

Research Article

Analysis of Humoral Immunity SARS-CoV-2 Infection Model with ACE2 Receptor and Latent Phase

Ahmed M. Elaiw^{1*}, Amani S. AlSulami^{1,2}, Aatef D. Hobiny¹

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

²Department of Mathematics and Statistics, Faculty of Science, University of Jeddah, P.O. Box 80327, Jeddah 21589, Saudi Arabia

E-mail: aelaiwksu.edu.sa@kau.edu.sa

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Abstract: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is RNA virus which causes the coronavirus disease 2019 (COVID-19). SARS-CoV-2 infects the epithelial (target) cells by binding its spike protein, S, to the Angiotensin-Converting Enzyme 2 (ACE2) receptor on the surface of epithelial cells. ACE2 is an essential mediating factor in the SARS-CoV-2 infection pathway. In this study, we build a mathematical model for characterizing the dynamics of SARS-CoV-2 within the host while taking into account the impact of humoral immunity and the function of the ACE2 receptor. We incorporate the cells that are latently infected into the model. We consider three distributed delays: (i) delay in development 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 address the fundamental properties of the delayed system, then find all possible equilibria. We demonstrate the existence and stability of the equilibria on the basis of two threshold parameters, namely basic reproduction number (\mathfrak{R}_0) and humoral immune activation number (\mathfrak{R}_1). By building appropriate Lyapunov functions and applying LaSalle's invariance principle, we prove the global asymptotic stability for all equilibria. We do numerical simulations to demonstrate the theoretical conclusions. We do sensitivity analysis and determine the most vulnerable parameters. Discussion is had on how the dynamics of the SARS-CoV-2 are affected by ACE2 receptors, humoral immunity, latent phase and time delays. It is shown that vigorous activation of humoral immunity can suppress viral multiplication. We found that, \mathfrak{R}_0 is influenced by the rates of ACE2 receptor growth and degradation, and this may offer valuable guidance for the creation of potential receptor-targeted vaccinations and medications. Further, it is shown that, increasing time delays can effectively decrease \mathfrak{R}_0 and then inhibit the SARS-CoV-2 replication. Finally, we showed that, excluding the latently infected cells in the model would result in an overestimation of \mathfrak{R}_0 . Our findings may be useful in understanding the dynamics of SARS-CoV-2 infection in the host as well as in the development of novel therapies.

Keywords: SARS-CoV-2, ACE2 receptor, COVID-19, latent phase, distributed delay, Lyapunov method, global stability

MSC: 01A01, 22B22, 31K13

1. Introduction

As the spread of leading to death diseases has increased in recent times, we need more studies to help us find ways to reduce the spread of these diseases and the possibility of producing effective treatments to reduce the number of deaths caused by these viruses. An example of this is the recent spread of coronavirus disease 2019 (COVID-19), which the World Health Organization (WHO) has classified as a pandemic. Some of the symptoms of COVID-19 infection are well-known are common fever, cough, exhaustion, shortness of breath, loss of odor, and tastelessness. People who have co-morbid conditions such as diabetes, liver illness, kidney disease, or cardiovascular disease are more likely to get COVID-19 infected. Patients with pneumonia influenced COVID-19 infection will also have acute respiratory sickness, which will result in organ failure. In the earlier COVID-19 pandemic waves, it was found that a high percentage of those who were tolerant to the virus had moderate symptoms and recovered because of their immunity, almost 20 percent of them eventually died due to multiple organ failure [1]. The WHO reported on September 24, 2023, that there were more than 770 million confirmed illnesses and 6.9 million fatalities worldwide [2].

COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The virus attacks the epithelial (target) cells by binding its spike protein, S, to the Angiotensin-Converting Enzyme 2 (ACE2) receptor on the surface of epithelial cells [3, 4]. ACE2 receptor is used by SARS-CoV-2 to accurately enter host cells and helps to make the host cells more susceptible [5]. Even though type II alveolar epithelial cells of the lungs contain the better copious expression of ACE2, they are therefore thought to be the major target cells of SARS-CoV-2 infection [6, 7]. The immune response is crucial for stopping the spread of the illness and getting rid of the SARS-CoV-2 infection. CTL and antibody are the two primary immune responses to viral infections. While antibodies neutralize the viruses, CTLs are in charge of destroying virus-infected cells.

Since the disease first started to spread, scientists and researchers from a wide range of disciplines have joined forces to investigate and comprehend the interaction between the virus and target cell in order to develop antiviral drugs and vaccines. It can be challenging and expensive to experimentally assess interactions between SARS-CoV-2, epithelial cells, and immune cells. Understanding the dynamic behavior of the virus and its target cells as well as immune cells may be facilitated by mathematical modeling studies of the dynamics of SARS-CoV-2 infection within the host. This study also contributes to our understanding of the efficacy of drugs, both alone and in combination.

In [8, 9], a model of in-host SARS-CoV-2 infection was provided by assuming that the target cells are limited. The initial use of this model was to explain influenza virus infections [10]. Uninfected epithelial cells (E), infected cells (I), and free SARS-CoV-2 particles (S) make up the model's three compartments. The model was formulated as follows:

$$\dot{E} = -\eta ES, \quad (1)$$

$$\dot{I} = \eta ES - \delta_I I, \quad (2)$$

$$\dot{S} = \delta_I \nu I - \delta_S S, \quad (3)$$

where $E = E(t)$, $I = I(t)$ and $S = S(t)$ represent the concentrations of the model's compartments at time t . Parameters η and ν , respectively, denote the infection rate constant and the number of free SARS-CoV-2 particles generated during the course of an average infected cell's life. δ_I and δ_S , respectively, stand for the death and clearance rates of infected cells and viruses. The model was considered in several works (see e.g., [11–13]).

Experimental findings show that a lag in the period between a target cell's initial infection and the release of new SARS-CoV-2 particles exists [14]. Therefore, by dividing the infected cells into two populations, latently infected cells and actively (productively) infected cells, a SARS-CoV-2 infection model was created using ordinary differential equations (ODEs) [8, 9]. Viruses are present in latently infected cells, but they are not released until the cells are activated. The SARS-CoV-2 infection model with latent phase was provided as [8, 9]:

$$\dot{E} = -\eta ES, \quad (4)$$

$$\dot{L} = \eta ES - aL, \quad (5)$$

$$\dot{I} = aL - \delta_I I, \quad (6)$$

$$\dot{S} = \delta_I \nu I - \delta_S S, \quad (7)$$

where $L = L(t)$ is the concentration of latently infected cells. The latently infected cells are activated by rate a . The model was used in many works (see e.g., [13, 15–19]).

Li et al. [20] took into account the growth and decay of epithelial cells as:

$$\dot{E} = \delta_E (E(0) - E) - \eta ES,$$

where $E(0)$ is the concentration of epithelial cells that are virus-free. This approach was considered and/or extended in many works (see e.g., [5, 21–27]).

These works mentioned above did not take into account the kinetics of the ACE2 receptor on epithelial cells. The Middle East respiratory syndrome coronavirus (MERS-CoV) infection was modeled by the authors of [28, 29] to see how the dipeptidyl peptidase 4 (DPP4) receptor affects it. Chatterjee and Al Basir [30] studied the local stability of a system of ODEs for SARS-CoV-2 infection with ACE2 receptor. Lv et al. [31] formulated a system of delay differential equations (DDEs) for SARS-CoV-2 infection mediated by ACE2 receptor as:

$$\dot{E} = \lambda_E - \eta \Psi(A) ES - \delta_E E, \quad (8)$$

$$\dot{I} = e^{-\alpha_1 \tau_1} \eta \Psi(A_{\tau_1}) E_{\tau_1} S_{\tau_1} - \delta_I I, \quad (9)$$

$$\dot{S} = \delta_I \nu I - \delta_S S, \quad (10)$$

$$\dot{A} = \lambda_A - \kappa \eta \Psi(A) AS - \delta_A A, \quad (11)$$

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 . $\Psi(A)$ is the probability of successful entry of the SARS-CoV-2 into the epithelial cell mediated by the ACE2 receptors. When the concentration of ACE2 receptor is lower (higher), then $\Psi(A) \sim 0 (\sim 1)$ [31]. 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 κ 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, τ_1 represents the amount of time that has passed since SARS-CoV-2 particles had made contact with healthy epithelial cells before those cells become actively infected. The likelihood that infected cells will survive throughout the delay period is $e^{-\alpha_1 \tau_1}$.

Model (8)-(11) disregards the immune system's response to the SARS-CoV-2 infection. Further, the model disregards the latent class and assumes that all infected cells are active. Additionally, the model ignores the maturation delay and only

takes into account one type of discrete-time delay, τ_1 . Several mathematical models in both virology and epidemiology were developed by taking into account the time delay as a random variable drawn from the probability distribution function in order to avoid such (biologically implausible) assumption (see e.g., [32–35]). It is worth pointing out that the distributed delay is one of various time delays and is more general than discrete delay.

Accordingly, the purpose of this article is to modify and analyze model (8)-(11) presented in [31] by taking into account the following factors:

F1: Humoral immune response, which depends on the activation of the B cells to generate antibodies for neutralizing the viruses.

F2: Latently infected cells, which contain virions, but they are not released until the cells are activated.

F3: Three distributed-time delays, (i) delay in development 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. It is known that distributed-time delay is more general than discrete-time delay.

Before finding any equilibria and discussing their existence and global stability, we first examine the essential properties of the DDEs. To look at the asymptotic stability of all equilibria globally, we develop appropriate Lyapunov functions and apply LaSalle's invariance principle (LIP). We show the theoretical conclusions using numerical simulations. We wrap up by discussing the outcomes.

2. Model formulation

We propose the following SARS-CoV-2 infection model taking into account factors F1-F3 as:

$$\begin{cases} \dot{E} = \lambda_E - \eta \Psi(A)ES - \delta_E E, \\ \dot{L} = \eta \int_0^{h_1} f_1(\tau) e^{-\alpha_1 \tau} \Psi(A_\tau) E_\tau S_\tau d\tau - (a + \delta_L)L, \\ \dot{I} = a \int_0^{h_2} f_2(\tau) e^{-\alpha_2 \tau} L_\tau d\tau - \delta_I I, \\ \dot{S} = \delta_I \nu \int_0^{h_3} f_3(\tau) e^{-\alpha_3 \tau} I_\tau d\tau - \delta_S S - \gamma SB, \\ \dot{A} = \lambda_A - \kappa \eta \Psi(A)AS - \delta_A A, \\ \dot{B} = \rho SB - \delta_B B, \end{cases} \quad (12)$$

where $(E_\tau, L_\tau, I_\tau, S_\tau, A_\tau) = (E(t - \tau), L(t - \tau), I(t - \tau), S(t - \tau), A(t - \tau))$. The variable $B = B(t)$ represents the concentration of per unit volume of antibodies at time t . The antibodies are stimulated at rate ρSB , die at rate $\delta_B B$ and neutralize the SARS-CoV-2 particles at rate γSB . We take τ as a random variable from probability distributed functions $f_i(\tau)$, $i = 1, 2, 3$ over the intervals $[0, h_i]$, where h_i is the limit superior of the delay period. The likelihood that epithelial cells that were uninfected when the SARS-CoV-2 made contact with them at time $t - \tau$ survived for τ time units and acquired latent infection at time t is represented by $f_1(\tau)e^{-\alpha_1 \tau}$. The factor $f_2(\tau)e^{-\alpha_2 \tau}$ represents the likelihood that latently infected cells will survive throughout the interval $[t - \tau, t]$. The likelihood that an immature SARS-CoV-2 at time $t - \tau$ survives for τ time units to become a mature SARS-CoV-2 at time t is represented by $f_3(\tau)e^{-\alpha_3 \tau}$. A schematic representation of the model in (12) is illustrated in Figure 1.

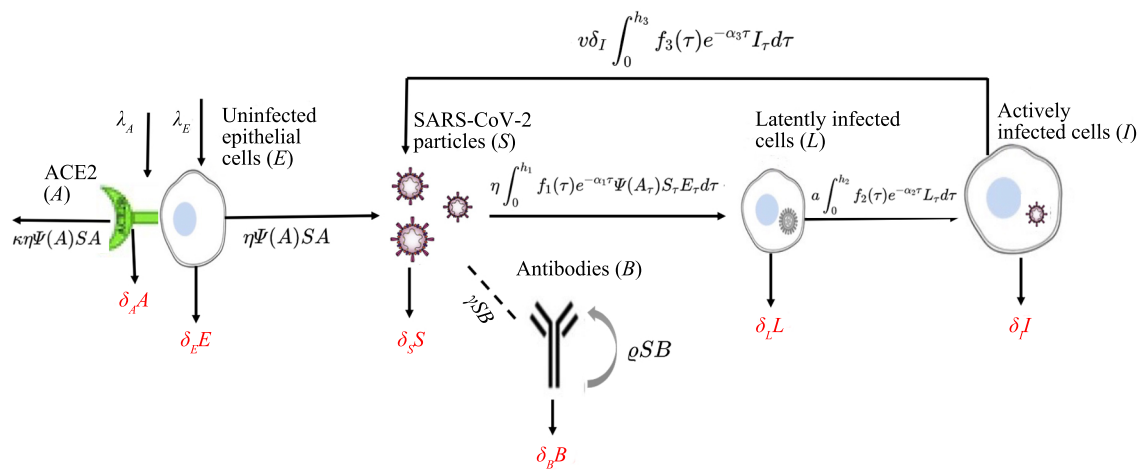


Figure 1. The schematic diagram of the SARS-CoV-2 infection

Function $f_i(\tau)$, satisfies the following conditions:

$$f_i(\tau) > 0, \quad \int_0^{h_i} f_i(\tau) d\tau = 1, \quad \int_0^{h_i} f_i(\tau) e^{\ell\tau} d\tau < \infty, \quad \text{where } \ell > 0, \quad i = 1, 2, 3.$$

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 $0 < \zeta_i \leq 1$. Usually $\Psi(A)$ 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 $n > 0$ is the Hill coefficient [31, 36]. The function $\Psi(A)$ is continuously differentiable on $[0, +\infty)$, strictly monotonically increasing.

The initial conditions for model (12) are given by:

$$\begin{aligned} E(\theta) &= \phi_1(\theta), \quad L(\theta) = \phi_2(\theta), \quad I(\theta) = \phi_3(\theta), \quad S(\theta) = \phi_4(\theta), \\ A(\theta) &= \phi_5(\theta), \quad B(\theta) = \phi_6(\theta), \quad \phi_i(\theta) \geq 0, \quad i = 1, 2, \dots, 6, \quad \theta \in [-\tau^*, 0], \end{aligned} \quad (13)$$

where, $\tau^* = \max\{h_1, h_2, h_3\}$, $\phi_i \in C([-\tau^*, 0], \mathbb{R}_{\geq 0})$ and C is the Banach space of continuous functions mapping from $[-\tau^*, 0]$ to $\mathbb{R}_{\geq 0}$ with the norm $\|\phi_i\| = \sup_{-\tau^* \leq \theta \leq 0} |\phi_i(\theta)|$ for $\phi_i \in C$, $i = 1, 2, \dots, 6$. We note that system (12) with initial conditions (13) has a unique solution [37]. All parameters of model (12) are positive.

3. Basic qualitative properties

This section proves the non-negativity and boundedness of the solutions of system (12).

Lemma 1 The solutions of model (12) with the initial states (13) are non-negative and ultimately bounded.

Proof. We have $\dot{E}|_{E=0} = \lambda_E > 0$, $\dot{A}|_{A=0} = \lambda_A > 0$ and $\dot{B}|_{B=0} = 0$. Hence, $E(t), A(t), B(t) \geq 0$, for all $t \geq 0$. From second, third and fourth equations of system (12) we have

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

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

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

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 and B are non-negative.

Now, we prove the ultimately boundedness of E , L , I , S , A and B . From the first equation of system (12) we have, $\limsup_{t \rightarrow \infty} E(t) \leq \frac{\lambda_E}{\delta_E} = \omega_1$. To prove the ultimate boundedness of L , we define

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

Then, we obtain

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

where, $p_1 = \min\{\delta_E, (a + \delta_L)\}$, then

$$\dot{\Pi}_1 \leq \lambda_E - p_1 \Pi_1.$$

It follows that, $\limsup_{t \rightarrow \infty} \Pi_1(t) \leq \frac{\lambda_E}{p_1} = \omega_2$. Since $E > 0$ and $L \geq 0$, then $\limsup_{t \rightarrow \infty} L(t) \leq \omega_2$. From the third equation we have

$$\begin{aligned}
\dot{I} &= a \int_0^{h_2} \chi_2(\tau) L_\tau d\tau - \delta_I I \\
&\leq a\omega_2 \zeta_2 - \delta_I I \\
&\leq a\omega_2 - \delta_I I.
\end{aligned}$$

Therefore, $\limsup_{t \rightarrow \infty} I(t) \leq \frac{a\omega_2}{\delta_I} = \omega_3$. Now let us define

$$\Pi_2 = S + \frac{\gamma}{\rho} B.$$

Then, we obtain

$$\begin{aligned}
\dot{\Pi}_2 &= \dot{S} + \frac{\gamma}{\rho} \dot{B} = \delta_I v \int_0^{h_3} \chi_3(\tau) I_\tau d\tau - \delta_S S - \gamma SB \\
&\quad + \frac{\gamma}{\rho} (\rho SB - \delta_B B) \\
&= \delta_I v \int_0^{h_3} \chi_3(\tau) I_\tau d\tau - \delta_S S - \frac{\gamma \delta_B}{\rho} B \\
&\leq \delta_I v \omega_3 \zeta_3 - p_2 \left[S + \frac{\gamma}{\rho} B \right] \\
&\leq \delta_I v \omega_3 - p_2 \left[S + \frac{\gamma}{\rho} B \right],
\end{aligned}$$

where, $p_2 = \min\{\delta_S, \delta_B\}$, then

$$\dot{\Pi}_2 \leq \delta_I v \omega_3 - p_2 \Pi_2.$$

Hence, $\limsup_{t \rightarrow \infty} \Pi_2(t) \leq \frac{\delta_I v \omega_3}{p_2} = \omega_4$. Since $S \geq 0$ and $B \geq 0$, then $\limsup_{t \rightarrow \infty} S(t) \leq \omega_4$ and $\limsup_{t \rightarrow \infty} B(t) \leq \frac{\rho}{\gamma} \omega_4 = \omega_6$. Finally, from fifth equation of system (12) we have, $\limsup_{t \rightarrow \infty} A(t) \leq \frac{\lambda_A}{\delta_A} = \omega_5$. Then E, L, I, S, A and B are ultimately bounded. \square

Based on Lemma 1, we can establish that $\Gamma = \{(E, L, I, S, A, B) \in C_{\geq 0}^6: \|E\| \leq \omega_1, \|L\| \leq \omega_2, \|I\| \leq \omega_3, \|S\| \leq \omega_4, \|A\| \leq \omega_5, \|B\| \leq \omega_6\}$ is positively invariant for system (12).

4. Equilibria

This section finds all equilibria of model (12) and the threshold parameters that determine the existence of these equilibria. Firstly, we compute the basic infection reproduction number \mathfrak{R}_0 for system (12) by using the next-generation matrix method [38]. We define the matrices F and V as follows:

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

where $E_0 = \lambda_E / \delta_E$ and $A_0 = \lambda_A / \delta_A$. Then \mathfrak{R}_0 , can be derived as the spectral radius of FV^{-1} , as:

$$\mathfrak{R}_0 = \frac{\eta a \nu \zeta_1 \zeta_2 \zeta_3 \Psi(A_0) E_0}{(a + \delta_L) \delta_S}. \quad (14)$$

Secondly, let $\Delta = (E, L, I, S, A, B)$ be any equilibrium of system (12) fulfilling the following system of nonlinear equations:

$$0 = \lambda_E - \eta \Psi(A) ES - \delta_E E, \quad (15)$$

$$0 = \eta \zeta_1 \Psi(A) ES - (a + \delta_L) L, \quad (16)$$

$$0 = a \zeta_2 L - \delta_I I, \quad (17)$$

$$0 = \delta_I \nu \zeta_3 I - \delta_S S - \gamma SB, \quad (18)$$

$$0 = \lambda_A - \kappa \eta \Psi(A) SA - \delta_A A, \quad (19)$$

$$0 = \rho SB - \delta_B B. \quad (20)$$

Equation (20) has two solutions, $B = 0$ and $S = \frac{\delta_B}{\rho}$. When $B = 0$, then from Equation (18) we get

$$\delta_I I = \frac{\delta_S}{\nu \zeta_3} S. \quad (21)$$

Substituting Equation (21) into Equation (17), we obtain

$$L = \frac{\delta_S}{a \nu \zeta_2 \zeta_3} S. \quad (22)$$

Substituting Equation (22) into Equation (16), we get

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

and then we have

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

If $S = 0$, then from Equations (15), (16), (17) and (19), we have $E = \lambda_E / \delta_E$, $L = 0$, $I = 0$ and $A = \lambda_A / \delta_A$. Then, we obtain the uninfected equilibrium $\Delta_0 = (E_0, 0, 0, 0, A_0, 0)$.

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

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

Therefore, we obtain

$$E = \frac{\lambda_E - (a + \delta_L) \zeta_1^{-1} L}{\delta_E}, \quad S = \frac{va \zeta_2 \zeta_3}{\delta_S} L, \quad I = \frac{a \zeta_2}{\delta_I} L \quad \text{and} \quad A = \frac{\lambda_A}{\delta_A + \kappa \zeta_1^{-1} (a + \delta_L) L / E}. \quad (23)$$

Substituting Equation (23) into Equation (16), we have

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

Since $L \neq 0$, then

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

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

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

We have

$$G(0) = \frac{\eta \nu a \zeta_1 \zeta_2 \zeta_3}{(a + \delta_L) \delta_S} \Psi \left(\frac{\lambda_A}{\delta_A} \right) \left(\frac{\lambda_E}{\delta_E} \right) - 1 = \Re_0 - 1 > 0, \quad \text{if } \Re_0 > 1,$$

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

and

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

So, we have

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

Then, there exists a unique $L_1 \in \left(0, \frac{\lambda_E \zeta_1}{a + \delta_L} \right)$ such that $G(L_1) = 0$.

Therefore, there exists a unique infected equilibrium $\Delta_1 = (E_1, L_1, I_1, S_1, A_1, 0)$ when $\Re_0 > 1$, where $E_1 = \frac{\lambda_E - (a + \delta_L) \zeta_1^{-1} L_1}{\delta_E} \in \left(0, \frac{\lambda_E}{\delta_E} \right)$, $I_1 = \frac{a \zeta_2}{\delta_I} L_1 \in \left(0, \frac{a \lambda_E \zeta_1 \zeta_2}{(a + \delta_L) \delta_I} \right)$, $S_1 = \frac{\nu a \zeta_2 \zeta_3}{\delta_S} L_1 \in \left(0, \frac{\nu a \lambda_E \zeta_1 \zeta_2 \zeta_3}{(a + \delta_L) \delta_S} \right)$ and $A_1 = \frac{\lambda_A}{\delta_A + \kappa \zeta_1^{-1} (a + \delta_L) L_1/E_1} \in \left(0, \frac{\lambda_A}{\delta_A} \right)$.

If $B \neq 0$ and $S = \frac{\delta_B}{\rho}$, therefore, we obtain

$$E = \frac{\lambda_E - (a + \delta_L) \zeta_1^{-1} L}{\delta_E}, \quad I = \frac{a \zeta_2}{\delta_I} L, \quad A = \frac{\lambda_A}{\delta_A + \kappa \zeta_1^{-1} (a + \delta_L) L/E} \quad (24)$$

$$\text{and } B = \frac{\delta_S}{\gamma} \left(\frac{\nu a \rho \zeta_2 \zeta_3}{\delta_S \delta_B} L - 1 \right).$$

Substituting Equation (24) into Equation (16), we obtain

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

Define a function $G^*(L)$ as:

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

We have

$$G^*(0) = \frac{\eta \delta_B \zeta_1}{\rho} \Psi \left(\frac{\lambda_A}{\delta_A} \right) \left(\frac{\lambda_E}{\delta_E} \right) > 0,$$

$$\lim_{L \rightarrow \frac{\lambda_E \zeta_1}{a + \delta_L}} G^*(L) = -\lambda_E \zeta_1 < 0.$$

Moreover,

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

So, we have

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

Then, there exists a unique $L_2 \in \left(0, \frac{\lambda_E \zeta_1}{a + \delta_L} \right)$ such that $G^*(L_2) = 0$. It follows that, there exists a unique infected equilibrium with antibody immune response $\Delta_2 = (E_2, L_2, I_2, S_2, A_2, B_2)$, when $\mathfrak{R}_1 > 1$, where $E_2 = \frac{\lambda_E - (a + \delta_L) \zeta_1^{-1} L_2}{\delta_E} \in \left(0, \frac{\lambda_E}{\delta_E} \right)$, $I_2 = \frac{a \zeta_2}{\delta_I} L_2 \in \left(0, \frac{a \lambda_E \zeta_1 \zeta_2}{(a + \delta_L) \delta_I} \right)$, $S_2 = \frac{\delta_B}{\rho}$, $A_2 = \frac{\lambda_A}{\delta_A + \kappa \zeta_1^{-1} (a + \delta_L) L_2 / E_2} \in \left(0, \frac{\lambda_A}{\delta_A} \right)$ and $B_2 = \frac{\delta_S}{\gamma} (\mathfrak{R}_1 - 1)$, where,

$$\mathfrak{R}_1 = \frac{\nu a \rho \zeta_2 \zeta_3}{\delta_S \delta_B} L_2.$$

Here, \mathfrak{R}_1 represents the humoral immunity activation number.

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

$$\begin{aligned} \mathfrak{R}_1 &= \frac{\nu a \rho \zeta_2 \zeta_3 L_2}{\delta_S \delta_B} = \frac{\nu a \rho \zeta_2 \zeta_3}{\delta_S \delta_B} \frac{\zeta_1 \eta \Psi(A_2) E_2 S_2}{a + \delta_L} \\ &= \frac{\nu a \zeta_1 \zeta_2 \zeta_3 \eta \Psi(A_2) E_2}{\delta_S (a + \delta_L)} < \frac{\nu a \zeta_1 \zeta_2 \zeta_3 \eta \Psi(A_0) E_0}{\delta_S (a + \delta_L)} = \mathfrak{R}_0. \end{aligned}$$

Now we can state the following lemma:

Lemma 2 For system (12), there exist two threshold parameters \mathfrak{R}_0 and \mathfrak{R}_1 such that

- (i) If $\mathfrak{R}_0 \leq 1$, then the uninfected equilibrium $\Delta_0 = (E_0, 0, 0, 0, A_0, 0)$ is the unique equilibrium,
- (ii) If $\mathfrak{R}_1 \leq 1 < \mathfrak{R}_0$, then there exists two equilibria Δ_0 and infected equilibrium without humoral immunity $\Delta_1 = (E_1, L_1, I_1, S_1, A_1, 0)$,
- (iii) If $\mathfrak{R}_1 > 1$, then there exist three equilibria Δ_0 , Δ_1 and infected equilibrium with humoral immunity $\Delta_2 = (E_2, L_2, I_2, S_2, A_2, B_2)$.

5. Global stability

This section formulates Lyapunov function and uses LIP to study the global asymptotic stability of equilibria. We follow the method presented in [39, 40]. 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

$$\Omega_j = \{(E, L, I, S, A, B) : \frac{d\Lambda_j}{dt} = 0\}, \quad j = 0, 1, 2,$$

where, $\Lambda_j(E, L, I, S, A, B)$ is a Lyapunov function candidate.

Theorem 1 Consider system (12) and suppose that $\mathfrak{R}_0 \leq 1$, then Δ_0 is globally asymptotically stable (G.A.S) and it is unstable when $\mathfrak{R}_0 > 1$.

Proof.

$$\begin{aligned} \Lambda_0 = & \zeta_1 E_0 \Phi\left(\frac{E}{E_0}\right) + L + \frac{a + \delta_L}{a\zeta_2} I + \frac{a + \delta_L}{a\nu\zeta_2\zeta_3} S + \frac{\zeta_1 E_0}{\kappa A_0} \left(A - A_0 - \int_{A_0}^A \frac{\Psi(A_0)}{\Psi(\xi)} d\xi \right) \\ & + \frac{\gamma(a + \delta_L)}{a\rho\nu\zeta_2\zeta_3} B + \eta \int_0^{h_1} \chi_1(\tau) \int_{t-\tau}^t \Psi(A(s)) E(s) S(s) ds d\tau \\ & + \frac{a + \delta_L}{\zeta_2} \int_0^{h_2} \chi_2(\tau) \int_{t-\tau}^t L(s) ds d\tau + \frac{\delta_I(a + \delta_L)}{a\zeta_2\zeta_3} \int_0^{h_3} \chi_3(\tau) \int_{t-\tau}^t I(s) ds d\tau. \end{aligned}$$

We note that, $\Lambda_0(E, L, I, S, A, B) > 0$ for all $E, L, I, S, A, B > 0$ and $\Lambda_0(E_0, 0, 0, 0, A_0, 0) = 0$. We calculate $\frac{d\Lambda_0}{dt}$ along the solutions of model (12) as:

$$\begin{aligned} \frac{d\Lambda_0}{dt} = & \zeta_1 \left(1 - \frac{E_0}{E} \right) \dot{E} + \dot{L} + \frac{a + \delta_L}{a\zeta_2} \dot{I} + \frac{a + \delta_L}{a\nu\zeta_2\zeta_3} \dot{S} + \frac{\zeta_1 E_0}{\kappa A_0} \left(1 - \frac{\Psi(A_0)}{\Psi(A)} \right) \dot{A} \\ & + \frac{\gamma(a + \delta_L)}{a\rho\nu\zeta_2\zeta_3} \dot{B} + \eta \frac{d}{dt} \int_0^{h_1} \chi_1(\tau) \int_{t-\tau}^t \Psi(A(s)) E(s) S(s) ds d\tau \\ & + \frac{a + \delta_L}{\zeta_2} \frac{d}{dt} \int_0^{h_2} \chi_2(\tau) \int_{t-\tau}^t L(s) ds d\tau + \frac{\delta_I(a + \delta_L)}{a\zeta_2\zeta_3} \frac{d}{dt} \int_0^{h_3} \chi_3(\tau) \int_{t-\tau}^t I(s) ds d\tau. \end{aligned}$$

Using system (12) we get

$$\begin{aligned}
\frac{d\Lambda_0}{dt} = & \zeta_1 \left(1 - \frac{E_0}{E} \right) [\lambda_E - \eta \Psi(A) ES - \delta_E E] \\
& + \eta \int_0^{h_1} \chi_1(\tau) \Psi(A_\tau) E_\tau S_\tau d\tau - (a + \delta_L) L \\
& + \frac{a + \delta_L}{a \zeta_2} \left[a \int_0^{h_2} \chi_2(\tau) L_\tau d\tau - \delta_I I \right] \\
& + \frac{a + \delta_L}{a v \zeta_2 \zeta_3} \left[\delta_I v \int_0^{h_3} \chi_3(\tau) I_\tau d\tau - \delta_S S - \gamma SB \right] \\
& + \frac{\zeta_1 E_0}{\kappa A_0} \left(1 - \frac{\Psi(A_0)}{\Psi(A)} \right) [\lambda_A - \kappa \eta \Psi(A) SA - \delta_A A] \\
& + \frac{\gamma(a + \delta_L)}{a \rho v \zeta_2 \zeta_3} [\rho SB - \delta_B B] \\
& + \eta \int_0^{h_1} \chi_1(\tau) [\Psi(A) ES - \Psi(A_\tau) E_\tau S_\tau] d\tau \\
& + \frac{a + \delta_L}{\zeta_2} \int_0^{h_2} \chi_2(\tau) [L - L_\tau] d\tau + \frac{\delta_I(a + \delta_L)}{a \zeta_2 \zeta_3} \int_0^{h_3} \chi_3(\tau) [I - I_\tau] d\tau.
\end{aligned}$$

Collecting terms we get

$$\begin{aligned}
\frac{d\Lambda_0}{dt} = & \zeta_1 \left(1 - \frac{E_0}{E} \right) [\lambda_E - \delta_E E] + \eta \zeta_1 \Psi(A) E_0 S \\
& - \frac{a + \delta_L}{a v \zeta_2 \zeta_3} \delta_S S + \eta \zeta_1 \Psi(A_0) E_0 S - \eta \zeta_1 \Psi(A_0) E_0 S \\
& + \frac{\zeta_1 E_0}{\kappa A_0} \left(1 - \frac{\Psi(A_0)}{\Psi(A)} \right) [\lambda_A - \delta_A A] - \frac{\zeta_1 E_0}{A_0} (\Psi(A) - \Psi(A_0)) \eta SA \\
& - \frac{\gamma(a + \delta_L) \delta_B}{a \rho v \zeta_2 \zeta_3} B
\end{aligned}$$

$$\begin{aligned}
&= \zeta_1 \left(\frac{E - E_0}{E} \right) [\lambda_E - \delta_E E] + \left(\eta \zeta_1 \Psi(A_0) E_0 - \frac{(a + \delta_L) \delta_S}{a \nu \zeta_2 \zeta_3} \right) S \\
&\quad + \eta \zeta_1 E_0 S (\Psi(A) - \Psi(A_0)) + \frac{\zeta_1 E_0}{\kappa A_0 \Psi(A)} (\Psi(A) - \Psi(A_0)) [\lambda_A - \delta_A A] \\
&\quad - \frac{\zeta_1 E_0}{A_0} (\Psi(A) - \Psi(A_0)) \eta S A - \frac{\gamma(a + \delta_L) \delta_B}{a \rho \nu \zeta_2 \zeta_3} B.
\end{aligned}$$

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

$$\begin{aligned}
\frac{d\Lambda_0}{dt} &= -\zeta_1 \delta_E \frac{(E - E_0)^2}{E} + \frac{(a + \delta_L) \delta_S}{a \nu \zeta_2 \zeta_3} \left(\frac{a \nu \zeta_1 \zeta_2 \zeta_3 \eta \Psi(A_0) E_0}{(a + \delta_L) \delta_S} - 1 \right) S \\
&\quad + \eta \zeta_1 E_0 S (\Psi(A) - \Psi(A_0)) \frac{A_0}{A_0} + \frac{\zeta_1 \delta_A E_0}{\kappa A_0 \Psi(A)} (\Psi(A) - \Psi(A_0)) (A_0 - A) \\
&\quad - \frac{\eta \zeta_1 E_0}{A_0} S (\Psi(A) - \Psi(A_0)) A - \frac{\gamma(a + \delta_L) \delta_B}{a \rho \nu \zeta_2 \zeta_3} B \\
&= -\zeta_1 \delta_E \frac{(E - E_0)^2}{E} + \frac{(a + \delta_L) \delta_S}{a \nu \zeta_2 \zeta_3} (\Re_0 - 1) S \\
&\quad + \left(\frac{\eta \zeta_1 E_0 S}{A_0} + \frac{\zeta_1 \delta_A E_0}{\kappa A_0 \Psi(A)} \right) (\Psi(A) - \Psi(A_0)) (A_0 - A) - \frac{\gamma(a + \delta_L) \delta_B}{a \rho \nu \zeta_2 \zeta_3} B.
\end{aligned}$$

Since $\Re_0 \leq 1$ and $(\Psi(A) - \Psi(A_0)) (A_0 - A) \leq 0$, then $\frac{d\Lambda_0}{dt} \leq 0$ for all $E, S, A, B > 0$. In addition $\frac{d\Lambda_0}{dt} = 0$ when $E = E_0$, $A = A_0$ and $S = B = 0$. Solutions of system (12) converge to $\tilde{\Omega}_0$ which contains elements with $S = 0$ [41]. Thus, $\dot{S} = 0$, the fourth equation of system (12) gives

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

Since $I = 0$, then $\dot{I} = 0$ and from the third equation of system (12) we have:

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

Therefore, $\tilde{\Omega}_0 = \{\Delta_0\}$ and applying LIP [42], we obtain that Δ_0 is G.A.S.

To show that instability of Δ_0 we calculate the characteristic equation of system (12) at Δ_0 as:

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

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

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

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

$$\mathcal{T}(0) = (a + \delta_L)\delta_I\delta_S\delta_A(1 - \Re_0) < 0, \text{ when } \Re_0 > 1,$$

$$\lim_{c \rightarrow \infty} \mathcal{T}(c) = \infty.$$

Hence, $\mathcal{T}(c)$ has a positive real root and thus Δ_0 is unstable. □

For confirming result on dynamics of Δ_1 , we require a additional assumptions [43]:

$$S_1 \leq \frac{\delta_B}{\rho}. \quad (\text{A})$$

Theorem 2 Suppose that $\Re_1 \leq 1 < \Re_0$ and Assumption (A) is satisfied, then Δ_1 is G.A.S.

Proof. Define Λ_1 as:

$$\Lambda_1 = \zeta_1 E_1 \Phi\left(\frac{E}{E_1}\right) + L_1 \Phi\left(\frac{L}{L_1}\right) + \frac{a + \delta_L}{a\zeta_2} I_1 \Phi\left(\frac{I}{I_1}\right) + \frac{a + \delta_L}{av\zeta_2\zeta_3} S_1 \Phi\left(\frac{S}{S_1}\right) \\ + \frac{\zeta_1 E_1}{\kappa A_1} \left(A - A_1 - \int_{A_1}^A \frac{\Psi(A_1)}{\Psi(\xi)} d\xi \right) + \frac{\gamma(a + \delta_L)}{\rho av\zeta_2\zeta_3} B \\ + \eta \Psi(A_1) E_1 S_1 \int_0^{h_1} \chi_1(\tau) \int_{t-\tau}^t \Phi\left(\frac{\Psi(A(s))E(s)S(s)}{\Psi(A_1)E_1 S_1}\right) ds d\tau \\ + \frac{a + \delta_L}{\zeta_2} L_1 \int_0^{h_2} \chi_2(\tau) \int_{t-\tau}^t \Phi\left(\frac{L(s)}{L_1}\right) ds d\tau \\ + \frac{(a + \delta_L)\delta_I}{a\zeta_2\zeta_3} I_1 \int_0^{h_3} \chi_3(\tau) \int_{t-\tau}^t \Phi\left(\frac{I(s)}{I_1}\right) ds d\tau.$$

We note that, $\Lambda_1(E, L, I, S, A, B) > 0$ for all $E, L, I, S, A, B > 0$ and $\Lambda_1(E_1, L_1, I_1, S_1, A_1, 0) = 0$. We calculate $\frac{d\Lambda_1}{dt}$ along the solutions of model (12) as:

$$\begin{aligned} \frac{d\Lambda_1}{dt} = & \zeta_1 \left(1 - \frac{E_1}{E}\right) \dot{E} + \left(1 - \frac{L_1}{L}\right) \dot{L} + \frac{a + \delta_L}{a\zeta_2} \left(1 - \frac{I_1}{I}\right) \dot{I} \\ & + \frac{a + \delta_L}{av\zeta_2\zeta_3} \left(1 - \frac{S_1}{S}\right) \dot{S} + \frac{\zeta_1 E_1}{\kappa A_1} \left(1 - \frac{\Psi(A_1)}{\Psi(A)}\right) \dot{A} + \frac{\gamma(a + \delta_L)}{\rho av\zeta_2\zeta_3} \dot{B} \\ & + \eta \Psi(A_1) E_1 S_1 \frac{d}{dt} \int_0^{h_1} \chi_1(\tau) \int_{t-\tau}^t \Phi \left(\frac{\Psi(A(s)) E(s) S(s)}{\Psi(A_1) E_1 S_1} \right) ds d\tau + \frac{a + \delta_L}{\zeta_2} L_1 \\ & \times \frac{d}{dt} \int_0^{h_2} \chi_2(\tau) \int_{t-\tau}^t \Phi \left(\frac{L(s)}{L_1} \right) ds d\tau + \frac{(a + \delta_L) \delta_I}{a\zeta_2\zeta_3} I_1 \frac{d}{dt} \int_0^{h_3} \chi_3(\tau) \int_{t-\tau}^t \Phi \left(\frac{I(s)}{I_1} \right) ds d\tau. \end{aligned}$$

Using system (12) we get

$$\begin{aligned} \frac{d\Lambda_1}{dt} = & \zeta_1 \left(1 - \frac{E_1}{E}\right) [\lambda_E - \eta \Psi(A) ES - \delta_E E] \\ & + \left(1 - \frac{L_1}{L}\right) \left[\eta \int_0^{h_1} \chi_1(\tau) \Psi(A_\tau) E_\tau S_\tau d\tau - (a + \delta_L) L \right] \\ & + \frac{a + \delta_L}{a\zeta_2} \left(1 - \frac{I_1}{I}\right) \left[a \int_0^{h_2} \chi_2(\tau) L_\tau d\tau - \delta_I I \right] \\ & + \frac{a + \delta_L}{av\zeta_2\zeta_3} \left(1 - \frac{S_1}{S}\right) \left[\delta_I v \int_0^{h_3} \chi_3(\tau) I_\tau d\tau - \delta_S S - \gamma SB \right] \\ & + \frac{\zeta_1 E_1}{\kappa A_1} \left(1 - \frac{\Psi(A_1)}{\Psi(A)}\right) [\lambda_A - \kappa \eta \Psi(A) SA - \delta_A A] + \frac{\gamma(a + \delta_L)}{\rho av\zeta_2\zeta_3} [\rho SB - \delta_B B] \\ & + \eta \Psi(A_1) E_1 S_1 \int_0^{h_1} \chi_1(\tau) \left[\frac{\Psi(A) ES}{\Psi(A_1) E_1 S_1} - \frac{\Psi(A_\tau) E_\tau S_\tau}{\Psi(A_1) E_1 S_1} + \ln \left(\frac{\Psi(A_\tau) E_\tau S_\tau}{\Psi(A) ES} \right) \right] d\tau \\ & + \frac{a + \delta_L}{\zeta_2} L_1 \int_0^{h_2} \chi_2(\tau) \left[\frac{L}{L_1} - \frac{L_\tau}{L_1} + \ln \left(\frac{L_\tau}{L} \right) \right] d\tau \\ & + \frac{(a + \delta_L) \delta_I}{a\zeta_2\zeta_3} I_1 \int_0^{h_3} \chi_3(\tau) \left[\frac{I}{I_1} - \frac{I_\tau}{I_1} + \ln \left(\frac{I_\tau}{I} \right) \right] d\tau. \end{aligned}$$

Collecting terms we get

$$\begin{aligned}
\frac{d\Lambda_1}{dt} = & \zeta_1 \left(1 - \frac{E_1}{E} \right) [\lambda_E - \delta_E E] + \zeta_1 \eta \Psi(A) E_1 S \\
& - \eta \int_0^{h_1} \chi_1(\tau) \Psi(A_\tau) E_\tau S_\tau \frac{L_1}{L} d\tau + (a + \delta_L) L_1 \\
& - \frac{a + \delta_L}{\zeta_2} \int_0^{h_2} \chi_2(\tau) L_\tau \frac{I_1}{I} d\tau + \frac{a + \delta_L}{a \zeta_2} \delta_I I_1 \\
& - \frac{a + \delta_L}{a \nu \zeta_2 \zeta_3} \delta_S S - \frac{a + \delta_L}{a \zeta_2 \zeta_3} \delta_I \int_0^{h_3} \chi_3(\tau) I_\tau \frac{S_1}{S} d\tau + \frac{a + \delta_L}{a \nu \zeta_2 \zeta_3} \delta_S S_1 \\
& + \frac{a + \delta_L}{a \nu \zeta_2 \zeta_3} \gamma S_1 B + \frac{\zeta_1 E_1}{\kappa A_1} \left(1 - \frac{\Psi(A_1)}{\Psi(A)} \right) [\lambda_A - \delta_A A] \\
& - \frac{\zeta_1 E_1}{A_1} \eta S A (\Psi(A) - \Psi(A_1)) - \frac{\gamma(a + \delta_L) \delta_B}{\rho a \nu \zeta_2 \zeta_3} B \\
& + \eta \Psi(A_1) E_1 S_1 \int_0^{h_1} \chi_1(\tau) \ln \left(\frac{\Psi(A_\tau) E_\tau S_\tau}{\Psi(A) E S} \right) d\tau \\
& + \frac{a + \delta_L}{\zeta_2} L_1 \int_0^{h_2} \chi_2(\tau) \ln \left(\frac{L_\tau}{L} \right) d\tau + \frac{(a + \delta_L) \delta_I}{a \zeta_2 \zeta_3} I_1 \int_0^{h_3} \chi_3(\tau) \ln \left(\frac{I_\tau}{I} \right) d\tau.
\end{aligned}$$

Using the equilibrium condition for Δ_1 :

$$\lambda_E = \eta \Psi(A_1) E_1 S_1 + \delta_E E_1, \quad (a + \delta_L) L_1 = \eta \zeta_1 \Psi(A_1) E_1 S_1,$$

$$\delta_I I_1 = a \zeta_2 L_1, \quad \delta_S S_1 = \delta_I \nu \zeta_3 I_1, \quad \lambda_A = \kappa \eta \Psi(A_1) S_1 A_1 + \delta_A A_1,$$

we obtain,

$$\begin{aligned}
\frac{d\Lambda_1}{dt} = & -\zeta_1 \delta_E \frac{(E - E_1)^2}{E} + 5(a + \delta_L) L_1 - (a + \delta_L) L_1 \frac{E_1}{E} + \zeta_1 \eta \Psi(A) E_1 S \\
& - \frac{a + \delta_L}{\zeta_1} L_1 \int_0^{h_1} \chi_1(\tau) \frac{\Psi(A_\tau) E_\tau S_\tau L_1}{\Psi(A_1) E_1 S_1 L} d\tau - \frac{a + \delta_L}{\zeta_2} L_1 \int_0^{h_2} \chi_2(\tau) \frac{L_\tau I_1}{L_1 I} d\tau
\end{aligned}$$

$$\begin{aligned}
& -\zeta_1 \eta \Psi(A_1) E_1 S - \frac{a + \delta_L}{\zeta_3} L_1 \int_0^{h_3} \chi_3(\tau) \frac{I_\tau S_1}{I_1 S} d\tau + \left(\frac{(a + \delta_L) \gamma}{a v \zeta_2 \zeta_3} S_1 - \frac{(a + \delta_L) \gamma \delta_B}{a \rho v \zeta_2 \zeta_3} \right) B \\
& + \frac{\zeta_1 \delta_A E_1}{\kappa A_1 \Psi(A)} (\Psi(A) - \Psi(A_1)) (A_1 - A) - (a + \delta_L) L_1 \frac{\Psi(A_1)}{\Psi(A)} \\
& - \frac{\eta \zeta_1 E_1}{A_1} (\Psi(A) - \Psi(A_1)) S A + \frac{a + \delta_L}{\zeta_1} L_1 \int_0^{h_1} \chi_1(\tau) \ln \left(\frac{\Psi(A_\tau) E_\tau S_\tau}{\Psi(A) E S} \right) d\tau \\
& + \frac{a + \delta_L}{\zeta_2} L_1 \int_0^{h_2} \chi_2(\tau) \ln \left(\frac{L_\tau}{L} \right) d\tau + \frac{a + \delta_L}{\zeta_3} L_1 \int_0^{h_3} \chi_3(\tau) \ln \left(\frac{I_\tau}{I} \right) d\tau \\
& = -\zeta_1 \delta_E \frac{(E - E_1)^2}{E} + 5(a + \delta_L) L_1 - (a + \delta_L) L_1 \frac{E_1}{E} + \eta \zeta_1 E_1 S (\Psi(A) - \Psi(A_1)) \\
& - \frac{a + \delta_L}{\zeta_1} L_1 \int_0^{h_1} \chi_1(\tau) \frac{\Psi(A_\tau) E_\tau S_\tau L_1}{\Psi(A_1) E_1 S_1 L} d\tau - \frac{a + \delta_L}{\zeta_2} L_1 \int_0^{h_2} \chi_2(\tau) \frac{L_\tau I_1}{L_1 I} d\tau \\
& - \frac{a + \delta_L}{\zeta_3} L_1 \int_0^{h_3} \chi_3(\tau) \frac{I_\tau S_1}{I_1 S} d\tau + \frac{(a + \delta_L) \gamma}{a v \zeta_2 \zeta_3} \left(S_1 - \frac{\delta_B}{\rho} \right) B \\
& + \frac{\zeta_1 \delta_A E_1}{\kappa A_1 \Psi(A)} (\Psi(A) - \Psi(A_1)) (A_1 - A) - (a + \delta_L) L_1 \frac{\Psi(A_1)}{\Psi(A)} \\
& - \frac{\eta \zeta_1 E_1}{A_1} (\Psi(A) - \Psi(A_1)) S A + \frac{a + \delta_L}{\zeta_1} L_1 \int_0^{h_1} \chi_1(\tau) \ln \left(\frac{\Psi(A_\tau) E_\tau S_\tau}{\Psi(A) E S} \right) d\tau \\
& + \frac{a + \delta_L}{\zeta_2} L_1 \int_0^{h_2} \chi_2(\tau) \ln \left(\frac{L_\tau}{L} \right) d\tau + \frac{a + \delta_L}{\zeta_3} L_1 \int_0^{h_3} \chi_3(\tau) \ln \left(\frac{I_\tau}{I} \right) d\tau.
\end{aligned}$$

Using equalities

$$\begin{aligned}
\ln \left(\frac{\Psi(A_\tau) E_\tau S_\tau}{\Psi(A) E S} \right) &= \ln \left(\frac{\Psi(A_\tau) E_\tau S_\tau L_1}{\Psi(A_1) E_1 S_1 L} \right) \\
&+ \ln \left(\frac{\Psi(A_1)}{\Psi(A)} \right) + \ln \left(\frac{L S_1}{L_1 S} \right) + \ln \left(\frac{E_1}{E} \right),
\end{aligned}$$

$$\ln\left(\frac{L\tau}{L}\right) = \ln\left(\frac{L\tau I_1}{L_1 I}\right) + \ln\left(\frac{L_1 I}{L I_1}\right),$$

$$\ln\left(\frac{I\tau}{I}\right) = \ln\left(\frac{I\tau S_1}{I_1 S}\right) + \ln\left(\frac{I_1 S}{I S_1}\right),$$

we obtain,

$$\begin{aligned} \frac{d\Lambda_1}{dt} = & -\zeta_1 \delta_E \frac{(E-E_1)^2}{E} - (a+\delta_L) L_1 \left[\Phi\left(\frac{E_1}{E}\right) + \frac{1}{\zeta_1} \int_0^{h_1} \chi_1(\tau) \right. \\ & \times \Phi\left(\frac{\Psi(A_\tau) E_\tau S_\tau L_1}{\Psi(A_1) E_1 S_1 L}\right) d\tau + \frac{1}{\zeta_2} \int_0^{h_2} \chi_2(\tau) \Phi\left(\frac{L\tau I_1}{L_1 I}\right) d\tau \\ & + \frac{1}{\zeta_3} \int_0^{h_3} \chi_3(\tau) \Phi\left(\frac{I\tau S_1}{I_1 S}\right) d\tau + \Phi\left(\frac{\Psi(A_1)}{\Psi(A)}\right) \left. \right] + \frac{(a+\delta_L)\gamma}{av\zeta_2\zeta_3} \left(S_1 - \frac{\delta_B}{\rho}\right) B \\ & + \left[\frac{\zeta_1 \delta_A E_1}{\kappa A_1 \Psi(A)} + \frac{\eta \zeta_1 E_1 S}{A_1} \right] (\Psi(A) - \Psi(A_1)) (A_1 - A). \end{aligned}$$

We have Since $S_1 \leq \frac{\delta_B}{\rho}$ and $(\Psi(A) - \Psi(A_1)) (A_1 - A) \leq 0$, then $\frac{d\Lambda_1}{dt} \leq 0$ for all $E, L, I, S, A, B > 0$. In addition, $\frac{d\Lambda_1}{dt} = 0$ when $E = E_1, L = L_1, I = I_1, S = S_1, A = A_1$ and $B = 0$. Therefore, $\tilde{\Omega}_1 = \{\Delta_1\}$ and applying LIP, we obtain that Δ_1 is G.A.S. \square

Theorem 3 For system (12), let $\Re_1 > 1$, then Δ_2 is G.A.S.

Proof. Consider

$$\begin{aligned} \Lambda_2 = & \zeta_1 E_2 \Phi\left(\frac{E}{E_2}\right) + L_2 \Phi\left(\frac{L}{L_2}\right) + \frac{a+\delta_L}{a\zeta_2} I_2 \Phi\left(\frac{I}{I_2}\right) \\ & + \frac{a+\delta_L}{av\zeta_2\zeta_3} S_2 \Phi\left(\frac{S}{S_2}\right) + \frac{\zeta_1 E_2}{\kappa A_2} \left(A - A_2 - \int_{A_2}^A \frac{\Psi(A_2)}{\Psi(\xi)} d\xi\right) \\ & + \frac{\gamma(a+\delta_L)}{\rho av\zeta_2\zeta_3} B_2 \Phi\left(\frac{B}{B_2}\right) + \eta \Psi(A_2) E_2 S_2 \int_0^{h_1} \chi_1(\tau) \int_{t-\tau}^t \Phi\left(\frac{\Psi(A(s)) E(s) S(s)}{\Psi(A_2) E_2 S_2}\right) ds d\tau \\ & + \frac{a+\delta_L}{\zeta_2} L_2 \int_0^{h_2} \chi_2(\tau) \int_{t-\tau}^t \Phi\left(\frac{L(s)}{L_2}\right) ds d\tau + \frac{(a+\delta_L)\delta_I}{a\zeta_2\zeta_3} I_2 \int_0^{h_3} \chi_3(\tau) \int_{t-\tau}^t \Phi\left(\frac{I(s)}{I_2}\right) ds d\tau. \end{aligned}$$

We note that, $\Lambda_2(E, L, I, S, A, B) > 0$ for all $E, L, I, S, A, B > 0$ and $\Lambda_2(E_2, L_2, I_2, S_2, A_2, B_2) = 0$.

We calculate $\frac{d\Lambda_2}{dt}$ as:

$$\begin{aligned}
\frac{d\Lambda_2}{dt} = & \zeta_1 \left(1 - \frac{E_2}{E}\right) \dot{E} + \left(1 - \frac{L_2}{L}\right) \dot{L} + \frac{a + \delta_L}{a\zeta_2} \left(1 - \frac{I_2}{I}\right) \dot{I} \\
& + \frac{a + \delta_L}{av\zeta_2\zeta_3} \left(1 - \frac{S_2}{S}\right) \dot{S} + \frac{\zeta_1 E_2}{\kappa A_2} \left(1 - \frac{\Psi(A_2)}{\Psi(A)}\right) \dot{A} + \frac{\gamma(a + \delta_L)}{\rho av\zeta_2\zeta_3} \left(1 - \frac{B_2}{B}\right) \dot{B} \\
& + \eta \Psi(A_2) E_2 S_2 \frac{d}{dt} \int_0^{h_1} \chi_1(\tau) \int_{t-\tau}^t \Phi \left(\frac{\Psi(A(s)) E(s) S(s)}{\Psi(A_2) E_2 S_2} \right) ds d\tau \\
& + \frac{a + \delta_L}{\zeta_2} L_2 \frac{d}{dt} \int_0^{h_2} \chi_2(\tau) \int_{t-\tau}^t \Phi \left(\frac{L(s)}{L_2} \right) ds d\tau \\
& + \frac{(a + \delta_L) \delta_I}{a\zeta_2\zeta_3} I_2 \frac{d}{dt} \int_0^{h_3} \chi_3(\tau) \int_{t-\tau}^t \Phi \left(\frac{I(s)}{I_2} \right) ds d\tau.
\end{aligned}$$

From system (12) we get

$$\begin{aligned}
\frac{d\Lambda_2}{dt} = & \zeta_1 \left(1 - \frac{E_2}{E}\right) [\lambda_E - \eta \Psi(A) ES - \delta_E E] \\
& + \left(1 - \frac{L_2}{L}\right) \left[\eta \int_0^{h_1} \chi_1(\tau) \Psi(A_\tau) E_\tau S_\tau d\tau - (a + \delta_L) L \right] \\
& + \frac{a + \delta_L}{a\zeta_2} \left(1 - \frac{I_2}{I}\right) \left[a \int_0^{h_2} \chi_2(\tau) L_\tau d\tau - \delta_I I \right] \\
& + \frac{a + \delta_L}{av\zeta_2\zeta_3} \left(1 - \frac{S_2}{S}\right) \left[\delta_I v \int_0^{h_3} \chi_3(\tau) I_\tau d\tau - \delta_S S - \gamma SB \right] \\
& + \frac{\zeta_1 E_2}{\kappa A_2} \left(1 - \frac{\Psi(A_2)}{\Psi(A)}\right) [\lambda_A - \kappa \eta \Psi(A) SA - \delta_A A] \\
& + \frac{\gamma(a + \delta_L)}{\rho av\zeta_2\zeta_3} \left(1 - \frac{B_2}{B}\right) [\rho SB - \delta_B B] + \eta \Psi(A_2) E_2 S_2 \int_0^{h_1} \chi_1(\tau) \\
& \times \left[\frac{\Psi(A) ES}{\Psi(A_2) E_2 S_2} - \frac{\Psi(A_\tau) E_\tau S_\tau}{\Psi(A_2) E_2 S_2} + \ln \left(\frac{\Psi(A_\tau) E_\tau S_\tau}{\Psi(A) ES} \right) \right] d\tau
\end{aligned}$$

$$\begin{aligned}
& + \frac{a + \delta_L}{\zeta_2} L_2 \int_0^{h_2} \chi_2(\tau) \left[\frac{L}{L_2} - \frac{L_\tau}{L_2} + \ln \left(\frac{L_\tau}{L} \right) \right] d\tau \\
& + \frac{(a + \delta_L) \delta_I}{a \zeta_2 \zeta_3} I_2 \int_0^{h_3} \chi_3(\tau) d\tau \left[\frac{I}{I_2} - \frac{I_\tau}{I_2} + \ln \left(\frac{I_\tau}{I} \right) \right] d\tau.
\end{aligned}$$

Collecting terms we get

$$\begin{aligned}
\frac{d\Lambda_2}{dt} = & \zeta_1 \left(1 - \frac{E_2}{E} \right) [\lambda_E - \delta_E E] + \eta \zeta_1 \Psi(A) E_2 S \\
& - \eta \int_0^{h_1} \chi_1(\tau) \Psi(A_\tau) E_\tau S_\tau \frac{L_2}{L} d\tau + (a + \delta_L) L_2 \\
& - \frac{a + \delta_L}{\zeta_2} \int_0^{h_2} \chi_2(\tau) L_\tau \frac{I_2}{I} d\tau + \frac{(a + \delta_L) \delta_I}{a \zeta_2} I_2 \\
& - \frac{(a + \delta_L) \delta_S}{a \nu \zeta_2 \zeta_3} S - \frac{(a + \delta_L) \delta_I}{a \zeta_2 \zeta_3} \int_0^{h_3} \chi_3(\tau) I_\tau \frac{S_2}{S} d\tau \\
& + \frac{(a + \delta_L) \delta_S}{a \nu \zeta_2 \zeta_3} S_2 + \frac{(a + \delta_L) \gamma}{a \nu \zeta_2 \zeta_3} S_2 B + \frac{\zeta_1 E_2}{\kappa A_2} \left(1 - \frac{\Psi(A_2)}{\Psi(A)} \right) [\lambda_A - \delta_A A] \\
& - \frac{\zeta_1 E_2}{A_2} (\Psi(A) - \Psi(A_2)) \eta S A - \frac{\gamma(a + \delta_L) \delta_B}{\rho a \nu \zeta_2 \zeta_3} B - \frac{\gamma(a + \delta_L)}{a \nu \zeta_2 \zeta_3} S B_2 \\
& + \frac{\gamma(a + \delta_L) \delta_B}{\rho a \nu \zeta_2 \zeta_3} B_2 + \eta \Psi(A_2) E_2 S_2 \int_0^{h_1} \chi_1(\tau) \ln \left(\frac{\Psi(A_\tau) E_\tau S_\tau}{\Psi(A) E S} \right) d\tau \\
& + \frac{a + \delta_L}{\zeta_2} L_2 \int_0^{h_2} \chi_2(\tau) \ln \left(\frac{L_\tau}{L} \right) d\tau + \frac{(a + \delta_L) \delta_I}{a \zeta_2 \zeta_3} I_2 \int_0^{h_3} \chi_3(\tau) \ln \left(\frac{I_\tau}{I} \right) d\tau.
\end{aligned}$$

Using the equilibrium condition for Δ_2 :

$$\lambda_E = \eta \Psi(A_2) E_2 S_2 + \delta_E E_2, \quad (a + \delta_L) L_2 = \eta \zeta_1 \Psi(A_2) E_2 S_2,$$

$$\delta_I I_2 = a \zeta_2 L_2, \quad \delta_S S_2 = \delta_I \nu \zeta_3 I_2 - \gamma S_2 B_2, \quad \lambda_A = \kappa \eta \Psi(A_2) S_2 A_2 + \delta_A A_2, \quad S_2 = \frac{\delta_B}{\rho},$$

we obtain,

$$\begin{aligned}
\frac{d\Lambda_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 \\
&\quad - \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_2 S_2 L} 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 \\
&\quad - \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)} \\
&\quad \times (\Psi(A) - \Psi(A_2))(A_2 - A) - (a+\delta_L)L_2 \frac{\Psi(A_2)}{\Psi(A)} - \frac{\zeta_1 E_2}{A_2} \eta S A (\Psi(A) - \Psi(A_2)) \\
&\quad + \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 \\
&\quad + \frac{a+\delta_L}{\zeta_3} L_2 \int_0^{h_3} \chi_3(\tau) \ln \left(\frac{I_\tau}{I} \right) d\tau \\
&= -\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_2 S (\Psi(A) - \Psi(A_2)) \\
&\quad - \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_2 S_2 L} 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 \\
&\quad - \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)} (\Psi(A) - \Psi(A_2))(A_2 - A) \\
&\quad - (a+\delta_L)L_2 \frac{\Psi(A_2)}{\Psi(A)} - \frac{\zeta_1 E_2}{A_2} \eta S A (\Psi(A) - \Psi(A_2)) \\
&\quad + \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) \\
&\quad \times \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.
\end{aligned}$$

Using equalities

$$\begin{aligned}\ln\left(\frac{\Psi(A_\tau)E_\tau S_\tau}{\Psi(A)ES}\right) &= \ln\left(\frac{\Psi(A_\tau)E_\tau S_\tau L_2}{\Psi(A_2)E_2 S_2 L}\right) + \ln\left(\frac{\Psi(A_2)}{\Psi(A)}\right) \\ &\quad + \ln\left(\frac{LS_2}{L_2 S}\right) + \ln\left(\frac{E_2}{E}\right), \\ \ln\left(\frac{L_\tau}{L}\right) &= \ln\left(\frac{L_\tau I_2}{L_2 I}\right) + \ln\left(\frac{L_2 I}{L I_2}\right), \\ \ln\left(\frac{I_\tau}{I}\right) &= \ln\left(\frac{I_\tau S_2}{I_2 S}\right) + \ln\left(\frac{I_2 S}{I S_2}\right),\end{aligned}$$

we obtain,

$$\begin{aligned}\frac{d\Lambda_2}{dt} &= -\delta_E \zeta_1 \frac{(E-E_2)^2}{E} - (a + \delta_L)L_2 \left[\Phi\left(\frac{E_2}{E}\right) + \frac{1}{\zeta_1} \int_0^{h_1} \chi_1(\tau) \right. \\ &\quad \times \Phi\left(\frac{\Psi(A_\tau)E_\tau S_\tau L_2}{\Psi(A_2)E_2 S_2 L}\right) d\tau + \frac{1}{\zeta_2} \int_0^{h_2} \chi_2(\tau) \Phi\left(\frac{L_\tau I_2}{L_2 I}\right) d\tau \\ &\quad \left. + \frac{1}{\zeta_3} \int_0^{h_3} \chi_3(\tau) \Phi\left(\frac{I_\tau S_2}{I_2 S}\right) + \Phi\left(\frac{\Psi(A_2)}{\Psi(A)}\right) \right] + \left[\frac{\zeta_1 \delta_A E_2}{\kappa A_2 \Psi(A)} + \frac{\zeta_1 \eta S E_2}{A_2} \right] \\ &\quad \times (\Psi(A) - \Psi(A_2))(A_2 - A).\end{aligned}$$

If $\Re_1 > 1$, we get $\frac{d\Lambda_2}{dt} \leq 0$ for all $E, L, I, S, A > 0$. Further, $\frac{d\Lambda_2}{dt} = 0$ when $E = E_2, L = L_2, I = I_2, S = S_2$, and $A = A_2$. Trajectories of system (12) converge to $\tilde{\Omega}_2$ which has $I = I_2$ and $S = S_2$. The fourth equation of system (12) provides

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

Therefore, $\tilde{\Omega}_2 = \{\Delta_2\}$. Applying LIP implies that Δ_2 is G.A.S. □

5.1 Comparison results

We examine model (12) under the influence of medication therapy for inhibiting the virus replication as an example to demonstrate the significance of including the latently infected cells and humoral immunity in our suggested model:

$$\begin{cases} \dot{E} = \lambda_E - \eta \Psi(A)ES - \delta_E E, \\ \dot{L} = \eta \int_0^{h_1} f_1(\tau) e^{-\alpha_1 \tau} \Psi(A_\tau) E_\tau S_\tau d\tau - (a + \delta_L)L, \\ \dot{I} = a \int_0^{h_2} f_2(\tau) e^{-\alpha_2 \tau} L_\tau d\tau - \delta_I I, \\ \dot{S} = (1 - \varepsilon) \delta_I v \int_0^{h_3} f_3(\tau) e^{-\alpha_3 \tau} I_\tau d\tau - \delta_S S - \gamma SB, \\ \dot{A} = \lambda_A - \kappa \eta \Psi(A)AS - \delta_A A, \\ \dot{B} = \rho SB - \delta_B B, \end{cases} \quad (25)$$

where $\varepsilon \in [0, 1]$ is the efficacy of drug therapy. The basic reproduction number of system (25) is:

$$\mathfrak{R}_0^\varepsilon = \frac{(1 - \varepsilon) \eta a v \zeta_1 \zeta_2 \zeta_3 \Psi(A_0) E_0}{(a + \delta_L) \delta_S} = (1 - \varepsilon) \mathfrak{R}_0.$$

Now, we calculate the drug efficacy ε that makes $\mathfrak{R}_0^\varepsilon \leq 1$ and stabilizes Δ_0 of system (25) as:

$$1 \geq \varepsilon \geq \tilde{\varepsilon}_{\min} = \max \left\{ 0, 1 - \frac{1}{\mathfrak{R}_0} \right\}. \quad (26)$$

When we ignore the latent phase in model (25) we obtain

$$\begin{cases} \dot{E} = \lambda_E - \eta \Psi(A)ES - \delta_E E, \\ \dot{I} = \eta \int_0^{h_1} f_1(\tau) e^{-\alpha_1 \tau} \Psi(A_\tau) E_\tau S_\tau d\tau - \delta_I I, \\ \dot{S} = (1 - \varepsilon) \delta_I v \int_0^{h_3} f_3(\tau) e^{-\alpha_3 \tau} I_\tau d\tau - \delta_S S - \gamma SB, \\ \dot{A} = \lambda_A - \kappa \eta \Psi(A)AS - \delta_A A, \\ \dot{B} = \rho SB - \delta_B B, \end{cases} \quad (27)$$

and the basic reproduction number of model (27) is given by

$$\hat{\mathfrak{R}}_0^\varepsilon = \frac{(1-\varepsilon)\eta v \zeta_1 \zeta_3 \Psi(A_0) E_0}{\delta_S} = (1-\varepsilon) \hat{\mathfrak{R}}_0$$

We determine the drug efficacy ε that makes $\hat{\mathfrak{R}}_0^\varepsilon \leq 1$ and stabilizes Δ_0 of system (27) as:

$$1 \geq \varepsilon \geq \hat{\varepsilon}_{\min} = \max \left\{ 0, 1 - \frac{1}{\hat{\mathfrak{R}}_0} \right\}. \quad (28)$$

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

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

In the SARS-CoV-2 dynamical model, excluding the latently infected cells would result in an overestimation of the basic reproduction number. By comparing Equations (26) and (28) we get that $\hat{\varepsilon}_{\min} > \tilde{\varepsilon}_{\min}$. As a result, when using a model with latent phase, less anti-SARS-CoV-2 medication will be required to maintain the system at the uninfected equilibrium and eradicate SARS-CoV-2 from the body.

In the absence of humoral immune response, system (12) becomes:

$$\begin{cases} \dot{E} = \lambda_E - \eta \Psi(A) E S - \delta_E E, \\ \dot{L} = \eta \int_0^{h_1} f_1(\tau) e^{-\alpha_1 \tau} \Psi(A_\tau) E_\tau S_\tau d\tau - (a + \delta_L) L, \\ \dot{I} = a \int_0^{h_2} f_2(\tau) e^{-\alpha_2 \tau} L_\tau d\tau - \delta_I I, \\ \dot{S} = \delta_I v \int_0^{h_3} f_3(\tau) e^{-\alpha_3 \tau} I_\tau d\tau - \delta_S S, \\ \dot{A} = \lambda_A - \kappa \eta \Psi(A) A S - \delta_A A. \end{cases} \quad (29)$$

This model has only two equilibria:

- (i) Uninfected equilibrium, $\bar{\Delta}_0 = (E_0, 0, 0, 0, A_0)$, where the SARS-CoV-2 infection is cleared,
- (ii) Infected equilibrium $\bar{\Delta}_1 = (E_1, L_1, I_1, S_1, A_1)$, where the SARS-CoV-2 infection is present.

Corollary 1 For system (29), the following statements hold true:

- (a) If $\hat{\mathfrak{R}}_0 \leq 1$, then $\bar{\Delta}_0$ is G.A.S.
- (b) If $\hat{\mathfrak{R}}_0 > 1$, then $\bar{\Delta}_1$ is G.A.S.

As a result, the SARS-CoV-2 infection model may not effectively represent SARS-CoV-2 infection if humoral immunity is ignored. Therefore, our proposed model are more relevant in describing the SARS-CoV-2 dynamics than the model presented in [31].

6. Numerical simulations

To demonstrate the theoretical conclusions in this part, we do a numerical simulation for model (12). We perform sensitivity analysis for the model. We show how humoral immunity and time delays affect the dynamics of SARS-CoV-2. Take a look at a specific type of probability distributed functions as

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

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

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

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 (12) becomes

$$\begin{aligned} \dot{E} &= \lambda_E - \eta \Psi(A) E S - \delta_E E, \\ \dot{L} &= \eta e^{-\alpha_1 \tau_1} \Psi(A_{\tau_1}) E_{\tau_1} S_{\tau_1} - (a + \delta_L) L, \\ \dot{I} &= a e^{-\alpha_2 \tau_2} L_{\tau_2} - \delta_I I, \\ \dot{S} &= \delta_I v e^{-\alpha_3 \tau_3} I_{\tau_3} - \delta_S S - \gamma S B, \\ \dot{A} &= \lambda_A - \kappa \eta \Psi(A) A S - \delta_A A, \\ \dot{B} &= \rho S B - \delta_B B. \end{aligned} \tag{30}$$

MATLAB's dde23 solver will be used to numerically solve the DDEs system (30). Table 1 contains the values of the parameters of model (30). We choose the function Ψ as $\Psi(A) = \frac{A^n}{\mathcal{A}_s^n + A^n}$. Then \mathfrak{R}_0 given by Equation (14) becomes

$$\mathfrak{R}_0 = \frac{\eta a v e^{-\alpha_1 \tau_1 - \alpha_2 \tau_2 - \alpha_3 \tau_3} E_0}{(a + \delta_L) \delta_S} \frac{A_0^n}{\mathcal{A}_s^n + A_0^n}. \quad (31)$$

Table 1. Model parameters

Parameter	Value	Parameter	Value
λ_E	5	ρ	Varied
δ_E	0.1	δ_B	0.1
η	Varied	\mathcal{A}_s	50
δ_I	0.1	α_1	1
ν	20	α_2	1
δ_S	0.1	α_3	1
γ	0.04	τ_1	Varied
λ_A	1	τ_2	Varied
κ	0.3	τ_3	Varied
a	0.2	δ_L	0.1
n	1	δ_A	0.1

We mentioned that, other numerical techniques, such as the finite difference approach, can also be used to solve system (12). We leave this for future work since more study is necessary.

6.1 Stability of the equilibria

We use the following three initials to demonstrate the global stability of the equilibrium points of system (30):

$$C1: (E(\theta), L(\theta), I(\theta), S(\theta), A(\theta), B(\theta)) = (35, 0.5, 0.5, 1, 7, 2),$$

$$C2: (E(\theta), L(\theta), I(\theta), S(\theta), A(\theta), B(\theta)) = (40, 1, 2, 3, 8, 2.5),$$

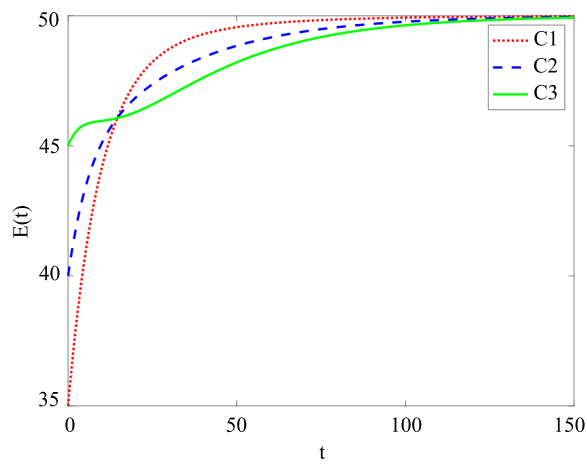
$$C3: (E(\theta), L(\theta), I(\theta), S(\theta), A(\theta), B(\theta)) = (45, 1.5, 3.5, 5, 9, 3),$$

where $\theta \in [-\max\{\tau_1, \tau_2, \tau_3\}, 0]$. Here, we set $\tau_i = 0.9$, $i = 1, 2, 3$ and select the values of η and ρ as:

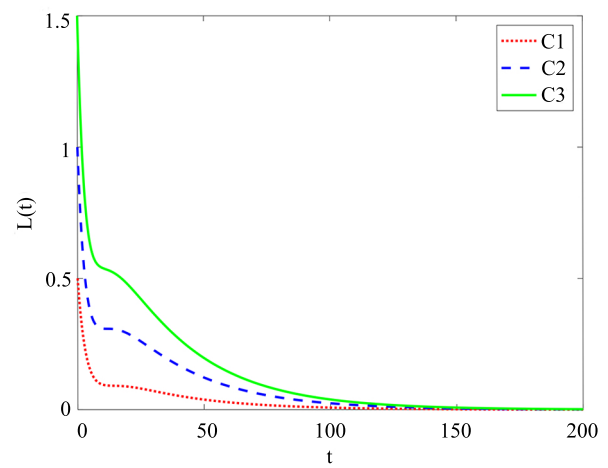
State 1 (Stability of Δ_0): $\eta = 0.005$ and $\rho = 0.0005$. These values give $\mathfrak{R}_0 = 0.373364 < 1$. Figure 2 demonstrates that for all starting values, the trajectories lead to the equilibrium $\Delta_0 = (50, 0, 0, 0, 10, 0)$. This demonstrates that Theorem 1's statement that Δ_0 is G.A.S. In this state, SARS-CoV-2 particles are eventually cleared.

State 2 (Stability of Δ_1): $\eta = 0.04$ and $\rho = 0.0005$. With such selection we obtain $\mathfrak{R}_1 = 0.189932 < 1 < 2.98691 = \mathfrak{R}_0$, $S_1 = 25.0488$ and $\frac{\delta_B}{\rho} = \frac{0.1}{0.0005} = 200$, then $S_1 < \frac{\delta_B}{\rho}$. The equilibrium point Δ_1 exists with $\Delta_1 = (22.0461, 3.7884, 3.0805, 25.0488, 7.2443, 0)$. Figure 3 clearly demonstrates that the trajectories eventually trend to Δ_1 for all initials, which is consistent with Theorem 2. This is the situation of an infected person when humoral immunity is not engaged.

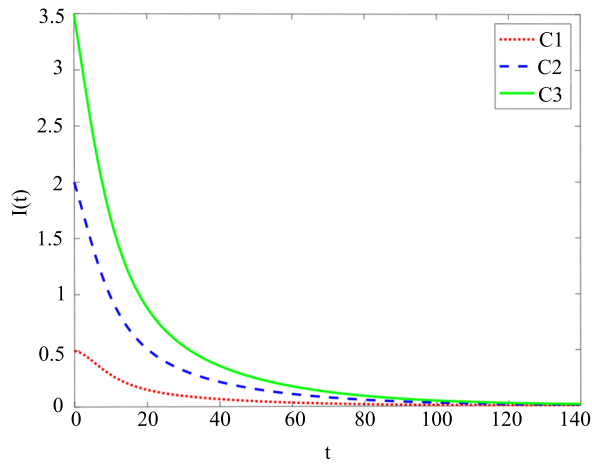
State 3 (Stability of Δ_2): $\eta = 0.04$ and $\rho = 0.05$. This gives $\mathfrak{R}_1 = 1.99231 > 1$. The numerical results show that, $\Delta_2 = (44.2806, 0.7751, 0.6303, 2, 9.62697, 3.9063)$ exists. Figure 4 shows that, for all initials, the trajectories eventually converge to Δ_2 , which is consistent with Theorem 3. This case depicts a person who has SARS-CoV-2 infection and active humoral immunity.



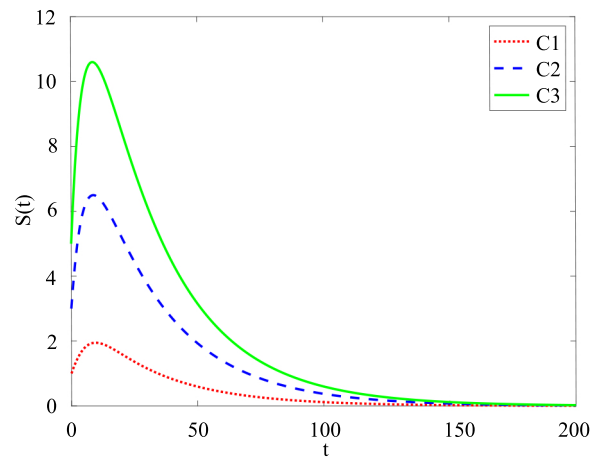
(a) Uninfected epithelial cells



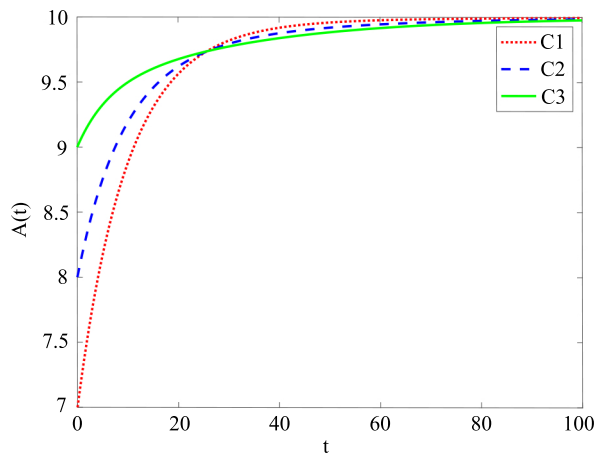
(b) Latently infected epithelial cells



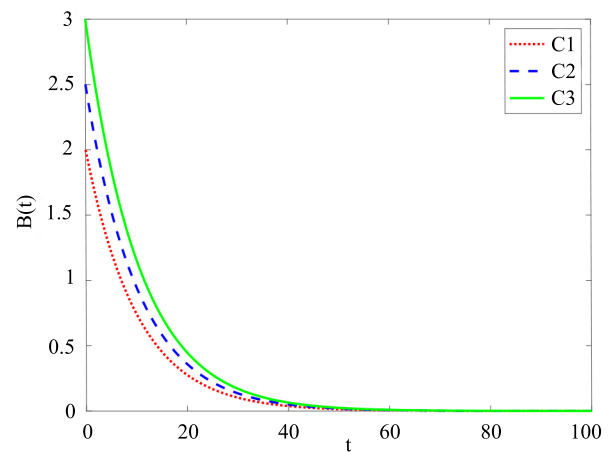
(c) Actively infected epithelial cells



(d) SARS-CoV-2 particles

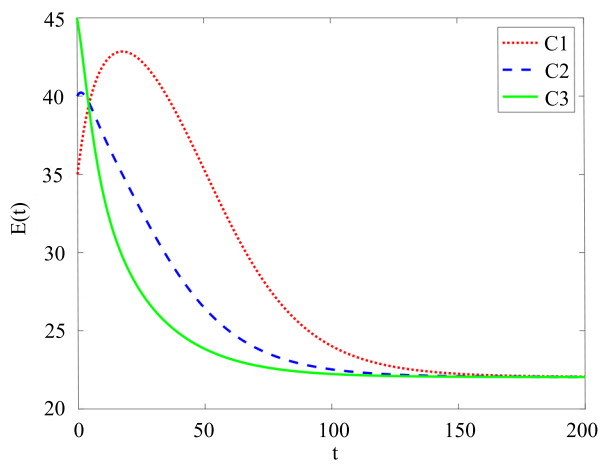


(e) ACE2 receptors

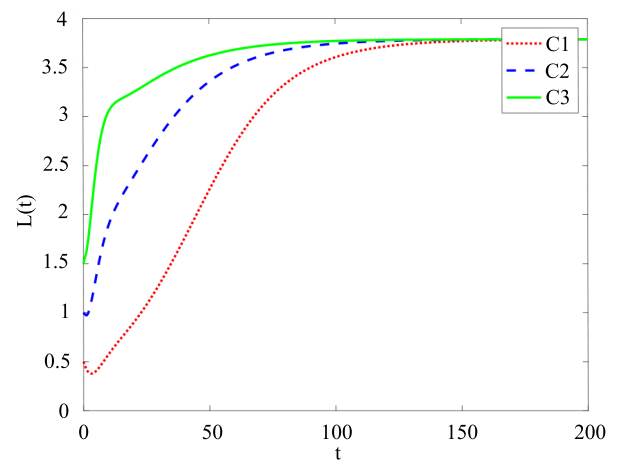


(f) Antibodies

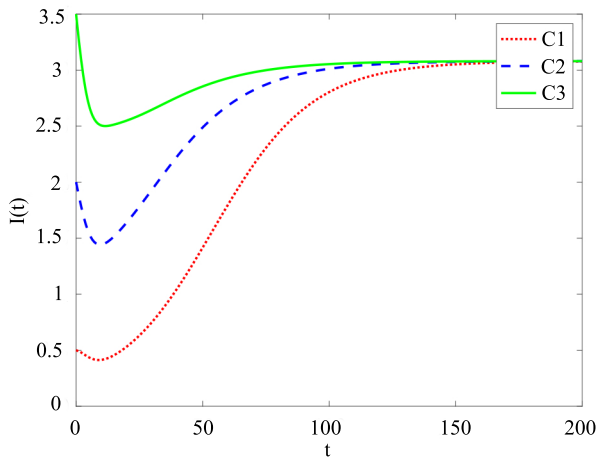
Figure 2. Solutions of model (30) with initials C1-C3 converge to $\Delta_0 = (50, 0, 0, 0, 10, 0)$ when $\mathfrak{R}_0 \leq 1$ (State 1)



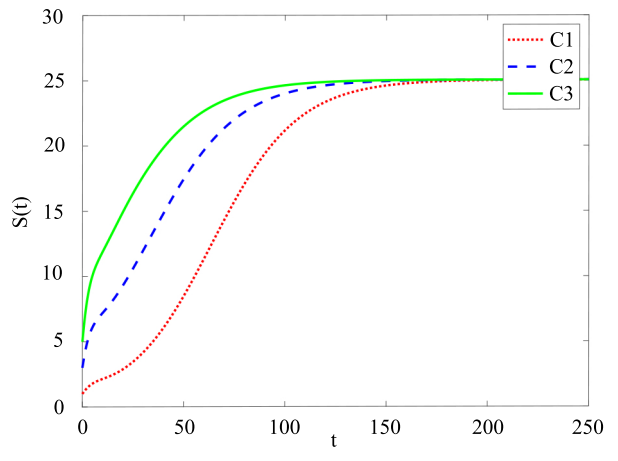
(a) Uninfected epithelial cells



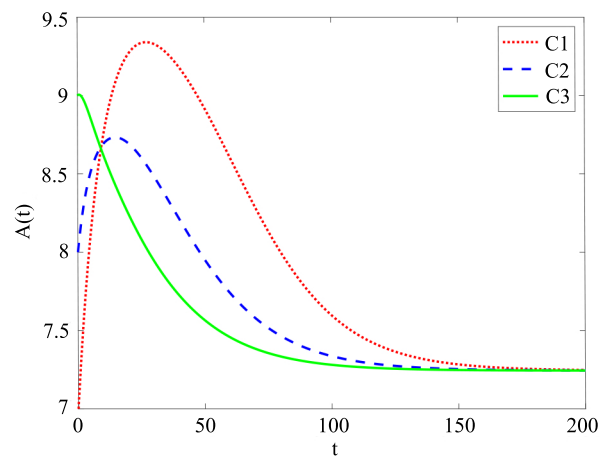
(b) Latently infected epithelial cells



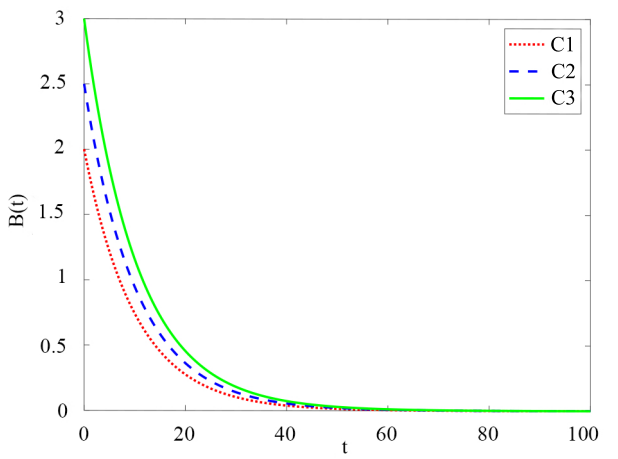
(c) Actively infected epithelial cells



(d) SARS-CoV-2 particles

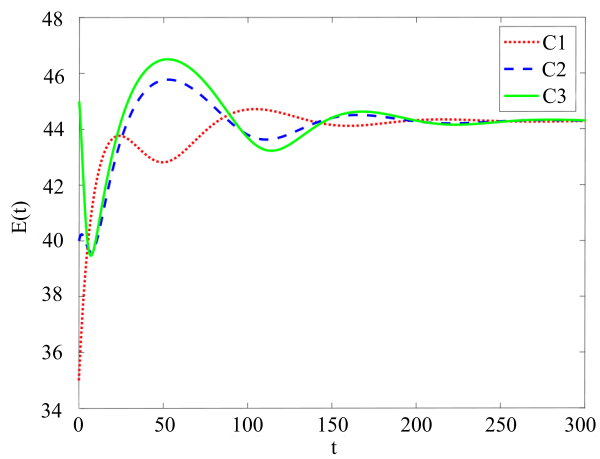


(e) ACE2 receptors

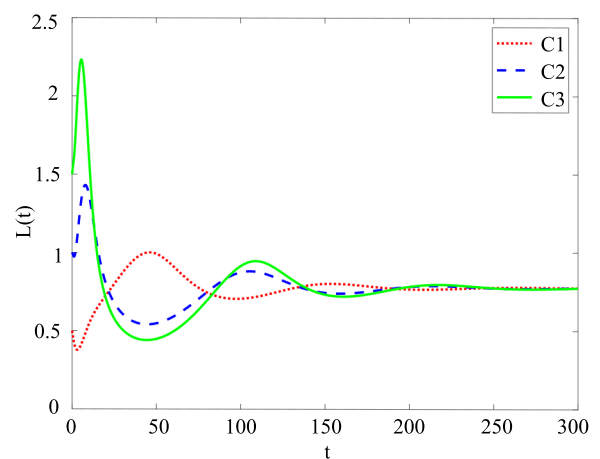


(f) Antibodies

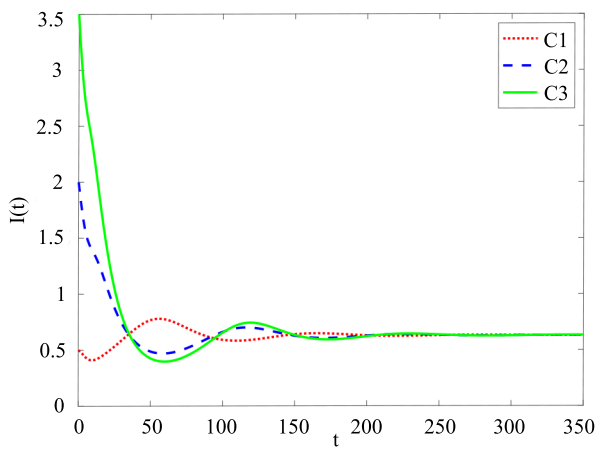
Figure 3. Solutions of model (30) with initials C1-C3 converge to $\Delta_1 = (22.0461, 3.7884, 3.0805, 25.0488, 7.2443, 0)$ when $\mathfrak{R}_0 > 1$ and $\mathfrak{R}_1 \leq 1$ (State 2)



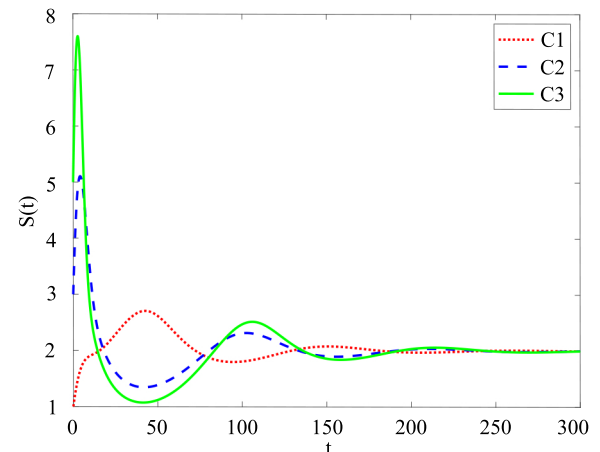
(a) Uninfected epithelial cells



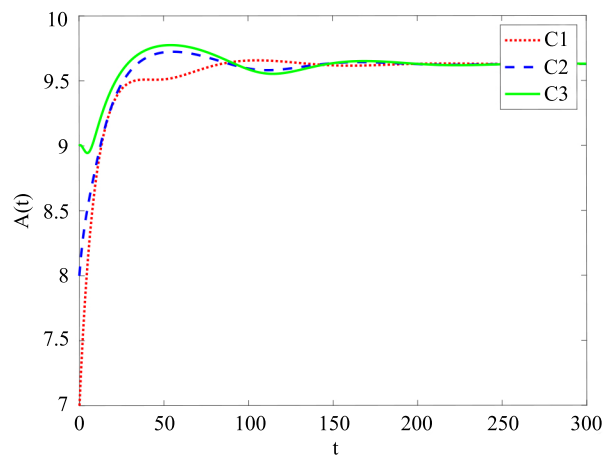
(b) Latently infected epithelial cells



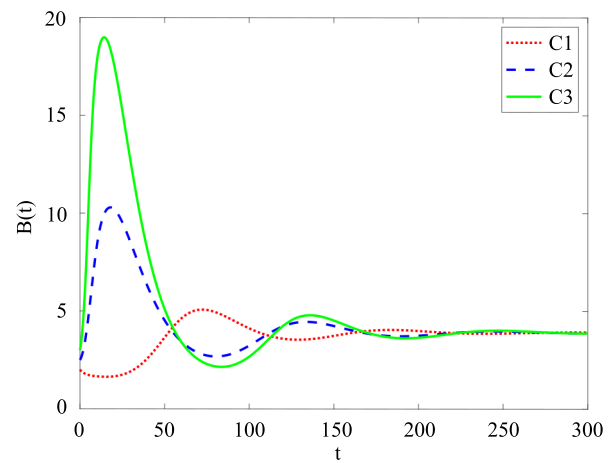
(c) Actively infected epithelial cells



(d) SARS-CoV-2 particles



(e) ACE2 receptors



(f) Antibodies

Figure 4. Solutions of model (30) with initials C1-C3 converge to $\Delta_2 = (44.2806, 0.7751, 0.6303, 2, 9.62697, 3.9063)$ when $\mathfrak{R}_1 > 1$ (State 3)

6.2 Impact of the time delay on the SARS-CoV-2 dynamics

We demonstrate how time delays parameters τ_1 , τ_2 and τ_3 affect the system's solutions and the stability of Δ_0 . From Equation (31), it is clear that while all other parameters are constant, the parameter \mathfrak{R}_0 is decreasing when the delay parameters τ_1 , τ_2 and τ_3 are increased. Therefore, depending on τ_1 , τ_2 and τ_3 , the stability of Δ_0 can be greatly altered. Let us fix $\eta = 0.01$, $\rho = 0.001$ and vary τ_1 , τ_2 and τ_3 as:

D1: $\tau_1 = \tau_2 = \tau_3 = 0$,

D2: $\tau_1 = \tau_2 = \tau_3 = 0.6$,

D3: $\tau_1 = \tau_2 = \tau_3 = 1.0$,

D4: $\tau_1 = \tau_2 = \tau_3 = 1.5$.

Additionally, we take the following initial.

$$C4: (E(\theta), L(\theta), I(\theta), S(\theta), A(\theta), B(\theta)) = (35, 5, 10, 50, 8, 3),$$

where $\theta \in [-\max\{\tau_1, \tau_2, \tau_3\}, 0]$. Assume that $\tau = \tau_1 = \tau_2 = \tau_3$, then for $n = 1$, \mathfrak{R}_0 is given by

$$\mathfrak{R}_0 = \frac{\eta a v e^{-(\alpha_1 + \alpha_2 + \alpha_3)\tau} \lambda_E \lambda_A}{(a + \delta_L) \delta_S (\mathcal{A}_S \delta_E \delta_A + \lambda_A \delta_E)}.$$

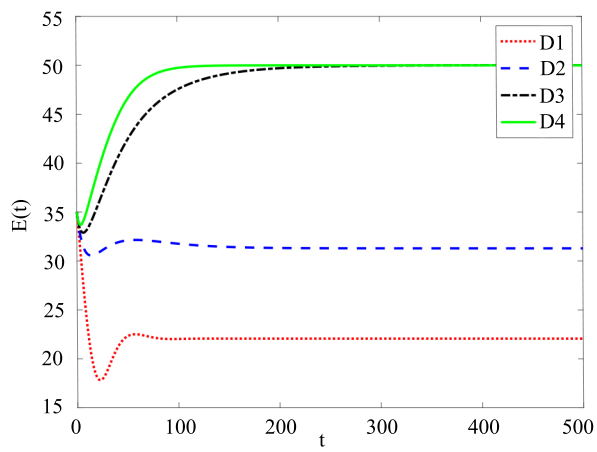
We see that, \mathfrak{R}_0 is a decreasing function of τ . Let τ_{cr} be such that $\mathfrak{R}_0(\tau_{cr}) = 1$. Consequently,

$$\mathfrak{R}_0 \leq 1 \text{ for all } \tau \geq \tau_{cr}.$$

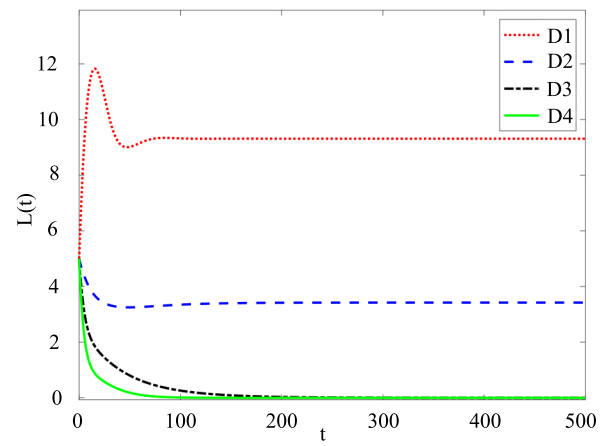
Hence, Δ_0 is G.A.S when $\tau \geq \tau_{cr}$. Using the values of the parameters we obtain, $\tau_{cr} = 0.802649$. Therefore, we have the following cases:

- (i) If $\tau \geq \tau_{cr}$, then $\mathfrak{R}_0 \leq 1$ and thus Δ_0 is G.A.S. Therefore, when τ is large enough, then Δ_0 can be stabilized.
- (ii) If $\tau < \tau_{cr}$, then $\mathfrak{R}_0 > 1$ and thus Δ_0 will be unstable.

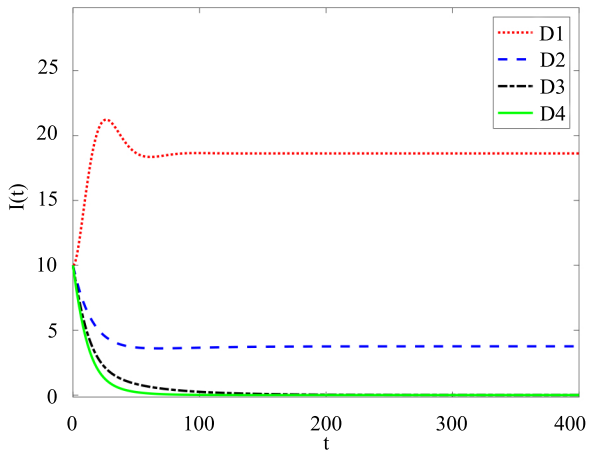
The impact of time delay on the system's trajectories is depicted in Figure 5. It is evident that as τ increases, the proportions of uninfected epithelial cells and the ACE2 receptor increase, whereas those of latently and actively infected epithelial cells, SARS-CoV-2 particles, and antibodies decrease.



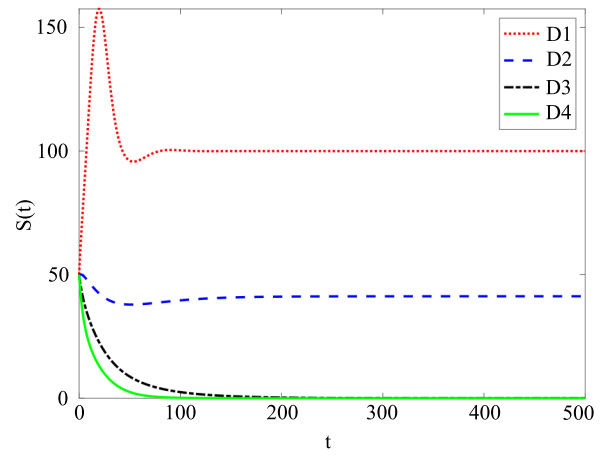
(a) Uninfected epithelial cells



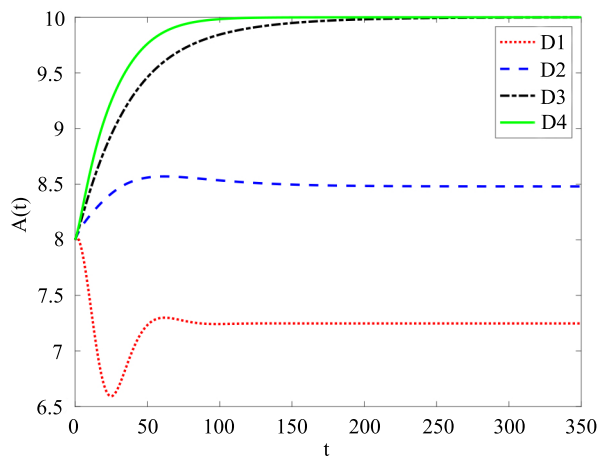
(b) Latently infected epithelial cells



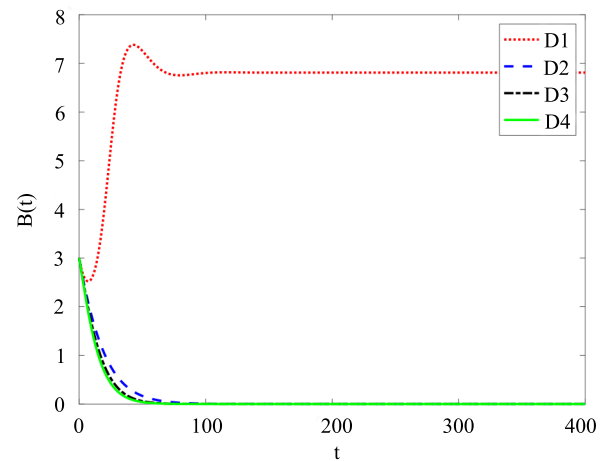
(c) Actively infected epithelial cells



(d) SARS-CoV-2 particles



(e) ACE2 receptors



(f) Antibodies

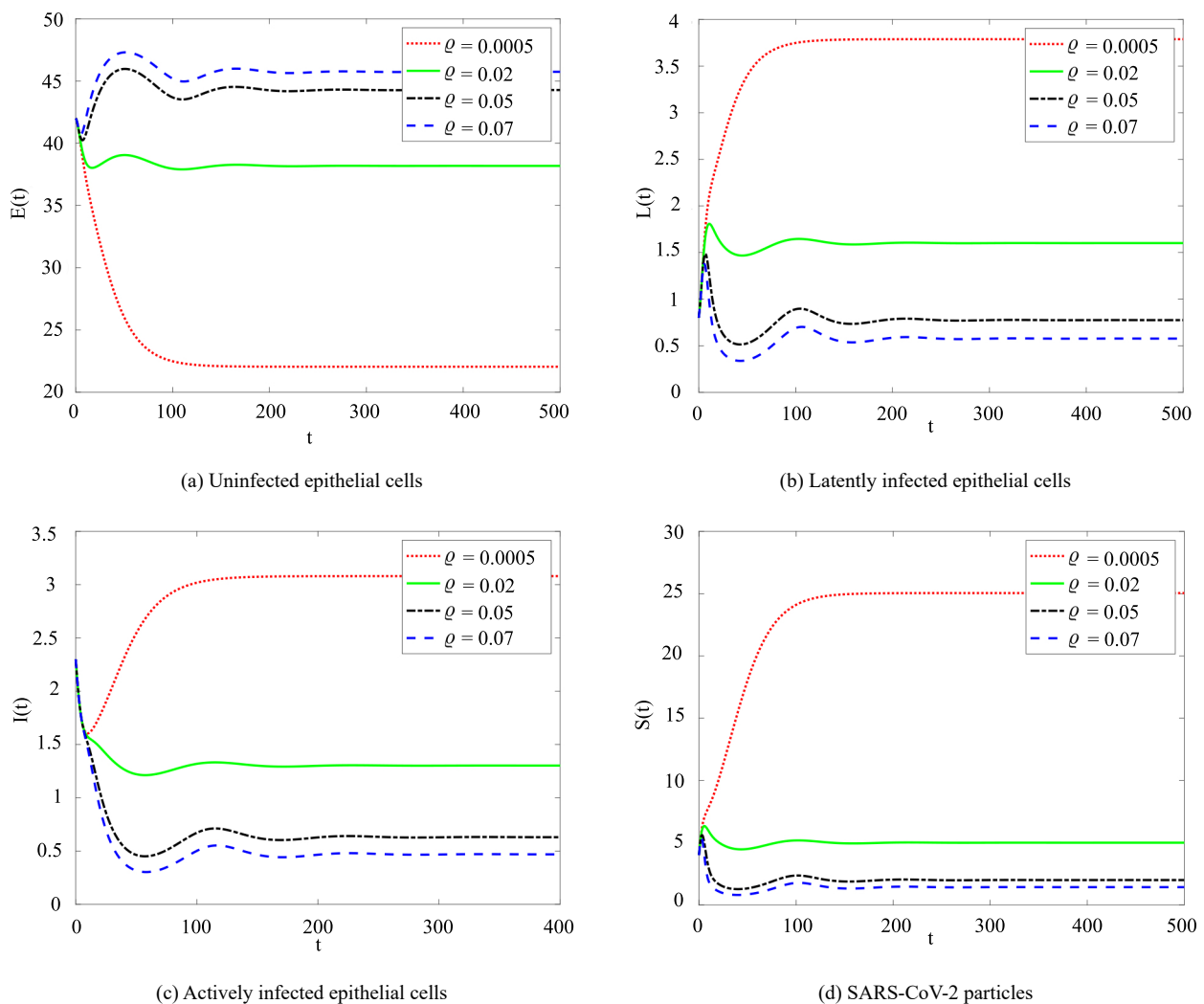
Figure 5. Solutions of model (30) under the impact of the time delay τ

6.3 Impact of humoral immunity on the SARS-CoV-2 infection

This part discusses how the dynamics of system (30) are affected by the stimulated rate constant ρ . We fix the parameters $\eta = 0.04$ and $\tau_1 = \tau_2 = \tau_3 = 0.9$ and vary the parameter ρ as: $\rho = 0.0005$, $\rho = 0.02$, $\rho = 0.05$ and $\rho = 0.07$. Further, we consider the initial condition:

$$C5: (E(\theta), L(\theta), I(\theta), S(\theta), A(\theta), B(\theta)) = (40, 1, 2, 6, 8, 3), \quad \theta \in [-0.9, 0]$$

Figure 6 illustrates how humoral immunity affected the SARS-CoV-2 infection. We see that when ρ is raised, the levels of uninfected epithelial cells, antibodies, and ACE2 receptors rise, whereas the levels of latently infected cells, actively infected cells, and SARS-CoV-2 particles fall. Therefore, the SARS-CoV-2 infection can be managed through humoral immunity. Keep in mind that because \mathcal{R}_0 does not depend on ρ , Δ_0 cannot be attained by raising ρ . This might contribute to the development of anti-SARS-CoV-2 treatments with the potential to boost humoral immunity.



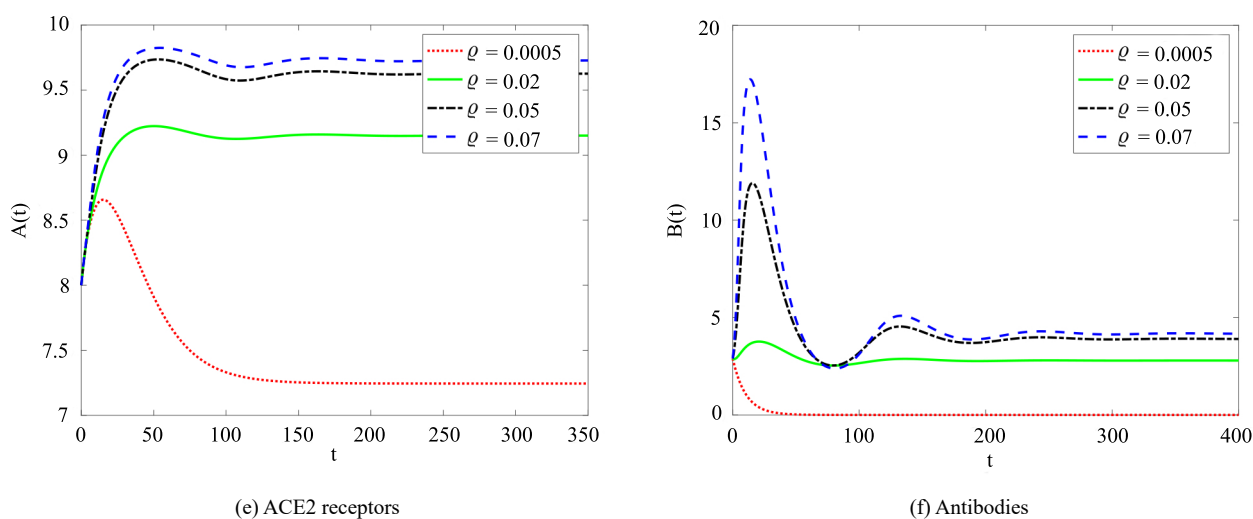


Figure 6. Solutions of model (30) under the impact of humoral immunity parameter ρ

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 \mathfrak{R}_0 is written in terms of the parameter m :

$$\mathcal{S}_m = \frac{m}{\mathfrak{R}_0} \frac{\partial \mathfrak{R}_0}{\partial m}. \quad (32)$$

Using the values given in Table 1 and $\eta = 0.003$, $\rho = 0.01$ and $\tau_1 = \tau_2 = \tau_3 = 0.9$, we present the sensitivity index \mathcal{S}_m in Table 2 and Figure 7. Obviously, λ_E , η , λ_A , a and v have positive indices. Clearly, λ_E , η and v , have the most positive sensitivity index. In this state, there is a positive relationship between the progression of COVID-19 and the parameters λ_E , η , λ_A , a and v , when all other parameters are fixed. Parameters δ_E , δ_S , δ_A , δ_L , τ_1 , τ_2 , τ_3 , α_1 , α_2 , α_3 , \mathcal{A}_s and n have negative indices, meaning that when the values of these parameters rise, the value of \mathfrak{R}_0 declines. Obviously, n has the most negative sensitivity index.

Table 2. Sensitivity index of \mathfrak{R}_0

m	\mathcal{S}_m	m	\mathcal{S}_m	m	\mathcal{S}_m
λ_E	1	δ_A	-0.833	α_1	-0.9
η	1	δ_L	-0.333	v	1
δ_E	-1	τ_1	-0.9	τ_3	-0.9
δ_S	-1	λ_A	0.833	α_2	-0.9
a	0.333	τ_2	-0.9	α_3	-0.9
n	-1.3412	\mathcal{A}_s	-0.833		

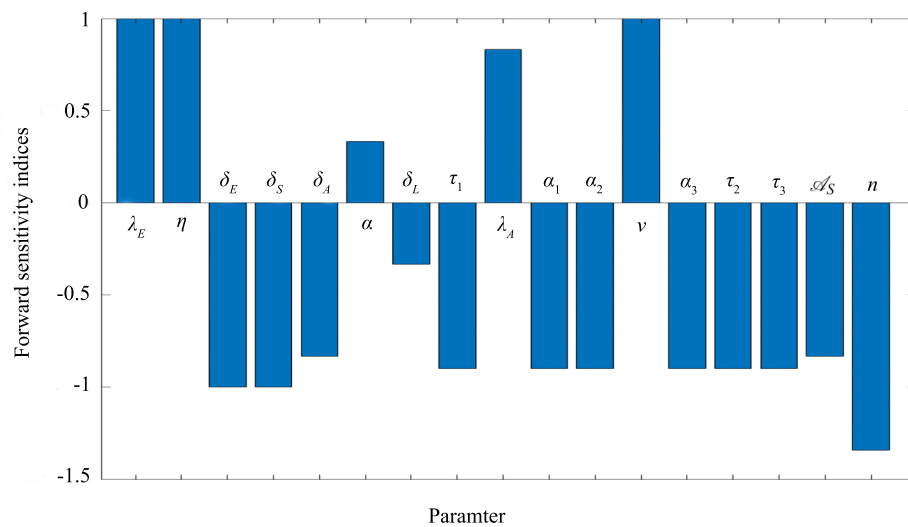


Figure 7. Forward sensitivity analysis of the parameters on \mathfrak{R}_0

7. Conclusion and discussions

In this study, we investigated a SARS-CoV-2 infection model that takes into account the function of the ACE2 receptor to characterize the dynamics of SARS-CoV-2 in the host. The effect of humoral immunity and latent phase on the SARS-CoV-2 infection was taken into consideration. Three distributed time-delays were incorporated: (i) delay in development 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 started by demonstrating the solutions' basic characteristics, nonnegativity and boundedness. Then, we established that the model have three equilibria, uninfected equilibrium, Δ_0 , infected equilibrium without humoral immunity, Δ_1 , and infected equilibrium with humoral immunity Δ_2 . The existence and global stability of the equilibria were demonstrated using the two threshold parameters \mathfrak{R}_0 and \mathfrak{R}_1 . We created appropriate Lyapunov functions and used LIP to demonstrate the three equilibria's global asymptotic stability. We proved the following:

- If $\mathfrak{R}_0 \leq 1$, then Δ_0 is the only equilibrium and it is G.A.S. In this state, the number of SARS-CoV-2 particles eventually converges to 0 and the COVID-19 patient will recover. Different control strategies can be applied to make

$$\mathfrak{R}_0 = \frac{\eta a v e^{-\alpha_1 \tau_1 - \alpha_2 \tau_2 - \alpha_3 \tau_3} \lambda_E \lambda_A}{(a + \delta_L) \delta_S (\mathcal{A}_S \delta_E \delta_A + \lambda_A \delta_E)} \leq 1.$$

These strategies such as: (i) reducing the parameter η as $(1 - \varepsilon_B)\eta$ by applying treatment for blocking the virus binding with drug efficacy $\varepsilon_B \in [0, 1]$ [46], (ii) reducing the parameter v as $(1 - \varepsilon_I)v$ by applying treatment for inhibiting the virus replication with drug efficacy $\varepsilon_I \in [0, 1]$ [46], (iii) enlarging the length of delay periods τ_1 , τ_2 and τ_3 [40], (iv) inhibiting the proliferation rate of ACE2 receptors λ_A , (v) increasing the degradation rate of ACE2 receptors δ_A . We see that \mathfrak{R}_0 is independent of humoral immunity parameters; as a result, humoral immunity only functions to regulate infection rather than to eradicate it.

- If $\mathfrak{R}_1 \leq 1 < \mathfrak{R}_0$, then there exist two equilibria Δ_0 and Δ_1 , where Δ_0 is unstable and Δ_1 is G.A.S. In this case, the infection is there, but the immune system is not responding. The reason for this is because when the viral concentration decreases (i.e. $S \leq \delta_B/\rho$), it may not be high enough to trigger an immune response.

• If $\mathfrak{R}_1 > 1$, then in addition to Δ_0 and Δ_1 , there exists Δ_2 and it is G.A.S. In this instance, the body has enough viruses (i.e., $S > \delta_B/\rho$) to trigger the immune system's response.

The model was numerically solved, the results were visually shown, and they agreed with our theoretical findings. We investigated the sensitivity analysis to see how the parameter \mathfrak{R}_0 is affected by the values of the model's parameters. We investigated the effects of ACE2 receptors, humoral immunity, time delay and latent phase on the SARS-CoV-2 infection. We showed that ACE2 receptor proliferation and degradation rates have an impact on \mathfrak{R}_0 , which may be useful information for the creation of potential receptor-targeted vaccinations and medications. We demonstrated that whereas humoral immunity plays a function in infection management, it does not ultimately remove SARS-CoV-2 particles. Additionally, lengthening the time delay can considerably reduce \mathfrak{R}_0 and hence impede the advancement of COVID-19. This makes it possible to develop various therapies that will extend the delay time. Finally, we showed that, excluding the latently infected cells in the model would result in an overestimation of \mathfrak{R}_0 .

Our inability to determine the values of the model's parameters using actual data from COVID-19 patients is the primary drawback of our study. The explanations are as follows: (i) Real data from infected individuals are still scarce; (ii) our results may not be very accurate when compared to a small number of real studies; (iii) it is difficult to gather real data from patients who have SARS-CoV-2 infection; and (iv) doing experiments to get real data is outside the purview of this study.

It is possible to extend the proposed model in several ways by considering immune response delay [21], CTL response [23, 47], reaction diffusion [48, 49] and memory effect [50, 51].

Conflict of interest

The authors declare no competing financial interest.

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