A generalized distributed delay model for HBV infection with two modes of transmission and adaptive immunity: A mathematical study

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Abstract

In this paper, we formulate a generalized hepatitis B virus (HBV) infection model with two modes of infection transmission and adaptive immunity, and investigate its dynamical properties. Both the virus-to-cell and cell-to-cell infection transmissions are modeled by general functions which satisfy some biologically motivated assumptions. Furthermore, the model incorporates three distributed time delays for the production of active infected hepatocytes, mature capsids and virions. The well-posedness of the proposed model is established by showing the non-negativity and boundedness of solutions. Five equilibria of the model are identified in terms of five threshold parameters R_0, R_1, R_2, R_3 and R_4. Further, the global stability analysis of each equilibrium under certain conditions is carried out by employing suitable Lyapunov function and LaSalle's invariance principle. Finally, we present an example with numerical simulations to illustrate the applicability of our study. Nonetheless, the results obtained in this study are valid for a wide class of HBV infection models.

Keywords: HBV infection; General incidence function; Adaptive immunity; Distributed delay; Global stability; Lyapunov function

1 Introduction

Hepatitis B is a dangerous viral infection caused by the hepatitis B virus (HBV) that attacks and injures liver cells called hepatocytes. It can cause both the acute and chronic illness, and it also represents a major global health problem during the last few years. For instance, the World Health Organization (WHO) estimated that 296 million people were living with chronic hepatitis B infection, and 820 000 people died in 2019 mainly due to cirrhosis and hepatocellular carcinoma (primary liver cancer) [1]. Chronic hepatitis B infection can be treated with medicines including oral antiviral agents. However, there is no specific treatment for acute hepatitis B.

Adaptive immunity plays a substantial role in the defense against HBV infection by using two fundamental arms, which are humoral and cellular immune responses [2, 3]. The first one is based on the antibodies that are produced by the B-cells and they are programmed to neutralize the HBV [2, 3]. Whereas, the second arm is mediated by cytotoxic T lymphocyte (CTL) cells in order to kill the infected hepatocytes [2, 3].

Modeling the role of adaptive immunity in HBV infection has attracted the attention of many researchers. One of the first models was introduced in [2] to explain mathematically the dysfunction of the adaptive immune response in patients infected with HBV, which was observed by Boni et al. [4] in 2007. Hattaf et al. [5, 6] extended the model of [2] in order to

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describe the dynamics of other viral infections such as human immunodeficiency virus (HIV) that often causes acquired immunodeficiency syndrome (AIDS). More recently, Manna and Hattaf [3] proposed an immunological model that incorporates the intracellular HBV DNA-containing capsids, three delays, adaptive immunity and general incidence rate that covers the bilinear incidence rate, the standard incidence, the Beddington-DeAngelis functional response, the Crowley-Martin functional response and the Hattaf-Yousfi functional response.

On the other hand, HBV infection in liver can spread via two different modes, one by virus-to-cell transmission and the other by cell-to-cell transmission through direct contact [7, 8, 9]. However, most of the mathematical models considered only the first classical mode of transmission of HBV [2, 10, 11, 12]. Furthermore, an experimental study in [13] showed that the direct cell-to-cell transmission can contributes to the viral persistence. Based on these biological reasons, Hattaf [14] proposed a class of immunological models with both modes of transmission but he did not consider the HBV DNA-containing capsids. However, both these components of HBV infection have been considered in [15], but the first arm of immunity mediated by antibodies was neglected. This paper aims to develop a generalized mathematical model that better describes the dynamics of HBV infection in presence of capsids, both arms of adaptive immunity, two modes of transmission, and three distributed delays.

Primary goal of this study is to provide dynamical properties of the generalized HBV infection model which is an amalgamation of several commonly used specific models. The organization of the rest of this paper is as follows. We introduce our generalized HBV infection model incorporating both modes of infection transmission and multiple distributed delays in the next section with a brief description. In Section 3, we establish the non-negativity and boundedness of solutions as well as the existence of possible equilibria depending upon the conditions in terms of threshold parameters. Global stability of all equilibria and associated conditions are obtained in Section 4. Further, in Section 5, we present an appropriate application of our study with numerical simulations. Finally, we end this paper with brief concluding remarks.

2 Model formulation

In this section, we propose and describe a generalized HBV infection model with two modes of infection transmission process (that is, virus-to-cell and cell-to-cell infection processes), adaptive immunity (that is, antibody B cell and CTL mediated immune responses), and multiple distributed delays. Our generalized model is the following system comprising of six delay differential equations:

$$
\begin{aligned}
\frac{dH}{dt} &= s - \mu H(t) - f\big(H(t), I(t), V(t)\big)V(t) - g\big(H(t), I(t)\big)I(t), \\
\frac{dI}{dt} &= \int_0^\infty f_1(\tau)e^{-\alpha_1\tau}\big[f\big(H(t-\tau), I(t-\tau), V(t-\tau)\big)V(t-\tau) + \\
&\quad g\big(H(t-\tau), I(t-\tau)\big)I(t-\tau)\big]d\tau - \delta I(t) - pI(t)Z(t), \\
\frac{dD}{dt} &= \kappa \int_0^\infty f_2(\tau)e^{-\alpha_2\tau}I(t-\tau)d\tau - (\beta + \delta)D(t), \quad\quad (1) \\
\frac{dV}{dt} &= \beta \int_0^\infty f_3(\tau)e^{-\alpha_3\tau}D(t-\tau)d\tau - \nu V(t) - qV(t)W(t), \\
\frac{dW}{dt} &= aV(t)W(t) - \sigma W(t), \\
\frac{dZ}{dt} &= bI(t)Z(t) - \eta Z(t),
\end{aligned}
$$

where $H(t)$, $I(t)$, $D(t)$, $V(t)$, $W(t)$ and $Z(t)$ are the densities of the uninfected hepatocytes, infected hepatocytes, capsids, virions, antibodies and CTL cells at time t, respectively. The parameters s and μ represent the constant production and natural death rates of the uninfected hepatocytes, respectively. The infected hepatocytes are assumed to die naturally at a rate δ and to get neutralized by CTL immune responses at a rate p. On the other hand, capsids replicate at a rate κ and get converted to virions at a rate β. The effective decay rate of capsids is thus represented by $(\beta + \delta)$. The natural and antibody-induced death rates of virions are denoted by ν and q, respectively. Both the antibody and CTL immune responses are respectively activated at rates a and b, while the parameters σ and η stand for the respective decay rates. In model (1), both the virus-to-cell and cell-to-cell infection processes in their general forms are characterized by the terms $f(H,I,V)V$ and $g(H,I)I$, respectively. In this case, the incidence functions $f(H,I,V)$ and $g(H,I)$ for both these modes of infection are assumed to be continuously differentiable and to satisfy the following biologically feasible hypotheses [3, 15, 16, 17]:

(A_1) $f(0,I,V) = 0$ for all $I \geq 0$ and $V \geq 0$.

(A_2) $f(H,I,V)$ is a strictly increasing function with respect to H for fixed $I \geq 0$ and $V \geq 0$ (i.e., $\frac{\partial f}{\partial H} > 0$).

(A_3) $f(H,I,V)$ is a monotone decreasing function with respect to I and V (i.e, $\frac{\partial f}{\partial I} \leq 0$ and $\frac{\partial f}{\partial V} \leq 0$).

(A_4) $g(0,I) = 0$ for all $I \geq 0$; $\frac{\partial g}{\partial H} > 0$ and $\frac{\partial g}{\partial I} \leq 0$ for all $H, I \geq 0$.

We can explain the above hypotheses within the periphery of biology as follows. The first hypothesis (A_1) indicates that the incidence rate for the virus-to-cell infection transmission becomes zero in the absence of uninfected hepatocytes. The next two hypotheses (A_2) and (A_3) mean that the incidence rate for this mode of transmission increases with the increasing density of uninfected hepatocytes, while it decreases with the increasing densities of both the infected hepatocytes and virions. Similarly, the last hypothesis (A_4) indicates that the incidence rate for the cell-to-cell infection transmission becomes zero in the absence of uninfected hepatocytes, becomes increasing with the increasing density of uninfected hepatocytes, and decreases with the increasing density of infected hepatocytes. Overall, the higher density of uninfected hepatocytes puts the infection process in fast-track, however, the higher densities of infected hepatocytes and/or virions cause to decline the infection rate. It should be noted that several commonly used incidence rates in the literature follow the above-mentioned hypotheses. We will exhibit one such example in Section 5.

In model (1), the term $\int_0^\infty f_1(\tau_1)e^{-\alpha_1\tau_1}\big[f\big(H(t-\tau_1),I(t-\tau_1),V(t-\tau_1)\big)V(t-\tau_1) + g\big(H(t-\tau_1),I(t-\tau_1)\big)I(t-\tau_1)\big]d\tau_1$ describes the newly activated infected hepatocytes at time t which are infected through at least one of the two modes of transmission τ_1 time ago [15]. In this case, $e^{-\alpha_1\tau_1}$ represents the survival rate of latently infected hepatocytes during time period $[t-\tau_1,t]$ with a probability distribution $f_1(\tau_1)$. Similarly, the terms $\kappa \int_0^\infty f_2(\tau_2)e^{-\alpha_2\tau_2}I(t-\tau_2)d\tau_2$ and $\beta \int_0^\infty f_3(\tau_3)e^{-\alpha_3\tau_3}D(t-\tau_3)d\tau_3$ respectively account for the mature capsids and virions produced at time t [15]. Here, $e^{-\alpha_2\tau_2}$ and $e^{-\alpha_3\tau_3}$ respectively indicate the survival rates of immature capsids during time period $[t-\tau_2,t]$ and mature capsids during time period $[t-\tau_3,t]$ with corresponding probability distributions $f_2(\tau_2)$ and $f_3(\tau_3)$. Without any loss of generality, we have denoted τ_1, τ_2 and τ_3 by τ in model (1) as they are all integration dummy variables. Also, the probability distributions $f_i(\tau) : [0,\infty) \to [0,\infty)$ are assumed to have compact supports, $f_i(\tau) \geq 0$, and $\int_0^\infty f_i(\tau)d\tau = 1$ for $i = 1, 2, 3$.

The model (1) is supplemented with the following non-negative initial conditions:

$$H(\theta) = \phi_1(\theta) \geq 0, \ I(\theta) = \phi_2(\theta) \geq 0, \ D(\theta) = \phi_3(\theta) \geq 0, \ V(\theta) = \phi_4(\theta) \geq 0,$$

$$W(\theta) = \phi_5(\theta) \geq 0, \ Z(\theta) = \phi_6(\theta) \geq 0, \ \text{for } \theta \in (-\infty, 0]. \tag{2}$$

Now, we define the Banach space of fading memory type as follows [18, 19, 20]:

$$\mathcal{C} := \left\{ \varphi \in C((-\infty, 0], \mathbb{R}) | \varphi(\theta) e^{r\theta} \text{ is uniformly continuous for } \theta \in (-\infty, 0] \text{ and } \|\varphi\| < \infty \right\},$$

where the norm $\|\varphi\| = \sup_{\theta \leq 0} |\varphi(\theta)| e^{r\theta}$ with r being a positive constant. The corresponding non-negative cone of $\mathcal{C}$ is defined by $\mathcal{C}_+ = \mathcal{C}((-\infty, 0], \mathbb{R}_+)$. We also define $\varphi_t \in \mathcal{C}_+$ as $\varphi_t(\theta) = \varphi(t + \theta)$ for $\theta \in (-\infty, 0]$ and $\varphi \in \mathcal{C}_+$. In this case, the initial conditions for model (1), $\phi = (\phi_1, \phi_2, \phi_3, \phi_4, \phi_5, \phi_6) \in \mathcal{C}_+^6 := \mathcal{C}_+ \times \mathcal{C}_+ \times \mathcal{C}_+ \times \mathcal{C}_+ \times \mathcal{C}_+ \times \mathcal{C}_+$. All the model parameters are assumed to be positive from their biological considerations.

3   Preliminaries

The model (1) along with an initial condition of the type (2) admits a unique solution for $t > 0$ and it can be easily proved by the standard theory of functional differential equations [20, 21]. In what follows, we prove the non-negativity and boundedness of solutions of the system (1)-(2). Further, we find the possible biologically feasible equilibria of the model (1) and their existential criteria.

Theorem 3.1. *All solutions of the model (1) along with initial conditions (2) are non-negative and ultimately uniformly bounded for $t \geq 0$.*

Proof. First, we show that $H(t) > 0$ for all $t \geq 0$ by the method of contradiction. Let us consider $H(t_1) = 0$ for some $t_1 > 0$ and $H(t) > 0$ for $t \in [0, t_1)$. Then the first equation of the model (1) implies that $\frac{dH(t_1)}{dt} = s > 0$. Thus, $H(t) < 0$ for $t \in (t_1 - \varepsilon, t_1)$ with sufficiently small $\varepsilon > 0$. This contradicts the fact that $H(t) > 0$ for $t \in [0, t_1)$, and it follows that $H(t) > 0$ for all $t \geq 0$. Also from the last two equations of the model (1), we have $\frac{dW}{dt}\big|_{W=0} = 0$ and $\frac{dZ}{dt}\big|_{Z=0} = 0$. This implies that $W(t) \geq 0$ and $Z(t) \geq 0$ for all $t \geq 0$. From the remaining three equations of the model (1), we obtain

$$
\begin{aligned}
I(t) &= \phi_2(0) e^{-\int_0^t (\delta + pZ(\xi)) d\xi} + \int_0^t e^{-\int_\zeta^t (\delta + pZ(\xi)) d\xi} \int_0^\infty f_1(\tau) e^{-\alpha_1 \tau} \\
&\quad \left[f\big(H(\zeta - \tau), I(\zeta - \tau), V(\zeta - \tau)\big) V(\zeta - \tau) + g\big(H(\zeta - \tau), I(\zeta - \tau)\big) I(\zeta - \tau) \right] d\tau d\zeta, \\
D(t) &= \left[\phi_3(0) + \kappa \int_0^t e^{(\beta + \delta)\zeta} \int_0^\infty f_2(\tau) e^{-\alpha_2 \tau} I(\zeta - \tau) d\tau d\zeta \right] e^{-(\beta + \delta)t}, \\
V(t) &= \phi_4(0) e^{-\int_0^t (\nu + qW(\xi)) d\xi} + \beta \int_0^t e^{-\int_\zeta^t (\nu + qW(\xi)) d\xi} \int_0^\infty f_3(\tau) e^{-\alpha_3 \tau} D(\zeta - \tau) d\tau d\zeta,
\end{aligned}
$$

which imply that $I(t) \geq 0$, $D(t) \geq 0$ and $V(t) \geq 0$ for small $t > 0$. If possible, we assume that $t_2 > 0$ is the first time such that $\min\{I(t_2), D(t_2), V(t_2)\} < 0$. If $I(t_2) < 0$, $I(t) \geq 0$ for $0 \leq t < t_2$, and $D(t) \geq 0$ and $V(t) \geq 0$ for $0 \leq t \leq t_2$, then we obtain

$$
\begin{aligned}
\frac{dI(t_2)}{dt} &= \int_0^\infty f_1(\tau) e^{-\alpha_1 \tau} \left[f\big(H(t_2 - \tau), I(t_2 - \tau), V(t_2 - \tau)\big) V(t_2 - \tau) + \right. \\
&\quad \left. g\big(H(t_2 - \tau), I(t_2 - \tau)\big) I(t_2 - \tau) \right] d\tau - \delta I(t_2) - pI(t_2)Z(t_2) > 0.
\end{aligned}
$$

This contradicts the fact that $I(t_2) < 0$ and $I(t) \geq 0$ for $0 \leq t < t_2$. Also if $D(t_2) < 0$, $D(t) \geq 0$ for $0 \leq t < t_2$, and $I(t) \geq 0$ and $V(t) \geq 0$ for $0 \leq t \leq t_2$, then we have

$$\frac{dD(t_2)}{dt} = \kappa \int_0^\infty f_2(\tau) e^{-\alpha_2 \tau} I(t_2 - \tau) d\tau - (\beta + \delta)D(t_2) > 0,$$

which amounts to another contradiction. Finally, if $V(t_2) < 0$, $V(t) \geq 0$ for $0 \leq t < t_2$, and $I(t) \geq 0$ and $D(t) \geq 0$ for $0 \leq t \leq t_2$, then we have

$$\frac{dV(t_2)}{dt} = \beta \int_0^\infty f_3(\tau) e^{-\alpha_3 \tau} D(t_2 - \tau) d\tau - \nu V(t_2) - q V(t_2) W(t_2) > 0,$$

which is again a contradiction. Therefore, we obtain $I(t) \geq 0$, $D(t) \geq 0$ and $V(t) \geq 0$ for all $t \geq 0$.

Now, we prove the boundedness of solutions. From the first equation of the model (1), we obtain $\frac{dH}{dt} \leq s - \mu H(t)$ and this implies $\limsup_{t \to \infty} H(t) \leq \frac{s}{\mu}$. Let us define

$$X(t) = \int_0^\infty f_1(\tau) e^{-\alpha_1 \tau} H(t - \tau) d\tau + I(t) + \frac{p}{b} Z(t).$$

Then, we have

$$\frac{dX}{dt} = s \int_0^\infty f_1(\tau) e^{-\alpha_1 \tau} d\tau - \mu \int_0^\infty f_1(\tau) e^{-\alpha_1 \tau} H(t - \tau) d\tau - \delta I(t) - \frac{p\eta}{b} Z(t)$$

$$\leq s \int_0^\infty f_1(\tau) e^{-\alpha_1 \tau} d\tau - m X(t),$$

where $m = \min\{\mu, \delta, \eta\}$. Hence, it follows that $\limsup_{t \to \infty} X(t) \leq \frac{s}{m} \int_0^\infty f_1(\tau) e^{-\alpha_1 \tau} d\tau :=$ M_1. As a consequence, we obtain $\limsup_{t \to \infty} I(t) \leq M_1$ and $\limsup_{t \to \infty} Z(t) \leq M_1$. Now using the bound for $I(t)$ in the third equation of model (1), we have

$$\frac{dD}{dt} \leq \kappa M_1 \int_0^\infty f_2(\tau) e^{-\alpha_2 \tau} d\tau - (\beta + \delta) D(t).$$

This implies that $\limsup_{t \to \infty} D(t) \leq \frac{\kappa M_1}{(\beta + \delta)} \int_0^\infty f_2(\tau) e^{-\alpha_2 \tau} d\tau := M_2$. Further, we define $Y(t) = V(t) + \frac{q}{a} W(t)$. Thus, we have

$$\frac{dY}{dt} = \beta \int_0^\infty f_3(\tau) e^{-\alpha_3 \tau} D(t - \tau) d\tau - \nu V(t) - \frac{q\sigma}{a} W(t)$$

$$\leq \beta M_2 \int_0^\infty f_3(\tau) e^{-\alpha_3 \tau} d\tau - \nu V(t) - \frac{q\sigma}{a} W(t)$$

$$\leq \beta M_2 \int_0^\infty f_3(\tau) e^{-\alpha_3 \tau} d\tau - n Y(t),$$

where $n = \min\{\nu, \sigma\}$. Hence, it follows that $\limsup_{t \to \infty} Y(t) \leq \frac{\beta M_2}{n} \int_0^\infty f_3(\tau) e^{-\alpha_3 \tau} d\tau :=$ M_3. As a result, we have $\limsup_{t \to \infty} V(t) \leq M_3$ and $\limsup_{t \to \infty} W(t) \leq M_3$. Therefore, $H(t)$, $I(t)$, $D(t)$, $V(t)$, $W(t)$ and $Z(t)$ are ultimately uniformly bounded. $\qquad \square$

Now, we derive all possible equilibria of the model (1). A typical equilibrium point $E = (\widetilde{H}, \widetilde{I}, \widetilde{D}, \widetilde{V}, \widetilde{W}, \widetilde{Z})$ of the model (1) satisfies the following system of algebraic equations:

$$\begin{aligned} s - \mu \widetilde{H} - f(\widetilde{H}, \widetilde{I}, \widetilde{V}) \widetilde{V} - g(\widetilde{H}, \widetilde{I}) \widetilde{I} &= 0, \\ \Gamma_1 [f(\widetilde{H}, \widetilde{I}, \widetilde{V}) \widetilde{V} + g(\widetilde{H}, \widetilde{I}) \widetilde{I}] - \delta \widetilde{I} - p \widetilde{I} \widetilde{Z} &= 0, \\ \kappa \Gamma_2 \widetilde{I} - (\beta + \delta) \widetilde{D} &= 0, \\ \beta \Gamma_3 \widetilde{D} - \nu \widetilde{V} - q \widetilde{V} \widetilde{W} &= 0, \\ a \widetilde{V} \widetilde{W} - \sigma \widetilde{W} &= 0, \\ b \widetilde{I} \widetilde{Z} - \eta \widetilde{Z} &= 0, \end{aligned} \tag{3}$$

where

$$\Gamma_i := \int_0^\infty f_i(\tau)e^{-\alpha_i\tau}d\tau \text{ for } i = 1, 2, 3. \tag{4}$$

We can easily deduce from the above system (3) that the model (1) always admits a unique infection-free equilibrium point $E_0 = (H_0, 0, 0, 0, 0, 0)$ with $H_0 = \frac{s}{\mu}$. This equilibrium point E_0 basically indicates that either an infected individual is completely cured from the HBV infection or an individual without any exposure to the infection. Now, we define the basic reproduction number of the model (1) by

$$R_0 := \frac{\kappa\beta\Gamma_1\Gamma_2\Gamma_3}{\nu\delta(\beta+\delta)}f(H_0, 0, 0) + \frac{\Gamma_1}{\delta}g(H_0, 0). \tag{5}$$

The basic reproduction number, R_0, provides a measure for the average number of secondary infections and it has been represented as a sum of two quantities due to two modes of transmission of the infection process. To be specific, the term $\frac{\kappa\beta\Gamma_1\Gamma_2\Gamma_3}{\nu\delta(\beta+\delta)}f(H_0, 0, 0) := R_0^{(1)}$ represents the basic reproduction number for virus-to-cell transmission and the term $\frac{\Gamma_1}{\delta}g(H_0, 0) := R_0^{(2)}$ represents the same for cell-to-cell transmission.

If we take $\widetilde{W} = 0$ and $\widetilde{Z} = 0$, then we have $\widetilde{I} = \frac{\Gamma_1}{\delta}(s - \mu\widetilde{H})$, $\widetilde{D} = \frac{\kappa\Gamma_1\Gamma_2}{\delta(\beta+\delta)}(s - \mu\widetilde{H})$, $\widetilde{V} = \frac{\kappa\beta\Gamma_1\Gamma_2\Gamma_3}{\nu\delta(\beta+\delta)}(s - \mu\widetilde{H})$ and

$$\kappa\beta\Gamma_1\Gamma_2\Gamma_3 f\left(\widetilde{H}, \frac{\Gamma_1}{\delta}(s - \mu\widetilde{H}), \frac{\kappa\beta\Gamma_1\Gamma_2\Gamma_3}{\nu\delta(\beta+\delta)}(s - \mu\widetilde{H})\right) + \nu(\beta+\delta)\Gamma_1 g\left(\widetilde{H}, \frac{\Gamma_1}{\delta}(s - \mu\widetilde{H})\right)$$
$$= \nu\delta(\beta+\delta).$$

Of course $\widetilde{I}$ is biologically feasible if and only if $\widetilde{I} \geq 0$ and it implies $\widetilde{H} \leq \frac{s}{\mu}$. Let us define a function Φ_1 on the closed interval $[0, s/\mu]$ as follows

$$\begin{aligned}\Phi_1(H) &= \kappa\beta\Gamma_1\Gamma_2\Gamma_3 f\left(H, \frac{\Gamma_1}{\delta}(s - \mu H), \frac{\kappa\beta\Gamma_1\Gamma_2\Gamma_3}{\nu\delta(\beta+\delta)}(s - \mu H)\right) \\ &\quad + \nu(\beta+\delta)\Gamma_1 g\left(H, \frac{\Gamma_1}{\delta}(s - \mu H)\right) - \nu\delta(\beta+\delta).\end{aligned}$$

Then, we obtain $\Phi_1(0) = -\nu\delta(\beta+\delta) < 0$, $\Phi_1\left(\frac{s}{\mu}\right) = \nu\delta(\beta+\delta)(R_0 - 1) > 0$ for $R_0 > 1$, and

$$\begin{aligned}\Phi_1'(H) &= \kappa\beta\Gamma_1\Gamma_2\Gamma_3\left[\frac{\partial f}{\partial H} - \frac{\mu\Gamma_1}{\delta}\frac{\partial f}{\partial I} - \frac{\kappa\beta\mu\Gamma_1\Gamma_2\Gamma_3}{\nu\delta(\beta+\delta)}\frac{\partial f}{\partial V}\right] \\ &\quad + \nu(\beta+\delta)\Gamma_1\left[\frac{\partial g}{\partial H} - \frac{\mu\Gamma_1}{\delta}\frac{\partial g}{\partial I}\right].\end{aligned}$$

Using the hypotheses (A_2)-(A_4), we have $\Phi_1'(H) > 0$ and this implies that Φ_1 is a strictly increasing function of H. Therefore, there exists a unique immune-free equilibrium point $E_1 = (H_1, I_1, D_1, V_1, 0, 0)$ with $H_1 \in \left(0, \frac{s}{\mu}\right)$, $I_1 = \frac{\Gamma_1}{\delta}(s - \mu H_1)$, $D_1 = \frac{\kappa\Gamma_1\Gamma_2}{\delta(\beta+\delta)}(s - \mu H_1)$ and $V_1 = \frac{\kappa\beta\Gamma_1\Gamma_2\Gamma_3}{\nu\delta(\beta+\delta)}(s - \mu H_1)$ whenever $R_0 > 1$. On the other hand, the consideration $R_0 < 1$ leads to $\Phi_1\left(\frac{s}{\mu}\right) < 0$, and hence, the equilibrium point E_1 does not exist in this case.

Further, if we consider $\widetilde{W} \neq 0$ and $\widetilde{Z} = 0$, then we have $\widetilde{V} = \frac{\sigma}{a}$, $\widetilde{I} = \frac{\Gamma_1}{\delta}(s - \mu\widetilde{H})$, $\widetilde{D} = \frac{\kappa\Gamma_1\Gamma_2}{\delta(\beta+\delta)}(s - \mu\widetilde{H})$ and $\widetilde{W} = \frac{a\kappa\beta\Gamma_1\Gamma_2\Gamma_3}{q\delta\sigma(\beta+\delta)}(s - \mu\widetilde{H}) - \frac{\nu}{q}$. Similarly, $\widetilde{W}$ is biologically feasible if and only if $\widetilde{W} \geq 0$ and it implies $\widetilde{H} \leq \frac{s}{\mu} - \frac{\delta\nu\sigma(\beta+\delta)}{a\kappa\beta\mu\Gamma_1\Gamma_2\Gamma_3}$. Also, we obtain

$$\delta\sigma f\left(\widetilde{H}, \frac{\Gamma_1}{\delta}(s - \mu\widetilde{H}), \frac{\sigma}{a}\right) + a\Gamma_1(s - \mu\widetilde{H})g\left(\widetilde{H}, \frac{\Gamma_1}{\delta}(s - \mu\widetilde{H})\right) = a\delta(s - \mu\widetilde{H}).$$

In this case, let us define a function Φ_2 on the closed interval $\left[0, \frac{s}{\mu} - \frac{\delta\nu\sigma(\beta+\delta)}{a\kappa\beta\mu\Gamma_1\Gamma_2\Gamma_3}\right]$ as follows

$$\Phi_2(H) = \delta\sigma f\left(H, \frac{\Gamma_1}{\delta}(s - \mu H), \frac{\sigma}{a}\right) + a\Gamma_1(s - \mu H)g\left(H, \frac{\Gamma_1}{\delta}(s - \mu H)\right) - a\delta(s - \mu H).$$

We can easily observe that $\Phi_2(0) = -a\delta s < 0$ and

$$
\begin{aligned}
\Phi_2'(H) &= \delta\sigma\left[\frac{\partial f}{\partial H} - \frac{\mu\Gamma_1}{\delta}\frac{\partial f}{\partial I}\right] + a\Gamma_1(s - \mu H)\left[\frac{\partial g}{\partial H} - \frac{\mu\Gamma_1}{\delta}\frac{\partial g}{\partial I}\right] \\
&\quad + a\mu\left[\delta - \Gamma_1 g\left(H, \frac{\Gamma_1}{\delta}(s - \mu H)\right)\right].
\end{aligned}
$$

Using the hypotheses (A_1)-(A_4), we have $\Phi_2'(H) > 0$ which implies that Φ_2 is a strictly increasing function of H. Now, we define the reproduction number for antibody immune response by

$$R_1 := \frac{a}{\sigma}V_1, \tag{6}$$

which provides a measure of the average number of antibodies activated by virus when CTL immune response has not been activated [3, 6]. Here, V_1 represents the density of virions at the immune-free equilibrium level, while other parameters a and $\frac{1}{\sigma}$ respectively indicate the activation rate of antibody immune response and the average life expectancy of antibody immune cells. If $R_1 > 1$, then we have $V_1 > \frac{\sigma}{a}$ and $H_1 < \frac{s}{\mu} - \frac{\delta\nu\sigma(\beta+\delta)}{a\kappa\beta\mu\Gamma_1\Gamma_2\Gamma_3}$. Thus, we obtain

$$
\begin{aligned}
\Phi_2\left(\frac{s}{\mu} - \frac{\delta\nu\sigma(\beta+\delta)}{a\kappa\beta\mu\Gamma_1\Gamma_2\Gamma_3}\right) &> \frac{\delta\sigma}{\kappa\beta\Gamma_1\Gamma_2\Gamma_3}\left[\kappa\beta\Gamma_1\Gamma_2\Gamma_3 f(H_1, I_1, V_1) + \nu(\beta+\delta)\Gamma_1 g(H_1, I_1)\right. \\
&\quad \left. - \nu\delta(\beta+\delta)\right] = \frac{\delta\sigma}{\kappa\beta\Gamma_1\Gamma_2\Gamma_3}\Phi_1(H_1) = 0.
\end{aligned}
$$

Therefore, there exists a unique infection equilibrium point with only antibody immune response $E_2 = (H_2, I_2, D_2, V_2, W_2, 0)$ with $H_2 \in \left(0, \frac{s}{\mu} - \frac{\delta\nu\sigma(\beta+\delta)}{a\kappa\beta\mu\Gamma_1\Gamma_2\Gamma_3}\right)$, $I_2 = \frac{\Gamma_1}{\delta}(s - \mu H_2)$, $D_2 = \frac{\kappa\Gamma_1\Gamma_2}{\delta(\beta+\delta)}(s - \mu H_2)$, $V_2 = \frac{\sigma}{a}$ and $W_2 = \frac{a\kappa\beta\Gamma_1\Gamma_2\Gamma_3}{q\delta\sigma(\beta+\delta)}(s - \mu H_2) - \frac{\nu}{q}$ whenever $R_1 > 1$. However, the condition $R_1 < 1$ implies that $V_1 < \frac{\sigma}{a}$ and $H_1 > \frac{s}{\mu} - \frac{\delta\nu\sigma(\beta+\delta)}{a\kappa\beta\mu\Gamma_1\Gamma_2\Gamma_3}$. Hence, we have

$$\Phi_2\left(\frac{s}{\mu} - \frac{\delta\nu\sigma(\beta+\delta)}{a\kappa\beta\mu\Gamma_1\Gamma_2\Gamma_3}\right) < \frac{\delta\sigma}{\kappa\beta\Gamma_1\Gamma_2\Gamma_3}\Phi_1(H_1) = 0.$$

Thus, the equilibrium point E_2 does not exist for $R_1 < 1$.

Now, we consider $\widetilde{W} = 0$ and $\widetilde{Z} \neq 0$. In this case, we obtain $\widetilde{I} = \frac{\eta}{b}$, $\widetilde{D} = \frac{\kappa\eta\Gamma_2}{b(\beta+\delta)}$, $\widetilde{V} = \frac{\kappa\beta\eta\Gamma_2\Gamma_3}{b\nu(\beta+\delta)}$ and $\widetilde{Z} = \frac{b\Gamma_1}{p\eta}(s - \mu\widetilde{H}) - \frac{\delta}{p}$. Since $\widetilde{Z}$ is biologically feasible if and only if $\widetilde{Z} \geq 0$, then we have $\widetilde{H} \leq \frac{s}{\mu} - \frac{\delta\eta}{b\mu\Gamma_1}$. Also, we have

$$\kappa\beta\eta\Gamma_2\Gamma_3 f\left(\widetilde{H}, \frac{\eta}{b}, \frac{\kappa\beta\eta\Gamma_2\Gamma_3}{b\nu(\beta+\delta)}\right) + \eta\nu(\beta+\delta)g\left(\widetilde{H}, \frac{\eta}{b}\right) = b\nu(\beta+\delta)(s - \mu\widetilde{H}).$$

Let us define a function Φ_3 on the closed interval $\left[0, \frac{s}{\mu} - \frac{\delta\eta}{b\mu\Gamma_1}\right]$ as follows

$$\Phi_3(H) = \kappa\beta\eta\Gamma_2\Gamma_3 f\left(H, \frac{\eta}{b}, \frac{\kappa\beta\eta\Gamma_2\Gamma_3}{b\nu(\beta+\delta)}\right) + \eta\nu(\beta+\delta)g\left(H, \frac{\eta}{b}\right) - b\nu(\beta+\delta)(s - \mu H).$$

Then, we can easily obtain that $\Phi_3(0) = -bs\nu(\beta + \delta) < 0$ and

$$\Phi_3'(H) = \kappa\beta\eta\Gamma_2\Gamma_3\frac{\partial f}{\partial H} + \eta\nu(\beta + \delta)\frac{\partial g}{\partial H} + b\mu\nu(\beta + \delta).$$

Using the hypotheses (A_2) and (A_4), we deduce that $\Phi_3'(H) > 0$ which indicates that Φ_3 is a strictly increasing function of H. Now, we define the reproduction number for CTL immune response by

$$R_2 := \frac{b}{\eta}I_1, \tag{7}$$

which provides a measure of the average number of CTL cells stimulated by infected hepatocytes when antibody immune response has not been activated [3, 6]. In this case, I_1 represents the density of infected hepatocytes at the immune-free equilibrium level, while other parameters b and $\frac{1}{\eta}$ respectively describe the activation rate of CTL immune response and the average life expectancy of CTL cells. Now, if $R_2 > 1$, then we have $I_1 > \frac{\eta}{b}$ and $H_1 < \frac{s}{\mu} - \frac{\delta\eta}{b\mu\Gamma_1}$. Thus, we obtain

$$\Phi_3\left(\frac{s}{\mu} - \frac{\delta\eta}{b\mu\Gamma_1}\right) > \frac{\eta}{\Gamma_1}\left[\kappa\beta\Gamma_1\Gamma_2\Gamma_3 f(H_1, I_1, V_1) + \nu(\beta + \delta)\Gamma_1 g(H_1, I_1) - \nu\delta(\beta + \delta)\right]$$

$$= \frac{\eta}{\Gamma_1}\Phi_3(H_1) = 0.$$

Therefore, there exists a unique infection equilibrium point with only CTL immune response $E_3 = (H_3, I_3, D_3, V_3, 0, Z_3)$ with $H_3 \in \left(0, \frac{s}{\mu} - \frac{\delta\eta}{b\mu\Gamma_1}\right)$, $I_3 = \frac{\eta}{b}$, $D_3 = \frac{\kappa\eta\Gamma_2}{b(\beta+\delta)}$, $V_3 = \frac{\kappa\beta\eta\Gamma_2\Gamma_3}{b\nu(\beta+\delta)}$ and $Z_3 = \frac{b\Gamma_1}{p\eta}(s - \mu H_3) - \frac{\delta}{p}$ whenever $R_2 > 1$. On the other hand, the consideration $R_2 < 1$ leads to $I_1 < \frac{\eta}{b}$ and $H_1 > \frac{s}{\mu} - \frac{\delta\eta}{b\mu\Gamma_1}$, and hence, we obtain

$$\Phi_3\left(\frac{s}{\mu} - \frac{\delta\eta}{b\mu\Gamma_1}\right) < \frac{\eta}{\Gamma_1}\Phi_3(H_1) = 0.$$

Thus, the equilibrium point E_3 does not exist for $R_2 < 1$.

Finally, we consider $\widetilde{W} \neq 0$ and $\widetilde{Z} \neq 0$. Then, we have $\widetilde{I} = \frac{\eta}{b}$, $\widetilde{D} = \frac{\kappa\eta\Gamma_2}{b(\beta+\delta)}$, $\widetilde{V} = \frac{\sigma}{a}$, $\widetilde{W} = \frac{a\kappa\beta\eta\Gamma_2\Gamma_3}{bq\sigma(\beta+\delta)} - \frac{\nu}{q}$, $\widetilde{Z} = \frac{b\Gamma_1}{p\eta}(s - \mu\widetilde{H}) - \frac{\delta}{p}$ and

$$b\sigma f\left(\widetilde{H}, \frac{\eta}{b}, \frac{\sigma}{a}\right) + a\eta g\left(\widetilde{H}, \frac{\eta}{b}\right) = ab(s - \mu\widetilde{H}).$$

Since the condition $\widetilde{Z} \geq 0$ is required for biologically feasible $\widetilde{Z}$, then we obtain $\widetilde{H} \leq \frac{s}{\mu} - \frac{\delta\eta}{b\mu\Gamma_1}$. In this case, let us define a function Φ_4 on the closed interval $\left[0, \frac{s}{\mu} - \frac{\delta\eta}{b\mu\Gamma_1}\right]$ by

$$\Phi_4(H) = b\sigma f\left(H, \frac{\eta}{b}, \frac{\sigma}{a}\right) + a\eta g\left(H, \frac{\eta}{b}\right) - ab(s - \mu H).$$

It is easy to notice that $\Phi_4(0) = -abs < 0$, and $\Phi_4'(H) = b\sigma\frac{\partial f}{\partial H} + a\eta\frac{\partial g}{\partial H} + ab\mu > 0$ due to the hypotheses (A_2) and (A_4). Now, we define two reproduction numbers for competitive CTL and antibody immune responses as

$$R_3 := \frac{b}{\eta}I_2 \text{ and } R_4 := \frac{a}{\sigma}V_3, \tag{8}$$

respectively. From the biological perspective, R_3 provides a measure for the average number of CTL cells activated by infected hepatocytes when the antibody immune response is already

at work, and R_4 describes the same for antibody immune cells activated by virions when the CTL immune response is already at work [3, 6]. Of course, $R_4 > 1$ implies that $\widetilde{W} = \frac{a\kappa\beta\eta\Gamma_2\Gamma_3}{bq\sigma(\beta+\delta)} - \frac{\nu}{q} = \frac{\nu}{q}(R_4 - 1) > 0$. On the other hand, $R_3 > 1$ implies that $I_2 > \frac{\eta}{b}$ and $H_2 < \frac{s}{\mu} - \frac{\delta\eta}{b\mu\Gamma_1}$. Then, we have

$$\Phi_4\left(\frac{s}{\mu} - \frac{\delta\eta}{b\mu\Gamma_1}\right) = \frac{b}{\delta}\Phi_2\left(\frac{s}{\mu} - \frac{\delta\eta}{b\mu\Gamma_1}\right) > \frac{b}{\delta}\Phi_2(H_2) = 0.$$

Therefore, there exists a unique infection equilibrium point with adaptive immune responses $E_4 = (H_4, I_4, D_4, V_4, W_4, Z_4)$ with $H_4 \in \left(0, \frac{s}{\mu} - \frac{\delta\eta}{b\mu\Gamma_1}\right)$, $I_4 = \frac{\eta}{b}$, $D_4 = \frac{\kappa\eta\Gamma_2}{b(\beta+\delta)}$, $V_4 = \frac{\sigma}{a}$, $W_4 = \frac{a\kappa\beta\eta\Gamma_2\Gamma_3}{bq\sigma(\beta+\delta)} - \frac{\nu}{q}$ and $Z_4 = \frac{b\Gamma_1}{p\eta}(s - \mu H_4) - \frac{\delta}{p}$ whenever $R_3 > 1$ and $R_4 > 1$. However, the equilibrium point E_4 does not exist if any one of R_3 and R_4 becomes less than unity.

Above discussions regarding the existence of possible equilibria of the model (1) can be summarized as the following result.

Theorem 3.2. *If $R_0 \leq 1$, then the infection-free equilibrium $E_0 = (H_0, 0, 0, 0, 0, 0)$ is the only equilibrium of the model (1) with $H_0 = \frac{s}{\mu}$. If $R_0 > 1$, then the model (1) admits another four equilibria along with E_0 and they are the following:*

(a) *The model (1) admits an immune-free equilibrium $E_1 = (H_1, I_1, D_1, V_1, 0, 0)$ with $H_1 \in \left(0, \frac{s}{\mu}\right)$, $I_1 = \frac{\Gamma_1}{\delta}(s - \mu H_1)$, $D_1 = \frac{\kappa\Gamma_1\Gamma_2}{\delta(\beta+\delta)}(s - \mu H_1)$ and $V_1 = \frac{\kappa\beta\Gamma_1\Gamma_2\Gamma_3}{\nu\delta(\beta+\delta)}(s - \mu H_1)$.*

(b) *If $R_1 > 1$, then the model (1) admits an infection equilibrium point with only antibody immune response $E_2 = (H_2, I_2, D_2, V_2, W_2, 0)$ with $H_2 \in \left(0, \frac{s}{\mu} - \frac{\delta\nu\sigma(\beta+\delta)}{a\kappa\beta\mu\Gamma_1\Gamma_2\Gamma_3}\right)$, $I_2 = \frac{\Gamma_1}{\delta}(s - \mu H_2)$, $D_2 = \frac{\kappa\Gamma_1\Gamma_2}{\delta(\beta+\delta)}(s - \mu H_2)$, $V_2 = \frac{\sigma}{a}$ and $W_2 = \frac{a\kappa\beta\Gamma_1\Gamma_2\Gamma_3}{q\delta\sigma(\beta+\delta)}(s - \mu H_2) - \frac{\nu}{q}$.*

(c) *If $R_2 > 1$, then the model (1) admits an infection equilibrium point with only CTL immune response $E_3 = (H_3, I_3, D_3, V_3, 0, Z_3)$ with $H_3 \in \left(0, \frac{s}{\mu} - \frac{\delta\eta}{b\mu\Gamma_1}\right)$, $I_3 = \frac{\eta}{b}$, $D_3 = \frac{\kappa\eta\Gamma_2}{b(\beta+\delta)}$, $V_3 = \frac{\kappa\beta\eta\Gamma_2\Gamma_3}{b\nu(\beta+\delta)}$ and $Z_3 = \frac{b\Gamma_1}{p\eta}(s - \mu H_3) - \frac{\delta}{p}$.*

(d) *If $R_1 > 1$, $R_2 > 1$, $R_3 > 1$ and $R_4 > 1$ hold simultaneously, then the model (1) admits an infection equilibrium point with adaptive immune responses $E_4 = (H_4, I_4, D_4, V_4, W_4, Z_4)$ with $H_4 \in \left(0, \frac{s}{\mu} - \frac{\delta\eta}{b\mu\Gamma_1}\right)$, $I_4 = \frac{\eta}{b}$, $D_4 = \frac{\kappa\eta\Gamma_2}{b(\beta+\delta)}$, $V_4 = \frac{\sigma}{a}$, $W_4 = \frac{a\kappa\beta\eta\Gamma_2\Gamma_3}{bq\sigma(\beta+\delta)} - \frac{\nu}{q}$ and $Z_4 = \frac{b\Gamma_1}{p\eta}(s - \mu H_4) - \frac{\delta}{p}$.*

4 Stability analysis of equilibria

In this section, we investigate the conditions for global stability and instability of all five equilibria of the generalized model (1) using suitable Lyapunov functions and linearization technique.

Theorem 4.1. *The infection-free equilibrium $E_0 = (H_0, 0, 0, 0, 0, 0)$ is globally asymptotically stable when $R_0 \leq 1$ and it becomes unstable when $R_0 > 1$.*

Proof. We first define a Lyapunov function $\mathcal{L}_0(t)$ as follows

$$\begin{aligned}
\mathcal{L}_0(t) &= \frac{1}{\Gamma_1}I(t) + \frac{\beta\Gamma_3 f(H_0, 0, 0)}{\nu(\beta+\delta)}D(t) + \frac{f(H_0, 0, 0)}{\nu}V(t) + \frac{qf(H_0, 0, 0)}{a\nu}W(t) + \frac{p}{b\Gamma_1}Z(t) \\
&\quad + \frac{1}{\Gamma_1}\int_0^\infty f_1(\tau)e^{-\alpha_1\tau}\int_{t-\tau}^t \left[f(H(\theta), I(\theta), V(\theta))V(\theta) + g(H(\theta), I(\theta))I(\theta)\right]d\theta d\tau
\end{aligned}$$

$$+\frac{\kappa\beta\Gamma_3 f\left(H_0,0,0\right)}{\nu(\beta+\delta)}\int_0^\infty f_2(\tau)e^{-\alpha_2\tau}\int_{t-\tau}^t I(\theta)d\theta d\tau +$$

$$\frac{\beta f\left(H_0,0,0\right)}{\nu}\int_0^\infty f_3(\tau)e^{-\alpha_3\tau}\int_{t-\tau}^t D(\theta)d\theta d\tau.$$

For the sake of convenience, we denote $N = N(t)$ and $N_\tau = N(t-\tau)$ for any $N \in \{H,I,D,V,W,Z\}$. Then, the time derivative of $\mathcal{L}_0(t)$ along solutions of the model (1) gives

$$
\begin{aligned}
\frac{d\mathcal{L}_0(t)}{dt} &= \frac{1}{\Gamma_1}\left[\int_0^\infty f_1(\tau)e^{-\alpha_1\tau}\left\{f(H_\tau,I_\tau,V_\tau)V_\tau + g(H_\tau,I_\tau)I_\tau\right\}d\tau - \delta I - pIZ\right] + \\
&\quad \frac{\beta\Gamma_3 f\left(H_0,0,0\right)}{\nu(\beta+\delta)}\left[\kappa\int_0^\infty f_2(\tau)e^{-\alpha_2\tau}I_\tau d\tau - (\beta+\delta)D\right] + \frac{f\left(H_0,0,0\right)}{\nu} \\
&\quad \left[\beta\int_0^\infty f_3(\tau)e^{-\alpha_3\tau}D_\tau d\tau - \nu D - qVW\right] + \frac{qf\left(H_0,0,0\right)}{a\nu}[aVW - \sigma W] + \\
&\quad \frac{p}{b\Gamma_1}[bIZ - \eta Z] + \left[f(H,I,V)V + g(H,I)I - \frac{1}{\Gamma_1}\int_0^\infty f_1(\tau)e^{-\alpha_1\tau}\right. \\
&\quad \left.\left\{f\left(H_\tau,I_\tau,V_\tau\right)V_\tau + g\left(H_\tau,I_\tau\right)I_\tau\right\}d\tau\right] + \frac{\kappa\beta\Gamma_3 f\left(H_0,0,0\right)}{\nu(\beta+\delta)}\left[\Gamma_2 I -\right. \\
&\quad \left.\int_0^\infty f_2(\tau)e^{-\alpha_2\tau}I_\tau d\tau\right] + \frac{\beta f\left(H_0,0,0\right)}{\nu}\left[\Gamma_3 D - \int_0^\infty f_3(\tau)e^{-\alpha_3\tau}D_\tau d\tau\right] \\
&= \left(f(H,I,V) - f(H_0,0,0)\right)V + \frac{\delta}{\Gamma_1}\left[\frac{\kappa\beta\Gamma_1\Gamma_2\Gamma_3}{\delta\nu(\beta+\delta)}f(H_0,0,0) + \frac{\Gamma_1}{\delta}g(H,I) - 1\right]I \\
&\quad -\frac{q\sigma f(H_0,0,0)}{a\nu}W - \frac{p\eta}{b\Gamma_1}Z.
\end{aligned}
$$

As we have already shown in the previous section that $\limsup_{t\to\infty} H(t) \le \frac{s}{\mu} \equiv H_0$, then it is sufficient to consider $H(t) \le H_0$. Then, using the hypotheses (A_1)-(A_4) we can write

$$
\begin{aligned}
\frac{d\mathcal{L}_0(t)}{dt} &\le \left(f(H,0,0) - f(H_0,0,0)\right)V + \frac{\delta}{\Gamma_1}\left[\frac{\kappa\beta\Gamma_1\Gamma_2\Gamma_3}{\delta\nu(\beta+\delta)}f(H_0,0,0) + \frac{\Gamma_1}{\delta}g(H_0,0) - 1\right]I \\
&\quad -\frac{q\sigma f(H_0,0,0)}{a\nu}W - \frac{p\eta}{b\Gamma_1}Z \\
&= \left(f(H,0,0) - f(H_0,0,0)\right)V + \frac{\delta}{\Gamma_1}\left(R_0 - 1\right)I - \frac{q\sigma f(H_0,0,0)}{a\nu}W - \frac{p\eta}{b\Gamma_1}Z.
\end{aligned}
$$

Thus, the condition $R_0 \le 1$ obviously leads to $\frac{d\mathcal{L}_0(t)}{dt} \le 0$. Further, we can observe that $\frac{d\mathcal{L}_0(t)}{dt} = 0$ if and only if $(f(H,0,0) - f(H_0,0,0))V = 0$, $\left(R_0 - 1\right)I = 0$, $W = 0$ and $Z = 0$. First, we assume $H = H_0$, and in this case, we obtain $I = 0$ and $V = 0$ from the first equation of model (1). Then, the fourth equation of model (1) yields $D = 0$. On the other hand, the assumption $H \ne H_0$ implies $V = 0$. In this case, the fourth and third equations of model (1) respectively yield $D = 0$ and $I = 0$. Then, the first equation of model (1) results in $\frac{dH}{dt} = s - \mu H$ which implies $H(t) \to \frac{s}{\mu} \equiv H_0$ as $t \to \infty$. Hence, the singleton set $\left\{E_0 = (H_0,0,0,0,0,0)\right\}$ is the largest invariant subset of $\left\{(H,I,D,V,W,Z) \in \mathbb{R}_+^6 \mid \frac{d\mathcal{L}_0}{dt} = 0\right\}$. Therefore, the infection-free equilibrium E_0 is globally asymptotically stable when $R_0 \le 1$ due to the LaSalle invariance principle [20, 21].

However, it remains to establish the instability of the infection-free equilibrium E_0 for $R_0 > 1$. The characteristic equation for the model (1) at the infection-free equilibrium E_0

is given by

$$(\lambda + \mu)(\lambda + \sigma)(\lambda + \eta)F_0(\lambda) = 0, \tag{9}$$

where

$$
\begin{aligned}
F_0(\lambda) &= \lambda^3 + \left[\beta + 2\delta + \nu - \widetilde{\Gamma_1}(\lambda)g\big(H_0, 0\big)\right]\lambda^2 + \Big[(\beta + \delta)(\delta + \nu) + \delta\nu - \widetilde{\Gamma_1}(\lambda)(\beta + \delta \\
&\quad + \nu)g\big(H_0, 0\big)\Big]\lambda + \delta\nu(\beta + \delta)\left[1 - \frac{\kappa\beta\widetilde{\Gamma_1}(\lambda)\widetilde{\Gamma_2}(\lambda)\widetilde{\Gamma_3}(\lambda)}{\delta\nu(\beta + \delta)}f\big(H_0, 0, 0\big) - \right. \\
&\quad \left. \frac{\widetilde{\Gamma_1}(\lambda)}{\delta}g\big(H_0, 0\big)\right].
\end{aligned}
$$

Note that

$$\widetilde{\Gamma}_i(\lambda) = \int_0^\infty f_i(\tau)e^{-(\alpha_i + \lambda)\tau}d\tau \le \int_0^\infty f_i(\tau)d\tau = 1, \tag{10}$$

and $\widetilde{\Gamma}_i(0) = \Gamma_i$ for $i = 1, 2, 3$. We can easily observe that the characteristic equation (9) admits three negative real roots $-\mu$, $-\sigma$ and $-\eta$. On the other hand, we have $\lim_{\lambda \to +\infty} F_0(\lambda) = +\infty$ and

$$F_0(0) = \delta\nu(\beta + \delta)\left[1 - \frac{\kappa\beta\Gamma_1\Gamma_2\Gamma_3}{\delta\nu(\beta + \delta)}f\big(H_0, 0, 0\big) - \frac{\Gamma_1}{\delta}g\big(H_0, 0\big)\right] = \delta\nu(\beta + \delta)\big(1 - R_0\big),$$

which becomes less than zero if $R_0 > 1$. Thus, the characteristic equation (9) possesses at least one positive real root when $R_0 > 1$ and this implies that the infection-free equilibrium E_0 becomes unstable in this case. □

Before going into the detailed results regarding stability of remaining equilibria of the model (1), we define a function $\mathbb{G}(U) = U - 1 - \ln(U)$ for $U > 0$. Then, it is easy to observe that $\mathbb{G}(U) \ge 0$ for all $U > 0$ and the equality occurs if and only if $U = 1$. Further, we assume that the incidence functions f and g satisfy the following hypotheses with $H, I, V > 0$:

(A_5) $\left(1 - \frac{f(H, I, V)}{f(H, I_i, V_i)}\right)\left(\frac{f(H, I_i, V_i)}{f(H, I, V)} - \frac{V}{V_i}\right) \le 0$,

(A_6) $\left(1 - \frac{f(H_i, I_i, V_i)g(H, I)}{f(H, I_i, V_i)g(H_i, I_i)}\right)\left(\frac{f(H, I_i, V_i)g(H_i, I_i)}{f(H_i, I_i, V_i)g(H, I)} - \frac{I}{I_i}\right) \le 0$,

where H_i, I_i and V_i denote the densities of uninfected hepatocyte, infected hepatocyte and virus at the equilibrium level E_i for $i = 1, 2, 3, 4$.

Theorem 4.2. *Let us consider $R_0 > 1$ and let the hypotheses (A_5)-(A_6) hold for equilibrium E_1. Then, the immune-free equilibrium $E_1 = \big(H_1, I_1, D_1, V_1, 0, 0\big)$ is globally asymptotically stable if both the conditions $R_1 \le 1$ and $R_2 \le 1$ are satisfied simultaneously. However, it becomes unstable if at least one of R_1 and R_2 is greater than unity.*

Proof. We define a Lyapunov function $\mathcal{L}_1(t)$ as follows

$$
\begin{aligned}
\mathcal{L}_1(t) &= \left(H(t) - H_1 - \int_{H_1}^{H(t)}\frac{f(H_1, I_1, V_1)}{f(U, I_1, V_1)}dU\right) + \frac{I_1}{\Gamma_1}\mathbb{G}\left(\frac{I(t)}{I_1}\right) + \\
&\quad \frac{f(H_1, I_1, V_1)V_1 D_1}{\kappa\Gamma_2 I_1}\mathbb{G}\left(\frac{D(t)}{D_1}\right) + \frac{(\beta + \delta)f(H_1, I_1, V_1)V_1^2}{\kappa\beta\Gamma_2\Gamma_3 I_1}\mathbb{G}\left(\frac{V(t)}{V_1}\right)
\end{aligned}
$$

$$+\frac{(\beta+\delta)qf(H_1,I_1,V_1)V_1}{a\kappa\beta\Gamma_2\Gamma_3 I_1}W(t)+\frac{p}{b\Gamma_1}Z(t)+$$

$$\frac{f(H_1,I_1,V_1)V_1}{\Gamma_1}\int_0^\infty f_1(\tau)e^{-\alpha_1\tau}\int_{t-\tau}^t \mathbb{G}\left(\frac{f(H(\theta),I(\theta),V(\theta))V(\theta)}{f(H_1,I_1,V_1)V_1}\right)d\theta d\tau$$

$$+\frac{g(H_1,I_1)I_1}{\Gamma_1}\int_0^\infty f_1(\tau)e^{-\alpha_1\tau}\int_{t-\tau}^t \mathbb{G}\left(\frac{g(H(\theta),I(\theta))I(\theta)}{g(H_1,I_1)I_1}\right)d\theta d\tau +$$

$$\frac{f(H_1,I_1,V_1)V_1}{\Gamma_2}\int_0^\infty f_2(\tau)e^{-\alpha_2\tau}\int_{t-\tau}^t \mathbb{G}\left(\frac{I(\theta)}{I_1}\right)d\theta d\tau +$$

$$\frac{f(H_1,I_1,V_1)V_1}{\Gamma_3}\int_0^\infty f_3(\tau)e^{-\alpha_3\tau}\int_{t-\tau}^t \mathbb{G}\left(\frac{D(\theta)}{D_1}\right)d\theta d\tau.$$

Then, the time derivative of $\mathcal{L}_1(t)$ along solutions of the model (1) yields

$$
\begin{aligned}
\frac{d\mathcal{L}_1(t)}{dt} =\ & \mu H_1\left(1-\frac{H}{H_1}\right)\left(1-\frac{f(H_1,I_1,V_1)}{f(H,I_1,V_1)}\right)+f(H_1,I_1,V_1)V_1\left[-1-\frac{V}{V_1}+\frac{f(H,I_1,V_1)}{f(H,I,V)}\right.\\
& +\left.\frac{f(H,I,V)V}{f(H,I_1,V_1)V_1}\right]+g(H_1,I_1)I_1\left[-1-\frac{I}{I_1}+\frac{f(H,I_1,V_1)g(H_1,I_1)}{f(H_1,I_1,V_1)g(H,I)}+\right.\\
& \left.\frac{f(H_1,I_1,V_1)g(H,I)I}{f(H,I_1,V_1)g(H_1,I_1)I_1}\right]+\frac{q(\beta+\delta)\sigma f(H_1,I_1,V_1)V_1}{a\kappa\beta\Gamma_2\Gamma_3 I_1}(R_1-1)W+\frac{p\eta}{b\Gamma_1}(R_2-1)Z\\
& -\frac{f(H_1,I_1,V_1)V_1}{\Gamma_1}\int_0^\infty f_1(\tau)e^{-\alpha_1\tau}\left[\mathbb{G}\left(\frac{f(H_1,I_1,V_1)}{f(H,I_1,V_1)}\right)+\mathbb{G}\left(\frac{f(H,I_1,V_1)}{f(H,I,V)}\right)+\right.\\
& \left.\mathbb{G}\left(\frac{f(H_\tau,I_\tau,V_\tau)V_\tau I_1}{f(H_1,I_1,V_1)V_1 I}\right)\right]d\tau-\frac{g(H_1,I_1)I_1}{\Gamma_1}\int_0^\infty f_1(\tau)e^{-\alpha_1\tau}\left[\mathbb{G}\left(\frac{f(H_1,I_1,V_1)}{f(H,I_1,V_1)}\right)\right.\\
& \left.+\mathbb{G}\left(\frac{g(H_\tau,I_\tau)I_\tau}{g(H_1,I_1)I}\right)+\mathbb{G}\left(\frac{f(H,I_1,V_1)g(H_1,I_1)}{f(H_1,I_1,V_1)g(H,I)}\right)\right]d\tau-\frac{f(H_1,I_1,V_1)V_1}{\Gamma_2}\\
& \int_0^\infty f_2(\tau)e^{-\alpha_2\tau}\mathbb{G}\left(\frac{D_1 I_\tau}{DI_1}\right)d\tau-\frac{f(H_1,I_1,V_1)V_1}{\Gamma_3}\int_0^\infty f_3(\tau)e^{-\alpha_3\tau}\mathbb{G}\left(\frac{V_1 D_\tau}{VD_1}\right)d\tau.
\end{aligned}
$$

As the incidence function f is strictly increasing with respect to H (see hypothesis (A_2)), then we have $\left(1-\frac{H}{H_1}\right)\left(1-\frac{f(H_1,I_1,V_1)}{f(H,I_1,V_1)}\right)\le 0$. Further, simple calculations and hypotheses (A_5)-(A_6) lead to

$$\left[-1-\frac{V}{V_1}+\frac{f(H,I_1,V_1)}{f(H,I,V)}+\frac{f(H,I,V)V}{f(H,I_1,V_1)V_1}\right]=\left(1-\frac{f(H,I,V)}{f(H,I_1,V_1)}\right)\left(\frac{f(H,I_1,V_1)}{f(H,I,V)}-\frac{V}{V_1}\right)\le 0,$$

$$\left[-1-\frac{I}{I_1}+\frac{f(H,I_1,V_1)g(H_1,I_1)}{f(H_1,I_1,V_1)g(H,I)}+\frac{f(H_1,I_1,V_1)g(H,I)I}{f(H,I_1,V_1)g(H_1,I_1)I_1}\right]$$
$$=\left(1-\frac{f(H_1,I_1,V_1)g(H,I)}{f(H,I_1,V_1)g(H_1,I_1)}\right)\left(\frac{f(H,I_1,V_1)g(H_1,I_1)}{f(H_1,I_1,V_1)g(H,I)}-\frac{I}{I_1}\right)\le 0.$$

Thus, the conditions $R_1\le 1$ and $R_2\le 1$ yield $\frac{d\mathcal{L}_1(t)}{dt}\le 0$. In this case, we can easily prove that the singleton set $\{E_1=(H_1,I_1,D_1,V_1,0,0)\}$ becomes the largest invariant subset of $\{(H,I,D,V,W,Z)\in\mathbb{R}_+^6\mid\frac{d\mathcal{L}_1}{dt}=0\}$, and therefore, the LaSalle invariance principle [20, 21] guarantees the global asymptotic stability of the immune-free equilibrium E_1 when $R_1\le 1$ and $R_2\le 1$.

It still remains to investigate the stability of the immune-free equilibrium E_1 if at least one of R_1 and R_2 becomes greater than unity. The characteristic equation for the model (1) at the immune-free equilibrium E_1 is given by

$$\left(\lambda+\sigma-aV_1\right)\left(\lambda+\eta-bI_1\right)F_1(\lambda)=0, \tag{11}$$

where

$$F_1(\lambda) = \begin{vmatrix} \lambda + \mu + C_1 & C_2 & 0 & C_3 \\ -\widetilde{\Gamma_1}(\lambda)C_1 & \lambda + \delta - \widetilde{\Gamma_1}(\lambda)C_2 & 0 & -\widetilde{\Gamma_1}(\lambda)C_3 \\ 0 & -\kappa\widetilde{\Gamma_2}(\lambda) & \lambda + \beta + \delta & 0 \\ 0 & 0 & -\beta\widetilde{\Gamma_3}(\lambda) & \lambda + \nu \end{vmatrix}$$

with $C_1 = \left(\frac{\partial f}{\partial H}V + \frac{\partial g}{\partial H}I\right)\Big|_{E_1}$, $C_2 = \left(\frac{\partial f}{\partial I}V + \frac{\partial g}{\partial I}I + g\right)\Big|_{E_1}$ and $C_3 = \left(\frac{\partial f}{\partial V}V + f\right)\Big|_{E_1}$. Then, we can easily observe that the characteristic equation (11) admits positive roots $\lambda = aV_1 - \sigma$ and $\lambda = bI_1 - \eta$ if $R_1 > 1$ and $R_2 > 1$, respectively. Therefore, the immune-free equilibrium E_1 is unstable whenever at least one of R_1 and R_2 becomes greater than unity. $\qquad\square$

Theorem 4.3. *Let us consider $R_0 > 1$ and $R_1 > 1$, and let the hypotheses (A_5)-(A_6) hold for equilibrium E_2. Then, the infection equilibrium with only antibody immune response $E_2 = (H_2, I_2, D_2, V_2, W_2, 0)$ is globally asymptotically stable if $R_3 \leq 1$. However, it becomes unstable whenever $R_3 > 1$.*

Proof. We define a Lyapunov function $\mathcal{L}_2(t)$ as follows

$$\begin{aligned}
\mathcal{L}_2(t) &= \left(H(t) - H_2 - \int_{H_2}^{H(t)} \frac{f(H_2, I_2, V_2)}{f(U, I_2, V_2)}dU\right) + \frac{I_2}{\Gamma_1}\mathbb{G}\left(\frac{I(t)}{I_2}\right) + \\
&\quad \frac{f(H_2, I_2, V_2)V_2 D_2}{\kappa\Gamma_2 I_2}\mathbb{G}\left(\frac{D(t)}{D_2}\right) + \frac{(\beta + \delta)f(H_2, I_2, V_2)V_2^2}{\kappa\beta\Gamma_2\Gamma_3 I_2}\mathbb{G}\left(\frac{V(t)}{V_2}\right) \\
&\quad + \frac{(\beta + \delta)qf(H_2, I_2, V_2)V_2 W_2}{a\kappa\beta\Gamma_2\Gamma_3 I_2}\mathbb{G}\left(\frac{W(t)}{W_2}\right) + \frac{p}{b\Gamma_1}Z(t) + \\
&\quad \frac{f(H_2, I_2, V_2)V_2}{\Gamma_1}\int_0^\infty f_1(\tau)e^{-\alpha_1\tau}\int_{t-\tau}^t \mathbb{G}\left(\frac{f(H(\theta), I(\theta), V(\theta))V(\theta)}{f(H_2, I_2, V_2)V_2}\right)d\theta d\tau \\
&\quad + \frac{g(H_2, I_2)I_2}{\Gamma_1}\int_0^\infty f_1(\tau)e^{-\alpha_1\tau}\int_{t-\tau}^t \mathbb{G}\left(\frac{g(H(\theta), I(\theta))I(\theta)}{g(H_2, I_2)I_2}\right)d\theta d\tau + \\
&\quad \frac{f(H_2, I_2, V_2)V_2}{\Gamma_2}\int_0^\infty f_2(\tau)e^{-\alpha_2\tau}\int_{t-\tau}^t \mathbb{G}\left(\frac{I(\theta)}{I_2}\right)d\theta d\tau + \\
&\quad \frac{f(H_2, I_2, V_2)V_2}{\Gamma_3}\int_0^\infty f_3(\tau)e^{-\alpha_3\tau}\int_{t-\tau}^t \mathbb{G}\left(\frac{D(\theta)}{D_2}\right)d\theta d\tau.
\end{aligned}$$

Then, the time derivative of $\mathcal{L}_2(t)$ along solutions of the model (1) yields

$$\begin{aligned}
\frac{d\mathcal{L}_2(t)}{dt} &= \mu H_2\left(1 - \frac{H}{H_2}\right)\left(1 - \frac{f(H_2, I_2, V_2)}{f(H, I_2, V_2)}\right) + f(H_2, I_2, V_2)V_2\left[-1 - \frac{V}{V_2} + \right. \\
&\quad \left. \frac{f(H, I_2, V_2)}{f(H, I, V)} + \frac{f(H, I, V)V}{f(H, I_2, V_2)V_2}\right] + g(H_2, I_2)I_2\left[-1 - \frac{I}{I_2} + \right. \\
&\quad \left. \frac{f(H, I_2, V_2)g(H_2, I_2)}{f(H_2, I_2, V_2)g(H, I)} + \frac{f(H_2, I_2, V_2)g(H, I)I}{f(H, I_2, V_2)g(H_2, I_2)I_2}\right] + \frac{p\eta}{b\Gamma_1}(R_3 - 1)Z - \\
&\quad \frac{f(H_2, I_2, V_2)V_2}{\Gamma_1}\int_0^\infty f_1(\tau)e^{-\alpha_1\tau}\left[\mathbb{G}\left(\frac{f(H_2, I_2, V_2)}{f(H, I_2, V_2)}\right) + \mathbb{G}\left(\frac{f(H, I_2, V_2)}{f(H, I, V)}\right) + \right. \\
&\quad \left. \mathbb{G}\left(\frac{f(H_\tau, I_\tau, V_\tau)V_\tau I_2}{f(H_2, I_2, V_2)V_2 I}\right)\right]d\tau - \frac{g(H_2, I_2)I_2}{\Gamma_1}\int_0^\infty f_1(\tau)e^{-\alpha_1\tau}\left[\mathbb{G}\left(\frac{f(H_2, I_2, V_2)}{f(H, I_2, V_2)}\right) \right. \\
&\quad \left. + \mathbb{G}\left(\frac{g(H_\tau, I_\tau)I_\tau}{g(H_2, I_2)I}\right) + \mathbb{G}\left(\frac{f(H, I_2, V_2)g(H_2, I_2)}{f(H_2, I_2, V_2)g(H, I)}\right)\right]d\tau - \frac{f(H_2, I_2, V_2)V_2}{\Gamma_2}
\end{aligned}$$

$$\int_0^\infty f_2(\tau)e^{-\alpha_2\tau}\mathbb{G}\left(\frac{D_2 I_\tau}{DI_2}\right)d\tau - \frac{f(H_2,I_2,V_2)V_2}{\Gamma_3}\int_0^\infty f_3(\tau)e^{-\alpha_3\tau}\mathbb{G}\left(\frac{V_2 D_\tau}{VD_2}\right)d\tau.$$

As discussed in the proof of the Theorem 4.2, the hypotheses (A_2), (A_5) and (A_6) lead to $\frac{d\mathcal{L}_2(t)}{dt} \le 0$ for $R_3 \le 1$. In this case, the singleton set $\{E_2 = (H_2, I_2, D_2, V_2, W_2, 0)\}$ becomes the largest invariant subset of $\{(H, I, D, V, W, Z) \in \mathbb{R}_+^6 \mid \frac{d\mathcal{L}_2}{dt} = 0\}$. Therefore, the global asymptotic stability of the infection equilibrium with only antibody immune response E_2 for $R_3 \le 1$ is guaranteed by the LaSalle invariance principle [20, 21].

Now, we investigate the stability of the infection equilibrium with only antibody immune response E_2 for $R_3 > 1$. The characteristic equation for the model (1) at the equilibrium E_2 is given by

$$\left(\lambda + \eta - bI_2\right)F_2(\lambda) = 0, \tag{12}$$

where

$$F_2(\lambda) = \begin{vmatrix} \lambda + \mu + \widetilde{C}_1 & \widetilde{C}_2 & 0 & \widetilde{C}_3 & 0 \\ -\widetilde{\Gamma_1}(\lambda)\widetilde{C}_1 & \lambda + \delta - \widetilde{\Gamma_1}(\lambda)\widetilde{C}_2 & 0 & -\widetilde{\Gamma_1}(\lambda)\widetilde{C}_3 & 0 \\ 0 & -\kappa\widetilde{\Gamma_2}(\lambda) & \lambda + \beta + \delta & 0 & 0 \\ 0 & 0 & -\beta\widetilde{\Gamma_3}(\lambda) & \lambda + \nu + qW_2 & qV_2 \\ 0 & 0 & 0 & -aW_2 & \lambda + \sigma - aV_2 \end{vmatrix}$$

with $\widetilde{C}_1 = \left(\frac{\partial f}{\partial H}V + \frac{\partial g}{\partial H}I\right)\big|_{E_2}$, $\widetilde{C}_2 = \left(\frac{\partial f}{\partial I}V + \frac{\partial g}{\partial I}I + g\right)\big|_{E_2}$ and $\widetilde{C}_3 = \left(\frac{\partial f}{\partial V}V + f\right)\big|_{E_2}$. Clearly, the characteristic equation (12) admits a positive root $\lambda = bI_2 - \eta$ when $R_3 > 1$. Therefore, the infection equilibrium with only antibody immune response E_2 is unstable whenever $R_3 > 1$. $\qquad\square$

Theorem 4.4. *Let us consider $R_0 > 1$ and $R_2 > 1$, and let the hypotheses (A_5)-(A_6) hold for equilibrium E_3. Then, the infection equilibrium with only CTL immune response $E_3 = \left(H_3, I_3, D_3, V_3, 0, Z_3\right)$ is globally asymptotically stable if $R_4 \le 1$. However, it becomes unstable whenever $R_4 > 1$.*

Proof. We define a Lyapunov function $\mathcal{L}_3(t)$ as follows

$$\begin{aligned} \mathcal{L}_3(t) &= \left(H(t) - H_3 - \int_{H_3}^{H(t)}\frac{f(H_3,I_3,V_3)}{f(U,I_3,V_3)}dU\right) + \frac{I_3}{\Gamma_1}\mathbb{G}\left(\frac{I(t)}{I_3}\right) + \\ &\quad \frac{f(H_3,I_3,V_3)V_3 D_3}{\kappa\Gamma_2 I_3}\mathbb{G}\left(\frac{D(t)}{D_3}\right) + \frac{(\beta+\delta)f(H_3,I_3,V_3)V_3^2}{\kappa\beta\Gamma_2\Gamma_3 I_3}\mathbb{G}\left(\frac{V(t)}{V_3}\right) \\ &\quad + \frac{(\beta+\delta)qf(H_3,I_3,V_3)V_3}{a\kappa\beta\Gamma_2\Gamma_3 I_3}W(t) + \frac{pZ_3}{b\Gamma_1}\mathbb{G}\left(\frac{Z(t)}{Z_3}\right) + \\ &\quad \frac{f(H_3,I_3,V_3)V_3}{\Gamma_1}\int_0^\infty f_1(\tau)e^{-\alpha_1\tau}\int_{t-\tau}^t\mathbb{G}\left(\frac{f(H(\theta),I(\theta),V(\theta))V(\theta)}{f(H_3,I_3,V_3)V_3}\right)d\theta d\tau \\ &\quad + \frac{g(H_3,I_3)I_3}{\Gamma_1}\int_0^\infty f_1(\tau)e^{-\alpha_1\tau}\int_{t-\tau}^t\mathbb{G}\left(\frac{g(H(\theta),I(\theta))I(\theta)}{g(H_3,I_3)I_3}\right)d\theta d\tau + \\ &\quad \frac{f(H_3,I_3,V_3)V_3}{\Gamma_2}\int_0^\infty f_2(\tau)e^{-\alpha_2\tau}\int_{t-\tau}^t\mathbb{G}\left(\frac{I(\theta)}{I_3}\right)d\theta d\tau + \\ &\quad \frac{f(H_3,I_3,V_3)V_3}{\Gamma_3}\int_0^\infty f_3(\tau)e^{-\alpha_3\tau}\int_{t-\tau}^t\mathbb{G}\left(\frac{D(\theta)}{D_3}\right)d\theta d\tau. \end{aligned}$$

Then, the time derivative of $\mathcal{L}_3(t)$ along solutions of the model (1) yields

$$
\begin{aligned}
\frac{d\mathcal{L}_3(t)}{dt} &= \mu H_3\left(1 - \frac{H}{H_3}\right)\left(1 - \frac{f(H_3, I_3, V_3)}{f(H, I_3, V_3)}\right) + f(H_3, I_3, V_3)V_3\left[-1 - \frac{V}{V_3} + \right. \\
&\quad \left. \frac{f(H, I_3, V_3)}{f(H, I, V)} + \frac{f(H, I, V)V}{f(H, I_3, V_3)V_3}\right] + g(H_3, I_3)I_3\left[-1 - \frac{I}{I_3} + \frac{f(H_3, I_3, V_3)g(H_3, I_3)}{f(H_3, I_3, V_3)g(H, I)}\right. \\
&\quad \left. + \frac{f(H_3, I_3, V_3)g(H, I)I}{f(H, I_3, V_3)g(H_3, I_3)I_3}\right] + \frac{q(\beta + \delta)\sigma f(H_3, I_3, V_3)V_3}{a\kappa\beta\Gamma_2\Gamma_3 I_3}(R_4 - 1)W - \\
&\quad \frac{f(H_3, I_3, V_3)V_3}{\Gamma_1}\int_0^\infty f_1(\tau)e^{-\alpha_1\tau}\left[\mathbb{G}\left(\frac{f(H_3, I_3, V_3)}{f(H, I_3, V_3)}\right) + \mathbb{G}\left(\frac{f(H, I_3, V_3)}{f(H, I, V)}\right) + \right. \\
&\quad \left. \mathbb{G}\left(\frac{f(H_\tau, I_\tau, V_\tau)V_\tau I_3}{f(H_3, I_3, V_3)V_3 I}\right)\right]d\tau - \frac{g(H_3, I_3)I_3}{\Gamma_1}\int_0^\infty f_1(\tau)e^{-\alpha_1\tau}\left[\mathbb{G}\left(\frac{f(H_3, I_3, V_3)}{f(H, I_3, V_3)}\right)\right. \\
&\quad \left. + \mathbb{G}\left(\frac{g(H_\tau, I_\tau)I_\tau}{g(H_3, I_3)I}\right) + \mathbb{G}\left(\frac{f(H, I_3, V_3)g(H_3, I_3)}{f(H_3, I_3, V_3)g(H, I)}\right)\right]d\tau - \frac{f(H_3, I_3, V_3)V_3}{\Gamma_2} \\
&\quad \int_0^\infty f_2(\tau)e^{-\alpha_2\tau}\mathbb{G}\left(\frac{D_3 I_\tau}{DI_3}\right)d\tau - \frac{f(H_3, I_3, V_3)V_3}{\Gamma_3}\int_0^\infty f_3(\tau)e^{-\alpha_3\tau}\mathbb{G}\left(\frac{V_3 D_\tau}{VD_3}\right)d\tau.
\end{aligned}
$$

As discussed earlier, the hypotheses (A_2), (A_5) and (A_6) imply $\frac{d\mathcal{L}_3(t)}{dt} \leq 0$ for $R_4 \leq 1$. In this case, the singleton set $\{E_3 = (H_3, I_3, D_3, V_3, 0, Z_3)\}$ becomes the largest invariant subset of $\left\{(H, I, D, V, W, Z) \in \mathbb{R}_+^6 \mid \frac{d\mathcal{L}_3}{dt} = 0\right\}$. Therefore, the global asymptotic stability of the infection equilibrium with only CTL immune response E_3 for $R_4 \leq 1$ is guaranteed by the LaSalle invariance principle [20, 21].

Now, we investigate the stability of the infection equilibrium with only CTL immune response E_3 for $R_4 > 1$. The characteristic equation for the model (1) at the equilibrium E_3 is given by

$$\big(\lambda + \sigma - aV_3\big)F_3(\lambda) = 0, \tag{13}$$

where

$$
F_3(\lambda) = \begin{vmatrix}
\lambda + \mu + \overline{C}_1 & \overline{C}_2 & 0 & \overline{C}_3 & 0 \\
-\widetilde{\Gamma}_1(\lambda)\overline{C}_1 & \lambda + \delta + pZ_3 - \widetilde{\Gamma}_1(\lambda)\overline{C}_2 & 0 & -\widetilde{\Gamma}_1(\lambda)\overline{C}_3 & pI_3 \\
0 & -\kappa\widetilde{\Gamma}_2(\lambda) & \lambda + \beta + \delta & 0 & 0 \\
0 & 0 & -\beta\widetilde{\Gamma}_3(\lambda) & \lambda + \nu & 0 \\
0 & -bZ_3 & 0 & 0 & \lambda + \eta - bI_3
\end{vmatrix}
$$

with $\overline{C}_1 = \left.\left(\frac{\partial f}{\partial H}V + \frac{\partial g}{\partial H}I\right)\right|_{E_3}$, $\overline{C}_2 = \left.\left(\frac{\partial f}{\partial I}V + \frac{\partial g}{\partial I}I + g\right)\right|_{E_3}$ and $\overline{C}_3 = \left.\left(\frac{\partial f}{\partial V}V + f\right)\right|_{E_3}$. Clearly, the characteristic equation (13) admits a positive root $\lambda = aV_3 - \sigma$ when $R_4 > 1$. Therefore, the infection equilibrium with only CTL immune response E_3 is unstable whenever $R_4 > 1$. $\square$

Theorem 4.5. *Let us consider $R_0 > 1$, $R_1 > 1$, $R_2 > 1$, $R_3 > 1$ and $R_4 > 1$. Also, we assume that the hypotheses (A_5)-(A_6) hold for equilibrium E_4. Then, the infection equilibrium with adaptive immune responses $E_4 = \big(H_4, I_4, D_4, V_4, W_4, Z_4\big)$ is globally asymptotically stable.*

Proof. We define a Lyapunov function $\mathcal{L}_4(t)$ as follows

$$
\mathcal{L}_4(t) = \left(H(t) - H_4 - \int_{H_4}^{H(t)} \frac{f(H_4, I_4, V_4)}{f(U, I_4, V_4)}dU\right) + \frac{I_4}{\Gamma_1}\mathbb{G}\left(\frac{I(t)}{I_4}\right) +
$$

$$\frac{f(H_4,I_4,V_4)V_4D_4}{\kappa\Gamma_2 I_4}\mathbb{G}\left(\frac{D(t)}{D_4}\right)+\frac{(\beta+\delta)f(H_4,I_4,V_4)V_4^2}{\kappa\beta\Gamma_2\Gamma_3 I_4}\mathbb{G}\left(\frac{V(t)}{V_4}\right)$$

$$+\frac{(\beta+\delta)qf(H_4,I_4,V_4)V_4W_4}{a\kappa\beta\Gamma_2\Gamma_3 I_4}\mathbb{G}\left(\frac{W(t)}{W_4}\right)+\frac{pZ_4}{b\Gamma_1}\mathbb{G}\left(\frac{Z(t)}{Z_4}\right)+$$

$$\frac{f(H_4,I_4,V_4)V_4}{\Gamma_1}\int_0^\infty f_1(\tau)e^{-\alpha_1\tau}\int_{t-\tau}^t\mathbb{G}\left(\frac{f(H(\theta),I(\theta),V(\theta))V(\theta)}{f(H_4,I_4,V_4)V_4}\right)d\theta d\tau$$

$$+\frac{g(H_4,I_4)I_4}{\Gamma_1}\int_0^\infty f_1(\tau)e^{-\alpha_1\tau}\int_{t-\tau}^t\mathbb{G}\left(\frac{g(H(\theta),I(\theta))I(\theta)}{g(H_4,I_4)I_4}\right)d\theta d\tau+$$

$$\frac{f(H_4,I_4,V_4)V_4}{\Gamma_2}\int_0^\infty f_2(\tau)e^{-\alpha_2\tau}\int_{t-\tau}^t\mathbb{G}\left(\frac{I(\theta)}{I_4}\right)d\theta d\tau+$$

$$\frac{f(H_4,I_4,V_4)V_4}{\Gamma_3}\int_0^\infty f_3(\tau)e^{-\alpha_3\tau}\int_{t-\tau}^t\mathbb{G}\left(\frac{D(\theta)}{D_4}\right)d\theta d\tau.$$

Then, the time derivative of $\mathcal{L}_4(t)$ along solutions of the model (1) yields

$$\begin{aligned}\frac{d\mathcal{L}_4(t)}{dt} &= \mu H_4\left(1-\frac{H}{H_4}\right)\left(1-\frac{f(H_4,I_4,V_4)}{f(H,I_4,V_4)}\right)+f(H_4,I_4,V_4)V_4\left[-1-\frac{V}{V_4}\right.\\ &+\frac{f(H,I_4,V_4)}{f(H,I,V)}+\frac{f(H,I,V)V}{f(H,I_4,V_4)V_4}\right]+g(H_4,I_4)I_4\left[-1-\frac{I}{I_4}\right.\\ &+\frac{f(H,I_4,V_4)g(H_4,I_4)}{f(H_4,I_4,V_4)g(H,I)}+\frac{f(H,I_4,V_4)g(H,I)I}{f(H,I_4,V_4)g(H_4,I_4)I_4}\right]-\\ &\frac{f(H_4,I_4,V_4)V_4}{\Gamma_1}\int_0^\infty f_1(\tau)e^{-\alpha_1\tau}\left[\mathbb{G}\left(\frac{f(H_4,I_4,V_4)}{f(H,I_4,V_4)}\right)+\mathbb{G}\left(\frac{f(H,I_4,V_4)}{f(H,I,V)}\right)+\right.\\ &\mathbb{G}\left(\frac{f(H_\tau,I_\tau,V_\tau)V_\tau I_4}{f(H_4,I_4,V_4)V_4 I}\right)\right]d\tau-\frac{g(H_4,I_4)I_4}{\Gamma_1}\int_0^\infty f_1(\tau)e^{-\alpha_1\tau}\left[\mathbb{G}\left(\frac{f(H_4,I_4,V_4)}{f(H,I_4,V_4)}\right)\right.\\ &+\mathbb{G}\left(\frac{g(H_\tau,I_\tau)I_\tau}{g(H_4,I_4)I}\right)+\mathbb{G}\left(\frac{f(H,I_4,V_4)g(H_4,I_4)}{f(H_4,I_4,V_4)g(H,I)}\right)\right]d\tau-\frac{f(H_4,I_4,V_4)V_4}{\Gamma_2}\\ &\int_0^\infty f_2(\tau)e^{-\alpha_2\tau}\mathbb{G}\left(\frac{D_4 I_\tau}{DI_4}\right)d\tau-\frac{f(H_4,I_4,V_4)V_4}{\Gamma_3}\int_0^\infty f_3(\tau)e^{-\alpha_3\tau}\mathbb{G}\left(\frac{V_4 D_\tau}{VD_4}\right)d\tau.\end{aligned}$$

As discussed earlier, the hypotheses (A_2), (A_5) and (A_6) imply $\frac{d\mathcal{L}_4(t)}{dt}\leq 0$. In this case, the singleton set $\{E_4=(H_4,I_4,D_4,V_4,W_4,Z_4)\}$ becomes the largest invariant subset of $\{(H,I,D,V,W,Z)\in\mathbb{R}_+^6\mid\frac{d\mathcal{L}_4}{dt}=0\}$. Therefore, the global asymptotic stability of the infection equilibrium with adaptive immune responses E_4 is guaranteed by the LaSalle invariance principle [20, 21]. This completes the proof. □

At this point, one might wonder about possible dynamics of the system (1) when the conditions $R_0 > 1$, $R_1 > 1$, $R_2 > 1$, $R_3 \leq 1$ and $R_4 \leq 1$ are satisfied simultaneously. We can observe that $H_2\in\left(0,\frac{s}{\mu}-\frac{\delta\nu\sigma(\beta+\delta)}{a\kappa\beta\mu\Gamma_1\Gamma_2\Gamma_3}\right)$ implies $I_2=\frac{\Gamma_1}{\delta}(s-\mu H_2)>\frac{\nu\sigma(\beta+\delta)}{a\kappa\beta\Gamma_2\Gamma_3}$. Thus, we have $R_3=\frac{b}{\eta}I_2>\frac{b\nu\sigma(\beta+\delta)}{a\kappa\beta\eta\Gamma_2\Gamma_3}$. On the other hand, $R_4=\frac{a}{\sigma}V_3=\frac{a\kappa\beta\eta\Gamma_2\Gamma_3}{b\nu\sigma(\beta+\delta)}$. Then, we obtain $R_3>\frac{1}{R_4}$, i.e., $R_3R_4>1$. However, the conditions $R_3\leq 1$ and $R_4\leq 1$ imply $R_3R_4\leq 1$. Hence, we arrive at a contradiction. Therefore, the results presented in this section effectively capture the complete dynamics of the system (1).

5 An application with numerical simulations

System (1) is considered to be a generalized model describing HBV infection in vivo with both modes of infection transmission and three distributed delay terms. Of course, the

biologically relevant assumptions (A_1)-(A_4) on incidence functions are valid for a widely variety of commonly used incidence functions [3, 15, 22]. Also, the probability distributions used to describe distributed delays can take different forms such as gamma distribution and Dirac delta functions [22, 23, 24]. In this section, we consider the specific forms of incidence functions as $f(H, I, V) = \frac{\gamma_1 H}{1+\rho_1 V}$ and $g(H, I) = \frac{\gamma_2 H}{1+\rho_2 I}$, and probability distributions as $f_i(\tau) = \Delta(\tau - \tau_i)$, the Dirac delta function, for $i = 1, 2, 3$. Then, the generalized model (1) reduces to the following system:

$$
\begin{aligned}
\frac{dH}{dt} &= s - \mu H(t) - \frac{\gamma_1 H(t)V(t)}{1+\rho_1 V(t)} - \frac{\gamma_2 H(t)I(t)}{1+\rho_2 I(t)}, \\
\frac{dI}{dt} &= e^{-\alpha_1\tau_1}\left(\frac{\gamma_1 H(t-\tau_1)V(t-\tau_1)}{1+\rho_1 V(t-\tau_1)} + \frac{\gamma_2 H(t-\tau_1)I(t-\tau_1)}{1+\rho_2 I(t-\tau_1)}\right) - \delta I(t) - pI(t)Z(t), \\
\frac{dD}{dt} &= \kappa e^{-\alpha_2\tau_2}I(t-\tau_2) - (\beta+\delta)D(t), \qquad\qquad (14)\\
\frac{dV}{dt} &= \beta e^{-\alpha_3\tau_3}D(t-\tau_3) - \nu V(t) - qV(t)W(t), \\
\frac{dW}{dt} &= aV(t)W(t) - \sigma W(t), \\
\frac{dZ}{dt} &= bI(t)Z(t) - \eta Z(t).
\end{aligned}
$$

The above model (14) is obviously a discrete-delay model where τ_i $(i = 1, 2, 3)$ represent the respective time delays and it arises due to the consideration of Dirac delta functions as probability distributions. Further, γ_i and ρ_i $(i = 1, 2)$ respectively denote the infection transmission and saturation rates for the corresponding mode of transmission.

The model (14) always admits the infection-free equilibrium $E_0 = (s/\mu, 0, 0, 0, 0, 0)$ and the basic reproduction number is given by

$$
R_0 = \frac{s\kappa\beta\gamma_1}{\delta\mu\nu(\beta+\delta)}e^{-(\alpha_1\tau_1+\alpha_2\tau_2+\alpha_3\tau_3)} + \frac{s\gamma_2}{\delta\mu}e^{-\alpha_1\tau_1}.
$$

However, it is difficult to obtain analytical expressions for other four equilibria of the model (14) and associated reproduction numbers. Hence, we rely on numerical computations to get them. Also for the chosen incidence functions, simple calculations lead to

$$
\left(1 - \frac{f(H, I, V)}{f(H, I_i, V_i)}\right)\left(\frac{f(H, I_i, V_i)}{f(H, I, V)} - \frac{V}{V_i}\right) = \frac{-\rho_1(V-V_i)^2}{(1+\rho_1 V)(1+\rho_1 V_i)V_i} \le 0,
$$

$$
\left(1 - \frac{f(H_i, I_i, V_i)g(H, I)}{f(H, I_i, V_i)g(H_i, I_i)}\right)\left(\frac{f(H, I_i, V_i)g(H_i, I_i)}{f(H_i, I_i, V_i)g(H, I)} - \frac{I}{I_i}\right) = \frac{-\rho_2(I-I_i)^2}{(1+\rho_2 I)(1+\rho_2 I_i)I_i} \le 0,
$$

where $i = 1, 2, 3, 4$. Thus, the hypotheses (A_5)-(A_6) are automatically satisfied for our chosen incidence functions. Therefore, stability properties for all the equilibria of the model (14) can directly be inferred from Theorems 4.1-4.5.

Now, we illustrate some numerical simulations of the model (14) to corroborate our analytical results regarding stability of equilibria. Note that the parameter values used for a particular simulation are mentioned in the caption of corresponding figure. In this regard, Figure 1 shows that the infection-free equilibrium $E_0 = (100, 0, 0, 0, 0, 0)$ is asymptotically stable when $R_0 = 0.83 < 1$, whereas stability of the immune-free equilibrium $E_1 = (47.82, 11.643, 4.017, 0.205, 0, 0)$ is encapsulated in Figure 2 for $R_0 = 22.706 > 1$, $R_1 = 0.123 < 1$ and $R_2 = 0.466 < 1$. Further, Figures 3 and 4 respectively illustrate the stable infection equilibria with only antibody immune response $E_2 = (48.477, 11.496, 3.967, 0.167, 2.734, 0)$ and with only CTL immune response $E_3 = (50.886, 2.5, 0.863, 0.335, 0, 1.692)$ for appropriate

values of the threshold parameters R_0, R_1, R_2, R_3 and R_4. Finally, Figure 5 encapsulates the stable infection equilibrium with adaptive immune response $E_4 = (53.165, 2.5, 0.863, 0.2, 1.275, 1.59)$ when all the threshold parameters are greater than unity. We would like to mention that obtained theoretical results have also been verified with other types of incidence functions and probability distributions. However, we refrained ourselves from incorporating those results in this paper for the sake of brevity.

6   Conclusions

Till date, a large class of mathematical models have been considered in literature to understand the within-host HBV infection. In this study, we have intended to provide results regarding dynamical properties of a generalized HBV infection model which can directly accommodate several models as special cases. Our model has six compartments such as uninfected and infected hepatocytes, capsids, virions, antibody and CTL immune responses. In order to model infection transmission process, we have considered both the virus-to-cell and cell-to-cell transmissions which are incorporated in the model through general functions constrained to some biologically feasible conditions (A_1)-(A_4). Further, we have considered three distributed delays accounting for the time needed in latently infected hepatocytes to become active, and capsids and virions to get matured. We have proved the non-negativity and boundedness of solutions to guarantee the well-posedness of the proposed model. Also, we have defined five reproduction numbers R_0, R_1, R_2, R_3 and R_4 which act as threshold parameters for the existence of all possible equilibria and take a crucial part in characterizing the system dynamics. Depending upon the values of these threshold parameters, our proposed model can admit at most five equilibria.

The conditions responsible for global stability of each equilibrium have been identified by using a suitable Lyapunov function and LaSalle's invariance principle. We have obtained that the infection-free equilibrium E_0 is globally asymptotically stable when $R_0 \leq 1$. This means that infection cannot persist in an infected individual, and as a result, the individual will become completely cured. Further, the immune-free equilibrium E_1 is globally asymptotically stable under the assumptions (A_5)-(A_6) when $R_0 > 1$, $R_1 \leq 1$ and $R_2 \leq 1$. In this case, both the viral load and infected hepatocyte level within an infected individual are unable to activate any kind of adaptive immune responses. On the other hand, the conditions $R_0 > 1$, $R_1 > 1$ and $R_3 \leq 1$ or $R_0 > 1$, $R_2 > 1$ and $R_4 \leq 1$ lead to the global stability of E_2 or E_3 when both the assumptions (A_5)-(A_6) are satisfied. This indicates that either viral load or infected hepatocyte level is such that only the corresponding arm of adaptive immune responses will be activated. Finally, the infection equilibrium with adaptive immune responses E_4 is globally asymptotically stable whenever it exists and the assumptions (A_5)-(A_6) are satisfied. In this case, both the arms of adaptive immunity will work together against the infection. Overall, the HBV infection persists if $R_0 > 1$ as one or both arms of adaptive immunity fails to eradicate the virus in this case. However, the presence of adaptive immunity is beneficial for an infected individual as it can effectively reduce the viral load and infected hepatocyte level to a certain extent.

Also, we can observe from the expression of R_0 (given in Section 3) that time delays are inversely related to R_0. Thus, sufficiently large time delays can effectively drive the value of R_0 below unity, and as a result, infection can be completely eliminated. Further, R_0 is defined to be a sum of basic reproduction numbers for both modes of transmission (that is, $R_0^{(1)}$ and $R_0^{(2)}$) in this study. Thus, we have $R_0 = R_0^{(1)} + R_0^{(2)} > R_0^{(1)}$. On the other hand, most of the existing HBV infection models in literature have ignored the cell-to-cell transmission. This could potentially lead to under-estimation of R_0. To this end, we would like to emphasize on the fact that all the results obtained in this study are robust
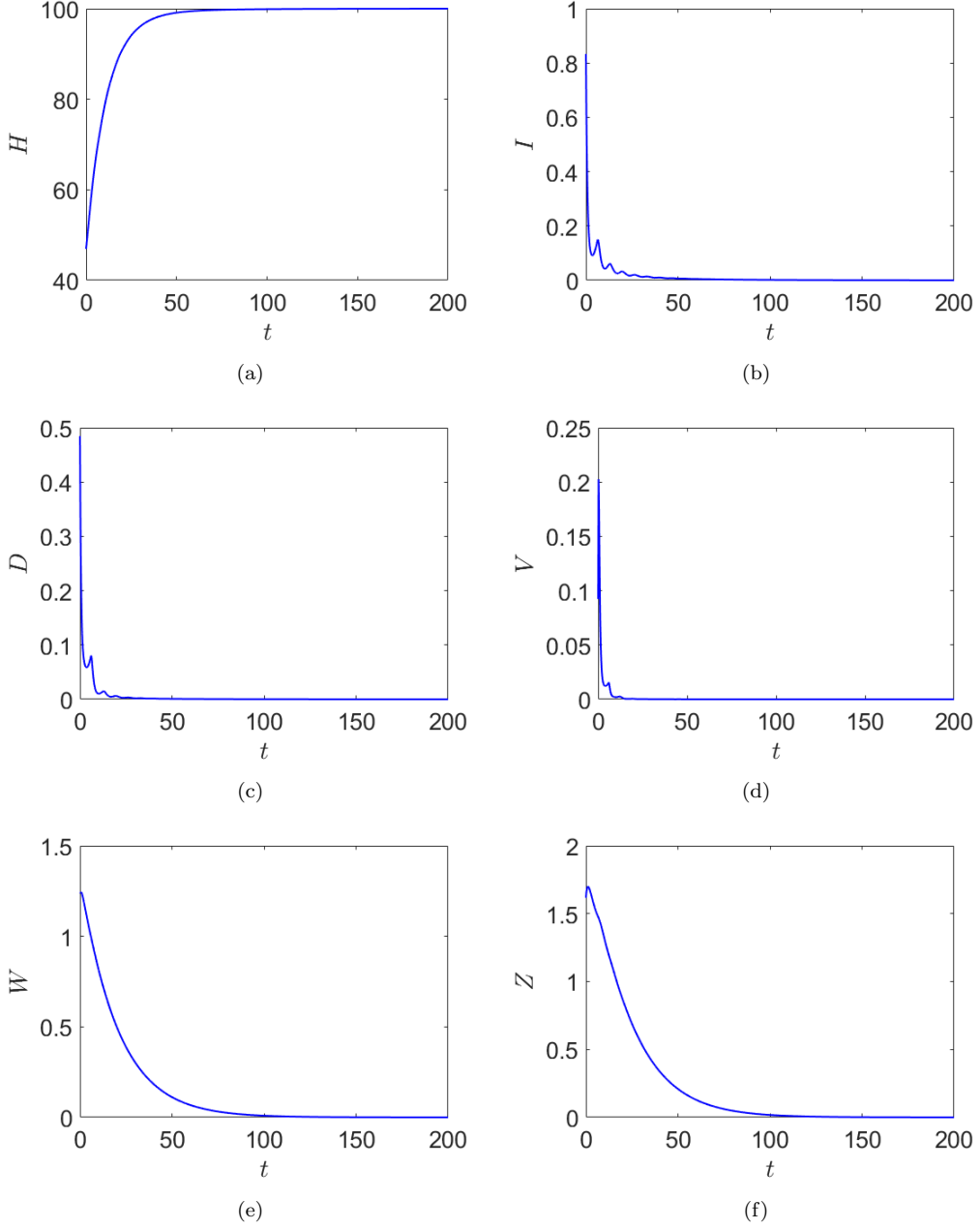
Figure 1: Temporal evolutions for components of the system (14) when $R_0 = 0.83 < 1$. The used parameter values are $s = 10$, $\mu = 0.1$, $\delta = 1$, $p = 0.2$, $\kappa = 1.2$, $\beta = 0.87$, $\nu = 4$, $q = 0.3$, $a = 0.3$, $\sigma = 0.05$, $b = 0.2$, $\eta = 0.05$, $\gamma_1 = \gamma_2 = 0.05$, $\rho_1 = \rho_2 = 1$, $\alpha_1 = \alpha_2 = \alpha_3 = 0.3$, and $\tau_1 = \tau_2 = \tau_3 = 6$.

with respect to a wide class of incidence functions and several probability distributions for distributed delays.
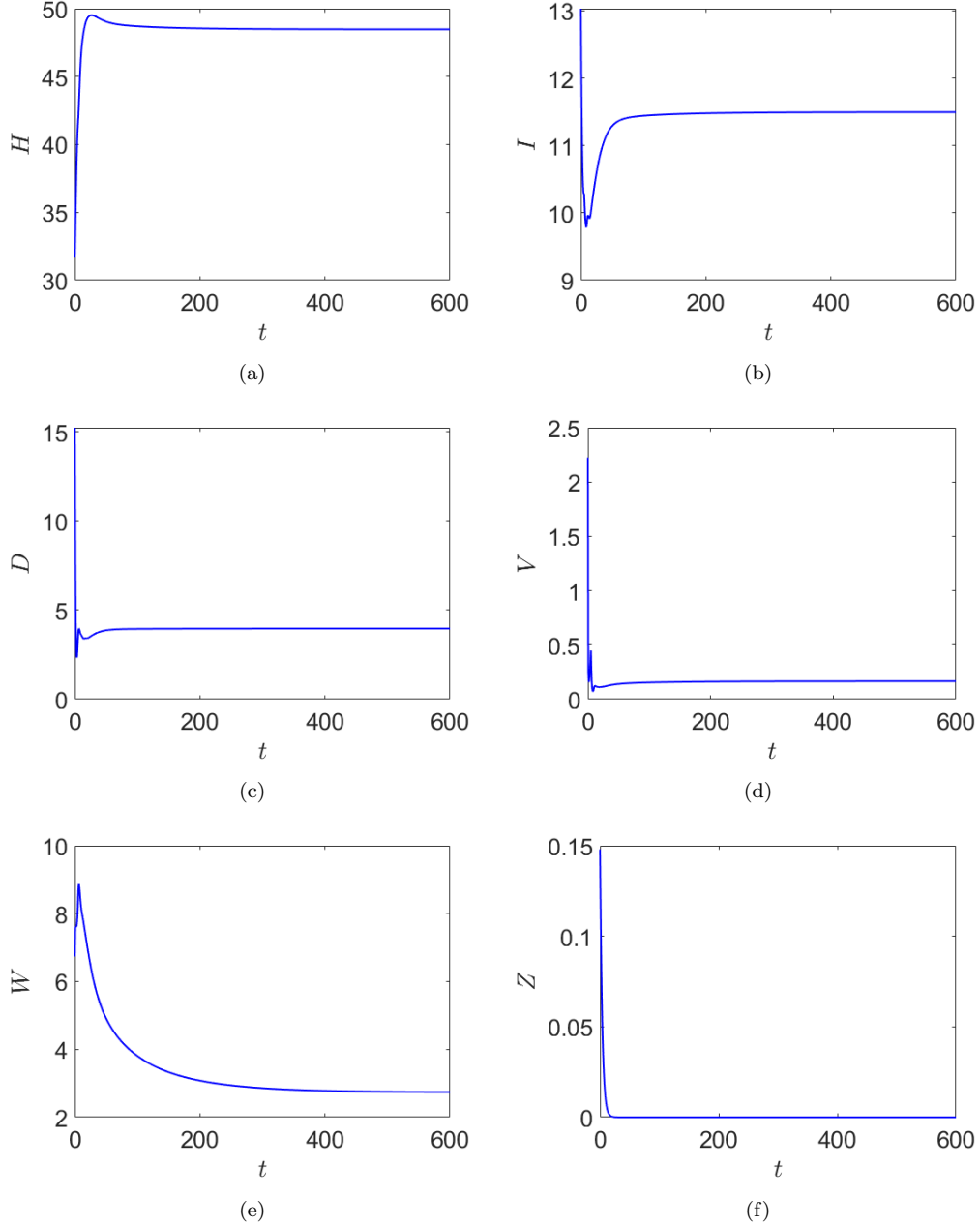
Figure 2: Temporal evolutions for components of the system (14) when $R_0 = 22.706 > 1$, $R_1 = 0.123 < 1$ and $R_2 = 0.466 < 1$. The used parameter values are $s = 10$, $\mu = 0.1$, $\delta = 0.1$, $p = 0.2$, $\kappa = 1.5$, $\beta = 0.87$, $\nu = 3.8$, $q = 0.3$, $a = 0.3$, $\sigma = 0.5$, $b = 0.02$, $\eta = 0.5$, $\gamma_1 = \gamma_2 = 0.1$, $\rho_1 = \rho_2 = 1$, $\alpha_1 = \alpha_2 = \alpha_3 = 0.3$, and $\tau_1 = \tau_2 = \tau_3 = 5$.

Acknowledgements

Figure 3: Temporal evolutions for components of the system (14) when $R_0 = 22.706 > 1$, $R_1 = 1.231 > 1$ and $R_3 = 0.46 < 1$. The used parameter values are $s = 10$, $\mu = 0.1$, $\delta = 0.1$, $p = 0.2$, $\kappa = 1.5$, $\beta = 0.87$, $\nu = 3.8$, $q = 0.3$, $a = 0.3$, $\sigma = 0.05$, $b = 0.02$, $\eta = 0.5$, $\gamma_1 = \gamma_2 = 0.1$, $\rho_1 = \rho_2 = 1$, $\alpha_1 = \alpha_2 = \alpha_3 = 0.3$, and $\tau_1 = \tau_2 = \tau_3 = 5$.

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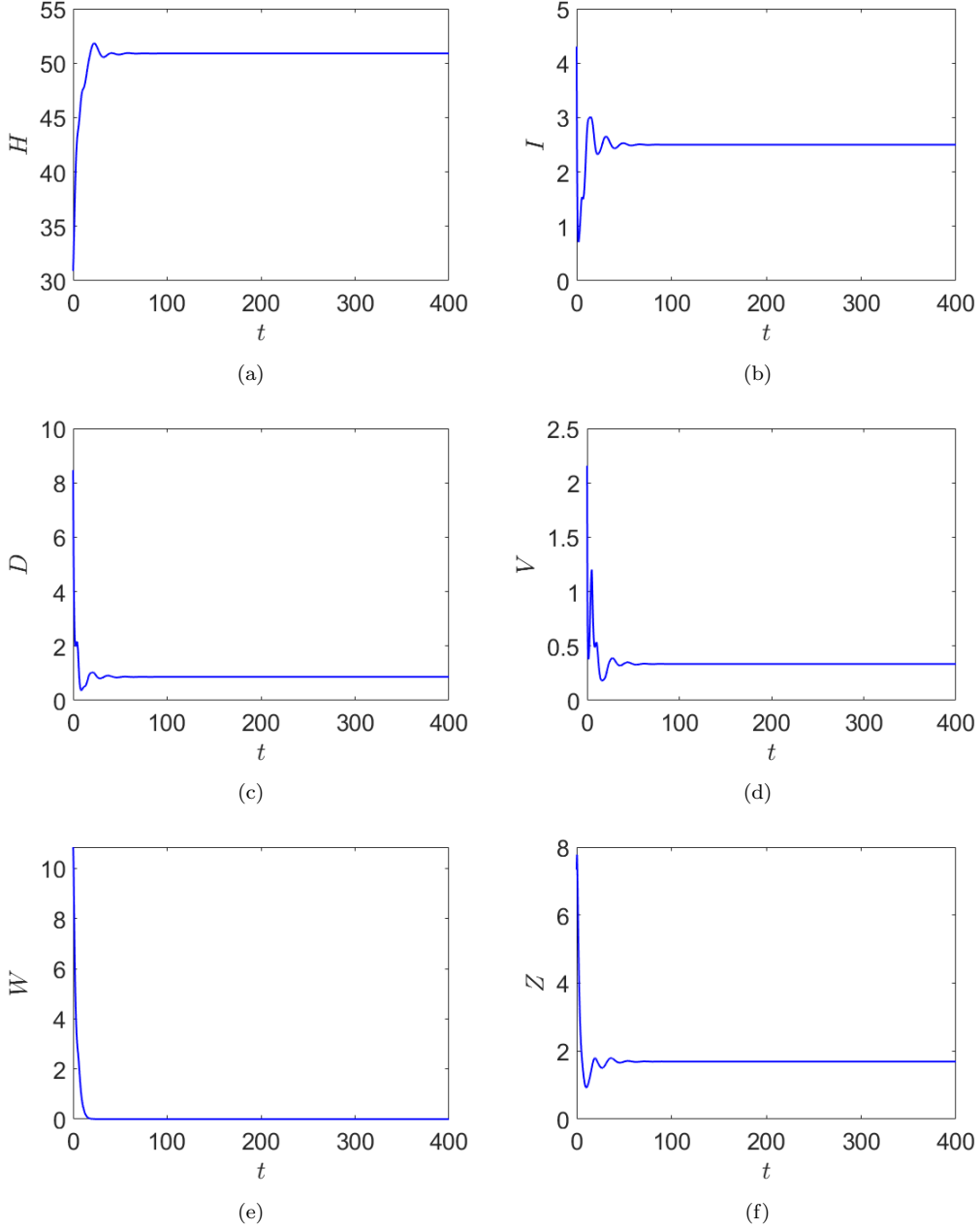https://www.who.int/news-room/fact-sheets/detail/hepatitis-b.

Figure 4: Temporal evolutions for components of the system (14) when $R_0 = 25.302 > 1$, $R_2 = 5.464 > 1$ and $R_4 = 0.201 < 1$. The used parameter values are $s = 10$, $\mu = 0.1$, $\delta = 0.1$, $p = 0.2$, $\kappa = 1.5$, $\beta = 0.87$, $\nu = 0.5$, $q = 0.3$, $a = 0.3$, $\sigma = 0.5$, $b = 0.2$, $\eta = 0.5$, $\gamma_1 = \gamma_2 = 0.1$, $\rho_1 = \rho_2 = 1$, $\alpha_1 = \alpha_2 = \alpha_3 = 0.3$, and $\tau_1 = \tau_2 = \tau_3 = 5$.

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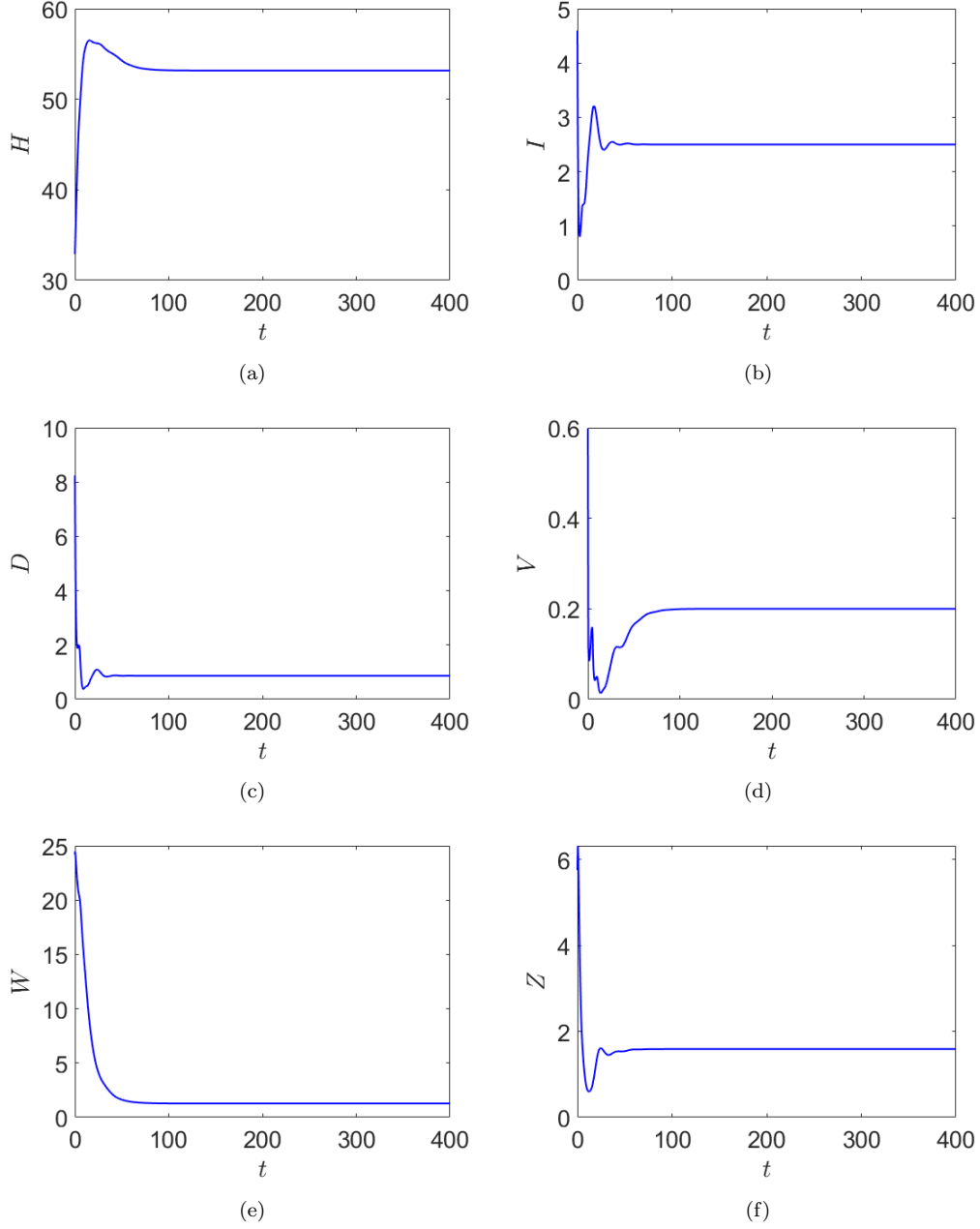[3] K. Manna, K. Hattaf, Spatiotemporal dynamics of a generalized HBV infection model

Figure 5: Temporal evolutions for components of the system (14) when $R_0 = 29.786 > 1$, $R_1 = 23.831 > 1$, $R_2 = 5.693 > 1$, $R_3 = 4.65 > 1$ and $R_4 = 4.186 > 1$. The used parameter values are $s = 10$, $\mu = 0.1$, $\delta = 0.1$, $p = 0.2$, $\kappa = 1.5$, $\beta = 0.87$, $\nu = 0.2$, $q = 0.5$, $a = 0.5$, $\sigma = 0.1$, $b = 0.2$, $\eta = 0.5$, $\gamma_1 = \gamma_2 = 0.1$, $\rho_1 = \rho_2 = 1$, $\alpha_1 = \alpha_2 = \alpha_3 = 0.3$, and $\tau_1 = \tau_2 = \tau_3 = 5$.

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