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DYNAMICS OF AN IMMUNOLOGICAL VIRAL INFECTION MODEL WITH LYTIC AND NON-LYTIC IMMUNE RESPONSE IN PRESENCE OF CELL-TO-CELL TRANSMISSION AND CURE OF INFECTED CELLS

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Abstract. In this paper, we propose a mathematical model that describes the dynamics of viral infection with both modes of transmission, virus-to-cell and cell-to-cell by taking into account the non-cytolytic cure of infected cells, the lytic and non-lytic humoral immune response. We first prove the non-negativity and boundedness of the solutions of the proposed model. Furthermore, the dynamical behaviors of the model including the local and global stability of equilibria are rigorously investigated.

Keywords: viral immunology; cell-to-cell transmission; mathematical modeling; Lyapunov function; stability.

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1. INTRODUCTION

The human body is exposed permanently to pathogenic agents, such as viruses which can induce viral infections. Viruses once entered the cell, they take over its machinery and metabolism to support their replication. Furthermore, viruses can spread by two different modes, either

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through cell-to-cell by contact of infected cells with healthy ones [1, 2, 3], or through classical virus-to-cell infection. In response to a viral infection, the organism initiates the immune system. There are two broad types of immune responses, the innate immunity and the adaptive immune response also called specific response. The last type of immunity has two arms, the cellular immunity based on cytotoxic T lymphocyte (CTL) cells which kill infected cells, and the humoral one that exercised by antibodies in order to neutralize the viruses.

During viral infection, infected cells can be killed or can also return to the uninfected state by loss of all covalently closed circular DNA (cccDNA) from their nucleus. Guidotti et al. [4] demonstrated that noncytopathic antiviral mechanisms contribute to viral clearance during acute viral hepatitis by purging hepatitis B virus (HBV) replicative intermediates from the cytoplasm and cccDNA from the nucleus of infected cells. The cure of infected cells are considered by many authors to model the dynamics of various viral infections [5, 6, 7, 8]. On the other hand, the immune response occurs in two ways, a lytic which kills the infected cells, and the another non-lytic which consists of inhibiting the infection transmission [9]. Antibodies are produced by B cells and proliferate as a result of stimulation by the virus, they play an important role in the immune system and participate significantly in lytic and non-lytic antiviral activity [10].

Based on the above biological and mathematical considerations, we propose a mathematical model that incorporates both modes of transmission, cure of infected cells as well as lytic and non-lytic humoral immune response. This model is formulated by the following nonlinear system

$$\begin{cases} U'(t) = \lambda - d_U U - \dfrac{\beta_1 UV}{1+q_1 A} - \dfrac{\beta_2 UI}{1+q_2 A} + \varepsilon I, \\ I'(t) = \dfrac{\beta_1 UV}{1+q_1 A} + \dfrac{\beta_2 UI}{1+q_2 A} - d_I I - \varepsilon I, \\ V'(t) = kI - d_V V - rVA, \\ A'(t) = \rho VA - d_A A, \end{cases} \tag{1}$$

where the uninfected cells (U) are generated at rate λ, die at rate $d_U U$ and become infected either by free virus particles at rate $\beta_1 UV$ or by direct contact with infected cells at rate $\beta_2 UI$. The two modes of transmission are inhibited by non-lytic humoral immune response at rate $1+q_1 A$ and $1+q_2 A$, respectively. The infected cells (I) die at rate $d_I I$ and return to the uninfected

state by loss of cccDNA from their nucleus at rate εI. Free viruses (V) are produced by infected cells at rate kI, cleared at rate $d_V V$ and neutralized by antibodies at rate rVA. Antibodies develop in response to free virus at rate ρVA and decay at rate $d_A A$.

It is important to note that if $q_1 = q_2 = 0$, then we find the model studied in [8]. Also, if $\beta_2 = 0$, then we get the model investigated by Dhar et al. in [7].

The remainder of this paper is outlined as follows. In the next section, we establish some preliminary results including the non-negativity and boundedness of solutions of system (1) as well as we discuss the existence of equilibria. In Section 3, we establish sufficient conditions for the local stability of the three equilibrium points. Section 4 is devoted to global stability of equilibria. The paper ends with a conclusion presented in Section 5.

2. Preliminary Results

Theorem 2.1. *All solutions for* (1) *with non-negative initial conditions, remain non-negative and bounded for all* $t \geq 0$.

Proof. We have

$$\begin{aligned}
\frac{dU}{dt}|_{U=0} &= \lambda + \varepsilon I \geq 0, \text{ for all } I \geq 0, \\
\frac{dI}{dt}|_{I=0} &= \frac{\beta_1 UV}{1+q_1 A} \geq 0, \text{ for all } U,V,A \geq 0, \\
\frac{dV}{dt}|_{V=0} &= kI \geq 0, \text{ for all } I \geq 0, \\
\frac{dA}{dt}|_{A=0} &= 0.
\end{aligned}$$

According to Proposition B.7 of [11], we deduce that the solutions U, I, V and A are non-negative.

To prove the boundedness of solutions, we consider the following function

$$X(t) = U(t) + I(t) + \frac{d_I}{2k} V(t) + \frac{rd_I}{2k\rho} A(t).$$

Then

$$\begin{aligned}
X'(t) &= \lambda - d_U U - \frac{d_I}{2} I(t) - \frac{d_I d_V}{2k} V - \frac{rd_I d_A}{2k\rho} A \\
&\leq \lambda - dX(t),
\end{aligned}$$

where $d = \min\{d_U, \frac{d_I}{2}, d_V, d_A\}$. Hence,

$$\limsup_{t\to+\infty} X(t) \leq \frac{\lambda}{d}.$$

Then $U(t)$, $I(t)$, $V(t)$ and $A(t)$ are bounded. This completes the proof. □

Next, we define two threshold parameters and establish the existence of three equilibrium points for (1). It is clear that the point $P_0(U_0,0,0,0)$, with $U_0 = \dfrac{\lambda}{d_U}$, is the unique infection-free equilibrium of model (1). Then we define the first threshold parameter which represents the basic reproduction number $\mathscr{R}_0$ of model (1) as follows:

$$\mathscr{R}_0 = \frac{\lambda(k\beta_1 + d_V\beta_2)}{d_U d_V(d_I+\varepsilon)} = \mathscr{R}_{01} + \mathscr{R}_{02}, \tag{2}$$

where $\mathscr{R}_{01} = \dfrac{\lambda k\beta_1}{d_U d_V(d_I+\varepsilon)}$ and $\mathscr{R}_{02} = \dfrac{\lambda\beta_2}{d_U(d_I+\varepsilon)}$ are the basic reproduction numbers associated to the virus-to-cell and cell-to-cell transmission modes, respectively.

In absence of humoral immune response and $\mathscr{R}_0 > 1$, the model (1) has the unique equilibrium point called the immune free-equilibrium and labeled by $P_1(U_1,I_1,V_1,0)$, where

$$U_1 = \frac{\lambda}{d_U\mathscr{R}_0},\ I_1 = \frac{\lambda(\mathscr{R}_0-1)}{d_I\mathscr{R}_0},\ V_1 = \frac{\lambda k(\mathscr{R}_0-1)}{d_V d_I\mathscr{R}_0}.$$

In presence of humoral immune response, we have $V = \dfrac{d_A}{\rho}$, $I = \dfrac{1}{d_I}(\lambda - d_U U)$ and $A = \dfrac{1}{r}\left(\dfrac{k\rho}{d_A d_I}(\lambda - d_U U) - d_V\right)$.

Since $A \geq 0$, we have $U \leq \dfrac{1}{d_U}\left(\lambda - \dfrac{d_V d_A d_I}{k\rho}\right)$. Hence, there is no biological equilibrium if $U > \dfrac{1}{d_U}\left(\lambda - \dfrac{d_V d_A d_I}{k\rho}\right)$ or $\dfrac{1}{d_U}\left(\lambda - \dfrac{d_V d_A d_I}{k\rho}\right) \leq 0$. We set $u^* = \dfrac{1}{d_U}\left(\lambda - \dfrac{d_V d_A d_I}{k\rho}\right)$ and we define on the closed interval $[0,u^*]$ the function h as follows

$$h(U) = \beta_1 V_2 \frac{U}{1+q_1 g(U)} + \beta_2 \frac{U f(U)}{1+q_2 g(U)} - (d_I+\varepsilon) f(U),$$

where $f(U) = \dfrac{1}{d_I}(\lambda - d_U U)$ and $g(U) = \dfrac{1}{r}\left(\dfrac{k\rho}{d_A d_I}(\lambda - d_U U) - d_V\right)$.

Then we have $h(0) = -(d_I+\varepsilon)\dfrac{\lambda}{d_I} < 0$ and

$$\begin{aligned} h'(U) &= \beta_1 V_2 \frac{1+q_1 g(U) - q_1 g'(U)U}{(1+q_1 g(U))^2} \\ &\quad +\beta_2 \frac{1+q_2 g(U) - U q_2 g'(U)}{(1+q_2 g(U))^2} f(U) \\ &\quad + \left(\beta_2 \frac{U}{1+q_2 g(U)} - (d_I+\varepsilon)\right) f'(U). \end{aligned}$$

When the humoral immune response has not established, we have from the last equation of model (1) that $\rho V_1 - d_A \leq 0$. Then we define the second threshold parameter which represents the antibody immune response reproduction number as follows

$$\mathscr{R}_1^A = \frac{\rho V_1}{d_A}. \tag{3}$$

Since $h(u^*) = \frac{d_V d_I d_A^2}{k^2 \rho^2 d_U}(k\beta_1 + \beta_2 d_V)\left(\mathscr{R}_1^A - 1\right)$, we deduce that when $\mathscr{R}_1^A > 1$ there exists a $U_2 \in (0, u^*)$ such that $h(U_2) = 0$. By the equalities

$$d_I + \varepsilon = \beta_1 \frac{U_2 V_2}{(1+q_2 A_2) I_2} + \beta_2 \frac{U_2}{1+q_2 A_2} \text{ and } g(U_2) = A_2,$$

we obtain

$$h'(U_2) = \beta_1 V_2 \frac{(1+q_1 A_2 - q_1 g'(U_2) U_2}{(1+q_1 A_2)^2} + \beta_2 \frac{1+q_2 A_2 - U q_2 g'(U_2)}{(1+q_2 A_2)^2} f(U_2) - \left(\beta_1 \frac{U_2 V_2}{(1+q_1 A_2) I_2}\right) f'(U_2).$$

As $g'(U_2) < 0$ and $f'(U_2) < 0$, we have $h'(U_2) > 0$. This establishes the uniqueness of U_2 and therefore our system has another infection equilibrium called the infection equilibrium with humoral immune response $P_2(U_2, I_2, V_2, A_2)$, where

$$I_2 = \frac{1}{d_I}(\lambda - d_U U_2),\ V_2 = \frac{d_A}{\rho},\ A_2 = \frac{1}{r}\left(\frac{k\rho}{d_I d_A}(\lambda - d_U U_2) - d_V\right).$$

3. Local Stability

In this section, we establish sufficient conditions for the local stability of the three equilibrium points.

The Jacobian matrix, $J(P)$, of system (1) at a point $P(U,I,V,A)$ is given by

$$J(P)=\begin{pmatrix} -d_U-\frac{\beta_1 V}{1+q_1A}-\frac{\beta_2 I}{1+q_2A} & -\frac{\beta_2 U}{1+q_2A}+\varepsilon & -\frac{\beta_1 U}{1+q_1A} & \frac{q_1\beta_1 UV}{(1+q_1A)^2}+\frac{\beta_2 q_2 UI}{(1+q_2A)^2} \\ \frac{\beta_1 V}{1+q_1A}+\frac{\beta_2 I}{1+q_2A} & \frac{\beta_2 U}{1+q_2A}-d_I-\varepsilon & \frac{\beta_1 U}{1+q_1A} & -\frac{q_1\beta_1 UV}{(1+q_1A)^2}-\frac{\beta_2 q_2 UI}{(1+q_2A)^2} \\ 0 & k & -d_V-rA & -rV \\ 0 & 0 & \rho A & \rho V-d_A \end{pmatrix}.$$

Theorem 3.1. *The infection-free equilibrium P_0 is locally asymptotically stable if $\mathscr{R}_0<1$ and becomes unstable if $\mathscr{R}_0>1$.*

Proof. The characteristic equation at P_0 is given by

$$(x+d_A)(x+d_U)(x^2+a_1x+a_2)=0, \tag{4}$$

where $a_1=d_I+\varepsilon+d_V-\frac{\lambda\beta_2}{d_U}$ and $a_2=d_V(d_I+\varepsilon-\frac{\lambda\beta_2}{d_U})-\frac{\lambda k\beta_1}{d_U}$.
Note that $x_1=-d_A<0$ and $x_2=-d_U<0$ are the roots of the equation (4). Also,

$$a_1=(d_I+\varepsilon)(1-\mathscr{R}_{02})+d_V>0 \text{ and } a_2=d_V(d_I+\varepsilon)(1-\mathscr{R}_0)>0, \text{ when } \mathscr{R}_0<1.$$

According to Routh-Hurwitz criterion [12, Theorem 4.4], the other two roots of the equation (4) have negative parts when $\mathscr{R}_0<1$. Hence, P_0 is locally asymptotically stable if $\mathscr{R}_0<1$.

When $\mathscr{R}_0>1$, we have $a_2<0$. Hence, the characteristic equation (4) admits at least one positive root. Thus, P_0 is unstable when $\mathscr{R}_0>1$. □

Theorem 3.2. *The immune-free equilibrium P_1 is locally asymptotically stable if $\mathscr{R}_1^A<1<\mathscr{R}_0$ and unstable if $\mathscr{R}_1^A>1$.*

Proof. The characteristic equation at the equilibrium point P_1 is given by

$$(x-\rho V_1+d_A)(x^3+a_1x^2+a_2x+a_3)=0, \tag{5}$$

where

$$\begin{aligned} a_1&=d_U+d_V+(d_I+\varepsilon)\frac{\mathscr{R}_{01}}{\mathscr{R}_0}+\frac{d_U(d_I+\varepsilon)}{d_I}(\mathscr{R}_0-1),\\ a_2&=d_Ud_V+d_U(d_I+\varepsilon)\frac{\mathscr{R}_{01}}{\mathscr{R}_0}+\frac{d_U(d_I+\varepsilon)}{d_I}(d_I+d_V)(\mathscr{R}_0-1),\\ a_3&=d_Vd_U(d_I+\varepsilon)(\mathscr{R}_0-1). \end{aligned}$$

Assume that $R_1^A < 1 < \mathscr{R}_0$. We have

$$\rho V_1 - d_A = d_A(\mathscr{R}_1^A - 1) < 0,$$

$$\begin{aligned} a_1a_2 - a_3 &= d_U d_V(d_U+d_V) + d_U(d_V+d_U)(d_I+d_\varepsilon)\frac{\mathscr{R}_{01}}{\mathscr{R}_0} + \frac{d_U^2(d_I+\varepsilon)^2}{d_I^2}(d_I+d_V)(\mathscr{R}_0-1)^2 \\ &+ \frac{d_U^2(d_I+\varepsilon)^2}{d_I}\frac{\mathscr{R}_{01}}{\mathscr{R}_0}(\mathscr{R}_0-1) + \frac{d_U(d_I+\varepsilon)}{d_I}(2d_Ud_V + d_V^3 + d_Ud_I)(\mathscr{R}_0-1) \\ &+ \left[d_U(d_I+\varepsilon)^2\frac{\mathscr{R}_{01}^2}{\mathscr{R}_0^2} + d_Ud_V(d_I+\varepsilon)\frac{\mathscr{R}_{01}}{\mathscr{R}_0} + \frac{d_U(d_I+\varepsilon)^2}{d_I}(d_I+d_V)\frac{\mathscr{R}_{01}}{\mathscr{R}_0}(\mathscr{R}_0-1)\right] > 0. \end{aligned}$$

From Routh-Hurwitz criterion, we deduce that all roots of the equation (5) have negative real parts. Hence, the immune-free equilibrium P_1 is locally asymptotically stable when $R_1^A < 1 < \mathscr{R}_0$.

If $\mathscr{R}_1^A > 1$, then $\rho V_1 - d_A$ is a positive root of the characteristic equation (5). Therfore, the immune-free equilibrium P_1 becomes unstable when $\mathscr{R}_1^A > 1$. □

Theorem 3.3. *If $\mathscr{R}_1^A > 1$, $d_U \le d_I \le \frac{3}{2}d_U$, $A_2 \le \frac{\beta_1}{\rho q_1}$, $U_2 \le \frac{r}{q_2\beta_2}$ and $(d_I+\varepsilon)I_2 - d_UU_2 \ge 0$, then the infection equilibrium with humoral immune response P_2 is locally asymptotically stable.*

Proof. The characteristic equation at P_2 is given by

$$x^4 + C_1x^3 + C_2x^2 + C_3x + C_4 = 0, \tag{6}$$

where

$$\begin{aligned} C_1 &= \left(d_U + \frac{\beta_1V_2}{1+q_1A_2} + \frac{\beta_2I_2}{1+q_2A_2} + \frac{kI_2}{V_2} + \frac{\beta_1U_2V_2}{(1+q_1A_2)I_2}\right), \\ C_2 &= \left(d_u\left(\frac{kI_2}{V_2} + \frac{\beta_1U_2V_2}{(1+q_1A_2)I_2}\right) + \left(\frac{\beta_1V_2}{1+q_1A_2} + \frac{\beta_2I_2}{1+q_2A_2}\right)(d_I + \frac{kI_2}{V_2}) + \rho A_2rV_2\right), \\ C_3 &= \rho A_2rV_2\frac{\beta_1U_2V_2}{(1+q_1A_2)I_2} + \rho A_2k\left(\frac{q_1\beta_1U_2V_2}{(1+q_1A_2)^2} + \frac{q_2U_2I_2}{(1+q_2A_2)^2}\right) \\ &+ d_U\rho A_2rV_2 + (\rho A_2rV_2 + d_I\frac{kI_2}{V_2})\left(\frac{\beta_1V_2}{1+q_1A_2} + \frac{\beta_2I_2}{1+q_2A_2}\right), \\ C_4 &= d_I\rho A_2rV_2\left(\frac{\beta_1V_2}{1+q_1A_2} + \frac{\beta_2I_2}{1+q_2A_2}\right) \\ &+ d_U\rho A_2\frac{V_2}{I_2}\left(rV_2\frac{\beta_1U_2}{1+q_1A_2} + k\frac{I_2}{V_2}\left(\frac{q_1\beta_1U_2V_2}{(1+q_1A_2)^2} + \frac{q_2\beta_1U_2I_2}{(1+q_2A_2)^2}\right)\right). \end{aligned}$$

Hence,

$$C_1 = d_U + c_1 + c_2 + c_3, \;\; C_2 = d_U(c_1+c_2) + d_Ic_3 + c_1c_3 + c_4,$$

$$C_3 = (d_U + c_2 + c_3)c_4 + d_I c_1 c_3 + c_1 c_2 c_4 c_5 + c_1 c_4 c_6 c_7,$$

$$C_4 = d_I c_3 c_4 + d_U c_2 c_4 + d_U c_1 c_2 c_4 c_5 + d_U c_1 c_4 c_6 c_7,$$

where $c_1 = \dfrac{kI_2}{V_2}$, $c_2 = \dfrac{\beta_1 U_2 V_2}{(1+q_1A_2)I_2}$, $c_3 = \dfrac{\beta_1 V_2}{1+q_1A_2} + \dfrac{\beta_2 I_2}{1+q_2A_2}$, $c_4 = \rho r A_2 V_2$, $c_5 = \dfrac{q_1}{r(1+q_1A_2)}$, $c_6 = \dfrac{q_2}{r(1+q_2A_2)}$ and $c_7 = \dfrac{\beta_2 U_2}{1+q_2A_2}$.

All coefficients C_1, C_2, C_3 and C_4 are positive, provided $\mathscr{R}_1^A > 1$. Further, we have

$(C_1C_2 - C_3)C_3 - C_1^2C_4 = c_1^3c_2c_3c_4c_5 + c_1^3c_3^2d_I + c_1^3c_3c_4c_6c_7 + c_1^3c_3d_Id_U + c_1^2c_2c_3^2c_4c_5 + c_1^2c_2c_3c_4c_6c_7 + c_1^2c_2c_3d_Id_U + c_1^2c_3^3d_I + c_1^2c_3^2c_4c_6c_7 + c_1^2c_3^2c_4 + 2c_1^2c_3^2d_Id_U + c_1^2c_3d_Id_U^2 + c_1c_2c_3^2d_I^2 + c_1c_3^3d_I^2 + c_1c_3^2d_I^2d_U + c_1c_2c_4(c_3^2 - c_4c_5d_U) + c_1c_3c_4(c_3^2 - c_6c_7d_U^2) + c_1c_3c_4c_6c_7d_U(d_I - d_U) + c_1^2c_2^2c_4c_5(c_3 - c_4c_5) + c_1^2c_2c_3d_I(c_3 - c_4c_5) + c_1^2c_3c_4(2d_U - c_6c_7d_I) + c_1^2c_2c_4(c_3 - c_4c_5c_6c_7) + c_1^2c_2c_4^2c_5(1 - c_6c_7) + c_1^2c_2d_U(c_3d_I - c_4c_5d_U) + (c_1^2c_4^2c_6c_7 + c_1^2c_4d_U^2)(1 - c_6c_7) + c_1c_2^2c_3c_4c_5(d_I - d_U) + c_1c_2^2c_4(c_3 - c_4c_5) + c_1c_2^2d_U(c_3d_I - c_5c_4d_U) + c_1c_2c_3^2c_4c_5(d_I - d_U) + c_1c_2c_3c_4(3d_U - 2d_I) + c_1c_2c_3c_4(c_3 - c_4c_5) + c_1c_2c_3d_U(c_3d_I - c_4c_5d_U) + c_1c_2c_3c_4c_5d_U(d_I - d_U) + c_1c_2c_3c_4c_6c_7(d_I - d_U) + c_1c_3c_4^2(1 - c_6c_7) + c_1c_2d_U^2(c_3d_I - c_4c_5d_U) + c_1c_3c_4d_U(3d_U - 2d_I) + (c_1c_4^2d_U + c_1c_4d_U^3)(1 - c_6c_7) + c_1c_3^2c_4c_6c_7(d_I - d_U) + c_1c_3^2c_4(3d_U - 2d_I) + c_1c_2c_4d_U^2(1 - c_6c_7) + c_1c_2c_4^2(1 - c_6c_7)$.

Hence, we deduce that if $d_U \leq d_I \leq \dfrac{3}{2}d_U$, $d_U \leq c_3$, $c_4c_5 \leq c_3$ and $c_6c_7 \leq 1$, then $(C_1C_2 - C_3)C_3 - C_1^2C_4 > 0$. It follows from the following equalities $c_3 - c_4c_5 = V_2\dfrac{\beta_1 - \rho q_1 A_2}{1+q_1A_2} + \dfrac{\beta_2 I_2}{1+q_2A_2}$, $1 - c_6c_7 = 1 - \dfrac{q_2\beta_2 U_2}{r(1+q_2A_2)^2}$ and $c_3 - d_U = \dfrac{(d_I+\varepsilon)I_2 - d_U U_2}{U_2}$ that if $d_U \leq d_I \leq \dfrac{3}{2}d_U$, $A_2 \leq \dfrac{\beta_1}{\rho q_1}$, $U_2 \leq \dfrac{r}{q_2\beta_2}$ and $(d_I+\varepsilon)I_2 - d_U U_2 \geq 0$, then $(C_1C_2 - C_3)C_3 - C_1^2C_4 > 0$. Based on Routh-Hurwitz criterion, we deduce that all roots of the equation (6) have negative real parts. □

4. Global Stability

In this section, we focus on the global stability analysis of the equilibria P_0, P_1, and P_3.

Theorem 4.1. *If $\mathscr{R}_0 \leq 1$, then the infection-free equilibrium P_0 is globally asymptotically stable.*

Proof. We define the Lyapunov function L_0 as

$$L_0(U,I,V,A) = U_0\phi\left(\frac{U}{U_0}\right) + I + \frac{\beta_1}{d_V}U_0V + \frac{\beta_1 r}{\rho d_V}U_0A + c((U-U_0)+I)^2,$$

where $\phi(x) = x - 1 - \ln(x)$ for $x > 0$, and c given by the following equality $2c(d_I + d_U) = \dfrac{\varepsilon}{U_0}$. Note that $\phi(x) \geq 0$ for all $x > 0$ and $\phi(x) = 0$ if and only if $x = 1$. Thus, $L_0(P) \geq 0$ for all $P \in \mathbb{R}^*_+ \times \mathbb{R}^3_+$ and $L_0(P) = 0$ if and only if $P = P_0$. Therefore, for all solution of the model system (1), we have

$$\begin{aligned}\frac{dL_0}{dt} &= \left(1 - \frac{U_0}{U}\right)\left(\lambda - d_U U - \frac{\beta_1}{1+q_1A}UV - \frac{\beta_2}{1+q_2A}UI + \varepsilon I\right)\\ &\quad + \left(\frac{\beta_1}{1+q_1A}UV + \frac{\beta_2}{1+q_2A}UI - (d_I+\varepsilon)I\right)\\ &\quad + \frac{\beta_1 k}{d_v}U_0 I - \beta_1 U_0 V - \frac{\beta_1 r}{d_V}U_0 VA - \frac{\beta_1 r}{\rho d_V}(\rho VA - d_A A)\\ &\quad + 2c(U - U_0 + I)(\lambda - d_U U - d_I I).\end{aligned}$$

Hence,

$$\frac{dL_0}{dt} = -\left(\frac{d_V}{U} + 2c + \frac{\varepsilon}{UU_0}\right)(U-U_0)^2 - \frac{q_1 A}{1+q_1A}\beta_1 U_0 V - 2cd_I I^2 + (d_I+\varepsilon)I(\mathscr{R}_0 - 1).$$

Thus, when $\mathscr{R}_0 \leq 1$, we have $\frac{dL_0}{dt} \leq 0$ with equality if and only if $U = U_0$, $I = 0$, $V = 0$ and $A = 0$. Therefore, it follows from LaSalle's invariance principle that P_0 is globally asymptotically stable when $\mathscr{R}_0 \leq 1$. □

To study the global stability for two infection equilibria P_1 and P_2, we consider the following condition

$$\text{(H)} \qquad \begin{cases} q_1(A - A_i)\left(\dfrac{1+q_1A}{1+q_1A_i} - \dfrac{V}{V_i}\right) \leq 0,\\ q_1(A - A_i)\left(\dfrac{1+q_1A}{1+q_1A_i} - \dfrac{I}{I_i}\right) \leq 0,\end{cases}$$

for all $i = 1,\ 2$.

Theorem 4.2. *If* (H) *holds for* P_1 *and* $\mathscr{R}_1^A \leq 1 < \mathscr{R}_0 \leq 1 + \dfrac{d_I}{\varepsilon}$, *then the immune-free equilibrium* P_1 *is globally asymptotically stable.*

Proof. We consider the Lyapunov functional L_1 as follows

$$\begin{aligned}L_1(U,I,V,A) &= U_1\phi\left(\frac{U}{U_1}\right) + I_1\phi\left(\frac{I}{I_1}\right) + \frac{\beta_1 U_1 V_1^2}{kI_1}\phi\left(\frac{V}{V_1}\right)\\ &\quad + \frac{\beta_1 r U_1 V_1}{\rho k I_1}A + \frac{\varepsilon}{2(d_U + d_I)U_1}[(U - U_1) + (I - I_1)]^2.\end{aligned}$$

Since $\lambda = d_U U_1 + \beta_1 U_1 V_1 + \beta_2 U_1 I_1 - \varepsilon I_1 = d_U U_1 + d_I I_1$ and $kI_1 = d_V V_1$, we get

$$\begin{aligned}
\frac{dL_1}{dt} &= -\left(d_U U_1 - \varepsilon I_1 + \varepsilon I + \frac{\varepsilon d_U U}{d_U + d_I}\right)\frac{(U-U_1)^2}{UU_1} \\
&\quad -\frac{\varepsilon d_I}{(d_U+d_I)U_1}(I-I_1)^2 + \frac{\beta_1 r d_A U_1}{\rho d_V}(\mathscr{R}_1^A - 1)A \\
&\quad +\beta_1 U_1 V_1\left(4 - \frac{U_1}{U} - \frac{IV_1}{I_1 V} - \frac{1}{1+q_1A}\frac{UVI_1}{U_1V_1I} - (1+q_1A)\right) \\
&\quad +\beta_1 U_1 V_1\left(-1 + (1+q_1A) - \frac{V}{V_1} + \frac{1}{1+q_1A}\frac{V}{V_1}\right) \\
&\quad +\beta_2 U_1 I_1\left(3 - \frac{U_1}{U} - \frac{1}{1+q_2A}\frac{U}{U_1} - (1+q_2A)\right) \\
&\quad +\beta_2 U_1 I_1\left(-1 + (1+q_2A) - \frac{I}{I_1} + \frac{1}{1+q_2A}\frac{I}{I_1}\right).
\end{aligned}$$

Form the condition (H) and using the equality $d_U U_1 - \varepsilon I_1 = \dfrac{\lambda}{d_I \mathscr{R}_0}(d_I + \varepsilon - \varepsilon \mathscr{R}_0)$, we deduce that if $\mathscr{R}_1^A \leq 1 < \mathscr{R}_0 \leq 1 + \dfrac{d_I}{\varepsilon}$, then $\dfrac{dL_1}{dt} \leq 0$ with equality if and only if $U = U_1$, $I = I_1$, $V = V_1$ and $A = 0$. From LaSalle's invariance principle, we deduce that P_1 is globally asymptotically stable when $\mathscr{R}_1^A \leq 1 < \mathscr{R}_0 \leq 1 + \dfrac{d_I}{\varepsilon}$. □

Theorem 4.3. *Assume that* (H) *holds for* P_2. *If* $\mathscr{R}_1^A > 1$ *and* $d_U U_2 - \varepsilon I_2 \geq 0$, *then the infection equilibrium with humoral immune response* P_2 *is globally asymptotically stable.*

Proof. To analyze the global stability of P_2, we consider the following Lyapunov function:

$$\begin{aligned}
L_2(U,I,V,A) &= U_2\phi\left(\frac{U}{U_2}\right) + I_2\phi\left(\frac{I}{I_2}\right) + \frac{\beta_1 U_2 V_2}{(1+q_1A)kI_2}V_2\phi\left(\frac{V}{V_2}\right) \\
&\quad + \frac{r\beta_1 U_2 V_2}{\rho k(1+q_1A_2)I_2}A_2\phi\left(\frac{A}{A_2}\right) + \frac{\varepsilon}{2(d_U+d_I)U_2}[(U-U_2)+(I-I_2)]^2.
\end{aligned}$$

Hence,

$$\begin{aligned}
\frac{dL_2}{dt} &= \left(1 - \frac{U_2}{U}\right)\left(\lambda - d_U U - \frac{\beta_1 UV}{1+q_A} - \frac{\beta_2 UI}{1+q_2A} + \varepsilon I\right) \\
&\quad + \left(1 - \frac{I_2}{I}\right)\left(\frac{\beta_1 UV}{1+q_1A} + \frac{\beta_2 UI}{1+q_2A} - (d_I+\varepsilon)I\right) \\
&\quad + \frac{\beta_1 U_2 V_2}{(1+q_1A_2)kI_2}\left(1 - \frac{V_2}{V}\right)(kI - d_V V - rVA)
\end{aligned}$$

$$+\frac{\beta_1 r U_2 V_2}{(1+q_1A_2)\rho k I_2}\left(1-\frac{A_2}{A}\right)(\rho VA - d_A A)$$
$$+\frac{\varepsilon}{(d_U+d_I)U_1}[(U-U_2)+(I-I_2)][\lambda - d_U U - d_I I].$$

Thus,

By the following equalities

$$\begin{cases} \lambda = \dfrac{\beta_1 U_2 V_2}{1+q_1A_2} + \dfrac{\beta_2 U_2 I_2}{1+q_2A_2} + d_U U_2 - \varepsilon I_2 = d_U U_2 + d_I I_2, \\ d_I + \varepsilon = \dfrac{\beta_1 U_2 V_2}{(1+q_1A_2)U_2} + \dfrac{\beta_2 U_2}{1+q_2A_2}, \\ d_V = \dfrac{kI_2}{V_2} + rA_2, \\ d_A = \rho V_2, \end{cases}$$

and by simple computations, we obtain

$$\frac{dL_2}{dt} = -\left(d_U U_2 - \varepsilon I_2 + \varepsilon I + \frac{\varepsilon d_U U}{d_U+d_I}\right)\frac{(U-U_2)^2}{UU_2} - \frac{\varepsilon d_I}{(d_U+d_I)U_2}(I-I_2)^2$$
$$+\frac{\beta_1 U_2 V_2}{1+q_1A_2}\left(4 - \frac{U_2}{U} - \frac{IV_2}{I_2V} - \frac{1+q_1A_2}{1+q_1A}\frac{UVI_2}{U_2V_2I} - \frac{1+q_1A}{1+q_1A_2}\right)$$
$$+\frac{\beta_1 U_2 V_2}{1+q_1A_2}\left(-1 + \frac{1+q_1A}{1+q_1A_2} - \frac{V}{V_2} + \frac{1+q_1A_2}{1+q_1A}\frac{V}{V_2}\right)$$
$$+\frac{\beta_2 U_2 I_2}{1+q_2A_2}\left(3 - \frac{U_2}{U} - \frac{1+q_2A_2}{1+q_2A}\frac{U}{U_2} - \frac{1+q_2A}{1+q_2A_2}\right)$$
$$+\frac{\beta_2 U_2 I_2}{1+q_2A_2}\left(-1 + \frac{1+q_2A}{1+q_2A_2} - \frac{I}{I_2} + \frac{1+q_2A_2}{1+q_2A}\frac{I}{I_2}\right).$$

Using the arithmetic-geometric inequality, we have

$$4 - \frac{U_2}{U} - \frac{IV_2}{I_2V} - \frac{1+q_1A_2}{1+q_1A}\frac{UVI_2}{U_2V_2I} - \frac{1+q_1A}{1+q_1A_2} \le 0,$$
$$3 - \frac{U_2}{U} - \frac{1+q_2A_2}{1+q_2A}\frac{U}{U_2} - \frac{1+q_2A}{1+q_2A_2} \le 0.$$

Moreover if (H) is holds for P_2, then

$$-1 + \frac{1+q_2A}{1+q_2A_2} - \frac{I}{I_2} + \frac{1+q_2A_2}{1+q_2A}\frac{I}{I_2} \le 0 \text{ and } -1 + \frac{1+q_1A}{1+q_1A_2} - \frac{V}{V_2} + \frac{1+q_1A_2}{1+q_1A}\frac{V}{V_2} \le 0.$$

Hence if $d_U U_2 - \varepsilon I_2 \geq 0$ and $\mathscr{R}_1^A > 1$, then $\dfrac{dL_2}{dt} \leq 0$ with equality if and only if $U = U_2$, $I = I_2$, $V = V_2$ and $A = A_2$. It follows from LaSalle's invariance principle that P_2 is globally asymptotically stable. This completes the proof. □

5. Conclusion

In this work, we have proposed and analyzed the dynamics of an immunological viral infection model with lytic and non-lytic immune response in presence of cell-to-cell transmission and cure of infected cells. We proved that the proposed model is mathematically and biologically well-posed. Also, we derived two threshold parameters that are the basic reproduction number $\mathscr{R}_0$ and the antibody immune response reproduction number $\mathscr{R}_1^A$. Such threshold parameters parameters characterize the dynamics of the model. In addition, the local and global stability of equilibria are fully established by means of direct and indirect Lyapunov method. Moreover, the models and results presented in [7, 8] are improved and generalized.

It is known that the adaptive immunity has two important characteristics that are specificity and memory. The first refers to ability of immune system to target specific pathogens. However, the second characteristic refers to the ability of immune system to quickly remember the antigens that previously activated it and launch a more intense immune reaction when encountering the same antigen a second time. Therefore, it will be more interesting to study the effect of immunological memory on the dynamics of the proposed model by using the new generalized Hattaf fractional (GHF) derivative and its properties presented [13, 14, 15]. This will be the main aim of our future works.

Conflict of Interests

The authors declare that there is no conflict of interests.

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