Review Article

Stability and Hopf Bifurcation of a Generalized Chikungunya Virus Infection Model with Two Modes of Transmission and Delays

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A generalized chikungunya virus (CHIKV) infection model with nonlinear incidence functions and two time delays is proposed and investigated. The model takes into account both modes of transmission that are virus-to-cell infection and cell-to-cell transmission. Furthermore, the local and global stabilities of the disease-free equilibrium and the chronic infection equilibrium are established by using the linearization and Lyapunov functional methods. Moreover, the existence of Hopf bifurcation is also analyzed. Finally, an application is presented in order to support the analytical results.

1. Introduction

The CHIKV belongs to the family Togaviridae, a term built from the Roman toga, to describe the draped appearance of their envelope [1]. Its genetic material consists of a single-stranded, thermosensitive RNA, about 15,000 nucleotides long. The multiplication of the viral genome in the cell is not strictly accurate, a common property of RNA viruses, which results in mutations that can affect not only the infective and pathogenic powers of the virus but also its passage from one kind of *Aedes* to another. Viral RNA of the infecting virion is included in a spherical particle made up of viral or nucleocapsid proteins assembled regularly and is of a size of around 70 nanometres. The virus multiplies with great ease in vitro, but also in vivo in mosquito cells, which explains the high infective power of contaminated *Aedes*. The female mosquito infects itself during a blood meal (necessary for laying) on a contaminated individual (man especially in the epidemic phase and also bats, monkeys, and other vertebrates). The virus proliferates in the insect. It is injected into a man or animal during a subsequent blood meal, during the initial phase of the bite, which includes the injection of "saliva" from the infected insect, before the blood meal itself [2].

In [3], the authors described the CHIKV replication cycle (see Figure 1) and the results of chikungunya virus infection particularly intense joint and muscle pain that forces patients to lean forward. After about one week of incubation, the pain appears, especially in the wrists, fingers, knees, ankles, and feet. The hips and shoulders are more rarely affected. These pains are accompanied by severe headaches, fever (over $38.5°C$), and rash in the chest and limbs, as well as lymph node swelling and conjunctivitis. Other symptoms sometimes appear, including bleeding of the gums or nose and neurological disorders.

Medical management is purely symptomatic, based on pain and anti-inflammatory treatments. However, these treatments have no preventive effect on the occurrence of a chronic evolution. First isolated in Uganda in 1953, CHIKV circulates mainly in the intertropical zone. This disease is particularly virulent in Africa and South Asia. However, cases were detected in the French territory as early as 2010 (in the south of France) and in 2013 and 2014 in the West Indies [4]. It can be responsible for important epidemics [5].
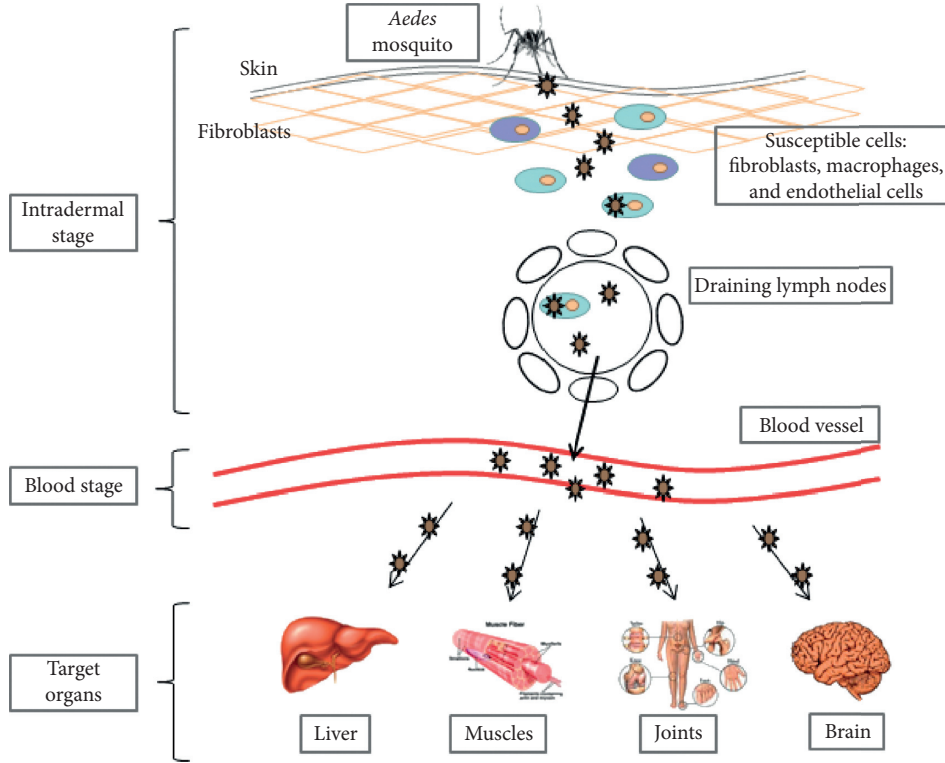
FIGURE 1: Schematic representation of CHIKV dissemination to different tissues and organs [3].

The risk of emergence in Europe is ever increasing due to the increase in "tiger mosquito," *Aedes albopictus* [6]. First observed in 2004 in the Alpes-Maritimes, the vector was established and active in 33 metropolitan departments in May 2017 [7]. This emergence has made it possible to highlight the need to strengthen the knowledge of health professionals with regard to arboviroses. Therefore, a few mathematical models have been established to describe dynamics of CHIKV viral infection, mostly focusing on virus-to-cell transmission [8, 9]. However, CHIKV can be spread by cell-to-cell transmission mode [10–13].

In view of this, we will formulate and analyse a generalized within-host CHIKV viral infection model taking into the account both modes of transmission and two discrete delays, in which the first delay τ_1 describes the time necessary for the newly produced virions to become mature and infectious and the second delay τ_2 represents the time needed to activate the humoral immune response. Then, the model is presented as follows:

$$\begin{cases} \dot{U} = s - d_1 U(t) - f(U(t), I(t), C(t))C(t) - g(U(t), I(t))I(t), \\ \dot{I} = f(U(t), I(t), C(t))C(t) + g(U(t), I(t))I(t) - d_2 I(t), \\ \dot{C} = vI(t - \tau_1) - d_3 C(t) - pA(t)C(t), \\ \dot{A} = \sigma + qA(t - \tau_2)C(t - \tau_2) - d_4 A(t), \end{cases}$$

(1)

where the general incidence functions $f(U, I, C)$ and $g(U, I)$ assumed to be continuously differentiable satisfy the following hypotheses [14, 15]:

(i) (H_0): $g(0, I) = 0$, for all $I \geq 0$; $(\partial g/\partial U)(U, I) \geq 0$ (or $g(U, I)$ is a monotone increasing function with respect to T when $f \equiv 0$), and $(\partial g/\partial I)(U, I) \leq 0$, for all $U \geq 0$ and $I \geq 0$

(ii) (H_1): $f(0, I, C) = 0$, for all $I \geq 0$ and $C \geq 0$

(iii) (H_2): $f(U, I, C)$ is a monotone increasing function with respect to U (or $(\partial f/\partial U)(U, I, C) \geq 0$ when $g(U, I)$ is a strictly monotone increasing function with respect to U), for any fixed $I \geq 0$ and $C \geq 0$

(iv) (H_3): $f(U, I, C)$ is a monotone decreasing function with respect to I and C

In biological terms, $U(t)$, $I(t)$, $C(t)$, and $A(t)$ indicate the densities of susceptible cells, infected cells, CHIKV particles, and antibodies at time t, respectively. The parameter s is the recruitment rate of uninfected cells, and v is the production rate of free CHIKV particles by infected cells. The CHIKV particles are attacked by the antibodies at rate pAC. The antibodies are created at rate σ and multiplicated at rate qAC. The parameters d_1, d_2, d_3, and d_4 are, respectively, the death rates of susceptible cells, infected cells, free CHIKV virions, and antibodies. Moreover, susceptible cells become infected either by free virus at rate $f(U, I, C)C$ or by direct contact with an infected cell at rate $g(U, I)I$. In addition, particular cases of the incidence function f and g are used by Elaiw et al. [16] to model the dynamics of CHIKV with cellular infection and delays. On the other hand, system (1) extends the model presented in [17] when $\tau_1 = \tau_2 = 0$ and the model proposed in [8] when $f(U, I, C) = \beta_1 U$ and $g(U, I) = 0$.

The rest of this paper is organized as follows. In Section 2, we provide some preliminary results concerning the existence, positivity, and boundedness of solutions. Also, we discuss the existence of equilibria. In Section 3, we analyse the stability for the equilibria. We investigate the existence of Hopf bifurcation in Section 4. An application is presented in Section 5. This paper ends with a conclusion in Section 6.

2. Preliminary Results

In this section, we first prove the existence, positivity, and boundedness of solutions. After that, we discuss the existence of equilibria.

2.1. Existence, Positivity, and Boundedness of Solutions.
According to biological meanings, the initial condition of system (1) is given as follows:

$$
\begin{aligned}
U(\theta) &= \phi_1(\theta) \geq 0, \\
I(\theta) &= \phi_2(\theta) \geq 0, \\
C(\theta) &= \phi_3(\theta) \geq 0, \\
A(\theta) &= \phi_4(\theta) \geq 0, \quad \theta \in [-\tau, 0],
\end{aligned} \tag{2}
$$

where $\tau = \max\{\tau_1, \tau_2\}$ and $(\phi_1(\theta), \phi_2(\theta), \phi_3(\theta), \phi_4(\theta)) (\in \mathscr{C}_+ = C([-\tau, 0], \mathrm{IR}_+^4))$. $\mathscr{C}_+$ is the Banach space of continuous functions mapping the interval $[-\tau, 0]$ into IR_+^4 with the topology of uniform convergence.

It follows from the fundamental theory of functional differential equations [18] that there exists a unique solution of system (1) with initial condition $(\phi_1, \phi_2, \phi_3, \phi_4) \in \mathscr{C}_+$.

Next, we investigate the positivity and boundedness of this solution under initial condition (2).

Theorem 1. *Under the initial condition (2), the solution of system (1) remains bounded and positive for all $t > 0$.*

Proof. We first demonstrate that $U(t) > 0$ for all $t \geq 0$. By contradiction, we assume that there exists a first time $t_1 > 0$ such that $U(t_1) = 0$ and $\dot{U}(t_1) \leq 0$. From the first equation of system (1), we have $\dot{U}(t_1) = s > 0$, which leads a contradiction. Then, $U(t) > 0$ for all $t \geq 0$. Since $\dot{A}(t) = \eta > 0$, and similar to the above, we deduce that $A(t) > 0$ for all $t \geq 0$. According to (1), we have

$$
\begin{aligned}
I(t) &= \phi_2(0)e^{-d_2 t \int_0^t g(U(\theta), I(\theta))\mathrm{d}\theta} + \int_0^t f(U(\xi), I(\xi), C(\xi))C(\xi)e^{-d_2(t-\xi)+\int_0^t g(U(\theta), I(\theta))\mathrm{d}\theta}\mathrm{d}\xi, \\
C(t) &= \phi_3(0)e^{-d_3 t - p\int_0^t A(\theta)\mathrm{d}\theta} + v\int_0^t I(\xi - \tau_1)e^{-d_3(t-\xi)-\int_0^t pA(\theta)\mathrm{d}\theta}\mathrm{d}\xi,
\end{aligned} \tag{3}
$$

which implies that $I(t)$ and $C(t)$ are nonnegative for all $t \geq 0$.

We consider the following function:

$$
N(t) = U(t) + I(t) + \frac{d_2}{2v}C(t + \tau_1) + \frac{pd_2}{2qv}A(t + \tau_1 + \tau_2). \tag{4}
$$

Then,

$$
\begin{aligned}
\dot{N}(t) &= s - d_1 U(t) - \frac{d_2}{2}I(t) - \frac{d_2 d_3}{2v}C(t + \tau_1) \\
&\quad + \frac{pd_2\sigma}{2qv} - \frac{pd_2 d_4}{2qv}A(t + \tau_1 + \tau_2) \leq s + \frac{pd_2\sigma}{2qv} - \delta N(t),
\end{aligned} \tag{5}
$$

where $\delta = \min\{d_1, (d_2/2), d_3, d_4\}$. Hence,

$$
\limsup_{t \to \infty} N(t) \leq \frac{s}{\delta} + \frac{pd_2\sigma}{2qv\delta}, \tag{6}
$$

which implies that all solutions of system (1) are bounded. This completes the proof.

2.2. Existence of the Equilibria.
Presently, we examine the existence of equilibria. By a basic calculation, system (1) has constantly one infection-free equilibrium of the form $Q_f((s/d_1), 0, 0, (\sigma/d_4))$. Thus, we characterize the basic reproduction number of our model as follows:

$$
R_0 = \frac{vf((s/d_1), 0, 0) + (d_3 + p(\sigma/d_4))g((s/d_1), 0)}{d_2(d_3 + p(\sigma/d_4))}. \tag{7}
$$

To locate different equilibria of (1), we solve the accompanying system:

$$
s - d_1 U - f(U, I, C)C - g(U, I)I = 0, \tag{8}
$$

$$
f(U, I, C)C + g(U, I)I - d_2 I = 0, \tag{9}
$$

$$
vI - d_3 C - pAC = 0, \tag{10}
$$

$$
\sigma + qAC - d_4 A = 0. \tag{11}
$$

From (8)–(11), we obtain $A = (\sigma/d_4 - qC)$, $I = ((d_3(d_4 - qC) + p\sigma)/v(d_4 - qC)C) = \varphi_1(C)$, $U = ((s - d_2\varphi_1(C))/d_1) = \varphi_2(C)$, and

$$v(d_4 - qC) f(\varphi_2(C), \varphi_1(C), C) + [d_3(d_4 - qC) + p\sigma] g(\varphi_2(C), \varphi_1(C)) = d_2 [d_3(d_4 - qC) + p\sigma]. \quad (12)$$

$A = \sigma/d_4 - qC \geq 0$ leads to $C < d_4/q$. Hence, there is no biological equilibrium when $C \geq d_4/q$. Accordingly, we consider the function ψ defined on $[0, (d_4/q))$ by

$$\psi(C) = v(d_4 - qC) f(\varphi_2(C), \varphi_1(C), C) + [d_3(d_4 - qC) + p\sigma] \\ \cdot g(\varphi_2(C), \varphi_1(C)) - d_2 [d_3(d_4 - qC) + p\sigma]. \quad (13)$$

We have $\varphi_2(0) = (s/d_1) > 0$ and

$$\lim_{C \longrightarrow (d_4/q)^-} \varphi_2(C) = -\infty \text{ and } \varphi_2'(C) = -\frac{d_2}{d_1} \varphi_1'(C) < 0, \quad (14)$$

with $\varphi_1'(C) = ((d_3(d_4 - qC)^2 + p\sigma d_4)/v(d_4 - qC)^2) > 0$. Then, the equation $\varphi_2(C) = 0$ admits a unique solution $\widetilde{C} \in (0, (d_4/q))$. Thus, $\widetilde{A} = (\sigma/(d_4 - q\widetilde{C})) > 0$ and $\psi(\widetilde{C}) = -d_2 [d_3(d_4 - q\widetilde{C}) + p\sigma] < 0$. Since $\psi(0) = d_2(d_3 d_4 + p\sigma)(R_0 - 1) > 0$ if $R_0 > 1$, we deduce that there exists $C^* \in (0, \widetilde{C})$ such that $\psi(C^*) = 0$.

From (10) and (11), we find $A^* = (\sigma/(d_4 - qC^*)) > 0$ and $I^* = ((d_3 + pA^*)/v)C^* > 0$.

Substitute $C = C^*$ and $I = I^*$ in (8), and define a function φ_3 as $\varphi_3(U) = s - d_1 U - f(U, I^*, C^*)C^* - g(U,$

$I^*)I^*$. Due to the fact that $\varphi_3(0) = s > 0$, $\varphi_3(s/d) = -f((s/d_1), I^*, C^*)C^* - g((s/d), I^*)I^* < 0$, and φ_3 is a strictly decreasing function of U, we deduce that there exists a unique $U^* \in (0, (s/d_1))$ such that $\varphi_3(U^*) = 0$. Therefore, model (1) has a unique chronic infection equilibrium $Q^*(U^*, I^*, C^*, A^*)$ when $R_0 > 1$.

The precedent conversations can be summed up in the accompanying outcome.

Theorem 2

(i) *For $R_0 \leq 1$, model (1) has one infection-free equilibrium $Q_f((s/d_1), 0, 0, (\sigma/d_4))$*

(ii) *For $R_0 > 1$, model (1) has a unique chronic infection equilibrium $Q^*(U^*, I^*, C^*, A^*)$ with $U^* \in (0, (s/d_1)), I^* > 0, C^* > 0,$ and $A^* > 0$*

3. Stability Analysis of Equilibria

In this section, we concentrate on the stability of infection-free equilibrium of system (1). The characteristic equation of system (1) is noted as

First, we have the following result.

Theorem 3. *For any τ_2 and $\tau_1 = 0$, the infection-free equilibrium Q_f is locally asymptotically stable if $R_0 < 1$ and becomes unstable if $R_0 > 1$.*

Proof. Examining (15) at Q_f, we obtain

$$\begin{vmatrix} -d_1 - C\dfrac{\partial f}{\partial U} - I\dfrac{\partial g}{\partial U} - \xi & -C\dfrac{\partial f}{\partial I} - I\dfrac{\partial g}{\partial I} - g(U,I) & -C\dfrac{\partial f}{\partial C} - f(U,I,C) & 0 \\[2mm] C\dfrac{\partial f}{\partial U} + I\dfrac{\partial g}{\partial U} & C\dfrac{\partial f}{\partial I} + I\dfrac{\partial g}{\partial I} + g(U,I) - d_2 - \xi & C\dfrac{\partial f}{\partial C} + f(U,I,C) & 0 \\[2mm] 0 & ve^{-\xi\tau_1} & -d_3 - pA - \xi & -pC \\[2mm] 0 & 0 & qAe^{-\xi\tau_2} & qCe^{-\xi\tau_2} - d_4 - \xi \end{vmatrix} = 0. \quad (15)$$

$$(\xi + d_1)(\xi + d_4) \left(\begin{array}{l} \xi^2 + \left[d_3 + d_2 + p\dfrac{\sigma}{d_4} - g\left(\dfrac{s}{d_1}, 0\right) \right]\xi - ve^{-\xi\tau_1} f\left(\dfrac{s}{d_1}, 0, 0\right) \\[3mm] \quad - \left(d_3 + p\dfrac{\sigma}{d_4} \right)\left(g\left(\dfrac{s}{d_1}, 0\right) - d_2 \right) \end{array} \right) = 0. \quad (16)$$

When $\tau_1 = 0$, from equation (16), we obtain

$$(\xi + d_1)(\xi + d_4)\left(\xi^2 + \left[d_3 + d_2 + p\dfrac{\sigma}{d_4} - g\left(\dfrac{s}{d_1}, 0\right) \right]\xi + d_2\left(d_3 + p\dfrac{\sigma}{d_4} \right)(1 - R_0) \right) = 0. \quad (17)$$

Therefore, the roots of this equation are

$$\xi_1 = -d_1,$$

$$\xi_2 = -d_4,$$

$$\xi_3 = \frac{-(d_2 + d_3 + p(\sigma/d_4) - g(s/d_1, 0)) - \sqrt{\Delta}}{2},$$ (18)

$$\xi_4 = \frac{-(d_2 + d_3 + p\sigma/d_4 - g(s/d_1, 0)) + \sqrt{\Delta}}{2},$$

of which $\Delta = (d_2 + d_3 + p\sigma/d_4 - g(s/d_1, 0))^2 - 4d_2$ $(d_3 + p\sigma/d_4)(1 - R_0)$. Obviously, $\xi_1, \xi_2,$ and ξ_3 are negative. Furthermore, ξ_4 is negative if $R_0 < 1$ and positive if $R_0 > 1$. Consequently, Q_f is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.

The following theorem characterizes the global stability of the infection-free equilibrium Q_f when $R_0 \leq 1$.

Theorem 4. *For any τ_1 and τ_2, the infection-free equilibrium Q_f is globally asymptotically stable if $R_0 \leq 1$.*

Proof. We establish a Lyapunov function as follows:

$$L(t) = I(t) + \frac{f((s/d_1), 0, 0)}{d_3 + p(\sigma/d_4)} C(t) + \frac{vf((s/d_1), 0, 0)}{d_3 + p(\sigma/d_4)} \int_{t-\tau_1}^{t} I(\theta) d\theta.$$ (19)

Computing the time derivative of L along the solutions of (1), we find

$$\frac{dL}{dt} = \left(f(U, I, C) - \frac{d_3 + pA}{d_3 + p(\sigma/d_4)} f\left(\frac{s}{d_1}, 0, 0\right) \right) C$$

$$+ d_2 \left(\frac{vf(s/d_1, 0, 0) + (d_2 + p(\sigma/d_4))g(U, I)}{d_2(d_3 + p(\sigma/d_4))} - 1 \right) I$$

$$\leq \left(f(U, 0, 0) - f\left(\frac{s}{d_1}, 0, 0\right) \right) C + a(R_0 - 1)I \leq a(R_0 - 1)I.$$ (20)

Given that $R_0 \leq 1$, we have $(dL/dt) \leq 0$. Likewise, it is not difficult to show that the largest invariant set in $\{(U, I, C, A) | (dL/dt) = 0\}$ is $\{Q_f\}$. By the LaSalle's invariance principle [19], Q_f is globally asymptotically stable for $R_0 \leq 1$.

Next, we focus on the global stability of the chronic infection equilibrium Q^* by assuming that $R_0 > 1$, and for all $U, I, C > 0$, we consider the following hypothesis:

$$\left(1 - \frac{f(U, I, C)}{f(U, I^*, C^*)} \right)\left(\frac{f(U, I^*, C^*)}{f(U, I, C)} - \frac{C}{C^*} \right) \leq 0,$$

$$\left(1 - \frac{f(U^*, I^*, C^*)g(U, I)}{f(U, I^*, C^*)g(U^*, I^*)} \right)\left(\frac{f(U, I^*, C^*)g(U^*, I^*)}{f(U^*, I^*, C^*)g(U, I)} - \frac{I}{I^*} \right) \leq 0.$$ (21)

Theorem 5. *Assume that (21) holds. For any τ_1, if $\tau_2 = 0$ and $R_0 > 1$, then the chronic infection equilibrium Q^* is globally asymptotically stable.*

Proof. Consider the following Lyapunov function:

$$W(t) = U(t) - U^* - \int_{U^*}^{U} \frac{f(U^*, I^*, C^*)}{f(X, I^*, C^*)} dX + I^* \Phi\left(\frac{I(t)}{I^*}\right) + \frac{f(U^*, I^*, C^*)C^*}{vI^*} C^* \Phi\left(\frac{C(t)}{C^*}\right)$$

$$+ \frac{qf(U^*, I^*, C^*)C^*}{qvI^*} A^* \Phi\left(\frac{A(t)}{A^*}\right) + f(U^*, I^*, C^*)C^* \int_{t-\tau_1}^{t} \Phi\left(\frac{I(\theta)}{I^*}\right) d\theta,$$ (22)

where $\Phi(x) = x - 1 - \ln x$, $x > 0$. Thus, the time derivative of W along the positive solutions of (1) satisfies

$$\frac{dW}{dt} = \left(1 - \frac{f(U^*, I^*, C^*)}{f(U, I^*, C^*)} \right)\dot{U} + \left(1 - \frac{I^*}{I} \right)\dot{I} + \frac{f(U^*, I^*, C^*)C^*}{vI^*}\left(1 - \frac{C^*}{C} \right)\dot{C}$$

$$\frac{pf(U^*, I^*, C^*)C^*}{qvI^*}\left(1 - \frac{A^*}{A} \right)\dot{A} + f(U^*, I^*, C^*)C^* \frac{d}{dt} \int_{t-\tau_1}^{t} \Phi\left(\frac{I(\theta)}{I^*}\right) d\theta,$$ (23)

where $(\mathrm{d}/\mathrm{d}t)\int_{t-\tau_1}^{t}\Phi(I(\theta)/I^*)\mathrm{d}\theta = (I - I(t - \tau_1)/I^*)$ $+\ln(I(t - \tau_1)/I)$. Therefore, we have

$$
\begin{aligned}
\frac{\mathrm{d}W}{\mathrm{d}t} &= \left(1 - \frac{f(U^*, I^*, C^*)}{f(U, I^*, C^*)}\right)(s - d_1 U - f(U, I, C)C - g(U, I)I) \\
&\quad + \left(1 - \frac{I^*}{I}\right)(f(U, I, C)C + g(U, I)I - d_2 I) + \frac{f(U^*, I^*, C^*)C^*}{vI^*}\left(1 - \frac{C^*}{C}\right)(vI(t - \tau_1) - d_3 C - pAC) \\
&\quad + \frac{pf(U^*, I^*, C^*)C^*}{qvI^*}\left(1 - \frac{A^*}{A}\right)(\sigma + qAC - d_4 A) + f(U^*, I^*, C^*)C^*\left(\frac{I - I(t - \tau_1)}{I^*} + \ln\frac{I(t - \tau_1)}{I}\right).
\end{aligned}
\tag{24}
$$

Substituting $s = d_1 U^* + f(U^*, I^*, C^*)C^* + g(U^*, I^*)I^*$, $vI^* = d_3 C^* + qA^* C^*$, and $\sigma = d_4 A^* - qA^* C^*$, we obtain

$$
\begin{aligned}
\frac{\mathrm{d}W}{\mathrm{d}t} &= d_1 U^*\left(1 - \frac{U}{U^*}\right)\left(1 - \frac{f(U^*, I^*, C^*)}{f(U, I^*, C^*)}\right) + f(U^*, I^*, C^*) \\
&\quad C^*\left(-1 - \frac{C}{C^*} + \frac{f(U, I, C)C}{f(U, I^*, C^*)C^*} + \frac{f(U, I^*, C^*)}{f(U, I, C)}\right) + f(U^*, I^*, C^*)C^* \\
&\quad \left(4 - \frac{f(U^*, I^*, C^*)}{f(U, I^*, C^*)} - \frac{f(U, I^*, C^*)}{f(U, I, C)} - \frac{f(U, I, C)CI^*}{f(U^*, I^*, C^*)C^* I} - \frac{C^* I(t - \tau_1)}{CI^*} + \ln\frac{I(t - \tau_1)}{I}\right) \\
&\quad + g(U^*, I^*)I^*\left(-1 - \frac{I}{I^*} - \frac{f(U^*, I^*, C^*)g(U, I)I}{f(U, I^*, C^*)g(U^*, I^*)I^*} + \frac{f(U, I^*, C^*)g(U^*, I^*)}{f(U^*, I^*, C^*)g(U, I)}\right) \\
&\quad + g(U^*, I^*)I^*\left(3 - \frac{f(U^*, I^*, C^*)}{f(U, I^*, C^*)} - \frac{f(U, I^*, C^*)g(U^*, I^*)}{f(U^*, I^*, C^*)g(U, I)} - \frac{g(U, I)}{g(U^*, I^*)}\right) \\
&\quad - \frac{p\sigma f(U^*, I^*, C^*)C^*}{qvI^* A^* A}(A - A^*)^2.
\end{aligned}
\tag{25}
$$

Thus,

$$
\begin{aligned}
\frac{\mathrm{d}W}{\mathrm{d}t} &= d_1 U^*\left(1 - \frac{U}{U^*}\right)\left(1 - \frac{f(U^*, I^*, C^*)}{f(U, I^*, C^*)}\right) \\
&\quad + f(U^*, I^*, C^*)C^*\left(-1 - \frac{C}{C^*} + \frac{f(U, I, C)C}{f(U, I^*, C^*)C^*} + \frac{f(U, I^*, C^*)}{f(U, I, C)}\right) \\
&\quad + g(U^*, I^*)I^*\left(-1 - \frac{I}{I^*} - \frac{f(U^*, I^*, C^*)g(U, I)I}{f(U, I^*, C^*)g(U^*, I^*)I^*} + \frac{f(U, I^*, C^*)g(U^*, I^*)}{f(U^*, I^*, C^*)g(U, I)}\right) \\
&\quad - f(U^*, I^*, C^*)C^*\left[\Phi\left(\frac{f(U^*, I^*, C^*)}{f(U, I^*, C^*)}\right) + \Phi\left(\frac{f(U, I^*, C^*)}{f(U, I, C)}\right) + \Phi\left(\frac{C^* I(t - \tau_1)}{CI^*}\right) + \Phi\left(\frac{f(U, I, C)CI^*}{f(U^*, I^*, C^*)C^* I}\right)\right] \\
&\quad - g(U^*, I^*)I^*\left[\Phi\left(\frac{f(U^*, I^*, C^*)}{f(U, I^*, C^*)}\right) + \Phi\left(\frac{f(U, I^*, C^*)g(U^*, I^*)}{f(U^*, I^*, C^*)g(U, I)}\right) + \Phi\left(\frac{g(U, I)}{g(U^*, I^*)}\right)\right] \\
&\quad - \frac{p\sigma f(U^*, I^*, C^*)C^*}{qvI^* A^* A}(A - A^*)^2.
\end{aligned}
\tag{26}
$$

By (H_2), we find that

$$\left(1 - \frac{U}{U^*}\right)\left(1 - \frac{f(U^*,I^*,C^*)}{f(U,I^*,C^*)}\right) \le 0. \qquad (27)$$

$$-1 - \frac{C}{C^*} + \frac{f(U,I,C)C}{f(U,I^*,C^*)C^*} + \frac{f(U,I^*,C^*)}{f(U,I,C)} = \left(1 - \frac{f(U,I,C)}{f(U,I^*,C^*)}\right)\left(\frac{f(U,I^*,C^*)}{f(U,I,C)} - \frac{C}{C^*}\right) \le 0,$$

$$-1 - \frac{I}{I^*} - \frac{f(U^*,I^*,C^*)g(U,I)I}{f(U,I^*,C^*)g(U^*,I^*)I^*} + \frac{f(U,I^*,C^*)g(U^*,I^*)}{f(U^*,I^*,C^*)g(U,I)} \qquad (28)$$

$$= \left(1 - \frac{f(U^*,I^*,C^*)g(U,I)}{f(U,I^*,C^*)g(U^*,I^*)}\right)\left(\frac{f(U,I^*,C^*)g(U^*,I^*)}{f(U^*,I^*,C^*)g(U,I)} - \frac{I}{I^*}\right) \le 0.$$

Since $\Phi(x) \ge 0$, we have $(dW/dt) \le 0$ with equality if and only if $U = U^*$, $I = I^*$, $C = C^*$, and $A = A^*$. From LaSalle's invariance principle, we deduce that the chronic infection equilibrium Q^* is globally asymptotically stable when $R_0 > 1$.

4. Hopf Bifurcation Analysis

In this section, we investigate the bifurcation at the infection equilibrium Q^*. By computing the characteristic equation for system (1) at Q^*, we find

By (21), we obtain

$$\xi^4 + a_1\xi^3 + a_2\xi^2 + a_3\xi + a_4 + \left(b_1\xi^3 + b_2\xi^2 + b_3\xi + b_4\right)e^{-\xi\tau_2}$$

$$+ \left(c_1\xi^2 + c_2\xi + c_3\right)e^{-\xi\tau_1} + \left(r_1\xi + r_2\right)e^{-\xi(\tau_1+\tau_2)} = 0, \qquad (29)$$

where

$$
\begin{aligned}
a_1 &= d_1 + d_3 + d_4 + M + A^* - N,\\
a_2 &= (d_1 + M - N)(d_3 + d_4 + pA^*) + d_4(d_3 + pA^*) + d_1(d_2 - N) + Md_2,\\
a_3 &= d_1(d_2 - N)(d_3 + d_4 + pA^*) + (d_3 + pA^*)[d_4(d_1 + M - N) + Md_2] + Md_2d_4,\\
a_4 &= d_4(d_3 + pA^*)[d_1(d_2 - N) + Md_2],\\
b_1 &= -qC^*,\\
b_2 &= -qC^*(d_1 + d_3 + M - N),\\
b_3 &= -qC^*[d_2(M - pA^*) + d_1(d_2 - N) + d_3(d_1 + M - N)],\\
b_4 &= -qC^*[pA^*(Nd_1 - Md_2 + (d_3 + pA^*)[d_1(d_2 - N) + Md_2]],\\
c_1 &= -vQ,\\
c_2 &= -vQ(d_4 + 1),\\
c_3 &= -vQd_4,\\
r_1 &= qC^*v,\\
r_2 &= qC^*vd_1,
\end{aligned}
\qquad (30)
$$

with $M = C^*(\partial f/\partial U)(U^*,I^*,C^*) + I^*(\partial g/\partial U)(U^*,I^*)$, $Q = C^*(\partial f/\partial C)(U^*,I^*,C^*) + f(U^*,I^*,C^*)$, and $N = C^*(\partial f/\partial I)(U^*,I^*,C^*) + I^*(\partial g/\partial I)(U^*,I^*) + g(U^*,I^*)$.

However, when $\tau_1 > 0$, equation (29) is too complicated. Therefore, in the following discussions, we assume that $\tau_1 = 0$ and $\tau_2 > 0$. Then, equation (29) is diminished to

$$\xi^4 + H_1\xi^3 + H_2\xi^2 + H_3\xi + H_4 + \left(I_1\xi^3 + I_2\xi^2 + I_3\xi + I_4\right)e^{-\xi\tau_2} = 0, \qquad (31)$$

where

$$
\begin{aligned}
H_1 &= a_1 = d_1 + d_3 + d_4 + M + A^* - N, \\
H_2 &= a_2 + c_1 = (d_1 + M - N)(d_3 + d_4 + pA^*) + d_4(d_3 + pA^*) + d_1(d_2 - N) + Md_2 - vQ, \\
H_3 &= a_3 + c_2 = d_1(d_2 - N)(d_3 + d_4 + pA^*) + (d_3 + pA^*)[d_4(d_1 + M - N) + Md_2] \\
    &\quad + Md_2 d_4 - vQ(d_4 + 1), \\
H_4 &= a_4 + c_3 = d_4(d_3 + pA^*)[d_1(d_2 - N) + Md_2] - vQd_4, \\
I_1 &= b_1 = -qC^*, \\
I_2 &= b_2 = -qC^*(d_1 + d_3 + M - N), \\
I_3 &= b_3 + r_1 = -qC^*[d_2(M - pA^*) + d_1(d_2 - N) + d_3(d_1 + M - N) - v], \\
I_4 &= b_4 + r_2 = -qC^*[pA^*(Nd_1 - Md_2 + (d_3 + pA^*)[d_1(d_2 - N) + Md_2] - vd_1].
\end{aligned}
\tag{32}
$$

Let $\xi = i\omega\,(\omega > 0)$ be a purely imaginary root of (31). Separating real and imaginary parts, it follows that

$$
\begin{cases}
\omega^4 - H_2\omega^2 + H_4 = (I_2\omega^2 - I_4)\cos(\tau_2\omega) + (I_1\omega^3 - I_3\omega)\sin(\tau_2\omega), \\
-H_1\omega^3 + H_3\omega = (I_1\omega^3 - I_3\omega)\cos(\tau_2\omega) - (I_2\omega^2 - I_4)\sin(\tau_2\omega).
\end{cases}
\tag{33}
$$

Squaring and adding the two equations of (33), it follows that

$$
\omega^8 + L_1\omega^6 + L_2\omega^4 + L_3\omega^2 + L_4 = 0,
\tag{34}
$$

where

$$
\begin{aligned}
L_1 &= H_1^2 - 2H_2 - I_1^2, \\
L_2 &= H_2^2 - 2H_1 H_3 + 2H_4 + 2I_1 I_3 - I_2^2, \\
L_3 &= H_3^2 - 2H_2 H_4 + 2I_2 I_4 - I_3^2, \\
L_4 &= H_4^2 - I_4^2.
\end{aligned}
\tag{35}
$$

Let $z = \omega^2$, then equation (34) becomes

$$
\Psi(z) := z^4 + L_1 z^3 + L_2 z^2 + L_3 z + L_4 = 0.
\tag{36}
$$

It is clear that when $L_4 < 0$, equation (36) has at least one positive root because $\Psi(0) = L_4 < 0$ and $\lim_{z \to +\infty}\Psi(z) = +\infty$. Moreover, we obtain

$$
\Psi'(z) = 4z^3 + 3L_1 z^2 + 2L_2 z + L_3.
\tag{37}
$$

Denote that

$$
\begin{aligned}
\gamma_1 &= \frac{8L_2 - 3L_1^2}{16}, \\
\delta_1 &= \frac{L_1^3 - 4L_1 L_2 + 8L_2}{32}, \\
\Delta &= \left(\frac{\gamma_1}{2}\right)^3 + \left(\frac{\delta_1}{2}\right)^3, \\
j &= e^{i(2\pi/3)} = -\frac{1}{2} + i\frac{\sqrt{3}}{2}.
\end{aligned}
\tag{38}
$$

Applying the Cardano formula, the cubic equation (37) has the following roots:

$$
\begin{aligned}
\nu_1 &= \sqrt[3]{-\frac{\delta_1}{2} + \sqrt{\Delta}} + \sqrt[3]{-\frac{\delta_1}{2} + \sqrt{\Delta}} - \frac{L_1}{4}, \\
\nu_2 &= j\sqrt[3]{-\frac{\delta_1}{2} + \sqrt{\Delta}} + j^2\sqrt[3]{-\frac{\delta_1}{2} + \sqrt{\Delta}} - \frac{L_1}{4}, \\
\nu_3 &= j^2\sqrt[3]{-\frac{\delta_1}{2} + \sqrt{\Delta}} + j\sqrt[3]{-\frac{\delta_1}{2} + \sqrt{\Delta}} - \frac{L_1}{4}.
\end{aligned}
\tag{39}
$$

When $\Delta > 0$, the first root ν_1 is a real number and the other two, ν_2 and ν_3, are conjugate complex numbers. In this situation,

$$
\Psi'(z) = 4(z - \nu_1)\left(z^2 - 2\mathrm{Re}(\nu_2)z + |\nu_2|^2\right).
\tag{40}
$$

We assume that $\Psi(z)$ is a decreasing function on the interval $(-\infty, \nu_1]$ and increasing function on $[\nu_1, +\infty)$. Since $z^2 - 2\mathrm{Re}(\nu_2)z + |\nu_2|^2 > 0$ for all $z \in \mathbb{R}$, it attains its strict global minimum at $z = \nu_1$.

When $\Delta = 0$, all roots are real with $\nu_1 = (3\gamma_1/\delta_1) - (L_1/4)$ and $\nu_2 = \nu_3 = (3\gamma_1/2\delta_1) - (L_1/4)$. Then,

$$
\Psi'(z) = 4(z - \nu_1)(z - \nu_2)^2.
\tag{41}
$$

Hence, $\Psi(z)$ is a decreasing function on $(-\infty, \nu_1]$ and increasing function on $[\nu_1, +\infty)$. Also, it attains its strict global minimum at $z = \nu_1$. Consequently, if $L_4 \geq 0$ and $\Delta \geq 0$, then equation (36) has a positive root if and only if $\nu_1 > 0$ and $\Psi(\nu_1) \leq 0$.

When $\Delta < 0$, all three roots are real and distinct. In this case, $\Psi'(z)$ can be changed as

$$
\Psi'(z) = 4(z - \nu_1)(z - \nu_2)(z - \nu_3).
\tag{42}
$$

Similarly, we obtain that if $L_4 \geq 0$ and $\Delta < 0$, then equation (36) has a positive root if and only if there exists at least one $\nu^* \in \{\nu_1, \nu_2, \nu_3\}$ such that $\nu^* > 0$ and $\Psi(\nu^*) \leq 0$.

Outlining the above discussions, we obtain the following lemma.

Lemma 1. *For the polynomial equation (36), the following results are true:*

(i) *If $L_4 < 0$, then equation (36) has at least one positive root*

(ii) *If $L_4 \geq 0$ and $\Delta \geq 0$, then equation (36) has positive root if and only if $\nu_1 > 0$ and $\Psi(\nu_1) \leq 0$*

(iii) *If $L_4 \geq 0$ and $\Delta < 0$, then equation (36) has a positive root if and only if there exists at least one $\nu^* \in \{\nu_1, \nu_2, \nu_3\}$ such that $\nu^* > 0$ and $\Psi(\nu^*) \leq 0$*

In light of this lemma, we acknowledge the following conditions:

(a) $L_4 < 0$

(b) $L_4 \geq 0$, $\Delta \geq 0$, $\nu_1 > 0$, and $\Psi(\nu_1) \leq 0$

(c) $L_4 \geq 0$, $\Delta < 0$, and there exists at least one $\nu^* \in \{\nu_1, \nu_2, \nu_3\}$ such that $\nu^* > 0$ and $\Psi(\nu^*) \leq 0$

In the case that the conditions $(a) - (c)$ are not fulfilled, then equation (14) has no positive roots. Consequently, the infection equilibrium Q^* is locally asymptotically stable for all delay $\tau_2 \geq 0$. As a result, the existence of Hopf bifurcation is preposterous.

Presently, we expect that one of the conditions, $(a) - (c)$, is fulfilled. We suppose that equation (36) has k_0 positive roots, where $k_0 \in \{1, 2, 3, 4\}$. Denote the positive root of (36) by $z_k, k = 1, 2, \ldots, k_0$. Then, equation (34) has positive roots $\omega_k = \sqrt{z_k}$. In accordance with (33), we obtain

$$
\cos(\omega_k \tau_2) = \frac{\left(\omega_k^4 - H_2\omega_k^2 + H_4\right)\left(I_2\omega_k^2 - I_4\right) + \left(-H_1\omega_k^3 + H_3\omega_k\right)\left(I_1\omega_k^3 - I_3\omega_k\right)}{\left(I_2\omega_k^2 - I_4\right)^2 + \left(I_1\omega_k^3 - I_3\omega_k\right)^2} = \Upsilon_1(\omega_k),
$$

$$
\sin(\omega_k \tau_2) = \frac{\left(\omega_k^4 - H_2\omega_k^2 + H_4\right)\left(I_1\omega_k^3 - I_3\omega_k\right) - \left(-H_1\omega_k^3 + H_3\omega_k\right)\left(I_2\omega_k^2 - I_4\right)}{\left(I_2\omega_k^2 - I_4\right)^2 + \left(I_1\omega_k^3 - I_3\omega_k\right)^2} = \Upsilon_2(\omega_k).
$$

(43)

Define

$$
\tau_{2,k}^{(n)} = \begin{cases} \dfrac{1}{\omega_k}\left[\arccos(\Upsilon_1(\omega_k)) + 2n\pi\right], & \text{If } \Upsilon_2(\omega_k) \geq 0, \\[3mm] \dfrac{1}{\omega_k}\left[2\pi - \arccos(\Upsilon_1(\omega_k)) + 2n\pi\right], & \text{If } \Upsilon_2(\omega_k) < 0, \end{cases}
$$

(44)

where $k = 1, 2, \ldots, k_0$ and $n \in \mathbb{N}$. Hence,

$$
\tau_0 = \tau_{2,k_0}^{(0)} = \min_{1 \leq k < k_0}\left\{\tau_{2,k}^{(0)}\right\},
$$

$$
\omega_0 = \omega_{k_0} \text{ and } z_0 = z_{k_0}.
$$

(45)

Let $\xi(\tau) = \alpha(\tau) + i\omega(\tau)$ be the root of equation (31) at $\tau = \tau_0$ satisfying $\alpha(\tau_0) = 0$ and $\omega(\tau_0) = \omega_0$. Then, we obtain the following result.

Lemma 2. *If $\Psi'(\nu_0) \neq 0$, then $d\operatorname{Re}\xi(\tau_2)/d\tau_2|_{\tau_2=\tau_0}$ and $\Psi'(\tau_2)$ have the same sign.*

Proof. Differentiating both sides of equation (31) with respect to τ_2 and noticing that ξ is a function of τ yield

$$
\left(\frac{d\xi}{d\tau_2}\right)^{-1} = \frac{4\xi^3 + 3H_1\xi^2 + 2H_2\xi + H_3}{-\xi e^{-\xi\tau_2}\left(I_1\xi^3 + I_2\xi^2 + I_3\xi + I_4\right)} + \frac{3I_1\xi^2 + 2I_2\xi + I_3}{\xi I_1\xi^3 + I_2\xi^2 + I_3\xi + I_4} - \frac{\tau_2}{\xi}
$$

$$
= \frac{4\xi^3 + 3H_1\xi^2 + 2H_2\xi + H_3}{-\xi\left(\xi^4 + H_1\xi^3 + H_2\xi^2 + H_3\xi + H_4\right)} + \frac{3I_1\xi^2 + 2I_2\xi + I_3}{\xi\left(I_1\xi^3 + I_2\xi^2 + I_3\xi + I_4\right)} - \frac{\tau_2}{\xi}
$$

$$
\left(4\xi^3 + 3H_1\xi^2 + 2H_2\xi + H_3\right)\frac{d\xi}{d\tau_2} + e^{-\xi\tau_2}\left(3I_1\xi^2 + 2I_2\xi + I_3\right)\frac{d\xi}{d\tau_2}
$$

$$
- e^{-\xi\tau_2}\left(I_1\xi^3 + I_2\xi^2 + I_3\xi + I_4\right)\left(\tau_2\frac{d\xi}{d\tau_2} + \xi\right) = 0.
$$

(46)

The fact that

$$\text{sign}\left[\frac{d\text{Re}\xi(\tau_2)}{d\tau_2}\Big|_{\tau_2=\tau_0}\right] = \text{sign}\left[\text{Re}\left(\frac{d\xi(\tau_2)}{d\tau_2}\right)^{-1}\Big|_{\tau_2=\tau_0}\right], \quad (47)$$

leads to

$$
\begin{aligned}
\text{sign}\left[\frac{d\text{Re}\xi(\tau_2)}{d\tau_2}\Big|_{\tau_2=\tau_0}\right] &= \text{sign}\left[\text{Re}\left[\frac{4\xi^3 + 3H_1\xi^2 + 2H_2\xi + H_3}{-\xi(\xi^4 + H_1\xi^3 + H_2\xi^2 + H_3\xi + H_4)}\right]\Big|_{\tau_2=\tau_0}\right.\\
&\quad \left.+\text{Re}\left[\frac{3I_1\xi^2 + 2I_2\xi + I_3}{\xi(I_1\xi^3 + I_2\xi^2 + I_3\xi + I_4)}\right]\Big|_{\xi=i\omega_0}\right] = \text{sign}\left[\frac{4\omega_0^6 + 3L_1\omega_0^4 + 2L_2\omega_0^2 + L_3}{(I_2\omega_0^2 - I_4)^2 + (I_1\omega_0^3 - I_3\omega_0)^2}\right]\\
&= \text{sign}\left[\frac{\Psi'(\omega_0^2)}{(I_2\omega_0^2 - I_4)^2 + (I_1\omega_0^3 - I_3\omega_0)^2}\right] = \text{sign}\left[\frac{\Psi'(z_0)}{(I_2\omega_0^2 - I_4)^2 + (I_1\omega_0^3 - I_3\omega_0)^2}\right].
\end{aligned}
\quad (48)
$$

Thus, $\text{sign}\{d\text{Re}\xi(\tau_2)/d\tau_2|_{\tau_2=\tau_0}\} = \text{sign}\{\Psi'(z_0)\}$.

Summarizing the above and the Hopf bifurcation theorem [20] allows us to state the following results.

Theorem 6. *If $R_0 > 1$ and (21) are satisfied, then the following results hold:*

(i) *If the conditions $(a) - (c)$ are all not satisfied, then the infection equilibrium Q^* is locally asymptotically stable for all delay $\tau_2 \geq 0$, which is called the delay-independent stability*

(ii) *If one of the conditions $(a) - (c)$ is satisfied, then the infection equilibrium Q^* is locally asymptotically stable for all $\tau \in (0, \tau_0)$*

(iii) *If one of the conditions $(a) - (c)$ is satisfied and $\Psi'(z_0) \neq 0$, then the transversality condition holds and model (1) undergoes a Hopf bifurcation at infection equilibrium Q^* when $\tau_2 = \tau_0$*

From Lemma 2, we see that, to ensure the condition of transversality, it is mandatory that the positive roots of equation (36) are simple. First, we need the following lemma given by Hattaf [21].

Lemma 3. *Let $P(x)$ be a polynomial of degree 4 with real coefficients:*

(i) *If the quartic equation $P(x) = 0$ has only a single positive and simple root x_1, then $P'(x_1) > 0$*

(ii) *If the quartic equation $P(x) = 0$ has only two positive and simple roots x_1 and x_2 (setting $x_2 < x_1$), then $P'(x_1) > 0$ and $P'(x_2) < 0$*

(iii) *If the quartic equation $P(x) = 0$ has only three positive and simple roots $x_3 < x_2 < x_1$, then $P'(x_1) > 0$, $P'(x_2) < 0$, and $P'(x_3) > 0$*

(iv) *If the quartic equation $P(x) = 0$ has only four positive roots $x_4 < x_3 < x_2 < x_1$, then $P'(x_1) > 0$, $P'(x_2) < 0$, $P'(x_3) > 0$, and $P'(x_4) < 0$*

Theorem 7. *Assume that $R_0 > 1$ and (21) holds. Define $\tau_{2,k_0}^{(n)}$ by (45).*

(i) *If equation (36) has only a single positive and simple root z_1, then Q^* is locally asymptotically stable for $\tau_2 \in (0, \tau_{2,1}^{(0)})$ and unstable for $\tau_2 > \tau_{2,1}^{(0)}$. Besides, a Hopf bifurcation happens when $\tau_2 > \tau_{2,1}^{(n)}$, $n \in \mathbb{N}$.*

(ii) *If equation (36) has only two positive and simple roots z_1 and z_2 with $z_2 < z_1$, then there exists a finite number of intervals such that if the delay τ_2 is fixed in these intervals, the equilibrium Q^* is locally asymptotically stable, while unstable if τ_2 does not belong to the ones. In this case, Q^* changes from stability to instability.*

(iii) *If equation (36) has a minimum of three positive and simple roots, then there exists at least one stability change.*

Proof. According to Theorem 5, Q^* is locally asymptotically stable for $\tau_2 = 0$. Then, equation (31) has complex roots with negative real parts for $\tau_2 = 0$. If equation (36) has only one positive and simple root z_1, then $\pm i\omega_1$ is a pair of purely imaginary roots of equation (31) with $\tau_2 = \tau_{2,1}^{(n)}$.

By applying Lemmas 2 and 3, we obtain

$$\text{sign}\left\{\frac{d\text{Re}\xi(\tau_2)}{d\tau_2}\Big|_{\tau_2=\tau_{2,1}^{(n)}}\right\} = \text{sign}\{\Psi'(z_0)\} > 0. \quad (49)$$

Then, all roots of (31) have negative real parts for $\tau_2 \in [0, \tau_{2,1}^{(0)})$ and it has at least one root with positive real part for $\tau_2 > \tau_{2,1}^{(0)}$. Therefore, we obtain (i).

For (ii), we have $z_2 < z_1$. From (44), we find that there exists $l \in \mathbb{N}$ such that $\tau_{2,1}^{(l)} - \tau_{2,1}^{(l-1)} = (2\pi/\omega_1) < (2\pi/\omega_2) = \tau_{2,2}^{(l)} - \tau_{2,2}^{(l-2)}$. From Lemma 2, we obtain that $\Psi'(z_1) > 0$ and $\Psi'(z_2) < 0$. Hence, $d\text{Re}\xi(\tau_2)/d\tau_2|_{\tau_2=\tau_{2,1}^{(n)}} > 0$ and $d\text{Re}\xi(\tau_2)/d\tau_2|_{\tau_2=\tau_{2,2}^{(n)}} < 0$. We deduce that l switches from stability to instability when the parameters $\tau_{2,1}^{(0)} < \tau_{2,2}^{(0)} < \tau_{2,1}^{(1)} < \cdots < \tau_{2,1}^{(l-1)} < \tau_{2,2}^{(l-1)} < \tau_{2,1}^{(l)}$; Q^* is locally asymptotically stable when

$\tau_2 \in [0, \tau_{2,1}^{(0)}] \cup [\tau_{2,2}^{(0)}, \tau_{2,1}^{(1)}] \cup \ldots, \cup [\tau_{2,2}^{(l-1)}, \tau_{2,1}^{(l)}]$ and unstable when $\tau_2 \in [\tau_{2,1}^{(0)}, \tau_{2,2}^{(0)}] \cup [\tau_{2,1}^{(1)}, \tau_{2,2}^{(1)}] \cup \ldots, \cup [\tau_{2,1}^{(l-1)}, \tau_{2,2}^{(l-1)}] \cup [\tau_{2,1}^{(l)}, +\infty]$. This demonstrates (ii) and, additionally, we can undoubtedly obtain the outcome yielding (iii).

5. Application

The purpose of this section is to illustrate our theoretical results to the following model, which is a special case of system (1) by letting $f(U, I, C) = (\beta_1 U / 1 + \alpha_1 C)$ and $g(U, I) = (\beta_2 U / 1 + \alpha_2 I)$:

$$
\begin{cases}
\dot{U} = s - d_1 U(t) - \dfrac{\beta_1 U(t) C(t)}{1 + \alpha_1 C(t)} - \dfrac{\beta_2 U(t) I(t)}{1 + \alpha_2 I(t)}, \\[2ex]
\dot{I} = \dfrac{\beta_1 U(t) C(t)}{1 + \alpha_1 C(t)} + \dfrac{\beta_2 U(t) I(t)}{1 + \alpha_2 I(t)} - d_2 I(t), \\[2ex]
\dot{C} = v I(t - \tau_1) - d_3 C(t) - p A(t) C(t), \\[2ex]
\dot{A} = \sigma + q A(t - \tau_2) C(t - \tau_2) - d_4 A(t),
\end{cases}
\tag{50}
$$

where α_1 and α_2 are positive constants that measure the saturation effect, β_1 is the virus-to-cell infection rate, and β_2 is the cell-to-cell transmission rate. Apparently, the hypotheses (H_0)–(H_3) hold and we have

$$
\left(1 - \frac{f(U, I, C)}{f(U, I^*, C^*)}\right)\left(\frac{f(U, I^*, C^*)}{f(U, I, C)} - \frac{C}{C^*}\right) = \frac{-\alpha_1 (C - C^*)^2}{C^*(1 + \alpha_1 C)(1 + \alpha_1 C^*)} \le 0,
$$
$$
\left(1 - \frac{f(U^*, I^*, C^*) g(U, I)}{f(U, I^*, C^*) g(U^*, I^*)}\right)\left(\frac{f(U, I^*, C^*) g(U^*, I^*)}{f(U^*, I^*, C^*) g(U, I)} - \frac{I}{I^*}\right) = \frac{-\alpha_2 (I - I^*)^2}{I^*(1 + \alpha_2 I)(1 + \alpha_2 I^*)} \le 0.
\tag{51}
$$

Therefore, hypothesis (21) is verified. From Theorems 4 and 5, we have the following result.

Corollary 1

(i) If $R_0 \le 1$, then the infection-free equilibrium Q_f of system (50) is globally asymptotically stable

(ii) If $R_0 > 1$, then the infection-free equilibrium Q_f becomes unstable and the chronic infection equilibrium Q^* of system (50) is globally asymptotically stable for $\tau_2 = 0$

Furthermore, theorem 7 holds true for system (50).

6. Conclusion

In this paper, we have presented a delayed CHIKV infection model with general incidence functions that include various forms existing in the literature. Initially, we have examined the nonnegativity, boundedness of the solutions, and the existence of equilibria. By building appropriate Lyapunov function, utilizing Lyapunov–LaSalle invariance principle and Hopf bifurcation theory, we have demonstrated the following outcomes: (i) when $R_0 \le 1$, the infection-free equilibrium Q_f is globally asymptotically stable for any time delays $\tau_1 \ge 0$ and $\tau_2 \ge 0$, which naturally implies that the virus is cleared and the infection vanishes; (ii) when $R_0 > 1$ and (H_4) holds, the chronic infection equilibrium Q^* is globally asymptotically stable for anytime delay $\tau_1 \ge 0$ and $\tau_2 = 0$, meaning that the infection perseveres in the host; (iii) when $\tau_2 > 0$ and $\tau_1 = 0$, we obtain the sufficient conditions on the existence of Hopf bifurcation at Q^*.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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