau)d\tau - \pi_1 y_1(t) \\ (1-q_2)\lambda_2 \int_0^{l_2} f_2(\tau)e^{-m_2\tau}s_2(t-\tau)p(t-\tau)d\tau - \pi_2 y_2(t) \\ q_1\lambda_1 \int_0^{l_1} f_1(\tau)e^{-m_1\tau}s_1(t-\tau)p(t-\tau)d\tau - \omega_1 u_1(t) \\ q_2\lambda_2 \int_0^{l_2} f_2(\tau)e^{-m_2\tau}s_2(t-\tau)p(t-\tau)d\tau - \omega_2 u_2(t) \\ \sum_{i=1}^{2}\left(N_i\pi_i \int_0^{e_i} g_i(\tau)e^{-n_i\tau}y_i(t-\tau)d\tau + M_i\omega_i \int_0^{\vartheta_i} h_i(\tau)e^{-r_i\tau}u_i(t-\tau)d\tau\right) \\ -cp(t) - bp(t)z(t) \\ \nu p(t)z(t) - \mu z(t) \end{pmatrix}.$$

We have

$$J_j(Q(t))\big|_{Q_i(t)\in\mathbb{R}^8_{>0}} \geqslant 0, \quad j = 1, ..., 8. \tag{2.7}$$

Using lemma 2 in [33], the solutions of system (2.1)-(2.5) with the initial states (2.6) satisfy $Q(t) \in \mathbb{R}^8_{\geq 0}$ for all $t \geq 0$. The nonnegativity of the model's solution implies that $\limsup_{t\to\infty} s_i(t) \leq \dfrac{\rho_i}{\beta_i}$,$i = 1, 2$.

Let $T_i(t) = \int_0^{l_i} \Theta_i(\tau)s_i(t-\tau)d\tau + y_i(t) + u_i(t)$, $i = 1, 2$ then:

$$\begin{aligned} \dot{T}_i(t) &= F_i\rho_i - \beta_i \int_0^{l_i} \Theta_i(\tau)s_i(t-\tau)d\tau - \pi_i y_i(t) - \omega_i u_i(t) \\ &\leq F_i\rho_i - \sigma_i\left(\int_0^{l_i} \Theta_i(\tau)s_i(t-\tau)d\tau + y_i(t) + u_i(t)\right) \\ &\leq \rho_i - \sigma_i T_i(t), \end{aligned}$$

where $\sigma_i = \min\{\beta_i, \pi_i, \omega_i\}$, $i = 1, 2$. Hence, $\limsup_{t\to\infty} T_i(t) \leq L_i$, where $L_i = \rho_i/\sigma_i, i = 1, 2$. Since $s_i(t)$, $y_i(t)$ and $u_i(t)$ are all non-negative, then $\limsup_{t\to\infty} y_i(t) \leq L_i$ and $\limsup_{t\to\infty} u_i(t) \leq L_i$ for all $t \geq 0$.

Moreover, we let $T_3(t) = p(t) + \frac{b}{\nu} z(t)$, then:

$$\begin{aligned}\dot{T}_3(t) &\leq \sum_{i=1}^{2} \left(N_i \pi_i G_i + M_i \omega_i C_i\right) L_i - cp + \frac{b\mu}{\nu} z(t)\\ &\leq \sum_{i=1}^{2} \left(N_i \pi_i G_i + M_i \omega_i C_i\right) L_i - \sigma_3 T_3(t),\end{aligned}$$

where $\sigma_3 = \min\{c, \mu\}$.

Hence $\limsup_{t\to\infty} T_3(t) \leq L_3$, for all $t \geq 0$, where $L_3 = \sum_{i=1}^{2} \frac{(N_i\pi_i G_i + M_i\omega_i C_i)L_i}{\sigma_3}$. Since $p(t) \geq 0$ and $z(t) \geq 0$ then, $\limsup_{t\to\infty} p(t) \leq L_3$ and $\limsup_{t\to\infty} z(t) \leq L_4$ where $L_4 = \frac{\nu}{b} L_3$ for all $t \geq 0$. Therefore, $s_i(t),\ y_i(t),\ u_i(t),\ p(t)$ and $z(t)$ are ultimately bounded, $i = 1, 2$.

According to Lemma 1, we can show that the region

$$\begin{aligned}\Omega = \big\{&(s_i, y_i, u_i, p, z) \in C^8 : \|s_i\| \leq L_i, \|y\| \leq L_i, \|u\| \leq L_i,\\ &\|p\| \leq L_3, \|z\| \leq L_4\big\},\end{aligned}$$

is positively invariant with respect to system (2.1)-(2.5). □

Lemma 2. *For system (2.1)-(2.5) there exist two bifurcation parameters R_0^B and R_1^B with $R_0^B > R_1^B > 0$ such that*

(i) if $R_0^B \leq 1$, then the system has only one nonnegative steady state Π_0,

(ii) if $R_1^B \leq 1 < R_0^B$, then the system has only two nonnegative steady states Π_0 and Π_1,

(iii) if $R_1^B > 1$, then the system has three nonnegative steady states Π_0, Π_1 and Π_2.

Proof. System (2.1)-(2.5) has the following steady states:

(i) Infection-free steady state $\Pi_0 = (s_1^0, s_2^0, 0, 0, 0, 0, 0, 0)$ where $s_i^0 = \rho_i/\beta_i$, $i = 1, 2$,

(ii) Humoral-inactivated infection steady state $\Pi_1 = (\tilde{s}_1, \tilde{s}_2, \tilde{y}_1, \tilde{y}_2, \tilde{u}_1, \tilde{u}_2, \tilde{p}, 0)$ where

$$\begin{aligned}\tilde{s}_i &= \frac{s_i^0}{1 + \eta_i \tilde{p}} > 0, \quad \tilde{y}_i = \frac{(1 - q_i) F_i \lambda_i s_i^0}{\pi_i (1 + \eta_i \tilde{p})} \tilde{p} > 0,\\ \tilde{u}_i &= \frac{q_i F_i \lambda_i s_i^0}{\omega_i (1 + \eta_i \tilde{p})} \tilde{p} > 0, \quad \tilde{p} = \frac{-B + \sqrt{B^2 + 4AC}}{2A},\end{aligned}$$

$$\begin{aligned}&A = \eta_1 \eta_2,\ B = \eta_1 R_{01}^B + \eta_2 R_{02}^B + (1 - R_0^B)(\eta_1 + \eta_2),\\ &C = R_0^B - 1,\ \eta_i = \frac{\lambda_i}{\beta_i},\ i = 1, 2,\end{aligned}$$

$R_0^B = \sum_{i=1}^{2} \frac{\gamma_i \lambda_i s_i^0}{c}$, represents the basic reproduction number for system (2.1)-(2.5) and $\gamma_i = ((1 - q_i) G_i N_i + q_i C_i M_i) F_i$.

(iii) Humoral-activated infection steady state $\Pi_2 = (\bar{s}_1, \bar{s}_2, \bar{y}_1, \bar{y}_2, \bar{u}_1, \bar{u}_2, \bar{p}, \bar{z})$ where

$$\bar{s}_i = \frac{\nu\rho_i}{\nu\beta_i + \mu\lambda_i} > 0,\ \bar{y}_i = \frac{(1-q_i)F_i\rho_i\lambda_i\mu}{\pi_i(\nu\beta_i + \mu\lambda_i)} > 0,\ \bar{u}_i = \frac{q_iF_i\rho_i\lambda_i\mu}{\omega_i(\nu\beta_i + \mu\lambda_i)} > 0,\ i = 1, 2,$$
$$\bar{p} = \frac{\mu}{\nu} > 0,\ \ \bar{z} = \frac{c}{b}\left(R_1^B - 1\right),$$

and $R_1^B = \sum_{i=1}^{2} \frac{\gamma_i\lambda_i\rho_i\nu}{c(\nu\beta_i+\mu\lambda_i)} = \sum_{i=1}^{2} \frac{R_0^B}{1+\frac{\mu\lambda_i}{\nu\beta_i}}$, denotes the humoral immunity activation number for system (2.1)-(2.5). □

We will use the following equalities throughout the paper :

$$\begin{aligned}
\ln\left(\frac{\phi_i(s_i(t-\tau), p(t-\tau))}{\phi_i(s_i, p)}\right) &= \ln\left(\frac{\phi_i(s_i^*, p^*)}{\phi_i(s_i, p^*)}\right) + \ln\left(\frac{y_i^*\phi_i(s_i(t-\tau), p(t-\tau))}{y_i\phi_i(s_i^*, p^*)}\right) \\
&\quad + \ln\left(\frac{p\phi_i(s_i, p^*)}{p^*\phi_i(s_i, p)}\right) + \ln\left(\frac{p^*y_i}{py_i^*}\right), \\
\ln\left(\frac{y_i(t-\tau)}{y_i}\right) &= \ln\left(\frac{p^*y_i(t-\tau)}{py_i^*}\right) + \ln\left(\frac{py_i^*}{p^*y_i}\right), \\
\ln\left(\frac{\phi_i(s_i(t-\tau), p(t-\tau))}{\phi_i(s_i, p)}\right) &= \ln\left(\frac{\phi_i(s_i^*, p^*)}{\phi_i(s_i, p^*)}\right) + \ln\left(\frac{u_i^*\phi_i(s_i(t-\tau), p(t-\tau))}{u_i\phi_i(s_i^*, p^*)}\right) \\
&\quad + \ln\left(\frac{p\phi_i(s_i, p^*)}{p^*\phi_i(s_i, p)}\right) + \ln\left(\frac{p^*u_i}{pu_i^*}\right), \\
\ln\left(\frac{u_i(t-\tau)}{u_i}\right) &= \ln\left(\frac{p^*u_i(t-\tau)}{pu_i^*}\right) + \ln\left(\frac{pu_i^*}{p^*u_i}\right).
\end{aligned} \tag{2.8}$$

2.2. **Global stability analysis.** The following theorems investigate the global stability of the steady states of system (2.1)-(2.5). We will use a function $H : (0,\infty) \to [0,\infty)$ as: $H(\nu) = \nu - 1 - \ln\nu$ throughout the paper.

Theorem 2.1. *For system (2.1)-(2.5), if $R_0^B \leq 1$, then Π_0 is globally asymptotically stable (GAS).*

Proof. We construct a Lyapunov functional V_0 as:

$$V_0 = \sum_{i=1}^{2}\gamma_i\left[s_i^0 H\left(\frac{s_i}{s_i^0}\right) + \frac{N_iG_i}{\gamma_i}y_i + \frac{M_iC_i}{\gamma_i}u_i + \frac{\lambda_i}{F_i}\int_0^{l_i}\Theta_i(\tau)\int_0^{\tau} s_i(t-\theta)p(t-\theta)d\theta d\tau\right.$$
$$\left. + \frac{N_i\pi_i}{\gamma_i}\int_0^{e_i}\Lambda_i(\tau)\int_0^{\tau} y_i(t-\theta)d\theta d\tau + \frac{M_i\omega_i}{\gamma_i}\int_0^{\vartheta_i}\Delta_i(\tau)\int_0^{\tau} u_i(t-\theta)d\theta d\tau\right] + p + \frac{b}{\nu}z.$$

We calculate $\frac{dV_0}{dt}$ along the trajectories of system (2.1)-(2.5) as:

$$\frac{dV_0}{dt} = \sum_{i=1}^{2}\gamma_i\left[\left(1 - \frac{s_i^0}{s_i}\right)(\rho_i - \beta_i s_i - \lambda_i s_i p)\right.$$

$$+\frac{N_iG_i}{\gamma_i}\left((1-q_i)\lambda_i\int\limits_0^{l_i}\Theta_i(\tau)s_i(t-\tau)p(t-\tau)d\tau-\pi_iy_i(t)\right)$$
$$+\frac{M_iC_i}{\gamma_i}\left(q_i\lambda_i\int_0^{l_i}\Theta_i(\tau)s_i(t-\tau)p(t-\tau)d\tau-\omega_iu_i(t)\right)$$
$$+\frac{\lambda_i}{F_i}\int_0^{l_i}\Theta_i(\tau)(s_ip-s_i(t-\tau)p(t-\tau))d\tau$$
$$\left.+\frac{N_i\pi_i}{\gamma_i}\int_0^{e_i}\Lambda_i(\tau)\left(y_i-y_i(t-\tau)\right)d\tau+\frac{M_i\omega_i}{\gamma_i}\int_0^{\vartheta_i}\Delta_i(\tau)\left(u_i-u_i(t-\tau)\right)d\tau\right]$$
$$+\sum_{i=1}^{2}\left(N_i\pi_i\int_0^{e_i}\Lambda_i(\tau)y_i(t-\tau)d\tau+M_i\omega_i\int_0^{\vartheta_i}\Delta_i(\tau)u_i(t-\tau)d\tau\right)$$
$$-cp-bpz+\frac{b}{\nu}\left(\nu pz-\mu z\right), \tag{2.9}$$

collecting Eq. (2.9) we get:

$$\begin{aligned}\frac{dV_0}{dt}&=-\sum_{i=1}^{2}\gamma_i\beta_i\frac{(s_i-s_i^0)^2}{s_i}+\sum_{i=1}^{2}\gamma_i\lambda_is_i^0p-cp-\frac{b\mu}{\nu}z\\&=-\sum_{i=1}^{2}\gamma_i\beta_i\frac{(s_i-s_i^0)^2}{s_i}+\left(\sum_{i=1}^{2}\frac{\gamma_i\lambda_is_i^0}{c}-1\right)cp-\frac{b\mu}{\nu}z\\&=-\sum_{i=1}^{2}\gamma_i\beta_i\frac{(s_i-s_i^0)^2}{s_i}+(R_0^B-1)cp-\frac{b\mu}{\nu}z.\end{aligned} \tag{2.10}$$

Therefore, if $R_0^B\le 1$,then $\frac{dV_0}{dt}\le 0$ for all $s_1,s_2,p,z>0$. Clearly, $\frac{dV_0}{dt}=0$ at Π_0. Applying LaSalle's invariance principle (LIP), we get that Π_0 is GAS. □

Theorem 2.2. *If $R_1^B\le 1<R_0^B$, then Π_1 is GAS.*

Proof. Let

$$V_1=\sum_{i=1}^{2}\gamma_i\left[\tilde{s}_iH\left(\frac{s_i}{\tilde{s}_i}\right)+\frac{N_iG_i}{\gamma_i}\tilde{y}_iH\left(\frac{y_i}{\tilde{y}_i}\right)+\frac{M_iC_i}{\gamma_i}\tilde{u}_iH\left(\frac{u_i}{\tilde{u}_i}\right)\right.$$
$$+\frac{\lambda_i\tilde{s}_i\tilde{p}}{F_i}\int_0^{l_i}\Theta_i(\tau)\int_0^{\tau}H\left(\frac{s_i(t-\theta)p(t-\theta)}{\tilde{s}_i\tilde{p}}\right)d\theta d\tau$$
$$+\frac{N_i\pi_i\tilde{y}_i}{\gamma_i}\int_0^{e_i}\Lambda_i(\tau)\int_0^{\tau}H\left(\frac{y_i(t-\theta)}{\tilde{y}_i}\right)d\theta d\tau$$
$$\left.+\frac{M_i\omega_i\tilde{u}_i}{\gamma_i}\int_0^{\vartheta_i}\Delta_i(\tau)\int_0^{\tau}H\left(\frac{u_i(t-\theta)}{\tilde{u}_i}\right)d\theta d\tau\right]+\tilde{p}H\left(\frac{p}{\tilde{p}}\right)+\frac{b}{\nu}z.$$

Calculating $\frac{dV_1}{dt}$ along the solutions of system (2.1)-(2.5) we obtain:

$$
\begin{aligned}
\frac{dV_1}{dt} &= \sum_{i=1}^{2}\gamma_i \Bigg[\left(1-\frac{\tilde{s}_i}{s_i}\right)(\rho_i-\beta_i s_i-\lambda_i s_i p) \\
&+ \frac{N_i G_i}{\gamma_i}\left(1-\frac{\tilde{y}_i}{y_i}\right)\left((1-q_i)\lambda_i\int_0^{l_i}\Theta_i(\tau)s_i(t-\tau)p(t-\tau)d\tau-\pi_i y_i\right) \\
&+ \frac{M_i C_i}{\gamma_i}\left(1-\frac{\tilde{u}_i}{u_i}\right)\left(q_i\lambda_i\int_0^{l_i}\Theta_i(\tau)s_i(t-\tau)p(t-\tau)d\tau-\omega_i u_i\right) \\
&+ \frac{\lambda_i\tilde{s}_i\tilde{p}}{F_i}\int_0^{l_i}\Theta_i(\tau)\left(\frac{s_i p}{\tilde{s}_i\tilde{p}}-\frac{s_i(t-\tau)p(t-\tau)}{\tilde{s}_i\tilde{p}}+\ln\left(\frac{s_i(t-\tau)p(t-\tau)}{s_i p}\right)\right)d\tau \\
&+ \frac{N_i\pi_i\tilde{y}_i}{\gamma_i}\int_0^{e_i}\Lambda_i(\tau)\left(\frac{y_i}{\tilde{y}_i}-\frac{y_i(t-\tau)}{\tilde{y}_i}+\ln\left(\frac{y_i(t-\tau)}{y_i}\right)\right)d\tau \\
&+ \frac{M_i\omega_i\tilde{u}_i}{\gamma_i}\int_0^{\vartheta_i}\Delta_i(\tau)\left(\frac{u_i}{\tilde{u}_i}-\frac{u_i(t-\tau)}{\tilde{u}_i}+\ln\left(\frac{u_i(t-\tau)}{u_i}\right)\right)d\tau\Bigg] \\
&+ \left(1-\frac{\tilde{p}}{p}\right)\left(\sum_{i=1}^{2}(N_i\pi_i\int_0^{e_i}\Lambda_i(\tau)y_i(t-\tau)d\tau+M_i\omega_i\int_0^{\vartheta_i}\Delta_i(\tau)u_i(t-\tau)d\tau)-cp-bpz\right) \\
&+ \frac{b}{\nu}(\nu pz-\mu z)
\end{aligned} \tag{2.11}
$$

Collecting terms of Eq. (2.11) and using the conditions of the steady state Π_1

$$
\rho_i=\beta_i\tilde{s}_i+\lambda_i\tilde{s}_i\tilde{p}, \qquad (1-q_i)F_i\lambda_i\tilde{s}_i\tilde{p}=\pi_i\tilde{y}_i, \qquad q_iF_i\lambda_i\tilde{s}_i\tilde{p}=\omega_i\tilde{u}_i,
$$
$$
c\tilde{p}=\sum_{i=1}^{2}(N_i\pi_iG_i\tilde{y}_i+M_i\omega_iC_i\tilde{u}_i)=\sum_{i=1}^{2}\gamma_i\lambda_i\tilde{s}_i\tilde{p}, \quad cp=\sum_{i=1}^{2}\gamma_i\lambda_i\tilde{s}_i p,
$$

we get

$$
\begin{aligned}
\frac{dV_1}{dt} &= \sum_{i=1}^{2}\gamma_i\Bigg[\left(1-\frac{\tilde{s}_i}{s_i}\right)(\beta_i\tilde{s}_i-\beta_i s_i)+\lambda_i\tilde{s}_i\tilde{p}\left(1-\frac{\tilde{s}_i}{s_i}\right) \\
&+ \frac{2N_iG_i\pi_i}{\gamma_i}\tilde{y}_i-\frac{N_iG_i\pi_i\tilde{y}_i}{\gamma_iF_i}\int_0^{l_i}\Theta_i(\tau)\frac{\tilde{y}_is_i(t-\tau)p(t-\tau)}{y_i\tilde{s}_i\tilde{p}}d\tau \\
&- \frac{M_iC_i\omega_i\tilde{u}_i}{\gamma_iF_i}\int_0^{l_i}\Theta_i(\tau)\frac{\tilde{u}_is_i(t-\tau)p(t-\tau)}{u_i\tilde{s}_i\tilde{p}}d\tau+\frac{2M_iC_i\omega_i}{\gamma_i}\tilde{u}_i \\
&- \frac{N_i\pi_i\tilde{y}_i}{\gamma_i}\int_0^{e_i}\Lambda_i(\tau)\frac{\tilde{p}y_i(t-\tau)}{p\tilde{y}_i}d\tau-\frac{M_i\omega_i\tilde{u}_i}{\gamma_i}\int_0^{\vartheta_i}\Delta_i(\tau)\frac{\tilde{p}u_i(t-\tau)}{p\tilde{u}_i}d\tau \\
&+ \left(\frac{N_iG_i\pi_i\tilde{y}_i+M_iC_i\omega_i\tilde{u}_i}{\gamma_iF_i}\right)\int_0^{l_i}\Theta_i(\tau)\ln\left(\frac{s_i(t-\tau)p(t-\tau)}{s_ip}\right)d\tau
\end{aligned}
$$

$$+\frac{N_i\pi_i\tilde{y}_i}{\gamma_i}\int_0^{e_i}\Lambda_i(\tau)\ln\left(\frac{y_i(t-\tau)}{y_i}\right)d\tau$$
$$+\frac{M_i\omega_i\tilde{u}_i}{\gamma_i}\int_0^{\vartheta_i}\Delta_i(\tau)\ln\left(\frac{u_i(t-\tau)}{u_i}\right)d\tau\Bigg]+b\left(\tilde{p}-\frac{\mu}{\nu}\right)z.$$

Using Eqs. (2.8) with $\phi_i(s_i,p)=\lambda_i s_i p$, $s_i^*=\tilde{s}_i$, $y_i^*=\tilde{y}_i$, $u_i^*=\tilde{u}_i$ and $p^*=\tilde{p}$, we can obtain

$$\frac{dV_1}{dt}=\sum_{i=1}^{2}\Bigg[-\gamma_i\frac{\beta_i(s_i-\tilde{s}_i)^2}{s_i}-\gamma_i\lambda_i\tilde{s}_i\tilde{p}H\left(\frac{\tilde{s}_i}{s_i}\right)$$
$$-\frac{N_iG_i\pi_i\tilde{y}_i}{F_i}\int_0^{l_i}\Theta_i(\tau)H\left(\frac{\tilde{y}_i s_i(t-\tau)p(t-\tau)}{y_i\tilde{s}_i\tilde{p}}\right)d\tau$$
$$-N_i\pi_i\tilde{y}_i\int_0^{e_i}\Lambda_i(\tau)H\left(\frac{\tilde{p}y_i(t-\tau)}{p\tilde{y}_i}\right)d\tau$$
$$-\frac{M_iC_i\omega_i\tilde{u}_i}{F_i}\int_0^{l_i}\Theta_i(\tau)H\left(\frac{\tilde{u}_i s_i(t-\tau)p(t-\tau)}{u_i\tilde{s}_i\tilde{p}}\right)d\tau$$
$$-M_i\omega_i\tilde{u}_i\int_0^{\vartheta_i}\Delta_i(\tau)H\left(\frac{\tilde{p}u_i(t-\tau)}{p\tilde{u}_i}\right)d\tau\Bigg]+b\left(\tilde{p}-\bar{p}\right)z.$$

From the conditions of the steady state Π_1 we have $\sum_{i=1}^{2}\frac{\gamma_i\lambda_i\rho_i}{c\beta_i(1+\eta_i\bar{p})}=1$, then

$$\begin{aligned}R_1^B-1&=\sum_{i=1}^{2}\frac{\gamma_i\lambda_i\rho_i\nu}{c(\nu\beta_i+\mu\lambda_i)}-\sum_{i=1}^{2}\frac{\gamma_i\lambda_i\rho_i}{c\beta_i(1+\eta_i\bar{p})}\\&=\sum_{i=1}^{2}\frac{\gamma_i\lambda_i\rho_i}{c\beta_i(1+\eta_i\bar{p})}-\sum_{i=1}^{2}\frac{\gamma_i\lambda_i\rho_i}{c\beta_i(1+\eta_i\tilde{p})}\\&=(\tilde{p}-\bar{p})\sum_{i=1}^{2}\frac{\gamma_i\lambda_i\rho_i\eta_i}{c\beta_i(1+\eta_i\bar{p})(1+\eta_i\tilde{p})}=\zeta\left(\tilde{p}-\bar{p}\right)\end{aligned}\tag{2.12}$$

Eq. (2.12) implies that $(\tilde{p}-\bar{p})=\frac{1}{\zeta}(R_1^B-1)$, where, $\zeta=\sum_{i=1}^{2}\frac{\gamma_i\lambda_i\rho_i\eta_i}{c\beta_i(1+\eta_i\bar{p})(1+\eta_i\tilde{p})}$. Therefore, $R_1^B\leq 1$ ensure $\frac{dV_1}{dt}\leq 0$ for all $s_i,y_i,u_i,p,z>0$. It follows that for all $s_i,y_i,u_i,p,z>0$ we have $\frac{dV_1}{dt}\leq 0$ and $\frac{dV_1}{dt}=0$ at Π_1. By LIP Π_1 is GAS. □

Theorem 2.3. *If* $R_1^B>1$ *then* Π_2 *is GAS.*

Proof. Consider

$$V_2=\sum_{i=1}^{2}\gamma_i\left[\bar{s}_iH\left(\frac{s_i}{\bar{s}_i}\right)+\frac{N_iG_i}{\gamma_i}\bar{y}_iH\left(\frac{y_i}{\bar{y}_i}\right)+\frac{M_iC_i}{\gamma_i}\bar{u}_iH\left(\frac{u_i}{\bar{u}}\right)\right.$$

$$+\frac{\lambda_i\bar{s}_i\bar{p}}{F_i}\int_0^{l_i}\Theta_i(\tau)\int_0^{\tau}H\left(\frac{s_i(t-\theta)p(t-\theta)}{\bar{s}_i\bar{p}}\right)d\theta d\tau$$
$$+\frac{N_i\pi_i\bar{y}_i}{\gamma_i}\int_0^{e_i}\Lambda_i(\tau)\int_0^{\tau}H\left(\frac{y_i(t-\theta)}{\bar{y}_i}\right)d\theta d\tau$$
$$+\frac{M_i\omega_i\bar{u}}{\gamma_i}\int_0^{\vartheta_i}\Delta_i(\tau)\int_0^{\tau}H\left(\frac{u_i(t-\theta)}{\bar{u}}\right)d\theta d\tau\Bigg]+\bar{p}H\left(\frac{p}{\bar{p}}\right)+\frac{b}{\nu}\bar{z}F\left(\frac{z}{\bar{z}}\right).$$

Calculating $\frac{dV_2}{dt}$ along the solutions of model (2.1)-(2.5) we obtain:

$$\frac{dV_2}{dt}=\sum_{i=1}^{2}\gamma_i\left[\left(1-\frac{\bar{s}_i}{s_i}\right)(\rho_i-\beta_i s_i)+\lambda_i\bar{s}_i p+\frac{N_iG_i\pi_i}{\gamma_i}\bar{y}_i+\frac{M_iC_i\omega_i}{\gamma_i}\bar{u}_i\right.$$
$$-\frac{(1-q_i)N_iG_i\lambda_i}{\gamma_i}\int_0^{l_i}\Theta_i(\tau)\frac{\bar{y}_is_i(t-\tau)p(t-\tau)}{y_i}d\tau$$
$$-\frac{q_iM_iC_i\lambda_i}{\gamma_i}\int_0^{l_i}\Theta_i(\tau)\frac{\bar{u}_is_i(t-\tau)p(t-\tau)}{u_i}d\tau$$
$$+\frac{\lambda_i\bar{s}_i\bar{p}}{F_i}\int_0^{l_i}\Theta_i(\tau)\ln\left(\frac{s_i(t-\tau)p(t-\tau)}{s_ip}\right)d\tau+\frac{N_i\pi_i\bar{y}_i}{\gamma_i}\int_0^{e_i}\Lambda_i(\tau)\ln\left(\frac{y_i(t-\tau)}{y_i}\right)d\tau$$
$$\left.+\frac{M_i\omega_i\bar{u}_i}{\gamma_i}\int_0^{\vartheta_i}\Delta_i(\tau)\ln\left(\frac{u_i(t-\tau)}{u_i}\right)d\tau\right]-\sum_{i=1}^{2}N_i\pi_i\int_0^{e_i}\Lambda_i(\tau)\frac{\bar{p}y_i(t-\tau)}{p}d\tau$$
$$-\sum_{i=1}^{2}M_i\omega_i\int_0^{\vartheta_i}\Delta_i(\tau)\frac{\bar{p}u_i(t-\tau)}{p}d\tau-cp+c\bar{p}+b\bar{p}z-b\frac{\mu}{\nu}z-bp\bar{z}+b\frac{\mu}{\nu}\bar{z}.$$

By the conditions of the steady state Π_2

$$\rho_i=\beta_i\bar{s}_i+\lambda_i\bar{s}_i\bar{p},\quad (1-q_i)F_i\lambda_i\bar{s}_i\bar{p}=\pi_i\bar{y}_i,\quad q_iF_i\lambda_i\bar{s}_i\bar{p}=\omega_i\bar{u}_i,$$
$$c\bar{p}=\sum_{i=1}^{2}\left(N_i\pi_iG_i\bar{y}_i+M_i\omega_iC_i\bar{u}_i\right)-b\bar{p}\bar{z},\ \ cp=\sum_{i=1}^{2}\gamma_i\lambda_i\bar{s}_ip-bp\bar{z},\ \ \bar{p}=\frac{\mu}{\nu},$$

and using the inequalities (2.8) with $s_i^*=\bar{s}_i,\ y_i^*=\bar{y}_i,\ u_i^*=\bar{u}_i$ and $p^*=\bar{p}$ we find

$$\frac{dV_2}{dt}=\sum_{i=1}^{2}\left[-\gamma_i\frac{\beta_i(s_i-\bar{s}_i)^2}{s_i}-\gamma_i\lambda_i\bar{s}_i\bar{p}H\left(\frac{\bar{s}_i}{s_i}\right)\right.$$
$$-\frac{N_iG_i\pi_i\bar{y}_i}{F_i}\int_0^{l_i}\Theta_i(\tau)H\left(\frac{\bar{y}_is_i(t-\tau)p(t-\tau)}{y_i\bar{s}_i\bar{p}}\right)d\tau-N_i\pi_i\bar{y}_i\int_0^{e_i}\Lambda_i(\tau)H\left(\frac{\bar{p}y_i(t-\tau)}{p\bar{y}_i}\right)d\tau$$
$$\left.-\frac{M_iC_i\omega_i\bar{u}_i}{F_i}\int_0^{l_i}\Theta_i(\tau)H\left(\frac{\bar{u}_is_i(t-\tau)p(t-\tau)}{u_i\bar{s}_i\bar{p}}\right)d\tau-M_i\omega_i\bar{u}_i\int_0^{\vartheta_i}\Delta_i(\tau)H\left(\frac{\bar{p}u_i(t-\tau)}{p\bar{u}_i}\right)d\tau\right].$$

Thus if $R_1^B>1$, then $\bar{s}_i,\bar{y}_i,\bar{u}_i,\bar{p},\bar{z}>0.$ Therefore we get $\frac{dV_2}{dt}\leq 0$ and $\frac{dV_2}{dt}=0$ at $\Pi_2.$ LIP implies that Π_2 is GAS. □

3. MODEL WITH SATURATION INCIDENCE RATE

We consider a model with a saturation incidence rate and humoral immunity as:

$$\dot{s}_i(t) = \rho_i - \beta_i s_i(t) - \frac{\lambda_i s_i(t)p(t)}{1+\alpha_i p(t)}, \qquad i = 1,2, \tag{3.1}$$

$$\dot{y}_i(t) = (1-q_i)\lambda_i \int_0^{l_i} \Theta_i(\tau)\frac{s_i(t-\tau)p(t-\tau)}{1+\alpha_i p(t-\tau)}d\tau - \pi_i y_i(t), \qquad i = 1,2, \tag{3.2}$$

$$\dot{u}_i(t) = q_i\lambda_i \int_0^{l_i} \Theta_i(\tau)\frac{s_i(t-\tau)p(t-\tau)}{1+\alpha_i p(t-\tau)}d\tau - \omega_i u_i(t), \qquad i = 1,2, \tag{3.3}$$

$$\dot{p}(t) = \sum_{i=1}^{2}\left(N_i\pi_i \int_0^{e_i} \Lambda_i(\tau)y_i(t-\tau)d\tau + M_i\omega_i \int_0^{\vartheta_i} \Delta_i(\tau)u_i(t-\tau)d\tau\right)$$
$$- cp(t) - bp(t)z(t), \tag{3.4}$$

$$\dot{z}(t) = \nu p(t)z(t) - \mu z(t). \tag{3.5}$$

where $\alpha_i > 0$. As the same to the previous section it's easy to show the non-negativity and boundedness of the solutions.

Lemma 3. *For system (3.1)-(3.5) there exist two bifurcation parameters R_0^S and R_1^S with $R_0^S > R_1^S > 0$ such that*
(i) if $R_0^S \le 1$, then the system has only one nonnegative steady state Π_0,
(ii) if $R_1^S \le 1 < R_0^S$, then the system has only two nonnegative steady states Π_0 and Π_1,
(iii) if $R_1^S > 1$, then the system has three nonnegative steady states Π_0, Π_1 and Π_2.

Proof. System (3.1)-(3.5) has the following steady states:
(i) Infection-free steady state $\Pi_0 = (s_1^0, s_2^0, 0,0,0,0,0,0)$ where $s_i^0 = \frac{\rho_i}{\beta_i}$, $i = 1,2$,
(ii) Humoral-inactivated infection steady state $\Pi_1 = (\tilde{s}_1, \tilde{s}_2, \tilde{y}_1, \tilde{y}_2, \tilde{u}_1, \tilde{u}_2, \tilde{p}, 0)$ where

$$\tilde{s}_i = \frac{s_i^0(1+\alpha_i\tilde{p})}{1+\xi_i\tilde{p}}, \quad \tilde{y}_i = \frac{(1-q_i)F_i\lambda_i s_i^0\tilde{p}}{\pi_i(1+\xi_i\tilde{p})},$$
$$\tilde{u}_i = \frac{q_iF_i\lambda_i s_i^0\tilde{p}}{\omega_i(1+\xi_i\tilde{p})}, \ \tilde{p} = \frac{-\hat{B}+\sqrt{\hat{B}^2+4\hat{A}\hat{C}}}{2\hat{A}},$$

where,

$$\hat{A} = \xi_1\xi_2, \ \hat{B} = \xi_1 R_{01}^S + \xi_2 R_{02}^S + (1-R_0^S)(\xi_1+\xi_2),$$
$$\hat{C} = R_0^S - 1, \quad \xi_i = \alpha_i + \frac{\lambda_i}{\beta_i}, \ i = 1,2,$$

and $R_0^S = \sum_{i=1}^{2}\frac{\gamma_i\lambda_i s_i^0}{c}$, is the basic reproduction number for model (3.1)-(3.5).

(iii) Humoral-activated infection steady state $\Pi_2 = (\bar{s}_1, \bar{s}_2, \bar{y}_1, \bar{y}_2, \bar{u}_1, \bar{u}_2, \bar{p}, \bar{z})$, where

$$\bar{s}_i = \frac{\rho_i(\nu + \mu\alpha_i)}{\beta_i(\nu + \mu\xi_i)} > 0,\ \bar{y}_i = \frac{(1-q_i)F_i\rho_i\lambda_i\mu}{\beta_i\pi_i(\nu + \mu\xi_i)} > 0,$$
$$\bar{u}_i = \frac{q_iF_i\rho_i\lambda_i\mu}{\omega_i\beta_i(\nu + \mu\xi_i)} > 0,\ i = 1,2,\ \bar{p} = \frac{\mu}{\nu} > 0,\ \bar{z} = \frac{c}{b}\left(R_1^S - 1\right),$$

and $R_1^S = \sum_{i=1}^{2} \frac{\gamma_i\lambda_i\rho_i\nu}{c\beta_i(\nu+\mu\xi_i)}$, is the humoral immunity activation number for system (3.1)-(3.5). □

3.1. **Global stability analysis.**

Theorem 3.1. *For system (3.1)-(3.5), if $R_0^S \le 1$, then Π_0 is GAS.*

Proof. We consider a Lyapunov function U_0 as:

$$U_0 = \sum_{i=1}^{2}\gamma_i\left[s_i^0 H\left(\frac{s_i}{s_i^0}\right) + \frac{N_iG_i}{\gamma_i}y_i + \frac{M_iC_i}{\gamma_i}u_i + \frac{\lambda_i}{F_i}\int_0^{l_i}\Theta_i(\tau)\int_0^{\tau}\frac{s_i(t-\theta)p(t-\theta)}{1+\alpha_i p(t-\theta)}d\theta d\tau\right.$$
$$\left.+\frac{N_i\pi_i}{\gamma_i}\int_0^{e_i}\Lambda_i(\tau)\int_0^{\tau}y_i(t-\theta)d\theta d\tau + \frac{M_i\omega_i}{\gamma_i}\int_0^{\vartheta_i}\Delta_i(\tau)\int_0^{\tau}u_i(t-\theta)d\theta d\tau\right] + p + \frac{b}{\nu}z.$$

Calculating $\frac{dU_0}{dt}$ along the trajectories of (3.1)-(3.5) we get:

$$\frac{dU_0}{dt} = -\sum_{i=1}^{2}\gamma_i\beta_i\frac{(s_i - s_i^0)^2}{s_i} + \left(\sum_{i=1}^{2}\frac{\gamma_i\lambda_i s_i^0}{c(1+\alpha_i p)} - 1\right)cp - \frac{b\mu}{\nu}z$$
$$= -\sum_{i=1}^{2}\gamma_i\beta_i\frac{(s_i - s_i^0)^2}{s_i} - \sum_{i=1}^{2}\frac{R_{0i}^S\alpha_i c p^2}{(1+\alpha_i p)} + (R_0^S - 1)cp - \frac{b\mu}{\nu}z.$$

Thus if $R_0^S \le 1$, then $\frac{dU_0}{dt} \le 0$ for all $s_1, s_2, p, z > 0$. Clearly $\frac{dU_0}{dt} = 0$ at Π_0. Applying (LIP), we get that Π_0 is GAS. □

Theorem 3.2. *For system (3.1)-(3.5) if $R_1^S \le 1 < R_0^S$, then Π_1 is GAS.*

Proof. Construct

$$U_1 = \sum_{i=1}^{2}\gamma_i\left[\tilde{s}_i H\left(\frac{s_i}{\tilde{s}_i}\right) + \frac{N_iG_i}{\gamma_i}\tilde{y}_i H\left(\frac{y_i}{\tilde{y}_i}\right) + \frac{M_iC_i}{\gamma_i}\tilde{u}_i H\left(\frac{u_i}{\tilde{u}_i}\right)\right.$$
$$+\frac{1}{F_i}\frac{\lambda_i\tilde{s}_i\tilde{p}}{(1+\alpha_i\tilde{p})}\int_0^{l_i}\Theta_i(\tau)\int_0^{\tau}H\left(\frac{s_i(t-\theta)p(t-\theta)(1+\alpha_i\tilde{p})}{\tilde{s}_i\tilde{p}(1+\alpha_i p(t-\theta))}\right)d\theta d\tau$$
$$+\frac{N_i\pi_i\tilde{y}_i}{\gamma_i}\int_0^{e_i}\Lambda_i(\tau)\int_0^{\tau}H\left(\frac{y_i(t-\theta)}{\tilde{y}_i}\right)d\theta d\tau$$

$$+\frac{M_i\omega_i\tilde{u}_i}{\gamma_i}\int_0^{\vartheta_i}\Delta_i(\tau)\int_0^{\tau}H\left(\frac{u_i(t-\theta)}{\tilde{u}_i}\right)d\theta d\tau\Bigg]+\tilde{p}H\left(\frac{p}{\tilde{p}}\right)+\frac{b}{\nu}z.$$

Calculating $\frac{dU_1}{dt}$ along the solutions of system (3.1)-(3.5), we get

$$\begin{aligned}\frac{dU_1}{dt}=&\sum_{i=1}^{2}\gamma_i\Bigg[\left(1-\frac{\tilde{s}_i}{s_i}\right)(\rho_i-\beta_i s_i)+\frac{\lambda_i\tilde{s}_i p}{1+\alpha_i p}+\frac{N_iG_i\pi_i}{\gamma_i}\tilde{y}_i\\&+\frac{M_iC_i\omega_i}{\gamma_i}\tilde{u}_i-\frac{q_iM_iC_i\lambda_i}{\gamma_i}\int_0^{l_i}\Theta_i(\tau)\frac{\tilde{u}_i s_i(t-\tau)p(t-\tau)}{u_i(1+\alpha_i p(t-\tau))}d\tau\\&-\frac{(1-q_i)N_iG_i\lambda_i}{\gamma_i}\int_0^{l_i}\Theta_i(\tau)\frac{\tilde{y}_i s_i(t-\tau)p(t-\tau)}{y_i(1+\alpha_i p(t-\tau))}d\tau\\&+\frac{N_i\pi_i\tilde{y}_i}{\gamma_i}\int_0^{e_i}\Lambda_i(\tau)\ln\left(\frac{y_i(t-\tau)}{y_i}\right)d\tau\\&+\frac{1}{F_i}\frac{\lambda_i\tilde{s}_i\tilde{p}}{(1+\alpha_i\tilde{p})}\int_0^{l_i}\Theta_i(\tau)\ln\left(\frac{s_i(t-\tau)p(t-\tau)(1+\alpha_i p)}{s_i p(1+\alpha_i p(t-\tau))}\right)d\tau\\&+\frac{M_i\omega_i\tilde{u}_i}{\gamma_i}\int_0^{\vartheta_i}\Delta_i(\tau)\ln\left(\frac{u_i(t-\tau)}{u_i}\right)d\tau\Bigg]\\&-\sum_{i=1}^{2}N_i\pi_i\int_0^{e_i}\Lambda_i(\tau)\frac{\tilde{p}y_i(t-\tau)}{p}d\tau-\sum_{i=1}^{2}M_i\omega_i\int_0^{\vartheta_i}\Delta_i(\tau)\frac{\tilde{p}u_i(t-\tau)}{p}d\tau\\&-cp+c\tilde{p}+b\tilde{p}z-\frac{b\mu}{\nu}z.\end{aligned}$$

From the steady state conditions of Π_1:

$$\rho_i=\beta_i\tilde{s}_i+\frac{\lambda_i\tilde{s}_i\tilde{p}}{1+\alpha_i\tilde{p}},\quad(1-q_i)F_i\frac{\lambda_i\tilde{s}_i\tilde{p}}{1+\alpha_i\tilde{p}}=\pi_i\tilde{y}_i,\quad q_iF_i\frac{\lambda_i\tilde{s}_i\tilde{p}}{1+\alpha_i\tilde{p}}=\omega_i\tilde{u}_i,$$
$$c\tilde{p}=\sum_{i=1}^{2}(N_i\pi_iG_i\tilde{y}_i+M_i\omega_iC_i\tilde{u}_i)=\sum_{i=1}^{2}\gamma_i\frac{\lambda_i\tilde{s}_i\tilde{p}}{1+\alpha_i\tilde{p}},\quad cp=\frac{p}{\tilde{p}}\sum_{i=1}^{2}\gamma_i\frac{\lambda_i\tilde{s}_i\tilde{p}}{1+\alpha_i\tilde{p}},$$

we obtain:

$$\begin{aligned}\frac{dU_1}{dt}=&\sum_{i=1}^{2}\gamma_i\Bigg[\left(1-\frac{\tilde{s}_i}{s_i}\right)(\beta_i\tilde{s}_i-\beta_i s_i)+\frac{\lambda_i\tilde{s}_i\tilde{p}}{1+\alpha_i\tilde{p}}\left(1-\frac{\tilde{s}_i}{s_i}\right)\\&+\frac{\lambda_i\tilde{s}_i\tilde{p}}{1+\alpha_i\tilde{p}}\left(\frac{p(1+\alpha_i\tilde{p})}{\tilde{p}(1+\alpha_i p)}-\frac{p}{\tilde{p}}\right)+\frac{2N_i\pi_iG_i}{\gamma_i}\tilde{y}_i+\frac{2M_i\omega_iC_i}{\gamma_i}\tilde{u}_i\\&-\frac{N_i\pi_iG_i\tilde{y}_i}{\gamma_iF_i}\int_0^{l_i}\Theta_i(\tau)\frac{\tilde{y}_i s_i(t-\tau)p(t-\tau)(1+\alpha_i\tilde{p})}{y_i\tilde{s}_i\tilde{p}(1+\alpha_i p(t-\tau))}d\tau\end{aligned}$$

$$
\begin{aligned}
&-\frac{M_i\omega_iC_i\tilde{u}_i}{\gamma_iF_i}\int\limits_0^{l_i}\Theta_i(\tau)\frac{\tilde{u}_is_i(t-\tau)p(t-\tau)(1+\alpha_i\tilde{p})}{u_i\tilde{s}_i\tilde{p}(1+\alpha_ip(t-\tau))}d\tau\\
&-\frac{N_i\pi_i\tilde{y}_i}{\gamma_i}\int_0^{e_i}\Lambda_i(\tau)\frac{\tilde{p}y_i(t-\tau)}{p\tilde{y}_i}d\tau\\
&-\frac{M_i\omega_i\tilde{u}_i}{\gamma_i}\int_0^{\vartheta_i}\Delta_i(\tau)\frac{\tilde{p}u_i(t-\tau)}{p\tilde{u}_i}d\tau+\frac{N_i\pi_i\tilde{y}_i}{\gamma_i}\int_0^{e_i}\Lambda_i(\tau)\ln\left(\frac{y_i(t-\tau)}{y_i}\right)d\tau\\
&+\left(\frac{N_i\pi_iG_i\tilde{y}_i+M_i\omega_iC_i\tilde{u}_i}{\gamma_iF_i}\right)\int_0^{l_i}\Theta_i(\tau)\ln\left(\frac{s_i(t-\tau)p(t-\tau)(1+\alpha_ip)}{s_ip(1+\alpha_ip(t-\tau))}\right)d\tau\\
&+\frac{M_i\omega_i\tilde{u}_i}{\gamma_i}\int_0^{\vartheta_i}\Delta_i(\tau)\ln\left(\frac{u_i(t-\tau)}{u_i}\right)d\tau\Bigg]+b\left(\tilde{p}-\frac{\mu}{\nu}\right)z.
\end{aligned}
$$

Using Eqs. (2.8) with $\phi_i(s_i,p)=\frac{\lambda_is_ip}{1+\alpha_ip},\ s_i^*=\tilde{s}_i,\ y_i^*=\tilde{y}_i,\ u_i^*=\tilde{u}_i$ and $p^*=\tilde{p}$, then we have:

$$
\begin{aligned}
\frac{dU_1}{dt}=\sum_{i=1}^{2}\Bigg[&-\gamma_i\frac{\beta_i(s_i-\tilde{s}_i)^2}{s_i}-\gamma_i\frac{\lambda_i\tilde{s}_i\tilde{p}}{1+\alpha_i\tilde{p}}\left(\frac{\alpha_i(p-\tilde{p})^2}{\tilde{p}(1+\alpha_ip)(1+\alpha_i\tilde{p})}\right)\\
&-\gamma_i\frac{\lambda_i\tilde{s}_i\tilde{p}}{1+\alpha_i\tilde{p}}\left(H\left(\frac{\tilde{s}_i}{s_i}\right)+H\left(\frac{1+\alpha_ip}{1+\alpha_i\tilde{p}}\right)\right)\\
&-\frac{N_i\pi_iG_i\tilde{y}_i}{F_i}\int_0^{l_i}\Theta_i(\tau)H\left(\frac{\tilde{y}_is_i(t-\tau)p(t-\tau)(1+\alpha_i\tilde{p})}{y_i\tilde{s}_i\tilde{p}(1+\alpha_ip(t-\tau))}\right)d\tau\\
&-N_i\pi_i\tilde{y}_i\int_0^{e_i}\Lambda_i(\tau)H\left(\frac{\tilde{p}y_i(t-\tau)}{p\tilde{y}_i}\right)d\tau\\
&-\frac{M_i\omega_iC_i\tilde{u}_i}{F_i}\int_0^{l_i}\Theta_i(\tau)H\left(\frac{\tilde{u}_is_i(t-\tau)p(t-\tau)(1+\alpha_i\tilde{p})}{u_i\tilde{s}_i\tilde{p}(1+\alpha_ip(t-\tau))}\right)d\tau\\
&-M_i\omega_i\tilde{u}_i\int_0^{\vartheta_i}\Delta_i(\tau)H\left(\frac{\tilde{p}u_i(t-\tau)}{p\tilde{u}_i}\right)d\tau\Bigg]+b\left(\tilde{p}-\frac{\mu}{\nu}\right)z.
\end{aligned}
$$

Similar to proof of Eq. (2.12) we can get $(\tilde{p}-\bar{p})=\frac{1}{Q}(R_1^S-1)$ where, $Q_1=\sum\limits_{i=1}^{2}\frac{\gamma_i\lambda_i\rho_i\xi_i}{c\beta_i(1+\xi_i\bar{p})(1+\xi_i\tilde{p})}$. Thus, if $R_1^S\le 1$ then $\tilde{p}\le\frac{\mu}{\nu}=\bar{p}$.

If $R_1^S\le 1$, then $\frac{dU_1}{dt}\le 0$ for all $s_i,y_i,u_i,p,z>0$ where equality occurs at Π_1. LIP implies the global stability of Π_1. □

Theorem 3.3. *For system (3.1)-(3.5) if* $R_1^S>1$, *then* Π_2 *is GAS.*

Proof. Define:

$$\begin{aligned}
U_2 = \sum_{i=1}^{2}\gamma_i \Bigg[&\bar{s}_i H\left(\frac{s_i}{\bar{s}_i}\right) + \frac{N_i G_i}{\gamma_i}\bar{y}_i H\left(\frac{y_i}{\bar{y}_i}\right) + \frac{M_i C_i}{\gamma_i}\bar{u}_i H\left(\frac{u_i}{\bar{u}_i}\right) \\
&+ \frac{1}{F_i}\frac{\lambda_i \bar{s}_i \bar{p}}{1+\alpha_i \bar{p}}\int_0^{l_i}\Theta_i(\tau)\int_0^{\tau} H\left(\frac{s_i(t-\theta)p(t-\theta)(1+\alpha_i\bar{p})}{\bar{s}_i\bar{p}(1+\alpha_i p(t-\theta))}\right)d\theta d\tau \\
&+ \frac{N_i\pi_i\bar{y}_i}{\gamma_i}\int_0^{e_i}\Lambda_i(\tau)\int_0^{\tau} H\left(\frac{y_i(t-\theta)}{\bar{y}_i}\right)d\theta d\tau \\
&+ \frac{M_i\omega_i\bar{u}_i}{\gamma_i}\int_0^{\vartheta_i}\Delta_i(\tau)\int_0^{\tau} H\left(\frac{u_i(t-\theta)}{\bar{u}_i}\right)d\theta d\tau\Bigg] + \bar{p}H\left(\frac{p}{\bar{p}}\right) + \frac{b}{\nu}\bar{z}H(\frac{z}{\bar{z}}).
\end{aligned}$$

The time derivative of U_2 along the trajectories of system (3.1)-(3.5) is obtained by:

$$\begin{aligned}
\frac{dU_2}{dt} = \sum_{i=1}^{2}\gamma_i \Bigg[&\left(1-\frac{\bar{s}_i}{s_i}\right)(\rho_i - \beta_i s_i) + \frac{\lambda_i \bar{s}_i p}{1+\alpha_i p} + \frac{N_i G_i}{\gamma_i}\pi_i \bar{y}_i \\
&+ \frac{M_i C_i}{\gamma_i}\omega_i\bar{u}_i - \frac{(1-q_i)N_i G_i \lambda_i}{\gamma_i}\int_0^{l_i}\Theta_i(\tau)\frac{\bar{y}_i s_i(t-\tau)p(t-\tau)}{y_i\left(1+\alpha_i p(t-\tau)\right)}d\tau \\
&- \frac{q_i M_i C_i \lambda_i}{\gamma_i}\int_0^{l_i}\Theta_i(\tau)\frac{\bar{u}_i s_i(t-\tau)p(t-\tau)}{u_i\left(1+\alpha_i p(t-\tau)\right)}d\tau \\
&+ \frac{1}{F_i}\frac{\lambda_i\bar{s}_i\bar{p}}{(1+\alpha_i\bar{p})}\int_0^{l_i}\Theta_i(\tau)\ln\left(\frac{s_i(t-\tau)p(t-\tau)(1+\alpha_i p)}{s_i p(1+\alpha_i p(t-\tau)}\right)d\tau \\
&+ \frac{N_i\pi_i\bar{y}_i}{\gamma_i}\int_0^{e_i}\Lambda_i(\tau)\ln\left(\frac{y_i(t-\tau)}{y_i}\right)d\tau \\
&+ \frac{M_i\omega_i\bar{u}_i}{\gamma_i}\int_0^{\vartheta_i}\Delta_i(\tau)\ln\left(\frac{u_i(t-\tau)}{u_i}\right)d\tau\Bigg] - \sum_{i=1}^{2}N_i\pi_i\int_0^{e_i}\Lambda_i(\tau)\frac{\bar{p}y_i(t-\tau)}{p}d\tau \\
&- \sum_{i=1}^{2}M_i\omega_i\int_0^{\vartheta_i}\Delta_i(\tau)\frac{\bar{p}u_i(t-\tau)}{p}d\tau - cp + c\bar{p} + b\bar{p}z - bp\bar{z} - \frac{b\mu}{\nu}z + \frac{b\mu}{\nu}\bar{z}. \qquad (3.6)
\end{aligned}$$

Using the steady state conditions of Π_2:

$$\begin{aligned}
&\rho_i = \beta_i\bar{s}_i + \frac{\lambda_i\bar{s}_i\bar{p}}{1+\alpha_i\bar{p}},\ \ (1-q_i)F_i\frac{\lambda_i\bar{s}_i\bar{p}}{1+\alpha_i\bar{p}} = \pi_i\bar{y}_i,\ \ q_i F_i\frac{\lambda_i\bar{s}_i\bar{p}}{1+\alpha_i\bar{p}} = \omega_i\bar{u}_i, \\
&c\bar{p} = \sum_{i=1}^{2}\left(N_i\pi_i G_i\bar{y}_i + M_i\omega_i C_i\bar{u}_i\right) - b\bar{p}\bar{z},\ \ cp = \frac{p}{\bar{p}}\sum_{i=1}^{2}\gamma_i\frac{\lambda_i\bar{s}_i\bar{p}}{1+\alpha_i p} - bp\bar{z},\ \ \bar{p} = \frac{\mu}{\nu},
\end{aligned}$$

and applying Eqs. (2.8) with $\phi_i(s_i,p)=\frac{\lambda_i s_i p}{1+\alpha_i p},\ s_i^*=\bar{s}_i,\ y_i^*=\bar{y}_i,\ u_i^*=\bar{u}_i^*$ and $p^*=\bar{p}$, we find:

$$\begin{aligned}
\frac{dU_2}{dt} &= \sum_{i=1}^{2}\Bigg[-\gamma_i\frac{\beta_i(s_i-\bar{s}_i)^2}{s_i}-\gamma_i\frac{\lambda_i\bar{s}_i\bar{p}}{1+\alpha_i\bar{p}}\left(\frac{\alpha_i(p-\bar{p})^2}{\bar{p}(1+\alpha_i p)(1+\alpha_i\bar{p})}\right)\\
&\quad-\gamma_i\frac{\lambda_i\bar{s}_i\bar{p}}{1+\alpha_i\bar{p}}\left(H\left(\frac{\bar{s}_i}{s_i}\right)+H\left(\frac{1+\alpha_i p}{1+\alpha_i\bar{p}}\right)\right)-N_i\pi_i\bar{y}_i\int_0^{e_i}\Lambda_i(\tau)H\left(\frac{\bar{p}y_i(t-\tau)}{p\bar{y}_i}\right)d\tau\\
&\quad-\frac{N_i\pi_i G_i\bar{y}_i}{F_i}\int_0^{l_i}\Theta_i(\tau)H\left(\frac{\bar{y}_i s_i(t-\tau)p(t-\tau)(1+\alpha_i p)}{y_i\bar{s}_i\bar{p}(1+\alpha_i p(t-\tau))}\right)d\tau\\
&\quad-\frac{M_i\omega_i C_i\bar{u}_i}{F_i}\int_0^{l_i}\Theta_i(\tau)H\left(\frac{\bar{u}_i s_i(t-\tau)p(t-\tau)(1+\alpha_i p)}{u_i\bar{s}_i\bar{p}(1+\alpha_i p(t-\tau))}\right)d\tau\\
&\quad-M_i\omega_i\bar{u}_i\int_0^{\vartheta_i}\Delta_i(\tau)H\left(\frac{\bar{p}u_i(t-\tau)}{p\bar{u}_i}\right)d\tau\Bigg].
\end{aligned}$$

Thus, if $R_1^S>1$ then $\bar{s}_i,\bar{y}_i,\bar{u}_i,\bar{p},\bar{z}>0$. Therefore $\frac{dU_2}{dt}\le 0$. Applying LIP one can show that Π_2 is GAS. □

4. MODEL WITH GENERAL INCIDENCE RATE

We consider a model with general incidence and neutralization rates as:

$$\dot{s}_i(t)=\rho_i-\beta_i s_i(t)-\phi_i(s_i(t),p(t)),\qquad i=1,2, \tag{4.1}$$

$$\dot{y}_i(t)=(1-q_i)\int_0^{l_i}\Theta_i(\tau)\phi_i(s_i(t-\tau),p(t-\tau))d\tau-\pi_i y_i(t),\quad i=1,2, \tag{4.2}$$

$$\dot{u}_i(t)=q_i\int_0^{l_i}\Theta_i(\tau)\phi_i(s_i(t-\tau),p(t-\tau))d\tau-\omega_i u_i(t),\qquad i=1,2, \tag{4.3}$$

$$\begin{aligned}\dot{p}(t)&=\sum_{i=1}^{2}\left(N_i\pi_i\int_0^{e_i}\Lambda_i(\tau)y_i(t-\tau)d\tau+M_i\omega_i\int_0^{\vartheta_i}\Delta_i(\tau)u_i(t-\tau)d\tau\right)\\
&\quad-cp(t)-bp(t)\psi(z(t)),\end{aligned} \tag{4.4}$$

$$\dot{z}(t)=\nu p(t)\psi(z(t))-\mu\psi(z(t)). \tag{4.5}$$

All the parameters are positive. Function $\phi_i(s_i,p)$, $i=1,2$ represents the incidence rate where, $\phi_1(s_1,p)=(1-\varepsilon)\bar{\phi}_1(s_1,p)$, and $\phi_2(s_2,p)=(1-f\varepsilon)\bar{\phi}_2(s_2,p)$. Also, $bp\psi(z)$, $\nu p\psi(z)$ and $\mu\psi(z)$, represent, the neutralize rate of viruses, the activation rate of B cells and the removal rate of B cells, respectively. For model (4.1)-(4.5) the initial conditions are given by Eq. (2.6). Suppose that functions ϕ_i and ψ are continuously differentiable such that:

Assumption (A1) Function ϕ_i satisfies:

(i) $\phi_i(s_i,p)>0$, $\phi_i(s_i,0)=\phi_i(0,p)=0$, for all $s_i>0, p>0$,

(ii) $\frac{\partial \phi_i(s_i,p)}{\partial p} > 0$, $\frac{\partial \phi_i(s_i,p)}{\partial s_i} > 0$, for any s_i, $p > 0$. Further, $\frac{\partial \phi_i(s_i,0)}{\partial p} > 0$ for any $s_i > 0$, $i = 1, 2$.

Assumption (A2) Function ϕ_i satisfies:

(i) $\phi_i(s_i, p) \leq p\frac{\partial \phi_i(s_i,0)}{\partial p}$, for all $p > 0$,

(ii) $\frac{d}{ds_i}\left(\frac{\partial \phi_i(s_i,0)}{\partial p}\right) \geqslant 0$ for all $s_i > 0$, $i = 1, 2$.

Assumption (A3). Function ϕ_i satisfies:

$\left(\frac{\phi_i(s_i,p)}{\phi_i(s_i,p^*)} - \frac{p}{p^*}\right)\left(1 - \frac{\phi_i(s_i,p^*)}{\phi_i(s_i,p)}\right) \leq 0,\ s_i, p > 0, i = 1, 2$, where $p^* = \tilde{p}$ or $p^* = \bar{p}$.

Assumption (A4). Function ψ satisfies: (i) $\psi(z) > 0$, for all $z > 0$, $\psi(0) = 0$,

(ii) $\psi'(z) > 0$, for all $z \geqslant 0$ and

(iii) there is $\varpi > 0$ such that $\psi(z) > \varpi z$ for all $z > 0$.

The non-negativity of the solutions of system (4.1)-(4.5) can easily be shown. Similar to proof of Lemma 1 we get $\limsup_{t\to\infty} s_i(t) \leq \frac{\rho_i}{\beta_i}$, $\limsup_{t\to\infty} y_i(t) \leq L_i$, and $\limsup_{t\to\infty} u_i(t) \leq L_i$ for all $t \geq 0$, and $\sigma_i = \min\{\beta_i, \pi_i, \omega_i\}$, $i = 1, 2$. From (A4)(iii), let $T(t) = p(t) + \frac{b}{\nu}z(t)$, then

$$\dot{T}(t) = \sum_{i=1}^{2}\left(N_i\pi_i\int_0^{e_i}\Lambda_i(\tau)y_i(t-\tau)d\tau + M_i\omega_i\int_0^{\vartheta_i}\Delta_i(\tau)u_i(t-\tau)d\tau\right) - cp(t) - \frac{b\mu}{\nu}\psi(z(t))$$

$$\leq \sum_{i=1}^{2}\left(N_i\pi_iG_i + M_i\omega_iC_i\right)L_i - \sigma_3\left(p\left(t\right) + \frac{b}{\nu}\psi\left(z\left(t\right)\right)\right)$$

where $\sigma_3 = \min\{c, \mu\varpi\}$. Therefore $\limsup_{t\to\infty} T(t) \leq L_3$, where $L_3 = \sum_{i=1}^{2}\frac{(N_i\pi_iG_i + M_i\omega_iC_i)L_i}{\sigma_3}$.

The non-negativity of $p(t) \geq 0$ and $z(t) \geq 0$ implies that $\limsup_{t\to\infty} p(t) \leq L_3$ and $\limsup_{t\to\infty} z(t) \leq L_4$ where $L_4 = \frac{\nu}{b}L_3$ for all $t \geq 0$. Hence, $s_i(t), y_i(t), u_i(t)$, $i = 1, 2$, $p(t)$ and $z(t)$ are ultimately bounded.

4.1. **Steady states.**

Lemma 4. *For system (4.1)-(4.5) there exist two bifurcation parameters R_0^G and R_1^G with $R_0^G > R_1^G > 0$ such that*

(i) if $R_0^G \leq 1$, then the system has only one nonnegative steady state Π_0,

(ii) if $R_1^G \leq 1 < R_0^G$, then the system has only two nonnegative steady states Π_0 and Π_1,

(iii) if $R_1^G > 1$, then the system has three nonnegative steady states Π_0, Π_1 and Π_2.

Proof. Let Assumptions (A1)-(A4) are valid, and $\Pi\left(s_1, s_2, y_1, y_2, u_1, u_2, p, z\right)$ be any steady state satisfying the following equations:

$$\rho_i - \beta_i s_i - \phi_i(s_i, p) = 0, \quad i = 1, 2, \tag{4.6}$$

$$(1 - q_i)F_i\phi_i(s_i, p) - \pi_i y_i = 0, \quad i = 1, 2, \tag{4.7}$$

$$q_iF_i\phi_i(s_i, p) - \omega_i u_i = 0, \quad i = 1, 2, \tag{4.8}$$

$$\sum_{i=1}^{2}(N_i\pi_i G_i y_i + M_i\omega_i C_i u_i) - cp - bp\psi(z) = 0, \tag{4.9}$$

$$\nu p\psi(z) - \mu\psi(z) = 0. \tag{4.10}$$

From Eq. (4.10) we have $\psi(z) = 0$ or $p = \frac{\mu}{\nu}$. First, we consider the case $\psi(z) = 0$, then from Assumption (A4) we have $z = 0$. Let $z = 0$ in Eqs. (4.6)-(4.9) we have:

$$\sum_{i=1}^{2}\gamma_i\phi_i(s_i, p) - cp = 0. \tag{4.11}$$

Eq. (4.11) has two solutions, $p = 0$ and $p \neq 0$. If $p = 0$ we get $\Pi_0 = (s_1^0, s_2^0, 0, 0, 0, 0, 0, 0)$ where $s_i^0 = \frac{\rho_i}{\beta_i}$, $i = 1, 2$. If $p \neq 0$, then we obtain a humoral-inactivated infection steady stat $\Pi_1 = (\tilde{s}_1, \tilde{s}_2, \tilde{y}_1, \tilde{y}_2, \tilde{u}_1, \tilde{u}_2, \tilde{p}, 0)$ where the coordinates satisfy the equalities:

$$\begin{aligned} \rho_i &= \beta_i\tilde{s}_i + \phi_i(\tilde{s}_i, \tilde{p}), \quad (1 - q_i)F_i\phi_i(\tilde{s}_i, \tilde{p}) = \pi_i\tilde{y}_i, \\ c\tilde{p} &= \sum_{i=1}^{2}\gamma_i\phi_i(\tilde{s}_i, \tilde{p}), \quad q_iF_i\phi_i(\tilde{s}_i, \tilde{p}) = \omega_i\tilde{u}_i, \end{aligned} \tag{4.12}$$

The other solution of Eq. (4.10) is $\bar{p} = \frac{\mu}{\nu}$. Substituting $p = \bar{p}$ in Eq. (4.6) and letting

$$\Psi(s_i) = \rho_i - \beta_i s_i - \phi_i(s_i, \bar{p}) = 0. \tag{4.13}$$

According to Assumption (A1), Ψ is a decreasing function of s_i. Besides $\Psi(0) = \rho_i > 0$ and $\Psi(s_i^0) = -\phi_i(s_i^0, \bar{p}) < 0$. Thus, there exists a unique $\bar{s}_i \in \left(0, s_i^0\right)$ such that $\Psi(\bar{s}_i) = 0$. It follows from Eqs. (4.7)-(4.9) that:

$$\begin{aligned} \bar{y}_i &= \frac{(1 - q_i)F_i\phi_i(\bar{s}_i, \bar{p})}{\pi_i}, \quad \bar{u}_i = \frac{q_iF_i\phi_i(\bar{s}_i, \bar{p})}{\omega_i}, \\ \bar{z} &= \psi^{-1}\left(\frac{c}{b}\left(\sum_{i=1}^{2}\frac{\gamma_i}{c}\frac{\phi_i(\bar{s}_i, \bar{p})}{\bar{p}} - 1\right)\right). \end{aligned}$$

Thus, $\bar{z} > 0$ when $\frac{\gamma_i}{c}\frac{\phi_i(\bar{s}_i, \bar{p})}{\bar{p}} > 1$. Let us define the parameter R_1^G as:

$$R_1^G = \sum_{i=1}^{2}\frac{\gamma_i}{c}\frac{\phi_i(\bar{s}_i, \bar{p})}{\bar{p}}.$$

If $R_1^G > 1$, then $\bar{z} = \psi^{-1}\left(\frac{c}{b}\left(R_1^G - 1\right)\right)$ and there exists a humoral-activated infection steady state $\Pi_2 = (\bar{s}_1, \bar{s}_2, \bar{y}_1, \bar{y}_2, \bar{u}_1, \bar{u}_2, \bar{p}, \bar{z})$.

By studying the local stability of Π_0, we can easily prove that Π_0 is locally if $\sum_{i=1}^{2} \frac{\gamma_i}{c} \frac{\partial \phi_i(s_i^0,0)}{\partial p} \leq 1$. Then, the basic reproduction number R_0^G of system (4.1)-(4.5) can be defined as:

$$R_0^G = \sum_{i=1}^{2} \frac{\gamma_i}{c} \frac{\partial \phi_i(s_i^0, 0)}{\partial p}.$$

□

Clearly from Assumptions (A1) and (A2), we have:

$$R_1^G = \sum_{i=1}^{2} \frac{\gamma_i}{c} \frac{\phi_i(\bar{s}_i, \bar{p})}{\bar{p}} \leq \sum_{i=1}^{2} \frac{\gamma_i}{c} \frac{\bar{p}\partial \phi_i(\bar{s}_i, 0)}{\partial \bar{p}} \leq \sum_{i=1}^{2} \frac{\gamma_i}{c} \frac{\partial \phi_i(s_i^0, 0)}{\partial p} = R_0^G.$$

4.2. **Global stability analysis.**

Theorem 4.1. *If $R_0^G \leq 1$ and Assumptions (A1) and (A2) are hold true for system (4.1)-(4.5), then Π_0 is GAS.*

Proof. Construct a Lyapunov functional K_0 as follows:

$$K_0 = \sum_{i=1}^{2} \gamma_i \Bigg[s_i - s_i^0 - \int_{s_i^0}^{s_i} \lim_{p \to 0^+} \frac{\phi_i(s_i^0, p)}{\phi_i(\nu, p)} d\nu + \frac{N_i G_i}{\gamma_i} y_i + \frac{M_i C_i}{\gamma_i} u_i$$
$$+ \frac{1}{F_i} \int_0^{l_i} \Theta_i(\tau) \int_0^{\tau} \phi_i(s_i(t-\theta), p(t-\theta)) d\theta d\tau$$
$$+ \frac{N_i \pi_i}{\gamma_i} \int_0^{e_i} \Lambda_i(\tau) \int_0^{\tau} y_i(t-\theta) d\theta d\tau + \frac{M_i \omega_i}{\gamma_i} \int_0^{\vartheta_i} \Delta_i(\tau) \int_0^{\tau} u_i(t-\theta) d\theta d\tau \Bigg] + p + \frac{b}{\nu} z.$$

We evaluate $\frac{dK_0}{dt}$ along the solutions of (4.1)-(4.5) as:

$$\frac{dK_0}{dt} = \sum_{i=1}^{2} \gamma_i \left[\left(1 - \frac{\partial \phi_i(s_i^0, 0)/\partial p}{\partial \phi_i(s_i, 0)/\partial p} \right) (\rho_i - \beta_i s_i) + \phi_i(s_i, p) \frac{\partial \phi_i(s_i^0, 0)/\partial p}{\partial \phi_i(s_i, 0)/\partial p} \right] - cp - \frac{b\mu}{\nu} \psi(z)$$
$$= \sum_{i=1}^{2} \gamma_i \rho_i \left(1 - \frac{s_i}{s_i^0} \right) \left(1 - \frac{\partial \phi_i(s_i^0, 0)/\partial p}{\partial \phi_i(s_i, 0)/\partial p} \right) + \sum_{i=1}^{2} \gamma_i \phi_i(s_i, p) \frac{\partial \phi_i(s_i^0, 0)/\partial p}{\partial \phi_i(s_i, 0)/\partial p} - cp - \frac{b\mu}{\nu} \psi(z)$$
$$\leq \sum_{i=1}^{2} \gamma_i \rho_i \left(1 - \frac{s_i}{s_i^0} \right) \left(1 - \frac{\partial \phi_i(s_i^0, 0)/\partial p}{\partial \phi_i(s_i, 0)/\partial p} \right) + \sum_{i=1}^{2} \gamma_i p \frac{\partial \phi_i(s_i^0, 0)}{\partial p} - cp - \frac{b\mu}{\nu} \psi(z)$$
$$= \sum_{i=1}^{2} \gamma_i \rho_i \left(1 - \frac{s_i}{s_i^0} \right) \left(1 - \frac{\partial \phi_i(s_i^0, 0)/\partial p}{\partial \phi_i(s_i, 0)/\partial p} \right) + (R_0^G - 1) cp - \frac{b\mu}{\nu} \psi(z). \tag{4.14}$$

From Assumptions (A1) and (A2), we have

$$\left(1-\frac{s_i}{s_i^0}\right)\left(1-\frac{\partial\phi_i(s_i^0,0)/\partial p}{\partial\phi_i(s_i,0)/\partial p}\right)\leq 0,\ s_i,\ p>0,\ i=1,2.$$

Therefore, if $R_0^G\leq 1$, then $\frac{dK_0}{dt}\leq 0$ and $\frac{dK_0}{dt}=0$ at Π_0. Thus, Π_0 is GAS. □

Lemma 5. *If $R_0^G>1$ and Assumptions (A1)-(A3) are valid, then:*

$$sgn\,(\bar{s}_i-\tilde{s}_i)=sgn\,(\tilde{p}-\bar{p})=sgn\left(R_1^G-1\right).$$

Proof. Using Assumptions (A1)-(A2), that for $\bar{s}_i,\tilde{s}_i,\bar{p},\tilde{p}>0$, we find:

$$(\phi_i(\bar{s}_i,\bar{p})-\phi_i(\tilde{s}_i,\bar{p}))\,(\bar{s}_i-\tilde{s}_i)>0,\quad (\phi_i(\tilde{s}_i,\bar{p})-\phi_i(\tilde{s}_i,\tilde{p}))\,(\bar{p}-\tilde{p})>0. \tag{4.15}$$

By the inequality (4.15) and Assumption (A3) with $s_i=\tilde{s}_i$ and $p=\bar{p}$ and $p^*=\tilde{p}$ we obtain:

$$((\phi_i(\tilde{s}_i,\bar{p})\tilde{p}-\phi_i(\tilde{s}_i,\tilde{p})\bar{p}))\,(\tilde{p}-\bar{p})>0. \tag{4.16}$$

Suppose that, $sgn\,(\bar{s}_i-\tilde{s}_i)=sgn\,(\bar{p}-\tilde{p})$. From the conditions of the steady states Π_1 and Π_2 we get:

$$\begin{aligned}(\rho_i-\beta_i\bar{s}_i)-(\rho_i-\beta_i\tilde{s}_i)&=\phi_i(\bar{s}_i,\bar{p})-\phi_i(\tilde{s}_i,\tilde{p})\\&=\phi_i(\bar{s}_i,\bar{p})-\phi_i(\bar{s}_i,\tilde{p})+\phi_i(\bar{s}_i,\tilde{p})-\phi_i(\tilde{s}_i,\tilde{p}).\end{aligned}$$

Therefore, from inequalities (4.15) we obtain $sgn\,(\bar{s}_i-\tilde{s}_i)=sgn\,(\tilde{s}_i-\bar{s}_i)$, which is a contradiction, hence, $sgn\,(\bar{s}_i-\tilde{s}_i)=sgn\,(\tilde{p}-\bar{p})$. Using Eq. (4.12) and the definition of R_1^G we get

$$\begin{aligned}R_1^G-1&=\sum_{i=1}^{2}\frac{\gamma_i}{c}\left(\frac{\phi_i(\bar{s}_i,\bar{p})}{\bar{p}}-\frac{\phi_i(\tilde{s}_i,\tilde{p})}{\tilde{p}}\right)\\&=\sum_{i=1}^{2}\frac{\gamma_i}{c}\left(\frac{1}{\bar{p}}\left(\phi_i(\bar{s}_i,\bar{p})-\phi_i(\tilde{s}_i,\bar{p})\right)+\frac{1}{\tilde{p}\bar{p}}\left(\phi_i(\tilde{s}_i,\bar{p})\tilde{p}-\phi_i(\tilde{s}_i,\tilde{p})\bar{p}\right)\right).\end{aligned}$$

Thus, from Eqs. (4.15) and (4.16) we obtain $sgn\left(R_1^G-1\right)=sgn\,(\tilde{p}-\bar{p})$. □

Theorem 4.2. *For system (4.1)-(4.5), if $R_1^G\leq 1<R_0^G$ and Assumptions (A1)-(A4) are valid, then Π_1 is GAS.*

Proof. Consider

$$\begin{aligned}K_1=\sum_{i=1}^{2}\gamma_i\Bigg[&s_i-\tilde{s}_i-\int_{\tilde{s}_i}^{s_i}\frac{\phi_i(\tilde{s}_i,\tilde{p})}{\phi_i(\nu,\tilde{p})}d\nu+\frac{N_iG_i}{\gamma_i}\tilde{y}_iH(\frac{y_i}{\tilde{y}_i})+\frac{M_iC_i}{\gamma_i}\tilde{u}_iH(\frac{u_i}{\tilde{u}_i})\\&+\frac{1}{F_i}\phi_i(\tilde{s}_i,\tilde{p})\int_0^{l_i}\Theta_i(\tau)\int_0^{\tau}H\left(\frac{\phi_i(s_i(t-\theta),p(t-\theta))}{\phi_i(\tilde{s}_i,\tilde{p})}\right)d\theta d\tau\\&+\frac{N_i\pi_i\tilde{y}_i}{\gamma_i}\int_0^{e_i}\Lambda_i(\tau)\int_0^{\tau}H\left(\frac{y_i(t-\theta)}{\tilde{y}_i}\right)d\theta d\tau\end{aligned}$$

$$+\frac{M_i\omega_i\tilde{u}_i}{\gamma_i}\int_0^{\vartheta_i}\Delta_i(\tau)\int_0^{\tau}H\left(\frac{u_i(t-\theta)}{\tilde{u}_i}\right)d\theta d\tau\Bigg]+\tilde{p}H\left(\frac{p}{\tilde{p}}\right)+\frac{b}{\nu}z.$$

Calculating $\frac{dK_1}{dt}$ along the solutions of system (4.1)-(4.5) we get:

$$\begin{aligned}\frac{dK_1}{dt}&=\sum_{i=1}^{2}\gamma_i\left[\left(1-\frac{\phi_i(\tilde{s}_i,\tilde{p})}{\phi_i(s_i,\tilde{p})}\right)(\rho_i-\beta_i s_i)+\phi_i(s_i,p)\frac{\phi_i(\tilde{s}_i,\tilde{p})}{\phi_i(s_i,\tilde{p})}+\frac{N_iG_i\pi_i}{\gamma_i}\tilde{y}_i\right.\\&+\frac{M_iC_i\omega_i}{\gamma_i}\tilde{u}_i-\frac{(1-q_i)N_iG_i}{\gamma_i}\int_0^{l_i}\Theta_i(\tau)\frac{\tilde{y}_i\phi_i(s_i(t-\tau),p(t-\tau))}{y_i}d\tau\\&-\frac{q_iM_iC_i}{\gamma_i}\int_0^{l_i}\Theta_i(\tau)\frac{\tilde{u}_i\phi_i(s_i(t-\tau),p(t-\tau))}{u_i}d\tau\\&+\frac{\phi_i(\tilde{s}_i,\tilde{p})}{F_i}\int_0^{l_i}\Theta_i(\tau)\ln\left(\frac{\phi_i(s_i(t-\tau),p(t-\tau))}{\phi_i(s_i,p)}\right)d\tau\\&\left.+\frac{N_i\pi_i\tilde{y}_i}{\gamma_i}\int_0^{e_i}\Lambda_i(\tau)\ln\left(\frac{y_i(t-\tau)}{y_i}\right)d\tau+\frac{M_i\omega_i\tilde{u}_i}{\gamma_i}\int_0^{\vartheta_i}\Delta_i(\tau)\ln\left(\frac{u_i(t-\tau)}{u_i}\right)d\tau\right]\\&-\sum_{i=1}^{2}N_i\pi_i\int_0^{e_i}\Lambda_i(\tau)\frac{\tilde{p}y_i(t-\tau)}{p}d\tau-\sum_{i=1}^{2}M_i\omega_i\int_0^{\vartheta_i}\Delta_i(\tau)\frac{\tilde{p}u_i(t-\tau)}{p}d\tau\\&-cp+c\tilde{p}+b\tilde{p}\psi(z)-\frac{b\mu}{\nu}\psi(z).\end{aligned}$$

From the conditions of the steady state Π_1, we find:

$$\rho_i=\beta_i\tilde{s}_i+\phi_i(\tilde{s}_i,\tilde{p}),\quad(1-q_i)F_i\phi_i(\tilde{s}_i,\tilde{p})=\pi_i\tilde{y}_i,\quad q_iF_i\phi_i(\tilde{s}_i,\tilde{p})=\omega_i\tilde{u}_i,$$

$$c\tilde{p}=\sum_{i=1}^{2}(N_i\pi_iG_i\tilde{y}_i+M_i\omega_iC_i\tilde{u}_i)=\sum_{i=1}^{2}\gamma_i\phi_i(\tilde{s}_i,\tilde{p}),\quad cp=\frac{p}{\tilde{p}}\sum_{i=1}^{2}\gamma_i\phi_i(\tilde{s}_i,\tilde{p}),$$

and using inequalities (2.8) with $s_i^*=\tilde{s}_i,\ y_i^*=\tilde{y}_i,\ u_i^*=\tilde{u}_i$ and $p^*=\tilde{p}$, we get

$$\begin{aligned}\frac{dK_1}{dt}&=\sum_{i=1}^{2}\left[\gamma_i\beta_i\tilde{s}_i\left(1-\frac{s_i}{\tilde{s}_i}\right)\left(1-\frac{\phi_i(\tilde{s}_i,\tilde{p})}{\phi_i(s_i,\tilde{p})}\right)\right.\\&+\gamma_i\phi_i(\tilde{s}_i,\tilde{p})\left(\frac{\phi_i(s_i,p)}{\phi_i(s_i,\tilde{p})}-\frac{p}{\tilde{p}}\right)\left(1-\frac{\phi_i(s_i,\tilde{p})}{\phi_i(s_i,p)}\right)\\&-\gamma_i\phi_i(\tilde{s}_i,\tilde{p})\left(H\left(\frac{\phi_i(\tilde{s}_i,\tilde{p})}{\phi_i(s_i,\tilde{p})}\right)+H\left(\frac{p\phi_i(s_i,\tilde{p})}{p\phi_i(s_i,p)}\right)\right)\\&-\frac{N_iG_i\pi_i\tilde{y}_i}{F_i}\int_0^{l_i}\Theta_i(\tau)H\left(\frac{\tilde{y}_i\phi_i(s_i(t-\tau),p(t-\tau))}{y_i\phi_i(\tilde{s}_i,\tilde{p})}\right)d\tau\\&-N_i\pi_i\tilde{y}_i\int_0^{e_i}\Lambda_i(\tau)H\left(\frac{\tilde{p}y_i(t-\tau)}{p\tilde{y}_i}\right)d\tau-M_i\omega_i\tilde{u}_i\int_0^{\vartheta_i}\Delta_i(\tau)H\left(\frac{\tilde{p}u_i(t-\tau)}{p\tilde{u}_i}\right)d\tau\end{aligned}$$

$$-\frac{M_iC_i\omega_i\tilde{u}_i}{F_i}\int_0^{l_i}\Theta_i(\tau)H\left(\frac{\tilde{u}_i\phi_i(s_i(t-\tau),p(t-\tau))}{u_i\phi_i(\tilde{s}_i,\tilde{p})}\right)d\tau\Bigg]+b(\tilde{p}-p)\psi(z). \quad (4.17)$$

Assumptions (A1), (A4), Lemma 5 and the condition $R_1^G \le 1$ imply that $\frac{dK_1}{dt} \le 0$ for all $s_i, y_i, u_i, p, z > 0$ and $\frac{dK_1}{dt} = 0$ at Π_1. By LIP Π_1 is GAS. □

Theorem 4.3. *For system (4.1)-(4.5), if $R_1^G > 1$ and Assumptions (A1)-(A4) are valid, then Π_2 is GAS.*

Proof. Constructing a Lyapunov functional as:

$$K_2=\sum_{i=1}^{2}\gamma_i\Bigg[s_i-\bar{s}_i-\int_{\bar{s}_i}^{s_i}\frac{\phi_i(\bar{s}_i,\bar{p})}{\phi_i(\nu,\bar{p})}d\nu+\frac{N_iG_i}{\gamma_i}\bar{y}_iH(\frac{y_i}{\bar{y}_i})+\frac{M_iC_i}{\gamma_i}\bar{u}_iH(\frac{u_i}{\bar{u}_i})$$
$$+\frac{1}{F_i}\phi_i(\bar{s}_i,\bar{p})\int_0^{l_i}\Theta_i(\tau)\int_0^{\tau}H\left(\frac{\phi_i(s_i(t-\theta),p(t-\theta))}{\phi_i(\bar{s}_i,\bar{p})}\right)d\theta d\tau$$
$$+\frac{N_i\pi_i\bar{y}_i}{\gamma_i}\int_0^{e_i}\Lambda_i(\tau)\int_0^{\tau}H\left(\frac{y_i(t-\theta)}{\bar{y}_i}\right)d\theta d\tau$$
$$+\frac{M_i\omega_i\bar{u}_i}{\gamma_i}\int_0^{\vartheta_i}\Delta_i(\tau)\int_0^{\tau}H\left(\frac{u_i(t-\theta)}{\bar{u}_i}\right)d\theta d\tau\Bigg]+\bar{p}H\left(\frac{p}{\bar{p}}\right)+\frac{b}{\nu}\left(z-\bar{z}-\int_{\bar{z}}^{z}\frac{\psi(\bar{z})}{\psi(\theta)}d\theta\right).$$

Calculating $\frac{dK_2}{dt}$ along the solutions of system (4.1)-(4.5) we obtain:

$$\frac{dK_2}{dt}=\sum_{i=1}^{2}\gamma_i\Bigg[\left(1-\frac{\phi_i(\bar{s}_i,\bar{p})}{\phi_i(s_i,\bar{p})}\right)(\rho_i-\beta_is_i)+\phi_i(s_i,p)\frac{\phi_i(\bar{s}_i,\bar{p})}{\phi_i(s_i,\bar{p})}+\frac{N_iG_i}{\gamma_i}\pi_i\bar{y}_i$$
$$+\frac{M_iC_i}{\gamma_i}\omega_i\bar{u}_i-\frac{(1-q_i)N_iG_i}{\gamma_i}\int_0^{l_i}\Theta_i(\tau)\frac{\bar{y}_i\phi_i(s_i(t-\tau),p(t-\tau))}{y_i}d\tau$$
$$-\frac{q_iM_iC_i}{\gamma_i}\int_0^{l_i}\Theta_i(\tau)\frac{\bar{u}_i\phi_i(s_i(t-\tau),p(t-\tau))}{u_i}d\tau$$
$$+\frac{\phi_i(\bar{s}_i,\bar{p})}{F_i}\int_0^{l_i}\Theta_i(\tau)\ln\left(\frac{\phi_i(s_i(t-\tau),p(t-\tau))}{\phi_i(s_i,p)}\right)d\tau$$
$$+\frac{N_i\pi_i\bar{y}_i}{\gamma_i}\int_0^{e_i}\Lambda_i(\tau)\ln\left(\frac{y_i(t-\tau)}{y_i}\right)d\tau+\frac{M_i\omega_i\bar{u}_i}{\gamma_i}\int_0^{\vartheta_i}\Delta_i(\tau)\ln\left(\frac{u_i(t-\tau)}{u_i}\right)d\tau\Bigg]$$
$$-\sum_{i=1}^{2}N_i\pi_i\int_0^{e_i}\Lambda_i(\tau)\frac{\bar{p}y_i(t-\tau)}{p}d\tau-\sum_{i=1}^{2}M_i\omega_i\int_0^{\vartheta_i}\Delta_i(\tau)\frac{\bar{p}u_i(t-\tau)}{p}d\tau$$
$$-cp+c\bar{p}+b\bar{p}\psi(z)-\frac{b\mu}{\nu}\psi(z)-bp\psi(\bar{z})+\frac{b\mu}{\nu}\psi(\bar{z}). \quad (4.18)$$

By using the steady state conditions of Π_2 :

$$\rho_i=\beta_i\bar{s}_i+\phi_i(\bar{s}_i,\bar{p}), \quad (1-q_i)F_i\phi_i(\bar{s}_i,\bar{p})=\pi_i\bar{y}_i, \quad q_iF_i\phi_i(\bar{s}_i,\bar{p})=\omega_i\bar{u}_i,$$

$$c\bar{p} = \sum_{i=1}^{2} (N_i\pi_i G_i \bar{y}_i + M_i\omega_i C_i \bar{u}_i) - b\bar{p}\psi(\bar{z}), \quad cp = \frac{p}{\bar{p}}\sum_{i=1}^{2}\gamma_i\phi_i(\bar{s}_i,\bar{p}) - bp\psi(\bar{z}),$$

and the inequalities (2.8) with $s_i^* = \bar{s}_i,\ y_i^* = \bar{y}_i,\ u_i^* = \bar{u}_i$ and $p^* = \bar{p}$, we find

$$\begin{aligned}
\frac{dK_2}{dt} = \sum_{i=1}^{2} \Bigg[& \gamma_i\beta_i\bar{s}_i\left(1 - \frac{s_i}{\bar{s}_i}\right)\left(1 - \frac{\phi_i(\bar{s}_i,\bar{p})}{\phi_i(s_i,\bar{p})}\right) \\
& + \gamma_i\phi_i(\bar{s}_i,\bar{p})\left(\frac{\phi_i(s_i,p)}{\phi_i(s_i,\bar{p})} - \frac{p}{\bar{p}}\right)\left(1 - \frac{\phi_i(s_i,\bar{p})}{\phi_i(s_i,p)}\right) \\
& - \gamma_i\phi_i(\bar{s}_i,\bar{p})\left(H\left(\frac{\phi_i(\bar{s}_i,\bar{p})}{\phi_i(s_i,\bar{p})}\right) + H\left(\frac{p\phi_i(s_i,\bar{p})}{\bar{p}\phi_i(s_i,p)}\right)\right) \\
& - \frac{N_i G_i \pi_i \bar{y}_i}{F_i}\int_0^{l_i}\Theta_i(\tau) H\left(\frac{\bar{y}_i\phi_i(s_i(t-\tau),p(t-\tau))}{y_i\phi_i(\bar{s}_i,\bar{p})}\right)d\tau \\
& - N_i\pi_i\bar{y}_i\int_0^{e_i}\Lambda_i(\tau) H\left(\frac{\bar{p}y_i(t-\tau)}{p\bar{y}_i}\right)d\tau \\
& - \frac{M_i C_i \omega_i \bar{u}_i}{F_i}\int_0^{l_i}\Theta_i(\tau) H\left(\frac{\bar{u}_i\phi_i(s_i(t-\tau),p(t-\tau))}{u_i\phi_i(\bar{s}_i,\bar{p})}\right)d\tau \\
& - M_i\omega_i\bar{u}_i\int_0^{\vartheta_i}\Delta_i(\tau) H\left(\frac{\bar{p}u_i(t-\tau)}{p\bar{u}_i}\right)d\tau\Bigg].
\end{aligned}$$

According to Assumptions (A1),(A2) and (A4) we get $\frac{dK_2}{dt} \leq 0$ and $\frac{dK_2}{dt} = 0$ at Π_2. LIP implies that Π_2 is GAS. □

5. NUMERICAL SIMULATIONS

We now perform some computer simulations on the following application. The incidence rate is given by Crowley-Martin (CM) functional response:

$$\phi_i(s_i,p) = \frac{\lambda_i s_i p}{(1+\mu_i s_i)(1+\alpha_i p)}, \qquad i = 1,2, \tag{5.1}$$

where $\mu_i \geq 0,\ i = 1,2$, and $\lambda_1 = (1-\varepsilon)\overline{\lambda}_1$, $\lambda_2 = (1-f\varepsilon)\overline{\lambda}_2$. Then, the general model (4.1)-(4.5) with incidence rate given in (5.1) can be described as:

$$\dot{s}_i(t) = \rho_i - \beta_i s_i(t) - \frac{\lambda_i s_i(t)p(t)}{(1+\mu_i s_i(t))(1+\alpha_i p(t))}, \qquad i = 1,2, \tag{5.2}$$

$$\dot{y}_i(t) = (1-q_i)\lambda_i\int_0^{l_i}\Theta_i(\tau)\frac{s_i(t-\tau)p(t-\tau)}{(1+\mu_i s_i(t-\tau))(1+\alpha_i p(t-\tau))}d\tau - \pi_i y_i(t),\ i = 1,2, \tag{5.3}$$

$$\dot{u}_i(t) = q_i\lambda_i\int_0^{l_i}\Theta_i(\tau)\frac{\lambda_i s_i(t-\tau)p(t-\tau)}{(1+\mu_i s_i(t-\tau))(1+\alpha_i p(t-\tau))}d\tau - \omega_i u_i(t), \quad i = 1,2, \tag{5.4}$$

$$\dot{p}(t) = \sum_{i=1}^{2}\left(N_i\pi_i\int_0^{e_i}\Lambda_i(\tau)y_i(t-\tau_i)d\tau + M_i\omega_i\int_0^{\vartheta_i}\Delta_i(\tau)u_i(t-\tau_i)d\tau\right)$$
$$- cp(t) - bp(t)z(t), \tag{5.5}$$
$$\dot{z}(t) = \nu p(t)z(t) - \mu z(t). \tag{5.6}$$

To verify Assumptions (A1)-(A4), we have:

$$\phi_i(s_i,p) > 0,\ \phi_i(s_i,0) = \phi_i(0,p) = 0,\ \frac{\partial\phi_i(s_i,p)}{\partial s_i} = \frac{\lambda_i p}{(1+\mu_i s_i)^2(1+\alpha_i p)} > 0,$$
$$\frac{\partial\phi_i(s_i,p)}{\partial p} = \frac{\lambda_i s_i}{(1+\mu_i s_i)(1+\alpha_i p)^2} > 0, \frac{\partial\phi_i(s_i,0)}{\partial p} = \frac{\lambda_i s_i}{1+\mu_i s_i} > 0,$$
$$\phi_i(s_i,p) = \frac{\lambda_i s_i p}{(1+\mu_i s_i)(1+\alpha_i p)} \le \frac{\lambda_i s_i p}{1+\mu_i s_i} = p\frac{\partial\phi_i(s_i,0)}{\partial p},$$
$$\left(\frac{\phi_i(s_i,p)}{\phi_i(s_i,p^*)} - \frac{p}{p^*}\right)\left(1 - \frac{\phi_i(s_i,p^*)}{\phi_i(s_i,p)}\right) = \frac{-\alpha_i(p-p^*)^2}{p^*(1+\alpha_i p^*)(1+\alpha_i p)} \le 0,\ \text{for all } s_i,\ p > 0.$$

Then Assumptions (A1)-(A3) are valid. Moreover, Assumption (A4) is also valid where $\psi(z) = z$.

Next, we shall perform simulation studies for model (4.1)-(4.5) with the incidence rate given by Eq. (5.1) and particular form of the probability distributed functions as:

$$f_i(\tau) = \delta(\tau-\tau_i),\quad g_i(\tau) = \delta(\tau-\tau_i),\quad h_i(\tau) = \delta(\tau-\tau_i),\quad i = 1,2, \tag{5.7}$$

where $\delta(.)$ is the Dirac delta function and $\tau_i \in [0,l_i]$, $\varkappa_i \in [0,e_i]$, $\iota_i \in [0,\vartheta_i]$, $i = 1,2$, are constants. When l_i, e_i and $\vartheta_i \to \infty$, we have:

$$\int_0^\infty f_i(\tau)d\tau = \int_0^\infty g_i(\tau)d\tau = \int_0^\infty h_i(\tau)d\tau = 1, \qquad i = 1,2. \tag{5.8}$$

Using the properties of Dirac delta function we get:

$$F_i = \int_0^\infty \delta(\tau-\tau_i)e^{-m_i\tau}d\tau = e^{-m_i\tau_i}, G_i = \int_0^\infty \delta(\tau-\varkappa_i)e^{-n_i\tau}d\tau = e^{-n_i\varkappa_i},$$
$$C_i = \int_0^\infty \delta(\tau-\iota_i)e^{-r_i\tau}d\tau = e^{-r_i\iota_i},\ i = 1,2.$$

Moreover,

$$\int_0^\infty \delta(\tau-\tau_i)e^{-m_i\tau}\frac{\lambda_i s_i(t-\tau)p(t-\tau)}{(1+\mu_i s_i(t-\tau))\,(1+\alpha_i p(t-\tau))}d\tau$$
$$= \frac{e^{-m_i\tau_i}\lambda_i s_i(t-\tau_i)p(t-\tau_i)}{(1+\mu_i s_i(t-\tau_i))\,(1+\alpha_i p(t-\tau_i))},\ i = 1,2,$$
$$\int_0^\infty \delta(\tau-\varkappa_i)e^{-n_i\tau}y_i(t-\tau)d\tau = e^{-n_i\varkappa_i}y_i(t-\varkappa_i),$$

$$\int_0^\infty \delta(\tau-\iota_i)e^{-r_i\tau}u_i(t-\tau)d\tau \;=\; e^{-r_i\varkappa_i}u_i(t-\varkappa_i),\; i=1,2.$$

Hence, model (4.1)-(4.5) with incidence rate given by Eq. (5.1), becomes:

$$\dot{s}_i(t)=\rho_i-\beta_i s_i(t)-\frac{\lambda_i s_i(t)p(t)}{(1+\mu_i s_i(t))(1+\alpha_i p(t))}, \qquad i=1,2, \tag{5.9}$$

$$\dot{y}_i(t)=(1-q_i)e^{-m_i\tau_i}\frac{\lambda_i s_i(t-\tau_i)p(t-\tau_i)}{(1+\mu_i s_i(t-\tau_i))(1+\alpha_i p(t-\tau_i))}-\pi_i y_i(t), \quad i=1,2, \tag{5.10}$$

$$\dot{u}_i(t)=q_i e^{-m_i\tau_i}\frac{\lambda_i s_i(t-\tau_i)p(t-\tau_i)}{(1+\mu_i s_i(t-\tau_i))(1+\alpha_i p(t-\tau_i))}-\omega_i u_i(t), \qquad i=1,2, \tag{5.11}$$

$$\dot{p}(t)==\sum_{i=1}^{2}\left(N_i\pi_i e^{-n_i\varkappa_i}y_i(t-\varkappa_i)+M_i\omega_i e^{-r_i\iota_i}u_i(t-\iota_i)\right)-cp(t)-bp(t)z(t), \tag{5.12}$$

$$\dot{z}(t)=\nu p(t)z(t)-\mu z(t). \tag{5.13}$$

The parameters R_0^{CM} and R_1^{CM} will be:

$$R_0^{CM}=\sum_{i=1}^{2}\frac{((1-q_i)N_i e^{-n_i\varkappa_i}+q_i M_i e^{-r_i\iota_i})e^{-m_i\tau_i}\lambda_i s_i^0}{c(1+\mu_i s_i^0)},$$

$$R_1^{CM}=\sum_{i=1}^{2}\frac{((1-q_i)N_i e^{-n_i\varkappa_i}+q_i M_i e^{-r_i\iota_i})e^{-m_i\tau_i}\lambda_i \bar{s}_i}{c(1+\mu_i \bar{s}_i)(1+\alpha_i\bar{p})},$$

where

$$\bar{s}_i=\frac{1}{2\mu_i(1+\alpha_i\bar{p})}\left[-B+\sqrt{B^2+4\mu_i s_i^0\,(1+\alpha_i\bar{p})^2}\right],$$

$$\bar{p}=\frac{\mu}{\nu},\; \zeta_i=\alpha_i+\frac{\lambda_i}{\beta_i},\; i=1,2,$$

$$B=(1+\zeta_i\bar{p})-\mu_i s_i^0(1+\alpha_i\bar{p}).$$

Now we are ready to perform some numerical simulations for system (5.9)-(5.13). The data of system (5.9)-(5.13) are provided in Table 1. We let $\tau_e=\tau_i=\varkappa_i=\iota_i,\; i=1,2$.

TABLE 1. Values of some parameters of system (5.9)-(5.13).

Parameter	ρ_1	ρ_2	m_1	m_2	μ_1	μ_2	α_1	α_2	N_1	N_2
Value	10	0.03198	1	1	0.03	0.01	0.03	0.01	100	30
Parameter	β_1	β_2	n_1	n_2	ω_1	ω_2	r_1	r_2	π_1	π_2
Value	0.01	0.005	1	1	0.25	0.05	1	1	0.3	0.03
Parameter	M_1	M_2	q_1	q_2	b	f	μ	c		
Value	50	10	0.5	0.5	0.01	0.3	0.05	3		

• **Effect of the parameters λ_1, λ_2 and ν on the stability of the steady states:** The initial conditions have been considered as: $\varphi_1(\theta) = 600$, $\varphi_2(\theta) = 0.1$, $\varphi_3(\theta) = 10$, $\varphi_4(\theta) = 0.1$, $\varphi_5(\theta) = 5$, $\varphi_6(\theta) = 0.1$, $\varphi_7(\theta) = 50$, $\varphi_8(\theta) = 60$, $\theta \in [-\tau_e, 0]$. Let us address three cases for the parameters λ_1, λ_2 and ν. We assume that $\varepsilon = 0$ (there is no treatment) and $\tau_e = 0.5$.

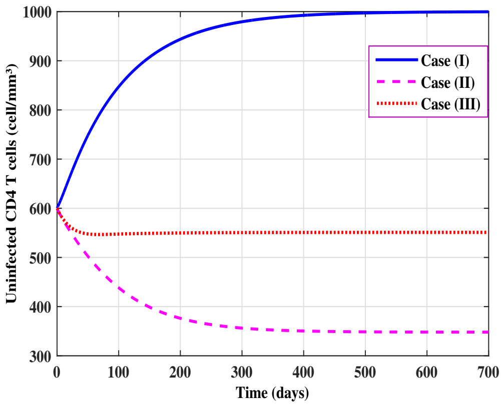

FIGURE 1. The concentration of uninfected CD4$^+$T cells.

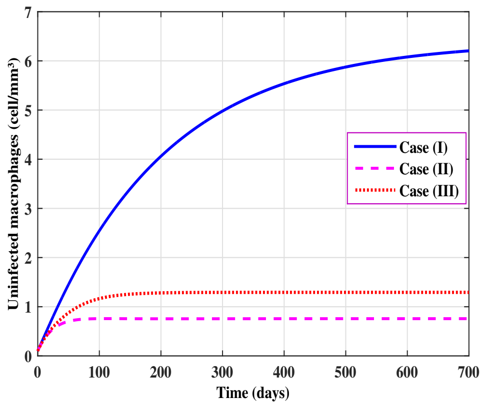

FIGURE 2. The concentration of uninfected macrophages.

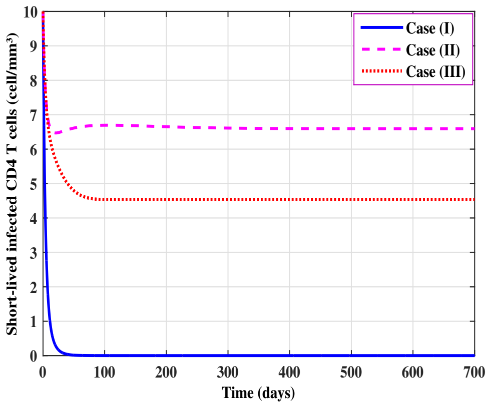

FIGURE 3. The concentration of short-lived infected CD4$^+$T cells.

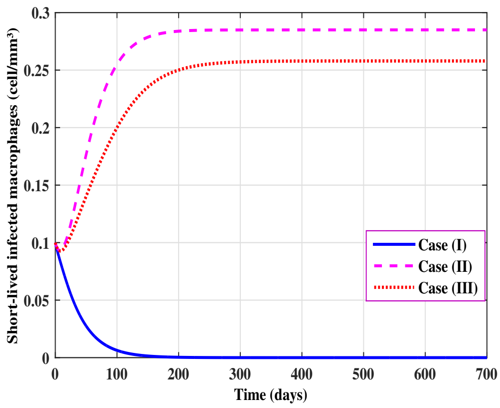

FIGURE 4. The concentration of short-lived infected macrophages.

Case (I): Choose $\lambda_1 = 0.002$, $\lambda_2 = 0.0005$ and $\nu = 0.0005$ which give $R_0^{CM} = 0.6007 < 1$ and $R_1^{CM} = 0.1481 < 1$. Therefore, based on Lemma 4 and Theorems 4.1 the system has unique steady state, that is Π_0 and it is GAS. As we can see from Figures 1-8 that the concentration of the uninfected cells is increased and approached its normal value before infection that is $s_1^0 = 1000$ and $s_2^0 = 6.396$ while concentrations of the other compartments converge to zero for the initial condition. As a result, the HIV1 is removed from the plasma.

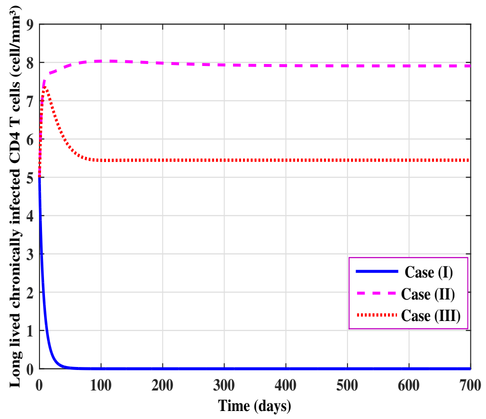

FIGURE 5. The concentration of long-lived infected CD4$^+$T cells.

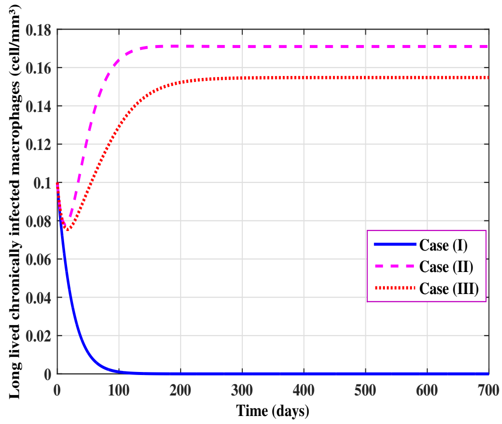

FIGURE 6. The concentration of long-lived infected macrophages.

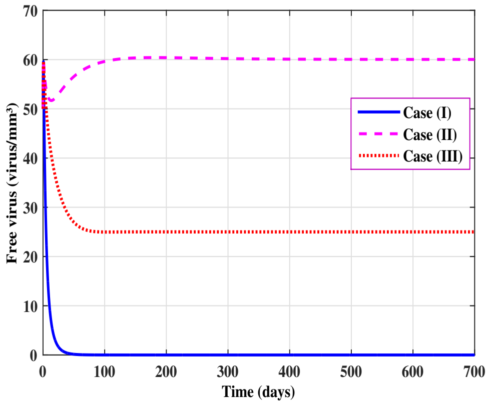

FIGURE 7. The concentration of free virus particles.

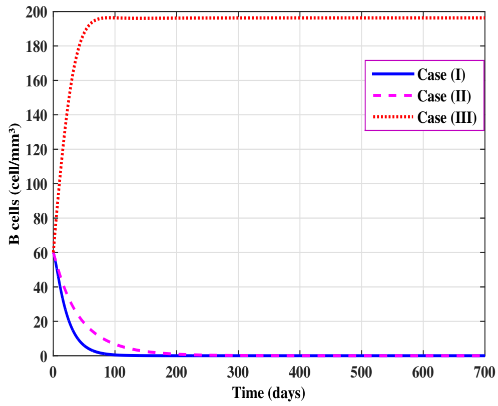

FIGURE 8. The concentration of B cells.

Case (II): We take the following values: $\lambda_1 = 0.01$, $\lambda_2 = 0.001$ and $\nu = 0.0005$. For these values $R_1^{CM} = 0.6803 < 1 < R_0^{CM} = 2.9815$. Consequently, based on Lemma 4 and Theorems 4.2, the humoral-inactivated infection steady state Π_1 is positive and is GAS. Figures 1-8 confirm that the numerical results support the theoretical results presented in Theorem 4.2. It can be observed that, the variables of the model eventually converge to Π_1 $(348.03, 0.76, 6.59, 0.29, 7.91, 0.17, 60.03, 0)$ for the initial conditions. This case corresponds to a chronic HIV-1 infection in the absence of immune response.

Case (III): $\lambda_1 = 0.01,\ \lambda_2 = 0.001$ and $\nu = 0.002$. Then, we calculate $R_0^{CM} = 2.9815 > 1$ and $R_1^{CM} = 1.6544 > 1$. We can see from Figure 1-8 that, there is a consistency between the numerical results and theoretical results of Theorem 4.3.

The states of the system converge to $\Pi_2(550.98, 1.29, 4.54, 0.26, 5.45, 0.15, 25, 196.31)$ for the initial conditions. In this case the humoral immune response is activated and can control the disease.

• **Effect of the drug efficacy ε on the stability of the steady states:** We take $\tau_e = 0.5$, $\lambda_1 = 0.01,\ \lambda_2 = 0.001$ and $\nu = 0.001$. In Figures 9-16 we show the effect of the drug efficacy ε on the HIV dynamics. Also, we can observe that, as the drug efficacy ε is increased, the concentration of uninfected cells is increased, while the concentrations of free virus particles and the three types of infected cells are decreased. Table 2 shows that, the values of R_0^{CM} and R_1^{CM} are decreased as ε is increased. Therefore, the results of Theorems 4.1-4.3 and the results of numerical simulation are compatible. Thus, we can say that treatment with sufficient drug efficacy can success to clear the HIV from the plasma.

TABLE 2. Values of steady states, R_0^{CM} and R_1^{CM} for system (5.9)-(5.13)with different values of ε.

drug	steady states	R_0^{CM}	R_1^{CM}
$\varepsilon = 0.0$	$\Pi_2(386.29, 0.84, 6.20, 0.28, 7.44, 0.17, 50, 39.07)$	2.9815	1.1302
$\varepsilon = 0.12623$	$\Pi_1(457.08, 0.87, 5.49, 0.28, 6.59, 0.17, 50, 0)$	2.6064	1.0000
$\varepsilon = 0.2$	$\Pi_1(525.97, 0.96, 4.79, 0.27, 5.75, 0.16, 43.66, 0)$	2.3873	0.9211
$\varepsilon = 0.4$	$\Pi_1(724.23, 1.42, 2.79, 0.25, 3.35, 0.15, 25.42, 0)$	1.7930	0.6996
$\varepsilon = 0.666908$	$\Pi_0(1000, 6.396, 0, 0, 0, 0, 0, 0)$	1.0000	0.3932
$\varepsilon = 0.8$	$\Pi_0(1000, 6.396, 0, 0, 0, 0, 0, 0)$	0.6046	0.2375

TABLE 3. Values of steady states, R_0^{CM} and R_1^{CM} for system (5.9)-(5.13) with different values of τ_e.

drug	steady states	R_0^{CM}	R_1^{CM}
$\tau_e = 0.001$	$\Pi_2(620.40, 0.94, 6.32, 0.45, 7.58, 0.27, 50, 269.36)$	4.8642	1.8978
$\tau_e = 0.1$	$\Pi_2(620.40, 0.94, 5.72, 0.41, 6.87, 0.25, 50, 167.08)$	3.9905	1.5570
$\tau_e = 0.3$	$\Pi_2(620.40, 0.94, 4.69, 0.34, 5.62, 0.20, 50, 13.10)$	2.6749	1.0437
$\tau_e = 0.321363$	$\Pi_1(620.40, 0.94, 4.59, 0.33, 5.51, 0.20, 50, 0)$	2.5630	1.0000
$\tau_e = 0.5$	$\Pi_1(724.23, 1.42, 2.79, 0.25, 3.35, 0.15, 25.42, 0)$	1.7930	0.6996
$\tau_e = 0.791955$	$\Pi_0(1000, 6.396, 0, 0, 0, 0, 0, 0)$	1.0000	0.3902
$\tau_e = 0.9$	$\Pi_0(1000, 6.396, 0, 0, 0, 0, 0, 0)$	0.8057	0.3143
$\tau_e = 1.0$	$\Pi_0(1000, 6.396, 0, 0, 0, 0, 0, 0)$	0.6596	0.2574
$\tau_e = 2.0$	$\Pi_0(1000, 6.396, 0, 0, 0, 0, 0, 0)$	0.0892	0.0348

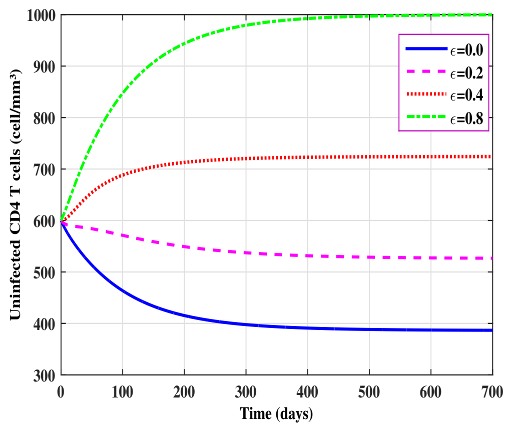

FIGURE 9. The concentration of uninfected CD4$^+$T cells.

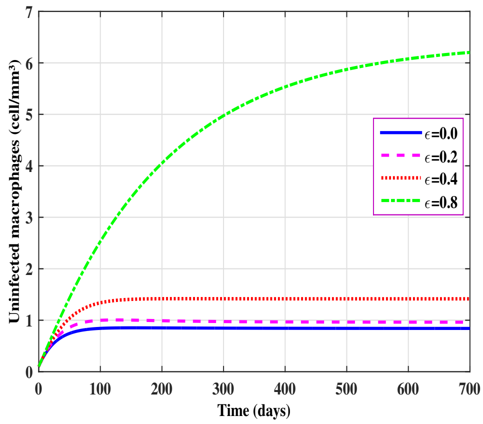

FIGURE 10. The concentration of uninfected macrophages.

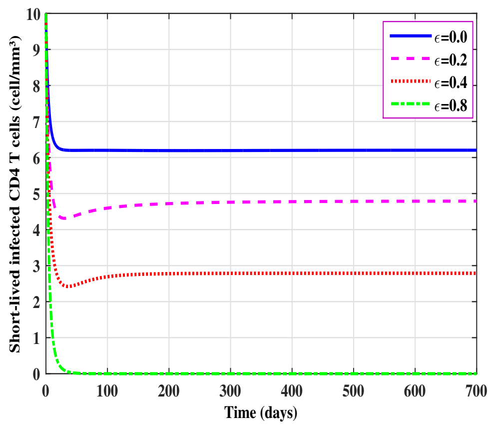

FIGURE 11. The concentration of short-lived infected CD4$^+$T cells.

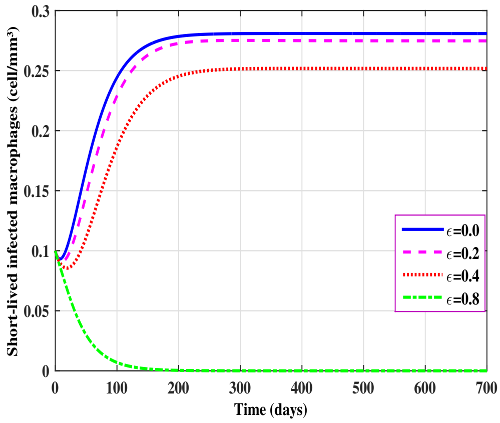

FIGURE 12. The concentration of short-lived infected macrophages.

- **Effect of the time delay on the stability of the system:** Choosing $\varepsilon = 0.4$, $\lambda_1 = 0.01, \lambda_2 = 0.001$ and $\nu = 0.001$. Figures 17-24 and Table 3 show the effect of the time delay parameter τ_e on the stability of Π_0, Π_1 and Π_2. Clearly, the parameter τ_e has similar effect as the drug efficacy parameters ε.

5.1. **Conclusion.** In this paper, we have proposed and analyzed three HIV infection models. We have considered four types of infected cells: short-lived infected CD4$^+$T cells, long-lived chronically infected CD4$^+$T cells, short-lived infected macrophages and long-lived chronically

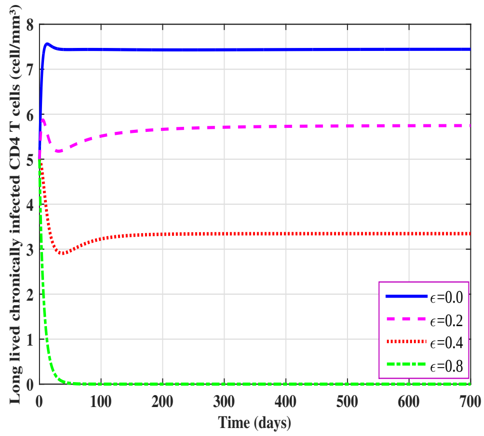

FIGURE 13. The concentration of long-lived infected CD4$^+$T cells.

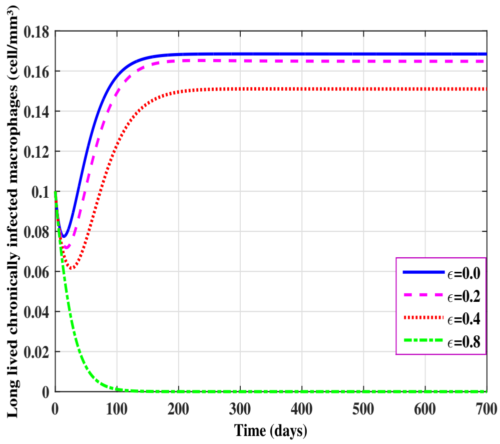

FIGURE 14. The concentration of long-lived infected macrophages.

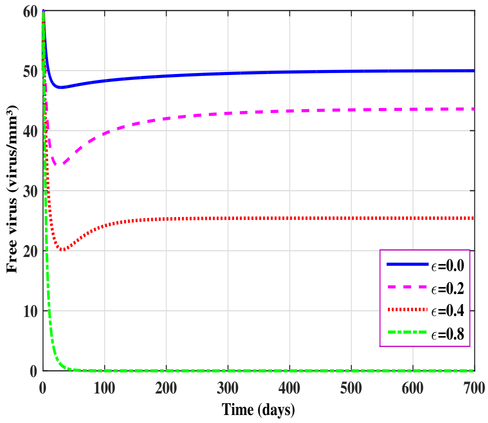

FIGURE 15. The concentration of free virus particles.

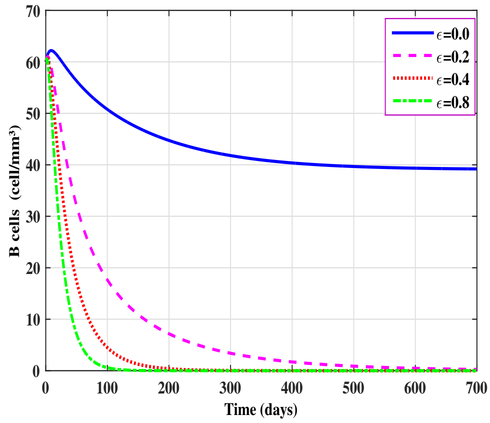

FIGURE 16. The concentration of B cells.

infected macrophages. We have incorporated three distributed time delays into the models. We have represented the HIV-target incidence rate by bilinear and saturation functional response for the first two models while, for the third model, we have considered more general nonlinear functions for both the HIV-target incidence rate and neutralization rate of viruses and we have derived a set of conditions on these general functions. We have proved the nonnegativity and ultimate boundedness of the model's solutions and the existence and stability of the model's steady states. We have determined two threshold parameters: the basic reproduction number and the humoral immune response activation number. Using Lyapunov functionals, we have

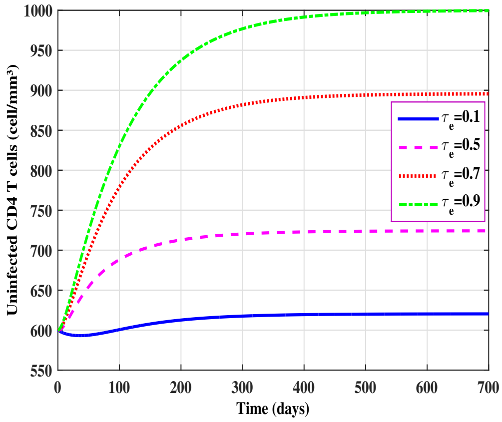

FIGURE 17. The concentration of uninfected CD4$^+$T cells.

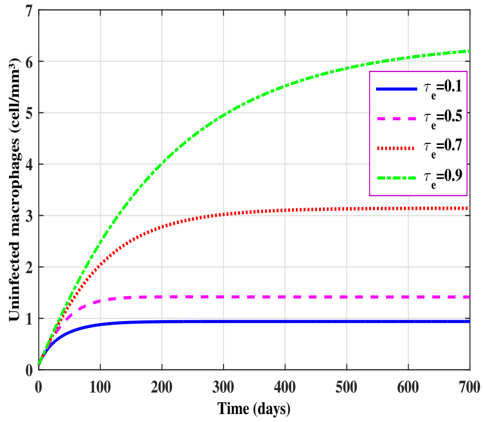

FIGURE 18. The concentration of uninfected macrophages.

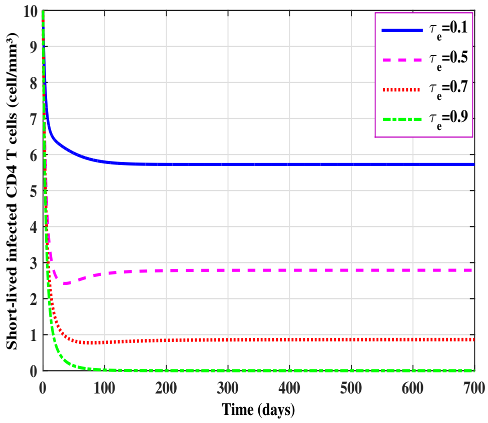

FIGURE 19. The concentration of short-lived infected CD4$^+$T cells.

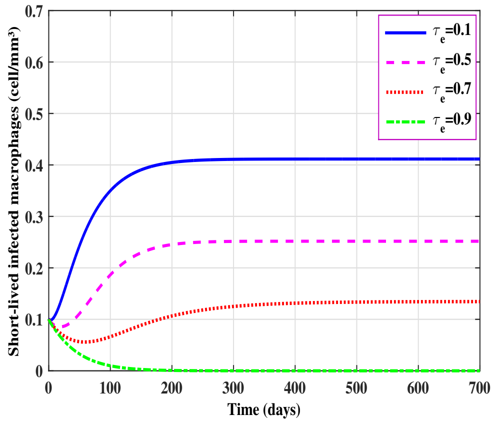

FIGURE 20. The concentration of short-lived infected macrophages.

established the global stability of the three steady states of the models. We have presented an example and performed some numerical simulations to support our theoretical results.

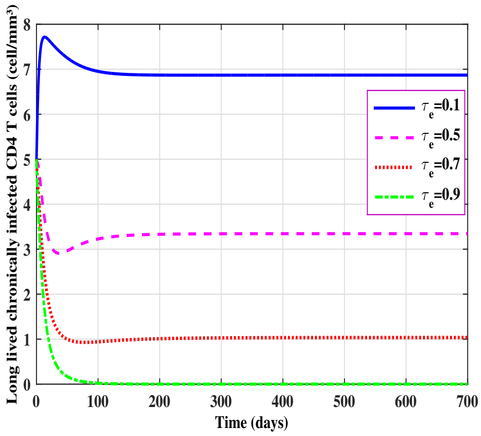

FIGURE 21. The concentration of long-lived infected CD4$^+$T cells.

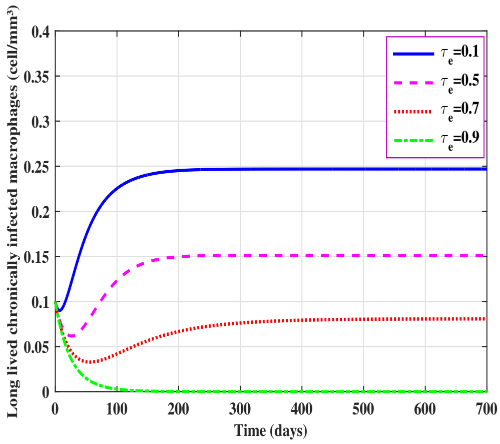

FIGURE 22. The concentration of long-lived infected macrophages.

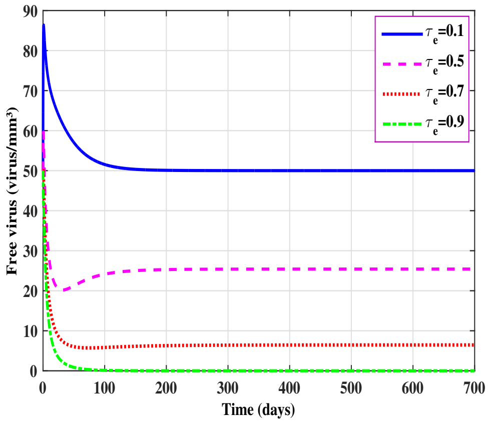

FIGURE 23. The concentration of free virus particles.

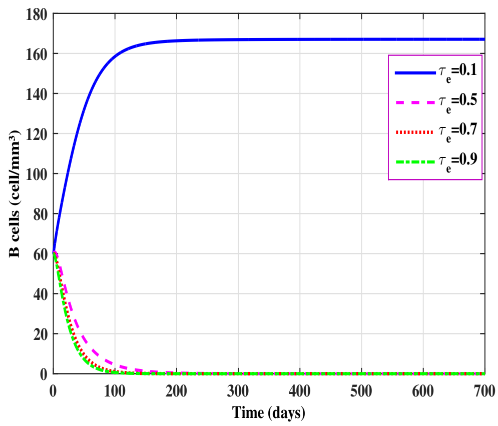

FIGURE 24. The concentration of B cells.

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