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# Global Stability of a Delayed Model for the Interaction of SARS-CoV-2/ACE2 and Adaptive Immunity

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**Abstract.** The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the culprit behind the coronavirus disease 2019 (COVID-19), which has killed millions of people. SARS-CoV-2 binds its spike (S) protein to the angiotensin-converting enzyme 2 (ACE2) receptor to inter the epithelial cells in the respiratory tracts. ACE2 is a crucial mediator in the SARS-CoV-2 infection pathway. In this paper, we construct a mathematical model to describe the SARS-CoV-2/ACE2 interaction and the adaptive immunological response. The model predicts the effects of latently infected cells as well as immunological responses from cytotoxic T lymphocytes (CTLs) and antibodies. The model is incorporated with three distributed time delays: (i) delay in the formation of latently infected epithelial cells, (ii) delay in the activation of latently infected epithelial cells, (iii) delay in the maturation of new released SARS-CoV-2 virions. We show that the model is well-posed and it admits five equilibria. The stability and existence of the equilibria are precisely controlled by four threshold parameters $\Re_i$, $i = 0, 1, 2, 3$. By formulating suitable Lyapunov functions and applying LaSalle's invariance principle, we show the global asymptotic stability for all equilibria. To demonstrate the theoretical results, we conduct numerical simulations. We do sensitivity analysis and identify the most sensitive parameters. We look at how the latent phase, ACE2 receptors, antibody and CTL responses, time delays affect the dynamical behavior of SARS-CoV-2. Although the basic reproduction number $\Re_0$ is unaffected by the parameters of antibody and CTL responses, it is shown that viral replication can be hampered by immunological activation of antibody and CTL responses. Further, our findings indicate that $\Re_0$ is affected by the rates at which the ACE2 receptor grows and degrades. This could provide valuable guidance for the development of receptor-targeted vaccines and medications. Furthermore, it is shown that, increasing time delays can effectively decrease $\Re_0$ and then inhibit the SARS-CoV-2 replication. Finally, we show that, excluding the latently infected cells in the model would result in an overestimation of $\Re_0$.

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# 1. Introduction

A new virus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first appeared in Wuhan, China, near the end of 2019. SARS-CoV-2 is the causative agent of coronavirus disease 2019 (COVID-19) that has killed millions of people worldwide. A multitude of symptoms may be exhibited by the majority of individuals who are symptomatic following infection, encompassing fever, a dry cough, diarrhea, muscular discomfort, fatigue, dysphagia, cephalalgia, and emesis [1]. Individuals with severe infections may develop acute respiratory distress syndrome (ARDS), which is characterized by respiratory difficulties and hypoxemia [2]. Consequently, the severity of the illness and the mortality of the patients are dependent upon both the viral infection and the host's reactions [2]. In addition to the vaccination efforts, dedicated scientists and researchers are diligently engaged in the development of novel and efficacious drugs interventions for patients suffering from COVID-19.

SARS-CoV-2 is a single-stranded RNA virus. It is classified as a member of the Coronaviridae family. SARS-CoV-2 virus infect the epithelial cells by binding its spike (S) protein to the angiotensin-converting enzyme 2 (ACE2) receptor [3], [4]. Epithelial cells are located in the respiratory tract, including the lungs, nasal passages, and trachea/bronchial tissues [5]. An effective immune response is crucial for controlling disease progression and eliminating the SARS-CoV-2 infection. The adaptive immune response relies on cytotoxic T lymphocytes (CTLs) to eliminate virus-infected cells, as well as on antibodies that neutralize the viruses.

Researchers can better understanding the SARS-CoV-2 replication cycle and the immune system's reaction to the viral infection by using mathematical models. Additionally, these models make it possible to evaluate the benefits of various antiviral medication regimens in relation to specific COVID-19 patients [7]. The dynamics of SARS-CoV-2 within the host have attracted the interest of many scientists (see the review paper [6]). The target cell-limited model for SARS-CoV-2 infection was published in [8] and [9], and is as follows:

$$\begin{cases} \dot{E} = -\eta ES, \\ \dot{I} = \eta ES - \delta_I I, \\ \dot{S} = \delta_I \nu I - \delta_S S, \end{cases} \tag{1.1}$$

where $E = E(t)$, $I = I(t)$ and $S = S(t)$ are the concentrations of uninfected epithelial cells, infected cells, and free SARS-CoV-2 particles at a given time $t$, respectively. The infection rate constant is denoted by $\eta$, while $\nu$ represents the number of free SARS-CoV-2 particles generated during the average of lifespan of infected cell. $\delta_I$ denotes the average lifetime of $I$. Parameter $\delta_S$ signifies the rate at which viruses are eliminated. Numerous investigations were dedicated to expand the model by distinguishing between two populations of infected cells: latently infected cells and actively (productively) infected cells (we refer to, for instance, [7], [8], [9], [10], [12], [13], [14] and [15]). Li et al. [16] proposed a SARS-CoV-2 infection model by incorporating the growth and decay of epithelial cells as:

$$\begin{cases} \dot{E} = \delta_E(E_0 - E) - \eta ES, \\ \dot{I} = \eta ES - \delta_I I, \\ \dot{S} = \delta_I \nu I - \delta_S S, \end{cases} \tag{1.2}$$

where $E_0 = E(0)$ is the concentration of epithelial cells that are virus-free. $\delta_E$ denotes the average lifetime of $E$. Many works have considered and/or expanded this model (see e.g., [5], [11], [17], [18], [19], [20], [23], [26] and [27]).

The kinetics of the ACE2 receptor on epithelial cells were not taken into account by the works mentioned above. The authors of papers [29]- [32] simulated the Middle East respiratory syndrome coronavirus (MERS-CoV) infection to observe how the dipeptidyl peptidase 4 (DPP4) receptor affects it. The local stability of an ODE system for SARS-CoV-2 infection in the ACE2 receptor was studied by Chatterjee and Al Basir [33]. Lv and Ma [34] proposed a system of delay differential equations (DDEs) for SARS-CoV-2 infection mediated by ACE2 receptor as:

$$\begin{cases} \dot{E} = \lambda_E - \eta \Psi(A) ES - \delta_E E, \\ \dot{I} = e^{-\alpha_1 \tau_1} \eta \Psi(A_{\tau_1}) E_{\tau_1} S_{\tau_1} - \delta_I I, \\ \dot{S} = \delta_I \nu I - \delta_S S, \\ \dot{A} = \lambda_A - \kappa \eta \Psi(A) AS - \delta_A A, \end{cases} \tag{1.3}$$

where $(E_{\tau_1}, S_{\tau_1}, A_{\tau_1}) = (E(t-\tau_1), S(t-\tau_1), A(t-\tau_1))$. The variable $A = A(t)$ represents the concentration of per unit volume of ACE2 receptors at time $t$. $\Psi(A)$ represents the probability of successful entry of the virion into the epithelial cell mediated by the receptor ACE2. When the concentration of the epithelial cell receptor ACE2 is lower (higher), there are $\Psi(A) \sim 0 (\sim 1)$ [34]. The term $\eta \Psi(A) ES$ represents the reduction rate of epithelial cells by SARS-CoV-2 and ACE2. The term $\kappa \eta \Psi(A) AS$, where $\kappa$ is a constant, shows the rate of decrease in ACE2 receptors as a result of the reduction in uninfected epithelial cells (induced by free SARS-CoV-2). Here, $\tau_1$ represents the amount of time that has passed since SARS-CoV-2 particles had made contact with uninfected epithelial cells before those cells become actively infected. The likelihood that infected cells will survive throughout the delay period is $e^{-\alpha_1 \tau_1}$. In [33], the reduction rates of epithelial cells and ACE2 receptors were given by $\eta AES$ and $\kappa \eta AES$, respectively.

One of the most powerful tools for researchers is stability analysis of within-host SARS-CoV-2 dynamics models. This can provide us with a better understanding of the virus's dynamics and how the immune system controls and clears it. Local and/or global stability of different within-host SARS-CoV-2 infection models were investigated in several works (see [11], [18], [19], [21], [27], [33], [34], [35] and [36]).

We noted that, model (1.3) neglect the adaptive immune response, latent phase, and the delayed maturity of recently released virions. Moreover, the model only considers one type of discrete-time delay. Therefore, our aim in this article is to propose and analyze a model for SARS-CoV-2 infection mediated by ACE2 receptor while taking into consideration the following factors:

F1. CTL response, which act for killing the actively infected cells.

F2. Antibody response, which act for neutralizing the SARS-CoV-2 particles.

F3. Latently infected cells, which contain virions, but they are not released until the cells are activated.

F4. Three distributed-time delays, (i) delay in formation of latently infected epithelial cells, (ii) delay in the latently infected epithelium cells' activation, and (iii) delay in the maturation of recently released SARS-CoV-2 virions.

We first examine the essential properties of the DDEs, find the model's equilibria and investigating their existence and global stability. We formulate suitable Lyapunov functions and employ LaSalle's invariance principle (LIP) to prove the global asymptotic stability of all equilibria. We show the theoretical conclusions using numerical simulations. We wrap up by discussing the outcomes.

## 2. Model formulation

We formulate a DDEs model for SARS-CoV-2 infection mediated by ACE2 receptor taking into account factors F1-F4. Let $L = L(t)$, $B = B(t)$ and $U = U(t)$ be the concentrations of per unit volume of latently infected cells, antibodies and CTLs, respectively at time $t$. We denote $(E_\tau, L_\tau, I_\tau, S_\tau, A_\tau) = (E(t-\tau), L(t-\tau), I(t-\tau), S(t-\tau), A(t-\tau))$, where $\tau$ as a random variable from probability distributed function $f_i(\tau)$, $i = 1, 2, 3$ over the interval $[0, h_i]$, where $h_i$ is the limit superior of the delay period. Our proposed model is given by:

$$\dot{E} = \lambda_E - \eta\Psi(A)ES - \delta_E E, \tag{2.1}$$

$$\dot{L} = \eta \int_0^{h_1} f_1(\tau)e^{-\alpha_1\tau}\Psi(A_\tau)E_\tau S_\tau d\tau - (a + \delta_L)L, \tag{2.2}$$

$$\dot{I} = a \int_0^{h_2} f_2(\tau)e^{-\alpha_2\tau}L_\tau d\tau - \delta_I I - \gamma_U IU, \tag{2.3}$$

$$\dot{S} = \delta_I \nu \int_0^{h_3} f_3(\tau)e^{-\alpha_3\tau}I_\tau d\tau - \delta_S S - \gamma_B SB, \tag{2.4}$$

$$\dot{A} = \lambda_A - \kappa\eta\Psi(A)AS - \delta_A A, \tag{2.5}$$

$$\dot{B} = \varrho_B SB - \delta_B B, \tag{2.6}$$

$$\dot{U} = \varrho_U IU - \delta_U U. \tag{2.7}$$

The latently infected cells die at rate $\delta_L L$ and are activated at rate $aL$. The responsiveness and death rates of the CTLs are denoted by $\varrho_U IU$ and $\delta_U U$, respectively. The killing rate of infected cells by CTLs is represented by $\gamma_U IU$. The antibodies are stimulated at rate $\varrho_B SB$, die at rate $\delta_B B$ and neutralize the SARS-CoV-2 particles at rate $\gamma_B SB$. The factor $f_1(\tau)e^{-\alpha_1\tau}$ represents the probability that uninfected epithelial cells contacted by the SARS-CoV-2 at time $t-\tau$ survived $\tau$ time units and become latently infected at time $t$. The factor $f_2(\tau)e^{-\alpha_2\tau}$ denotes the probability of latently infected cells at time $t-\tau$ survived $\tau$ time units and become actively infected cells. The factor $f_3(\tau)e^{-\alpha_3\tau}$

is the probability that an immature SARS-CoV-2 particle at time $t-\tau$ survives $\tau$ time units to be mature at time $t$. A schematic representation of the model in (2.1)-(2.7) is illustrated in Figure 1.

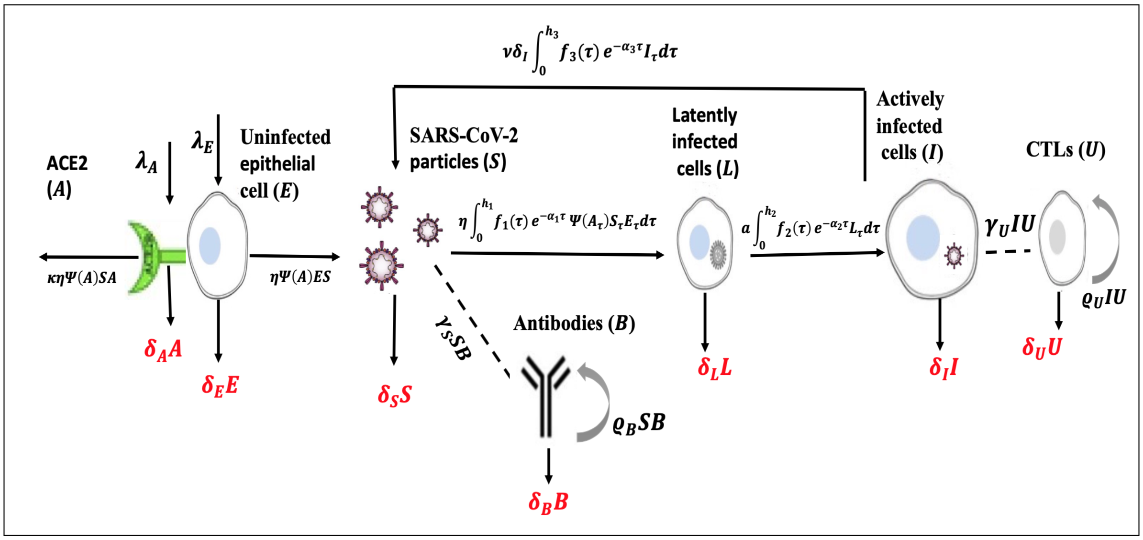



Figure 1. The schematic diagram of the SARS-CoV-2 infection.

Functions $f_i(\tau)$, $i = 1,2,3$, satisfy the following conditions:

$$f_i(\tau) > 0, \quad \int_0^{h_i} f_i(\tau)d\tau = 1, \quad \int_0^{h_i} f_i(\tau)e^{\ell\tau}d\tau < \infty, \quad \text{where} \quad \ell > 0.$$

Let $\chi_i(\tau) = f_i(\tau)e^{-\alpha_i\tau}$ and $\zeta_i = \int_0^{h_i} \chi_i(\tau)d\tau$, $i = 1,2,3$, thus $0 < \zeta_i \le 1$. Usually function $\Psi(A)$ is chosen as the classic Hill function: $\Psi(A) = \frac{A^n}{\mathcal{A}_s^n + A^n}$, where $\mathcal{A}_s$ is the half-saturation constant and $n$ is the Hill coefficient [34], [37]. The function $\Psi(A)$ is continuously differentiable on $[0,+\infty)$ and strictly monotonically increasing.

The initial conditions for model (2.1)-(2.7) are given by:

$$E(\theta) = \phi_1(\theta), \; L(\theta) = \phi_2(\theta), \; I(\theta) = \phi_3(\theta), \; S(\theta) = \phi_4(\theta), \; A(\theta) = \phi_5(\theta),$$
$$B(\theta) = \phi_6(\theta), \; U(\theta) = \phi_7(\theta), \quad \phi_i(\theta) \ge 0, \; i = 1,2,...,7, \; \theta \in [-\tau^*, 0], \tag{2.8}$$

where, $\tau^* = \max\{h_1,h_2,h_3\}$, $\phi_i \in C([-\tau^*,0],\mathbb{R}_{\ge 0})$ and $C$ is the Banach space of continuous functions mapping from $[-\tau^*,0]$ to $\mathbb{R}_{\ge 0}$ with the norm $\|\phi_i\| = \sup_{-\tau^* \le \theta \le 0} |\phi_i(\theta)|$ for $\phi_i \in C$, $i = 1,2,...,7$. We note that system (2.1)-(2.7) with initial conditions (2.8) has a unique solution [38]. All parameters of model (2.1)-(2.7) are positive.

## 3. Basic qualitative properties

This section proves the non-negativity and boundedness of the solutions of system (2.1)-(2.7).

**Lemma 1.** The solutions of model (2.1)-(2.7) with the initial states (2.8) are non-negative and ultimately bounded.

**Proof**. We have $\dot{E}\mid_{E=0}=\lambda_E>0$, $\dot{A}\mid_{A=0}=\lambda_A>0$, $\dot{B}\mid_{B=0}=0$ and $\dot{U}\mid_{U=0}=0$. Hence, $E(t)>0$, $A(t)>0$, $B(t)\geq 0$ and $U(t)\geq 0$, for all $t\geq 0$. From Eqs, (2.2)-(2.4) we have

$$L(t)=e^{-(a+\delta_L)t}\phi_2(0)+\eta\int_0^t\int_0^{h_1}\chi_1(\tau)\Psi(A(\theta-\tau))E(\theta-\tau)S(\theta-\tau)e^{-(a+\delta_L)(t-\theta)}d\tau d\theta\geq 0,$$

$$I(t)=e^{-\int_0^t(\delta_I+\gamma_U U(r))dr}\phi_3(0)+a\int_0^t\int_0^{h_2}\chi_2(\tau)L(\theta-\tau)e^{-\int_\theta^t(\delta_I+\gamma_U U(r))dr}d\tau d\theta\geq 0,$$

$$S(t)=e^{-\int_0^t(\delta_S+\gamma_B B(r))dr}\phi_4(0)+\delta_I\nu\int_0^t\int_0^{h_3}\chi_3(\tau)I(\theta-\tau)e^{-\int_\theta^t(\delta_S+\gamma_B B(r))dr}d\tau d\theta\geq 0,$$

for all $t\in[0,\tau^*]$. Hence, by recursive argumentation, we obtain that $L(t),I(t),S(t)\geq 0$ for all $t\geq 0$. Hence, $E,L,I,S,A,B$ and $U$ are non-negative.

Now, we prove the ultimately boundedness $E$, $L$, $I$, $S$, $A$, $B$ and $U$. From Eq. (2.1) we have, $\lim\limits_{t\to\infty}\sup E(t)\leq\frac{\lambda_E}{\delta_E}=\omega_1$. To prove the ultimate boundedness of $L(t)$, we define

$$\Pi_1=\int_0^{h_1}\chi_1(\tau)E_\tau d\tau+L.$$

Then, we obtain

$$\begin{aligned}\dot{\Pi}_1=\int_0^{h_1}\chi_1(\tau)\dot{E}_\tau d\tau+\dot{L}&=\int_0^{h_1}\chi_1(\tau)\{\lambda_E-\eta\Psi(A_\tau)E_\tau S_\tau\\&-\delta_E E_\tau\}d\tau+\eta\int_0^{h_1}\chi_1(\tau)\Psi(A_\tau)E_\tau S_\tau d\tau-(a+\delta_L)L\\&=\lambda_E\int_0^{h_1}\chi_1(\tau)d\tau-\delta_E\int_0^{h_1}\chi_1(\tau)E_\tau d\tau-(a+\delta_L)L\\&\leq\lambda_E\zeta_1-p_1\left[\int_0^{h_1}\chi_1(\tau)E_\tau d\tau+L\right]\\&\leq\lambda_E-p_1\left[\int_0^{h_1}\chi_1(\tau)E_\tau d\tau+L\right]\\&=\lambda_E-p_1\Pi_1,\end{aligned}$$

where, $p_1=\min\{\delta_E,(a+\delta_L)\}$. It follows that, $\lim\limits_{t\to\infty}\sup\Pi_1(t)\leq\frac{\lambda_E}{p_1}=\omega_2$ and then $\lim\limits_{t\to\infty}\sup L(t)\leq\omega_2$. Define

$$\Pi_2=I+\frac{\gamma_U}{\varrho_U}U.$$

Then, we obtain

$$\begin{aligned}\dot{\Pi}_2 &= \dot{I} + \frac{\gamma_U}{\varrho_U}\dot{U} = a\int_0^{h_2} \chi_2(\tau)L_\tau d\tau - \delta_I I - \gamma_U IU + \frac{\gamma_U}{\varrho_U}(\varrho_U IU - \delta_U U)\\
&= a\int_0^{h_2} \chi_2(\tau)L_\tau d\tau - \delta_I I - \frac{\gamma_U\delta_U}{\varrho_U}U\\
&\le a\omega_2\zeta_2 - p_2\left[I + \frac{\gamma_U}{\varrho_U}U\right]\\
&\le a\omega_2 - p_2\left[I + \frac{\gamma_U}{\varrho_U}U\right]\\
&= a\omega_2 - p_2\Pi_2,\end{aligned}$$

where, $p_2 = \min\{\delta_I, \delta_U\}$. Hence, $\limsup_{t\to\infty} \Pi_2(t) \le \frac{a\omega_2}{p_2} = \omega_3$ and this gives $\limsup_{t\to\infty} I(t) \le \omega_3$ and $\limsup_{t\to\infty} U(t) \le \frac{\varrho_U}{\gamma_U}\omega_3 = \omega_7$. We define

$$\Pi_3 = S + \frac{\gamma_B}{\varrho_B}B.$$

Then, we obtain

$$\begin{aligned}\dot{\Pi}_3 &= \dot{S} + \frac{\gamma_B}{\varrho_B}\dot{B} = \delta_I\nu\int_0^{h_3} \chi_3(\tau)I_\tau d\tau - \delta_S S - \gamma_B SB + \frac{\gamma_B}{\varrho_B}(\varrho_B SB - \delta_B B)\\
&= \delta_I\nu\int_0^{h_3} \chi_3(\tau)I_\tau d\tau - \delta_S S - \frac{\gamma_B\delta_B}{\varrho_B}B\\
&\le \delta_I\nu\omega_3\zeta_3 - p_3\left[S + \frac{\gamma_B}{\varrho_B}B\right]\\
&\le \delta_I\nu\omega_3 - p_3\left[S + \frac{\gamma_B}{\varrho_B}B\right],\\
&= \delta_I\nu\omega_3 - p_3\Pi_3,\end{aligned}$$

where, $p_3 = \min\{\delta_S, \delta_B\}$. Hence, $\limsup_{t\to\infty} \Pi_3(t) \le \frac{\delta_I\nu\omega_3}{p_3} = \omega_4$ and then $\limsup_{t\to\infty} S(t) \le \omega_4$ and $\limsup_{t\to\infty} B(t) \le \frac{\varrho_B}{\gamma_B}\omega_4 = \omega_6$. Finally, Eq. (2.5) implies $\limsup_{t\to\infty} A(t) \le \frac{\lambda_A}{\delta_A} = \omega_5$.□

Based on Lemma 1, we can be show that the domain $\Gamma = \{(E, L, I, S, A, B, U) \in C^7_{\ge 0} : \|E\| \le \omega_1$, $\|L\| \le \omega_2$, $\|I\| \le \omega_3$, $\|S\| \le \omega_4$, $\|A\| \le \omega_5$, $\|B\| \le \omega_6$ $\|U\| \le \omega_7\}$ is positively invariant for system (2.1)-(2.7).

**Remark 1.** When the latently infected cells are not included, model (2.1)-(2.7) becomes

$$\begin{cases}\dot{E} = \lambda_E - \eta\Psi(A)ES - \delta_E E,\\
\dot{I} = \eta\int_0^{h_1} f_1(\tau)e^{-\alpha_1\tau}\Psi(A_\tau)E_\tau S_\tau d\tau - \delta_I I - \gamma IU,\\
\dot{S} = \delta_I\nu\int_0^{h_3} f_3(\tau)e^{-\alpha_3\tau}I_\tau d\tau - \delta_S S - \gamma_B SB,\\
\dot{A} = \lambda_A - \kappa\eta\Psi(A)AS - \delta_A A,\\
\dot{B} = \varrho_B SB - \delta_B B,\\
\dot{U} = \varrho IU - \delta_U U.\end{cases} \tag{3.1}$$

The basic reproduction number of model (3.1) can be calculated as:

$$\hat{\Re}_0 = \frac{\eta \nu \zeta_1 \zeta_3 \Psi(A_0) E_0}{\delta_S}.$$

Since $0 < \zeta_2 \leq 1$, then

$$\Re_0 = \frac{\eta a \nu \zeta_1 \zeta_2 \zeta_3 \Psi(A_0) E_0}{(a+\delta_L)\delta_S} \leq \frac{\eta a \nu \zeta_1 \zeta_3 \Psi(A_0) E_0}{(a+\delta_L)\delta_S} < \frac{\eta \nu \zeta_1 \zeta_3 \Psi(A_0) E_0}{\delta_S} = \hat{\Re}_0.$$

Therefore, excluding the latently infected cells in the model would result in an overestimation of the basic reproduction number.

## 4. Equilibria

This section finds all equilibria of the model (2.1)-(2.7) also the threshold parameters that guarantee their existence. First, by applying the next-generation matrix approach [39], we compute the fundamental infection reproduction number $\Re_0$ for system (2.1)-(2.7). We define the matrices $F$ and $V$ as follows:

$$F = \begin{pmatrix} 0 & 0 & \eta \zeta_1 \Psi(A_0) E_0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}, \qquad V = \begin{pmatrix} a+\delta_L & 0 & 0 \\ -a\zeta_2 & \delta_I & 0 \\ 0 & -\zeta_3 \delta_I \nu & \delta_S \end{pmatrix},$$

where $E_0 = \lambda_E/\delta_E$ and $A_0 = \lambda_A/\delta_A$.

The basic reproduction number $\Re_0$, can be derived as the spectral radius of $FV^{-1}$, as:

$$\Re_0 = \frac{\eta a \nu \zeta_1 \zeta_2 \zeta_3 \Psi(A_0) E_0}{(a+\delta_L)\delta_S}. \tag{4.1}$$

A second step is to define $\Delta = (E, L, I, S, A, B, U)$ as any equilibrium of system (2.1)-(2.7) that may be solved by the set of nonlinear equations that follows:

$$0 = \lambda_E - \eta \Psi(A) E S - \delta_E E, \tag{4.2}$$

$$0 = \eta \zeta_1 \Psi(A) E S - (a+\delta_L) L, \tag{4.3}$$

$$0 = a\zeta_2 L - \delta_I I - \gamma_U I U, \tag{4.4}$$

$$0 = \delta_I \nu \zeta_3 I - \delta_S S - \gamma_B S B, \tag{4.5}$$

$$0 = \lambda_A - \kappa \eta \Psi(A) S A - \delta_A A, \tag{4.6}$$

$$0 = \varrho_B S B - \delta_B B, \tag{4.7}$$

$$0 = \varrho_U I U - \delta_U U. \tag{4.8}$$

Eq. (4.8) has two solutions, $U = 0$ and $I = \frac{\delta_U}{\varrho_U}$, Also Eq. (4.7) has two solutions, $B = 0$ and $S = \frac{\delta_B}{\varrho_B}$. We have the following cases:

(i) $U = 0$ and $B = 0$. From Eq. (4.4) we get

$$\delta_I I = a\zeta_2 L. \tag{4.9}$$

Substituting Eq. (4.9) into Eq. (4.5), we obtain

$$L = \frac{\delta_S}{a\nu\zeta_2\zeta_3} S. \tag{4.10}$$

Substituting Eq. (4.10) into Eq. (4.3), we get

$$\left[\eta\zeta_1\Psi(A)E - \frac{(a+\delta_L)\delta_S}{\nu a\zeta_2\zeta_3}\right] S = 0,$$

and then we have

$$S = 0, \quad \text{or} \quad \eta\zeta_1\Psi(A)E - \frac{(a+\delta_L)\delta_S}{\nu a\zeta_2\zeta_3} = 0.$$

If $S = 0$, then from Eqs. (4.2), (4.3), (4.5) and (4.6), we have $E = \lambda_E/\delta_E$, $L = 0$, $I = 0$ and $A = \lambda_A/\delta_A$. Then, we obtain the uninfected equilibrium $\Delta_0 = (E_0, 0, 0, 0, A_0, 0, 0)$.

If $S \neq 0$, then $L \neq 0$ and

$$\eta\zeta_1\Psi(A)E = \frac{(a+\delta_L)\delta_S}{\nu a\zeta_2\zeta_3}.$$

Therefore, we obtain

$$E = \frac{\lambda_E - (a+\delta_L)\zeta_1^{-1}L}{\delta_E}, \quad S = \frac{\nu a\zeta_2\zeta_3}{\delta_S}L, \quad I = \frac{a\zeta_2}{\delta_I}L \quad \text{and} \quad A = \frac{\lambda_A}{\delta_A + \kappa\zeta_1^{-1}(a+\delta_L)L/E}. \tag{4.11}$$

Substituting Eq. (4.11) into Eq. (4.3), we have

$$\eta\zeta_1\Psi\left(\frac{\lambda_A}{\delta_A + \kappa\zeta_1^{-1}(a+\delta_L)L/E}\right)\left(\frac{\lambda_E - (a+\delta_L)\zeta_1^{-1}L}{\delta_E}\right)\left(\frac{\nu a\zeta_2\zeta_3}{\delta_S}L\right) - (a+\delta_L)L = 0,$$

Since $L \neq 0$, then

$$\eta\zeta_1\Psi\left(\frac{\lambda_A}{\delta_A + \kappa\zeta_1^{-1}(a+\delta_L)L/E}\right)\left(\frac{\lambda_E - (a+\delta_L)\zeta_1^{-1}L}{\delta_E}\right)\left(\frac{\nu a\zeta_2\zeta_3}{\delta_S}\right) - (a+\delta_L) = 0.$$

We define a function $G_1(L)$ as:

$$G_1(L) = \eta\zeta_1\Psi\left(\frac{\lambda_A}{\delta_A + \kappa\zeta_1^{-1}(a+\delta_L)L/E}\right)\left(\frac{\lambda_E - (a+\delta_L)\zeta_1^{-1}L}{\delta_E}\right)\left(\frac{\nu a\zeta_2\zeta_3}{(a+\delta_L)\delta_S}\right) - 1 = 0.$$

We have

$$G_1(0) = \frac{\eta\nu a\zeta_1\zeta_2\zeta_3}{(a+\delta_L)\delta_S}\Psi\left(\frac{\lambda_A}{\delta_A}\right)\left(\frac{\lambda_E}{\delta_E}\right) - 1 = \mathfrak{R}_0 - 1 > 0, \quad \text{if} \quad \mathfrak{R}_0 > 1,$$

$$\lim_{L \to \frac{\lambda_E\zeta_1}{a+\delta_L}} G_1(L) = -1 < 0,$$

and

$$\frac{d}{dL}\left[\Psi\left(\frac{\lambda_A}{\delta_A + \kappa\zeta_1^{-1}(a+\delta_L)L/E}\right)\right] = -\frac{\kappa(a+\delta_L)\delta_E\lambda_A\lambda_E\zeta_1^{-1}}{[\delta_A\lambda_E + (a+\delta_L)\zeta_1^{-1}L(\kappa\delta_E - \delta_A)]^2}$$
$$\times\Psi_L\left(\frac{\lambda_A}{\delta_A + \kappa\zeta_1^{-1}(a+\delta_L)L/E}\right) = \Theta_1 < 0.$$

So, we have

$$\frac{dG_1(L)}{dL} = \frac{\eta\nu a\zeta_1\zeta_2\zeta_3}{(a+\delta_L)\delta_S}\left(\frac{\lambda_E-(a+\delta_L)\zeta_1^{-1}L}{\delta_E}\right)\Theta_1 - \frac{\eta\nu a\zeta_2\zeta_3}{\delta_S\delta_E}\Psi\left(\frac{\lambda_A}{\delta_A+\kappa\zeta_1^{-1}(a+\delta_L)L/E}\right) < 0.$$

Then, there exists a unique $L_1 \in \left(0, \frac{\lambda_E\zeta_1}{a+\delta_L}\right)$ such that $G_1(L_1) = 0$.
Therefore, there exists a unique infected equilibrium without immune response $\Delta_1 = (E_1, L_1, I_1, S_1, A_1, 0, 0)$ when $\Re_0 > 1$, where

$$E_1 = \frac{\lambda_E-(a+\delta_L)\zeta_1^{-1}L_1}{\delta_E} \in \left(0, \frac{\lambda_E}{\delta_E}\right), \quad I_1 = \frac{a\zeta_2}{\delta_I}L_1 \in \left(0, \frac{a\lambda_E\zeta_1\zeta_2}{(a+\delta_L)\delta_I}\right),$$
$$S_1 = \frac{\nu a\zeta_2\zeta_3}{\delta_S}L_1 \in \left(0, \frac{\nu a\lambda_E\zeta_1\zeta_2\zeta_3}{(a+\delta_L)\delta_S}\right), \quad A_1 = \frac{\lambda_A}{\delta_A+\kappa\zeta_1^{-1}(a+\delta_L)L_1/E_1} \in \left(0, \frac{\lambda_A}{\delta_A}\right).$$

(ii) $U = 0$ and $S = \frac{\delta_B}{\varrho_B}$. In this case we obtain

$$E = \frac{\lambda_E-(a+\delta_L)\zeta_1^{-1}L}{\delta_E}, \quad I = \frac{a\zeta_2}{\delta_I}L,$$
$$A = \frac{\lambda_A}{\delta_A+\kappa\zeta_1^{-1}(a+\delta_L)L/E}, \quad B = \frac{\delta_S}{\gamma_B}\left(\frac{\nu a\varrho_B\zeta_2\zeta_3}{\delta_S\delta_B}L - 1\right). \tag{4.12}$$

Substituting Eq. (4.12) into Eq. (4.3), we obtain

$$\frac{\eta\delta_B\zeta_1}{\varrho_B}\Psi\left(\frac{\lambda_A}{\delta_A+\kappa\zeta_1^{-1}(a+\delta_L)L/E}\right)\left(\frac{\lambda_E-(a+\delta_L)\zeta_1^{-1}L}{\delta_E}\right) - (a+\delta_L)L = 0.$$

Define a function $G_2(L)$ as:

$$G_2(L) = \frac{\eta\delta_B\zeta_1}{\varrho_B}\Psi\left(\frac{\lambda_A}{\delta_A+\kappa\zeta_1^{-1}(a+\delta_L)L/E}\right)\left(\frac{\lambda_E-(a+\delta_L)\zeta_1^{-1}L}{\delta_E}\right) - (a+\delta_L)L.$$

We have

$$G_2(0) = \frac{\eta\delta_B\zeta_1}{\varrho_B}\Psi\left(\frac{\lambda_A}{\delta_A}\right)\left(\frac{\lambda_E}{\delta_E}\right) > 0,$$
$$\lim_{L\to\frac{\lambda_E\zeta_1}{a+\delta_L}} G_2(L) = -\lambda_E\zeta_1 < 0.$$

Moreover,

$$\frac{d}{dL}\left[\Psi\left(\frac{\lambda_A}{\delta_A+\kappa\zeta_1^{-1}(a+\delta_L)L/E}\right)\right] = -\frac{\kappa(a+\delta_L)\delta_E\lambda_A\lambda_E\zeta_1^{-1}}{[\delta_A\lambda_E+(a+\delta_L)\zeta_1^{-1}L(\kappa\delta_E-\delta_A)]^2}$$
$$\times\Psi_L\left(\frac{\lambda_A}{\delta_A+\kappa\zeta_1^{-1}(a+\delta_L)L/E}\right) = \Theta_2 < 0.$$

So, we have

$$\frac{dG_2(L)}{dL} = \frac{\eta\delta_B\zeta_1}{\varrho_B}\left(\frac{\lambda_E-(a+\delta_L)\zeta_1^{-1}L}{\delta_E}\right)\Theta_2 - \frac{\eta\delta_B(a+\delta_L)}{\varrho_B\delta_E}\Psi\left(\frac{\lambda_A}{\delta_A+\kappa\zeta_1^{-1}(a+\delta_L)L/E}\right)$$
$$-(a+\delta_L) < 0.$$

Then, there exists a unique $L_2 \in \left(0, \frac{\lambda_E \zeta_1}{a+\delta_L}\right)$ such that $G_2(L_2) = 0$. It follows that, there exists a unique infected equilibrium with only antibody response $\Delta_2 = (E_2, L_2, I_2, S_2, A_2, B_2, 0)$, when $\Re_1 > 1$, where

$$E_2 = \frac{\lambda_E - (a+\delta_L)\zeta_1^{-1} L_2}{\delta_E} \in \left(0, \frac{\lambda_E}{\delta_E}\right), \quad I_2 = \frac{a\zeta_2}{\delta_I} L_2 \in \left(0, \frac{a\lambda_E \zeta_1 \zeta_2}{(a+\delta_L)\delta_I}\right),$$
$$S_2 = \frac{\delta_B}{\varrho_B}, \quad A_2 = \frac{\lambda_A}{\delta_A + \kappa \zeta_1^{-1}(a+\delta_L) L_2/E_2} \in \left(0, \frac{\lambda_A}{\delta_A}\right), \quad B_2 = \frac{\delta_S}{\gamma_B}\left(\Re_1 - 1\right),$$

where,

$$\Re_1 = \frac{\nu a \varrho_B \zeta_2 \zeta_3}{\delta_S \delta_B} L_2.$$

Here, $\Re_1$ represents the the antibody immunity activation number.

(iii) $B = 0$ and $I = \frac{\delta_U}{\varrho_U}$. In the case we obtain

$$E = \frac{\lambda_E - (a+\delta_L)\zeta_1^{-1} L}{\delta_E}, \quad S = \frac{\nu \zeta_3 \delta_I \delta_U}{\varrho_U \delta_S},$$
$$A = \frac{\lambda_A}{\delta_A + \kappa \zeta_1^{-1}(a+\delta_L) L/E}, \; U = \frac{\delta_I}{\gamma_U}\left(\frac{a \varrho_U \zeta_2}{\delta_I \delta_U} L - 1\right). \tag{4.13}$$

Substituting Eq. (4.13) into Eq. (4.3), we obtain

$$\frac{\nu \eta \zeta_1 \zeta_3 \delta_I \delta_U}{\varrho_U \delta_S} \Psi\left(\frac{\lambda_A}{\delta_A + \kappa \zeta_1^{-1}(a+\delta_L) L/E}\right)\left(\frac{\lambda_E - (a+\delta_L)\zeta_1^{-1} L}{\delta_E}\right) - (a+\delta_L) L = 0.$$

Define a function $G_3(L)$ as:

$$G_3(L) = \frac{\nu \eta \zeta_1 \zeta_3 \delta_I \delta_U}{\varrho_U \delta_S} \Psi\left(\frac{\lambda_A}{\delta_A + \kappa \zeta_1^{-1}(a+\delta_L) L/E}\right)\left(\frac{\lambda_E - (a+\delta_L)\zeta_1^{-1} L}{\delta_E}\right) - (a+\delta_L) L.$$

We have

$$G_3(0) = \frac{\nu \eta \zeta_1 \zeta_3 \delta_I \delta_U}{\varrho_U \delta_S} \Psi\left(\frac{\lambda_A}{\delta_A}\right)\left(\frac{\lambda_E}{\delta_E}\right) > 0,$$
$$\lim_{L \to \frac{\lambda_E \zeta_1}{a+\delta_L}} G_3(L) = -\lambda_E \zeta_1 < 0.$$

Moreover,

$$\frac{d}{dL}\left[\Psi\left(\frac{\lambda_A}{\delta_A + \kappa \zeta_1^{-1}(a+\delta_L) L/E}\right)\right] = -\frac{\kappa (a+\delta_L)\delta_E \lambda_A \lambda_E \zeta_1^{-1}}{[\delta_A \lambda_E + (a+\delta_L)\zeta_1^{-1} L(\kappa \delta_E - \delta_A)]^2}$$
$$\times \Psi_L\left(\frac{\lambda_A}{\delta_A + \kappa \zeta_1^{-1}(a+\delta_L) L/E}\right) = \Theta_3 < 0.$$

So, we have

$$\frac{dG_3(L)}{dL} = \frac{\nu \eta \zeta_1 \zeta_3 \delta_I \delta_U}{\varrho_U \delta_S}\left(\frac{\lambda_E - (a+\delta_L)\zeta_1^{-1} L}{\delta_E}\right)\Theta_3 - \left(\frac{\nu \eta \zeta_3 \delta_I \delta_U (a+\delta_L)}{\varrho_U \delta_S \delta_E}\right)$$
$$\times \Psi\left(\frac{\lambda_A}{\delta_A + \kappa \zeta_1^{-1}(a+\delta_L) L/E}\right) - (a+\delta_L) < 0.$$

Then, there exists a unique $L_3 \in \left(0, \frac{\lambda_E \zeta_1}{a+\delta_L}\right)$ such that $G_3(L_3) = 0$. It follows that, there exists a unique infected equilibrium with only CTL response $\Delta_3 = (E_3, L_3, I_3, S_3, A_3, 0, U_3)$, when $\Re_2 > 1$, where

$$E_3 = \frac{\lambda_E - (a+\delta_L)\zeta_1^{-1} L_3}{\delta_E} \in \left(0, \frac{\lambda_E}{\delta_E}\right), \; I_3 = \frac{\delta_U}{\varrho_U}, \; S_3 = \frac{\nu \zeta_3 \delta_I \delta_U}{\varrho_U \delta_S},$$
$$A_3 = \frac{\lambda_A}{\delta_A + \kappa \zeta_1^{-1}(a+\delta_L) L_3 / E_3} \in \left(0, \frac{\lambda_A}{\delta_A}\right), \; U_3 = \frac{\delta_I}{\gamma_U}\left(\Re_2 - 1\right),$$

where,

$$\Re_2 = \frac{a \varrho_U \zeta_2}{\delta_I \delta_U} L_3.$$

Here, $\Re_2$ represents the CTL response activation number.

(iv) $B \neq 0$ and $U \neq 0$. In this case $S = \frac{\delta_B}{\varrho_B}$ and $I = \frac{\delta_U}{\varrho_U}$, therefore, we obtain

$$E = \frac{\lambda_E - (a+\delta_L)\zeta_1^{-1} L}{\delta_E}, \quad A = \frac{\lambda_A}{\delta_A + \kappa \zeta_1^{-1}(a+\delta_L) L / E},$$
$$B = \frac{\delta_S}{\gamma_B}\left(\frac{\nu \delta_I \delta_U \varrho_B \zeta_3}{\delta_S \delta_B \varrho_U} - 1\right), \quad U = \frac{\delta_I}{\gamma_U}\left(\frac{a \varrho_U \zeta_2}{\delta_I \delta_U} L - 1\right). \tag{4.14}$$

Substituting Eq. (4.14) into Eq. (4.3), we obtain

$$\frac{\eta \zeta_1 \delta_B}{\varrho_B} \Psi\left(\frac{\lambda_A}{\delta_A + \kappa \zeta_1^{-1}(a+\delta_L) L / E}\right)\left(\frac{\lambda_E - (a+\delta_L)\zeta_1^{-1} L}{\delta_E}\right) - (a+\delta_L) L = 0.$$

Define a function $G_4(L)$ as:

$$G_4(L) = \frac{\eta \zeta_1 \delta_B}{\varrho_B} \Psi\left(\frac{\lambda_A}{\delta_A + \kappa \zeta_1^{-1}(a+\delta_L) L / E}\right)\left(\frac{\lambda_E - (a+\delta_L)\zeta_1^{-1} L}{\delta_E}\right) - (a+\delta_L) L.$$

Clearly $G_4(L) = G_2(L)$. Then, there exists a unique $L_4 = L_2 \in \left(0, \frac{\lambda_E \zeta_1}{a+\delta_L}\right)$ such that $G_4(L_4) = 0$. It follows that, there exists a unique infected equilibrium with both antibody and CTL responses $\Delta_4 = (E_4, L_4, I_4, S_4, A_4, B_4, U_4)$, when $\frac{\nu \delta_I \delta_U \varrho_B \zeta_3}{\delta_S \delta_B \varrho_U} > 1$ and $\frac{a \varrho_U \zeta_2}{\delta_I \delta_U} L_4 > 1$, where

$$E_4 = \frac{\lambda_E - (a+\delta_L)\zeta_1^{-1} L_4}{\delta_E} \in \left(0, \frac{\lambda_E}{\delta_E}\right), \qquad I_4 = \frac{\delta_U}{\varrho_U}, \; S_4 = \frac{\delta_B}{\varrho_B},$$
$$A_4 = \frac{\lambda_A}{\delta_A + \kappa \zeta_1^{-1}(a+\delta_L) L_4 / E_4} \in \left(0, \frac{\lambda_A}{\delta_A}\right), \; B_4 = \frac{\delta_S}{\gamma_B}\left(\frac{\nu \delta_I \delta_U \varrho_B \zeta_3}{\delta_S \delta_B \varrho_U} - 1\right),$$
$$U_4 = \frac{\delta_I}{\gamma_U}\left(\frac{a \varrho_U \zeta_2}{\delta_I \delta_U} L_4 - 1\right).$$

We see that $B_4$ and $U_4$ exist when $\frac{\nu \delta_I \delta_U \varrho_B \zeta_3}{\delta_S \delta_B \varrho_U} > 1$ and $\frac{a \varrho_U \zeta_2}{\delta_I \delta_U} L_4 > 1$. Now, we define

$$\Re_3 = \frac{a \varrho_U \zeta_2}{\delta_I \delta_U} L_4.$$

Hence $B_4$ and $U_4$ can be rewritten as:

$$B_4 = \frac{\delta_S}{\gamma_B}\left(\frac{\Re_1}{\Re_3} - 1\right), \; U_4 = \frac{\delta_I}{\gamma_U}\left(\Re_3 - 1\right).$$

Therefore, $\Delta_4$ exists when $\Re_1 > \Re_3$ and $\Re_3 > 1$. Here, $\Re_3$ refers to the competed CTL immunity number.

We have $\Psi(A_2) < \Psi(A_0)$ and $E_2 < E_0$. Therefore

$$\begin{aligned}\Re_1 &= \frac{\nu a \varrho_B \zeta_2 \zeta_3 L_2}{\delta_S \delta_B} = \frac{\nu a \varrho_B \zeta_2 \zeta_3}{\delta_S \delta_B} \frac{\zeta_1 \eta \Psi(A_2) E_2 S_2}{a+\delta_L} \\ &= \frac{\nu a \zeta_1 \zeta_2 \zeta_3 \eta \Psi(A_2) E_2}{\delta_S(a+\delta_L)} < \frac{\nu a \zeta_1 \zeta_2 \zeta_3 \eta \Psi(A_0) E_0}{\delta_S(a+\delta_L)} = \Re_0.\end{aligned}$$

We have $\Psi(A_3) < \Psi(A_0)$ and $E_3 < E_0$. Therefore

$$\begin{aligned}\Re_2 &= \frac{a \varrho_U \zeta_2 L_3}{\delta_I \delta_U} = \frac{a \varrho_U \zeta_2}{\delta_I \delta_U} \frac{\zeta_1 \eta \Psi(A_3) E_3 S_3}{a+\delta_L} \\ &= \frac{\nu a \zeta_1 \zeta_2 \zeta_3 \eta \Psi(A_3) E_3}{\delta_S(a+\delta_L)} < \frac{\nu a \zeta_1 \zeta_2 \zeta_3 \eta \Psi(A_0) E_0}{\delta_S(a+\delta_L)} = \Re_0.\end{aligned}$$

Now we can state the following lemma:

**Lemma 2**: For system (2.1)-(2.7), there exist four threshold parameters $\Re_0$, $\Re_1$, $\Re_2$ and $\Re_3$ such that

(i) If $\Re_0 \leq 1$, then the uninfected equilibrium $\Delta_0 = (E_0, 0, 0, 0, A_0, 0, 0)$ is the unique equilibrium,

(ii) If $\Re_1 \leq 1 < \Re_0$, then there exists two equilibria $\Delta_0$ and infected equilibrium without antibody and CTL responses $\Delta_1 = (E_1, L_1, I_1, S_1, A_1, 0, 0)$,

(iii) If $\Re_1 > 1$, then there exist three equilibria $\Delta_0$, $\Delta_1$ and infected equilibrium with only antibody response $\Delta_2 = (E_2, L_2, I_2, S_2, A_2, B_2, 0)$.

(iv) If $\Re_2 > 1$, then there exist four equilibria $\Delta_0$, $\Delta_1$, $\Delta_2$ and infected equilibrium with only CTL response $\Delta_3 = (E_3, L_3, I_3, S_3, A_3, 0, U_3)$.

(v) If $\Re_1 > \Re_3 > 1$, then there exist five equilibria $\Delta_0$, $\Delta_1$, $\Delta_2$, $\Delta_3$ and infected equilibrium with both antibody and CTL responses $\Delta_4 = (E_4, L_4, I_4, S_4, A_4, B_4, U_4)$.

## 5. Global stability

This section formulates Lyapunov function and uses LIP to prove the global asymptotic stability of equilibria. We follow the method presented in [40] and [41]. We define a function $\Phi(x) = x - 1 - \ln x$. Clearly, $\Phi(1) = 0$ and $\Phi(x) \geq 0$ for $x > 0$. Let $\tilde{\Omega}_j$ be the largest invariant subset of

$$\Omega_j = \{(E, L, I, S, A, B, U) : \frac{d\mathcal{G}_j}{dt} = 0\}, \quad j = 0, 1, 2, 3, 4,$$

where, $\mathcal{G}_j(E, L, I, S, A, B, U)$ is a Lyapunov function candidate. The following equalities, should be used in the subsequent theorems:

$$\ln\left(\frac{\Psi(A_\tau)E_\tau S_\tau}{\Psi(A)ES}\right)=\ln\left(\frac{\Psi(A_\tau)E_\tau S_\tau L_k}{\Psi(A_k)E_kS_kL}\right)+\ln\left(\frac{\Psi(A_k)}{\Psi(A)}\right)+\ln\left(\frac{LS_k}{L_kS}\right)+\ln\left(\frac{E_k}{E}\right),$$

$$\ln\left(\frac{L_\tau}{L}\right)=\ln\left(\frac{L_\tau I_k}{L_kI}\right)+\ln\left(\frac{L_kI}{LI_k}\right),$$

$$\ln\left(\frac{I_\tau}{I}\right)=\ln\left(\frac{I_\tau S_k}{I_kS}\right)+\ln\left(\frac{I_kS}{IS_k}\right),\text{ where }k=1,2,3,4. \tag{5.1}$$

**Theorem 1.** Suppose that $\Re_0\le 1$, then $\Delta_0$ is globally asymptotically stable (G.A.S) and it is unstable when $\Re_0>1$.

**Proof.** Define

$$\begin{aligned}\mathcal{G}_0&=\zeta_1E_0\Phi\left(\frac{E}{E_0}\right)+L+\frac{a+\delta_L}{a\zeta_2}I+\frac{a+\delta_L}{a\nu\zeta_2\zeta_3}S+\frac{\zeta_1E_0}{\kappa A_0}\left(A-A_0-\int_{A_0}^{A}\frac{\Psi(A_0)}{\Psi(\xi)}d\xi\right)\\&+\frac{\gamma_B(a+\delta_L)}{a\varrho_B\nu\zeta_2\zeta_3}B+\frac{\gamma_U(a+\delta_L)}{a\varrho_U\zeta_2}U+\eta\int_0^{h_1}\chi_1(\tau)\int_{t-\tau}^{t}\Psi(A(s))E(s)S(s)dsd\tau\\&+\frac{a+\delta_L}{\zeta_2}\int_0^{h_2}\chi_2(\tau)\int_{t-\tau}^{t}L(s)dsd\tau+\frac{\delta_I(a+\delta_L)}{a\zeta_2\zeta_3}\int_0^{h_3}\chi_3(\tau)\int_{t-\tau}^{t}I(s)dsd\tau.\end{aligned}$$

We note that, $\mathcal{G}_0(E,L,I,S,A,B,U)>0$ for all $E,L,I,S,A,B,U>0$ and $\mathcal{G}_0(E_0,0,0,0,A_0,0,0)=0$. We calculate $\frac{d\mathcal{G}_0}{dt}$ along the solutions of model (2.1)-(2.7) as:

$$\begin{aligned}\frac{d\mathcal{G}_0}{dt}&=\zeta_1\left(1-\frac{E_0}{E}\right)\dot{E}+\dot{L}+\frac{a+\delta_L}{a\zeta_2}\dot{I}+\frac{a+\delta_L}{a\nu\zeta_2\zeta_3}\dot{S}+\frac{\zeta_1E_0}{\kappa A_0}\left(1-\frac{\Psi(A_0)}{\Psi(A)}\right)\dot{A}\\&+\frac{\gamma_B(a+\delta_L)}{a\varrho_B\nu\zeta_2\zeta_3}\dot{B}+\frac{\gamma_U(a+\delta_L)}{a\varrho_U\zeta_2}\dot{U}+\eta\frac{d}{dt}\int_0^{h_1}\chi_1(\tau)\int_{t-\tau}^{t}\Psi(A(s))E(s)S(s)dsd\tau\\&+\frac{a+\delta_L}{\zeta_2}\frac{d}{dt}\int_0^{h_2}\chi_2(\tau)\int_{t-\tau}^{t}L(s)dsd\tau+\frac{\delta_I(a+\delta_L)}{a\zeta_2\zeta_3}\frac{d}{dt}\int_0^{h_3}\chi_3(\tau)\int_{t-\tau}^{t}I(s)dsd\tau.\end{aligned}$$

Using system (2.1)-(2.7) we get

$$\begin{aligned}\frac{d\mathcal{G}_0}{dt}&=\zeta_1\left(1-\frac{E_0}{E}\right)[\lambda_E-\eta\Psi(A)ES-\delta_EE]\\&+\eta\int_0^{h_1}\chi_1(\tau)\Psi(A_\tau)E_\tau S_\tau d\tau-(a+\delta_L)L\\&+\frac{a+\delta_L}{a\zeta_2}\left[a\int_0^{h_2}\chi_2(\tau)L_\tau d\tau-\delta_II-\gamma_UIU\right]\\&+\frac{a+\delta_L}{a\nu\zeta_2\zeta_3}\left[\delta_I\nu\int_0^{h_3}\chi_3(\tau)I_\tau d\tau-\delta_SS-\gamma_BSB\right]\\&+\frac{\zeta_1E_0}{\kappa A_0}\left(1-\frac{\Psi(A_0)}{\Psi(A)}\right)[\lambda_A-\kappa\eta\Psi(A)SA-\delta_AA]\end{aligned}$$

$$+\frac{\gamma_B(a+\delta_L)}{a\varrho_B\nu\zeta_2\zeta_3}[\varrho_B SB-\delta_B B]+\frac{\gamma_U(a+\delta_L)}{a\varrho_U\zeta_2}[\varrho_U IU-\delta_U U]$$
$$+\eta\int_0^{h_1}\chi_1(\tau)\left[\Psi(A)ES-\Psi(A_\tau)E_\tau S_\tau\right]d\tau$$
$$+\frac{a+\delta_L}{\zeta_2}\int_0^{h_2}\chi_2(\tau)[L-L_\tau]d\tau+\frac{\delta_I(a+\delta_L)}{a\zeta_2\zeta_3}\int_0^{h_3}\chi_3(\tau)[I-I_\tau]d\tau.$$

Collecting terms we get

$$\begin{aligned}\frac{d\mathcal{G}_0}{dt}&=\zeta_1\left(1-\frac{E_0}{E}\right)[\lambda_E-\delta_E E]+\eta\zeta_1\Psi(A)E_0S\\
&-\frac{a+\delta_L}{a\nu\zeta_2\zeta_3}\delta_S S+\eta\zeta_1\Psi(A_0)E_0S-\eta\zeta_1\Psi(A_0)E_0S\\
&+\frac{\zeta_1E_0}{\kappa A_0}\left(1-\frac{\Psi(A_0)}{\Psi(A)}\right)[\lambda_A-\delta_A A]-\frac{\zeta_1E_0}{A_0}\left(\Psi(A)-\Psi(A_0)\right)\eta SA\\
&-\frac{\gamma_B(a+\delta_L)}{a\varrho_B\nu\zeta_2\zeta_3}\delta_B B-\frac{\gamma_U(a+\delta_L)}{a\varrho_U\zeta_2}\delta_U U\\
&=\zeta_1\left(\frac{E-E_0}{E}\right)[\lambda_E-\delta_E E]+\left(\eta\zeta_1\Psi(A_0)E_0-\frac{(a+\delta_L)\delta_S}{a\nu\zeta_2\zeta_3}\right)S\\
&+\eta\zeta_1E_0S(\Psi(A)-\Psi(A_0))+\frac{\zeta_1E_0}{\kappa A_0\Psi(A)}\left(\Psi(A)-\Psi(A_0)\right)[\lambda_A-\delta_A A]\\
&-\frac{\zeta_1E_0}{A_0}\left(\Psi(A)-\Psi(A_0)\right)\eta SA-\frac{\gamma_B(a+\delta_L)}{a\varrho_B\nu\zeta_2\zeta_3}\delta_B B-\frac{\gamma_U(a+\delta_L)}{a\varrho_U\zeta_2}\delta_U U.\end{aligned}$$

Using the equilibrium condition $\lambda_E=\delta_E E_0$, and $\lambda_A=\delta_A A_0$, we get:

$$\begin{aligned}\frac{d\mathcal{G}_0}{dt}&=-\zeta_1\delta_E\frac{(E-E_0)^2}{E}+\frac{(a+\delta_L)\delta_S}{a\nu\zeta_2\zeta_3}\left(\frac{a\nu\zeta_1\zeta_2\zeta_3\eta\Psi(A_0)E_0}{(a+\delta_L)\delta_S}-1\right)S\\
&+\eta\zeta_1E_0S(\Psi(A)-\Psi(A_0))\frac{A_0}{A_0}+\frac{\zeta_1\delta_AE_0}{\kappa A_0\Psi(A)}\left(\Psi(A)-\Psi(A_0)\right)(A_0-A)\\
&-\frac{\eta\zeta_1E_0}{A_0}S\left(\Psi(A)-\Psi(A_0)\right)A-\frac{\gamma_B(a+\delta_L)}{a\varrho_B\nu\zeta_2\zeta_3}\delta_B B-\frac{\gamma_U(a+\delta_L)}{a\varrho_U\zeta_2}\delta_U U\\
&=-\zeta_1\delta_E\frac{(E-E_0)^2}{E}+\frac{(a+\delta_L)\delta_S}{a\nu\zeta_2\zeta_3}(\mathfrak{R}_0-1)S\\
&+\left(\frac{\eta\zeta_1E_0S}{A_0}+\frac{\zeta_1\delta_AE_0}{\kappa A_0\Psi(A)}\right)\left(\Psi(A)-\Psi(A_0)\right)(A_0-A)\\
&-\frac{\gamma_B(a+\delta_L)}{a\varrho_B\nu\zeta_2\zeta_3}\delta_B B-\frac{\gamma_U(a+\delta_L)}{a\varrho_U\zeta_2}\delta_U U.\end{aligned}$$

Since $\mathfrak{R}_0\le 1$ and $\left(\Psi(A)-\Psi(A_0)\right)(A_0-A)\le 0$, then $\frac{d\mathcal{G}_0}{dt}\le 0$ for all $E,S,A,B,U>0$. In addition $\frac{d\mathcal{G}_0}{dt}=0$ when $E=E_0$, $A=A_0$ and $S=B=U=0$. Solutions of system (2.1)-(2.7) converge to $\tilde{\Omega}_0$, where $E=E_0$, $A=A_0$ and $S=U=0$ [42]. Thus, $\dot{S}=0$ and Eq. (2.4) gives

$$0=\dot{S}=\delta_I\nu\int_0^{h_3}\chi_3(\tau)I_\tau d\tau\Longrightarrow I=0,\ \text{for all } t.$$

Since $I=0$, then $\dot{I}=0$ and from Eq. (2.3) we have

$$0=\dot{I}=a\int_0^{h_2}\chi_2(\tau)L_\tau d\tau \Longrightarrow L=0, \text{ for all } t.$$

Therefore, $\tilde{\Omega}_0=\{\Delta_0\}$ and applying LIP [43], we obtain that $\Delta_0$ is G.A.S.

To show that instability of $\Delta_0$ we calculate the characteristic equation of system (2.1)-(2.7) at $\Delta_0$ as:

$$\begin{aligned}0=&(c+\delta_E)(c+\delta_B)(c+\delta_U)+\Big[c^4+(a+\delta_L+\delta_I+\delta_S+\delta_A)c^3+[(a+\delta_L)(\delta_I+\delta_S+\delta_A)\\&+\delta_S\delta_A+\delta_I(\delta_S+\delta_A)]c^2+(\delta_I\delta_S\delta_A-\eta a\bar{\zeta}_1\bar{\zeta}_2\bar{\zeta}_3\delta_I\nu\Psi(A_0)E_0)c\\&+(a+\delta_L)\delta_I\delta_S\delta_A-\eta a\bar{\zeta}_1\bar{\zeta}_2\bar{\zeta}_3\delta_I\nu\delta_A\Psi(A_0)E_0\Big].\end{aligned}$$

Define a function where $\mathcal{T}(c)$ as:

$$\begin{aligned}\mathcal{T}(c)=&c^4+(a+\delta_L+\delta_I+\delta_S+\delta_A)c^3+[(a+\delta_L)(\delta_I+\delta_S+\delta_A)+\delta_S\delta_A+\delta_I(\delta_S+\delta_A)]c^2\\&+(\delta_I\delta_S\delta_A-\eta a\bar{\zeta}_1\bar{\zeta}_2\bar{\zeta}_3\delta_I\nu\Psi(A_0)E_0)c+(a+\delta_L)\delta_I\delta_S\delta_A-\eta a\bar{\zeta}_1\bar{\zeta}_2\bar{\zeta}_3\delta_I\nu\delta_A\Psi(A_0)E_0\end{aligned}$$

where $\bar{\zeta}_i=\int_0^{h_i}f_i(\tau)e^{-(c+\alpha_i)\tau}d\tau,\ i=1,2,3,$ which is continuous on $[0,\infty)$. We have

$$\begin{aligned}&\mathcal{T}(0)=(a+\delta_L)\delta_I\delta_S\delta_A(1-\mathfrak{R}_0)\ <0, \quad \text{when } \ \mathfrak{R}_0>1,\\&\lim_{c\to\infty}\mathcal{T}(c)=\infty.\end{aligned}$$

Hence, $\mathcal{T}(c)$ has a positive real root and thus $\Delta_0$ is unstable. □

**Theorem 2.** If $\mathfrak{R}_1\le 1<\mathfrak{R}_0$ and $\mathfrak{R}_2\le 1$, then $\Delta_1$ is G.A.S.

**Proof.** Define $\mathcal{G}_1$ as:

$$\begin{aligned}\mathcal{G}_1=&\zeta_1E_1\Phi\left(\frac{E}{E_1}\right)+L_1\Phi\left(\frac{L}{L_1}\right)+\frac{a+\delta_L}{a\zeta_2}I_1\Phi\left(\frac{I}{I_1}\right)+\frac{a+\delta_L}{a\nu\zeta_2\zeta_3}S_1\Phi\left(\frac{S}{S_1}\right)\\&+\frac{\zeta_1E_1}{\kappa A_1}\left(A-A_1-\int_{A_1}^{A}\frac{\Psi(A_1)}{\Psi(\xi)}d\xi\right)+\frac{\gamma_B(a+\delta_L)}{\varrho_Ba\nu\zeta_2\zeta_3}B+\frac{\gamma_U(a+\delta_L)}{\varrho_Ua\zeta_2}U\\&+\eta\Psi(A_1)E_1S_1\int_0^{h_1}\chi_1(\tau)\int_{t-\tau}^{t}\Phi\left(\frac{\Psi(A(s))E(s)S(s)}{\Psi(A_1)E_1S_1}\right)dsd\tau+\frac{a+\delta_L}{\zeta_2}L_1\\&\times\int_0^{h_2}\chi_2(\tau)\int_{t-\tau}^{t}\Phi\left(\frac{L(s)}{L_1}\right)dsd\tau+\frac{(a+\delta_L)\delta_I}{a\zeta_2\zeta_3}I_1\int_0^{h_3}\chi_3(\tau)\int_{t-\tau}^{t}\Phi\left(\frac{I(s)}{I_1}\right)dsd\tau.\end{aligned}$$

We note that, $\mathcal{G}_1(E,L,I,S,A,B,U)>0$ for all $E,L,I,S,A,B,U>0$ and $\mathcal{G}_1(E_1,L_1,I_1,S_1,A_1,0,0)=0$. We calculate $\frac{d\mathcal{G}_1}{dt}$ as:

$$\begin{aligned}\frac{d\mathcal{G}_1}{dt}=&\zeta_1\left(1-\frac{E_1}{E}\right)\dot{E}+\left(1-\frac{L_1}{L}\right)\dot{L}+\frac{a+\delta_L}{a\zeta_2}\left(1-\frac{I_1}{I}\right)\dot{I}\\&+\frac{a+\delta_L}{a\nu\zeta_2\zeta_3}\left(1-\frac{S_1}{S}\right)\dot{S}+\frac{\zeta_1E_1}{\kappa A_1}\left(1-\frac{\Psi(A_1)}{\Psi(A)}\right)\dot{A}+\frac{\gamma_B(a+\delta_L)}{\varrho_Ba\nu\zeta_2\zeta_3}\dot{B}\end{aligned}$$

$$+\frac{\gamma_U(a+\delta_L)}{\varrho_U a\zeta_2}\dot{U}+\eta\Psi(A_1)E_1S_1\frac{d}{dt}\int_0^{h_1}\chi_1(\tau)\int_{t-\tau}^{t}\Phi\left(\frac{\Psi(A(s))E(s)S(s)}{\Psi(A_1)E_1S_1}\right)dsd\tau$$
$$+\frac{a+\delta_L}{\zeta_2}L_1\frac{d}{dt}\int_0^{h_2}\chi_2(\tau)\int_{t-\tau}^{t}\Phi\left(\frac{L(s)}{L_1}\right)dsd\tau$$
$$+\frac{(a+\delta_L)\delta_I}{a\zeta_2\zeta_3}I_1\frac{d}{dt}\int_0^{h_3}\chi_3(\tau)\int_{t-\tau}^{t}\Phi\left(\frac{I(s)}{I_1}\right)dsd\tau.$$

Using system (2.1)-(2.7) we get

$$\begin{aligned}\frac{d\mathcal{G}_1}{dt}&=\zeta_1\left(1-\frac{E_1}{E}\right)[\lambda_E-\eta\Psi(A)ES-\delta_E E]\\
&+\left(1-\frac{L_1}{L}\right)\left[\eta\int_0^{h_1}\chi_1(\tau)\Psi(A_\tau)E_\tau S_\tau d\tau-(a+\delta_L)L\right]\\
&+\frac{a+\delta_L}{a\zeta_2}\left(1-\frac{I_1}{I}\right)\left[a\int_0^{h_2}\chi_2(\tau)L_\tau d\tau-\delta_I I-\gamma_U IU\right]\\
&+\frac{a+\delta_L}{a\nu\zeta_2\zeta_3}\left(1-\frac{S_1}{S}\right)\left[\delta_I\nu\int_0^{h_3}\chi_3(\tau)I_\tau d\tau-\delta_S S-\gamma_B SB\right]\\
&+\frac{\zeta_1E_1}{\kappa A_1}\left(1-\frac{\Psi(A_1)}{\Psi(A)}\right)[\lambda_A-\kappa\eta\Psi(A)SA-\delta_A A]\\
&+\frac{\gamma_B(a+\delta_L)}{\varrho_B a\nu\zeta_2\zeta_3}[\varrho_B SB-\delta_B B]+\frac{\gamma_U(a+\delta_L)}{\varrho_U a\zeta_2}[\varrho_U IU-\delta_U U]\\
&+\eta\Psi(A_1)E_1S_1\int_0^{h_1}\chi_1(\tau)\left[\frac{\Psi(A)ES}{\Psi(A_1)E_1S_1}-\frac{\Psi(A_\tau)E_\tau S_\tau}{\Psi(A_1)E_1S_1}+\ln\left(\frac{\Psi(A_\tau)E_\tau S_\tau}{\Psi(A)ES}\right)\right]d\tau\\
&+\frac{a+\delta_L}{\zeta_2}L_1\int_0^{h_2}\chi_2(\tau)\left[\frac{L}{L_1}-\frac{L_\tau}{L_1}+\ln\left(\frac{L_\tau}{L}\right)\right]d\tau\\
&+\frac{(a+\delta_L)\delta_I}{a\zeta_2\zeta_3}I_1\int_0^{h_3}\chi_3(\tau)\left[\frac{I}{I_1}-\frac{I_\tau}{I_1}+\ln\left(\frac{I_\tau}{I}\right)\right]d\tau.\end{aligned}$$

Collecting terms we get

$$\begin{aligned}\frac{d\mathcal{G}_1}{dt}&=\zeta_1\left(1-\frac{E_1}{E}\right)[\lambda_E-\delta_E E]+\zeta_1\eta\Psi(A)E_1S\\
&-\eta\int_0^{h_1}\chi_1(\tau)\Psi(A_\tau)E_\tau S_\tau\frac{L_1}{L}d\tau+(a+\delta_L)L_1\\
&-\frac{a+\delta_L}{\zeta_2}\int_0^{h_2}\chi_2(\tau)L_\tau\frac{I_1}{I}d\tau+\frac{a+\delta_L}{a\zeta_2}\delta_I I_1\\
&+\frac{a+\delta_L}{a\zeta_2}\gamma_U I_1U-\frac{a+\delta_L}{a\nu\zeta_2\zeta_3}\delta_S S-\frac{a+\delta_L}{a\zeta_2\zeta_3}\delta_I\int_0^{h_3}\chi_3(\tau)I_\tau\frac{S_1}{S}d\tau\\
&+\frac{a+\delta_L}{a\nu\zeta_2\zeta_3}\delta_S S_1+\frac{a+\delta_L}{a\nu\zeta_2\zeta_3}\gamma_B S_1B+\frac{\zeta_1E_1}{\kappa A_1}\left(1-\frac{\Psi(A_1)}{\Psi(A)}\right)[\lambda_A-\delta_A A]\end{aligned}$$

$$
\begin{aligned}
&-\frac{\zeta_1 E_1}{A_1}\eta SA\left(\Psi(A)-\Psi(A_1)\right)-\frac{\gamma_B(a+\delta_L)}{\varrho_B a\nu\zeta_2\zeta_3}\delta_B B-\frac{\gamma_U(a+\delta_L)}{\varrho_U a\zeta_2}\delta_U U\\
&+\eta\Psi(A_1)E_1S_1\int_0^{h_1}\chi_1(\tau)\ln\left(\frac{\Psi(A_\tau)E_\tau S_\tau}{\Psi(A)ES}\right)d\tau\\
&+\frac{a+\delta_L}{\zeta_2}L_1\int_0^{h_2}\chi_2(\tau)\ln\left(\frac{L_\tau}{L}\right)d\tau+\frac{(a+\delta_L)\delta_I}{a\zeta_2\zeta_3}I_1\int_0^{h_3}\chi_3(\tau)\ln\left(\frac{I_\tau}{I}\right)d\tau.
\end{aligned}
$$

Using the equilibrium condition for $\Delta_1$:

$$
\begin{aligned}
&\lambda_E=\eta\Psi(A_1)E_1S_1+\delta_E E_1,\ \ (a+\delta_L)L_1=\eta\zeta_1\Psi(A_1)E_1S_1,\\
&\delta_I I_1=a\zeta_2 L_1,\ \ \delta_S S_1=\delta_I\nu\zeta_3 I_1,\ \ \lambda_A=\kappa\eta\Psi(A_1)S_1A_1+\delta_A A_1,
\end{aligned}
$$

we obtain,

$$
\begin{aligned}
\frac{d\mathcal{G}_1}{dt}&=-\zeta_1\delta_E\frac{(E-E_1)^2}{E}+5(a+\delta_L)L_1-(a+\delta_L)L_1\frac{E_1}{E}+\zeta_1\eta\Psi(A)E_1S\\
&-\frac{a+\delta_L}{\zeta_1}L_1\int_0^{h_1}\chi_1(\tau)\frac{\Psi(A_\tau)E_\tau S_\tau L_1}{\Psi(A_1)E_1S_1L}d\tau-\frac{a+\delta_L}{\zeta_2}L_1\int_0^{h_2}\chi_2(\tau)\frac{L_\tau I_1}{L_1 I}d\tau\\
&-\zeta_1\eta\Psi(A_1)E_1S-\frac{a+\delta_L}{\zeta_3}L_1\int_0^{h_3}\chi_3(\tau)\frac{I_\tau S_1}{I_1S}d\tau\\
&+\left(\frac{(a+\delta_L)\gamma_B}{a\nu\zeta_2\zeta_3}S_1-\frac{(a+\delta_L)\gamma_B\delta_B}{\varrho_B a\nu\zeta_2\zeta_3}\right)B+\left(\frac{(a+\delta_L)\gamma_U}{a\zeta_2}I_1-\frac{(a+\delta_L)\gamma_U\delta_U}{a\varrho_U\zeta_2}\right)U\\
&+\frac{\zeta_1\delta_A E_1}{\kappa A_1\Psi(A)}\left(\Psi(A)-\Psi(A_1)\right)(A_1-A)-(a+\delta_L)L_1\frac{\Psi(A_1)}{\Psi(A)}\\
&-\frac{\eta\zeta_1E_1}{A_1}\left(\Psi(A)-\Psi(A_1)\right)SA+\frac{a+\delta_L}{\zeta_1}L_1\int_0^{h_1}\chi_1(\tau)\ln\left(\frac{\Psi(A_\tau)E_\tau S_\tau}{\Psi(A)ES}\right)d\tau\\
&+\frac{a+\delta_L}{\zeta_2}L_1\int_0^{h_2}\chi_2(\tau)\ln\left(\frac{L_\tau}{L}\right)d\tau+\frac{a+\delta_L}{\zeta_3}L_1\int_0^{h_3}\chi_3(\tau)\ln\left(\frac{I_\tau}{I}\right)d\tau.
\end{aligned}
$$

Then we get

$$
\begin{aligned}
\frac{d\mathcal{G}_1}{dt}&=-\zeta_1\delta_E\frac{(E-E_1)^2}{E}+5(a+\delta_L)L_1-(a+\delta_L)L_1\frac{E_1}{E}+\eta\zeta_1E_1S(\Psi(A)-\Psi(A_1))\\
&-\frac{a+\delta_L}{\zeta_1}L_1\int_0^{h_1}\chi_1(\tau)\frac{\Psi(A_\tau)E_\tau S_\tau L_1}{\Psi(A_1)E_1S_1L}d\tau-\frac{a+\delta_L}{\zeta_2}L_1\int_0^{h_2}\chi_2(\tau)\frac{L_\tau I_1}{L_1I}d\tau\\
&-\frac{a+\delta_L}{\zeta_3}L_1\int_0^{h_3}\chi_3(\tau)\frac{I_\tau S_1}{I_1S}d\tau+\frac{(a+\delta_L)\gamma_B}{a\nu\zeta_2\zeta_3}[S_1-\frac{\delta_B}{\varrho_B}]B+\frac{(a+\delta_L)\gamma_U}{a\zeta_2}[I_1-\frac{\delta_U}{\varrho_U}]U\\
&+\frac{\zeta_1\delta_A E_1}{\kappa A_1\Psi(A)}\left(\Psi(A)-\Psi(A_1)\right)(A_1-A)-(a+\delta_L)L_1\frac{\Psi(A_1)}{\Psi(A)}\\
&-\frac{\eta\zeta_1E_1}{A_1}\left(\Psi(A)-\Psi(A_1)\right)SA+\frac{a+\delta_L}{\zeta_1}L_1\int_0^{h_1}\chi_1(\tau)\ln\left(\frac{\Psi(A_\tau)E_\tau S_\tau}{\Psi(A)ES}\right)d\tau\\
&+\frac{a+\delta_L}{\zeta_2}L_1\int_0^{h_2}\chi_2(\tau)\ln\left(\frac{L_\tau}{L}\right)d\tau+\frac{a+\delta_L}{\zeta_3}L_1\int_0^{h_3}\chi_3(\tau)\ln\left(\frac{I_\tau}{I}\right)d\tau.
\end{aligned}
$$

Using the equalities given by (5.1) in case of $k = 1$, we get,

$$\frac{d\mathcal{G}_1}{dt} = -\zeta_1\delta_E\frac{(E-E_1)^2}{E} - (a+\delta_L)L_1\left[\Phi\left(\frac{E_1}{E}\right) + \frac{1}{\zeta_1}\int_0^{h_1}\chi_1(\tau)\right.$$
$$\times\Phi\left(\frac{\Psi(A_\tau)E_\tau S_\tau L_1}{\Psi(A_1)E_1S_1L}\right)d\tau + \frac{1}{\zeta_2}\int_0^{h_2}\chi_2(\tau)\Phi\left(\frac{L_\tau I_1}{L_1 I}\right)d\tau$$
$$\left.+\frac{1}{\zeta_3}\int_0^{h_3}\chi_3(\tau)\Phi\left(\frac{I_\tau S_1}{I_1 S}\right)d\tau + \Phi\left(\frac{\Psi(A_1)}{\Psi(A)}\right)\right]$$
$$+\frac{(a+\delta_L)\gamma_B}{a\nu\zeta_2\zeta_3}[S_1 - S_2]B + \frac{(a+\delta_L)\gamma_U}{a\zeta_2}[I_1 - I_3]U$$
$$+\left[\frac{\zeta_1\delta_A E_1}{\kappa A_1\Psi(A)} + \frac{\eta\zeta_1 E_1 S}{A_1}\right](\Psi(A) - \Psi(A_1))(A_1 - A).$$

Since $\Re_1 \le 1$, and $(\Psi(A) - \Psi(A_1))(A_1 - A) \le 0$ then $B_2 = \frac{\delta_S}{\gamma_B}(\Re_1 - 1) \le 0$ and $\Delta_2$ dose not exists. It follows that $\dot{B} = \varrho_B(S - \frac{\delta_B}{\varrho_B})B = \varrho_B(S - S_2)B \le 0$, then $S_1 \le S_2$. Moreover, since $\Re_2 \le 1$, then $U_3 = \frac{\delta_I}{\gamma_U}(\Re_2 - 1) \le 0$ and $\Delta_3$ dose not exists. It follows that $\dot{U} = \varrho_U(I - \frac{\delta_U}{\varrho_U})U = \varrho_U(I - I_3)U \le 0$, then $I_1 \le I_3$ and this gives $\frac{d\mathcal{G}_1}{dt} \le 0$ for all $E, L, I, S, A, B, U > 0$. In addition, $\frac{d\mathcal{G}_1}{dt} = 0$ when $E = E_1$, $L = L_1, I = I_1, S = S_1, A = A_1, B = 0$ and $U = 0$. Therefore, $\tilde{\Omega}_1 = \{\Delta_1\}$ and applying LIP, we obtain that $\Delta_1$ is G.A.S. □

**Theorem 3.** Suppose that $\Re_1 > 1$ and $\Re_3 \le 1$ then $\Delta_2$ is G.A.S.

**Proof.** Consider

$$\mathcal{G}_2 = \zeta_1 E_2\Phi\left(\frac{E}{E_2}\right) + L_2\Phi\left(\frac{L}{L_2}\right) + \frac{a+\delta_L}{a\zeta_2}I_2\Phi\left(\frac{I}{I_2}\right)$$
$$+\frac{a+\delta_L}{a\nu\zeta_2\zeta_3}S_2\Phi\left(\frac{S}{S_2}\right) + \frac{\zeta_1 E_2}{\kappa A_2}\left(A - A_2 - \int_{A_2}^{A}\frac{\Psi(A_2)}{\Psi(\xi)}d\xi\right)$$
$$+\frac{\gamma_B(a+\delta_L)}{\varrho_B a\nu\zeta_2\zeta_3}B_2\Phi\left(\frac{B}{B_2}\right) + \frac{\gamma_U(a+\delta_L)}{\varrho_U a\zeta_2}U + \eta\Psi(A_2)E_2S_2\int_0^{h_1}\chi_1(\tau)$$
$$\times\int_{t-\tau}^{t}\Phi\left(\frac{\Psi(A(s))E(s)S(s)}{\Psi(A_2)E_2S_2}\right)ds d\tau + \frac{a+\delta_L}{\zeta_2}L_2\int_0^{h_2}\chi_2(\tau)\int_{t-\tau}^{t}\Phi\left(\frac{L(s)}{L_2}\right)ds d\tau$$
$$+\frac{(a+\delta_L)\delta_I}{a\zeta_2\zeta_3}I_2\int_0^{h_3}\chi_3(\tau)\int_{t-\tau}^{t}\Phi\left(\frac{I(s)}{I_2}\right)ds d\tau.$$

Clearly, $\mathcal{G}_2(E, L, I, S, A, B, U) > 0$ for all $E, L, I, S, A, B, U > 0$ and $\mathcal{G}_2(E_2, L_2, I_2, S_2, A_2, B_2, 0) = 0$. We calculate $\frac{d\mathcal{G}_2}{dt}$ as:

$$\frac{d\mathcal{G}_2}{dt} = \zeta_1\left(1 - \frac{E_2}{E}\right)\dot{E} + \left(1 - \frac{L_2}{L}\right)\dot{L} + \frac{a+\delta_L}{a\zeta_2}\left(1 - \frac{I_2}{I}\right)\dot{I}$$
$$+\frac{a+\delta_L}{a\nu\zeta_2\zeta_3}\left(1 - \frac{S_2}{S}\right)\dot{S} + \frac{\zeta_1 E_2}{\kappa A_2}\left(1 - \frac{\Psi(A_2)}{\Psi(A)}\right)\dot{A} + \frac{\gamma_B(a+\delta_L)}{\varrho_B a\nu\zeta_2\zeta_3}\left(1 - \frac{B_2}{B}\right)\dot{B}$$

$$+\frac{\gamma_U(a+\delta_L)}{\varrho_U a\zeta_2}\dot{U}+\eta\Psi(A_2)E_2S_2\frac{d}{dt}\int_0^{h_1}\chi_1(\tau)\int_{t-\tau}^{t}\Phi\left(\frac{\Psi(A(s))E(s)S(s)}{\Psi(A_2)E_2S_2}\right)dsd\tau$$
$$+\frac{a+\delta_L}{\zeta_2}L_2\frac{d}{dt}\int_0^{h_2}\chi_2(\tau)\int_{t-\tau}^{t}\Phi\left(\frac{L(s)}{L_2}\right)dsd\tau$$
$$+\frac{(a+\delta_L)\delta_I}{a\zeta_2\zeta_3}I_2\frac{d}{dt}\int_0^{h_3}\chi_3(\tau)\int_{t-\tau}^{t}\Phi\left(\frac{I(s)}{I_2}\right)dsd\tau.$$

From system (2.1)-(2.7) we get

$$\frac{d\mathcal{G}_2}{dt}=\zeta_1\left(1-\frac{E_2}{E}\right)[\lambda_E-\eta\Psi(A)ES-\delta_E E]$$
$$+\left(1-\frac{L_2}{L}\right)\left[\eta\int_0^{h_1}\chi_1(\tau)\Psi(A_\tau)E_\tau S_\tau d\tau-(a+\delta_L)L\right]$$
$$+\frac{a+\delta_L}{a\zeta_2}\left(1-\frac{I_2}{I}\right)\left[a\int_0^{h_2}\chi_2(\tau)L_\tau d\tau-\delta_I I-\gamma_U IU\right]$$
$$+\frac{a+\delta_L}{a\nu\zeta_2\zeta_3}\left(1-\frac{S_2}{S}\right)\left[\delta_I\nu\int_0^{h_3}\chi_3(\tau)I_\tau d\tau-\delta_S S-\gamma_B SB\right]$$
$$+\frac{\zeta_1E_2}{\kappa A_2}\left(1-\frac{\Psi(A_2)}{\Psi(A)}\right)[\lambda_A-\kappa\eta\Psi(A)SA-\delta_A A]$$
$$+\frac{\gamma_B(a+\delta_L)}{\varrho_B a\nu\zeta_2\zeta_3}\left(1-\frac{B_2}{B}\right)[\varrho_B SB-\delta_B B]+\frac{\gamma_U(a+\delta_L)}{\varrho_U a\zeta_2}[\varrho_U IU-\delta_U U]$$
$$+\eta\Psi(A_2)E_2S_2\int_0^{h_1}\chi_1(\tau)\left[\frac{\Psi(A)ES}{\Psi(A_2)E_2S_2}-\frac{\Psi(A_\tau)E_\tau S_\tau}{\Psi(A_2)E_2S_2}+\ln\left(\frac{\Psi(A_\tau)E_\tau S_\tau}{\Psi(A)ES}\right)\right]d\tau$$
$$+\frac{a+\delta_L}{\zeta_2}L_2\int_0^{h_2}\chi_2(\tau)\left[\frac{L}{L_2}-\frac{L_\tau}{L_2}+\ln\left(\frac{L_\tau}{L}\right)\right]d\tau$$
$$+\frac{(a+\delta_L)\delta_I}{a\zeta_2\zeta_3}I_2\int_0^{h_3}\chi_3(\tau)d\tau\left[\frac{I}{I_2}-\frac{I_\tau}{I_2}+\ln\left(\frac{I_\tau}{I}\right)\right]d\tau$$

Collecting terms we get

$$\frac{d\mathcal{G}_2}{dt}=\zeta_1\left(1-\frac{E_2}{E}\right)[\lambda_E-\delta_E E]+\eta\zeta_1\Psi(A)E_2S$$
$$-\eta\int_0^{h_1}\chi_1(\tau)\Psi(A_\tau)E_\tau S_\tau\frac{L_2}{L}d\tau+(a+\delta_L)L_2$$
$$-\frac{a+\delta_L}{\zeta_2}\int_0^{h_2}\chi_2(\tau)L_\tau\frac{I_2}{I}d\tau+\frac{(a+\delta_L)\delta_I}{a\zeta_2}I_2+\frac{(a+\delta_L)\gamma_U}{a\zeta_2}I_2U$$
$$-\frac{(a+\delta_L)\delta_S}{a\nu\zeta_2\zeta_3}S-\frac{(a+\delta_L)\delta_I}{a\zeta_2\zeta_3}\int_0^{h_3}\chi_3(\tau)I_\tau\frac{S_2}{S}d\tau+\frac{(a+\delta_L)\delta_S}{a\nu\zeta_2\zeta_3}S_2$$
$$+\frac{(a+\delta_L)\gamma_B}{a\nu\zeta_2\zeta_3}S_2B+\frac{\zeta_1E_2}{\kappa A_2}\left(1-\frac{\Psi(A_2)}{\Psi(A)}\right)[\lambda_A-\delta_A A]$$
$$-\frac{\zeta_1E_2}{A_2}\left(\Psi(A)-\Psi(A_2)\right)\eta SA-\frac{\gamma_B(a+\delta_L)}{\varrho_B a\nu\zeta_2\zeta_3}\delta_B B$$

$$- \frac{\gamma_B(a+\delta_L)}{a\nu\zeta_2\zeta_3}SB_2 + \frac{\gamma_B(a+\delta_L)}{\varrho_B a\nu\zeta_2\zeta_3}\delta_B B_2 - \frac{\gamma_U(a+\delta_L)}{\varrho_U a\zeta_2}\delta_U U$$
$$+ \eta\Psi(A_2)E_2S_2\int_0^{h_1}\chi_1(\tau)\ln\left(\frac{\Psi(A_\tau)E_\tau S_\tau}{\Psi(A)ES}\right)d\tau$$
$$+ \frac{a+\delta_L}{\zeta_2}L_2\int_0^{h_2}\chi_2(\tau)\ln\left(\frac{L_\tau}{L}\right)d\tau + \frac{(a+\delta_L)\delta_I}{a\zeta_2\zeta_3}I_2\int_0^{h_3}\chi_3(\tau)\ln\left(\frac{I_\tau}{I}\right)d\tau.$$

Using the equilibrium condition for $\Delta_2$:

$$\lambda_E = \eta\Psi(A_2)E_2S_2 + \delta_E E_2, \qquad (a+\delta_L)L_2 = \eta\zeta_1\Psi(A_2)E_2S_2,$$
$$\delta_I I_2 = a\zeta_2 L_2,\ \ \delta_S S_2 = \delta_I\nu\zeta_3 I_2 - \gamma_B S_2 B_2,\ \ \lambda_A = \kappa\eta\Psi(A_2)S_2A_2 + \delta_A A_2,\ \ S_2 = \frac{\delta_B}{\varrho_B}$$

we obtain,

$$\frac{d\mathcal{G}_2}{dt} = -\delta_E\zeta_1\frac{(E-E_2)^2}{E} + 5(a+\delta_L)L_2 - (a+\delta_L)L_2\frac{E_2}{E} + \zeta_1\eta\Psi(A)E_2S$$
$$- \frac{a+\delta_L}{\zeta_1}L_2\int_0^{h_1}\chi_1(\tau)\frac{\Psi(A_\tau)E_\tau S_\tau L_2}{\Psi(A_2)E_2S_2L}d\tau - \frac{a+\delta_L}{\zeta_2}L_2\int_0^{h_2}\chi_2(\tau)\frac{L_\tau I_2}{L_2 I}d\tau$$
$$- \eta\zeta_1\Psi(A_2)E_2S - \frac{a+\delta_L}{\zeta_3}L_2\int_0^{h_3}\chi_3(\tau)\frac{I_\tau S_2}{I_2 S}d\tau$$
$$+ \frac{\zeta_1\delta_A E_2}{\kappa A_2\Psi(A)}\left(\Psi(A)-\Psi(A_2)\right)(A_2-A) - (a+\delta_L)L_2\frac{\Psi(A_2)}{\Psi(A)}$$
$$- \frac{\zeta_1 E_2}{A_2}\eta SA\left(\Psi(A)-\Psi(A_2)\right) - \frac{\gamma_U(a+\delta_L)}{\varrho_U a\zeta_2}\delta_U U + \frac{(a+\delta_L)\gamma_U}{a\zeta_2}I_2U$$
$$+ \frac{a+\delta_L}{\zeta_1}L_2\int_0^{h_1}\chi_1(\tau)\ln\left(\frac{\Psi(A_\tau)E_\tau S_\tau}{\Psi(A)ES}\right)d\tau + \frac{a+\delta_L}{\zeta_2}L_2\int_0^{h_2}\chi_2(\tau)\ln\left(\frac{L_\tau}{L}\right)d\tau$$
$$+ \frac{a+\delta_L}{\zeta_3}L_2\int_0^{h_3}\chi_3(\tau)\ln\left(\frac{I_\tau}{I}\right)d\tau.$$

Finally we get

$$\frac{d\mathcal{G}_2}{dt} = -\delta_E\zeta_1\frac{(E-E_2)^2}{E} + 5(a+\delta_L)L_2 - (a+\delta_L)L_2\frac{E_2}{E} + \zeta_1\eta E_2S(\Psi(A)-\Psi(A_2))$$
$$- \frac{a+\delta_L}{\zeta_1}L_2\int_0^{h_1}\chi_1(\tau)\frac{\Psi(A_\tau)E_\tau S_\tau L_2}{\Psi(A_2)E_2S_2L}d\tau - \frac{a+\delta_L}{\zeta_2}L_2\int_0^{h_2}\chi_2(\tau)\frac{L_\tau I_2}{L_2 I}d\tau$$
$$- \frac{a+\delta_L}{\zeta_3}L_2\int_0^{h_3}\chi_3(\tau)\frac{I_\tau S_2}{I_2 S}d\tau + \frac{\zeta_1\delta_A E_2}{\kappa A_2\Psi(A)}\left(\Psi(A)-\Psi(A_2)\right)(A_2-A)$$
$$- (a+\delta_L)L_2\frac{\Psi(A_2)}{\Psi(A)} - \frac{\zeta_1 E_2}{A_2}\eta SA\left(\Psi(A)-\Psi(A_2)\right)$$
$$+ \frac{a+\delta_L}{\zeta_1}L_2\int_0^{h_1}\chi_1(\tau)\ln\left(\frac{\Psi(A_\tau)E_\tau S_\tau}{\Psi(A)ES}\right)d\tau + \frac{a+\delta_L}{\zeta_2}L_2\int_0^{h_2}\chi_2(\tau)\ln\left(\frac{L_\tau}{L}\right)d\tau$$
$$+ \frac{a+\delta_L}{\zeta_3}L_2\int_0^{h_3}\chi_3(\tau)\ln\left(\frac{I_\tau}{I}\right)d\tau + \frac{(a+\delta_L)\gamma_U}{a\zeta_2}\left[I_2 - \frac{\delta_U}{\varrho_U}\right]U.$$

We have $L_2 = L_4$ and then $I_2 - \frac{\delta_U}{\varrho_U} = \frac{a\zeta_2 L_4}{\delta_I} - \frac{\delta_U}{\varrho_U} = \frac{\delta_U}{\varrho_U}\left(\frac{a\zeta_2\varrho_U L_4}{\delta_I\delta_U} - 1\right) = \frac{\delta_U}{\varrho_U}(\Re_3 - 1)$, and using the equalities given by (5.1) in case of $k = 2$, we obtain,

$$\begin{aligned}\frac{d\mathcal{G}_2}{dt} &= -\delta_E\zeta_1\frac{(E-E_2)^2}{E} - (a+\delta_L)L_2\left[\Phi\left(\frac{E_2}{E}\right) + \frac{1}{\zeta_1}\int_0^{h_1}\chi_1(\tau)\Phi\left(\frac{\Psi(A_\tau)E_\tau S_\tau L_2}{\Psi(A_2)E_2S_2L}\right)d\tau\right.\\&\left.+\frac{1}{\zeta_2}\int_0^{h_2}\chi_2(\tau)\Phi\left(\frac{L_\tau I_2}{L_2 I}\right)d\tau + \frac{1}{\zeta_3}\int_0^{h_3}\chi_3(\tau)\Phi\left(\frac{I_\tau S_2}{I_2 S}\right)d\tau + \Phi\left(\frac{\Psi(A_2)}{\Psi(A)}\right)\right]\\&+\left[\frac{\zeta_1\delta_A E_2}{\kappa A_2\Psi(A)} + \frac{\zeta_1\eta S E_2}{A_2}\right](\Psi(A)-\Psi(A_2))\,(A_2 - A) - \frac{(a+\delta_L)\gamma_U\delta_U}{a\zeta_2\varrho_U}(\Re_3 - 1)U.\end{aligned}$$

If $\Re_1 > 1$ and $\Re_3 \le 1$ we get $\frac{d\mathcal{G}_2}{dt} \le 0$ for all $E, L, I, S, A, U > 0$. Further, $\frac{d\mathcal{G}_2}{dt} = 0$ when $E = E_2$, $L = L_2$, $I = I_2$, $S = S_2$, $A = A_2$ and $U = 0$. Solutions of system (2.1)-(2.7) converge to $\tilde{\Omega}_2$ where, $I = I_2$ and $S = S_2$. Thus, $\dot{S} = 0$ and Eq. (2.4) provides

$$0 = \dot{S} = \delta_I\nu\zeta_3 I_2 - \delta_S S_2 - \gamma S_2 B \Longrightarrow B = B_2, \text{ for all } t.$$

Therefore, $\tilde{\Omega}_2 = \{\Delta_2\}$. Applying LIP, we get $\Delta_2$ is G.A.S. □

**Theorem 4.** Suppose that $\Re_2 > 1$ and $\Re_1 \le \Re_3$, then $\Delta_3$ is G.A.S.

**Proof.** Consider

$$\begin{aligned}\mathcal{G}_3 &= \zeta_1 E_3\Phi\left(\frac{E}{E_3}\right) + L_3\Phi\left(\frac{L}{L_3}\right) + \frac{a+\delta_L}{a\zeta_2}I_3\Phi\left(\frac{I}{I_3}\right)\\&+\left(\frac{a+\delta_L}{a\nu\zeta_2\zeta_3} + \frac{\gamma_U(a+\delta_L)U_3}{a\nu\zeta_2\zeta_3\delta_I}\right)S_3\Phi\left(\frac{S}{S_3}\right) + \frac{\zeta_1 E_3}{\kappa A_3}\left(A - A_3 - \int_{A_3}^{A}\frac{\Psi(A_3)}{\Psi(\xi)}d\xi\right)\\&+\left(\frac{\gamma_B(a+\delta_L)}{a\nu\zeta_2\zeta_3\varrho_B} + \frac{\gamma_B\gamma_U(a+\delta_L)U_3}{a\nu\zeta_2\zeta_3\delta_I\varrho_B}\right)B + \frac{\gamma_U(a+\delta_L)}{\varrho_U a\zeta_2}U_3\Phi\left(\frac{U}{U_3}\right)\\&+\eta\Psi(A_3)E_3S_3\int_0^{h_1}\chi_1(\tau)\int_{t-\tau}^{t}\Phi\left(\frac{\Psi(A(s))E(s)S(s)}{\Psi(A_3)E_3S_3}\right)ds\,d\tau\\&+\frac{a+\delta_L}{\zeta_2}L_3\int_0^{h_2}\chi_2(\tau)\int_{t-\tau}^{t}\Phi\left(\frac{L(s)}{L_3}\right)ds\,d\tau\\&+\left(\frac{(a+\delta_L)\delta_I}{a\zeta_2\zeta_3} + \frac{\gamma_U(a+\delta_L)U_3}{a\zeta_2\zeta_3}\right)I_3\int_0^{h_3}\chi_3(\tau)\int_{t-\tau}^{t}\Phi\left(\frac{I(s)}{I_3}\right)ds\,d\tau.\end{aligned}$$

We note that, $\mathcal{G}_3(E, L, I, S, A, B, U) > 0$ for all $E, L, I, S, A, B, U > 0$ and $\mathcal{G}_3(E_3, L_3, I_3, S_3, A_3, 0, U_3) = 0$. We calculate $\frac{d\mathcal{G}_3}{dt}$ as:

$$\begin{aligned}\frac{d\mathcal{G}_3}{dt} &= \zeta_1\left(1 - \frac{E_3}{E}\right)\dot{E} + \left(1 - \frac{L_3}{L}\right)\dot{L} + \frac{a+\delta_L}{a\zeta_2}\left(1 - \frac{I_3}{I}\right)\dot{I}\\&+\left(\frac{a+\delta_L}{a\nu\zeta_2\zeta_3} + \frac{\gamma_U(a+\delta_L)U_3}{a\nu\zeta_2\zeta_3\delta_I}\right)\left(1 - \frac{S_3}{S}\right)\dot{S} + \frac{\zeta_1 E_3}{\kappa A_3}\left(1 - \frac{\Psi(A_3)}{\Psi(A)}\right)\dot{A}\\&+\left(\frac{\gamma_B(a+\delta_L)}{a\nu\zeta_2\zeta_3\varrho_B} + \frac{\gamma_B\gamma_U(a+\delta_L)U_3}{a\nu\zeta_2\zeta_3\delta_I\varrho_B}\right)\dot{B} + \frac{\gamma_U(a+\delta_L)}{\varrho_U a\zeta_2}\left(1 - \frac{U_3}{U}\right)\dot{U}\end{aligned}$$

$$+\eta\Psi(A_3)E_3S_3\frac{d}{dt}\int_0^{h_1}\chi_1(\tau)\times\int_{t-\tau}^{t}\Phi\left(\frac{\Psi(A(s))E(s)S(s)}{\Psi(A_3)E_3S_3}\right)dsd\tau$$
$$+\frac{a+\delta_L}{\zeta_2}L_3\frac{d}{dt}\int_0^{h_2}\chi_2(\tau)\int_{t-\tau}^{t}\Phi\left(\frac{L(s)}{L_3}\right)dsd\tau$$
$$+\left(\frac{(a+\delta_L)\delta_I}{a\zeta_2\zeta_3}+\frac{\gamma_U(a+\delta_L)U_3}{a\zeta_2\zeta_3}\right)I_3\frac{d}{dt}\int_0^{h_3}\chi_3(\tau)\int_{t-\tau}^{t}\Phi\left(\frac{I(s)}{I_3}\right)dsd\tau.$$

From system (2.1)-(2.7) we get

$$\begin{aligned}\frac{d\mathcal{G}_3}{dt}&=\zeta_1\left(1-\frac{E_3}{E}\right)[\lambda_E-\eta\Psi(A)ES-\delta_EE]\\
&+\left(1-\frac{L_3}{L}\right)\left[\eta\int_0^{h_1}\chi_1(\tau)\Psi(A_\tau)E_\tau S_\tau d\tau-(a+\delta_L)L\right]\\
&+\frac{a+\delta_L}{a\zeta_2}\left(1-\frac{I_3}{I}\right)\left[a\int_0^{h_2}\chi_2(\tau)L_\tau d\tau-\delta_II-\gamma_UUI\right]\\
&+\left(\frac{a+\delta_L}{a\nu\zeta_2\zeta_3}+\frac{\gamma_U(a+\delta_L)U_3}{a\nu\zeta_2\zeta_3\delta_I}\right)\left(1-\frac{S_3}{S}\right)\left[\delta_I\nu\int_0^{h_3}\chi_3(\tau)I_\tau d\tau-\delta_SS-\gamma_BSB\right]\\
&+\frac{\zeta_1E_3}{\kappa A_3}\left(1-\frac{\Psi(A_3)}{\Psi(A)}\right)[\lambda_A-\kappa\eta\Psi(A)SA-\delta_AA]\\
&+\left(\frac{\gamma_B(a+\delta_L)}{a\nu\zeta_2\zeta_3\varrho_B}+\frac{\gamma_B\gamma_U(a+\delta_L)U_3}{a\nu\zeta_2\zeta_3\delta_I\varrho_B}\right)[\varrho_BSB-\delta_BB]+\frac{\gamma_U(a+\delta_L)}{\varrho_Ua\zeta_2}\left(1-\frac{U_3}{U}\right)\\
&\times[\varrho_UIU-\delta_UU]+\eta\Psi(A_3)E_3S_3\int_0^{h_1}\chi_1(\tau)\left[\frac{\Psi(A)ES}{\Psi(A_3)E_3S_3}\right.\\
&\left.-\frac{\Psi(A_\tau)E_\tau S_\tau}{\Psi(A_3)E_3S_3}+\ln\left(\frac{\Psi(A_\tau)E_\tau S_\tau}{\Psi(A)ES}\right)\right]d\tau\\
&+\frac{a+\delta_L}{\zeta_2}L_3\int_0^{h_2}\chi_2(\tau)\left[\frac{L}{L_3}-\frac{L_\tau}{L_3}+\ln\left(\frac{L_\tau}{L}\right)\right]d\tau\\
&+\left(\frac{(a+\delta_L)\delta_I}{a\zeta_2\zeta_3}+\frac{\gamma_U(a+\delta_L)U_3}{a\zeta_2\zeta_3}\right)I_3\int_0^{h_3}\chi_3(\tau)\left[\frac{I}{I_3}-\frac{I_\tau}{I_3}+\ln\left(\frac{I_\tau}{I}\right)\right]d\tau\end{aligned}$$

Collecting terms we get

$$\begin{aligned}\frac{d\mathcal{G}_3}{dt}&=\zeta_1\left(1-\frac{E_3}{E}\right)[\lambda_E-\delta_EE]+\eta\zeta_1\Psi(A)E_3S\\
&-\eta\int_0^{h_1}\chi_1(\tau)\Psi(A_\tau)E_\tau S_\tau\frac{L_3}{L}d\tau+(a+\delta_L)L_3\\
&-\frac{a+\delta_L}{\zeta_2}\int_0^{h_2}\chi_2(\tau)L_\tau\frac{I_3}{I}d\tau+\frac{(a+\delta_L)\delta_I}{a\zeta_2}I_3+\frac{\gamma_U(a+\delta_L)}{a\zeta_2}I_3U\\
&-\left(\frac{a+\delta_L}{a\nu\zeta_2\zeta_3}+\frac{\gamma_U(a+\delta_L)U_3}{a\nu\zeta_2\zeta_3\delta_I}\right)\delta_SS-\left(\frac{(a+\delta_L)\delta_I}{a\zeta_2\zeta_3}+\frac{\gamma_U(a+\delta_L)U_3}{a\zeta_2\zeta_3}\right)\end{aligned}$$

$$\times\int_0^{h_3}\chi_3(\tau)I_\tau\frac{S_3}{S}d\tau+\left(\frac{a+\delta_L}{a\nu\zeta_2\zeta_3}+\frac{\gamma_U(a+\delta_L)U_3}{a\nu\zeta_2\zeta_3\delta_I}\right)\delta_S S_3$$
$$+\left(\frac{a+\delta_L}{a\nu\zeta_2\zeta_3}+\frac{\gamma_U(a+\delta_L)U_3}{a\nu\zeta_2\zeta_3\delta_I}\right)\gamma_B S_3 B+\frac{\zeta_1 E_3}{\kappa A_3}\left(1-\frac{\Psi(A_3)}{\Psi(A)}\right)[\lambda_A-\delta_A A]$$
$$-\frac{\zeta_1 E_3}{A_3}\left(\Psi(A)-\Psi(A_3)\right)\eta SA-\left(\frac{(a+\delta_L)\gamma_B}{a\nu\zeta_2\zeta_3\varrho_B}+\frac{\gamma_B\gamma_U(a+\delta_L)U_3}{a\nu\zeta_2\zeta_3\delta_I\varrho_B}\right)\delta_B B$$
$$-\frac{\gamma_U(a+\delta_L)}{\varrho_U a\zeta_2}\delta_U U+\frac{\gamma_U(a+\delta_L)\delta_U}{\varrho_U a\zeta_2}U_3$$
$$+\eta\Psi(A_3)E_3S_3\int_0^{h_1}\chi_1(\tau)\ln\left(\frac{\Psi(A_\tau)E_\tau S_\tau}{\Psi(A)ES}\right)d\tau$$
$$+\frac{a+\delta_L}{\zeta_2}L_3\int_0^{h_2}\chi_2(\tau)\ln\left(\frac{L_\tau}{L}\right)d\tau$$
$$+\left(\frac{(a+\delta_L)\delta_I}{a\zeta_2\zeta_3}+\frac{\gamma_U(a+\delta_L)U_3}{a\zeta_2\zeta_3}\right)I_3\int_0^{h_3}\chi_3(\tau)\ln\left(\frac{I_\tau}{I}\right)d\tau.$$

Using the equilibrium condition for $\Delta_3$:

$$\lambda_E=\eta\Psi(A_3)E_3S_3+\delta_E E_3,\qquad (a+\delta_L)L_3=\eta\zeta_1\Psi(A_3)E_3S_3,$$
$$a\zeta_2 L_3=\delta_I I_3+\gamma_U I_3 U_3,\ \ \delta_S S_3=\delta_I\nu\zeta_3 I_3,\ \ \lambda_A=\kappa\eta\Psi(A_3)S_3A_3+\delta_A A_3,\ \ I_3=\frac{\delta_U}{\varrho_U},$$

we obtain,

$$\frac{d\mathcal{G}_3}{dt}=-\delta_E\zeta_1\frac{(E-E_3)^2}{E}+5(a+\delta_L)L_3-(a+\delta_L)L_3\frac{E_3}{E}+\zeta_1\eta\Psi(A)E_3S$$
$$-\frac{a+\delta_L}{\zeta_1}L_3\int_0^{h_1}\chi_1(\tau)\frac{\Psi(A_\tau)E_\tau S_\tau L_3}{\Psi(A_3)E_3S_3L}d\tau-\frac{a+\delta_L}{\zeta_2}L_3\int_0^{h_2}\chi_2(\tau)$$
$$\times\frac{L_\tau I_3}{L_3 I}d\tau-\eta\zeta_1\Psi(A_3)E_3S-\frac{a+\delta_L}{\zeta_3}L_3\int_0^{h_3}\chi_3(\tau)\frac{I_\tau S_3}{I_3 S}d\tau$$
$$+\frac{\gamma_B(a+\delta_L)L_3}{\nu\zeta_3\delta_I I_3}\left[S_3-\frac{\delta_B}{\varrho_B}\right]B+\frac{\zeta_1\delta_A E_3}{\kappa A_3\Psi(A)}\left(\Psi(A)-\Psi(A_3)\right)(A_3-A)$$
$$-(a+\delta_L)L_3\frac{\Psi(A_3)}{\Psi(A)}-\frac{\zeta_1 E_3}{A_3}\eta SA\left(\Psi(A)-\Psi(A_3)\right)$$
$$+\frac{a+\delta_L}{\zeta_1}L_3\int_0^{h_1}\chi_1(\tau)\ln\left(\frac{\Psi(A_\tau)E_\tau S_\tau}{\Psi(A)ES}\right)d\tau+\frac{a+\delta_L}{\zeta_2}L_3\int_0^{h_2}\chi_2(\tau)\ln\left(\frac{L_\tau}{L}\right)d\tau$$
$$+\frac{a+\delta_L}{\zeta_3}L_3\int_0^{h_3}\chi_3(\tau)\ln\left(\frac{I_\tau}{I}\right)d\tau.$$

This yields

$$\frac{d\mathcal{G}_3}{dt}=-\delta_E\zeta_1\frac{(E-E_3)^2}{E}+5(a+\delta_L)L_3-(a+\delta_L)L_3\frac{E_3}{E}+\zeta_1\eta E_3S(\Psi(A)-\Psi(A_3))$$
$$-\frac{a+\delta_L}{\zeta_1}L_3\int_0^{h_1}\chi_1(\tau)\frac{\Psi(A_\tau)E_\tau S_\tau L_3}{\Psi(A_3)E_3S_3L}d\tau-\frac{a+\delta_L}{\zeta_2}L_3\int_0^{h_2}\chi_2(\tau)\frac{L_\tau I_3}{L_3 I}d\tau$$

$$
\begin{aligned}
&-\frac{a+\delta_L}{\zeta_3}L_3\int_0^{h_3}\chi_3(\tau)\frac{I_\tau S_3}{I_3 S}d\tau+\frac{\gamma_B(a+\delta_L)L_3}{\nu\zeta_3\delta_I I_3}\left(\frac{\delta_I\delta_U\nu\zeta_3}{\delta_S\varrho_U}-\frac{\delta_B}{\varrho_B}\right)B\\
&+\frac{\zeta_1\delta_A E_3}{\kappa A_3\Psi(A)}\left(\Psi(A)-\Psi(A_3)\right)(A_3-A)-(a+\delta_L)L_3\frac{\Psi(A_3)}{\Psi(A)}\\
&-\frac{\zeta_1 E_3}{A_3}\eta SA\left(\Psi(A)-\Psi(A_3)\right)+\frac{a+\delta_L}{\zeta_1}L_3\int_0^{h_1}\chi_1(\tau)\ln\left(\frac{\Psi(A_\tau)E_\tau S_\tau}{\Psi(A)ES}\right)d\tau\\
&+\frac{a+\delta_L}{\zeta_2}L_3\int_0^{h_2}\chi_2(\tau)\ln\left(\frac{L_\tau}{L}\right)d\tau+\frac{a+\delta_L}{\zeta_3}L_3\int_0^{h_3}\chi_3(\tau)\ln\left(\frac{I_\tau}{I}\right)d\tau.
\end{aligned}
$$

It follows that

$$
\begin{aligned}
\frac{d\mathcal{G}_3}{dt}&=-\delta_E\zeta_1\frac{(E-E_3)^2}{E}+5(a+\delta_L)L_3-(a+\delta_L)L_3\frac{E_3}{E}\\
&+\frac{\zeta_1 E_3}{A_3}\eta SA\left(\Psi(A)-\Psi(A_3)\right)(A_3-A)\\
&-\frac{a+\delta_L}{\zeta_1}L_3\int_0^{h_1}\chi_1(\tau)\frac{\Psi(A_\tau)E_\tau S_\tau L_3}{\Psi(A_3)E_3S_3L}d\tau-\frac{a+\delta_L}{\zeta_2}L_3\int_0^{h_2}\chi_2(\tau)\frac{L_\tau I_3}{L_3 I}d\tau\\
&-\frac{a+\delta_L}{\zeta_3}L_3\int_0^{h_3}\chi_3(\tau)\frac{I_\tau S_3}{I_3 S}d\tau+\frac{\gamma_B(a+\delta_L)L_3}{\nu\zeta_3\delta_I I_3}\frac{\delta_B}{\varrho_B}\left(\frac{\varrho_B\delta_I\delta_U\nu\zeta_3}{\delta_B\delta_S\varrho_U}-1\right)B\\
&+\frac{\zeta_1\delta_A E_3}{\kappa A_3\Psi(A)}\left(\Psi(A)-\Psi(A_3)\right)(A_3-A)-(a+\delta_L)L_3\frac{\Psi(A_3)}{\Psi(A)}\\
&+\frac{a+\delta_L}{\zeta_1}L_3\int_0^{h_1}\chi_1(\tau)\ln\left(\frac{\Psi(A_\tau)E_\tau S_\tau}{\Psi(A)ES}\right)d\tau+\frac{a+\delta_L}{\zeta_2}L_3\int_0^{h_2}\chi_2(\tau)\\
&\times\ln\left(\frac{L_\tau}{L}\right)d\tau+\frac{a+\delta_L}{\zeta_3}L_3\int_0^{h_3}\chi_3(\tau)\ln\left(\frac{I_\tau}{I}\right)d\tau.
\end{aligned}
$$

Using the equalities given by (5.1) in case of $k=3$, we get

$$
\begin{aligned}
\frac{d\mathcal{G}_3}{dt}&=-\delta_E\zeta_1\frac{(E-E_3)^2}{E}-(a+\delta_L)L_3\left[\Phi\left(\frac{E_3}{E}\right)+\frac{1}{\zeta_1}\int_0^{h_1}\chi_1(\tau)\right.\\
&\times\Phi\left(\frac{\Psi(A_\tau)E_\tau S_\tau L_3}{\Psi(A_3)E_3S_3L}\right)d\tau+\frac{1}{\zeta_2}\int_0^{h_2}\chi_2(\tau)\Phi\left(\frac{L_\tau I_3}{L_3 I}\right)d\tau\\
&\left.+\frac{1}{\zeta_3}\int_0^{h_3}\chi_3(\tau)\Phi\left(\frac{I_\tau S_3}{I_3 S}\right)d\tau+\Phi\left(\frac{\Psi(A_3)}{\Psi(A)}\right)\right]\\
&+\left[\frac{\zeta_1\delta_A E_3}{\kappa A_3\Psi(A)}+\frac{\zeta_1\eta SE_3}{A_3}\right]\left(\Psi(A)-\Psi(A_3)\right)(A_3-A)\\
&+\frac{\gamma_B(a+\delta_L)L_3}{\nu\zeta_3\delta_I I_3}\frac{\delta_B}{\varrho_B}\left(\frac{\mathfrak{R}_1}{\mathfrak{R}_3}-1\right)B.
\end{aligned}
$$

Since $\mathfrak{R}_2>1$ and $\mathfrak{R}_1\leq\mathfrak{R}_3$, we get $\frac{d\mathcal{G}_3}{dt}\leq 0$ for all $E,L,I,S,A,B>0$. Further, $\frac{d\mathcal{G}_3}{dt}=0$ when $E=E_3$, $L=L_3$, $I=I_3$, $S=S_3$, $A=A_3$ and $B=0$. Solutions of system (2.1)-(2.7) converge to $\tilde{\Omega}_3$ where $L=L_3$ and $I=I_3$. Then $\dot{I}=0$, and (2.3) provides

$$0=\dot{I}=a\zeta_2L_3-\delta_I I_3-\gamma_U I_3 U\Longrightarrow U=U_3,\ \text{for all } t.$$

Therefore, $\tilde{\Omega}_3 = \{\Delta_3\}$. Applying LIP, we get $\Delta_3$ is G.A.S. □

**Theorem 5.** Suppose that $\Re_1 > \Re_3 > 1$, then $\Delta_4$ is G.A.S.

**Proof.** Consider

$$\begin{aligned}
\mathcal{G}_4 &= \zeta_1 E_4 \Phi\left(\frac{E}{E_4}\right) + L_4 \Phi\left(\frac{L}{L_4}\right) + \frac{a+\delta_L}{a\zeta_2} I_4 \Phi\left(\frac{I}{I_4}\right) \\
&+ \left(\frac{a+\delta_L}{a\nu\zeta_2\zeta_3} + \frac{\gamma_U(a+\delta_L)U_4}{a\nu\zeta_2\zeta_3\delta_I}\right) S_4 \Phi\left(\frac{S}{S_4}\right) + \frac{\zeta_1 E_4}{\kappa A_4}\left(A - A_4 - \int_{A_4}^{A} \frac{\Psi(A_4)}{\Psi(\xi)} d\xi\right) \\
&+ \left(\frac{\gamma_B(a+\delta_L)}{a\nu\zeta_2\zeta_3\varrho_B} + \frac{\gamma_B\gamma_U(a+\delta_L)U_4}{a\nu\zeta_2\zeta_3\delta_I\varrho_B}\right) B_4 \Phi\left(\frac{B}{B_4}\right) + \frac{\gamma_U(a+\delta_L)}{\varrho_U a\zeta_2} U_4 \Phi\left(\frac{U}{U_4}\right) \\
&+ \eta\Psi(A_4)E_4S_4 \int_0^{h_1} \chi_1(\tau) \int_{t-\tau}^{t} \Phi\left(\frac{\Psi(A(s))E(s)S(s)}{\Psi(A_4)E_4S_4}\right) ds d\tau \\
&+ \frac{a+\delta_L}{\zeta_2} L_4 \int_0^{h_2} \chi_2(\tau) \int_{t-\tau}^{t} \Phi\left(\frac{L(s)}{L_4}\right) ds d\tau \\
&+ \left(\frac{(a+\delta_L)\delta_I}{a\zeta_2\zeta_3} + \frac{\gamma_U(a+\delta_L)U_4}{a\zeta_2\zeta_3}\right) I_4 \int_0^{h_3} \chi_3(\tau) \int_{t-\tau}^{t} \Phi\left(\frac{I(s)}{I_4}\right) ds d\tau.
\end{aligned}$$

We note that, $\mathcal{G}_4(E, L, I, S, A, B, U) > 0$ for all $E, L, I, S, A, B, U > 0$ and $\mathcal{G}_4(E_4, L_4, I_4, S_4, A_4, B_4, U_4) = 0$. We calculate $\frac{d\mathcal{G}_4}{dt}$ as:

$$\begin{aligned}
\frac{d\mathcal{G}_4}{dt} &= \zeta_1\left(1 - \frac{E_4}{E}\right)\dot{E} + \left(1 - \frac{L_4}{L}\right)\dot{L} + \frac{a+\delta_L}{a\zeta_2}\left(1 - \frac{I_4}{I}\right)\dot{I} \\
&+ \left(\frac{a+\delta_L}{a\nu\zeta_2\zeta_3} + \frac{\gamma_U(a+\delta_L)U_4}{a\nu\zeta_2\zeta_3\delta_I}\right)\left(1 - \frac{S_4}{S}\right)\dot{S} + \frac{\zeta_1 E_4}{\kappa A_4}\left(1 - \frac{\Psi(A_4)}{\Psi(A)}\right)\dot{A} \\
&+ \left(\frac{\gamma_B(a+\delta_L)}{a\nu\zeta_2\zeta_3\varrho_B} + \frac{\gamma_B\gamma_U(a+\delta_L)U_4}{a\nu\zeta_2\zeta_3\delta_I\varrho_B}\right)\left(1 - \frac{B_4}{B}\right)\dot{B} + \frac{\gamma_U(a+\delta_L)}{\varrho_U a\zeta_2}\left(1 - \frac{U_4}{U}\right)\dot{U} \\
&+ \eta\Psi(A_4)E_4S_4 \frac{d}{dt}\int_0^{h_1} \chi_1(\tau) \int_{t-\tau}^{t} \Phi\left(\frac{\Psi(A(s))E(s)S(s)}{\Psi(A_4)E_4S_4}\right) ds d\tau \\
&+ \frac{a+\delta_L}{\zeta_2} L_4 \frac{d}{dt}\int_0^{h_2} \chi_2(\tau) \int_{t-\tau}^{t} \Phi\left(\frac{L(s)}{L_4}\right) ds d\tau \\
&+ \left(\frac{(a+\delta_L)\delta_I}{a\zeta_2\zeta_3} + \frac{\gamma_U(a+\delta_L)U_4}{a\zeta_2\zeta_3}\right) I_4 \frac{d}{dt}\int_0^{h_3} \chi_3(\tau) \int_{t-\tau}^{t} \Phi\left(\frac{I(s)}{I_4}\right) ds d\tau.
\end{aligned}$$

From system (2.1)-(2.7) we get

$$\begin{aligned}
\frac{d\mathcal{G}_4}{dt} &= \zeta_1\left(1 - \frac{E_4}{E}\right)\left[\lambda_E - \eta\Psi(A)ES - \delta_E E\right] \\
&+ \left(1 - \frac{L_4}{L}\right)\left[\eta\int_0^{h_1} \chi_1(\tau)\Psi(A_\tau)E_\tau S_\tau d\tau - (a+\delta_L)L\right] \\
&+ \frac{a+\delta_L}{a\zeta_2}\left(1 - \frac{I_4}{I}\right)\left[a\int_0^{h_2} \chi_2(\tau)L_\tau d\tau - \delta_I I - \gamma_U UI\right] \\
&+ \left(\frac{a+\delta_L}{a\nu\zeta_2\zeta_3} + \frac{\gamma_U(a+\delta_L)U_4}{a\nu\zeta_2\zeta_3\delta_I}\right)\left(1 - \frac{S_4}{S}\right)\left[\delta_I\nu\int_0^{h_3} \chi_3(\tau)I_\tau d\tau - \delta_S S - \gamma_B SB\right]
\end{aligned}$$

$$
\begin{aligned}
&+ \frac{\zeta_1 E_4}{\kappa A_4}\left(1-\frac{\Psi(A_4)}{\Psi(A)}\right)[\lambda_A - \kappa\eta\Psi(A)SA - \delta_A A] \\
&+ \left(\frac{\gamma_B(a+\delta_L)}{av\zeta_2\zeta_3\varrho_B} + \frac{\gamma_B\gamma_U(a+\delta_L)U_4}{av\zeta_2\zeta_3\delta_I\varrho_B}\right)\left(1-\frac{B_4}{B}\right)[\varrho_B SB - \delta_B B] \\
&+ \frac{\gamma_U(a+\delta_L)}{\varrho_U a\zeta_2}\left(1-\frac{U_4}{U}\right)[\varrho_U IU - \delta_U U] + \eta\Psi(A_4)E_4S_4\int_0^{h_1}\chi_1(\tau)\left[\frac{\Psi(A)ES}{\Psi(A_4)E_4S_4}\right. \\
&\left. -\frac{\Psi(A_\tau)E_\tau S_\tau}{\Psi(A_4)E_4S_4} + \ln\left(\frac{\Psi(A_\tau)E_\tau S_\tau}{\Psi(A)ES}\right)\right]d\tau \\
&+ \frac{a+\delta_L}{\zeta_2}L_4\int_0^{h_2}\chi_2(\tau)\left[\frac{L}{L_4} - \frac{L_\tau}{L_4} + \ln\left(\frac{L_\tau}{L}\right)\right]d\tau \\
&+ \left(\frac{(a+\delta_L)\delta_I}{a\zeta_2\zeta_3} + \frac{\gamma_U(a+\delta_L)U_4}{a\zeta_2\zeta_3}\right)I_4\int_0^{h_3}\chi_3(\tau)d\tau\left[\frac{I}{I_4} - \frac{I_\tau}{I_4} + \ln\left(\frac{I_\tau}{I}\right)\right]d\tau.
\end{aligned}
$$

Collecting terms we get

$$
\begin{aligned}
\frac{d\mathcal{G}_4}{dt} &= \zeta_1\left(1-\frac{E_4}{E}\right)[\lambda_E - \delta_E E] + \eta\zeta_1\Psi(A)E_4S \\
&- \eta\int_0^{h_1}\chi_1(\tau)\Psi(A_\tau)E_\tau S_\tau\frac{L_4}{L}d\tau + (a+\delta_L)L_4 \\
&- \frac{a+\delta_L}{\zeta_2}\int_0^{h_2}\chi_2(\tau)L_\tau\frac{I_4}{I}d\tau + \frac{(a+\delta_L)\delta_I}{a\zeta_2}I_4 + \frac{\gamma_U(a+\delta_L)}{a\zeta_2}I_4U \\
&- \left(\frac{a+\delta_L}{av\zeta_2\zeta_3} + \frac{\gamma_U(a+\delta_L)U_4}{av\zeta_2\zeta_3\delta_I}\right)\delta_S S - \left(\frac{(a+\delta_L)\delta_I}{a\zeta_2\zeta_3} + \frac{\gamma_U(a+\delta_L)U_4}{a\zeta_2\zeta_3}\right) \\
&\times\int_0^{h_3}\chi_3(\tau)I_\tau\frac{S_4}{S}d\tau + \left(\frac{a+\delta_L}{av\zeta_2\zeta_3} + \frac{\gamma_U(a+\delta_L)U_4}{av\zeta_2\zeta_3\delta_I}\right)\delta_S S_4 \\
&+ \left(\frac{a+\delta_L}{av\zeta_2\zeta_3} + + \frac{\gamma_U(a+\delta_L)U_4}{av\zeta_2\zeta_3\delta_I}\right)\gamma_B S_4 B + \frac{\zeta_1E_4}{\kappa A_4}\left(1-\frac{\Psi(A_4)}{\Psi(A)}\right)[\lambda_A - \delta_A A] \\
&- \frac{\zeta_1E_4}{A_4}\left(\Psi(A) - \Psi(A_4)\right)\eta SA + \left(\frac{\gamma_B(a+\delta_L)}{av\varrho_B\zeta_2\zeta_3} - \frac{\gamma_U\gamma_B(a+\delta_L)U_4}{av\varrho_B\zeta_2\zeta_3\delta_I}\right)\delta_B B \\
&- \left(\frac{\gamma_B(a+\delta_L)}{av\zeta_2\zeta_3} + \frac{\gamma_U\gamma_B(a+\delta_L)U_4}{av\zeta_2\zeta_3\delta_I}\right)SB_4 + \left(\frac{\gamma_B(a+\delta_L)}{av\varrho_B\zeta_2\zeta_3} + \frac{\gamma_U\gamma_B(a+\delta_L)U_4}{av\varrho_B\zeta_2\zeta_3\delta_I}\right)\delta_B B_4 \\
&- \frac{\gamma_U(a+\delta_L)}{\varrho_U a\zeta_2}\delta_U U + \frac{\gamma_U(a+\delta_L)\delta_U}{\varrho_U a\zeta_2}U_4 + \eta\Psi(A_4)E_4S_4\int_0^{h_1}\chi_1(\tau) \\
&\times\ln\left(\frac{\Psi(A_\tau)E_\tau S_\tau}{\Psi(A)ES}\right)d\tau + \frac{a+\delta_L}{\zeta_2}L_4\int_0^{h_2}\chi_2(\tau)\ln\left(\frac{L_\tau}{L}\right)d\tau \\
&+ \left(\frac{(a+\delta_L)\delta_I}{a\zeta_2\zeta_3} + \frac{\gamma_U(a+\delta_L)U_4}{a\zeta_2\zeta_3}\right)I_4\int_0^{h_3}\chi_3(\tau)\ln\left(\frac{I_\tau}{I}\right)d\tau.
\end{aligned}
$$

Using the equilibrium condition for $\Delta_4$:

$$
\lambda_E = \eta\Psi(A_4)E_4S_4 + \delta_E E_4, \quad (a+\delta_L)L_4 = \eta\zeta_1\Psi(A_4)E_4S_4, \quad I_4 = \frac{\delta_U}{\varrho_U}, \quad S_4 = \frac{\delta_B}{\varrho_B}
$$

$$a\zeta_2 L_4 = \delta_I I_4 + \gamma_U I_4 U_4, \quad \delta_S S_4 = \delta_I \nu \zeta_3 I_4 - \gamma_B S_4 B_4, \quad \lambda_A = \kappa\eta\Psi(A_4) S_4 A_4 + \delta_A A_4,$$

we obtain,

$$\begin{aligned}\frac{d\mathcal{G}_4}{dt} &= -\delta_E \zeta_1 \frac{(E-E_4)^2}{E} + 5(a+\delta_L)L_4 - (a+\delta_L)L_4 \frac{E_4}{E} + \zeta_1 \eta \Psi(A) E_4 S \\ &- \frac{a+\delta_L}{\zeta_1} L_4 \int_0^{h_1} \chi_1(\tau) \frac{\Psi(A_\tau) E_\tau S_\tau L_4}{\Psi(A_4) E_4 S_4 L} d\tau - \frac{a+\delta_L}{\zeta_2} L_4 \int_0^{h_2} \chi_2(\tau) \frac{L_\tau I_4}{L_4 I} d\tau \\ &- \eta \zeta_1 \Psi(A_4) E_4 S - \frac{a+\delta_L}{\zeta_3} L_4 \int_0^{h_3} \chi_3(\tau) \frac{I_\tau S_4}{I_4 S} d\tau \\ &+ \frac{\zeta_1 \delta_A E_4}{\kappa A_4 \Psi(A)} \left(\Psi(A) - \Psi(A_4)\right)(A_4 - A) - (a+\delta_L) L_4 \frac{\Psi(A_4)}{\Psi(A)} \\ &- \frac{\zeta_1 E_4}{A_4} \eta S A \left(\Psi(A) - \Psi(A_4)\right) + \frac{a+\delta_L}{\zeta_1} L_4 \int_0^{h_1} \chi_1(\tau) \\ &\times \ln\left(\frac{\Psi(A_\tau) E_\tau S_\tau}{\Psi(A) E S}\right) d\tau + \frac{a+\delta_L}{\zeta_2} L_4 \int_0^{h_2} \chi_2(\tau) \ln\left(\frac{L_\tau}{L}\right) d\tau \\ &+ \frac{a+\delta_L}{\zeta_3} L_4 \int_0^{h_3} \chi_3(\tau) \ln\left(\frac{I_\tau}{I}\right) d\tau\end{aligned}$$

It follows that

$$\begin{aligned}\frac{d\mathcal{G}_4}{dt} &= -\delta_E \zeta_1 \frac{(E-E_4)^2}{E} + 5(a+\delta_L)L_4 - (a+\delta_L)L_4 \frac{E_4}{E} + \zeta_1 \eta E_4 S (\Psi(A) - \Psi(A_4)) \\ &- \frac{a+\delta_L}{\zeta_1} L_4 \int_0^{h_1} \chi_1(\tau) \frac{\Psi(A_\tau) E_\tau S_\tau L_4}{\Psi(A_4) E_4 S_4 L} d\tau - \frac{a+\delta_L}{\zeta_2} L_4 \int_0^{h_2} \chi_2(\tau) \frac{L_\tau I_4}{L_4 I} d\tau \\ &- \frac{a+\delta_L}{\zeta_3} L_4 \int_0^{h_3} \chi_3(\tau) \frac{I_\tau S_4}{I_4 S} d\tau + \frac{\zeta_1 \delta_A E_4}{\kappa A_4 \Psi(A)} \left(\Psi(A) - \Psi(A_4)\right)(A_4 - A) \\ &- (a+\delta_L) L_4 \frac{\Psi(A_4)}{\Psi(A)} - \frac{\zeta_1 E_4}{A_4} \eta S A \left(\Psi(A) - \Psi(A_4)\right) \\ &+ \frac{a+\delta_L}{\zeta_1} L_4 \int_0^{h_1} \chi_1(\tau) \ln\left(\frac{\Psi(A_\tau) E_\tau S_\tau}{\Psi(A) E S}\right) d\tau + \frac{a+\delta_L}{\zeta_2} L_4 \int_0^{h_2} \chi_2(\tau) \\ &\times \ln\left(\frac{L_\tau}{L}\right) d\tau + \frac{a+\delta_L}{\zeta_3} L_4 \int_0^{h_3} \chi_3(\tau) \ln\left(\frac{I_\tau}{I}\right) d\tau.\end{aligned}$$

Using the equalities given by (5.1) in case of $k = 4$, we get

$$\begin{aligned}\frac{d\mathcal{G}_4}{dt} &= -\delta_E \zeta_1 \frac{(E-E_4)^2}{E} - (a+\delta_L) L_4 \left[\Phi\left(\frac{E_4}{E}\right) + \frac{1}{\zeta_1} \int_0^{h_1} \chi_1(\tau) \right. \\ &\times \Phi\left(\frac{\Psi(A_\tau) E_\tau S_\tau L_4}{\Psi(A_4) E_4 S_4 L}\right) d\tau + \frac{1}{\zeta_2} \int_0^{h_2} \chi_2(\tau) \Phi\left(\frac{L_\tau I_4}{L_4 I}\right) d\tau \\ &+ \left. \frac{1}{\zeta_3} \int_0^{h_3} \chi_3(\tau) \Phi\left(\frac{I_\tau S_4}{I_4 S}\right) d\tau + \Phi\left(\frac{\Psi(A_4)}{\Psi(A)}\right)\right] \\ &+ \left[\frac{\zeta_1 \delta_A E_4}{\kappa A_4 \Psi(A)} + \frac{\zeta_1 \eta S E_4}{A_4}\right] \left(\Psi(A) - \Psi(A_4)\right)(A_4 - A).\end{aligned}$$

Since $\mathfrak{R}_1 > \mathfrak{R}_3 > 1$, we get $\frac{d\mathcal{G}_4}{dt} \le 0$ for all $E, L, I, S, A > 0$. Further, $\frac{d\mathcal{G}_4}{dt} = 0$ when $E = E_4$, $L = L_4$, $I = I_4$, $S = S_4$ and $A = A_4$. Solutions of system (2.1)-(2.7) converge to $\tilde{\Omega}_4$ which has $L = L_4$, $I = I_4$ and $S = S_4$. Then $\dot{I} = 0$, $\dot{S} = 0$ and Eqs (2.3)-(2.4) provide

$$0 = \dot{I} = a\zeta_2 L_4 - \delta_I I_4 - \gamma_U I_4 U \Longrightarrow U = U_4, \text{ for all } t.$$

$$0 = \dot{S} = \delta_I \nu \zeta_3 I_4 - \delta_S S_4 - \gamma_B S_4 B \Longrightarrow B = B_4, \text{ for all } t.$$

Therefore, $\tilde{\Omega}_4 = \{\Delta_4\}$. Applying LIP, we get $\Delta_4$ is G.A.S. □

Now we able to summarize the existence and stability conditions of the model's equilibria (see Table 1):

Table 1. Conditions of existence and global stability of equilibria.

| Equilibrium point | Existence conditions | Global stability conditions |
|---|---|---|
| $\Delta_0 = (E_0, 0, 0, 0, A_0, 0, 0)$ | None | $\mathfrak{R}_0 \le 1$ |
| $\Delta_1 = (E_1, L_1, I_1, S_1, A_1, 0, 0)$ | $\mathfrak{R}_0 > 1$ | $\mathfrak{R}_1 \le 1 < \mathfrak{R}_0$ and $\mathfrak{R}_2 \le 1$ |
| $\Delta_2 = (E_2, L_2, I_2, S_2, A_2, B_2, 0)$ | $\mathfrak{R}_1 > 1$ | $\mathfrak{R}_1 > 1$ and $\mathfrak{R}_3 \le 1$ |
| $\Delta_3 = (E_3, L_3, I_3, S_3, A_3, 0, U_3)$ | $\mathfrak{R}_2 > 1$ | $\mathfrak{R}_2 > 1$ and $\mathfrak{R}_1 \le \mathfrak{R}_3$ |
| $\Delta_4 = (E_4, L_4, I_4, S_4, A_4, B_4, U_4)$ | $\mathfrak{R}_1 > \mathfrak{R}_3 > 1$ | $\mathfrak{R}_1 > \mathfrak{R}_3 > 1$ |

## 6. Numerical simulations

In this section, we conduct numerical simulation for model (2.1)-(2.7) to illustrate the theoretical findings. We perform sensitivity analysis for the model. We demonstrate the effect of antibody and CTL responses and time delays on the SARS-CoV-2 dynamics. Let us take a particular form of the probability distributed functions as.

$$f_i(\tau) = F(\tau - \tau_i), \; i = 1, 2, 3.$$

where $F(.)$ is the Dirac delta function. When $h_i \to \infty$, $i = 1, 2, 3$, we have

$$\int_0^\infty f_i(\tau) d\tau = 1 \;\text{ and }\; \int_0^\infty F(\tau - \tau_i) e^{-\alpha_i \tau} d\tau = e^{-\alpha_i \tau_i}, \; i = 1, 2, 3.$$

Moreover

$$\int_0^\infty F(\tau - \tau_1) e^{-\alpha_1 \tau} \Psi(A_\tau) E_\tau S_\tau d\tau = e^{-\alpha_1 \tau_1} \Psi(A_{\tau_1}) E_{\tau_1} S_{\tau_1},$$
$$\int_0^\infty F(\tau - \tau_2) e^{-\alpha_2 \tau} L_\tau d\tau = e^{-\alpha_2 \tau_2} L_{\tau_2},$$
$$\int_0^\infty F(\tau - \tau_3) e^{-\alpha_3 \tau} I_\tau d\tau = e^{-\alpha_3 \tau_3} I_{\tau_3}.$$

Then, model (2.1)-(2.7) becomes

$$\begin{cases} \dot{E} = \lambda_E - \eta\Psi(A)ES - \delta_E E, \\ \dot{L} = \eta e^{-\alpha_1\tau_1}\Psi(A_{\tau_1})E_{\tau_1}S_{\tau_1} - (a+\delta_L)L, \\ \dot{I} = e^{-\alpha_2\tau_2}aL_{\tau_2} - \delta_I I - \gamma_U IU, \\ \dot{S} = \delta_I \nu e^{-\alpha_3\tau_3}I_{\tau_3} - \delta_S S - \gamma_B SB, \\ \dot{A} = \lambda_A - \kappa\eta\Psi(A)AS - \delta_A A, \\ \dot{B} = \varrho_B SB - \delta_B B, \\ \dot{U} = \varrho_U UI - \delta_U U. \end{cases} \tag{6.1}$$

MATLAB's dde23 solver will be used to numerically solve the DDEs system (6.1). Table 2 contains the values of the parameters of model (6.1). We choose the function $\Psi$ as $\Psi(A) = \frac{A^n}{\mathcal{A}_s^n + A^n}$. For $n = 1$ we have

$$\Re_0 = \frac{\eta a\nu e^{-\alpha_1\tau_1-\alpha_2\tau_2-\alpha_3\tau_3}\Psi(A_0)E_0}{(a+\delta_L)\delta_S} = \frac{\eta a\nu e^{-\alpha_1\tau_1-\alpha_2\tau_2-\alpha_3\tau_3}\lambda_E\lambda_A}{(a+\delta_L)\delta_S(\mathcal{A}_s\delta_E\delta_A + \lambda_A\delta_E)}. \tag{6.2}$$

Table 2. Model parameters.

| Parameter | Value | Parameter | Value |
|---|---|---|---|
| $\lambda_E$ | 5 | $\varrho_U$ | Varied |
| $\delta_E$ | 0.1 | $\delta_I$ | 0.1 |
| $\eta$ | Varied | $\mathcal{A}_s$ | 50 |
| $\delta_S$ | 0.1 | $\alpha_1$ | 1 |
| $\nu$ | 20 | $\alpha_2$ | 1 |
| $\delta_L$ | 0.1 | $\alpha_3$ | 1 |
| $\gamma_B$ | 0.04 | $\tau_1$ | Varied |
| $\lambda_A$ | 1 | $\tau_2$ | Varied |
| $\kappa$ | 0.3 | $\tau_3$ | Varied |
| $a$ | 0.2 | $\delta_U$ | 0.1 |
| $n$ | 1 | $\delta_A$ | 0.1 |
| $\varrho_B$ | Varied | $\delta_B$ | 0.1 |
| $\gamma_U$ | 0.04 | | |

6.1. **Stability of the equilibria.** To show the global stability of the equilibria of system (6.1) we take three initials as:

$$C1 : (E(\theta), L(\theta), I(\theta), S(\theta), A(\theta), B(\theta), U(\theta)) = (20, 0.9, 1, 10, 8, 2, 0.1),$$

$$C2 : (E(\theta), L(\theta), I(\theta), S(\theta), A(\theta), B(\theta), U(\theta)) = (30, 1.5, 2, 20, 8.5, 2.6, 0.5),$$

$$C3 : (E(\theta), L(\theta), I(\theta), S(\theta), A(\theta), B(\theta), U(\theta)) = (40, 2.1, 3, 30, 9, 3.2, 0.9),$$

where $\theta \in [-\max\{\tau_1, \tau_2, \tau_3\}, 0]$. Here, we set $\tau_i = 0.7,\ i = 1, 2, 3$ and select the values of $\eta$, $\varrho_B$ and $\varrho_U$ as:

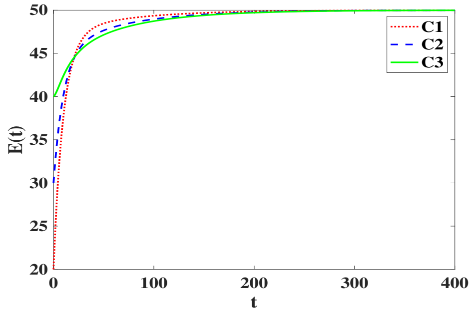
**State 1 (Stability of $\Delta_0$)*:*** $\eta = 0.005$, $\varrho_B = 0.0003$ and $\varrho_U = 0.02$. These values give $\Re_0 = 0.680313 < 1$. Figure 2 demonstrates that for all starting values, the trajectories lead to the equilibrium $\Delta_0 = (50, 0, 0, 0, 10, 0, 0)$. This demonstrates the statement of Theorem 1's that $\Delta_0$ is G.A.S. In this state, the viruses are eventually cleared.

**State 2 (Stability of $\Delta_1$)*:*** $\eta = 0.02$, $\varrho_B = 0.0003$ and $\varrho_U = 0.02$. With such selection we obtain $\Re_1 = 0.203822 < 1 < 2.72125 = \Re_0$ and $\Re_2 = 0.916236 < 1$. The equilibrium point $\Delta_1$ exists with $\Delta_1 = (23.538, 4.3802, 4.3503, 43.2059, 7.4779, 0, 0)$. Figure 3 clearly demonstrates that the trajectories eventually trend to $\Delta_1$ for all initials, which is consistent with Theorem 2. This is the situation of an infected person when both antibody and CTL responses are not engaged.

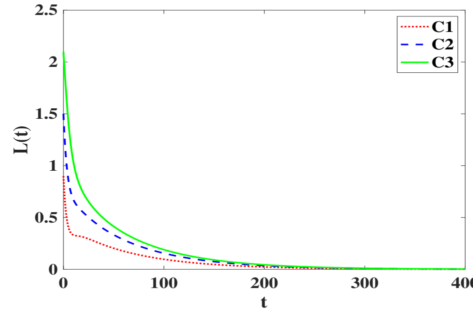
**State 3 (Stability of $\Delta_2$)*:*** $\eta = 0.02$, $\varrho_B = 0.011$ and $\varrho_U = 0.02$. This gives $\Re_1 = 1.98082 > 1$ and $\Re_3 = 0.362631 < 1$ The numerical results show that, $\Delta_2 = (38.9709, 1.8256, 1.8132, 9.0909, 9.2174, 2.4521, 0)$ exists. Figure 4 shows that, for all initials, the trajectories eventually converge to $\Delta_2$, which is consistent with Theorem 3. This case depicts a person who has SARS-CoV-2 infection and only active antibody response.

**State 4 (Stability of $\Delta_3$ )*:*** $\eta = 0.02$, $\varrho_B = 0.0003$ and $\varrho_U = 0.2$. With such selection we obtain $\Re_2 = 2.25768 > 1$ and $\Re_1 = 0.203822 < 13.6815 = \Re_3$. The equilibrium point $\Delta_3$ exists with $\Delta_3 = (43.1335, 1.1366, 0.5, 4.9659, 9.5442, 0, 3.1442)$. Figure 5 clearly demonstrates that the trajectories eventually trend to $\Delta_3$ for all initials, which is consistent with Theorem 4. This state depicts a person who has SARS-CoV-2 infection and only active CTL response.

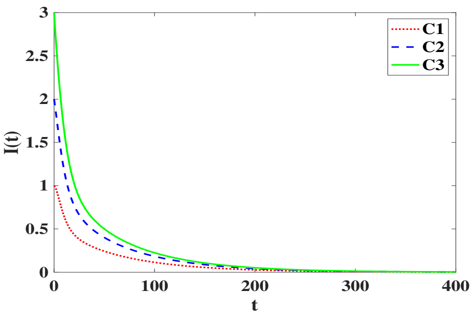
**State 5 (Stability of $\Delta_4$ )*:*** $\eta = 0.02$, $\varrho_B = 0.07$ and $\varrho_U = 0.3$. This gives $\Re_1 = 6.7694 > 1$ and $\Re_3 = 2.9211 > 1$ and then $\Re_1 > \Re_3 > 1$. The numerical results show that, $\Delta_4 = (47.7525, 0.372, 0.3333, 1.4286, 9.8608, 3.2935, 0.2711)$ exists. Figure 6 clearly demonstrates that the trajectories eventually trend to $\Delta_4$ for all initials, which is consistent with Theorem 5. In this situation both antibody and CTL responses are active against the SARS-CoV-2-infection.



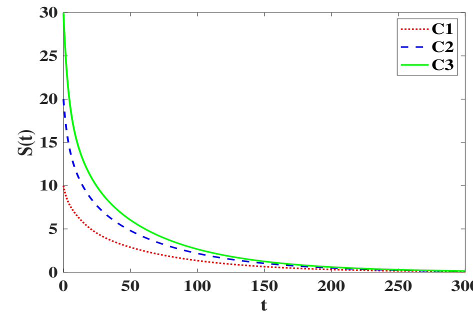

(A) Uninfected epithelial cells



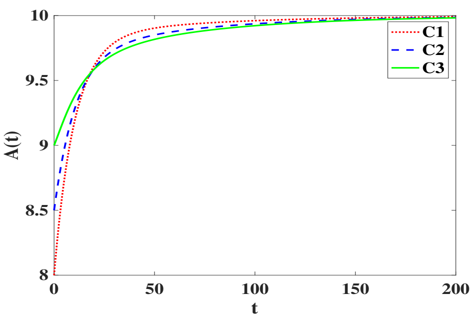

(B) Latently infected epithelial cells



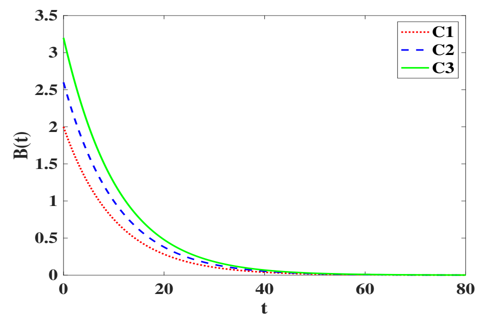

(C) Actively infected epithelial cells



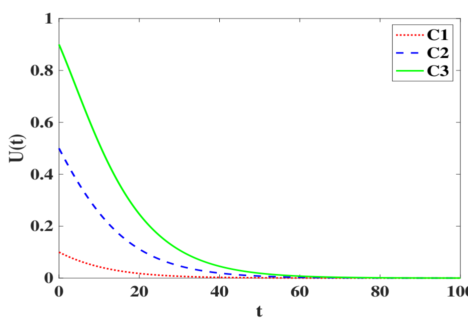

(D) SARS-CoV-2 particles




(E) ACE2 receptors

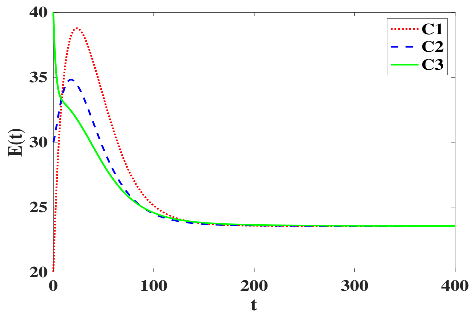



(F) Antibodies

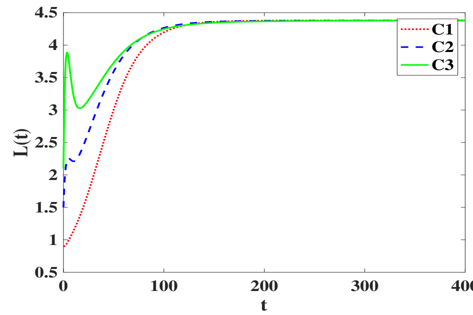



(G) CTLs

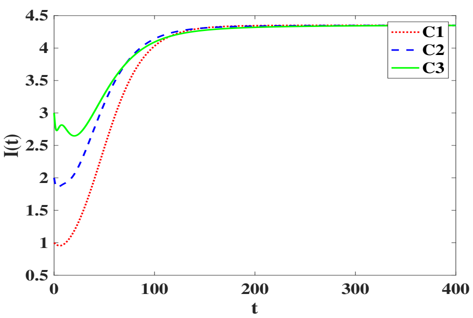
FIGURE 2. Solutions of model (6.1) with initials C1-C3 converge to $\Delta_0 = (50, 0, 0, 0, 10, 0, 0)$ when $\Re_0 \leq 1$ (State 1).



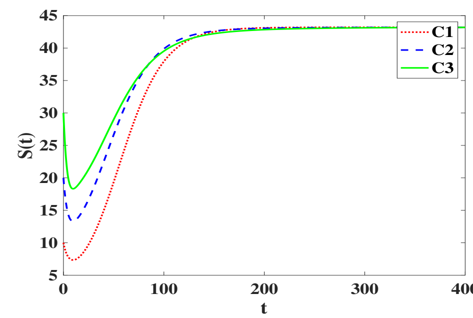

(A) Uninfected epithelial cells



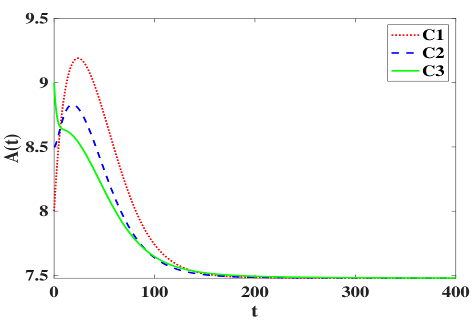

(B) Latently infected epithelial cells



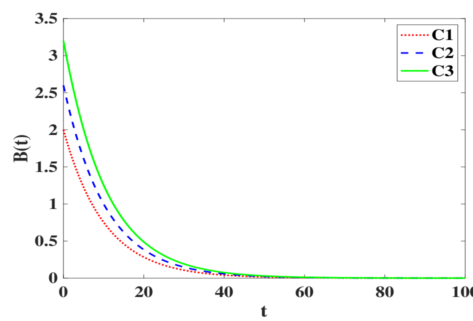

(C) Actively infected epithelial cells



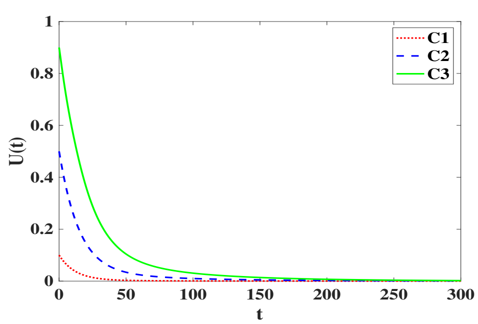

(D) SARS-CoV-2 particles




(E) ACE2 receptors

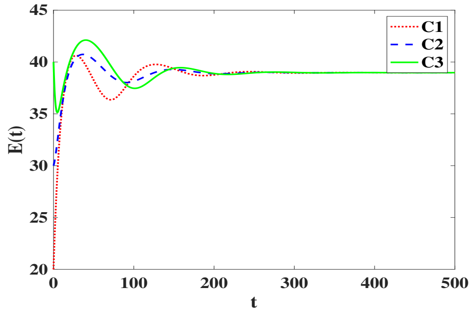



(F) Antibodies

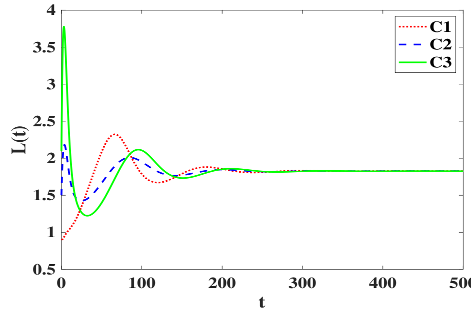



(G) CTLs

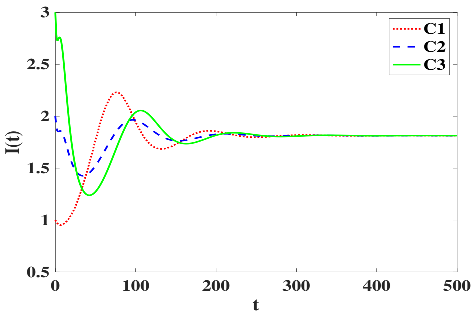
Figure 3. Solutions of model (6.1) with initials C1-C3 converge to $\Delta_1 = (23.538, 4.3802, 4.3503, 43.2059, 7.47793, 0, 0)$ when $\Re_1 \leq 1 < \Re_0$ and $\Re_2 \leq 1$ (State 2).



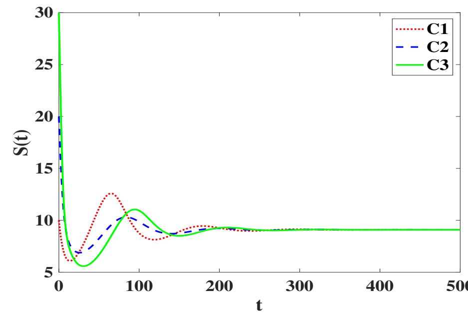

(a) Uninfected epithelial cells



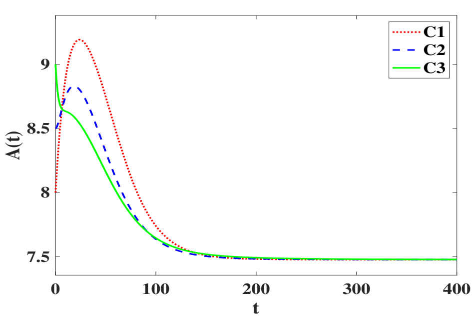

(b) Latently infected epithelial cells



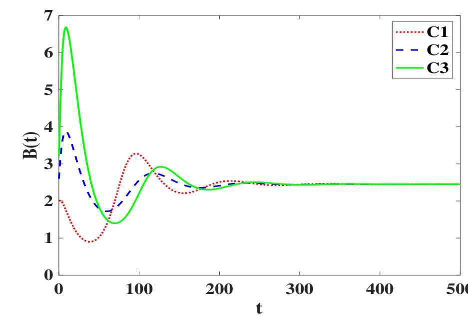

(c) Actively infected epithelial cells



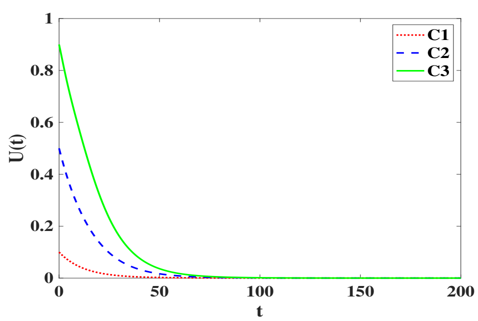

(d) SARS-CoV-2 particles




(e) ACE2 receptors

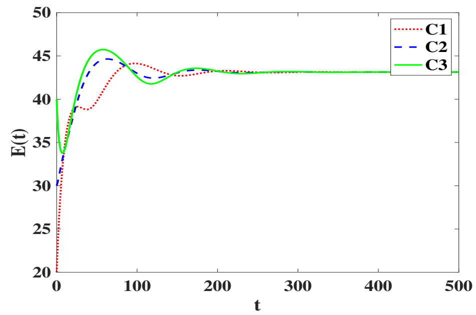



(f) Antibodies

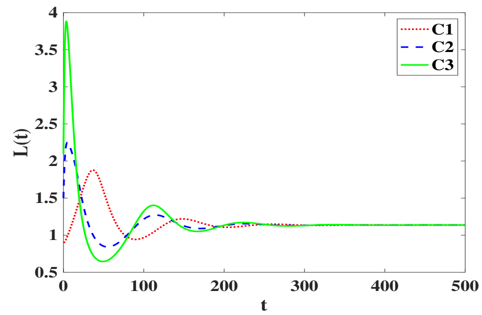



(g) CTLs

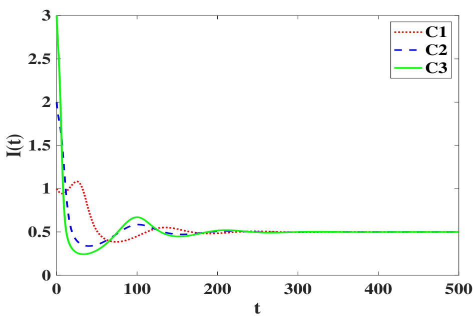
Figure 4. Solutions of model (6.1) with initials C1-C3 converge to $\Delta_2 = (38.9709, 1.8256, 1.8132, 9.0909, 9.2174, 2.4521, 0)$ when $\Re_1 > 1$ and $\Re_3 \leq 1$ (State 3).



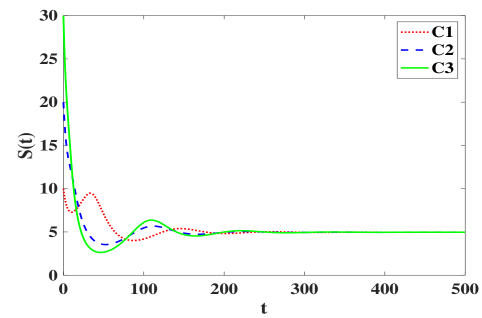

(A) Uninfected epithelial cells



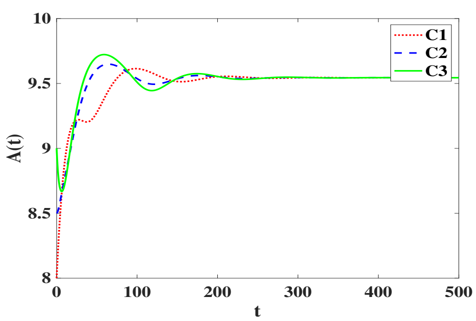

(B) Latently infected epithelial cells



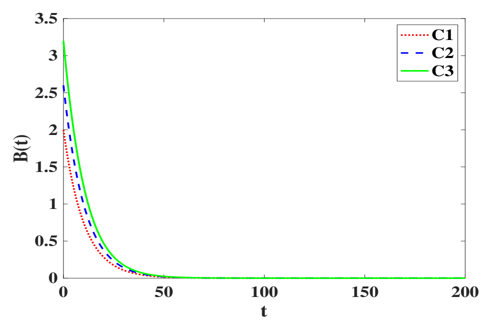

(C) Actively infected epithelial cells



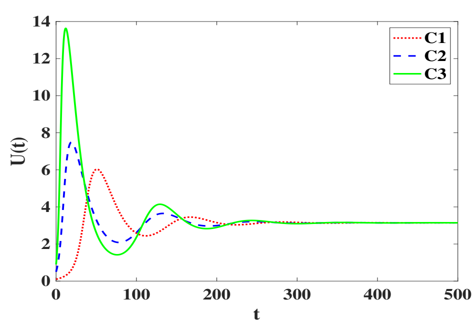

(D) SARS-CoV-2 particles




(E) ACE2 receptors

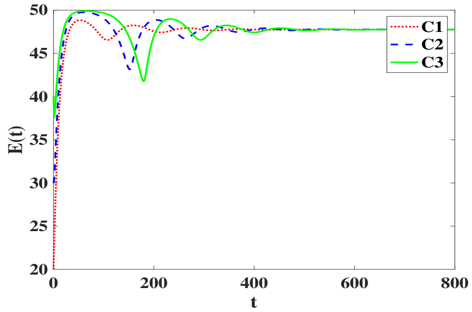



(F) Antibodies

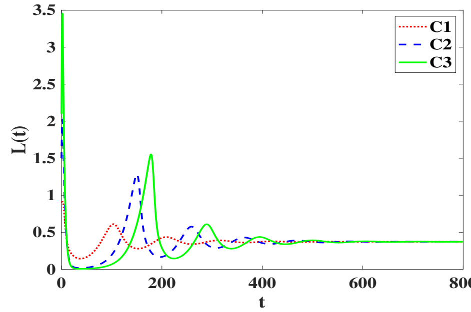



(G) CTLs

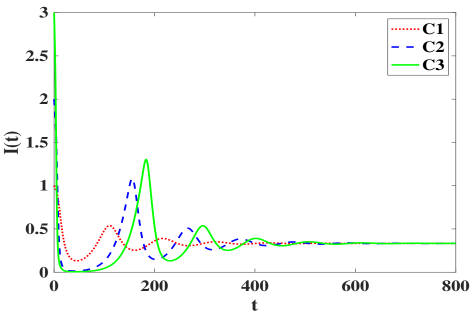
FIGURE 5. Solutions of model (6.1) with initials C1-C3 converge to $\Delta_3 = (43.1335, 1.1366, 0.5, 4.9659, 9.5442, 0, 3.1442)$ when $\Re_2 > 1$ and $\Re_1 \leq \Re_3$(State 4).



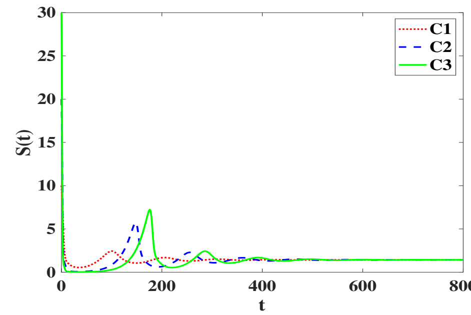

(A) Uninfected epithelial cells



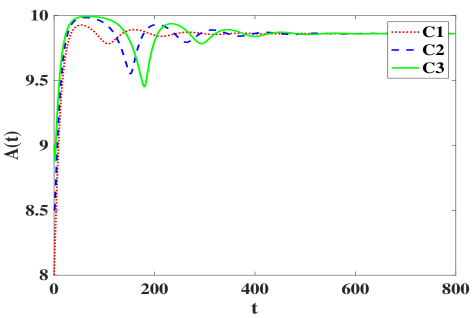

(B) Latently infected epithelial cells



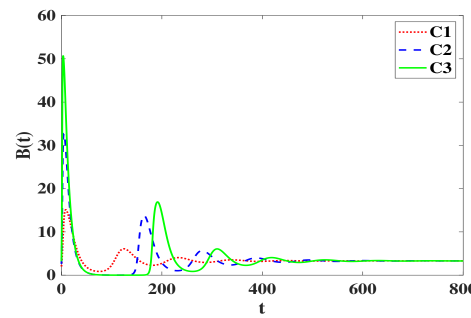

(C) Actively infected epithelial cells



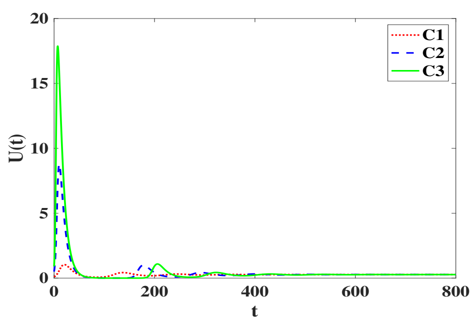

(D) SARS-CoV-2 particles




(E) ACE2 receptors




(F) Antibodies




(G) CTLs

Figure 6. Solutions of model (6.1) with initials C1-C3 converge to $\Delta_4 = (47.7525, 0.372, 0.3333, 1.4286, 9.8608, 3.2935, 0.2711)$ when $\Re_1 > \Re_3 > 1$ (State 5).

6.2. **Impact of the time delay on the SARS-CoV-2 dynamics.** We show the impact of time delays $\tau_1,\ \tau_2$ and $\tau_3$ on solutions of the system as well as stability of $\Delta_0$. We can see from Eq. (6.2) that the parameter $\Re_0$ is decreasing by increasing of the delay parameters $\tau_1,\ \tau_2$ and $\tau_3$ when all other parameters are fixed. Therefore, stability of $\Delta_0$ can significantly be changed based on $\tau_1,\ \tau_2$ and $\tau_3$. Let us fix $\eta = 0.007,\ \varrho_B = 0.0005,\ \varrho_U = 0.01$ and vary $\tau_1,\ \tau_2$ and $\tau_3$ as:

D1: $\tau_1 = \tau_2 = \tau_3 = 0$,
D2: $\tau_1 = \tau_2 = \tau_3 = 0.5$,
D3: $\tau_1 = \tau_2 = \tau_3 = 1$,
D4: $\tau_1 = \tau_2 = \tau_3 = 1.5$.

Further, we consider the initial condition:

$$C4 : (E(\theta), L(\theta), I(\theta), S(\theta), A(\theta), B(\theta), U\theta)) = (25, 5, 5, 100, 8, 2.5, 1.5),$$

where $\theta \in [-\max\{\tau_1, \tau_2, \tau_3\}, 0]$. Assume that $\tau = \tau_1 = \tau_2 = \tau_3$, then $\Re_0$ is given by

$$\Re_0 = \frac{\eta a v e^{-(\alpha_1+\alpha_2+\alpha_3)\tau}\lambda_E\lambda_A}{(a+\delta_L)\delta_S(\mathcal{A}_s\delta_E\delta_A + \lambda_A\delta_E)}.$$

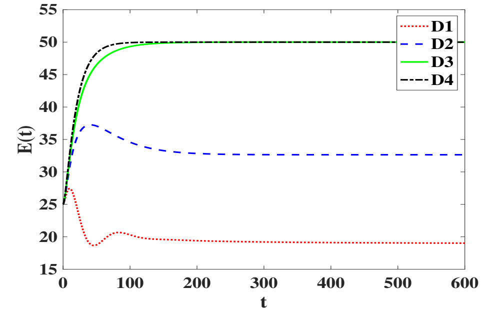
We see that $\Re_0$ is a decreasing function of $\tau$. Let $\tau_{cr}$ be such that $\Re_0(\tau_{cr}) = 1$. Consequently,

$$\Re_0 \leq 1 \text{ for all } \tau \geq \tau_{cr}.$$

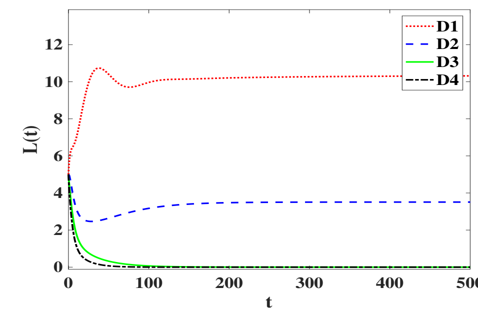
Hence, $\Delta_0$ is G.A.S when $\tau \geq \tau_{cr}$. Using the values of the parameters we obtain, $\tau_{cr} = 0.683757$. Therefore, we have the following cases:

(i) If $\tau \geq \tau_{cr}$, then $\Re_0 \leq 1$ and thus $\Delta_0$ is G.A.S.
(ii) If $\tau < \tau_{cr}$, then $\Re_0 > 1$ and thus $\Delta_0$ will lose its stability. Therefore, sufficiently large time delay can stabilize the system around the equilibrium $\Delta_0$.

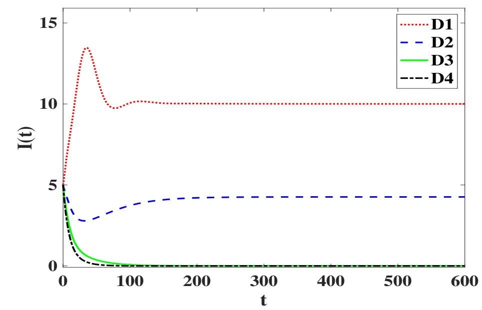
The impact of time delay on the system's trajectories is depicted in Figure 7. It is evident that as $\tau$ increases, the concentrations of uninfected epithelial cells and ACE2 receptor increase, whereas those of latently and actively infected cells, SARS-CoV-2 particles, antibodies and CTLs decrease.



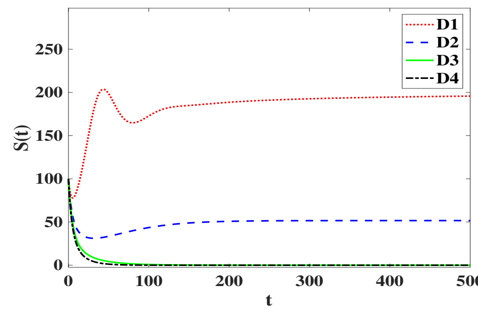

(A) Uninfected epithelial cells



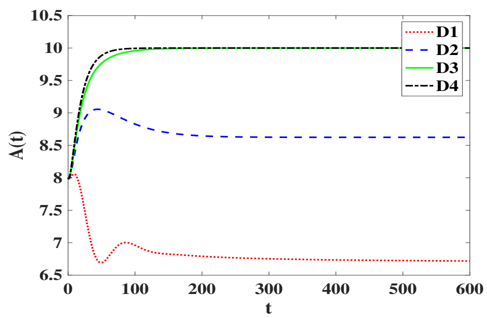

(B) Latently infected epithelial cells



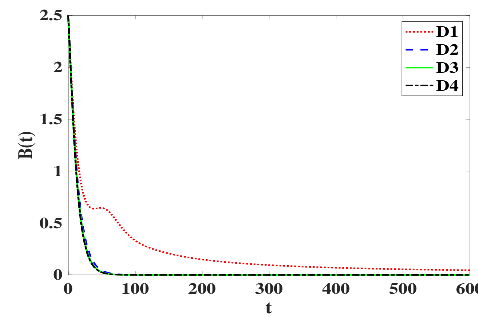

(C) Actively infected epithelial cells



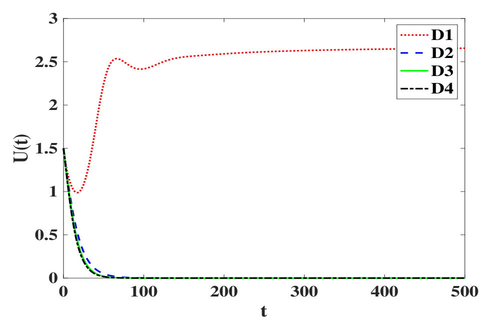

(D) SARS-CoV-2 particles




(E) ACE2 receptors




(F) Antibodies




(G) CTLs

Figure 7. Solutions of model (6.1) under the impact of the time delays $\tau$.

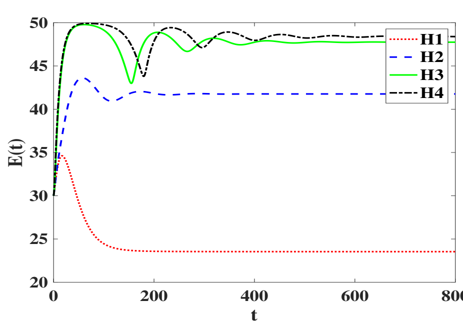
6.3. **Impact of adaptive immune response on the SARS-CoV-2 infection.** This subsection addresses the effect of stimulated rate constants $\varrho_B$ and $\varrho_U$ on the dynamics of system (6.1). We fix the parameters $\eta = 0.02$ and $\tau_1 = \tau_2 = \tau_3 = 0.7$ and vary the parameter $\varrho_B$ and $\varrho_U$ as:

H1: $\varrho_B = 0.0003,\ \varrho_U = 0.02,$
H2: $\varrho_B = 0.0035,\ \varrho_U = 0.16,$
H3: $\varrho_B = 0.07,\ \varrho_U = 0.3,$
H4: $\varrho_B = 0.1,\ \varrho_U = 0.44.$

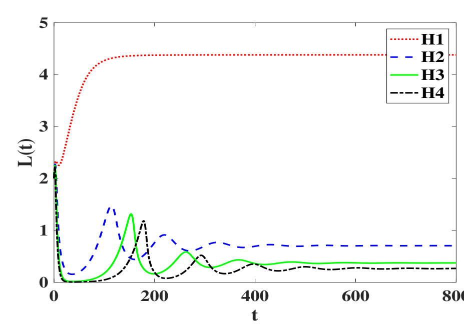
Further, we consider the initial condition:

$$C5 : (E(\theta), L(\theta), I(\theta), S(\theta), A(\theta), B(\theta), U(\theta)) = (30, 2, 2, 20, 8, 2.5, 0.5),\ \theta \in [-0.7, 0].$$

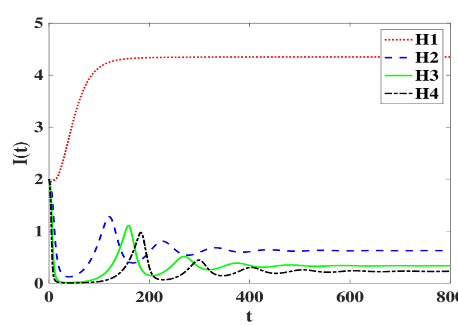
The impact of antibody and CTL responses can be seen in Figure 8. We observe that, as $\varrho_B$ and $\varrho_U$ are increased, the concentrations of uninfected epithelial cells and ACE2 receptors are increased, while concentrations of latently infected cells, actively infected cells and SARS-CoV-2 particles are decreased. Therefore, antibody and CTL responses can control the SARS-CoV-2 infection. Note that, $\Re_0$ does not depend on $\varrho_B$ and $\varrho_U$, therefore $\Delta_0$ can not be reached by increasing $\varrho_B$ and $\varrho_U$. This might contribute to the development of treatments for SARS-CoV-2 with the potential to boost antibody and CTL responses.



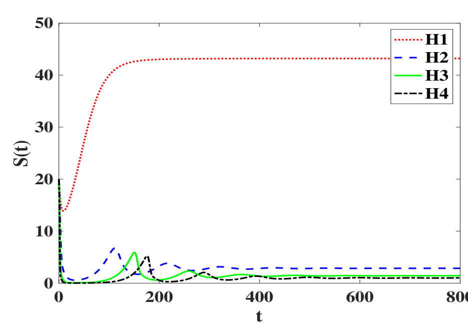
(A) Uninfected epithelial cells



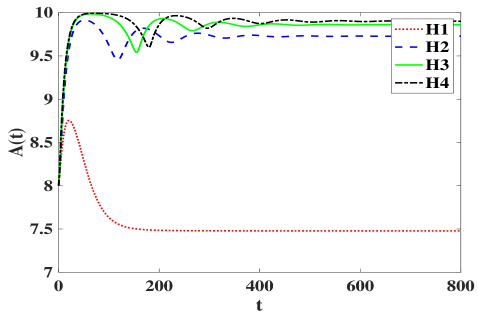
(B) Latently infected epithelial cells



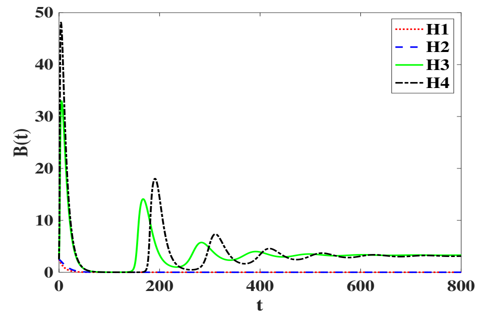
(C) Actively infected epithelial cells



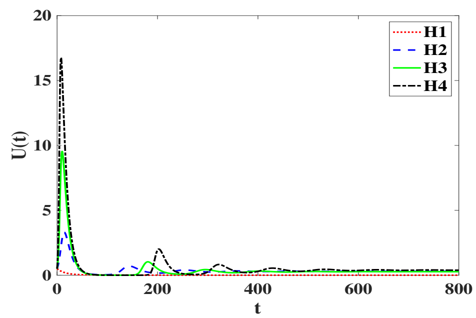
(D) SARS-CoV-2 particles




(E) ACE2 receptors




(F) Antibodies




(G) CTLs

FIGURE 8. Solutions of model (6.1) under the impact of adaptive immune response.

6.4. **Sensitivity analysis.** Sensitivity analysis is crucial in pathology and epidemiology when modeling complex interactions [44]. Sensitivity analysis can help us assess how well we are able to prevent the progression of the disease between-hosts and within-host. Three techniques may be used to determine sensitivity indices: directly by direct differentiation, with the use of a Latin hypercube sampling technique, or by linearizing the system and resolving the resultant equations [44], [45]. With the use of direct differentiation, the indices in this study may be stated analytically. When variables fluctuate dependent on parameters, you may get the sensitivity index by using partial derivatives. The normalized forward sensitivity index of $\Re_0$ is written in terms of a parameter $m$ as:

$$\mathcal{S}_m = \frac{m}{\Re_0}\frac{\partial \Re_0}{\partial m}. \tag{6.3}$$

Using the values given in Table 2 and $\eta = 0.005$, $\varrho_B = 0.0003$, $\varrho_U = 0.002$ and $\tau_1 = \tau_2 = \tau_3 = 0.7$, we present the sensitivity index $\mathcal{S}_m$ in Table 3 and Figure 9. Obviously, $\lambda_E$, $\eta$, $\lambda_A$, $a$ and $\nu$ have positive indices. Clearly, $\lambda_E$, $\eta$ and $\nu$, have the most positive sensitivity index. In this state, there is a positive relationship between the progression of COVID-19 and the parameters $\lambda_E$, $\eta$, $\lambda_A$, $a$ and $\nu$, when all other parameters are fixed. Parameters $\delta_E$, $\delta_S$, $\delta_A$, $\delta_L$, $\tau_1$, $\tau_2$, $\tau_3$, $\alpha_1$, $\alpha_2$, $\alpha_3$, $\mathcal{A}_s$ and $n$ have negative indices, meaning that when the values of these parameters rise, the value of $\Re_0$ declines. Obviously, $n$ has the most negative sensitivity index. As for, $\varrho_B$, $\varrho_U$, $\kappa$, $\delta_I$, $\delta_B$, $\delta_U$, $\gamma_B$ and $\gamma_U$ do not affect $\Re_0$.

TABLE 3. Sensitivity index of $\Re_0$.

| $m$ | $\mathcal{S}_m$ | $m$ | $\mathcal{S}_m$ | $m$ | $\mathcal{S}_m$ |
|---|---|---|---|---|---|
| $\lambda_E$ | 1 | $\delta_A$ | −0.833 | $\alpha_1$ | −0.7 |
| $\eta$ | 1 | $\delta_L$ | −0.333 | $\nu$ | 1 |
| $\delta_E$ | −1 | $\tau_1$ | −0.7 | $\alpha_2$ | −0.7 |
| $\delta_S$ | −1 | $\lambda_A$ | 0.833 | $\alpha_3$ | −0.7 |
| $a$ | 0.333 | $\tau_2$ | −0.7 | $\tau_3$ | −0.7 |
| $n$ | −1.3412 | $\mathcal{A}_s$ | −0.833 | | |

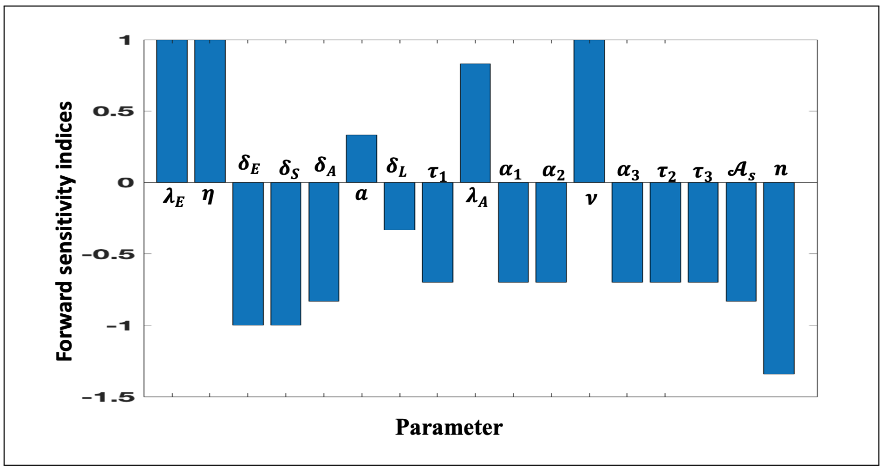



FIGURE 9. Forward sensitivity analysis of the parameters on $\Re_0$.

## 7. Discussion

Recent studies have demonstrated that the ACE2 receptor is crucial for the entry of the SARS-CoV-2 virus into the target cell. Thus, there is an urgent need to comprehend the function of the ACE2 receptor in the dynamics of SARS-CoV-2 under the effect of the adaptive immune response. In this paper we develop a SARS-CoV-2 dynamics model with ACE2 receptor and adaptive immune response. The model admits five equilibrium points as the following:

- Uninfected equilibrium ($\Delta_0$) which is usually exists. It is G.A.S when $\Re_0 \leq 1$ and unstable otherwise. In this state, the concentration of SARS-CoV-2 particles eventually converges to 0 and the COVID-19 patient will recover. Different control strategies can be applied to make

$$\Re_0 = \frac{\eta a v e^{-\alpha_1\tau_1-\alpha_2\tau_2-\alpha_3\tau_3}\lambda_E\lambda_A}{(a+\delta_L)\delta_S(\mathcal{A}_s\delta_E\delta_A+\lambda_A\delta_E)} \leq 1.$$

Examples of these strategies as:

(i) using reverse transcriptase inhibitor (RTI) drugs with drug efficacy $\epsilon_{RTI} \in [0,1]$ which lower the parameter $\eta$ as $(1-\epsilon_{RTI})\eta$ [25];

(ii) employing protease inhibitor (PI) drugs with drug efficacy $\epsilon_{PI} \in [0,1]$ to reduce the parameter $\nu$ as $(1-\epsilon_{PI})\nu$ [25];

(iii) using antiviral remdesivir (RDV) with drug efficacy $\epsilon_{RDV} \in [0,1]$ to reduce the parameter $a$ as $(1-\epsilon_{RDV})a$ [24];

(iv) developing new treatment which may enlarge the length of delay periods $\tau_1$ or $\tau_2$ or $\tau_3$ [41];

(v) developing new receptor-targeted drugs which may inhibit the proliferation rate of ACE2 receptors $\lambda_A$ [34];

(vi) developing new receptor-targeted drugs which may increase the degradation rate of ACE2 receptors $\delta_A$ [34].

We note that $\Re_0$ is independent of the parameters that characterizing the antibody and CTL responses. As a result, antibody and CTL responses only function to regulate infection rather than to eradicate it.

- Infected equilibrium without immune response ($\Delta_1$) exists when $\Re_0 > 1$ and it is G.A.S when $\Re_1 \leq 1 < \Re_0$ and $\Re_2 \leq 1$. In this case, the infection is there, but the immune system is not responding. The reason for this is because when the concentrations of the viruses and infected cells not be high enough to trigger an immune response (i.e. $S \leq \delta_B/\varrho_B$ and $I \leq \delta_U/\varrho_U$).
- Infected equilibrium with only antibody response ($\Delta_2$) exists when $\Re_1 > 1$. Moreover, $\Delta_2$ is G.A.S when $\Re_3 \leq 1 < \Re_1$. For this case, the body has enough number of viruses (i.e. $S > \delta_B/\varrho_B$) which trigger the antibody response. However, the number of infected cells still not enough to activate the CTL response ($I \leq \delta_U/\varrho_U$).
- Infected equilibrium with only CTL response ($\Delta_3$) exists when $\Re_2 > 1$. Moreover, $\Delta_3$ is G.A.S when $\Re_2 > 1$ and $\Re_1 \leq \Re_3$. For this case, the body has enough infected cells (i.e. $I > \delta_U/\varrho_U$) to trigger the CTL immune system's response. However, the number of viruses still not enough to activate the CTL response (i.e. $S \leq \delta_B/\varrho_B$).
- Infected equilibrium with both antibody and CTL responses ($\Delta_4$) exists and is G.A.S when $\Re_1 > \Re_3 > 1$. For this case, the concentrations of viruses and infected are high enough to trigger the antibody and CTL responses (i.e. $S > \delta_B/\varrho_B$ and $I > \delta_U/\varrho_U$).

## 8. Conclusion

In this paper, we formulated a SARS-CoV-2 infection model to get an insight on SARS-CoV-2 dynamics taking the role of ACE2 receptor under consideration. The effect of latently infected cells and both antibody and CTL responses on the SARS-CoV-2 infection was included. We toke into account three distributed delays, including (i) the formation of latently infected epithelial cells, (ii) the activation of latently infected epithelial cells, and (iii) the maturation of newly released SARS-CoV-2 virions. We began by displaying the fundamental properties of the solutions, nonnegativity and boundedness. We derived four threshold parameters, $\Re_i$, $i = 0,1,2,3$, which completely determine the existence and global stability of the model's equilibria. We used Lyapunov method to prove the global asymptotic stability for all equilibria. We solved the model numerically and presented the results graphically. We found an agreement between the numerical and theoretical findings. Sensitivity analysis was performed to establish how the values of the model's parameters affect the basic reproduction number $\Re_0$. We discussed the effect of ACE2 receptors, time delays, adaptive immunity and latently infected cells on the SARS-CoV-2 dynamics. We established that the proliferation and degradation rates of ACE2 receptors affect $\Re_0$, which may be important knowledge for the development of potentially receptor-targeted vaccines and drugs. We showed that the activation rate of the latently infected cells affect $\Re_0$, which may be important for suggesting the use of RDV treatment. We demonstrated that while antibody and CTL responses play the roles in controlling the SARS-CoV-2 infection, the viruses are not eventually eliminated by them. Furthermore, extending the time delay can significantly lower $\Re_0$ and inhibit the development of COVID-19. This enables the development of numerous medicines that will lengthen the delay period.

**Conflicts of Interest:** The authors declare that there are no conflicts of interest regarding the publication of this paper.

## References


[1] C. Huang, Y. Wang, X. Li, et al. Clinical Features of Patients Infected With 2019 Novel Coronavirus in Wuhan, China, The Lancet. 395 (2020), 497–506. https://doi.org/10.1016/s0140-6736(20)30183-5.

[2] M.Z. Tay, C.M. Poh, L. Renia, P.A. MacAry, L.F.P. Ng, The Trinity of COVID-19: Immunity, Inflammation and Intervention, Nat. Rev. Immunol. 20 (2020), 363–374. https://doi.org/10.1038/s41577-020-0311-8.

[3] P. Zhou, X.L. Yang, X.G. Wang, et al. A Pneumonia Outbreak Associated With a New Coronavirus of Probable Bat Origin, Nature. 579 (2020), 270–273. https://doi.org/10.1038/s41586-020-2012-7.

[4] Z. Varga, A.J. Flammer, P. Steiger, et al. Endothelial Cell Infection and Endotheliitis in COVID-19, The Lancet. 395 (2020), 1417–1418. https://doi.org/10.1016/s0140-6736(20)30937-5.

[5] S.Q. Du, W. Yuan, Mathematical Modeling of Interaction Between Innate and Adaptive Immune Responses in COVID-19 and Implications for Viral Pathogenesis, J. Med. Virol. 92 (2020), 1615–1628. https://doi.org/10.1002/jmv.25866.

[6] A.S. Perelson, R. Ke, Mechanistic Modeling of SARS-CoV-2 and Other Infectious Diseases and the Effects of Therapeutics, Clin. Pharma. Therapeutics. 109 (2021), 829–840. https://doi.org/10.1002/cpt.2160.

[7] F. Fatehi, R.J. Bingham, E.C. Dykeman, P.G. Stockley, R. Twarock, Comparing Antiviral Strategies Against COVID-19 via Multiscale Within-Host Modelling, R. Soc. Open Sci. 8 (2021), 210082. https://doi.org/10.1098/rsos.210082.

[8] E.A. Hernandez-Vargas, J.X. Velasco-Hernandez, In-host Mathematical Modelling of COVID-19 in Humans, Ann. Rev. Control. 50 (2020), 448–456. https://doi.org/10.1016/j.arcontrol.2020.09.006.

[9] S. Wang, Y. Pan, Q. Wang, H. Miao, A.N. Brown, L. Rong, Modeling the Viral Dynamics of SARS-CoV-2 Infection, Math. Biosci. 328 (2020), 108438. https://doi.org/10.1016/j.mbs.2020.108438.

[10] R. Ke, C. Zitzmann, D.D. Ho, R.M. Ribeiro, A.S. Perelson, In Vivo Kinetics of SARS-CoV-2 Infection and Its Relationship With a Person's Infectiousness, Proc. Natl. Acad. Sci. U.S.A. 118 (2021), e2111477118. https://doi.org/10.1073/pnas.2111477118.

[11] I. Al-Darabsah, K.L. Liao, S. Portet, A Simple In-Host Model for COVID-19 With Treatments: Model Prediction and Calibration, J. Math. Biol. 86 (2023), 20. https://doi.org/10.1007/s00285-022-01849-6.

[12] M. Sadria, A.T. Layton, Modeling Within-Host SARS-CoV-2 Infection Dynamics and Potential Treatments, Viruses. 13 (2021), 1141. https://doi.org/10.3390/v13061141.

[13] L. Pinky, H.M. Dobrovolny, SARS-CoV-2 Coinfections: Could Influenza and the Common Cold Be Beneficial?, J. Med. Virol. 92 (2020), 2623–2630. https://doi.org/10.1002/jmv.26098.

[14] N. Neant, G. Lingas, Q. Le Hingrat, et al. Modeling SARS-CoV-2 Viral Kinetics and Association With Mortality in Hospitalized Patients From the French COVID Cohort, Proc. Natl. Acad. Sci. U.S.A. 118 (2021), e2017962118. https://doi.org/10.1073/pnas.2017962118.

[15] A. Goncalves, J. Bertrand, R. Ke, et al. Timing of Antiviral Treatment Initiation is Critical to Reduce SARS-CoV-2 Viral Load, CPT Pharmacom. Syst. Pharma. 9 (2020), 509–514. https://doi.org/10.1002/psp4.12543.

[16] C. Li, J. Xu, J. Liu, Y. Zhou, The within-host viral kinetics of SARS-CoV-2, Math. Biosci. Eng. 17 (2020), 2853–2861. https://doi.org/10.3934/mbe.2020159.

[17] I. Ghosh, Within Host Dynamics of SARS-CoV-2 in Humans: Modeling Immune Responses and Antiviral Treatments, SN Comput. Sci. 2 (2021), 482. https://doi.org/10.1007/s42979-021-00919-8.

[18] J. Mondal, P. Samui, A.N. Chatterjee, Dynamical Demeanour of SARS-CoV-2 Virus Undergoing Immune Response Mechanism in COVID-19 Pandemic, Eur. Phys. J. Spec. Top. 231 (2022), 3357–3370. https://doi.org/10.1140/epjs/s11734-022-00437-5.

[19] K. Hattaf, N. Yousfi, Dynamics of SARS-CoV-2 Infection Model With Two Modes of Transmission and Immune Response, Math. Biosci. Eng. 17 (2020), 5326–5340. https://doi.org/10.3934/mbe.2020288.

[20] A.M. Elaiw, A.D. Al Agha, S.A. Azoz, E. Ramadan, Global Analysis of Within-Host SARS-CoV-2/HIV Coinfection Model With Latency, Eur. Phys. J. Plus. 137 (2022), 174. https://doi.org/10.1140/epjp/s13360-022-02387-2.

[21] A.E.S. Almocera, G. Quiroz, E.A. Hernandez-Vargas, Stability Analysis in COVID-19 Within-Host Model With Immune Response, Commun. Nonlinear Sci. Numer. Simul. 95 (2021), 105584. https://doi.org/10.1016/j.cnsns.2020.105584.

[22] A.M. Elaiw, A.J. Alsaedi, A.D. Hobiny, S. Aly, Stability of a Delayed SARS-CoV-2 Reactivation Model With Logistic Growth and Adaptive Immune Response, Physica A: Stat. Mech. Appl. 616 (2023), 128604. https://doi.org/10.1016/j.physa.2023.128604.

[23] C. Leon, A. Tokarev, A. Bouchnita, V. Volpert, Modelling of the Innate and Adaptive Immune Response to SARS Viral Infection, Cytokine Storm and Vaccination, Vaccines. 11 (2023), 127. https://doi.org/10.3390/vaccines11010127.

[24] H.M. Dobrovolny, Quantifying the Effect of Remdesivir in Rhesus Macaques Infected With SARS-CoV-2, Virology. 550 (2020), 61–69. https://doi.org/10.1016/j.virol.2020.07.015.

[25] P. Abuin, A. Anderson, A. Ferramosca, E.A. Hernandez-Vargas, A.H. Gonzalez, Characterization of SARS-CoV-2 Dynamics in the Host, Ann. Rev. Control. 50 (2020), 457–468. https://doi.org/10.1016/j.arcontrol.2020.09.008.

[26] B. Chhetri, V.M. Bhagat, D.K.K. Vamsi, et al. Within-Host Mathematical Modeling on Crucial Inflammatory Mediators and Drug Interventions in COVID-19 Identifies Combination Therapy to Be Most Effective and Optimal, Alexandria Eng. J. 60 (2021), 2491–2512. https://doi.org/10.1016/j.aej.2020.12.011.

[27] T. Song, Y. Wang, X. Gu, S. Qiao, Modeling the Within-Host Dynamics of SARS-CoV-2 Infection Based on Antiviral Treatment, Mathematics. 11 (2023), 3485. https://doi.org/10.3390/math11163485.

[28] A.L. Jenner, R.A. Aogo, S. Alfonso, et al. COVID-19 Virtual Patient Cohort Suggests Immune Mechanisms Driving Disease Outcomes, PLoS Pathog. 17 (2021), e1009753. https://doi.org/10.1371/journal.ppat.1009753.

[29] S. Tang, W. Ma, P. Bai, A Novel Dynamic Model Describing the Spread of the MERS-CoV and the Expression of Dipeptidyl Peptidase 4, Comput. Math. Methods Med. 2017 (2017), 5285810. https://doi.org/10.1155/2017/5285810.

[30] T. Keyoumu, W. Ma, K. Guo, Existence of Positive Periodic Solutions for a Class of In-Host MERS-CoV Infection Model With Periodic Coefficients, AIMS Math. 7 (2022), 3083–3096. https://doi.org/10.3934/math.2022171.

[31] T. Keyoumu, K. Guo, W. Ma, Periodic Oscillation for a Class of In-Host MERS-CoV Infection Model With CTL Immune Response, Math. Biosci. Eng. 19 (2022), 12247–12259. https://doi.org/10.3934/mbe.2022570.

[32] T. Keyoumu, W. Ma, K. Guo, Global Stability of a MERS-CoV Infection Model with CTL Immune Response and Intracellular Delay, Mathematics. 11 (2023), 1066. https://doi.org/10.3390/math11041066.

[33] A.N. Chatterjee, F. Al Basir, A Model for SARS-CoV-2 Infection with Treatment, Comput. Math. Methods Med. 2020 (2020), 1352982. https://doi.org/10.1155/2020/1352982.

[34] J. Lv, W. Ma, Global Asymptotic Stability of a Delay Differential Equation Model for SARS-CoV-2 Virus Infection Mediated by ACE2 Receptor Protein, Appl. Math. Lett. 142 (2023), 108631. https://doi.org/10.1016/j.aml.2023.108631.

[35] B.J. Nath, K. Dehingia, V.N. Mishra, Y.M. Chu, H.K. Sarmah, Mathematical Analysis of a Within-Host Model of SARS-CoV-2, Adv. Differ. Equ. 2021 (2021), 113. https://doi.org/10.1186/s13662-021-03276-1.

[36] A. Danchin, O. Pagani-Azizi, G. Turinici, G. Yahiaoui, COVID-19 Adaptive Humoral Immunity Models: Weakly Neutralizing Versus Antibody-Disease Enhancement Scenarios, Acta Biotheor. 70 (2022), 23. https://doi.org/10.1007/s10441-022-09447-1.

[37] N. Bairagi, D. Adak, Global Analysis of HIV-1 Dynamics With Hill Type Infection Rate and Intracellular Delay, Appl. Math. Model. 38 (2014), 5047–5066. https://doi.org/10.1016/j.apm.2014.03.010.

[38] Y. Kuang, Delay Differential Equations With Applications in Population Dynamics, Academic Press, Boston, 1993.

[39] P. van den Driessche, J. Watmough, Reproduction Numbers and Sub-Threshold Endemic Equilibria for Compartmental Models of Disease Transmission, Math. Biosci. 180 (2002), 29–48. https://doi.org/10.1016/s0025-5564(02)00108-6.

[40] A. Korobeinikov, Global Properties of Basic Virus Dynamics Models, Bull. Math. Biol. 66 (2004), 879–883. https://doi.org/10.1016/j.bulm.2004.02.001.

[41] G. Huang, Y. Takeuchi, W. Ma, Lyapunov Functionals for Delay Differential Equations Model of Viral Infections, SIAM J. Appl. Math. 70 (2010), 2693–2708. https://doi.org/10.1137/090780821.

[42] J.K. Hale, S.M.V. Lunel, Introduction to Functional Differential Equations, Springer-Verlag, New York, 1993.

[43] H.K. Khalil, Nonlinear Systems, Prentice Hall, Upper Saddle River, 2002.

[44] S. Marino, I.B. Hogue, C.J. Ray, D.E. Kirschner, A Methodology for Performing Global Uncertainty and Sensitivity Analysis in Systems Biology, J. Theor. Biol. 254 (2008), 178–196. https://doi.org/10.1016/j.jtbi.2008.04.011.

[45] A. Khan, R. Zarin, G. Hussain, N.A. Ahmad, M.H. Mohd, A. Yusuf, Stability Analysis and Optimal Control of COVID-19 With Convex Incidence Rate in Khyber Pakhtunkhawa (Pakistan), Results Phys. 20 (2021), 103703. https://doi.org/10.1016/j.rinp.2020.103703.