



Research article

Stability of delayed HCV model with two target cells and Beddington-DeAngelis infection function and saturated CTL immune response

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Abstract: In this paper, we present a mathematical model that describes the dynamics of a hepatitis C virus infection. The model takes two classes of target cells (hepatocytes and extrahepatic cells) into account as well as a saturated Cytotoxic T lymphocytes (CTLs) immune response in the liver. We found that the system solutions are positive and bounded, and the equilibrium points are computed. Through a careful examination of the model, we demonstrated that it exhibits global threshold dynamics that are fully captured by the threshold parameters. Numerical simulations were carried out to demonstrate the stability results.

Keywords: hepatitis C virus; global stability; Beddington-DeAngelis infection rate; time delay; CTL immune response

1. Introduction

Hepatitis C is a contagious liver disease caused by the hepatitis C virus (HCV) and is most often transmitted through direct contact with the blood of an infected individual [1]. About 58 million people worldwide are chronically infected with the HCV with about 1.5 million new infections occurring per year, and more than 290,000 people died in 2019 from hepatitis C-related liver diseases [2]. After exposure to HCV, the host mounts a strong immune response. Cytotoxic T lymphocytes (CTLs) play a key role by directly killing infected cells. Once a cell becomes infected, it serves as a site for the production of new virus particles. Viral proteins within the infected cell are processed and displayed on the cell surface in association with major histocompatibility complex class I (MHC I) molecules, which are expressed on nearly all human cells. When a CTL with a matching T cell receptor recognizes these viral antigens on the infected cell, it binds to the cell and becomes activated. Activated CD8 T cells

then release cytotoxic substances that lead to the destruction of the target cell. Following activation, CTLs proliferate and differentiate into effector and memory cells, similar to the process observed in B-cell activation. Effector cells eliminate infected cells, while memory cells persist in the host to provide protection against future infections.

Mathematical models that are utilized to examine the dynamics of viral infection transmission have attracted significant attention. These mathematical models consist of a system of ordinary differential equations, some of these models have been presented to elucidate the interactions between HCV and immune system cells in humans. Early models of HCV epidemics were proposed [3–6]. Qesmi et al. [7] considered the infection in liver and blood cell populations and included inter-compartmental interactions mediated by viral particles circulating between the liver and blood. The model was further extended to account for the age of infection in [8]. However references [7, 8] did not take into account immune response. Hu [9] and Njagarah [10] extended the model in [7] to include a CTL immune response. Thus mathematical models of viral infections have increasingly incorporated heterogeneous cellular populations and immune-mediated mechanisms to provide a more realistic description of viral dynamics. For example, Li et al. [11] developed a multi-compartment HIV-1 model involving five different cell populations and three interconnected compartments, including peripheral blood, lymph nodes, and the central nervous system, thereby emphasizing the importance of distinguishing cellular and anatomical compartments in viral infection models. Moreover, Chen et al. [12] incorporated latent infection, apoptosis, macrophage dynamics, CD4⁺ T-cell-mediated immunity, and specific immune responses into a viral dynamical model, demonstrating that interactions between infected cells and immune components can substantially influence the resulting dynamical behavior. These studies highlight the importance of considering cellular heterogeneity, tissue compartments, and immune responses when developing mathematical models of viral infections. Meng et al. [13] developed an HIV infection model incorporating cell-to-cell transmission, two immune responses, and induced apoptosis. Moreover, Yang et al. [14] proposed a delayed HIV reaction-diffusion model that incorporates viral maturation delay and immune impairment. In particular, the researchers considered immune-unactivated and immune-activated reproduction numbers and investigated the global threshold dynamics using Lyapunov functionals and LaSalle's invariance principle. Motivated by these approaches, we focus on HCV infection in hepatic and extrahepatic tissues and incorporate a Beddington–DeAngelis incidence function, a saturated immune response, and a time delay to describe key features of HCV infection dynamics. Yang et al. [15] extended the model of [9] to include the saturation incidence rate for CTL immune response and distributed delay; their model is presented as follows:

$$\begin{aligned}\dot{x}_1(t) &= \lambda_1 - d_1 x_1 - \frac{\beta_1 x_1 v}{x_1 + v}, \\ \dot{y}_1(t) &= \int_0^{\tau_1} f_1(\sigma_1) e^{-\mu_1 \sigma_1} \frac{\beta_1 x_1(t - \sigma_1) v(t - \sigma_1)}{x_1(t - \sigma_1) + v(t - \sigma_1)} d\sigma_1 - a_1 y_1 - p y_1 z, \\ \dot{x}_2(t) &= \lambda_2 - d_2 x_2 - \frac{\beta_2 x_2 v}{x_2 + v}, \\ \dot{y}_2(t) &= \int_0^{\tau_2} f_2(\sigma_2) e^{-\mu_2 \sigma_2} \frac{\beta_2 x_2(t - \sigma_2) v(t - \sigma_2)}{x_2(t - \sigma_2) + v(t - \sigma_2)} d\sigma_2 - a_2 y_2,\end{aligned}$$

$$\begin{aligned}\dot{v}(t) &= k_1 e^{-\mu_3 \tau_3} y_1(t - \tau_3) + k_2 e^{-\mu_4 \tau_4} y_2(t - \tau_4) - \gamma v, \\ \dot{z}(t) &= q y_1 z - r z,\end{aligned}$$

where x_1 and x_2 denote the populations of healthy hepatocytes and healthy extrahepatic cells, respectively, y_1 and y_2 represent the corresponding infected cell populations. The variable v denotes the concentration of free virus particles, and z represents the cytotoxic T lymphocyte (CTL) immune response in the liver. Healthy hepatocytes and extrahepatic cells are produced at rates $\Lambda_i (i = 1, 2)$, die naturally at rates $d_i x_i (i = 1, 2)$, and become infected at rates $\frac{\beta_i x_i v}{x_i + v} (i = 1, 2)$. Infected cells die at rates $a_i y_i (i = 1, 2)$, while free virus particles are cleared at rate γv . The term $p y_1 z$ describes the clearance of infected hepatocytes mediated by the CTL immune response. All model parameters are assumed to be positive constants. Li et al. [16] presented a five-dimensional viral model incorporating distributed delay, a general nonlinear infection rate, state-dependent clearance rates, and CTL and humoral immune responses, along with five reproduction numbers and a global analysis using Lyapunov functions. We acknowledge that the model of Li et al. is more general in several respects, particularly through its incorporation of CTL and humoral immune responses, general nonlinear incidence and state-dependent removal functions. The proposed model is developed for HCV infection and introduces a biologically distinct two-target-cell structure. In particular, our model explicitly distinguishes healthy hepatocytes x_1 and healthy extrahepatic cells x_2 , together with their corresponding infected populations y_1 and y_2 . This structure enables us to describe potentially different infection and viral-production dynamics in hepatic and extrahepatic cellular compartments, which cannot be represented by a single target-cell population. Furthermore, our model employs a Beddington-DeAngelis incidence function for each target-cell population and distinguishes distributed delays associated with infection processes and discrete delays associated with virus production. Thus, the proposed formulation provides a biologically differentiated delay structure tailored to the HCV dynamic.

During this manuscript, we present a model of HCV infection, which is a modification of the model presented by Yang et al. [15], where we replace saturated incidence with a Beddington-DeAngelis incidence in infection transmission terms. Additionally, we extend Yang's model to include saturation of the CTL immune response. The model consists of a system of ordinary differential equations. For this model, the solutions nonnegativity and boundedness have been proved, and we derive the basic reproduction numbers and the prospective equilibrium points along with their existence conditions. We examine the global stability of the equilibria by using appropriate Lyapunov functions and applying the LaSalle invariance principle. Finally, numerical simulations are carried out to investigate key parameters and the impact of time delays on system dynamics and to corroborate the theoretical analysis.

2. Model formulation

A mathematical framework is presented and analyzed in this section to describe the dynamics of HCV with two co-circulating populations of target cells, distributed time delays, and Beddington-DeAngelis incidence function. The model is given by

$$\dot{x}_1(t) = \Lambda_1 - d_1 x_1 - \frac{\beta_1 x_1 v}{1 + \alpha_1 x_1 + \zeta_1 v}, \quad (2.1)$$

$$\dot{y}_1(t) = \int_0^{\tau_1} f_1(\sigma_1) e^{-\mu_1 \sigma_1} \frac{\beta_1 x_1(t - \sigma_1) v(t - \sigma_1)}{1 + \alpha_1 x_1(t - \sigma_1) + \zeta_1 v(t - \sigma_1)} d\sigma_1 - a_1 y_1 - p y_1 z, \quad (2.2)$$

$$\dot{x}_2(t) = \Lambda_2 - d_2 x_2 - \frac{\beta_2 x_2 v}{1 + \alpha_2 x_2 + \zeta_2 v}, \quad (2.3)$$

$$\dot{y}_2(t) = \int_0^{\tau_2} f_2(\sigma_2) e^{-\mu_2 \sigma_2} \frac{\beta_2 x_2(t - \sigma_2) v(t - \sigma_2)}{1 + \alpha_2 x_2(t - \sigma_2) + \zeta_2 v(t - \sigma_2)} d\sigma_2 - a_2 y_2, \quad (2.4)$$

$$\dot{v}(t) = k_1 e^{-\mu_3 \tau_3} y_1(t - \tau_3) + k_2 e^{-\mu_4 \tau_4} y_2(t - \tau_4) - \gamma v, \quad (2.5)$$

$$\dot{z}(t) = \frac{q y_1 z}{h + z} - r z. \quad (2.6)$$

All variables and parameters have the same meaning as those in the model proposed by Yang et al. [15]. Here, h determines the strength of saturation, while $1/h$ represents the CTL level at which the immune response reaches half of its maximum value p/h . Thus, h characterizes the saturation level of CTL-mediated immune activity. Additionally, uninfected target cells in the two compartments become infected through the Beddington–DeAngelis incidence rate $\frac{\beta_i x_i v}{1 + \alpha_i x_i + \zeta_i v}$, where $i = 1, 2$. The infection process is assumed to involve a distributed intracellular delay. Specifically, an uninfected target cell is exposed to the virus at time $t - \tau_i$ ($i = 1, 2$) and enters the infected-cell compartment at time t , where τ_i is a random variable with probability density function $f_i(\tau_i)$ over the time interval $[0, \tau_i]$, and $i = 1, 2$ is the limit superior over the delay period, where $f_i(\tau_i) \geq 0$ and $\int_0^{\tau_i} f_i(\sigma_i) d\sigma_i = 1$. $e^{-\mu_i \tau_i}$ represents the probability that a cell survives before transitioning to the infected state, where μ_i ($i = 1, 2$) are constants.

Following infection, infected hepatocytes and extrahepatic cells produce a free virus with delays τ_3 and τ_4 , respectively. $e^{-\mu_3 \tau_3}$ and $e^{-\mu_4 \tau_4}$ represent the probabilities that infected cells survive during these viral-production delays, where $(\mu_3, \mu_4 > 0)$ are the corresponding loss rates. Thus, the delayed viral-production terms account for the loss of infected cells during the periods between infection and the release of newly produced virions so $e^{-\mu_j \tau_j}$, where $\mu_j > 0$, $j = 3, 4$ represent the loss of the infected cells during the delay period.

2.1. Preliminaries

To ensure the boundedness of the system solutions, we suppose that $\Upsilon = \max\{\tau_1, \tau_2, \tau_3, \tau_4\}$, where C is the Banach space of continuous functions mapping the interval $[-\Upsilon, 0]$ into $\mathbb{R}_{\geq 0}^6$. Then the system in Eqs (2.1)–(2.6) has the initial conditions:

$$\begin{aligned} x_1(\theta) &= \phi_1(\theta), \quad y_1(\theta) = \phi_2(\theta), \quad x_2(\theta) = \phi_3(\theta), \\ y_2(\theta) &= \phi_4(\theta), \quad v(\theta) = \phi_5(\theta), \quad z(\theta) = \phi_6(\theta), \\ \phi_n(\theta) &\geq 0, n = 1, \dots, 6, \quad \theta \in [-\Upsilon, 0], \end{aligned} \quad (2.7)$$

where $(\phi_1(\theta), \dots, \phi_6(\theta)) \in C([-\Upsilon, 0], \mathbb{R}_{\geq 0}^6)$. Thus, there exists a unique solution for system in Eqs (2.1)–(2.6) with initial conditions in Eq (2.7) (see [17]).

Lemma 1. *Solutions of system in Eqs (2.1)–(2.6) satisfying the initial conditions in Eq (2.7) are non-negative and ultimately bounded for $t \geq 0$.*

Proof. The existence and uniqueness of solutions follow from standard results for functional differential equations. Since all state variables represent biologically meaningful quantities, we first establish the invariance of the non-negative region.

Suppose, by contradiction, that $x_i(t)$, $i = 1, 2$, loses non-negativity on the interval of existence. Then there exists $t_i^* > 0$, such that $x_i(t_i^*) = 0$. From Eqs (2.1) and (2.3), we have

$$\dot{x}_i(t_i^*) = \Lambda_i > 0, \quad i = 1, 2,$$

which contradicts the possibility of crossing the boundary of the non-negative region. Hence,

$$x_i(t) \geq 0, \quad i = 1, 2.$$

Furthermore, from Eqs (2.2), (2.4), and (2.5), the variation-of-constants formulas give

$$y_1(t) = \phi_2(0)e^{-\left(a_1 t + p \int_0^t z(s) ds\right)} + \beta_1 \int_0^t e^{-\left(a_1(t-\theta) + p \int_0^{t-\theta} z(s) ds\right)} d\theta,$$

$$\int_0^{\tau_1} f_1(\sigma_1) \frac{e^{-\mu_1 \sigma_1} x_1(\theta - \sigma_1) v(\theta - \sigma_1)}{1 + \alpha_1 x_1(\theta - \sigma_1) + \zeta_1 v(\theta - \sigma_1)} d\sigma_1 d\theta \geq 0,$$

and similarly,

$$y_2(t) \geq 0, \quad v(t) \geq 0.$$

Moreover, Eq (2.6) implies

$$z(t) \geq z(0)e^{-rt} \geq 0.$$

Therefore, the non-negative region is invariant [18, 19]. It remains to prove the ultimate boundedness. To prove the boundedness of the solutions, Eq (2.1) implies that $\sup_{t \rightarrow \infty} x_i(t) \leq \frac{\Lambda_i}{d_i}$, $i = 1, 2$ and let us define

$$\varkappa(t) = \int_0^{\tau_1} f_1(\sigma_1) e^{-\mu_1 \sigma_1} x_1(t - \sigma_1) d\sigma_1 + y_1(t) + \int_0^{\tau_2} f_2(\sigma_2) e^{-\mu_2 \sigma_2} x_2(t - \sigma_2) d\sigma_2 + y_2(t) + \frac{ph}{q} z(t).$$

Then

$$\dot{\varkappa}(t) = \int_0^{\tau_1} f_1(\sigma_1) e^{-\mu_1 \sigma_1} [\Lambda_1 - d_1 x_1(t - \sigma_1)] d\sigma_1 - a_1 y_1(t) - p y_1(t) z$$

$$+ \int_0^{\tau_2} f_2(\sigma_2) e^{-\mu_2 \sigma_2} [\Lambda_2 - d_2 x_2(t - \sigma_2)] d\sigma_2 - a_2 y_2(t) + \frac{ph}{q} \left[\frac{q y_1(t) z}{h + z} - r z(t) \right]$$

$$\begin{aligned}
&= \Lambda_1 F_1 - d_1 \int_0^{\tau_1} f_1(\sigma_1) e^{-\mu_1 \sigma_1} x_1(t - \sigma_1) d\sigma_1 - a_1 y_1(t) + \Lambda_2 F_2 - d_2 \int_0^{\tau_2} f_2(\sigma_2) e^{-\mu_2 \sigma_2} x_2(t - \sigma_2) d\sigma_2 \\
&\quad - a_2 y_2(t) - \frac{p y_1(t) z^2}{h + z} - \frac{p h}{q} r z(t) \\
&\leq \Lambda_1 F_1 + \Lambda_2 F_2 - \left[d_1 \int_0^{\tau_1} f_1(\sigma_1) e^{-\mu_1 \sigma_1} x_1(t - \sigma_1) d\sigma_1 + a_1 y_1(t) + d_2 \int_0^{\tau_2} f_2(\sigma_2) e^{-\mu_2 \sigma_2} x_2(t - \sigma_2) d\sigma_2 \right. \\
&\quad \left. + a_2 y_2(t) + \frac{p h}{q} r z(t) \right] \\
&\leq \Lambda_1 F_1 + \Lambda_2 F_2 - \delta \kappa(t),
\end{aligned}$$

where $F_1 = \int_0^{\tau_1} f_1(\sigma_1) e^{-\mu_1 \sigma_1} d\sigma_1$, $F_2 = \int_0^{\tau_2} f_2(\sigma_2) e^{-\mu_2 \sigma_2} d\sigma_2$ and $\delta = \min\{d_1, a_1, d_2, a_2, r\}$. Hence, $\limsup_{t \rightarrow \infty} \kappa(t) \leq M_1$, $\limsup_{t \rightarrow \infty} y_i(t) \leq M_1$, and $\limsup_{t \rightarrow \infty} z(t) \leq M_2$, for all $t \geq 0$, where $i = 1, 2$, and $M_1 = \frac{\Lambda_1 F_1 + \Lambda_2 F_2}{\delta}$ and $M_2 = \frac{q}{ph} M_1$. From the fourth equation, we have

$$\begin{aligned}
\dot{v}(t) &= k_1 e^{-\mu_3 \tau_3} y_1(t - \tau_3) + k_2 e^{-\mu_4 \tau_4} y_2(t - \tau_4) - \gamma v(t) \\
&\leq (k_1 e^{-\mu_3 \tau_3} + k_2 e^{-\mu_4 \tau_4}) M_1 - \gamma v(t),
\end{aligned}$$

which yields $\limsup_{t \rightarrow \infty} v(t) \leq M_3$, where $M_3 = \frac{(k_1 + k_2) M_1}{\gamma}$.

3. Biological threshold and equilibria

In this section, we compute all possible equilibria of system in Eqs (2.1)–(2.6) and the threshold parameters that guarantee the existence of these equilibria.

3.1. The basic reproduction number $\mathcal{R}_0$

The basic reproduction number $\mathcal{R}_0$ represents the expected number of newly infected target cells generated by a typical infectious source during its infectious period when the infection is introduced into an otherwise infection-free environment. Biologically, it measures the invasion potential of HCV in the absence of an established infection. The basic reproduction number $\mathcal{R}_0$ of the system's in Eqs (2.1)–(2.6) can be calculated using the next-generation matrix method [20]. Let us define the Jacobian matrix $\mathcal{F}$ of infection rates by the following

$$\mathcal{F} = \begin{bmatrix} 0 & 0 & \frac{\beta_1 F_1 x_1^0}{1 + \alpha_1 x_1^0} \\ 0 & 0 & \frac{\beta_2 F_2 x_2^0}{1 + \alpha_2 x_2^0} \\ 0 & 0 & 0 \end{bmatrix},$$

where $x_i^0 = \frac{\Lambda_i}{d_i}$, $i = 1, 2$. The recovery rates of Jacobian matrix ∇ is given by:

$$\nabla = \begin{bmatrix} a_1 & 0 & 0 \\ 0 & a_2 & 0 \\ -k_1 e^{-\mu_3 \tau_3} & -k_2 e^{-\mu_4 \tau_4} & \gamma \end{bmatrix}.$$

The basic reproduction number is given by

$$\mathcal{R}_0 = \rho(\mathcal{F}\nabla^{-1}),$$

where

$$\nabla^{-1} = \begin{bmatrix} \frac{1}{a_1} & 0 & 0 \\ 0 & \frac{1}{a_2} & 0 \\ \frac{k_1 e^{-\mu_3 \tau_3}}{a_1 \gamma} & \frac{k_2 e^{-\mu_4 \tau_4}}{a_2 \gamma} & \frac{1}{\gamma} \end{bmatrix},$$

then

$$\mathcal{F}\nabla^{-1} = \begin{bmatrix} \frac{\beta_1 F_1 k_1 x_1^0 e^{-\mu_3 \tau_3}}{a_1 \gamma (1 + \alpha_1 x_1^0)} & \frac{\beta_1 F_1 k_2 x_1^0 e^{-\mu_4 \tau_4}}{a_2 \gamma (1 + \alpha_1 x_1^0)} & \frac{\beta_1 F_1 x_1^0}{\gamma (1 + \alpha_1 x_1^0)} \\ \frac{\beta_2 F_2 k_1 x_2^0 e^{-\mu_3 \tau_3}}{a_1 \gamma (1 + \alpha_2 x_2^0)} & \frac{\beta_2 F_2 k_2 x_2^0 e^{-\mu_4 \tau_4}}{a_2 \gamma (1 + \alpha_2 x_2^0)} & \frac{\beta_2 F_2 x_2^0}{\gamma (1 + \alpha_2 x_2^0)} \\ 0 & 0 & 0 \end{bmatrix},$$

and $\rho(\mathcal{F}\nabla^{-1})$ denote the spectral radius of a matrix $\mathcal{F}\nabla^{-1}$. Thus, the basic reproduction number for the system in Eqs (2.1)–(2.6) is given by

$$\mathcal{R}_0 = \frac{\beta_1 F_1 k_1 x_1^0 e^{-\mu_3 \tau_3}}{a_1 \gamma (1 + \alpha_1 x_1^0)} + \frac{\beta_2 F_2 k_2 x_2^0 e^{-\mu_4 \tau_4}}{a_2 \gamma (1 + \alpha_2 x_2^0)} = \mathcal{R}_0^1 + \mathcal{R}_0^2.$$

Where $\mathcal{R}_0$ incorporates the contributions from both infection pathways. Specifically, $\mathcal{R}_0^1$ represents the contribution of the hepatic infection pathway associated with the first target-cell population, whereas $\mathcal{R}_0^2$ represents the contribution of the extrahepatic infection pathway associated with the second target-cell population. Thus, $\mathcal{R}_0$ reflects the combined infection-generating potential of HCV through the hepatic and extrahepatic compartments. Moreover, if $\mathcal{R}_0 < 1$, each infectious source produces, on average, fewer than one new infection, and the infection cannot invade the infection-free population. Conversely, if $\mathcal{R}_0 > 1$, the infection can successfully invade and persist.

3.2. Equilibria

Let $(x_1, y_1, x_2, y_2, v, z)$ be any equilibrium satisfying

$$0 = \Lambda_1 - d_1 x_1 - \frac{\beta_1 x_1 v}{1 + \alpha_1 x_1 + \zeta_1 v}, \quad (3.1)$$

$$0 = \frac{\beta_1 F_1 x_1 v}{1 + \alpha_1 x_1 + \zeta_1 v} - a_1 y_1 - p y_1 z, \quad (3.2)$$

$$0 = \Lambda_2 - d_2 x_2 - \frac{\beta_2 x_2 v}{1 + \alpha_2 x_2 + \zeta_2 v}, \quad (3.3)$$

$$0 = \frac{\beta_2 F_2 x_2 v}{1 + \alpha_2 x_2 + \zeta_2 v} - a_2 y_2, \quad (3.4)$$

$$0 = k_1 e^{-\mu_3 \tau_3} y_1 + k_2 e^{-\mu_4 \tau_4} y_2 - \gamma v, \quad (3.5)$$

$$0 = \frac{q y_1 z}{h + z} - r z. \quad (3.6)$$

From Eq (3.6), the system has two possibilities $z = 0$, or $q y_1 = r(h + z)$. If $z = 0$ then the system has two positive equilibria as follows: (i) An infection-free equilibrium $\Pi_0 = (x_1^0, 0, x_2^0, 0, 0, 0)$.

(ii) Endemic equilibrium without immunity $\Pi^* = (x_1^*, y_1^*, x_2^*, y_2^*, v^*, 0)$ with the following values of each component:

$$\begin{aligned} x_i^* &= \frac{-B_i + \sqrt{B_i^2 + 4A_i C_i}}{2A_i}, \quad A_i = d_i \alpha_i, \quad i = 1, 2, \\ B_i &= d_i(1 + \zeta_i v^*) + \beta_i v^* - \alpha_i \Lambda_i, \quad C_i = -\Lambda_i(1 + \zeta_i v^*), \\ y_i^* &= \frac{F_i}{a_i} \frac{\beta_i x_i^* v^*}{(1 + \alpha_i x_i^* + \zeta_i v^*)}. \end{aligned} \quad (3.7)$$

Substituting Eqs (3.2) and (3.4) into Eq (3.5), we can determine v^* from the equation

$$\frac{k_1 e^{-\mu_3 \tau_3}}{a_1} \frac{\beta_1 F_1 x_1^*}{1 + \alpha_1 x_1^* + \zeta_1 v^*} + \frac{k_2 e^{-\mu_4 \tau_4}}{a_2} \frac{\beta_2 F_2 x_2^*}{1 + \alpha_2 x_2^* + \zeta_2 v^*} = \gamma.$$

The last equation is a function of v ; by solving it and substituting into Eq (3.7), the other variables of Π^* can be determined.

The other probability is $qy_1 = r(h + z)$, and we get a third equilibrium point $\tilde{\Pi} = (\tilde{x}_1, \tilde{y}_1, \tilde{x}_2, \tilde{y}_2, \tilde{v}, \tilde{z})$, where

$$\tilde{z} = h \left(\frac{q\tilde{y}_1}{hr} - 1 \right) = h(\mathcal{R}_c - 1),$$

where $\mathcal{R}_c = \frac{q\tilde{y}_1}{hr}$ is the threshold parameter with immunity, where $\tilde{y}_1$ is the number of infected hepatocyte cells at the third equilibrium point $\tilde{\Pi}$, and $\tilde{\Pi}$ exists only if $\mathcal{R}_c > 1$.

$$\begin{aligned} \tilde{x}_1 &= x_1^0 - \frac{rF_1(h + \tilde{z})(a_1 + p\tilde{z})}{qd_1}, \\ \tilde{x}_2 &= x_2^0 - \frac{a_2 r F_2(h + \tilde{z})}{qd_2}. \end{aligned}$$

3.3. Global properties

In what follows, we examine the global stability properties of the equilibria associated with the system in Eqs (2.1)–(2.6). Define a function $H : (0, \infty) \rightarrow [0, \infty)$ as $H(\ell) = \ell - 1 - \ln \ell$.

Theorem 1. *For the system in Eqs (2.1)–(2.6), if $\mathcal{R}_0 \leq 1$, then Π_0 is globally asymptotically stable (G.A.S).*

Proof. Let $\mathcal{R}_0 \leq 1$ and constructing a function $L_0(x_1, y_1, x_2, y_2, v, z)$ as:

$$\begin{aligned} L_0 &= \frac{F_1 x_1^0}{1 + \alpha_1 x_1^0} H\left(\frac{x_1}{x_1^0}\right) + y_1 + \frac{a_1 k_2 e^{-\mu_4 \tau_4}}{a_2 k_1 e^{-\mu_3 \tau_3}} \left[\frac{F_2 x_2^0}{1 + \alpha_2 x_2^0} H\left(\frac{x_2}{x_2^0}\right) + y_2 \right] + \frac{a_1}{k_1 e^{-\mu_3 \tau_3}} v + \frac{ph}{q} z \\ &+ \int_0^{\tau_1} f_1(\sigma_1) e^{-\mu_1 \sigma_1} \int_0^{\sigma_1} \frac{\beta_1 x_1(t - \theta) v(t - \theta)}{1 + \alpha_1 x_1(t - \theta) + \zeta_1 v(t - \theta)} d\theta d\sigma_1 + a_1 \int_0^{\tau_3} y_1(t - \theta) d\theta \end{aligned}$$

$$+ \frac{a_1 k_2 e^{-\mu_4 \tau_4}}{a_2 k_1 e^{-\mu_3 \tau_3}} \left[\int_0^{\tau_2} f_2(\sigma_2) e^{-\mu_2 \sigma_2} \int_0^{\sigma_2} \frac{\beta_2 x_2(t-\theta) v(t-\theta)}{1 + \alpha_2 x_2(t-\theta) + \zeta_2 v(t-\theta)} d\theta d\sigma_2 + a_2 \int_0^{\tau_4} y_2(t-\theta) d\theta \right].$$

Thus, $L_0(x_1, y_1, x_2, y_2, v, z) > 0$ for all $x_1, y_1, x_2, y_2, v, z \neq \Pi_0$, and $L_0(x_1^0, 0, x_2^0, 0, 0, 0) = 0$. Calculating $\frac{dL_0}{dt}$ along system in Eqs (2.1)–(2.6), we obtain

$$\begin{aligned} \frac{dL_0}{dt} = & \frac{F_1}{1 + \alpha_1 x_1^0} \left(1 - \frac{x_1^0}{x_1} \right) \dot{x}_1 + \dot{y}_1 + \frac{a_1 k_2 e^{-\mu_4 \tau_4}}{a_2 k_1 e^{-\mu_3 \tau_3}} \left[\frac{F_2}{1 + \alpha_2 x_2^0} \dot{x}_2 + \dot{y}_2 \right] + \frac{a_1}{k_1 e^{-\mu_3 \tau_3}} \dot{v} + \frac{ph}{q} \dot{z} \\ & + \int_0^{\tau_1} f_1(\sigma_1) e^{-\mu_1 \sigma_1} \left[\frac{\beta_1 x_1 v}{1 + \alpha_1 x_1 + \zeta_1 v} - \frac{\beta_1 x_1(t-\sigma_1) v(t-\sigma_1)}{1 + \alpha_1 x_1(t-\sigma_1) + \zeta_1 v(t-\sigma_1)} \right] d\sigma_1 \\ & + \frac{a_1 k_2 e^{-\mu_4 \tau_4}}{a_2 k_1 e^{-\mu_3 \tau_3}} \int_0^{\tau_2} f_2(\sigma_2) e^{-\mu_2 \sigma_2} \left[\frac{\beta_2 x_2 v}{1 + \alpha_2 x_1 + \zeta_2 v} - \frac{\beta_2 x_2(t-\sigma_2) v(t-\sigma_2)}{1 + \alpha_2 x_2(t-\sigma_2) + \zeta_2 v(t-\sigma_2)} \right] d\sigma_2 \\ & + a_1 [y_1 - y_1(t-\tau_3)] + \frac{a_1 k_2 e^{-\mu_4 \tau_4}}{k_1 e^{-\mu_3 \tau_3}} [y_2 - y_2(t-\tau_4)], \end{aligned}$$

$$\begin{aligned} \frac{dL_0}{dt} = & \frac{F_1}{1 + \alpha_1 x_1^0} \left(1 - \frac{x_1^0}{x_1} \right) \left(\Lambda_1 - d_1 x_1 - \frac{\beta_1 x_1 v}{1 + \alpha_1 x_1 + \zeta_1 v} \right) \\ & + \int_0^{\tau_1} f_1(\sigma_1) e^{-\mu_1 \sigma_1} \frac{\beta_1 x_1(t-\sigma_1) v(t-\sigma_1)}{1 + \alpha_1 x_1(t-\sigma_1) + \zeta_1 v(t-\sigma_1)} d\sigma_1 - a_1 y_1 - p y_1 z \\ & + \frac{a_1 k_2 e^{-\mu_4 \tau_4}}{a_2 k_1 e^{-\mu_3 \tau_3}} \frac{F_2}{1 + \alpha_2 x_2^0} \left(1 - \frac{x_2^0}{x_2} \right) \left(\Lambda_2 - d_2 x_2 - \frac{\beta_2 x_2 v}{1 + \alpha_2 x_2 + \zeta_2 v} \right) \\ & + \frac{a_1 k_2 e^{-\mu_4 \tau_4}}{a_2 k_1 e^{-\mu_3 \tau_3}} \left[\int_0^{\tau_2} f_2(\sigma_2) e^{-\mu_2 \sigma_2} \frac{\beta_2 x_2(t-\sigma_2) v(t-\sigma_2)}{1 + \alpha_2 x_2(t-\sigma_2) + \zeta_2 v(t-\sigma_2)} d\sigma_2 - a_2 y_2 \right] \\ & + \frac{a_1}{k_1 e^{-\mu_3 \tau_3}} (k_1 e^{-\mu_3 \tau_3} y_1(t-\tau_3) + k_2 e^{-\mu_4 \tau_4} y_2(t-\tau_4) - \gamma v) + \frac{ph}{q} \left(\frac{q y_1 z}{h + z} - r z \right) \\ & + \int_0^{\tau_1} f_1(\sigma_1) e^{-\mu_1 \sigma_1} \left[\frac{\beta_1 x_1 v}{1 + \alpha_1 x_1 + \zeta_1 v} - \frac{\beta_1 x_1(t-\sigma_1) v(t-\sigma_1)}{1 + \alpha_1 x_1(t-\sigma_1) + \zeta_1 v(t-\sigma_1)} \right] d\sigma_1 \\ & + \frac{a_1 k_2 e^{-\mu_4 \tau_4}}{a_2 k_1 e^{-\mu_3 \tau_3}} \int_0^{\tau_2} f_2(\sigma_2) e^{-\mu_2 \sigma_2} \left[\frac{\beta_2 x_2 v}{1 + \alpha_2 x_1 + \zeta_2 v} - \frac{\beta_2 x_2(t-\sigma_2) v(t-\sigma_2)}{1 + \alpha_2 x_2(t-\sigma_2) + \zeta_2 v(t-\sigma_2)} \right] d\sigma_2 \\ & + a_1 [y_1 - y_1(t-\tau_3)] + \frac{a_1 k_2 e^{-\mu_4 \tau_4}}{k_1 e^{-\mu_3 \tau_3}} [y_2 - y_2(t-\tau_4)]. \end{aligned} \tag{3.8}$$

Eliminating the terms of Eq (3.8) together and using the conditions $\Lambda_i = d_i x_i^0 (i = 1, 2)$, we obtain

$$\begin{aligned} \frac{dL_0}{dt} = & \frac{-F_1 d_1 (x_1 - x_1^0)^2}{x_1 (1 + \alpha_1 x_1^0)} - \frac{F_1}{1 + \alpha_1 x_1^0} \left(1 - \frac{x_1^0}{x_1}\right) \frac{\beta_1 x_1 v}{1 + \alpha_1 x_1 + \zeta_1 v} + \frac{F_1 \beta_1 x_1 v}{1 + \alpha_1 x_1 + \zeta_1 v} \\ & + \frac{a_1 k_2 e^{-\mu_4 \tau_4}}{a_2 k_1 e^{-\mu_3 \tau_3}} \left[\frac{-F_2 d_2 (x_2 - x_2^0)^2}{x_2 (1 + \alpha_2 x_2^0)} - \frac{F_2}{1 + \alpha_2 x_2^0} \left(1 - \frac{x_2^0}{x_2}\right) \frac{\beta_2 x_2 v}{1 + \alpha_2 x_2 + \zeta_2 v} + \frac{F_2 \beta_2 x_2 v}{1 + \alpha_2 x_2 + \zeta_2 v} \right] \\ & - \frac{a_1 \gamma v}{k_1 e^{-\mu_3 \tau_3}} - p y_1 z + \frac{p h}{q} \left(\frac{q y_1 z}{h + z} - r z \right). \end{aligned}$$

Then

$$\begin{aligned} \frac{dL_0}{dt} = & \frac{-F_1 d_1 (x_1 - x_1^0)^2}{x_1 (1 + \alpha_1 x_1^0)} - \frac{a_1 k_2 e^{-\mu_4 \tau_4}}{a_2 k_1 e^{-\mu_3 \tau_3}} \frac{F_2 d_2 (x_2 - x_2^0)^2}{x_2 (1 + \alpha_2 x_2^0)} + \frac{F_1 \beta_1 x_1^0 v (1 + \alpha_1 x_1)}{(1 + \alpha_1 x_1^0)(1 + \alpha_1 x_1 + \zeta_1 v)} \\ & + \frac{a_1 k_2 e^{-\mu_4 \tau_4}}{a_2 k_1 e^{-\mu_3 \tau_3}} \frac{F_2 \beta_2 x_2^0 v (1 + \alpha_2 x_2)}{(1 + \alpha_2 x_2^0)(1 + \alpha_2 x_2 + \zeta_2 v)} - \frac{a_1 \gamma v}{k_1 e^{-\mu_3 \tau_3}} - \frac{p y_1 z^2}{h + z} - \frac{p h r}{q} z, \\ \frac{dL_0}{dt} = & \frac{-F_1 d_1 (x_1 - x_1^0)^2}{x_1 (1 + \alpha_1 x_1^0)} - \frac{a_1 k_2 e^{-\mu_4 \tau_4}}{a_2 k_1 e^{-\mu_3 \tau_3}} \frac{F_2 d_2 (x_2 - x_2^0)^2}{x_2 (1 + \alpha_2 x_2^0)} + \frac{a_1 \gamma v (1 + \alpha_1 x_1)(1 + \alpha_2 x_2)(\mathcal{R}_0 - 1)}{k_1 e^{-\mu_3 \tau_3} (1 + \alpha_1 x_1 + \zeta_1 v)(1 + \alpha_2 x_2 + \zeta_2 v)} \\ & + \frac{a_1 \gamma \zeta_2 v^2 (1 + \alpha_1 x_1)(\mathcal{R}_0^1 - 1)}{k_1 e^{-\mu_3 \tau_3} (1 + \alpha_1 x_1 + \zeta_1 v)(1 + \alpha_2 x_2 + \zeta_2 v)} + \frac{a_1 \gamma \zeta_1 v^2 (1 + \alpha_2 x_2)(\mathcal{R}_0^2 - 1)}{k_1 e^{-\mu_3 \tau_3} (1 + \alpha_1 x_1 + \zeta_1 v)(1 + \alpha_2 x_2 + \zeta_2 v)} \\ & - \frac{a_1 \zeta_1 \zeta_2 \gamma v^3}{k_1 e^{-\mu_3 \tau_3} (1 + \alpha_1 x_1 + \zeta_1 v)(1 + \alpha_2 x_2 + \zeta_2 v)} - \frac{p y_1 z^2}{h + z} - \frac{p h r}{q} z. \end{aligned}$$

Consequently, when $\mathcal{R}_0 \leq 1$, the time derivative of L_0 is non-positive for all $x_1, y_1, x_2, y_2, v, z \in (0, \infty)$. Moreover, $\frac{dL_0}{dt} = 0$ holds only when $x_1(t) = x_1^0, x_2(t) = x_2^0, v(t) = 0$, and $z(t) = 0$, for every t . Define $\Gamma = \{(x_1, x_2, y_1, y_2, v, z) : \frac{dL_0}{dt} = 0\}$, and Γ_0 is the largest invariant subset of Γ . It is clear that the solutions of system in Eqs (2.1)–(2.6) approaches Γ_0 [17]. Moreover, Γ_0 is invariant and consists of trajectories for which $v(t) = 0$. Therefore, from Eq (2.5), it follows that

$$0 = \dot{v}(t) = k_1 e^{-\mu_3 \tau_3} y_1(t - \tau_3) + k_2 e^{-\mu_4 \tau_4} y_2(t - \tau_4).$$

This yields $y_i(t) = 0, i = 1, 2$. Hence, Γ_0 is the singleton $\{\Pi_0\}$, and we apply the invariance principle for delay differential systems, adapted from Lemma 3.1 of Saito et al. [21] and [22–24] to establish the global asymptotic stability of the equilibria. We get that Π_0 is G.A.S. from LaSalle's invariance principle, which completes the proof. $\square$

Theorem 2. For the system in Eqs (2.1)–(2.6), and if $\mathcal{R}_c < 1 < \mathcal{R}_0$, then Π^* is GAS.

Proof. Let

$$\Omega_1 = 1, \quad \Omega_2 = \frac{a_1 k_2 e^{-\mu_4 \tau_4}}{a_2 k_1 e^{-\mu_3 \tau_3}},$$

and define a function $L_1(x_1, y_1, x_2, y_2, v, z)$ be defined as:

$$\begin{aligned}
 L_1 = & \sum_{i=1}^2 \Omega_i \left[F_i \left(x_i - x_i^* - \int_{x_i^*}^{x_i} \frac{x_i^*(1 + \alpha_i \Theta + \zeta_i v^*)}{\Theta(1 + \alpha_i x_i^* + \zeta_i v^*)} d\Theta \right) + y_i^* H\left(\frac{y_i}{y_i^*}\right) \right. \\
 & + \frac{\beta_i x_i^* v^*}{(1 + \alpha_i x_i^* + \zeta_i v^*)} \int_0^{\tau_i} f_i(\sigma_i) e^{-\mu_i \sigma_i} \int_0^{\sigma_i} H\left(\frac{x_i(t - \theta)v(t - \theta)(1 + \alpha_i x_i^* + \zeta_i v^*)}{x_i^* v^* (1 + \alpha_i x_i(t - \theta) + \zeta_i v(t - \theta))}\right) d\theta d\sigma_i \\
 & \left. + a_i y_i^* \int_0^{\tau_{i+2}} H\left(\frac{y_i(t - \theta)}{y_i^*}\right) d\theta \right] + \frac{a_1}{k_1 e^{-\mu_3 \tau_3}} v^* H\left(\frac{v}{v^*}\right) + \frac{ph}{q} z.
 \end{aligned}$$

Thus, $L_1(x_1, y_1, x_2, y_2, v, z) > 0$ for all $x_1, y_1, x_2, y_2, v, z > 0$, and $L_1(x_1^*, y_1^*, x_2^*, y_2^*, v^*, 0) = 0$. Then

$$\begin{aligned}
 \frac{dL_1}{dt} = & \sum_{i=1}^2 \Omega_i \left[F_i \left(1 - \frac{x_i^* (1 + \alpha_i x_i + \zeta_i v^*)}{x_i (1 + \alpha_i x_i^* + \zeta_i v^*)} \right) \dot{x}_i + \left(1 - \frac{y_i^*}{y_i} \right) \dot{y}_i + \frac{F_i \beta_i x_i v}{1 + \alpha_i x_i + \zeta_i v} \right. \\
 & - \int_0^{\tau_i} f_i(\sigma_i) e^{-\mu_i \sigma_i} \frac{\beta_i x_i(t - \sigma_i) v(t - \sigma_i)}{1 + \alpha_i x_i(t - \sigma_i) + \zeta_i v(t - \sigma_i)} d\sigma_i \\
 & + \frac{\beta_i x_i^* v^*}{1 + \alpha_i x_i^* + \zeta_i v^*} \int_0^{\tau_i} f_i(\sigma_i) e^{-\mu_i \sigma_i} \ln \left(\frac{x_i(t - \sigma_i) v(t - \sigma_i) (1 + \alpha_i x_i + \zeta_i v)}{x_i v (1 + \alpha_i x_i(t - \sigma_i) + \zeta_i v(t - \sigma_i))} \right) d\sigma_i \\
 & \left. + a_i \left(y_i - y_i(t - \tau_{i+2}) + y_i^* \ln \left(\frac{y_i(t - \tau_{i+2})}{y_i} \right) \right) \right] + \frac{a_1}{k_1 e^{-\mu_3 \tau_3}} \left(1 - \frac{v^*}{v} \right) \dot{v} + \frac{ph}{q} \dot{z}. \quad (3.9)
 \end{aligned}$$

Then

$$\begin{aligned}
 \frac{dL_1}{dt} = & \sum_{i=1}^2 \Omega_i \left[F_i \left(1 - \frac{x_i^* (1 + \alpha_i x_i + \zeta_i v^*)}{x_i (1 + \alpha_i x_i^* + \zeta_i v^*)} \right) \left(\Lambda_i - d_i x_i - \frac{\beta_i x_i v}{1 + \alpha_i x_i + \zeta_i v} \right) \right. \\
 & + \frac{F_i \beta_i x_i v}{1 + \alpha_i x_i + \zeta_i v} - \int_0^{\tau_i} f_i(\sigma_i) e^{-\mu_i \sigma_i} \frac{\beta_i x_i(t - \sigma_i) v(t - \sigma_i)}{1 + \alpha_i x_i(t - \sigma_i) + \zeta_i v(t - \sigma_i)} d\sigma_i \\
 & + \frac{\beta_i x_i^* v^*}{1 + \alpha_i x_i^* + \zeta_i v^*} \int_0^{\tau_i} f_i(\sigma_i) e^{-\mu_i \sigma_i} \ln \left(\frac{x_i(t - \sigma_i) v(t - \sigma_i) (1 + \alpha_i x_i + \zeta_i v)}{x_i v (1 + \alpha_i x_i(t - \sigma_i) + \zeta_i v(t - \sigma_i))} \right) d\sigma_i \\
 & \left. + a_i \left(y_i - y_i(t - \tau_{i+2}) + y_i^* \ln \left(\frac{y_i(t - \tau_{i+2})}{y_i} \right) \right) \right] \\
 & + \left(1 - \frac{y_1^*}{y_1} \right) \left(\int_0^{\tau_1} f_1(\sigma_1) e^{-\mu_1 \sigma_1} \frac{\beta_1 x_1(t - \sigma_1) v(t - \sigma_1)}{1 + \alpha_1 x_1(t - \sigma_1) + \zeta_1 v(t - \sigma_1)} d\sigma_1 - a_1 y_1 - p y_1 z \right) \\
 & + \Omega_2 \left(1 - \frac{y_2^*}{y_2} \right) \left(\int_0^{\tau_2} f_2(\sigma_2) e^{-\mu_2 \sigma_2} \frac{\beta_2 x_2(t - \sigma_2) v(t - \sigma_2)}{1 + \alpha_2 x_2(t - \sigma_2) + \zeta_2 v(t - \sigma_2)} d\sigma_2 - a_2 y_2 \right)
 \end{aligned}$$

$$+ \frac{a_1}{k_1 e^{-\mu_3 \tau_3}} \left(1 - \frac{v^*}{v}\right) (k_1 e^{-\mu_3 \tau_3} y_1(t - \tau_3) + k_2 e^{-\mu_4 \tau_4} y_2(t - \tau_4) - \gamma v) + \frac{ph}{q} \left(\frac{qy_1 z}{h+z} - rz\right).$$

We Apply the following conditions for Π^* :

$$\begin{aligned}\Lambda_i &= d_i x_i^* + \frac{\beta_i x_i^* v^*}{1 + \alpha_i x_i^* + \zeta_i v^*}, \quad i = 1, 2, \\ a_i y_i^* &= \frac{F_i \beta_i x_i^* v^*}{1 + \alpha_i x_i^* + \zeta_i v^*}, \quad i = 1, 2, \\ \gamma v^* &= k_1 e^{-\mu_3 \tau_3} y_1^* + k_2 e^{-\mu_4 \tau_4} y_2^*.\end{aligned}$$

Calculating $\frac{dL_1}{dt}$ along the trajectories of Eqs (2.1)–(2.6), we get

$$\begin{aligned}\frac{dL_1}{dt} &= \sum_{i=1}^2 \Omega_i \left[F_i \left(1 - \frac{x_i^* (1 + \alpha_i x_i + \zeta_i v^*)}{x_i (1 + \alpha_i x_i^* + \zeta_i v^*)}\right) (d_i x_i^* - d_i x_i) + \frac{F_i \beta_i x_i^* v^*}{1 + \alpha_i x_i^* + \zeta_i v^*} \left(1 - \frac{x_i^* (1 + \alpha_i x_i + \zeta_i v^*)}{x_i (1 + \alpha_i x_i^* + \zeta_i v^*)}\right) \right. \\ &\quad + \frac{\beta_i x_i^* v}{1 + \alpha_i x_i + \zeta_i v} \frac{(1 + \alpha_i x_i + \zeta_i v^*)}{(1 + \alpha_i x_i^* + \zeta_i v^*)} - \frac{y_i^*}{y_i} \int_0^{\tau_i} f_i(\sigma_i) e^{-\mu_i \sigma_i} \frac{\beta_i x_i(t - \sigma_i) v(t - \sigma_i)}{1 + \alpha_i x_i(t - \sigma_i) + \zeta_i v(t - \sigma_i)} d\sigma_i + a_i y_i^* \\ &\quad + \frac{\beta_i x_i^* v^*}{1 + \alpha_i x_i^* + \zeta_i v^*} \int_0^{\tau_i} f_i(\sigma_i) e^{-\mu_i \sigma_i} \ln \left(\frac{x_i(t - \sigma_i) v(t - \sigma_i) (1 + \alpha_i x_i + \zeta_i v)}{x_i v (1 + \alpha_i x_i(t - \sigma_i) + \zeta_i v(t - \sigma_i))} \right) d\sigma_i + a_i y_i^* \ln \left(\frac{y_i(t - \tau_{i+2})}{y_i} \right) \\ &\quad \left. - \frac{v^*}{v} a_i y_i(t - \tau_{i+2}) \right] - p y_1 z + p y_1^* z - \frac{a_1}{k_1 e^{-\mu_3 \tau_3}} \gamma v + \frac{a_1}{k_1 e^{-\mu_3 \tau_3}} \gamma v^* + \frac{p h y_1 z}{h+z} - \frac{p h r}{q} z.\end{aligned}$$

Collecting the terms of last equation, we have

$$\begin{aligned}\frac{dL_1}{dt} &= \sum_{i=1}^2 \Omega_i \left[\frac{-F_i d_i (x_i - x_i^*)^2 (1 + \zeta_i v^*)}{x_i (1 + \alpha_i x_i^* + \zeta_i v^*)} + \frac{F_i \beta_i x_i^* v^*}{1 + \alpha_i x_i^* + \zeta_i v^*} \left(2 - \frac{x_i^* (1 + \alpha_i x_i + \zeta_i v^*)}{x_i (1 + \alpha_i x_i^* + \zeta_i v^*)} + \frac{v (1 + \alpha_i x_i + \zeta_i v^*)}{v^* (1 + \alpha_i x_i + \zeta_i v)}\right) \right. \\ &\quad - \frac{\beta_i x_i^* v^*}{1 + \alpha_i x_i^* + \zeta_i v^*} \int_0^{\tau_i} f_i(\sigma_i) e^{-\mu_i \sigma_i} \frac{y_i^*}{y_i} \frac{x_i(t - \sigma_i) v(t - \sigma_i) (1 + \alpha_i x_i^* + \zeta_i v^*)}{x_i^* v^* (1 + \alpha_i x_i(t - \sigma_i) + \zeta_i v(t - \sigma_i))} d\sigma_i \\ &\quad + \frac{\beta_i x_i^* v^*}{1 + \alpha_i x_i^* + \zeta_i v^*} \int_0^{\tau_i} f_i(\sigma_i) e^{-\mu_i \sigma_i} \ln \left(\frac{x_i(t - \sigma_i) v(t - \sigma_i) (1 + \alpha_i x_i + \zeta_i v)}{x_i v (1 + \alpha_i x_i(t - \sigma_i) + \zeta_i v(t - \sigma_i))} \right) d\sigma_i \\ &\quad + \frac{F_i \beta_i x_i^* v^*}{1 + \alpha_i x_i^* + \zeta_i v^*} \ln \left(\frac{y_i(t - \tau_{i+2})}{y_i} \right) - \frac{F_i \beta_i x_i^* v^*}{1 + \alpha_i x_i^* + \zeta_i v^*} \frac{v^* y_i(t - \tau_{i+2})}{v y_i^*} \left. \right] - \frac{p y_1 z^2}{h+z} \\ &\quad + \frac{p h r}{q} \left(\frac{q y_1^*}{h r} - 1 \right) z - \frac{a_1}{k_1 e^{-\mu_3 \tau_3}} \frac{v}{v^*} (k_1 e^{-\mu_3 \tau_3} y_1^* + k_2 e^{-\mu_4 \tau_4} y_2^*) + \frac{a_1}{k_1 e^{-\mu_3 \tau_3}} (k_1 e^{-\mu_3 \tau_3} y_1^* + k_2 e^{-\mu_4 \tau_4} y_2^*).\end{aligned}$$

Using the equalities

$$\ln \left(\frac{x_i(t - \sigma_i) v(t - \sigma_i) (1 + \alpha_i x_i + \zeta_i v)}{x_i v (1 + \alpha_i x_i(t - \sigma_i) + \zeta_i v(t - \sigma_i))} \right) = \ln \left(\frac{x_i^* (1 + \alpha_i x_i + \zeta_i v^*)}{x_i (1 + \alpha_i x_i^* + \zeta_i v^*)} \right) + \ln \left(\frac{1 + \alpha_i x_i + \zeta_i v}{1 + \alpha_i x_i + \zeta_i v^*} \right)$$

$$+ \ln\left(\frac{y_i v^*}{y_i^* v}\right) + \ln\left(\frac{y_i^* x_i(t - \sigma_i)v(t - \sigma_i)(1 + \alpha_i x_i^* + \zeta_i v^*)}{y_i x_i^* v^*(1 + \alpha_i x_i(t - \sigma_i) + \zeta_i v(t - \sigma_i))}\right),$$

$$\ln\left(\frac{y_i(t - \tau_{i+2})}{y_i}\right) = \ln\left(\frac{y_i(t - \tau_{i+2})v^*}{y_i^* v}\right) + \ln\left(\frac{y_i^* v}{y_i v^*}\right), \quad i = 1, 2.$$

Thus,

$$\begin{aligned} \frac{dL_1}{dt} = & \sum_{i=1}^2 \Omega_i \left[\frac{-F_i d_i (x_i - x_i^*)^2 (1 + \zeta_i v^*)}{x_i (1 + \alpha_i x_i^* + \zeta_i v^*)} - \frac{F_i \beta_i x_i^* v^*}{1 + \alpha_i x_i^* + \zeta_i v^*} \left[H\left(\frac{x_i^* (1 + \alpha_i x_i + \zeta_i v^*)}{x_i (1 + \alpha_i x_i^* + \zeta_i v^*)}\right) \right. \right. \\ & + H\left(\frac{v^* y_i(t - \tau_{i+2})}{v y_i^*}\right) + H\left(\frac{1 + \alpha_i x_i + \zeta_i v}{1 + \alpha_i x_i + \zeta_i v^*}\right) + 1 + \frac{v}{v^*} - \frac{1 + \alpha_i x_i + \zeta_i v}{1 + \alpha_i x_i + \zeta_i v^*} - \frac{v (1 + \alpha_i x_i + \zeta_i v^*)}{v^* (1 + \alpha_i x_i + \zeta_i v)} \Big] \\ & + \frac{\beta_i x_i^* v^*}{1 + \alpha_i x_i^* + \zeta_i v^*} \int_0^{\tau_i} f_i(\sigma_i) e^{-\mu_i \sigma_i} H\left(\frac{y_i^* x_i(t - \sigma_i)v(t - \sigma_i)(1 + \alpha_i x_i^* + \zeta_i v^*)}{y_i x_i^* v^*(1 + \alpha_i x_i(t - \sigma_i) + \zeta_i v(t - \sigma_i))}\right) d\sigma_i \Big] - \frac{p y_1 z^2}{h + z} \\ & + \frac{phr(\mathcal{R}_c - 1)}{q} z. \end{aligned}$$

However

$$\frac{v (1 + \alpha_i x_i + \zeta_i v^*)}{v^* (1 + \alpha_i x_i + \zeta_i v)} - 1 - \frac{v}{v^*} + \frac{1 + \alpha_i x_i + \zeta_i v}{1 + \alpha_i x_i + \zeta_i v^*} = \frac{-\zeta_i (1 + \alpha_i x_i)(v - v^*)^2}{v^* (1 + \alpha_i x_i + \zeta_i v)(1 + \alpha_i x_i + \zeta_i v^*)}.$$

Finally,

$$\begin{aligned} \frac{dL_1}{dt} = & \sum_{i=1}^2 \Omega_i \left[\frac{-F_i d_i (x_i - x_i^*)^2 (1 + \zeta_i v^*)}{x_i (1 + \alpha_i x_i^* + \zeta_i v^*)} - \frac{F_i \beta_i x_i^* v^*}{1 + \alpha_i x_i^* + \zeta_i v^*} \left[\frac{\zeta_i (1 + \alpha_i x_i)(v - v^*)^2}{v^* (1 + \alpha_i x_i + \zeta_i v)(1 + \alpha_i x_i + \zeta_i v^*)} \right. \right. \\ & + H\left(\frac{x_i^* (1 + \alpha_i x_i + \zeta_i v^*)}{x_i (1 + \alpha_i x_i^* + \zeta_i v^*)}\right) + H\left(\frac{v^* y_i(t - \tau_{i+2})}{v y_i^*}\right) + H\left(\frac{1 + \alpha_i x_i + \zeta_i v}{1 + \alpha_i x_i + \zeta_i v^*}\right) \Big] \\ & + \frac{\beta_i x_i^* v^*}{1 + \alpha_i x_i^* + \zeta_i v^*} \int_0^{\tau_i} f_i(\sigma_i) e^{-\mu_i \sigma_i} H\left(\frac{y_i^* x_i(t - \sigma_i)v(t - \sigma_i)(1 + \alpha_i x_i^* + \zeta_i v^*)}{y_i x_i^* v^*(1 + \alpha_i x_i(t - \sigma_i) + \zeta_i v(t - \sigma_i))}\right) d\sigma_i \Big] \\ & - \frac{p y_1 z^2}{h + z} + \frac{phr}{q} (\mathcal{R}_c - 1) z. \end{aligned}$$

We have $x_1^*, y_1^*, x_2^*, y_2^*, v^* > 0$ when $\mathcal{R}_0 > 1$, and if $\mathcal{R}_c < 1$, then $\frac{dL_1}{dt} \leq 0$ for all $x_1, y_1, x_2, y_2, v > 0$, and then solutions of system in Eqs (2.1)–(2.6) are limited to Π^* , the largest invariant subset of $\left\{ (x_1, x_2, y_1, y_2, v, z) : \frac{dL_1}{dt} = 0 \right\}$. It can be seen that, $\frac{dL_1}{dt} = 0$ if and only if $(x_1(t), x_2(t), y_1(t), y_2(t), v(t), z(t)) = (x_1^*, x_2^*, y_1^*, y_2^*, v^*, 0)$. By Lemma 3.1 of Saito et al. [21], which provides an appropriate invariance principle for delay differential systems, we have the largest invariant subset of the set, where $\frac{dL_1}{dt}$ is the endemic equilibrium without immunity. Therefore, based on the preceding analysis and LIP, the second equilibrium point Π^* is globally asymptotically stable. $\square$

Theorem 3. For the system's Eqs (2.1)–(2.6), if $\mathcal{R}_c > 1$, so $\tilde{\Pi}$ is GAS.

Proof. Let

$$\Psi_1 = 1, \quad \Psi_2 = \frac{(a_1 + p\tilde{z})k_2e^{-\mu_4\tau_4}}{a_2k_1e^{-\mu_3\tau_3}},$$

and define a function $L_2(x_1, y_1, x_2, y_2, v, z)$ as:

$$\begin{aligned} L_2 = & \sum_{i=1}^2 \Psi_i \left[F_i \left(x_i - \tilde{x}_i - \int_{\tilde{x}_i}^{x_i} \frac{\tilde{x}_i(1 + \alpha_i\Theta + \zeta_i\tilde{v})}{\Theta(1 + \alpha_i\tilde{x}_i + \zeta_i\tilde{v})} d\Theta \right) + \tilde{y}_i H\left(\frac{y_i}{\tilde{y}_i}\right) \right. \\ & + \frac{\beta_i\tilde{x}_i\tilde{v}}{(1 + \alpha_i\tilde{x}_i + \zeta_i\tilde{v})} \int_0^{\tau_i} f_i(\sigma_i)e^{-\mu_i\sigma_i} \int_0^{\sigma_i} H\left(\frac{x_i(t-\theta)v(t-\theta)(1 + \alpha_i\tilde{x}_i + \zeta_i\tilde{v})}{\tilde{x}_i\tilde{v}(1 + \alpha_i x_i(t-\theta) + \zeta_i v(t-\theta))}\right) d\theta d\sigma_i \Big] \\ & + \frac{(a_1 + p\tilde{z})}{k_1e^{-\mu_3\tau_3}} \tilde{v} H\left(\frac{v}{\tilde{v}}\right) + (a_1 + p\tilde{z})\tilde{y}_1 \int_0^{\tau_3} H\left(\frac{y_1(t-\theta)}{\tilde{y}_1}\right) d\theta \\ & + \Psi_2 a_2 \tilde{y}_2 \int_0^{\tau_4} H\left(\frac{y_2(t-\theta)}{\tilde{y}_2}\right) d\theta + \frac{p\tilde{y}_1}{r} \tilde{z} H\left(\frac{z}{\tilde{z}}\right). \end{aligned}$$

Thus, $L_2(x_1, y_1, x_2, y_2, v, z) > 0$ for all $x_1, y_1, x_2, y_2, v, z > 0$, and $L_2(\tilde{x}_1, \tilde{y}_1, \tilde{x}_2, \tilde{y}_2, \tilde{v}, \tilde{z}) = 0$. Then

$$\begin{aligned} \frac{dL_2}{dt} = & \sum_{i=1}^2 \Psi_i \left[F_i \left(1 - \frac{\tilde{x}_i(1 + \alpha_i x_i + \zeta_i \tilde{v})}{x_i(1 + \alpha_i \tilde{x}_i + \zeta_i \tilde{v})} \right) \dot{x}_i + \left(1 - \frac{\tilde{y}_i}{y_i} \right) \dot{y}_i + \frac{F_i \beta_i x_i v}{1 + \alpha_i x_i + \zeta_i v} \right. \\ & - \int_0^{\tau_i} f_i(\sigma_i)e^{-\mu_i\sigma_i} \frac{\beta_i x_i(t-\sigma_i)v(t-\sigma_i)}{1 + \alpha_i x_i(t-\sigma_i) + \zeta_i v(t-\sigma_i)} d\sigma_i \\ & + \frac{\beta_i \tilde{x}_i \tilde{v}}{1 + \alpha_i \tilde{x}_i + \zeta_i \tilde{v}} \int_0^{\tau_i} f_i(\sigma_i)e^{-\mu_i\sigma_i} \ln \left(\frac{x_i(t-\sigma_i)v(t-\sigma_i)(1 + \alpha_i x_i + \zeta_i v)}{x_i v(1 + \alpha_i x_i(t-\sigma_i) + \zeta_i v(t-\sigma_i))} \right) d\sigma_i \Big] \\ & + \frac{(a_1 + p\tilde{z})}{k_1e^{-\mu_3\tau_3}} \left(1 - \frac{\tilde{v}}{v} \right) \dot{v} + (a_1 + p\tilde{z}) \left[y_1 - y_1(t-\tau_3) + \tilde{y}_1 \ln \left(\frac{y_1(t-\tau_3)}{y_1} \right) \right] \\ & + \Psi_2 a_2 \left[y_2 - y_2(t-\tau_4) + \tilde{y}_2 \ln \left(\frac{y_2(t-\tau_4)}{y_2} \right) \right] + \frac{p\tilde{y}_1}{r} \left(1 - \frac{\tilde{z}}{z} \right) \dot{z}. \end{aligned} \quad (3.10)$$

Applying the following conditions for $\tilde{\Pi}$:

$$\begin{aligned} \Lambda_i &= d_i \tilde{x}_i + \frac{\beta_i \tilde{x}_i \tilde{v}}{1 + \alpha_i \tilde{x}_i + \zeta_i \tilde{v}}, \quad i = 1, 2, \\ (a_1 + p\tilde{z})\tilde{y}_1 &= \frac{F_1 \beta_1 \tilde{x}_1 \tilde{v}}{1 + \alpha_1 \tilde{x}_1 + \zeta_1 \tilde{v}}, \\ a_2 \tilde{y}_2 &= \frac{F_2 \beta_2 \tilde{x}_2 \tilde{v}}{1 + \alpha_2 \tilde{x}_2 + \zeta_2 \tilde{v}}, \\ \gamma \tilde{v} &= k_1 e^{-\mu_3 \tau_3} \tilde{y}_1 + k_2 e^{-\mu_4 \tau_4} \tilde{y}_2, \\ q \tilde{y}_1 &= r(h + \tilde{z}). \end{aligned}$$

Calculating $\frac{dL_2}{dt}$ along the trajectories of Eqs (2.1)–(2.6), we get

$$\begin{aligned} \frac{dL_2}{dt} = & \sum_{i=1}^2 \Psi_i \left[F_i \left(1 - \frac{\tilde{x}_i (1 + \alpha_i x_i + \zeta_i \tilde{v})}{x_i (1 + \alpha_i \tilde{x}_i + \zeta_i \tilde{v})} \right) (d_i \tilde{x}_i - d_i x_i) + \frac{F_i \beta_i \tilde{x}_i \tilde{v}}{1 + \alpha_i \tilde{x}_i + \zeta_i \tilde{v}} \left(1 - \frac{\tilde{x}_i (1 + \alpha_i x_i + \zeta_i \tilde{v})}{x_i (1 + \alpha_i \tilde{x}_i + \zeta_i \tilde{v})} \right) \right. \\ & + \frac{F_i \beta_i \tilde{x}_i \tilde{v}}{1 + \alpha_i x_i + \zeta_i \tilde{v}} \frac{(1 + \alpha_i x_i + \zeta_i \tilde{v})}{(1 + \alpha_i \tilde{x}_i + \zeta_i \tilde{v})} - \frac{\tilde{y}_i}{y_i} \int_0^{\tau_i} f_i(\sigma_i) e^{-\mu_i \sigma_i} \frac{\beta_i x_i(t - \sigma_i) v(t - \sigma_i)}{1 + \alpha_i x_i(t - \sigma_i) + \zeta_i v(t - \sigma_i)} d\sigma_i + a_i \tilde{y}_i \\ & + \frac{\beta_i \tilde{x}_i \tilde{v}}{1 + \alpha_i \tilde{x}_i + \zeta_i \tilde{v}} \int_0^{\tau_i} f_i(\sigma_i) e^{-\mu_i \sigma_i} \ln \left(\frac{x_i(t - \sigma_i) v(t - \sigma_i) (1 + \alpha_i x_i + \zeta_i v)}{x_i v (1 + \alpha_i x_i(t - \sigma_i) + \zeta_i v(t - \sigma_i))} \right) d\sigma_i \left. \right] - p y_1 z + p \tilde{y}_1 z \\ & + (a_1 + p \tilde{z}) \left(1 - \frac{\tilde{v}}{v} \right) y_1(t - \tau_3) + \Psi_2 a_2 \left(1 - \frac{v^*}{v} \right) y_2(t - \tau_4) + \frac{\Psi_2 a_2}{k_2 e^{-\mu_4 \tau_4}} (\gamma \tilde{v} - \gamma v) \\ & + \left[\frac{q \tilde{y}_1}{r} \frac{p y_1 z}{h + z} - p \tilde{y}_1 z - \frac{q \tilde{y}_1}{r} \frac{p y_1 \tilde{z}}{h + z} + p \tilde{y}_1 \tilde{z} \right] + (a_1 + p \tilde{z}) \left[\tilde{y}_1 \ln \left(\frac{y_1(t - \tau_3)}{y_1} \right) - y_1(t - \tau_3) \right] \\ & + \Psi_2 a_2 \left[\tilde{y}_2 \ln \left(\frac{y_2(t - \tau_4)}{y_2} \right) - y_2(t - \tau_4) \right]. \end{aligned}$$

We Collect the terms of the last equation and use the equality

$$\begin{aligned} \frac{q \tilde{y}_1}{r} \frac{p y_1 z}{h + z} - p y_1 z - \frac{q \tilde{y}_1}{r} \frac{p y_1 \tilde{z}}{h + z} + p y_1 \tilde{z} &= p y_1 z \frac{h + \tilde{z}}{h + z} - p y_1 z - p y_1 \tilde{z} \frac{h + \tilde{z}}{h + z} + p y_1 \tilde{z} \\ &= p y_1 z \frac{\tilde{z} - z}{h + z} - p y_1 \tilde{z} \frac{\tilde{z} - z}{h + z} = \frac{-p y_1 (z - \tilde{z})^2}{h + z}, \end{aligned}$$

and get

$$\begin{aligned} \frac{dL_2}{dt} = & \sum_{i=1}^2 \Psi_i \left[\frac{-F_i d_i (x_i - \tilde{x}_i)^2 (1 + \zeta_i \tilde{v})}{x_i (1 + \alpha_i \tilde{x}_i + \zeta_i \tilde{v})} + \frac{F_i \beta_i \tilde{x}_i \tilde{v}}{1 + \alpha_i \tilde{x}_i + \zeta_i \tilde{v}} \left(3 - \frac{\tilde{x}_i (1 + \alpha_i x_i + \zeta_i \tilde{v})}{x_i (1 + \alpha_i \tilde{x}_i + \zeta_i \tilde{v})} - \frac{v}{\tilde{v}} \right. \right. \\ & + \left. \frac{v (1 + \alpha_i x_i + \zeta_i \tilde{v})}{\tilde{v} (1 + \alpha_i x_i + \zeta_i \tilde{v})} \right) - \frac{\beta_i \tilde{x}_i \tilde{v}}{1 + \alpha_i \tilde{x}_i + \zeta_i \tilde{v}} \int_0^{\tau_i} f_i(\sigma_i) e^{-\mu_i \sigma_i} \frac{\tilde{y}_i x_i(t - \tau_i) v(t - \tau_i) (1 + \alpha_i \tilde{x}_i + \zeta_i \tilde{v})}{y_i \tilde{x}_i \tilde{v} (1 + \alpha_i x_i(t - \tau_i) + \zeta_i v(t - \tau_i))} d\sigma_i \\ & + \frac{\beta_i \tilde{x}_i \tilde{v}}{1 + \alpha_i \tilde{x}_i + \zeta_i \tilde{v}} \int_0^{\tau_i} f_i(\sigma_i) e^{-\mu_i \sigma_i} \ln \left(\frac{x_i(t - \tau_i) v(t - \tau_i) (1 + \alpha_i x_i + \zeta_i v)}{x_i v (1 + \alpha_i x_i(t - \tau_i) + \zeta_i v(t - \tau_i))} \right) d\sigma_i \left. \right] \\ & - \frac{p y_1 (z - \tilde{z})^2}{h + z} - (a_1 + p \tilde{z}) \frac{\tilde{v}}{v} y_1(t - \tau_3) - \Psi_2 a_2 \frac{\tilde{v}}{v} y_2(t - \tau_4) + (a_1 + p \tilde{z}) \tilde{y}_1 \ln \left(\frac{y_1(t - \tau_3)}{y_1} \right) \\ & + \Psi_2 a_2 \tilde{y}_2 \ln \left(\frac{y_2(t - \tau_4)}{y_2} \right). \end{aligned}$$

We use the equalities

$$\ln \left(\frac{x_i(t - \tau_i) v(t - \tau_i) (1 + \alpha_i x_i + \zeta_i v)}{x_i v (1 + \alpha_i x_i(t - \tau_i) + \zeta_i v(t - \tau_i))} \right) = \ln \left(\frac{\tilde{x}_i (1 + \alpha_i x_i + \zeta_i \tilde{v})}{x_i (1 + \alpha_i \tilde{x}_i + \zeta_i \tilde{v})} \right) + \ln \left(\frac{1 + \alpha_i x_i + \zeta_i v}{1 + \alpha_i x_i + \zeta_i \tilde{v}} \right)$$

$$+ \ln\left(\frac{y_i \tilde{v}}{\tilde{y}_i v}\right) + \ln\left(\frac{\tilde{y}_i x_i (t - \tau_i) v (t - \tau_i) (1 + \alpha_i \tilde{x}_i + \zeta_i \tilde{v})}{y_i \tilde{x}_i \tilde{v} (1 + \alpha_i x_i (t - \tau_i) + \zeta_i v (t - \tau_i))}\right),$$

$$\ln\left(\frac{y_i (t - \tau_{i+2})}{y_i}\right) = \ln\left(\frac{y_i (t - \tau_{i+2}) \tilde{v}}{\tilde{y}_i v}\right) + \ln\left(\frac{\tilde{y}_i v}{y_i \tilde{v}}\right), \quad i = 1, 2.$$

Thus,

$$\begin{aligned} \frac{dL_2}{dt} = & \sum_{i=1}^2 \Psi_i \left[\frac{-F_i d_i (x_i - \tilde{x}_i)^2 (1 + \zeta_i \tilde{v})}{x_i (1 + \alpha_i \tilde{x}_i + \zeta_i \tilde{v})} - \frac{F_i \beta_i \tilde{x}_i \tilde{v}}{1 + \alpha_i \tilde{x}_i + \zeta_i \tilde{v}} \left[H\left(\frac{\tilde{x}_i (1 + \alpha_i x_i + \zeta_i \tilde{v})}{x_i (1 + \alpha_i \tilde{x}_i + \zeta_i \tilde{v})}\right) - \frac{v (1 + \alpha_i x_i + \zeta_i \tilde{v})}{\tilde{v} (1 + \alpha_i x_i + \zeta_i v)} \right. \right. \\ & \left. \left. + 1 + \frac{v}{\tilde{v}} + H\left(\frac{1 + \alpha_i x_i + \zeta_i v}{1 + \alpha_i \tilde{x}_i + \zeta_i \tilde{v}}\right) - \frac{1 + \alpha_i x_i + \zeta_i v}{1 + \alpha_i \tilde{x}_i + \zeta_i \tilde{v}} \right] \right] + (a_1 + p\tilde{z}) \tilde{y}_1 H\left(\frac{\tilde{v} y_1 (t - \tau_3)}{v \tilde{y}_1}\right) \\ & + \sum_{i=1}^2 \Psi_i \frac{\beta_i \tilde{x}_i \tilde{v}}{1 + \alpha_i \tilde{x}_i + \zeta_i \tilde{v}} \int_0^{\tau_i} f_i(\sigma_i) e^{-\mu_i \sigma_i} H\left(\frac{\tilde{y}_i x_i (t - \tau_i) v (t - \tau_i) (1 + \alpha_i \tilde{x}_i + \zeta_i \tilde{v})}{y_i \tilde{x}_i \tilde{v} (1 + \alpha_i x_i (t - \tau_i) + \zeta_i v (t - \tau_i))}\right) d\sigma_i \\ & + \Psi_2 a_2 \tilde{y}_2 H\left(\frac{\tilde{v} y_2 (t - \tau_4)}{v \tilde{y}_2}\right) - \frac{p y_1 (z - \tilde{z})^2}{h + z}. \end{aligned}$$

We have

$$\frac{v (1 + \alpha_i x_i + \zeta_i \tilde{v})}{\tilde{v} (1 + \alpha_i x_i + \zeta_i v)} - 1 - \frac{v}{\tilde{v}} + \frac{1 + \alpha_i x_i + \zeta_i v}{1 + \alpha_i \tilde{x}_i + \zeta_i \tilde{v}} = \frac{-\zeta_i (1 + \alpha_i x_i) (v - \tilde{v})^2}{\tilde{v} (1 + \alpha_i x_i + \zeta_i v) (1 + \alpha_i \tilde{x}_i + \zeta_i \tilde{v})}.$$

Finally

$$\begin{aligned} \frac{dL_2}{dt} = & \sum_{i=1}^2 \Psi_i \left[\frac{-F_i d_i (x_i - \tilde{x}_i)^2 (1 + \zeta_i \tilde{v})}{x_i (1 + \alpha_i \tilde{x}_i + \zeta_i \tilde{v})} - \frac{F_i \beta_i \tilde{x}_i \tilde{v}}{1 + \alpha_i \tilde{x}_i + \zeta_i \tilde{v}} \left[H\left(\frac{\tilde{x}_i (1 + \alpha_i x_i + \zeta_i \tilde{v})}{x_i (1 + \alpha_i \tilde{x}_i + \zeta_i \tilde{v})}\right) + H\left(\frac{1 + \alpha_i x_i + \zeta_i v}{1 + \alpha_i \tilde{x}_i + \zeta_i \tilde{v}}\right) \right. \right. \\ & \left. \left. + H\left(\frac{\tilde{v} y_i (t - \tau_{i+2})}{v \tilde{y}_i}\right) + \frac{\zeta_i (1 + \alpha_i x_i) (v - \tilde{v})^2}{\tilde{v} (1 + \alpha_i x_i + \zeta_i v) (1 + \alpha_i \tilde{x}_i + \zeta_i \tilde{v})} \right] \right. \\ & \left. + \frac{\beta_i \tilde{x}_i \tilde{v}}{1 + \alpha_i \tilde{x}_i + \zeta_i \tilde{v}} \int_0^{\tau_i} f_i(\sigma_i) e^{-\mu_i \sigma_i} H\left(\frac{\tilde{y}_i x_i (t - \tau_i) v (t - \tau_i) (1 + \alpha_i \tilde{x}_i + \zeta_i \tilde{v})}{y_i \tilde{x}_i \tilde{v} (1 + \alpha_i x_i (t - \tau_i) + \zeta_i v (t - \tau_i))}\right) d\sigma_i \right] - \frac{p y_1 (z - \tilde{z})^2}{h + z}, \end{aligned}$$

where $\tilde{x}_1, \tilde{y}_1, \tilde{x}_2, \tilde{y}_2, \tilde{v}, \tilde{z} > 0$, so $\frac{dL_2}{dt} \leq 0$ for all $x_1, y_1, x_2, y_2, v, z > 0$, and then the solutions of the system Eqs (2.1)–(2.6) are limited to $\tilde{\Pi}$, with the largest invariant subset of $\left\{ (x_1, x_2, y_1, y_2, v, z) : \frac{dL_2}{dt} = 0 \right\}$. It can be seen that, $\frac{dL_2}{dt} = 0$ if and only if $(x_1(t), x_2(t), y_1(t), y_2(t), v(t), z(t)) = (\tilde{x}_1, \tilde{x}_2, \tilde{y}_1, \tilde{y}_2, \tilde{v}, \tilde{z})$. The global stability of $\tilde{\Pi}$ is satisfied from LIP. $\square$

4. Numerical simulations

In this section, we illustrate the behavior of system in Eqs (2.1)–(2.6) through numerical simulations, using the parameter values reported in Table 1 (see e.g. [25, 26]). To streamline the analysis, we assume that

$$\int_0^{\tau_i} f_1(\sigma_i) e^{-\mu_i \sigma_i} \frac{\beta_i x_i(t - \sigma_i) v(t - \sigma_i)}{1 + \alpha_i x_i(t - \sigma_i) + \zeta_i v(t - \sigma_i)} d\sigma_i = \frac{e^{-\mu_i \tau_i} \beta_i x_i(t - \tau_i) v(t - \tau_i)}{1 + \alpha_i x_i(t - \tau_i) + \zeta_i v(t - \tau_i)}, \quad i = 1, 2.$$

Table 1. The parameter values of model in Eqs (2.1)–(2.6).

Parameter	Value	Parameter	Value
Λ_1	10 cells mm ⁻³ day ⁻¹	Λ_2	0.3 cells mm ⁻³ day ⁻¹
d_1	0.01 day ⁻¹	d_2	0.01 day ⁻¹
β_1	varied	β_2	varied
α_1	0.001	α_2	0.0001
ζ_1	0.005 virus ⁻¹ mm ³	ζ_2	0.002 virus ⁻¹ mm ³
a_1	0.3	μ_1	1 day ⁻¹
p	0.04	μ_2	1 day ⁻¹
a_2	0.12	μ_3	1 day ⁻¹
k_1	5 virus cells ⁻¹	μ_4	1 day ⁻¹
k_2	3 virus cells ⁻¹	γ	3 day ⁻¹
q	0.025 day ⁻¹	h	0.3
r	2 day ⁻¹		

4.1. Sensitivity analysis of $\mathcal{R}_0$

A major goal in managing a HCV infection is to reduce the basic reproduction number, $\mathcal{R}_0$, below one. To achieve this, it is crucial to understand how different model parameters influence the value of $\mathcal{R}_0$. Identifying key parameters that impact infection control is important and can be achieved through sensitivity analysis. Forward sensitivity analysis is particularly useful in disease modeling as it offers insights into how factors influence disease dynamics [27]. To evaluate how sensitive $\mathcal{R}_0$ is to changes in the parameters of our proposed system in Eqs (2.1)–(2.6), we employ local sensitivity analysis. Specifically, we calculate the normalized forward sensitivity index, Ξ_ϱ . This index quantifies the impact of a parameter ϱ on $\mathcal{R}_0$. It is defined as follows:

$$\Xi_\varrho = \frac{\varrho}{\mathcal{R}_0} \frac{\partial \mathcal{R}_0}{\partial \varrho}. \quad (4.1)$$

Under the simplifying assumption introduced above, the distributed-delay factors F_i used in the numerical and sensitivity analysis are reduced to

$$F_i = e^{-\mu_i \tau_i}, \quad i = 1, 2.$$

Consequently, the basic reproduction number used in the sensitivity analysis takes the form

$$\mathcal{R}_0 = \frac{\beta_1 k_1 x_1^0 e^{-\mu_1 \tau_1} e^{-\mu_3 \tau_3}}{a_1 \gamma (1 + \alpha_1 x_1^0)} + \frac{\beta_2 k_2 x_2^0 e^{-\mu_2 \tau_2} e^{-\mu_4 \tau_4}}{a_2 \gamma (1 + \alpha_2 x_2^0)} = \mathcal{R}_0^1 + \mathcal{R}_0^2.$$

Applying definition (4.1) to our model yields the sensitivity indices presented in Table 2.

Table 2. Sensitivity indices of $\mathcal{R}_0$.

Parameter ϱ	Ξ_{ϱ}	Parameter ϱ	Ξ_{ϱ}	Parameter ϱ	Ξ_{ϱ}
β_1	$\frac{\mathcal{R}_0^1}{\mathcal{R}_0}$	μ_3	$-\mu_3 \tau_3 \frac{\mathcal{R}_0^1}{\mathcal{R}_0}$	γ	-1
k_1	$\frac{\mathcal{R}_0^1}{\mathcal{R}_0}$	τ_3	$-\mu_3 \tau_3 \frac{\mathcal{R}_0^1}{\mathcal{R}_0}$	β_2	$\frac{\mathcal{R}_0^2}{\mathcal{R}_0}$
Λ_1	$\frac{d_1 \mathcal{R}_0^1}{(\Lambda_1 \alpha_1 + d_1) \mathcal{R}_0}$	μ_4	$-\mu_4 \tau_4 \frac{\mathcal{R}_0^2}{\mathcal{R}_0}$	k_2	$\frac{\mathcal{R}_0^2}{\mathcal{R}_0}$
μ_1	$-\mu_1 \tau_1 \frac{\mathcal{R}_0^1}{\mathcal{R}_0}$	τ_4	$-\mu_4 \tau_4 \frac{\mathcal{R}_0^2}{\mathcal{R}_0}$	Λ_2	$\frac{d_2 \mathcal{R}_0^2}{(\Lambda_2 \alpha_2 + d_2) \mathcal{R}_0}$
τ_1	$-\mu_1 \tau_1 \frac{\mathcal{R}_0^1}{\mathcal{R}_0}$	d_1	$-\frac{d_1 \mathcal{R}_0^1}{(\Lambda_1 \alpha_1 + d_1) \mathcal{R}_0}$	d_2	$-\frac{d_2 \mathcal{R}_0^2}{(\Lambda_2 \alpha_2 + d_2) \mathcal{R}_0}$
μ_2	$-\mu_2 \tau_2 \frac{\mathcal{R}_0^2}{\mathcal{R}_0}$	α_1	$-\frac{\mathcal{R}_0^1}{\mathcal{R}_0}$	α_2	$-\frac{\mathcal{R}_0^2}{\mathcal{R}_0}$
τ_2	$-\mu_2 \tau_2 \frac{\mathcal{R}_0^2}{\mathcal{R}_0}$	α_1	$-\frac{\alpha_1 \Lambda_1 \mathcal{R}_0^1}{(\Lambda_1 \alpha_1 + d_1) \mathcal{R}_0}$	α_2	$-\frac{\alpha_2 \Lambda_2 \mathcal{R}_0^2}{(\Lambda_2 \alpha_2 + d_2) \mathcal{R}_0}$

The sensitivity indices presented in Table 2 quantify the impact of various parameters on $\mathcal{R}_0$ in the hepatitis C model. A positive sensitivity index indicates that a local increase in the corresponding parameter increases $\mathcal{R}_0$, whereas a negative sensitivity index indicates that a local increase in the corresponding parameter decreases $\mathcal{R}_0$. The negative sensitivity indices associated with the delay parameters indicate that, under the adopted parameter set and the reduced numerical model, increasing these delays decreases $\mathcal{R}_0$.

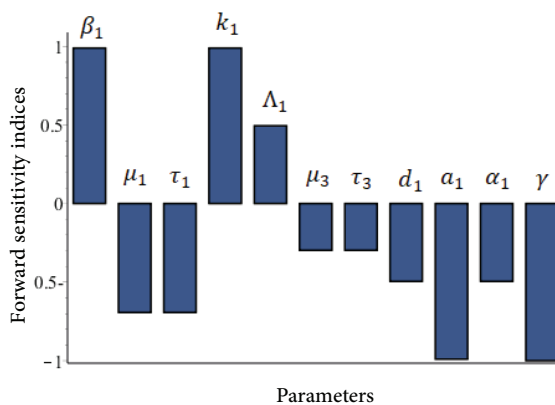
For numerical simulations, we assign $\beta_1 = 0.008$, $\beta_2 = 0.001$, $\tau_1 = 0.7$, $\tau_2 = 0.2$, $\tau_3 = 0.3$, and $\tau_4 = 0.9$. Tables 3 and 4, together with Figure 1, illustrate the sensitivity indices for various model parameters.

Table 3. Positive sensitivity indices of $\mathcal{R}_0$.

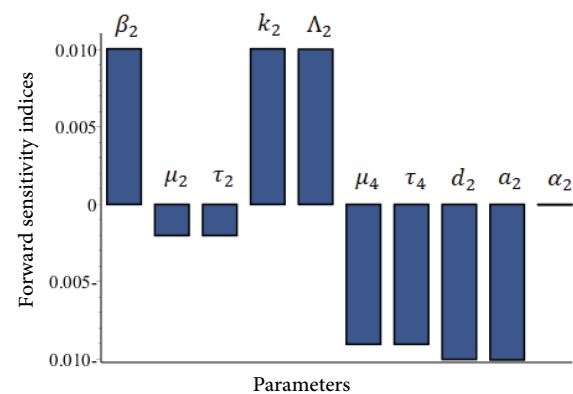
Parameter ϱ	Ξ_{ϱ}	Interpretation
β_1, β_2	0.990, 0.010	A 10% change in the incidence rates involving HCV and both the healthy cells x_1 and x_2 results in approximately a corresponding 9.9% and 0.1% change in $\mathcal{R}_0$, respectively
Λ_1, Λ_2	0.495, 0.010	A 10% change in the production rates of the healthy cells x_1 and x_2 results in approximately a corresponding 4.95% and 0.1% change in $\mathcal{R}_0$, respectively
k_1, k_2	0.990, 0.010	A 10% change in the production rates of free virus from HCV-infected cells y_1 and y_2 results in approximately a corresponding 9.9% and 0.1% change in $\mathcal{R}_0$, respectively

Table 4. Negative sensitivity indices of $\mathcal{R}_0$.

Parameter ϱ	Ξ_{ϱ}	Interpretation
$d_1, d_2, a_1, a_2, \gamma$	$-0.495, -0.010, -0.990, -0.010, -1$	A 10% increase in the death rates of x_1, x_2, y_1, y_2 and of the free virus v leads to a decrease in $\mathcal{R}_0$ by 4.95%, 0.1%, 9.90%, 0.1%, and 10%, respectively
α_1, α_2	$-0.495, -0.00003$	A 10% increase in the saturation coefficients for healthy cells x_1 and x_2 leads to a decrease in $\mathcal{R}_0$ by 4.95% and 0.0003%, respectively
$\tau_1, \tau_2, \tau_3, \tau_4$	$-0.693, -0.0020, -0.297, -0.0090$	A 10% increase in the time delay parameters τ_1, τ_2, τ_3 , and τ_4 leads to a decrease in $\mathcal{R}_0$ by 6.93%, 0.020%, 2.97% and 0.090%, respectively
$\mu_1, \mu_2, \mu_3, \mu_4$	$-0.693, -0.0020, -0.297, -0.0090$	A 10% increase in the parameters μ_1, μ_2, μ_3 , and μ_4 leads to a decrease in $\mathcal{R}_0$ by 6.93%, 0.020%, 2.97% and 0.090%, respectively



(a)



(b)

Figure 1. Forward sensitivity analysis for $\mathcal{R}_0$.

4.2. Stability of the equilibria

Assume that $\tau_1 = \tau_2 = \tau_3 = \tau_4 = \tau_c$, and choose the initial conditions as:

IC1: $\phi_1(\theta) = 700$, $\phi_2(\theta) = 20$, $\phi_3(\theta) = 15$, $\phi_4(\theta) = 0.0005$, $\phi_5(\theta) = 15$ and $\phi_6(\theta) = 1.5$,

IC2: $\phi_1(\theta) = 500$, $\phi_2(\theta) = 15$, $\phi_3(\theta) = 10$, $\phi_4(\theta) = 0.001$, $\phi_5(\theta) = 12$ and $\phi_6(\theta) = 1$,

IC3: $\phi_1(\theta) = 300$, $\phi_2(\theta) = 5$, $\phi_3(\theta) = 1$, $\phi_4(\theta) = 0.3$, $\phi_5(\theta) = 8$ and $\phi_6(\theta) = 0.5$, where $\theta \in [-\max\{\tau_1, \tau_2, \tau_3, \tau_4\}, 0]$.

Case I: Stability of the steady states:

Let $\tau_1 = \tau_2 = \tau_3 = \tau_4 = \tau_c = 0.7$. We have three subcases as follows:

(a) $\beta_1 = 2.3 \times 10^{-4}$ and $\beta_2 = 2 \times 10^{-4}$, then $\mathcal{R}_0 = 0.0847 < 1$. It follows that Π_0 is globally asymptotically stable. In this case, the HCV will be eliminated (Figure 2).

(b) $\beta_1 = 0.008$ and $\beta_2 = 0.001$ then $\mathcal{R}_0 = 2.5893 > 1$ and $\mathcal{R}_c = 0.6182 < 1$. Therefore, $\Pi^* = (103.58, 14.84, 13.46, 0.685, 12.62, 0)$ exists and is globally asymptotically stable. In this situation, the infection will be chronic (Figure 3).

(c) $\beta_1 = 0.008$ and $\beta_2 = 0.001$ and $q = 0.25$ then $\mathcal{R}_0 = 2.5893 > 1$ and $\mathcal{R}_c = 5.18 > 1$. Therefore, $\tilde{\Pi} = (121.43, 12.45, 14.72, 0.632, 10.62, 1.26)$ exists and is globally asymptotically stable (Figure 4).

Case II: Effect of h on the HCV dynamics:

In this case, we fix $\beta_1 = 0.008$ and $\beta_2 = 0.001$, $q = 0.25$ and $\tau_c = 0.5$ with a new set of initial conditions as $(120, 20, 15, 2, 10, 1)$, and then $\mathcal{R}_0 = 3.8628 > 1$. As h increases the infection increase and CTL immune response (Figure 5).

Case III: Effect of τ_c on the HCV dynamics:

In this case, we fix the infection rate constants as $\beta_1 = 0.002$ and $\beta_2 = 0.001$ and we consider the first set of initial conditions. Figure 6 shows that the stability of the steady states have been changed by changing the values of the delay parameter τ_c . Using the values of the parameters given in Table 1 we have if $\tau_c \leq 0.51625$, then $\mathcal{R} \leq 1$ and then Π_0 is globally asymptotically stable.

As a final step, we illustrate the global dynamics of the system's Eqs (2.1)–(2.6) using three-dimensional phase portraits. In these simulations, the distributed delays are preserved. Here, $f_i(\sigma) = 1/\tau_i$ is adopted in the simulations, and the parameter values are the same as those used in Case I(c).

The phase portraits are presented in Figure 7. In all cases of the initial conditions, the trajectories remain bounded and converge to a unique equilibrium, indicating global asymptotic stability. In particular, when $\mathcal{R}_0 > 1$ and $\mathcal{R}_c > 1$, the solutions approach the endemic equilibrium $\tilde{\Pi}$. These numerical findings are consistent with the theoretical analysis and support Theorems 1 and 2.

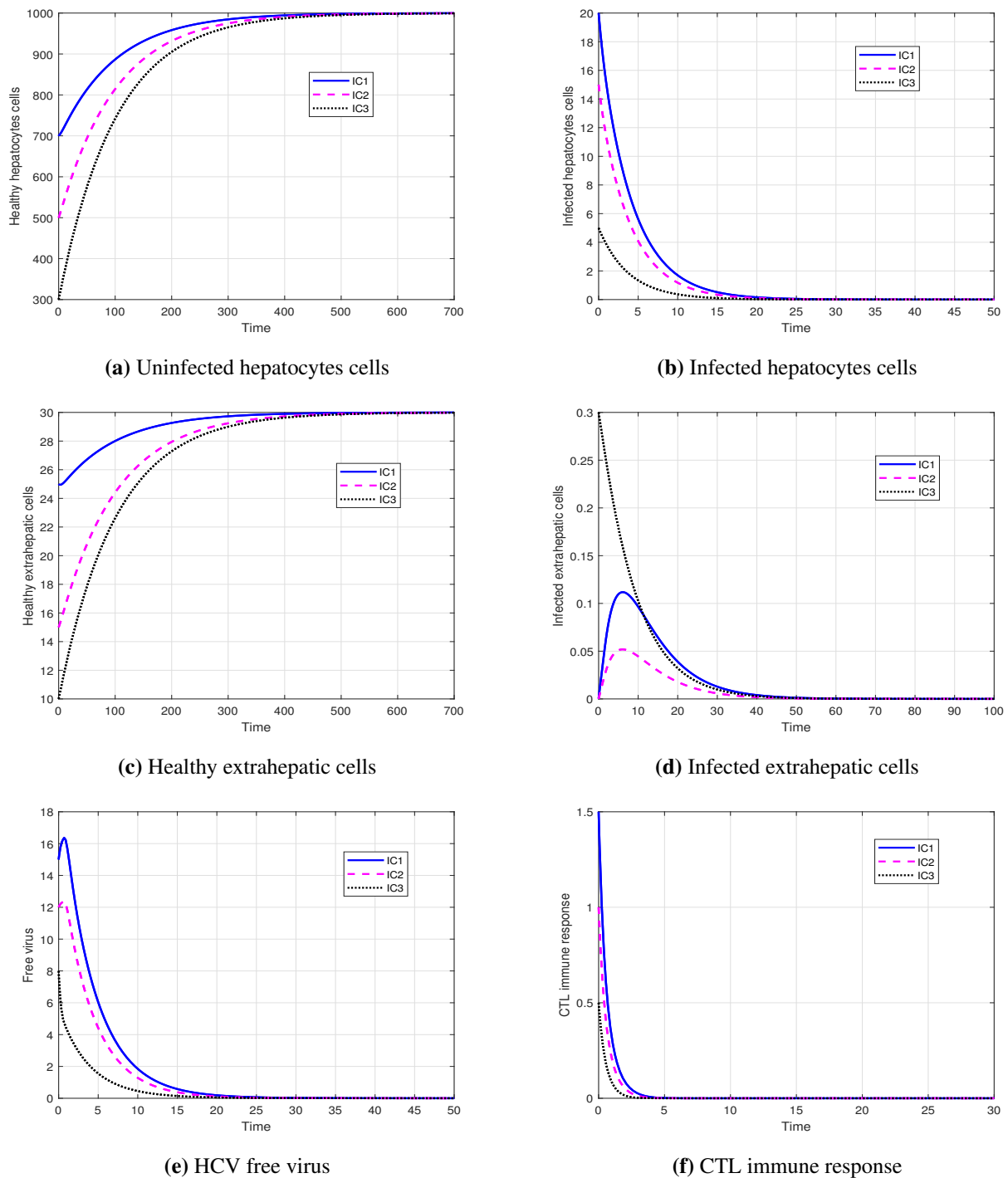


Figure 2. The system's Eqs (2.1)–(2.6) trajectories, showing the temporal dynamics of healthy and infected hepatocytes and extrahepatic cells, free HCV virus, and the CTL immune response for three different initial conditions for $\beta_1 = 0.00023$ and $\beta_2 = 0.0002$, $\mathcal{R}_0 = 0.03 < 1$. All solutions converge to the infection free equilibrium $\Pi_0 = (1000, 0, 30, 0, 0, 0)$, confirming its global asymptotic stability (G.A.S.).

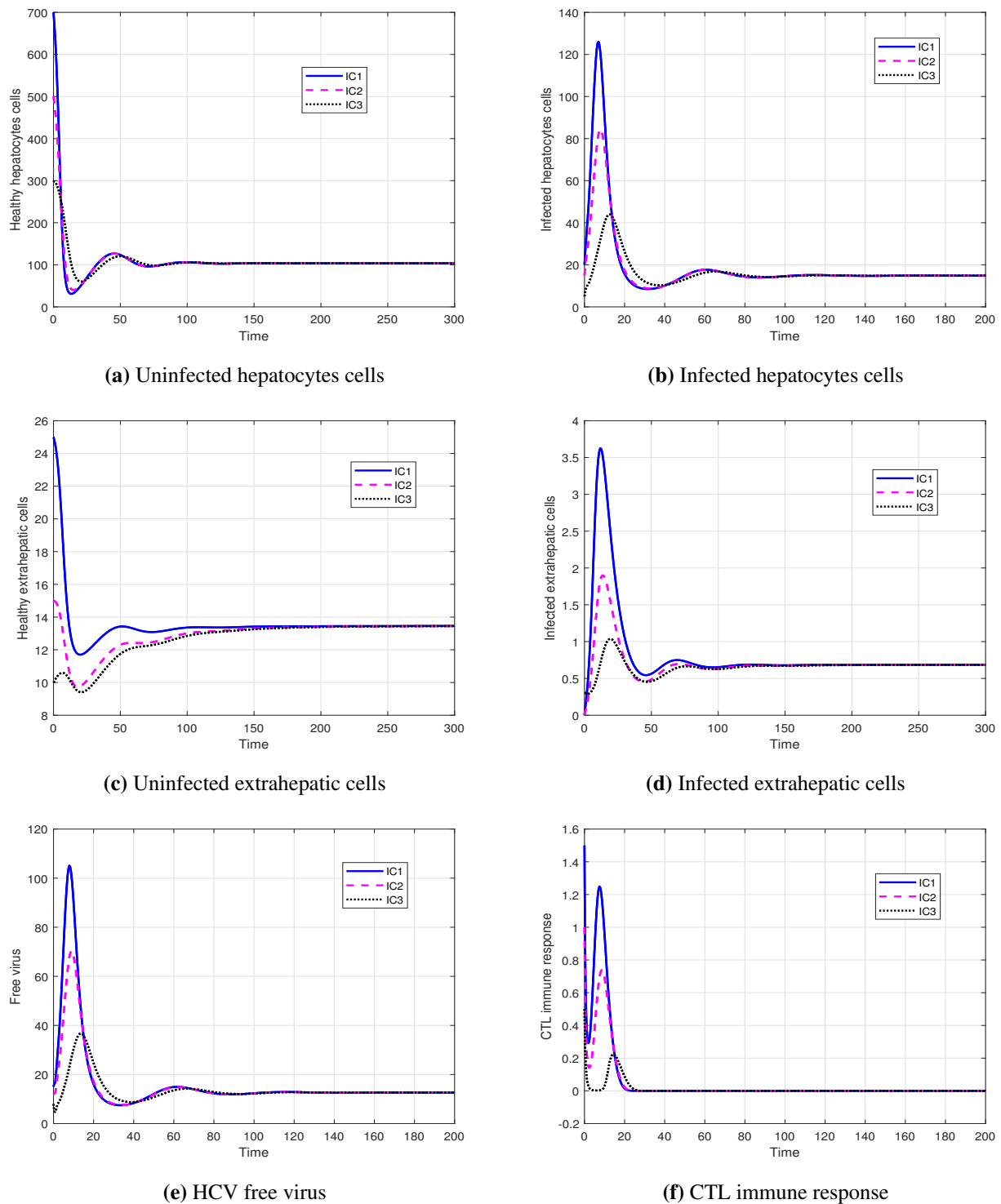


Figure 3. The system's Eqs (2.1)–(2.6) trajectories, showing the temporal dynamics of healthy and infected hepatocytes and extrahepatic cells, free HCV virus, and the CTL immune response for three initial conditions and for $\beta_1 = 0.008$, $\beta_2 = 0.001$, and $\mathcal{R}_C < 1 < \mathcal{R}_0$. All solutions converge to the endemic equilibrium without immunity $\Pi^* = (103.58, 14.84, 13.46, 0.685, 12.62, 0)$, confirming its global asymptotic stability (G.A.S.).

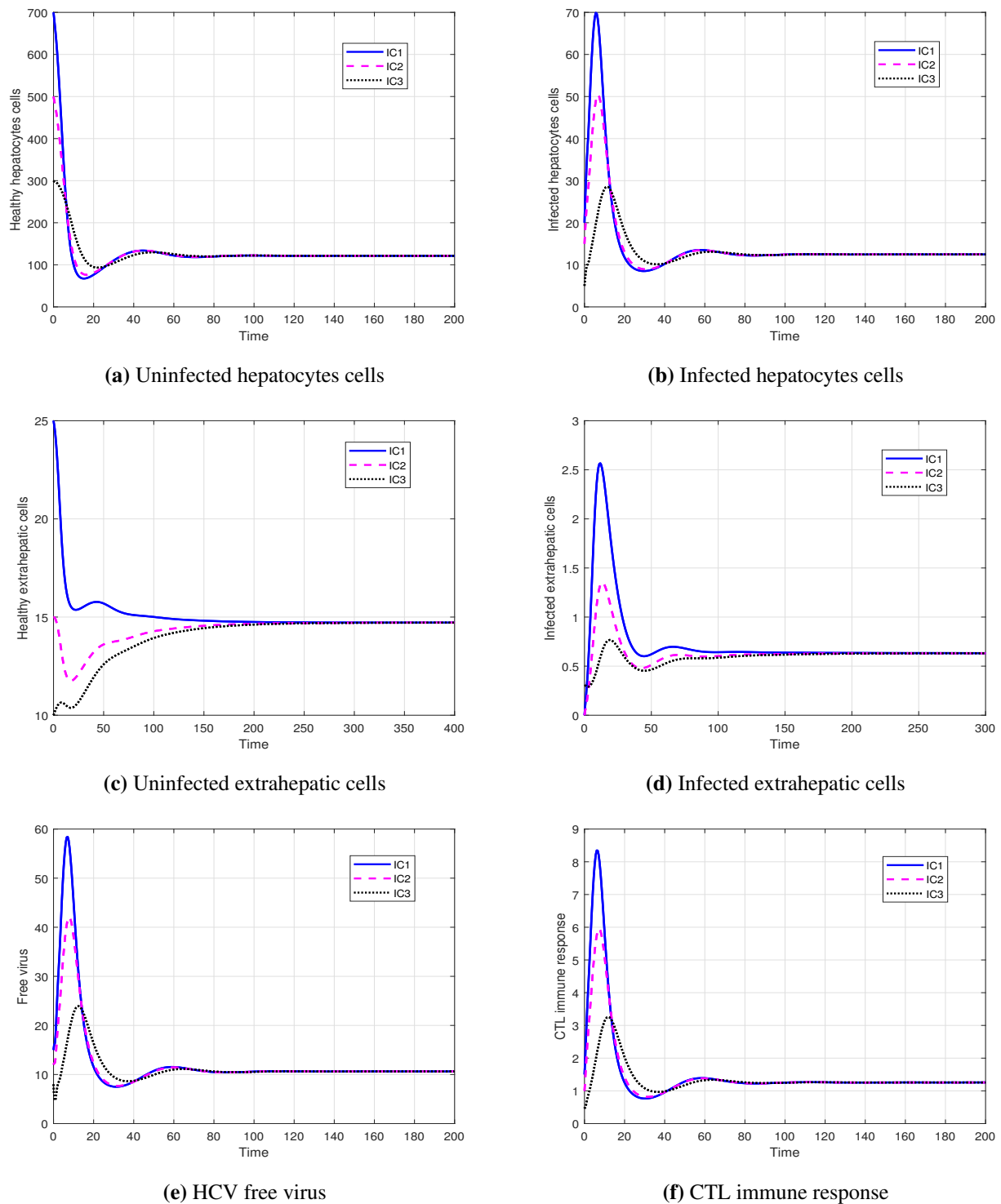
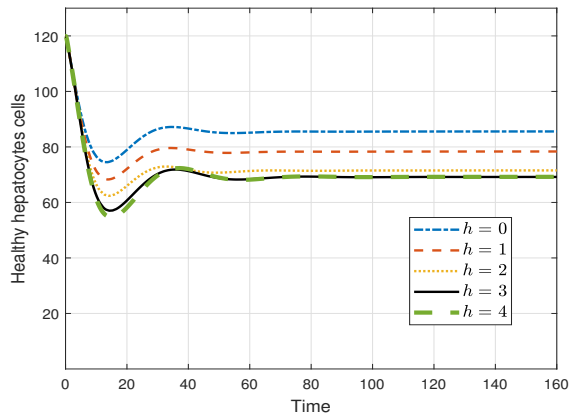
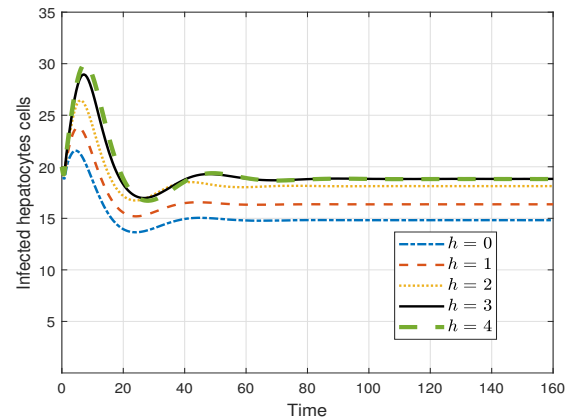


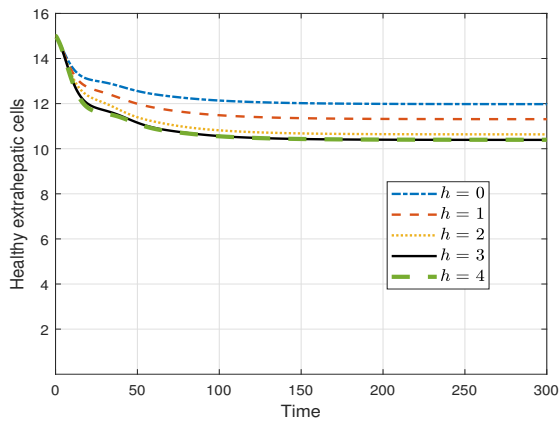
Figure 4. The system's Eqs (2.1)–(2.6) trajectories, showing the temporal dynamics of healthy and infected hepatocytes and extrahepatic cells, free HCV virus, and the CTL immune response for three initial conditions for $\beta_1 = 0.008$, $\beta_2 = 0.001$, and $\mathcal{R}_C > 1$. All solutions converge to $\tilde{\Pi} = (121.43, 12.45, 14.72, 0.632, 10.62, 1.26)$, confirming its global asymptotic stability (G.A.S.).



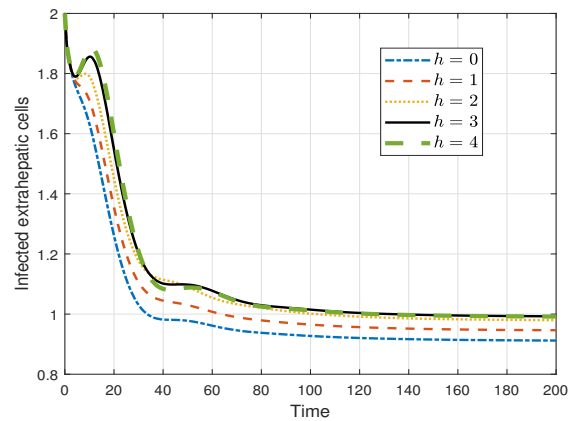
(a) Uninfected hepatocytes cells



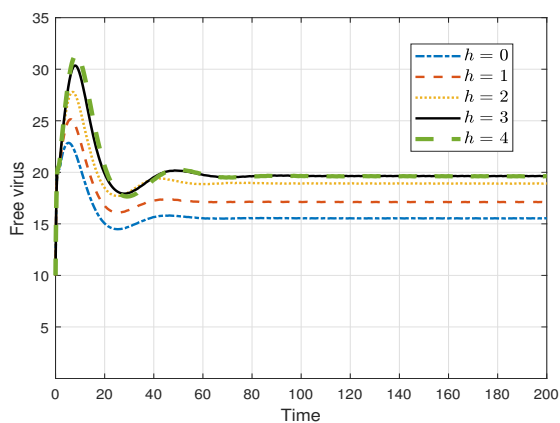
(b) Infected hepatocytes cells



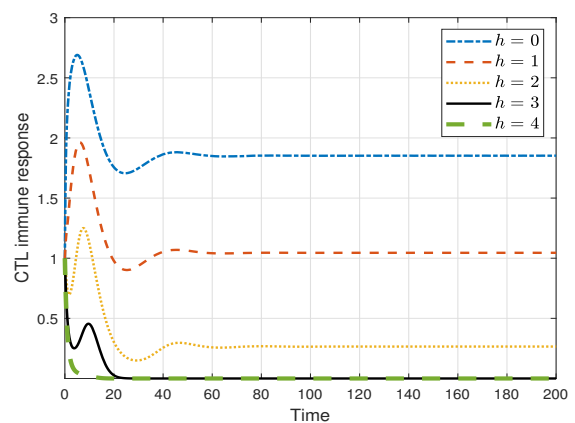
(c) Uninfected extrahepatic cells



(d) Infected extrahepatic cells

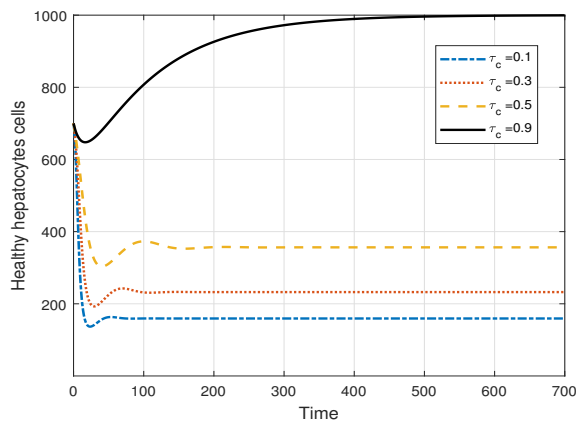


(e) HCV free virus

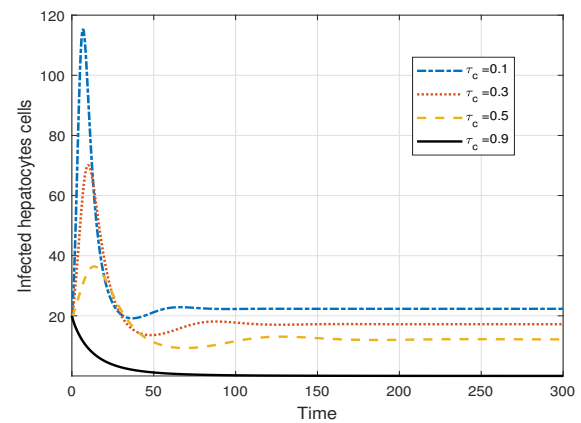


(f) CTL immune response

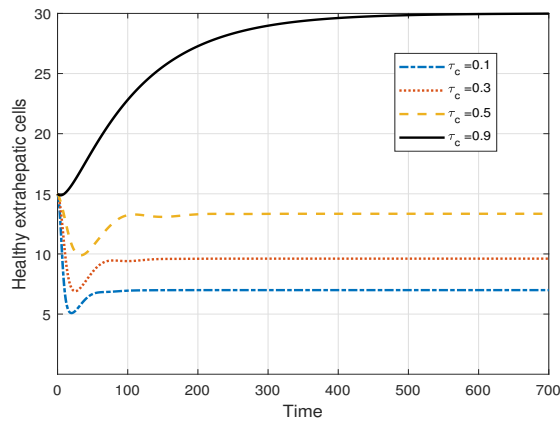
Figure 5. For $\beta_1 = 0.008$, and $\beta_2 = 0.001$, the system Eqs (2.1)–(2.6) trajectories, showing the temporal dynamics of healthy and infected hepatocytes and extrahepatic cells, free HCV virus, and the CTL immune response with different values of h .



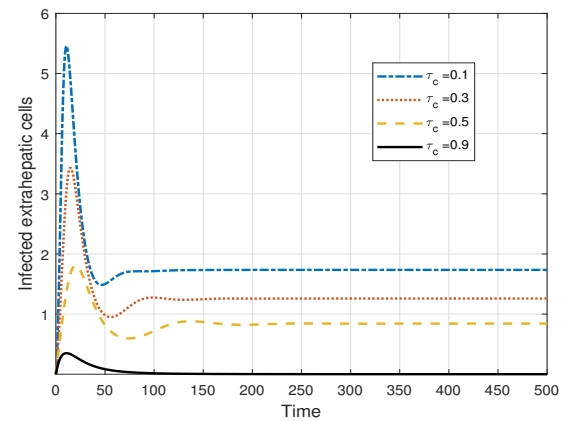
(a) Uninfected hepatocytes cells



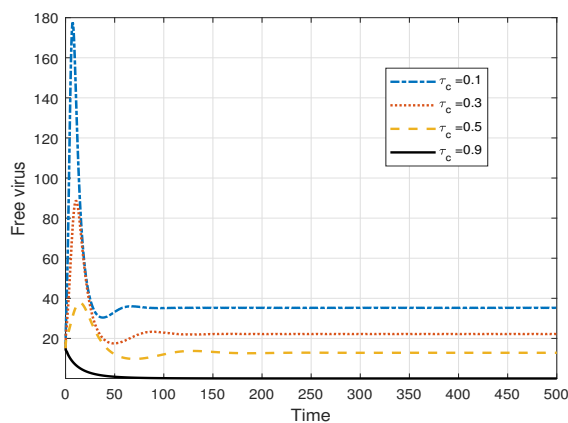
(b) Infected hepatocytes cells



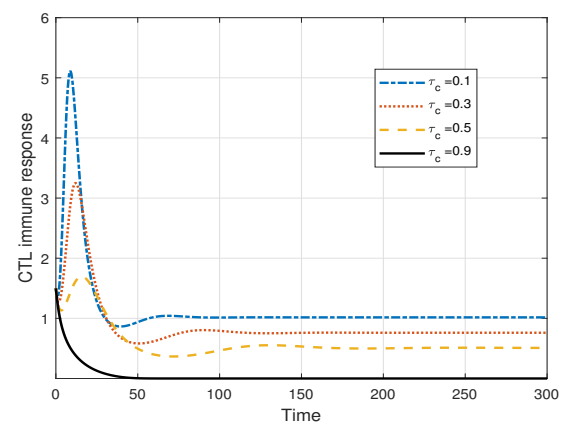
(c) Uninfected extrahepatic cells



(d) Infected extrahepatic cells



(e) HCV free virus



(f) CTL immune response

Figure 6. For $\beta_1 = 0.002$, and $\beta_2 = 0.001$, the system Eqs (2.1)–(2.6) trajectories, showing the temporal dynamics of healthy and infected hepatocytes and extrahepatic cells, free HCV virus, and the CTL immune response with different values of time delay parameter τ_c .

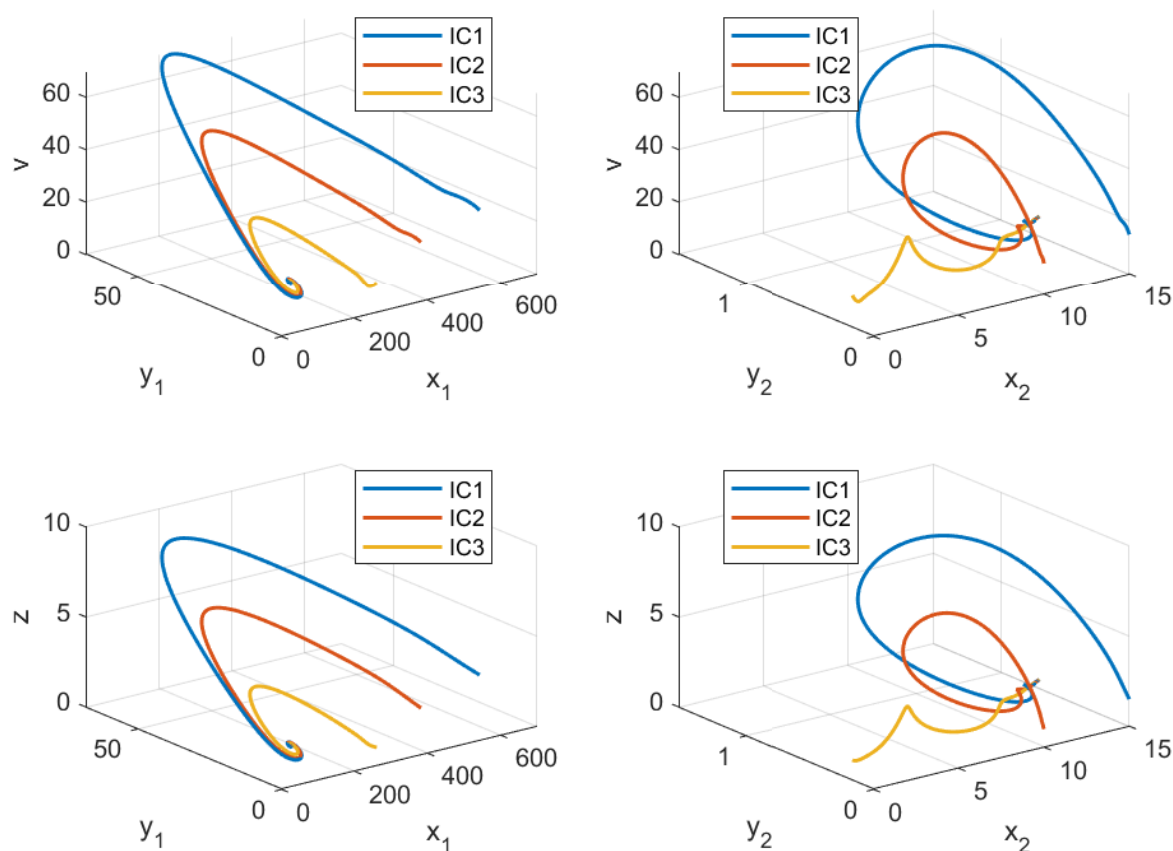


Figure 7. Global stability: Phase portraits of system in Eqs (2.1)–(2.6) are plotted taking different initial conditions. Parameter values are same as used in Case I(c).

5. Conclusions and future work

In this paper, a delayed HCV infection model in the liver and extrahepatic tissue is developed by incorporating Beddington–DeAngelis transmission instead of saturated transmission, together with a saturated immune response. We prove that the solutions of the proposed model are bounded and establish the existence of three possible equilibrium points depending on the threshold parameters $\mathcal{R}_0$ and $\mathcal{R}_C$. Using the Lyapunov direct method and LaSalle’s invariance principle, we prove that these threshold parameters govern the global dynamics of the model. Specifically, when $\mathcal{R}_0 < 1$, the infection-free equilibrium is globally asymptotically stable; when $\mathcal{R}_0 > 1$ and $\mathcal{R}_C < 1$, the endemic equilibrium without immunity is globally asymptotically stable; and when $\mathcal{R}_C > 1$, the endemic equilibrium with immunity is globally asymptotically stable. Numerical simulations are conducted to verify the theoretical results and investigate the effects of the time delay on the model solutions and the overall system dynamics. Moreover, sensitivity analysis shows that the HCV transmission rate β_1 and the viral production rate k_1 are among the most influential parameters, with sensitivity indices of 0.990, indicating that interventions that reduce HCV transmission and viral production

can substantially decrease $\mathcal{R}_0$. The results therefore highlight the importance of strengthening HCV prevention measures, including reducing exposure to infectious sources and improving early detection and treatment. In addition, parameters associated with the host immune response indicate that enhancing the effectiveness of the CTL-mediated immune response may contribute to improved control of HCV infection. These findings provide a practical interpretation of the mathematical results and suggest that combining strategies to reduce HCV transmission with approaches that promote effective antiviral immune responses may be important for achieving sustained HCV prevention and control.

Even though the inclusion of distributed delays enables the model to account for biological processes that require a nonzero time interval, the saturated immune response reflects the limited capacity of CTL-mediated immune activity. The corresponding immune threshold further determines whether a sustained CTL response can be established. Additionally, numerical simulations illustrate the biological consequences of these threshold conditions, including viral clearance and persistence as well as the role of immune-mediated control. The sensitivity analysis further indicates that parameters associated with viral transmission and production can have a substantial influence on $\mathcal{R}_0$. These findings suggest that reducing effective viral transmission and production may be important for controlling HCV infection. Thus, the model provides a theoretical framework for examining the interaction between delayed viral dynamics and immune-mediated control.

Despite these results, the model is deterministic and does not explicitly account for environmental fluctuations or biological uncertainty. An important direction for future research is therefore to incorporate stochastic environmental effects into the proposed HCV model. In particular, stochastic perturbations driven by Brownian motion or an Ornstein–Uhlenbeck process could be introduced to represent temporal fluctuations in transmission, viral production, and immune-response parameters. Such an extension would enable an investigation of the effects of environmental noise on infection persistence or extinction, threshold dynamics, and the stability of the infection-free and endemic states. Moreover, studies on stochastic epidemic models have shown that environmental fluctuations may significantly alter disease-transmission dynamics [28–33]. Therefore in future work, we will focus on developing a stochastic delayed HCV model and determine how environmental noise interacts with time delays and the saturated CTL immune response, thereby providing a more realistic framework for understanding HCV dynamics under fluctuating biological conditions.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Author contributions

Shaimaa A. Azoz: Conceptualization, model formulation, mathematical analysis, numerical simulations, writing the original draft, and manuscript editing. Aeshah A. Raezah: Methodology, numerical simulations, validation, and interpretation of results, supervision, and critical revision of the manuscript. All authors have read and approved the final version of the manuscript.

Conflict of interest

The authors declare there is no conflict of interest.

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