



Research article

Global stability and optimal control of an HBV/HCV coinfection model with humoral immunity and cell-to-cell transmission

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Abstract: In this study, we investigate the dynamics of a within-host model of hepatitis B virus (HBV) and hepatitis C virus (HCV) coinfection with two distinct transmission pathways: virus-to-cell and cell-to-cell transmission. The model incorporates both HBV-specific and HCV-specific humoral immunity. Using the next-generation matrix method, we derive the basic reproduction numbers for HBV mono-infection ($\mathcal{R}_0^B$), HCV mono-infection ($\mathcal{R}_0^C$), and HBV/HCV coinfection ($\mathcal{R}_0 = \max\{\mathcal{R}_0^B, \mathcal{R}_0^C\}$). We establish the fundamental qualitative properties of the model, identify eight possible equilibrium points, and investigate their global stability. The stability analysis is carried out using Lyapunov functions together with the Lyapunov–LaSalle invariance principle. The model is further formulated as a nonlinear control system, where anti-HBV and anti-HCV therapies serve as the control inputs. For each virus, two antiviral treatment strategies are considered: one that reduces virus-to-cell transmission and another that reduces cell-to-cell transmission. The results show that neglecting cell-to-cell transmission may underestimate the treatment effort required for viral clearance, highlighting the importance of incorporating this transmission pathway to obtain more realistic descriptions of within-host HBV/HCV dynamics. The optimal control problem is formulated to maximize the population of uninfected hepatocytes while minimizing treatment costs. Numerical simulations illustrate the theoretical results and demonstrate that the proposed control strategies can reduce viral infections and increase the population of uninfected hepatocytes under the considered parameter scenarios. Finally, sensitivity analysis of $\mathcal{R}_0^B$ and $\mathcal{R}_0^C$ identifies the parameters that have the greatest influence on the basic reproduction numbers, providing insights into the model mechanisms associated with viral persistence and clearance.

Keywords: hepatitis B virus; hepatitis C virus; global stability; Lyapunov function; optimal control

1. Introduction

A report from the World Health Organization (WHO) provides a comprehensive and up-to-date assessment of the global burden of hepatitis B and hepatitis C, which together account for more than 95% of deaths related to viral hepatitis [1]. Viral hepatitis is now considered to be the second leading infectious cause of death globally, causing about 1.3 million deaths each year, similar to the mortality associated with tuberculosis. Of these deaths, hepatitis B accounts for approximately 83%, while hepatitis C contributes about 17% [2]. Long-term infection with these viruses leads to serious liver complications such as cirrhosis and hepatocellular carcinoma [2].

Hepatitis B and hepatitis C are caused by hepatitis B virus (HBV) and hepatitis C virus (HCV), respectively. HBV is a DNA virus classified within the Hepadnaviridae family, and it replicates in the nucleus of hepatocytes. By comparison, HCV is an RNA virus that belongs to the Flaviviridae family and carries out its replication in the cytoplasm [3–5].

Coinfection with HBV and HCV is commonly observed in regions where both infections are endemic [4, 6]. Clinical and epidemiological studies indicate that coinfecting individuals are at a higher risk of developing severe liver disease and are more likely to progress to hepatocellular carcinoma than patients infected with either virus alone. In addition, partial immune suppression may occur in coinfecting patients. HBV/HCV coinfection can arise either through simultaneous transmission (cotransmission), in which both viruses are acquired at the same time via shared exposure routes such as contaminated blood transfusions, intravenous drug use, unsafe injection practices, or organ transplantation, or through superinfection, where an individual with a pre-existing chronic infection acquires the second virus [3, 4, 7].

When two viruses target the same cell population, their long-term coexistence may occur under specific biological conditions. These conditions may include: (i) Superinfection, in which one virus can infect cells already infected by another virus [8]; (ii) immune-mediated interactions, where cytotoxic T lymphocytes (CTLs) or antibodies introduce regulatory feedback that may allow both viruses to persist [9, 10]; (iii) viral saturation effects, where nonlinear infection mechanisms can reduce the intensity of inter-viral competition [11]; (iv) overlapping and distinct target-cell populations, where the viruses share some target-cell populations while also infecting distinct cell types [12, 13]; and (v) two competing viruses interacting across two target-cell populations, where each virus can infect both target-cell types, thereby creating cross-interactions that may permit viral coexistence [14]. These mechanisms demonstrate that competition for common target cells does not necessarily result in competitive exclusion and that viral coexistence can arise through interactions among transmission, immune responses, and target-cell availability.

Antiviral therapy for HBV is typically initiated early and primarily involves nucleoside analogues (NAs) and pegylated interferon (IFN- α). NAs suppress viral replication by inhibiting DNA synthesis, whereas IFN- α can contribute to viral suppression and immune-mediated control of HBV infection [15, 16]. In addition, IFN- α is a key component of innate immunity and is also used in the treatment of HCV infection [17]. More recently, direct-acting antivirals (DAAs) have become central to HCV therapy by targeting specific stages of the viral life cycle. During therapy, the viral load declines, leading to a corresponding reduction in viral replication within the liver [18]. For this reason, it is crucial to study the optimization of treatment for hepatitis viruses. Several mathematical models have discussed HBV treatment in [19, 20]. Additionally, HCV treatment has been discussed in [21, 22].

Mathematical modeling has become an essential approach for investigating viral dynamics and interactions within the host. These models help clarify the mechanisms governing infection at the cellular level and provide valuable insights into disease progression. They are also useful for improving antiviral therapies and vaccine strategies, as well as informing decisions on optimal treatment and prevention approaches. Furthermore, such models assist in identifying the critical parameters needed to interpret experimental findings and better understand biological systems. A number of studies have developed within-host models for HBV infection; for instance, Nowak and colleagues [23] proposed a foundational mathematical model describing HBV mono-infection:

$$\begin{aligned}\dot{H} &= \overbrace{\phi}^{\text{hepatocytes production}} - \overbrace{\sigma H}^{\text{natural death}} - \overbrace{\beta HV}^{\text{HBV infectious transmission}}, \\ \dot{Y} &= \overbrace{\beta HV}^{\text{HBV infectious transmission}} - \overbrace{\delta Y}^{\text{natural death}}, \\ \dot{V} &= \overbrace{\theta Y}^{\text{HBV production}} - \overbrace{\phi V}^{\text{natural death}},\end{aligned}$$

where $H = H(t)$, $Y = Y(t)$, and $V = V(t)$ represent, respectively, the densities of uninfected hepatocytes, hepatocytes infected with HBV, and free HBV particles at time t .

It is well established that the immune system combats viral infections through two main pathways: humoral immunity and cell-mediated immunity. The cell-mediated response is driven by cytotoxic T lymphocytes (CTLs), which target and destroy infected cells. In contrast, humoral immunity is mediated by antibodies produced by B lymphocytes, which function to neutralize circulating viral particles. The primary role of these antibodies is to block viral activity and prevent further infection [24]. Early mathematical models based on ordinary differential equations (ODEs) that incorporated both viral dynamics and the humoral immune response were proposed by Murase et al. [25] and Wang and Zou [26]. These studies introduced a fundamental modeling framework to represent how the humoral immune response interacts with HBV infection:

$$\begin{aligned}\dot{H} &= \overbrace{\phi}^{\text{hepatocytes production}} - \overbrace{\sigma H}^{\text{natural death}} - \overbrace{\beta HV}^{\text{HBV infectious transmission}}, \\ \dot{Y} &= \overbrace{\beta HV}^{\text{HBV infectious transmission}} - \overbrace{\delta Y}^{\text{natural death}}, \\ \dot{V} &= \overbrace{\theta Y}^{\text{HBV production}} - \overbrace{\phi V}^{\text{natural death}} - \overbrace{\gamma AV}^{\text{HBV neutralization}}, \\ \dot{A} &= \overbrace{\rho AV}^{\text{Proliferation of HBV-specific antibodies}} - \overbrace{\lambda A}^{\text{natural death}},\end{aligned}$$

where $A = A(t)$ represents the concentration of antibodies. The terms ρAV and λA denote the proliferation and death rates of antibodies, respectively, while γAV is the viral neutralization rate constant due to antibodies. Building on these, several mathematical models have been developed [27, 28] to describe HBV infection in the presence of antibody-mediated immune response. Foko and Tadmon [29] developed a diffusive within-host HBV model incorporating viral capsids, adaptive immunity, and exposed and productively infected hepatocytes, while Foko [30] investigated a

delayed within-host HBV model that further accounts for viral capsids, exposed infected hepatocytes, adaptive immune responses, and a general incidence rate.

Beyond the classical infection routes, it is widely recognized that viruses can also spread through a mechanism known as cell-to-cell transmission [31, 32]. In this process, viral particles are passed directly from an infected cell to adjacent susceptible cells through specialized contact structures called virological synapses [33, 34]. Recent studies have examined the combined impact of both virus-to-cell and direct cell-to-cell transmission pathways on overall viral dynamics [35, 36]. Motivated by these findings, mathematical models have been developed [37, 38] to characterize HBV monoinfection while explicitly accounting for cell-to-cell viral spread.

Several mathematical models have been proposed to better understand the dynamics of HCV infection [39–41]. These models incorporate a variety of biological mechanisms, adaptive immune responses [41–43], and cell-to-cell transmission [44–47]. In addition, more comprehensive multiscale models have been developed that simultaneously account for virus-to-cell and cell-to-cell transmission, as well as CTL and antibody-mediated immune response [48].

Antiviral treatment plays an important role in controlling HBV and HCV infections by suppressing viral replication and reducing the viral burden in infected individuals. Accordingly, mathematical models incorporating therapeutic interventions have been developed to evaluate treatment efficacy and investigate strategies for controlling these infections. Sadki et al. [49] developed a mathematical model of HCV dynamics that incorporates the effects of therapy, both modes of viral transmission, and adaptive immune responses, while Yosyingyong et al. [50] proposed a model for HBV dynamics that includes the effects of therapy, time delay, intracellular HBV DNA-containing capsids, and adaptive immunity.

A variety of mathematical models have been proposed to investigate the transmission co-dynamics of HBV and HCV at the population level [51, 52]. However, mathematical models describing the within-host co-dynamics of HBV and HCV have received much less attention. Within-host models of HBV/HCV coinfection have recently been developed by Elaiw et al. [53, 54], respectively. The model given in [53] considered HBV/HCV coinfection with antibody-mediated immunity as follows:

$$\begin{aligned}
 \dot{H} &= \overbrace{\phi}^{\text{hepatocytes production}} - \overbrace{\sigma H}^{\text{natural death}} - \overbrace{\beta_B H V^B}^{\text{HBV infectious transmission}} - \overbrace{\beta_C H V^C}^{\text{HCV infectious transmission}}, \\
 \dot{Y}^B &= \overbrace{\beta_B H V^B}^{\text{HBV infectious transmission}} - \overbrace{\delta_B Y^B}^{\text{natural death}}, \\
 \dot{Y}^C &= \overbrace{\beta_C H V^C}^{\text{HCV infectious transmission}} - \overbrace{\delta_C Y^C}^{\text{natural death}}, \\
 \dot{V}^B &= \overbrace{\theta_B Y^B}^{\text{HBV production}} - \overbrace{\phi_B V^B}^{\text{natural death}} - \overbrace{\gamma_B A^B V^B}^{\text{HBV neutralization}}, \\
 \dot{V}^C &= \overbrace{\theta_C Y^C}^{\text{HCV production}} - \overbrace{\phi_C V^C}^{\text{natural death}} - \overbrace{\gamma_C A^C V^C}^{\text{HCV neutralization}}, \\
 \dot{A}^B &= \overbrace{\rho_B A^B V^B}^{\text{Proliferation of HBV-specific antibodies}} - \overbrace{\lambda_B A^B}^{\text{natural death}}, \\
 \dot{A}^C &= \overbrace{\rho_C A^C V^C}^{\text{Proliferation of HCV-specific antibodies}} - \overbrace{\lambda_C A^C}^{\text{natural death}},
 \end{aligned}$$

where $H = H(t)$, $Y^B = Y^B(t)$, $Y^C = Y^C(t)$, $V^B = V^B(t)$, $V^C = V^C(t)$, $A^B = A^B(t)$, and $A^C =$

$A^C(t)$ denote the uninfected hepatocytes, hepatocytes infected with HBV, hepatocytes infected with HCV, free HBV particles, free HCV particles, antibodies targeting HBV, and antibodies targeting HCV, respectively, at time t .

The model presented in [54] considered HBV/HCV coinfection with CTL-mediated immunity. Neither of these studies considered cell-to-cell transmission. Conversely, cell-to-cell transmission has been incorporated into within-host models of HBV monoinfection [37, 38] and HCV monoinfection [44–46], but its simultaneous role in HBV/HCV coinfection has not been investigated. Thus, the present study extends these previous formulations by incorporating both virus-to-cell and cell-to-cell transmission into a within-host HBV/HCV coinfection model with antibody-mediated immunity.

For clarity, Table 1 summarizes the main differences between the previous within-host HBV/HCV coinfection models in [53, 54] and the present study. The comparison in Table 1 demonstrates that the mathematical contribution of the present study extends beyond the combination of previously investigated biological mechanisms. In particular, the simultaneous inclusion of virus-to-cell and cell-to-cell transmission leads to new threshold quantities, $\tilde{\mathcal{R}}_2^B$ and $\tilde{\mathcal{R}}_2^C$, together with the corresponding invasion conditions. Furthermore, unlike the models in [53, 54], the present study formulates and analyzes a nonlinear optimal-control problem. Therefore, the present work provides a mathematical assessment of how cell-to-cell transmission affects HBV/HCV coinfection dynamics and treatment optimization.

Table 1. Comparison of the main features of [53, 54], and the present work.

Feature	Ref. [53]	Ref. [54]	Present study
HBV/HCV coinfection	✓	✓	✓
Antibody-mediated immunity	✓	×	✓
CTL-mediated immunity	×	✓	×
Virus-to-cell transmission	✓	✓	✓
Cell-to-cell transmission	×	×	✓
Both transmission modes	×	×	✓
New thresholds $\tilde{\mathcal{R}}_2^B, \tilde{\mathcal{R}}_2^C$	×	×	✓
Globally asymptotically stable of single-antibody coinfection equilibria	×	×	✓
Optimal control	×	×	✓

In this work, we develop a within-host model of HBV/HCV coinfection that incorporates antibody-mediated immune responses and both virus-to-cell and cell-to-cell transmission. We establish the non-negativity and boundedness of the solutions, derive the relevant threshold quantities, determine all possible equilibria, and analyze their global stability. We further formulate a nonlinear optimal-control problem, which was not considered in [53] or [54], to maximize the population of uninfected hepatocytes while minimizing the treatment costs. Numerical simulations are conducted to validate the theoretical findings, compare the effects of virus-to-cell and cell-to-cell transmission, assess the impact of optimal treatment strategies on HBV/HCV co-dynamics, and demonstrate the importance of accounting for cell-to-cell transmission in treatment design.

2. Model formulation

This section presents a mathematical framework that captures the within-host dynamics of coinfection with HBV and HCV with both virus-to-cell and cell-to-cell transmission. A diagram illustrating these interactions is provided in Figure 1. The formulation of the model relies on the following assumptions:

- (A1) The model is composed of seven coupled state variables: uninfected hepatocytes (H), hepatocytes infected with HBV (Y^B), hepatocytes infected with HCV (Y^C), free HBV particles (V^B), free HCV particles (V^C), antibodies targeting HBV (A^B), and antibodies targeting HCV (A^C). Each variable represents the density of its corresponding population.
- (A2) Uninfected hepatocytes act as the primary target cells for infection by both viruses.
- (A3) The population of uninfected hepatocytes is maintained through a constant recruitment rate ϕ , while natural cell death occurs at a rate of σH . These cells become infected with HBV and HCV through virus-to-cell transmission at the rates of $\beta_B H V^B$ and $\beta_C H V^C$, respectively.
- (A4) Infection by HBV is driven by interactions between infected cells and susceptible hepatocytes, occurring through cell-to-cell transmission at a rate of $\alpha_B H Y^B$.
- (A5) Likewise, HCV transmission arises from contact between HCV-infected cells and healthy hepatocytes, through cell-to-cell transmission at a rate of $\alpha_C H Y^C$.
- (A6) HBV virions are produced by HBV-infected hepatocytes at a rate of $\theta_B Y^B$ and cleared at a rate of $\phi_B V^B$. Similarly, HCV virions are produced by HCV-infected hepatocytes at a rate of $\theta_C Y^C$ and cleared at a rate of $\phi_C V^C$.
- (A7) HBV-specific antibodies undergo virus-induced expansion in response to encounters with HBV virions at a rate of $\rho_B A^B V^B$, decay at a rate of $\lambda_B A^B$, and contribute to viral neutralization at a rate of $\gamma_B A^B V^B$. The bilinear term $\rho_B A^B V^B$ represents a virus–humoral immune interaction of a predator–prey type and has been used in mathematical models of virus–immune dynamics (see, e.g., [24]). Thus, the antibody compartment represents the amplification of a pre-existing HBV-specific humoral response rather than the generation of antibodies from an initially zero level.
- (A8) Similarly, HCV-specific antibodies undergo virus-induced expansion in response to encounters with HCV virions at a rate of $\rho_C A^C V^C$, decay at a rate of $\lambda_C A^C$, and contribute to viral neutralization at a rate of $\gamma_C A^C V^C$. The term $\rho_C A^C V^C$ likewise represents a virus–humoral immune interaction of predator–prey type, consistent with formulations used in virus–immune dynamics (see, e.g., [24]). Accordingly, A^C represents an aggregate HCV-specific humoral response that can be amplified in the presence of HCV rather than antibodies generated from an initially zero level.
- (A9) For mathematical tractability, HBV- and HCV-infected hepatocytes are represented by mutually exclusive compartments in the present model. Thus, the model does not explicitly include a compartment for hepatocytes simultaneously infected with both HBV and HCV. This assumption

is adopted to focus on the competition between the two viruses for uninfected hepatocytes and to investigate the effects of virus-to-cell and cell-to-cell transmission. Importantly, this assumption does not imply that simultaneous HBV/HCV infection at the cellular level is biologically impossible. Experimental studies (see e.g., [55, 56]) have demonstrated that HBV and HCV can coexist within the same hepatocyte, while HCV replication may suppress HBV replication. Therefore, the present formulation should be interpreted as an effective approximation of viral competition and interference at the within-host population level. Incorporating a doubly infected hepatocyte compartment and the corresponding intracellular interactions would provide a more detailed description of HBV/HCV coinfection and is left for future investigation.

Based on assumptions (A1)–(A9), the corresponding system of equations describing the within-host dynamics of HBV/HCV coinfection can be constructed as follows.

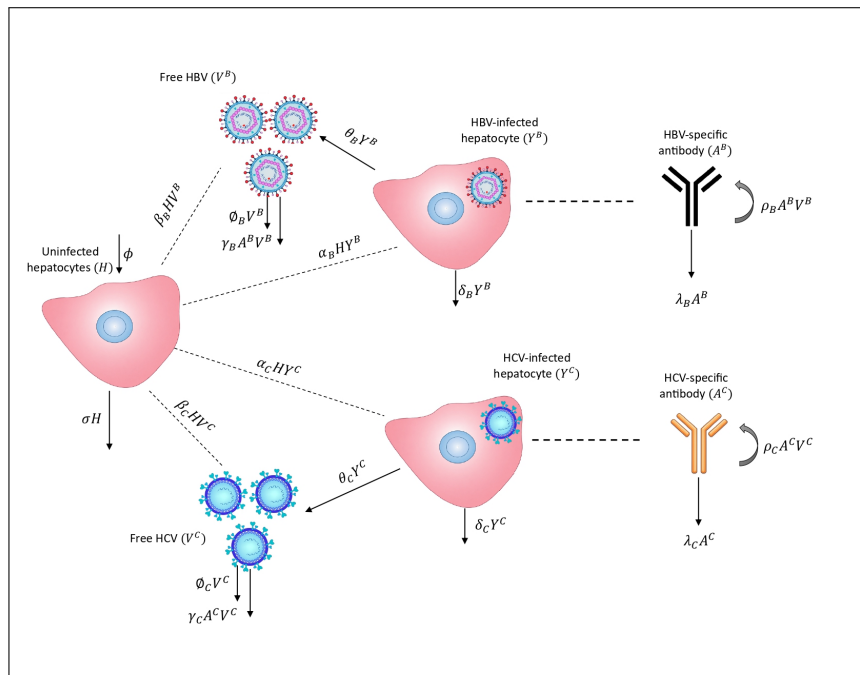


Figure 1. The schematic diagram of the HBV/HCV coinfection dynamics within-host.

$$\begin{aligned}
 \dot{H} &= \phi - \sigma H - \beta_B H V^B - \alpha_B H Y^B - \beta_C H V^C - \alpha_C H Y^C, \\
 \dot{Y}^B &= \beta_B H V^B + \alpha_B H Y^B - \delta_B Y^B, \\
 \dot{Y}^C &= \beta_C H V^C + \alpha_C H Y^C - \delta_C Y^C, \\
 \dot{V}^B &= \theta_B Y^B - \phi_B V^B - \gamma_B A^B V^B, \\
 \dot{V}^C &= \theta_C Y^C - \phi_C V^C - \gamma_C A^C V^C, \\
 \dot{A}^B &= \rho_B A^B V^B - \lambda_B A^B, \\
 \dot{A}^C &= \rho_C A^C V^C - \lambda_C A^C,
 \end{aligned} \tag{2.1}$$

where $(H, Y^B, Y^C, V^B, V^C, A^B, A^C) = (H(t), Y^B(t), Y^C(t), V^B(t), V^C(t), A^B(t), A^C(t))$. All variables

and parameters preserve the same biological meanings as introduced in the previous section. The units assigned to the model variables are as follows: time (t) is measured in days; (H) , (Y^B) , and (Y^C) represent cell concentrations (cells mm^{-3}); (V^B) and (V^C) denote viral concentrations (viruses mm^{-3}); and (A^B) and (A^C) represent antibody concentrations ($\mu\text{g mm}^{-3}$). The units associated with all model parameters are listed in Table 3.

It is important to clarify the biological interpretation of the antibody compartments. Because the antibody equations contain the factors A^B and A^C , respectively, an initially zero antibody population remains zero. Thus, the present formulation describes the amplification and persistence of a pre-existing humoral response rather than the generation of antibodies from an initially zero level. Consequently, the antibody-positive equilibria considered below should be interpreted as states in which a pre-existing humoral response is maintained or amplified in the presence of the corresponding virus. A more detailed representation of de novo antibody production would require additional immune-cell compartments and corresponding recruitment and differentiation mechanisms, which are beyond the scope of the present model.

It is important to clarify the biological interpretation of the HCV-specific antibody compartment A^C . Unlike anti-HBs, which is a clinically established marker associated with protection against HBV, anti-HCV antibodies do not generally indicate viral clearance or complete protective immunity, since HCV can persist despite substantial antibody responses. Nevertheless, neutralizing antibodies can arise during HCV infection, and some broadly neutralizing antibodies have demonstrated the ability to inhibit HCV infection and may contribute to partial protection against viral infection [57–59]. Therefore, A^C is interpreted in the present model as an aggregate HCV-specific humoral response rather than a direct measure of sterilizing immunity or complete viral protection. Accordingly, an increase in A^C in the numerical simulations should be interpreted as an enhanced modeled humoral response and not necessarily as evidence of HCV clearance.

3. Fundamental qualitative properties

This section investigates the fundamental properties of system (2.1). In particular, we establish the non-negativity and boundedness of the solutions of the system to ensure the biological feasibility and well-posedness of the model.

Lemma 1. *The solutions of system (2.1) are non-negative and bounded.*

Proof. We have

$$\begin{aligned}\dot{H} \big|_{(H=0)} &= \phi > 0, \\ \dot{Y}^B \big|_{(Y^B=0, H \geq 0, V^B \geq 0)} &= \beta_B H V^B \geq 0, \\ \dot{Y}^C \big|_{(Y^C=0, H \geq 0, V^C \geq 0)} &= \beta_C H V^C \geq 0, \\ \dot{V}^B \big|_{(V^B=0, Y^B \geq 0)} &= \theta_B Y^B \geq 0, \\ \dot{V}^C \big|_{(V^C=0, Y^C \geq 0)} &= \theta_C Y^C \geq 0, \\ \dot{A}^B \big|_{(A^B=0)} &= 0, \\ \dot{A}^C \big|_{(A^C=0)} &= 0.\end{aligned}$$

Thus, according to Proposition B.7 of [60], the non-negative orthant $R_{\geq 0}^7$ is positively invariant. Hence, for every initial condition $(H(0), Y^B(0), Y^C(0), V^B(0), V^C(0), A^B(0), A^C(0)) \in R_{\geq 0}^7$, the corresponding solution remains in $R_{\geq 0}^7$ for all $t \geq 0$. Let us define

$$\Psi = H + Y^B + Y^C + \frac{\delta_B}{2\theta_B} V^B + \frac{\delta_C}{2\theta_C} V^C + \frac{\delta_B \gamma_B}{2\theta_B \rho_B} A^B + \frac{\delta_C \gamma_C}{2\theta_C \rho_C} A^C.$$

Then, using system (2.1), we obtain

$$\dot{\Psi} = \phi - \sigma H - \frac{\delta_B}{2} Y^B - \frac{\delta_C}{2} Y^C - \frac{\delta_B \phi_B}{2\theta_B} V^B - \frac{\delta_C \phi_C}{2\theta_C} V^C - \frac{\delta_B \gamma_B \lambda_B}{2\theta_B \rho_B} A^B - \frac{\delta_C \gamma_C \lambda_C}{2\theta_C \rho_C} A^C.$$

Let $\varrho = \min\left\{\sigma, \frac{\delta_B}{2}, \frac{\delta_C}{2}, \phi_B, \phi_C, \lambda_B, \lambda_C\right\}$. Since all model parameters are positive, $\varrho > 0$. Therefore, we have

$$\begin{aligned} \dot{\Psi} &\leq \phi - \varrho \left[H + Y^B + Y^C + \frac{\delta_B}{2\theta_B} V^B + \frac{\delta_C}{2\theta_C} V^C + \frac{\delta_B \gamma_B}{2\theta_B \rho_B} A^B + \frac{\delta_C \gamma_C}{2\theta_C \rho_C} A^C \right], \\ &= \phi - \varrho \Psi. \end{aligned}$$

By the comparison principle

$$\Psi(t) \leq \Psi(0) e^{-\varrho t} + \frac{\phi}{\varrho} (1 - e^{-\varrho t}).$$

Consequently,

$$\Psi(t) \leq \max\left\{\Psi(0), \frac{\phi}{\varrho}\right\}.$$

Let

$$\Delta = \max\left\{\Psi(0), \frac{\phi}{\varrho}\right\}.$$

Since all state variables are non-negative and all their coefficients in Ψ are positive, we obtain $0 \leq H(t) \leq \Delta$, $0 \leq Y^B(t) \leq \Delta$, $0 \leq Y^C(t) \leq \Delta$, $0 \leq V^B(t) \leq \frac{2\theta_B}{\delta_B} \Delta$, $0 \leq V^C(t) \leq \frac{2\theta_C}{\delta_C} \Delta$, $0 \leq A^B(t) \leq \frac{2\theta_B \rho_B}{\delta_B \gamma_B} \Delta$, and $0 \leq A^C(t) \leq \frac{2\theta_C \rho_C}{\delta_C \gamma_C} \Delta$. Hence, all components of the solution are bounded for $t \geq 0$, and therefore, the solution is globally defined.

Consequently, if the initial condition satisfies $\Psi(0) \leq \Delta_1$, where $\Delta_1 = \frac{\phi}{\varrho}$, then the set

$$\Gamma = \left\{ (H, Y^B, Y^C, V^B, V^C, A^B, A^C) \in \mathbb{R}_{\geq 0}^7 : \Psi \leq \Delta_1 \right\},$$

is positively invariant with respect to system (2.1). Indeed, on the boundary $\Psi = \Delta_1$

$$\dot{\Psi} \leq \phi - \varrho \Delta_1 = 0.$$

Thus, trajectories cannot leave Γ through the boundary ($\Psi = \Delta_1$). Moreover, since Γ is closed and bounded in $R_{\geq 0}^7$, it is compact.

4. Equilibria

In this section, we establish the equilibrium points of system (2.1) and determine the conditions for the existence of the equilibria. For any equilibrium point $\Xi = (H, Y^B, Y^C, V^B, V^C, A^B, A^C)$, the following equations hold:

$$0 = \phi - \sigma H - \beta_B H V^B - \alpha_B H Y^B - \beta_C H V^C - \alpha_C H Y^C, \quad (4.1)$$

$$0 = \beta_B H V^B + \alpha_B H Y^B - \delta_B Y^B, \quad (4.2)$$

$$0 = \beta_C H V^C + \alpha_C H Y^C - \delta_C Y^C, \quad (4.3)$$

$$0 = \theta_B Y^B - \phi_B V^B - \gamma_B A^B V^B, \quad (4.4)$$

$$0 = \theta_C Y^C - \phi_C V^C - \gamma_C A^C V^C, \quad (4.5)$$

$$0 = \rho_B A^B V^B - \lambda_B A^B, \quad (4.6)$$

$$0 = \rho_C A^C V^C - \lambda_C A^C. \quad (4.7)$$

The system in Eqs (4.1)–(4.7) has the following equilibria:

- Infection-free equilibrium, $\Xi_0 = (H_0, 0, 0, 0, 0, 0, 0)$, where $H_0 = \phi/\sigma$.
- HBV monoinfection equilibrium without a positive antibody response, $\Xi_1 = (H_1, Y_1^B, 0, V_1^B, 0, 0, 0)$, where

$$H_1 = \frac{H_0}{\mathfrak{R}_0^B}, \quad Y_1^B = \frac{\sigma \phi_B}{\beta_B \theta_B + \alpha_B \phi_B} (\mathfrak{R}_0^B - 1), \quad V_1^B = \frac{\sigma \theta_B}{\beta_B \theta_B + \alpha_B \phi_B} (\mathfrak{R}_0^B - 1),$$

where

$$\mathfrak{R}_0^B = \frac{H_0 (\beta_B \theta_B + \alpha_B \phi_B)}{\delta_B \phi_B}$$

is the basic reproduction number for HBV monoinfection. It serves as the threshold quantity determining whether HBV infection can be established in a susceptible host. Consequently, the equilibrium Ξ_1 exists whenever $\mathfrak{R}_0^B > 1$.

Let us write

$$\mathfrak{R}_0^B = \mathfrak{R}_{01}^B + \mathfrak{R}_{02}^B = \frac{H_0 \beta_B \theta_B}{\delta_B \phi_B} + \frac{H_0 \alpha_B}{\delta_B},$$

where $\mathfrak{R}_{01}^B$ denotes the basic reproduction number for HBV monoinfection associated with the virus-to-cell transmission mode, while $\mathfrak{R}_{02}^B$ denotes the basic reproduction number associated with the cell-to-cell transmission mode.

- HCV monoinfection equilibrium without a positive antibody response, $\Xi_2 = (H_2, 0, Y_2^C, 0, V_2^C, 0, 0)$, where

$$H_2 = \frac{H_0}{\mathfrak{R}_0^C}, \quad Y_2^C = \frac{\sigma \phi_C}{\beta_C \theta_C + \alpha_C \phi_C} (\mathfrak{R}_0^C - 1), \quad V_2^C = \frac{\sigma \theta_C}{\beta_C \theta_C + \alpha_C \phi_C} (\mathfrak{R}_0^C - 1),$$

where

$$\mathfrak{R}_0^C = \frac{H_0 (\beta_C \theta_C + \alpha_C \phi_C)}{\delta_C \phi_C}$$

is the basic reproduction number for HCV monoinfection. It serves as the threshold quantity determining whether HCV infection can be established in a susceptible host. Consequently, the equilibrium Ξ_2 exists whenever $\mathfrak{R}_0^C > 1$.

Let us write

$$\mathfrak{R}_0^C = \mathfrak{R}_{01}^C + \mathfrak{R}_{02}^C = \frac{H_0\beta_C\theta_C}{\delta_C\phi_C} + \frac{H_0\alpha_C}{\delta_C},$$

where $\mathfrak{R}_{01}^C$ denotes the basic reproduction number for HCV monoinfection associated with the virus-to-cell transmission mode, while $\mathfrak{R}_{02}^C$ denotes the basic reproduction number associated with the cell-to-cell transmission mode.

- HBV monoinfection equilibrium with a positive HBV-specific antibody response, $\Xi_3 = (H_3, Y_3^B, 0, V_3^B, 0, A_3^B, 0)$, where

$$H_3 = \frac{\phi}{\sigma + \beta_B V_3^B + \alpha_B Y_3^B}, \quad V_3^B = \frac{\lambda_B}{\rho_B}, \quad A_3^B = \frac{\phi_B}{\gamma_B} \left[\frac{\rho_B \theta_B}{\lambda_B \phi_B} Y_3^B - 1 \right].$$

The component Y_3^B satisfies the quadratic equation

$$\widetilde{A} (Y_3^B)^2 + \widetilde{B} Y_3^B + \widetilde{C} = 0, \quad (4.8)$$

with

$$\begin{aligned} \widetilde{A} &= \delta_B \alpha_B, \\ \widetilde{B} &= \delta_B \left(\sigma + \frac{\beta_B \lambda_B}{\rho_B} \right) - \phi \alpha_B, \\ \widetilde{C} &= -\frac{\phi \beta_B \lambda_B}{\rho_B}. \end{aligned} \quad (4.9)$$

Since $\widetilde{A} > 0$ and $\widetilde{C} < 0$, Eq (4.8) has two real roots, the positive one is

$$Y_3^B = \frac{-\widetilde{B} + \sqrt{\widetilde{B}^2 - 4\widetilde{A}\widetilde{C}}}{2\widetilde{A}}.$$

Positivity of H_3 and A_3^B requires

$$\frac{\rho_B \theta_B}{\lambda_B \phi_B} Y_3^B > 1.$$

Define

$$\mathfrak{R}_1^B = \frac{\rho_B \theta_B}{\lambda_B \phi_B} Y_3^B.$$

Therefore, $A_3^B = \frac{\phi_B}{\gamma_B} (\mathfrak{R}_1^B - 1)$. Thus, $\mathfrak{R}_1^B$ determines the activation of the HBV-specific antibody immunity in the absence of HCV infection.

- HCV monoinfection equilibrium with a positive HCV-specific antibody response, $\Xi_4 = (H_4, 0, Y_4^C, 0, V_4^C, 0, A_4^C)$, where

$$H_4 = \frac{\phi}{\sigma + \beta_C V_4^C + \alpha_C Y_4^C}, \quad V_4^C = \frac{\lambda_C}{\rho_C}, \quad A_4^C = \frac{\phi_C}{\gamma_C} \left[\frac{\rho_C \theta_C}{\lambda_C \phi_C} Y_4^C - 1 \right].$$

The component Y_4^C satisfies the quadratic equation

$$\widehat{A}(Y_4^C)^2 + \widehat{B}Y_4^C + \widehat{C} = 0, \quad (4.10)$$

with

$$\begin{aligned} \widehat{A} &= \delta_C \alpha_C, \\ \widehat{B} &= \delta_C \left(\sigma + \frac{\beta_C \lambda_C}{\rho_C} \right) - \phi \alpha_C, \\ \widehat{C} &= -\frac{\phi \beta_C \lambda_C}{\rho_C}. \end{aligned} \quad (4.11)$$

Since $\widehat{A} > 0$ and $\widehat{C} < 0$, Eq (4.10) has two real roots; the positive one is

$$Y_4^C = \frac{-\widehat{B} + \sqrt{\widehat{B}^2 - 4\widehat{A}\widehat{C}}}{2\widehat{A}}.$$

Positivity of H_4 and A_4^C requires

$$\frac{\rho_C \theta_C}{\lambda_C \phi_C} Y_4^C > 1.$$

Define

$$\mathfrak{R}_1^C = \frac{\rho_C \theta_C}{\lambda_C \phi_C} Y_4^C.$$

Therefore, $A_4^C = \frac{\phi_C}{\gamma_C} (\mathfrak{R}_1^C - 1)$. Thus, $\mathfrak{R}_1^C$ determines the activation of the HCV-specific antibody immunity in the absence of HBV infection.

- HBV/HCV coexistence equilibrium with a positive HBV-specific antibody response and no positive HCV-specific antibody response, $\Xi_5 = (H_5, Y_5^B, Y_5^C, V_5^B, V_5^C, A_5^B, 0)$, where

$$\begin{aligned} H_5 = H_2 &= \frac{H_0}{\mathfrak{R}_0^C}, \quad Y_5^B = \frac{\beta_B H_5 V_5^B}{\delta_B - \alpha_B H_5}, \quad Y_5^C = \frac{\phi_C}{\theta_C} V_5^C, \\ V_5^B = V_3^B &= \frac{\lambda_B}{\rho_B}, \quad A_5^B = \frac{\phi_B \delta_B}{\gamma_B (\delta_B - \alpha_B H_5)} \left[\frac{\mathfrak{R}_0^B}{\mathfrak{R}_0^C} - 1 \right], \\ V_5^C &= \frac{\theta_C H_5 (\alpha_B Y_5^B + \beta_B V_5^B + \sigma)}{\delta_C \phi_C} \left[\frac{\phi}{H_5 (\alpha_B Y_5^B + \beta_B V_5^B + \sigma)} - 1 \right]. \end{aligned}$$

We note that Ξ_5 exists when,

$$\frac{\mathfrak{R}_0^B}{\mathfrak{R}_0^C} > 1, \quad \frac{\delta_B}{\alpha_B H_5} > 1 \quad \text{and} \quad \frac{\phi}{H_5(\alpha_B Y_5^B + \beta_B V_5^B + \sigma)} > 1.$$

We define two threshold parameters $\mathfrak{R}_2^B$ and $\tilde{\mathfrak{R}}_2^B$ as:

$$\mathfrak{R}_2^B = \frac{\phi}{H_5(\alpha_B Y_5^B + \beta_B V_5^B + \sigma)} \quad \text{and} \quad \tilde{\mathfrak{R}}_2^B = \frac{\delta_B \mathfrak{R}_0^C}{\alpha_B H_0}.$$

Hence,

$$Y_5^B = \frac{\beta_B V_5^B}{\alpha_B (\tilde{\mathfrak{R}}_2^B - 1)}, \quad Y_5^C = \frac{H_5(\alpha_B Y_5^B + \beta_B V_5^B + \sigma)}{\delta_C} (\mathfrak{R}_2^B - 1),$$

$$A_5^B = \frac{\phi_B \delta_B}{\gamma_B \alpha_B H_5 (\tilde{\mathfrak{R}}_2^B - 1)} \left[\frac{\mathfrak{R}_0^B}{\mathfrak{R}_0^C} - 1 \right], \quad V_5^C = \frac{\theta_C H_5 (\alpha_B Y_5^B + \beta_B V_5^B + \sigma)}{\delta_C \phi_C} (\mathfrak{R}_2^B - 1),$$

and then Ξ_5 exists if $\frac{\mathfrak{R}_0^B}{\mathfrak{R}_0^C} > 1$, $\tilde{\mathfrak{R}}_2^B > 1$, and $\mathfrak{R}_2^B > 1$.

- HBV/HCV coexistence equilibrium with a positive HCV-specific antibody response and no positive HBV-specific antibody response, $\Xi_6 = (H_6, Y_6^B, Y_6^C, V_6^B, V_6^C, 0, A_6^C)$, where

$$H_6 = H_1 = \frac{H_0}{\mathfrak{R}_0^B}, \quad Y_6^B = \frac{\phi_B}{\theta_B} V_6^B, \quad Y_6^C = \frac{\beta_C H_6 V_6^C}{\delta_C - \alpha_C H_6},$$

$$V_6^C = V_4^C = \frac{\lambda_C}{\rho_C}, \quad A_6^C = \frac{\phi_C \delta_C}{\gamma_C (\delta_C - \alpha_C H_6)} \left[\frac{\mathfrak{R}_0^C}{\mathfrak{R}_0^B} - 1 \right],$$

$$V_6^B = \frac{\theta_B H_6 (\alpha_C Y_6^C + \beta_C V_6^C + \sigma)}{\delta_B \phi_B} \left[\frac{\phi}{H_6 (\alpha_C Y_6^C + \beta_C V_6^C + \sigma)} - 1 \right].$$

We note that Ξ_6 exists when

$$\frac{\mathfrak{R}_0^C}{\mathfrak{R}_0^B} > 1, \quad \frac{\delta_C}{\alpha_C H_6} > 1 \quad \text{and} \quad \frac{\phi}{H_6 (\alpha_C Y_6^C + \beta_C V_6^C + \sigma)} > 1.$$

We define two threshold parameters $\mathfrak{R}_2^C$ and $\tilde{\mathfrak{R}}_2^C$ as follows:

$$\mathfrak{R}_2^C = \frac{\phi}{H_6 (\alpha_C Y_6^C + \beta_C V_6^C + \sigma)} \quad \text{and} \quad \tilde{\mathfrak{R}}_2^C = \frac{\delta_C \mathfrak{R}_0^B}{\alpha_C H_0}.$$

Hence, we have

$$Y_6^B = \frac{H_6 (\alpha_C Y_6^C + \beta_C V_6^C + \sigma)}{\delta_B} [\mathfrak{R}_2^C - 1], \quad Y_6^C = \frac{\beta_C V_6^C}{\alpha_C (\tilde{\mathfrak{R}}_2^C - 1)},$$

$$A_6^C = \frac{\phi_C \delta_C}{\gamma_C \alpha_C H_6 (\tilde{\mathfrak{R}}_2^C - 1)} \left[\frac{\mathfrak{R}_0^C}{\mathfrak{R}_0^B} - 1 \right], V_6^B = \frac{\theta_B H_6 (\alpha_C Y_6^C + \beta_C V_6^C + \sigma)}{\delta_B \phi_B} (\mathfrak{R}_2^C - 1),$$

and then Ξ_6 exists if $\frac{\mathfrak{R}_0^C}{\mathfrak{R}_0^B} > 1$, $\tilde{\mathfrak{R}}_2^C > 1$, and $\mathfrak{R}_2^C > 1$.

- HBV/HCV coexistence equilibrium with positive HBV- and HCV-specific antibody responses, $\Xi_7 = (H_7, Y_7^B, Y_7^C, V_7^B, V_7^C, A_7^B, A_7^C)$, where

$$\begin{aligned} Y_7^B &= \frac{\beta_B H_7 V_7^B}{\delta_B - \alpha_B H_7}, \quad Y_7^C = \frac{\beta_C H_7 V_7^C}{\delta_C - \alpha_C H_7}, \quad V_7^B = \frac{\lambda_B}{\rho_B}, \quad V_7^C = \frac{\lambda_C}{\rho_C}, \\ A_7^B &= \frac{\phi_B}{\gamma_B} \left[\frac{\theta_B \rho_B}{\phi_B \lambda_B} Y_7^B - 1 \right], \quad A_7^C = \frac{\phi_C}{\gamma_C} \left[\frac{\theta_C \rho_C}{\phi_C \lambda_C} Y_7^C - 1 \right], \end{aligned} \quad (4.12)$$

and H_7 is a solution of the following

$$\phi - \kappa H - \frac{\beta_B \alpha_B V_7^B H^2}{\delta_B - \alpha_B H} - \frac{\beta_C \alpha_C V_7^C H^2}{\delta_C - \alpha_C H} = 0, \quad (4.13)$$

where, $\kappa = \sigma + \beta_B V_7^B + \beta_C V_7^C$. Equation (4.13) yields

$$\frac{\bar{A}H^3 + \bar{B}H^2 + \bar{C}H + \bar{D}}{(\delta_B - \alpha_B H)(\delta_C - \alpha_C H)} = 0, \quad (4.14)$$

where

$$\begin{aligned} \bar{A} &= (\kappa - \beta_B V_7^B - \beta_C V_7^C) \alpha_B \alpha_C, \\ \bar{B} &= \delta_C \beta_B \alpha_B V_7^B + \delta_B \beta_C \alpha_C V_7^C - \phi \alpha_B \alpha_C - \delta_B \alpha_C \kappa - \delta_C \alpha_B \kappa, \\ \bar{C} &= \phi \delta_B \alpha_C + \phi \delta_C \alpha_B + \delta_B \delta_C \kappa, \\ \bar{D} &= -\phi \delta_B \delta_C. \end{aligned}$$

We define a function $G(H) = \bar{A}H^3 + \bar{B}H^2 + \bar{C}H + \bar{D}$, then we obtain

$$\begin{aligned} G(0) &= -\phi \delta_B \delta_C < 0, \\ G\left(\frac{\delta_B}{\alpha_B}\right) &= \frac{\beta_B \alpha_C \delta_B^2 V_7^B}{\alpha_B} \left(\frac{\delta_C}{\alpha_C} - \frac{\delta_B}{\alpha_B} \right), \\ G\left(\frac{\delta_C}{\alpha_C}\right) &= \frac{\alpha_B \beta_C \delta_C^2 V_7^C}{\alpha_C} \left(\frac{\delta_B}{\alpha_B} - \frac{\delta_C}{\alpha_C} \right), \\ \lim_{H \rightarrow \infty} G(H) &= \infty. \end{aligned}$$

We first consider the nondegenerate case

$$\frac{\delta_C}{\alpha_C} \neq \frac{\delta_B}{\alpha_B}.$$

It follows that,

$$\begin{aligned}\frac{\delta_C}{\alpha_C} > \frac{\delta_B}{\alpha_B} &\Rightarrow G\left(\frac{\delta_B}{\alpha_B}\right) > 0 \text{ and } G\left(\frac{\delta_C}{\alpha_C}\right) < 0, \\ \frac{\delta_C}{\alpha_C} < \frac{\delta_B}{\alpha_B} &\Rightarrow G\left(\frac{\delta_B}{\alpha_B}\right) < 0 \text{ and } G\left(\frac{\delta_C}{\alpha_C}\right) > 0.\end{aligned}$$

Hence, we have

$$G\left(\min\left\{\frac{\delta_B}{\alpha_B}, \frac{\delta_C}{\alpha_C}\right\}\right) > 0 \text{ and } G\left(\max\left\{\frac{\delta_B}{\alpha_B}, \frac{\delta_C}{\alpha_C}\right\}\right) < 0.$$

Therefore, the cubic equation has exactly three positive roots as follows:

$$\begin{aligned}H^* &\in \left(0, \min\left\{\frac{\delta_B}{\alpha_B}, \frac{\delta_C}{\alpha_C}\right\}\right), \\ \bar{H} &\in \left(\min\left\{\frac{\delta_B}{\alpha_B}, \frac{\delta_C}{\alpha_C}\right\}, \max\left\{\frac{\delta_B}{\alpha_B}, \frac{\delta_C}{\alpha_C}\right\}\right), \\ \tilde{H} &\in \left(\max\left\{\frac{\delta_B}{\alpha_B}, \frac{\delta_C}{\alpha_C}\right\}, \infty\right).\end{aligned}$$

From Eq (4.12), we observe that the solution $\bar{H}$ leads to $Y^B < 0$ or $Y^C < 0$; moreover, $\tilde{H}$ results in $Y^B < 0$ and $Y^C < 0$. Therefore, the only acceptable solution is $H_7 = H^*$, which gives:

$$\begin{aligned}Y_7^B &= \frac{\beta_B H_7 V_7^B}{\delta_B - \alpha_B H_7}, \quad Y_7^C = \frac{\beta_C H_7 V_7^C}{\delta_C - \alpha_C H_7}, \quad V_7^B = \frac{\lambda_B}{\rho_B}, \quad V_7^C = \frac{\lambda_C}{\rho_C}, \\ A_7^B &= \frac{\phi_B}{\gamma_B} \left[\frac{\theta_B \rho_B}{\phi_B \lambda_B} Y_7^B - 1 \right], \quad A_7^C = \frac{\phi_C}{\gamma_C} \left[\frac{\theta_C \rho_C}{\phi_C \lambda_C} Y_7^C - 1 \right].\end{aligned}$$

Hence, $A_7^B > 0$ and $A_7^C > 0$ when

$$\frac{\theta_B \rho_B}{\phi_B \lambda_B} Y_7^B > 1, \quad \frac{\theta_C \rho_C}{\phi_C \lambda_C} Y_7^C > 1.$$

Now we consider the degenerate case

$$\frac{\delta_C}{\alpha_C} = \frac{\delta_B}{\alpha_B}.$$

Let

$$\frac{\delta_C}{\alpha_C} = \frac{\delta_B}{\alpha_B} =: q,$$

thus $\delta_B = \alpha_B q$ and $\delta_C = \alpha_C q$ and this reduces exactly to

$$F(H) = \phi - \kappa H - \frac{(\beta_B V_7^B + \beta_C V_7^C) H^2}{q - H}.$$

Then

$$F(0) = \phi > 0, \quad \lim_{H \rightarrow q^-} F(H) = -\infty.$$

Since $F(H)$ is continuous on $(0, q)$, the intermediate value theorem guarantees the existence of at least one $H_7 \in (0, q)$ such that $F(H_7) = 0$. Then $\delta_B - \alpha_B H_7 > 0$ and $\delta_C - \alpha_C H_7 > 0$. It follows that

$$Y_7^B = \frac{\beta_B H_7 V_7^B}{\delta_B - \alpha_B H_7} > 0, \quad Y_7^C = \frac{\beta_C H_7 V_7^C}{\delta_C - \alpha_C H_7} > 0.$$

Thus, the degenerate case does not invalidate the existence argument. The common threshold

$$q = \frac{\delta_C}{\alpha_C} = \frac{\delta_B}{\alpha_B}$$

is not itself an admissible equilibrium root because the infected-cell expressions are singular there, but there exists at least one biologically admissible root in the interval $(0, q)$.

Finally, as in the nondegenerate cases, the equilibrium Ξ_7 has strictly positive antibody responses provided that

$$\frac{\theta_B \rho_B}{\phi_B \lambda_B} Y_7^B > 1, \quad \frac{\theta_C \rho_C}{\phi_C \lambda_C} Y_7^C > 1.$$

Now, we define:

$$\mathfrak{R}_3^B = \frac{\theta_B \rho_B}{\phi_B \lambda_B} Y_7^B, \quad \mathfrak{R}_3^C = \frac{\theta_C \rho_C}{\phi_C \lambda_C} Y_7^C.$$

Therefore, Ξ_7 exists when, $\mathfrak{R}_3^B > 1$ and $\mathfrak{R}_3^C > 1$.

5. Global stability

The analysis of stability plays a central role in the study of dynamical systems, since only stable states can be detected in practical observations. In this section, we investigate the global asymptotic stability of the system's equilibrium points. This is achieved through the construction of suitable Lyapunov functions [61] and the use of the Lyapunov-LaSalle asymptotic stability theorem (L-LAST) [62]. Moreover, we employ the arithmetic mean-geometric mean (AM-GM) inequality, which is given by

$$\sqrt[n]{(u_1)(u_2)\dots(u_n)} \leq \frac{u_1 + u_2 + \dots + u_n}{n}, \quad u_i > 0, \quad i = 1, 2, \dots, n. \quad (5.1)$$

Let a $\Lambda_j(H, Y^B, Y^C, V^B, V^C, A^B, A^C)$ denote a candidate Lyapunov function, and let $\tilde{\Omega}_j$ represent the largest invariant subset of

$$\Omega_j = \left\{ (H, Y^B, Y^C, V^B, V^C, A^B, A^C) : \frac{d\Lambda_j}{dt} = 0 \right\}, \quad j = 0, 1, 2, \dots, 7.$$

Define a function

$$F(v) = v - 1 - \ln v,$$

which satisfies $F(v) \geq 0$, $\forall v > 0$ and $F(1) = 0$.

Let $x = (H, Y^B, Y^C, V^B, V^C, A^B, A^C)$. We define the following subsets of Γ :

$$\Gamma_1 = \{x \in \Gamma : H > 0, Y^B > 0, V^B > 0, Y^C, V^C, A^B, A^C \geq 0\},$$

$$\begin{aligned}
\Gamma_2 &= \{x \in \Gamma : H > 0, Y^C > 0, V^C > 0, Y^B, V^B, A^B, A^C \geq 0\}, \\
\Gamma_3 &= \{x \in \Gamma : H > 0, Y^B > 0, V^B > 0, A^B > 0, Y^C, V^C, A^C \geq 0\}, \\
\Gamma_4 &= \{x \in \Gamma : H > 0, Y^C > 0, V^C > 0, A^C > 0, Y^B, V^B, A^B \geq 0\}, \\
\Gamma_5 &= \{x \in \Gamma : H > 0, Y^B > 0, Y^C > 0, V^B > 0, V^C > 0, A^B > 0, A^C \geq 0\}, \\
\Gamma_6 &= \{x \in \Gamma : H > 0, Y^B > 0, Y^C > 0, V^B > 0, V^C > 0, A^C > 0, A^B \geq 0\}, \\
\Gamma_7 &= \{x \in \Gamma : H > 0, Y^B > 0, Y^C > 0, V^B > 0, V^C > 0, A^C > 0, A^B > 0\}.
\end{aligned}$$

Theorem 1. If $\mathfrak{R}_0 = \max\{\mathfrak{R}_0^B, \mathfrak{R}_0^C\} \leq 1$, then Ξ_0 is GAS in Γ . If $\mathfrak{R}_0 > 1$, then Ξ_0 is unstable.

Proof. Define

$$\Lambda_0 = H_0 F\left(\frac{H}{H_0}\right) + Y^B + Y^C + \frac{\beta_B H_0}{\phi_B} V^B + \frac{\beta_C H_0}{\phi_C} V^C + \frac{\gamma_B \beta_B H_0}{\rho_B \phi_B} A^B + \frac{\gamma_C \beta_C H_0}{\rho_C \phi_C} A^C.$$

We note that, $\Lambda_0 > 0$ for all $H, Y^B, Y^C, V^B, V^C, A^B, A^C > 0$, and $\Lambda_0(\Xi_0) = 0$.

We calculate $\frac{d\Lambda_0}{dt}$ along the solutions of model (2.1) as follows:

$$\begin{aligned}
\frac{d\Lambda_0}{dt} &= \left(1 - \frac{H_0}{H}\right) [\phi - \sigma H - \beta_B H V^B - \alpha_B H Y^B - \beta_C H V^C - \alpha_C H Y^C] + \beta_B H V^B + \alpha_B H Y^B - \delta_B Y^B \\
&\quad + \beta_C H V^C + \alpha_C H Y^C - \delta_C Y^C + \frac{\beta_B H_0}{\phi_B} [\theta_B Y^B - \phi_B V^B - \gamma_B A^B V^B] \\
&\quad + \frac{\beta_C H_0}{\phi_C} [\theta_C Y^C - \phi_C V^C - \gamma_C A^C V^C] + \frac{\gamma_B \beta_B H_0}{\rho_B \phi_B} [\rho_B A^B V^B - \lambda_B A^B] \\
&\quad + \frac{\gamma_C \beta_C H_0}{\rho_C \phi_C} [\rho_C A^C V^C - \lambda_C A^C] \\
&= \left(1 - \frac{H_0}{H}\right) (\phi - \sigma H) + \left(\alpha_B H_0 + \frac{\beta_B H_0 \theta_B}{\phi_B} - \delta_B\right) Y^B + \left(\alpha_C H_0 + \frac{\beta_C H_0 \theta_C}{\phi_C} - \delta_C\right) Y^C \\
&\quad - \frac{\lambda_B \gamma_B \beta_B H_0}{\rho_B \phi_B} A^B - \frac{\lambda_C \gamma_C \beta_C H_0}{\rho_C \phi_C} A^C.
\end{aligned}$$

Using the equilibrium condition $\phi = \sigma H_0$, we get:

$$\frac{d\Lambda_0}{dt} = -\sigma \frac{(H - H_0)^2}{H} + \delta_B (\mathfrak{R}_0^B - 1) Y^B + \delta_C (\mathfrak{R}_0^C - 1) Y^C - \frac{\lambda_B \gamma_B \beta_B H_0}{\rho_B \phi_B} A^B - \frac{\lambda_C \gamma_C \beta_C H_0}{\rho_C \phi_C} A^C.$$

Since $\mathfrak{R}_0 \leq 1$, then $\frac{d\Lambda_0}{dt} \leq 0$ for all $H, Y^B, Y^C, A^B, A^C > 0$. In addition $\frac{d\Lambda_0}{dt} = 0$ when $H = H_0$, $A^B = A^C = 0$, $(\mathfrak{R}_0^B - 1) Y^B = 0$ and $(\mathfrak{R}_0^C - 1) Y^C = 0$. The solutions of system (2.1) converge to $\tilde{\Omega}_0$ [63]. Each element of $\tilde{\Omega}_0$ satisfies the condition $H = H_0$ and $A^B = A^C = 0$, and

$$(\mathfrak{R}_0^B - 1) Y^B = 0 \text{ and } (\mathfrak{R}_0^C - 1) Y^C = 0. \quad (5.2)$$

We have the following four cases:

Case 1 $\mathfrak{R}_0^B = 1$ and $\mathfrak{R}_0^C < 1$: Since $\mathfrak{R}_0^C < 1$ from Eq (5.2) leads to $Y^C = 0$. Hence, $\dot{Y}^C = 0$, and the third part of Eq (2.1) yields

$$0 = \dot{Y}^C = \beta_C H_0 V^C \implies V^C(t) = 0, \text{ for all } t. \quad (5.3)$$

From first part of Eq (2.1), we have

$$\begin{aligned} 0 &= \phi - \sigma H_0 - \beta_B H_0 V^B - \alpha_B H_0 Y^B, \\ \implies 0 &= \beta_B H_0 V^B + \alpha_B H_0 Y^B, \\ \implies V^B &= Y^B = 0. \end{aligned} \quad (5.4)$$

Hence, the set $\tilde{\Omega}_0$ reduces to $\{\Xi_0\}$.

Case 2 If $\mathfrak{R}_0^B < 1$ and $\mathfrak{R}_0^C = 1$: Since $\mathfrak{R}_0^B < 1$ from Eq (5.2) leads to $Y^B = 0$. Hence, $\dot{Y}^B = 0$, and the second part of Eq (2.1) yields

$$0 = \dot{Y}^B = \beta_B H_0 V^B \implies V^B(t) = 0, \text{ for all } t. \quad (5.5)$$

From first part of Eq (2.1), we have

$$\begin{aligned} 0 &= \phi - \sigma H_0 - \beta_C H_0 V^C - \alpha_C H_0 Y^C, \\ \implies 0 &= \beta_C H_0 V^C + \alpha_C H_0 Y^C, \\ \implies V^C &= Y^C = 0. \end{aligned} \quad (5.6)$$

Hence, the set $\tilde{\Omega}_0$ reduces to $\{\Xi_0\}$.

Case 3 If $\mathfrak{R}_0^B < 1$ and $\mathfrak{R}_0^C < 1$: From Eq (5.2), we get $Y^B = Y^C = 0$, and then from Eqs (5.3)–(5.6), we get that $\tilde{\Omega}_0 = \{\Xi_0\}$.

Case 4 If $\mathfrak{R}_0^B = 1$ and $\mathfrak{R}_0^C = 1$: From the first part of Eq (2.1), we have

$$\begin{aligned} 0 &= \phi - \sigma H_0 - \beta_B H_0 V^B - \alpha_B H_0 Y^B - \beta_C H_0 V^C - \alpha_C H_0 Y^C, \\ \implies 0 &= \beta_B H_0 V^B + \alpha_B H_0 Y^B + \beta_C H_0 V^C + \alpha_C H_0 Y^C, \\ \implies V^B &= Y^B = V^C = Y^C = 0. \end{aligned}$$

Hence, the set $\tilde{\Omega}_0 = \{\Xi_0\}$.

Therefore in all cases, $\tilde{\Omega}_0 = \{\Xi_0\}$ and applying L-LAST [62], it follows that Ξ_0 is GAS.

To establish the instability of Ξ_0 if $\mathfrak{R}_0 > 1$, we compute the Jacobian matrix as follows:

$$J = \begin{pmatrix} J_{11} & -\alpha_B H & -\alpha_C H & -\beta_B H & -\beta_C H & 0 & 0 \\ J_{21} & J_{22} & 0 & \beta_B H & 0 & 0 & 0 \\ J_{31} & 0 & J_{33} & 0 & \beta_C H & 0 & 0 \\ 0 & \theta_B & 0 & J_{44} & 0 & -\gamma_B V^B & 0 \\ 0 & 0 & \theta_C & 0 & J_{55} & 0 & -\gamma_C V^C \\ 0 & 0 & 0 & \rho_B A^B & 0 & J_{66} & 0 \\ 0 & 0 & 0 & 0 & \rho_C A^C & 0 & J_{77} \end{pmatrix}, \quad (5.7)$$

where $J_{11} = -(\sigma + \beta_B V^B + \alpha_B Y^B + \beta_C V^C + \alpha_C Y^C)$, $J_{21} = \beta_B V^B + \alpha_B Y^B$, $J_{31} = \beta_C V^C + \alpha_C Y^C$, $J_{22} = \alpha_B H - \delta_B$, $J_{33} = \alpha_C H - \delta_C$, $J_{44} = -\phi_B - \gamma_B A^B$, $J_{55} = -\phi_C - \gamma_C A^C$, $J_{66} = \rho_B V^B - \lambda_B$, and $J_{77} = \rho_C V^C - \lambda_C$.

We compute the Jacobian matrix at Ξ_0 as follows:

$$J(\Xi_0) = \begin{pmatrix} -\sigma & -\alpha_B H_0 & -\alpha_C H_0 & -\beta_B H_0 & -\beta_C H_0 & 0 & 0 \\ 0 & \alpha_B H_0 - \delta_B & 0 & \beta_B H_0 & 0 & 0 & 0 \\ 0 & 0 & \alpha_C H_0 - \delta_C & 0 & \beta_C H_0 & 0 & 0 \\ 0 & \theta_B & 0 & -\phi_B & 0 & 0 & 0 \\ 0 & 0 & \theta_C & 0 & -\phi_C & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -\lambda_B & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -\lambda_C \end{pmatrix}$$

and we calculate characteristic equation as follows:

$$(\xi + \sigma)(\xi + \lambda_B)(\xi + \lambda_C)G_1(\xi)G_2(\xi) = 0,$$

where

$$G_1(\xi) = \xi^2 + a_1\xi + a_0,$$

$$G_2(\xi) = \xi^2 + b_1\xi + b_0,$$

$$a_1 = (\delta_B(1 - \mathfrak{R}_{02}^B) + \phi_B),$$

$$a_0 = \delta_B\phi_B(1 - \mathfrak{R}_0^B),$$

$$b_1 = (\delta_C(1 - \mathfrak{R}_{02}^C) + \phi_C),$$

$$b_0 = \delta_C\phi_C(1 - \mathfrak{R}_0^C),$$

where ξ is the eigenvalue. We have $\xi_1 = -\sigma$, $\xi_2 = -\lambda_B$, and $\xi_3 = -\lambda_C$. Since $\mathfrak{R}_{02}^B < \mathfrak{R}_0^B$ and $\mathfrak{R}_{02}^C < \mathfrak{R}_0^C$, then if $\mathfrak{R}_0^B < 1$ and $\mathfrak{R}_0^C < 1$, then $a_1 > 0$, $a_0 > 0$, $b_1 > 0$, and $b_0 > 0$ and then Ξ_0 is locally asymptotically stable. If $\mathfrak{R}_0 > 1$, then $\mathfrak{R}_0^B > 1$ and/or $\mathfrak{R}_0^C > 1$, then $a_0 < 0$ and/or $b_0 < 0$, and $G_1(\xi)$ and/or $G_2(\xi)$ has a positive root, and hence Ξ_0 is unstable. $\square$

Lemma 2. If $\mathfrak{R}_1^B \leq 1$, then $V_1^B \leq V_3^B$.

Proof. Let $\mathfrak{R}_1^B \leq 1$, then $\frac{\rho_B\theta_B}{\lambda_B\phi_B}Y_3^B \leq 1$ and hence

$$\begin{aligned} Y_3^B &\leq \frac{\lambda_B\phi_B}{\rho_B\theta_B} \Rightarrow \frac{-\widetilde{B} + \sqrt{\widetilde{B}^2 - 4\widetilde{A}\widetilde{C}}}{2\widetilde{A}} \leq \frac{\lambda_B\phi_B}{\rho_B\theta_B}, \\ &\Rightarrow \sqrt{\widetilde{B}^2 - 4\widetilde{A}\widetilde{C}} \leq \frac{2\widetilde{A}\lambda_B\phi_B + \rho_B\theta_B\widetilde{B}}{\rho_B\theta_B}, \\ &\Rightarrow \left(\frac{2\widetilde{A}\lambda_B\phi_B + \rho_B\theta_B\widetilde{B}}{\rho_B\theta_B} \right)^2 + 4\widetilde{A}\widetilde{C} - \widetilde{B}^2 \geq 0. \end{aligned}$$

Using Eq (4.9), we obtain

$$\frac{4\alpha_B\delta_B^2\lambda_B\phi_B(\beta_B\theta_B + \alpha_B\phi_B)}{\rho_B\theta_B^2} (V_3^B - V_1^B) \geq 0.$$

Hence, $V_1^B \leq V_3^B$. $\square$

Theorem 2. Suppose that $\mathfrak{R}_0^B > 1$, $\mathfrak{R}_0^C/\mathfrak{R}_0^B \leq 1$ and $\mathfrak{R}_1^B \leq 1$, then Ξ_1 is GAS in Γ_1 . If $\mathfrak{R}_0^C/\mathfrak{R}_0^B > 1$, then Ξ_1 is unstable.

Proof. Let Λ_1 be

$$\begin{aligned}\Lambda_1 = & H_1 F\left(\frac{H}{H_1}\right) + Y_1^B F\left(\frac{Y^B}{Y_1^B}\right) + Y^C + \frac{\beta_B H_1}{\phi_B} V_1^B F\left(\frac{V^B}{V_1^B}\right) + \frac{\beta_C H_1}{\phi_C} V^C + \frac{\gamma_B \beta_B H_1}{\rho_B \phi_B} A^B \\ & + \frac{\gamma_C \beta_C H_1}{\rho_C \phi_C} A^C.\end{aligned}$$

We calculate $\frac{d\Lambda_1}{dt}$ as follows:

$$\begin{aligned}\frac{d\Lambda_1}{dt} = & \left(1 - \frac{H_1}{H}\right) [\phi - \sigma H - \beta_B H V^B - \alpha_B H Y^B - \beta_C H V^C - \alpha_C H Y^C] \\ & + \left(1 - \frac{Y_1^B}{Y^B}\right) [\beta_B H V^B + \alpha_B H Y^B - \delta_B Y^B] + \beta_C H V^C + \alpha_C H Y^C - \delta_C Y^C \\ & + \frac{\beta_B H_1}{\phi_B} \left(1 - \frac{V_1^B}{V^B}\right) [\theta_B Y^B - \phi_B V^B - \gamma_B A^B V^B] + \frac{\beta_C H_1}{\phi_C} [\theta_C Y^C - \phi_C V^C - \gamma_C A^C V^C] \\ & + \frac{\gamma_B \beta_B H_1}{\rho_B \phi_B} [\rho_B A^B V^B - \lambda_B A^B] + \frac{\gamma_C \beta_C H_1}{\rho_C \phi_C} [\rho_C A^C V^C - \lambda_C A^C].\end{aligned}\quad (5.8)$$

Simplifying Eq (5.8), we get:

$$\begin{aligned}\frac{d\Lambda_1}{dt} = & \left(1 - \frac{H_1}{H}\right) (\phi - \sigma H) + \alpha_B H_1 Y^B + \alpha_C H_1 Y^C - \delta_B Y^B - \beta_B H V^B \frac{Y_1^B}{Y^B} - \alpha_B H Y_1^B \\ & + \delta_B Y_1^B - \delta_C Y^C + \frac{\beta_B H_1 \theta_B}{\phi_B} Y^B - \frac{\beta_B H_1 \theta_B}{\phi_B} Y^B \frac{V_1^B}{V^B} + \beta_B H_1 V_1^B + \frac{\gamma_B \beta_B H_1}{\phi_B} A^B V_1^B \\ & + \frac{\beta_C H_1 \theta_C}{\phi_C} Y^C - \frac{\lambda_B \gamma_B \beta_B H_1}{\rho_B \phi_B} A^B - \frac{\lambda_C \gamma_C \beta_C H_1}{\rho_C \phi_C} A^C.\end{aligned}$$

Using the equilibrium conditions for Ξ_1 :

$$\phi = \sigma H_1 + \beta_B H_1 V_1^B + \alpha_B H_1 Y_1^B, \quad \beta_B H_1 V_1^B + \alpha_B H_1 Y_1^B = \delta_B Y_1^B \text{ and } \theta_B Y_1^B = \phi_B V_1^B.$$

We get

$$\left[\alpha_B H_1 + \frac{\beta_B H_1 \theta_B}{\phi_B} - \delta_B\right] Y^B = \left[\beta_B H_1 V_1^B + \alpha_B H_1 Y_1^B - \delta_B Y_1^B\right] \frac{Y^B}{Y_1^B} = 0.$$

Then,

$$\begin{aligned}\frac{d\Lambda_1}{dt} = & \left(1 - \frac{H_1}{H}\right) (\sigma H_1 - \sigma H) + \left(1 - \frac{H_1}{H}\right) (\beta_B H_1 V_1^B + \alpha_B H_1 Y_1^B) - \beta_B H_1 V_1^B \frac{H V^B Y_1^B}{H_1 V_1^B Y^B} \\ & - \alpha_B H Y_1^B + 2\beta_B H_1 V_1^B + \alpha_B H_1 Y_1^B - \beta_B H_1 V_1^B \frac{Y^B V_1^B}{Y_1^B V^B} + \frac{\gamma_B \beta_B H_1}{\phi_B} \left(V_1^B - \frac{\lambda_B}{\rho_B}\right) A^B \\ & - \frac{\lambda_C \gamma_C \beta_C H_1}{\rho_C \phi_C} A^C + \left(\alpha_C H_1 + \frac{\beta_C H_1 \theta_C}{\phi_C} - \delta_C\right) Y^C.\end{aligned}\quad (5.9)$$

Then collecting terms of Eq (5.9), we get:

$$\begin{aligned} \frac{d\Lambda_1}{dt} &= -\sigma \frac{(H - H_1)^2}{H} + \beta_B H_1 V_1^B \left[3 - \frac{H_1}{H} - \frac{H V_1^B Y_1^B}{H_1 V_1^B Y_1^B} - \frac{Y_1^B V_1^B}{Y_1^B V_1^B} \right] + \alpha_B H_1 Y_1^B \left[2 - \frac{H_1}{H} - \frac{H}{H_1} \right] \\ &\quad + \frac{\gamma_B \beta_B H_1}{\phi_B} (V_1^B - V_3^B) A^B + \delta_C \left(\frac{\mathfrak{R}_0^C}{\mathfrak{R}_0^B} - 1 \right) Y^C - \frac{\lambda_C \gamma_C \beta_C H_1}{\rho_C \phi_C} A^C \\ &= -\frac{\sigma + \alpha_B Y_1^B}{H} (H - H_1)^2 + \beta_B H_1 V_1^B \left[3 - \frac{H_1}{H} - \frac{H V_1^B Y_1^B}{H_1 V_1^B Y_1^B} - \frac{Y_1^B V_1^B}{Y_1^B V_1^B} \right] + \frac{\gamma_B \beta_B H_1}{\phi_B} (V_1^B - V_3^B) A^B \\ &\quad + \delta_C \left(\frac{\mathfrak{R}_0^C}{\mathfrak{R}_0^B} - 1 \right) Y^C - \frac{\lambda_C \gamma_C \beta_C H_1}{\rho_C \phi_C} A^C. \end{aligned}$$

Using inequality (5.1), we get:

$$3 - \frac{H_1}{H} - \frac{H V_1^B Y_1^B}{H_1 V_1^B Y_1^B} - \frac{Y_1^B V_1^B}{Y_1^B V_1^B} \leq 0.$$

Since $\mathfrak{R}_0^C/\mathfrak{R}_0^B \leq 1$ and $\mathfrak{R}_1^B \leq 1$, then $\frac{d\Lambda_1}{dt} \leq 0$ for all $H, Y^B, Y^C, V^B, A^B, A^C > 0$. In addition, $\frac{d\Lambda_1}{dt} = 0$ when $H = H_1$, $Y^B = Y_1^B$, $V^B = V_1^B$, $A^B = A^C = 0$, and $(\mathfrak{R}_0^C/\mathfrak{R}_0^B - 1)Y^C = 0$ and $(V_1^B - V_3^B)A^B = 0$. The solutions of system (2.1) converge to $\tilde{\Omega}_1$ [63]. Each element of $\tilde{\Omega}_1$ satisfies the condition $H = H_1$, $Y^B = Y_1^B$, $V^B = V_1^B$, $A^C = 0$, and

$$\left(\frac{\mathfrak{R}_0^C}{\mathfrak{R}_0^B} - 1 \right) Y^C = 0 \text{ and } (V_1^B - V_3^B) A^B = 0. \quad (5.10)$$

We have four cases:

Case 1 If $\mathfrak{R}_0^C/\mathfrak{R}_0^B < 1$ and $V_1^B < V_3^B$: From Eq (5.10) leads to $Y^C = 0$ and $A^B = 0$. Then $\dot{Y}^C = 0$ and the third Eq (2.1) implies

$$0 = \dot{Y}^C = \beta_C H_1 V^C \implies V^C(t) = 0, \text{ for all } t. \quad (5.11)$$

Thus, the set $\tilde{\Omega}_1$ reduces to $\{\Xi_1\}$.

Case 2 If $\mathfrak{R}_0^C/\mathfrak{R}_0^B < 1$ and $V_1^B = V_3^B$: Since $V^B = V_1^B$, then given $\dot{V}^B = 0$ and the fourth part of Eq (2.1), we have

$$\begin{aligned} 0 &= \theta_B Y_1^B - \phi_B V_1^B - \gamma_B A^B V_1^B, \\ \implies 0 &= \gamma_B A^B V_1^B, \\ \implies A^B &= 0. \end{aligned} \quad (5.12)$$

From Eqs (5.11) and (5.12), we get $\tilde{\Omega}_1 = \{\Xi_1\}$.

Case 3 If $\mathfrak{R}_0^C/\mathfrak{R}_0^B = 1$, and $V_1^B < V_3^B$: From the first part of Eq (2.1), we have

$$0 = \phi - \sigma H_1 - \beta_B H_1 V_1^B - \alpha_B H_1 Y_1^B - \beta_C H_1 V^C - \alpha_C H_1 Y^C,$$

$$\begin{aligned} \implies 0 &= \beta_C H_1 V^C + \alpha_C H_1 Y^C, \\ \implies V^C &= Y^C = 0. \end{aligned} \quad (5.13)$$

From Eqs (5.11), we get $\tilde{\Omega}_1 = \{\Xi_1\}$.

Case 4 If $\mathfrak{R}_0^C/\mathfrak{R}_0^B = 1$, and $V_1^B = V_3^B$: Then from Eqs (5.12) and (5.13), we get $\tilde{\Omega}_1 = \{\Xi_1\}$.

Therefore, in all cases, $\tilde{\Omega}_1 = \{\Xi_1\}$ is GAS by applying L-LAST [62].

To prove the instability of when $\mathfrak{R}_0^C/\mathfrak{R}_0^B > 1$, we calculate characteristic equation at Ξ_1 as follows:

$$(\xi + \lambda_C) \left(\xi + \lambda_B - \frac{(\mathfrak{R}_0^B - 1) \sigma \theta_B \rho_B}{\beta_B \theta_B + \alpha_B \phi_B} \right) Z_1(\xi) Z_2(\xi) = 0, \quad (5.14)$$

where

$$\begin{aligned} Z_1(\xi) &= \xi^3 + \hat{a}_2 \xi^2 + \hat{a}_1 \xi + \hat{a}_0, \\ Z_2(\xi) &= \hat{b}_2 \xi^2 + \hat{b}_1 \xi + \hat{b}_0, \\ \hat{a}_2 &= \frac{-H_0 \alpha_B + \mathfrak{R}_0^B (\mathfrak{R}_0^B \sigma + \delta_B) + \mathfrak{R}_0^B \phi_B}{\mathfrak{R}_0^B}, \\ \hat{a}_1 &= \frac{-H_0 \mathfrak{R}_0^B \beta_B \theta_B + \mathfrak{R}_0^B \left(-H_0 \sigma \alpha_B + (\mathfrak{R}_0^B)^2 \sigma \delta_B + (-H_0 \alpha_B + \mathfrak{R}_0^B \phi_B (\mathfrak{R}_0^B \sigma + \delta_B)) \right)}{(\mathfrak{R}_0^B)^2}, \\ \hat{a}_0 &= \sigma \delta_B \phi_B (\mathfrak{R}_0^B - 1), \\ \hat{b}_2 &= \frac{H_0 (\beta_B \theta_B + \alpha_B \phi_B)}{\delta_B \phi_B}, \\ \hat{b}_1 &= (\delta_C + \phi_C) \mathfrak{R}_0^B - H_0 \alpha_C, \\ \hat{b}_0 &= \frac{H_0 \delta_C \phi_C (\beta_B \theta_B + \alpha_B \phi_B)}{\delta_B \phi_B} \left(1 - \frac{\mathfrak{R}_0^C}{\mathfrak{R}_0^B} \right). \end{aligned}$$

where ξ is the eigenvalue. If $\mathfrak{R}_0^C/\mathfrak{R}_0^B > 1$, then $Z_2(0) < 0$ and $\lim_{\xi \rightarrow \infty} Z_2(\xi) = \infty$. Thus, Eq (5.14) has a positive root and hence Ξ_1 is unstable. $\square$

Lemma 3. If $\mathfrak{R}_1^C \leq 1$, then $V_2^C \leq V_4^C$.

Proof. Let $\mathfrak{R}_1^C \leq 1$, then $\frac{\rho_C \theta_C}{\lambda_C \phi_C} Y_4^C \leq 1$ and hence

$$\begin{aligned} Y_4^C &\leq \frac{\lambda_C \phi_C}{\rho_C \theta_C} \Rightarrow \frac{-B + \sqrt{\widehat{B}^2 - 4\widehat{A}\widehat{C}}}{2\widehat{A}} \leq \frac{\lambda_C \phi_C}{\rho_C \theta_C}, \\ &\Rightarrow \sqrt{\widehat{B}^2 - 4\widehat{A}\widehat{C}} \leq \frac{2\widehat{A}\lambda_C \phi_C + \rho_C \theta_C \widehat{B}}{\rho_C \theta_C}, \\ &\Rightarrow \left(\frac{2\widehat{A}\lambda_C \phi_C + \rho_C \theta_C \widehat{B}}{\rho_C \theta_C} \right)^2 + 4\widehat{A}\widehat{C} - \widehat{B}^2 \geq 0. \end{aligned}$$

Using Eq (4.11), we obtain

$$\frac{4\alpha_C\delta_C^2\lambda_C\phi_C(\beta_C\theta_C + \alpha_C\phi_C)}{\rho_C\theta_C^2}(V_4^C - V_2^C) \geq 0.$$

Hence, $V_2^C \leq V_4^C$. $\square$

Theorem 3. Let $\mathfrak{R}_0^C > 1$, $\mathfrak{R}_0^B/\mathfrak{R}_0^C \leq 1$ and $\mathfrak{R}_1^C \leq 1$, then Ξ_2 is GAS in Γ_2 . If $\mathfrak{R}_0^B/\mathfrak{R}_0^C > 1$, then Ξ_2 is unstable.

Proof. Consider

$$\begin{aligned}\Lambda_2 = & H_2F\left(\frac{H}{H_2}\right) + Y^B + Y_2^CF\left(\frac{Y^C}{Y_2^C}\right) + \frac{\beta_B H_2}{\phi_B}V^B + \frac{\beta_C H_2}{\phi_C}V_2^CF\left(\frac{V^C}{V_2^C}\right) \\ & + \frac{\gamma_B\beta_B H_2}{\rho_B\phi_B}A^B + \frac{\gamma_C\beta_C H_2}{\rho_C\phi_C}A^C.\end{aligned}$$

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

$$\begin{aligned}\frac{d\Lambda_2}{dt} = & \left(1 - \frac{H_2}{H}\right)[\phi - \sigma H - \beta_B H V^B - \alpha_B H Y^B - \beta_C H V^C - \alpha_C H Y^C] \\ & + \beta_B H V^B + \alpha_B H Y^B - \delta_B Y^B + \left(1 - \frac{Y_2^C}{Y^C}\right)[\beta_C H V^C + \alpha_C H Y^C - \delta_C Y^C] \\ & + \frac{\beta_B H_2}{\phi_B}[\theta_B Y^B - \phi_B V^B - \gamma_B A^B V^B] + \frac{\beta_C H_2}{\phi_C}\left(1 - \frac{V_2^C}{V^C}\right)[\theta_C Y^C - \phi_C V^C - \gamma_C A^C V^C] \\ & + \frac{\gamma_B\beta_B H_2}{\rho_B\phi_B}[\rho_B A^B V^B - \lambda_B A^B] + \frac{\gamma_C\beta_C H_2}{\rho_C\phi_C}[\rho_C A^C V^C - \lambda_C A^C].\end{aligned}\quad (5.15)$$

Then, by simplifying Eq (5.15), we get:

$$\begin{aligned}\frac{d\Lambda_2}{dt} = & \left(1 - \frac{H_2}{H}\right)(\phi - \sigma H) + \alpha_B H_2 Y^B + \alpha_C H_2 Y^C - \delta_B Y^B - \delta_C Y^C - \beta_C H V^C \frac{Y_2^C}{Y^C} \\ & - \alpha_C H Y_2^C + \delta_C Y_2^C + \frac{\beta_B H_2 \theta_B}{\phi_B} Y^B + \frac{\beta_C H_2 \theta_C}{\phi_C} Y^C - \frac{\beta_C H_2 \theta_C}{\phi_C} Y^C \frac{V_2^C}{V^C} + \beta_C H_2 V_2^C \\ & + \frac{\gamma_C \beta_C H_2}{\phi_C} \left(V_2^C - \frac{\lambda_C}{\rho_C}\right) A^C - \frac{\lambda_B \gamma_B \beta_B H_2}{\rho_B \phi_B} A^B.\end{aligned}$$

Using the equilibrium conditions for Ξ_2 :

$$\phi = \sigma H_2 + \beta_C H_2 V_2^C + \alpha_C H_2 Y_2^C, \quad \beta_C H_2 V_2^C + \alpha_C H_2 Y_2^C = \delta_C Y_2^C, \quad \theta_C Y_2^C = \phi_C V_2^C,$$

we get

$$\left[\alpha_C H_2 + \frac{\beta_C H_2 \theta_C}{\phi_C} - \delta_C\right] Y^C = \left[\frac{\beta_C H_2 \theta_C}{\phi_C} Y_2^C + \alpha_C H_2 Y_2^C - \delta_C Y_2^C\right] \frac{Y^C}{Y_2^C} = 0,$$

and we obtain

$$\frac{d\Lambda_2}{dt} = \left(1 - \frac{H_2}{H}\right)(\sigma H_2 - \sigma H) + \left(1 - \frac{H_2}{H}\right)(\beta_C H_2 V_2^C + \alpha_C H_2 Y_2^C)$$

$$\begin{aligned}
& -\beta_C H_2 V_2^C \frac{H V^C Y_2^C}{H_2 V_2^C Y^C} - \alpha_C H Y_2^C + \beta_C H_2 V_2^C + \alpha_C H_2 Y_2^C - \beta_C H_2 V_2^C \frac{Y^C V_2^C}{Y_2^C V^C} + \beta_C H_2 V_2^C \\
& + \frac{\gamma_C \beta_C H_2}{\phi_C} (V_2^C - V_4^C) A^C - \frac{\lambda_B \gamma_B \beta_B H_2}{\rho_B \phi_B} A^B + \delta_B \left(\frac{\mathfrak{R}_0^B}{\mathfrak{R}_0^C} - 1 \right) Y^B \\
& = -\sigma \frac{(H - H_2)^2}{H} + \beta_C H_2 V_2^C \left[3 - \frac{H_2}{H} - \frac{H V^C Y_2^C}{H_2 V_2^C Y^C} - \frac{Y^C V_2^C}{Y_2^C V^C} \right] + \alpha_C H_2 Y_2^C \left[2 - \frac{H_2}{H} - \frac{H}{H_2} \right] \\
& + \delta_B \left(\frac{\mathfrak{R}_0^B}{\mathfrak{R}_0^C} - 1 \right) Y^B + \frac{\gamma_C \beta_C H_2}{\phi_C} (V_2^C - V_4^C) A^C - \frac{\lambda_B \gamma_B \beta_B H_2}{\rho_B \phi_B} A^B \\
& = -\left(\frac{\sigma + \alpha_C Y_2^C}{H} \right) (H - H_2)^2 + \beta_C H_2 V_2^C \left[3 - \frac{H_2}{H} - \frac{H V^C Y_2^C}{H_2 V_2^C Y^C} - \frac{Y^C V_2^C}{Y_2^C V^C} \right] + \delta_B \left(\frac{\mathfrak{R}_0^B}{\mathfrak{R}_0^C} - 1 \right) Y^B \\
& + \frac{\gamma_C \beta_C H_2}{\phi_C} (V_2^C - V_4^C) A^C - \frac{\lambda_B \gamma_B \beta_B H_2}{\rho_B \phi_B} A^B.
\end{aligned}$$

Since $\mathfrak{R}_0^B/\mathfrak{R}_0^C \leq 1$ and $\mathfrak{R}_1^C \leq 1$, then $\frac{d\Lambda_2}{dt} \leq 0$ for all $H, Y^B, Y^C, V^C, A^B, A^C > 0$. In addition, $\frac{d\Lambda_2}{dt} = 0$ when $H = H_2, Y^C = Y_2^C, V^C = V_2^C, A^B = A^C = 0, (\mathfrak{R}_0^B/\mathfrak{R}_0^C - 1) Y^B = 0$, and $(V_2^C - V_4^C) A^C = 0$. The solutions of system (2.1) tend to $\tilde{\Omega}_2$ [63]. Each element of $\tilde{\Omega}_2$ satisfies the condition $H = H_2, Y^C = Y_2^C, V^C = V_2^C, A^B = 0$, and

$$\left(\frac{\mathfrak{R}_0^B}{\mathfrak{R}_0^C} - 1 \right) Y^B = 0 \text{ and } (V_2^C - V_4^C) A^C = 0. \quad (5.16)$$

We have four cases:

Case 1 If $\mathfrak{R}_0^B/\mathfrak{R}_0^C < 1$, and $V_2^C < V_4^C$: From Eq (5.16) leads to $Y^B = 0$ and $A^C = 0$. Then $\dot{Y}^B = 0$ and the second part of Eq (2.1), it follows that

$$0 = \dot{Y}^B = \beta_B H_2 V^B \implies V^B(t) = 0, \text{ for all } t. \quad (5.17)$$

Hence, the set $\tilde{\Omega}_2$ reduces to $\{\Xi_2\}$.

Case 2 If $\mathfrak{R}_0^B/\mathfrak{R}_0^C < 1$, and $V_2^C = V_4^C$: Since $V^C = V_2^C$, then $\dot{V}^C = 0$ and the fourth part of Eq (2.1), we have

$$\begin{aligned}
0 &= \theta_C Y_2^C - \phi_C V_2^C - \gamma_C A^C V_2^C, \\
&\implies 0 = \gamma_C A^C V_2^C, \\
&\implies A^C = 0.
\end{aligned} \quad (5.18)$$

From Eqs (5.17) and (5.18), we get $\tilde{\Omega}_2 = \{\Xi_2\}$.

Case 3 If $\mathfrak{R}_0^B/\mathfrak{R}_0^C = 1$, and $V_2^C < V_4^C$: From the first part of Eq (2.1), we have

$$\begin{aligned}
0 &= \phi - \sigma H_2 - \beta_B H_2 V^B - \alpha_B H_2 Y^B - \beta_C H_2 V_2^C - \alpha_C H_2 Y_2^C, \\
&\implies 0 = \beta_B H_2 V^B + \alpha_B H_2 Y^B, \\
&\implies V^B = Y^B = 0.
\end{aligned} \quad (5.19)$$

From Eq (5.17), we get $\tilde{\Omega}_2 = \{\Xi_2\}$.

Case 4 If $\mathfrak{R}_0^B/\mathfrak{R}_0^C = 1$, and $V_2^C = V_4^C$: Then from Eqs (5.18) and (5.19) we get that $\tilde{\Omega}_2 = \{\Xi_2\}$.

Therefore, in all cases, $\tilde{\Omega}_2 = \{\Xi_2\}$. Utilizing L-LAST, we conclude that Ξ_2 is GAS.

To determine whether Ξ_2 is unstable when $\mathfrak{R}_0^B/\mathfrak{R}_0^C > 1$, we calculate characteristic equation at Ξ_2 as follows:

$$(\xi + \lambda_B) \left[\theta_C (\beta_C \lambda_C - \sigma \rho_C (\mathfrak{R}_0^C - 1)) + \alpha_C \lambda_C \phi_C + \xi (\beta_C \theta_C + \alpha_C \phi_C) \right] T_1(\xi) T_2(\xi) = 0, \quad (5.20)$$

where

$$\begin{aligned} T_1(\xi) &= \tilde{a}_3 \xi^3 + \tilde{a}_2 \xi^2 + \tilde{a}_1 \xi + \tilde{a}_0, \\ T_2(\xi) &= \tilde{b}_2 \xi^2 + \tilde{b}_1 \xi + \tilde{b}_0, \\ \tilde{a}_3 &= \mathfrak{R}_0^C, \\ \tilde{a}_2 &= (\mathfrak{R}_0^C)^2 \sigma - H_0 \alpha_C + \mathfrak{R}_0^C \delta_C + \mathfrak{R}_0^C \phi_C, \\ \tilde{a}_1 &= -H_0 \beta_C \theta_C + (\mathfrak{R}_0^C)^2 \sigma \phi_C - H_0 \alpha_C (\sigma + \phi_C) + \mathfrak{R}_0^C \delta_C (\mathfrak{R}_0^C \sigma + \phi_C), \\ \tilde{a}_0 &= \mathfrak{R}_0^C \sigma \delta_C \phi_C - H_0 (\beta_C \theta_C + \alpha_C \phi_C) = \sigma \delta_B \phi_B (\mathfrak{R}_0^C - 1), \\ \tilde{b}_2 &= \mathfrak{R}_0^C, \\ \tilde{b}_1 &= (\delta_B + \phi_B) \mathfrak{R}_0^C - H_0 \alpha_B, \\ \tilde{b}_0 &= \mathfrak{R}_0^C \delta_B \phi_B \left(1 - \frac{\mathfrak{R}_0^B}{\mathfrak{R}_0^C} \right). \end{aligned}$$

where ξ is the eigenvalue. If $\mathfrak{R}_0^B/\mathfrak{R}_0^C > 1$, then $T_2(0) < 0$ and $\lim_{\xi \rightarrow \infty} T_2(\xi) = \infty$. Thus, Eq (5.20) has a positive root, and hence Ξ_2 is unstable. $\square$

Theorem 4. Suppose that $\mathfrak{R}_1^B > 1$ and $\mathfrak{R}_2^B \leq 1$, then Ξ_3 is GAS in Γ_3 .

Proof. Define

$$\begin{aligned} \Lambda_3 &= H_3 F \left(\frac{H}{H_3} \right) + Y_3^B F \left(\frac{Y^B}{Y_3^B} \right) + Y^C + \frac{\beta_B H_3}{\phi_B + \gamma_B A_3^B} V_3^B F \left(\frac{V^B}{V_3^B} \right) + \frac{\beta_C H_3}{\phi_C} V^C \\ &\quad + \frac{\gamma_B \beta_B H_3}{\rho_B (\phi_B + \gamma_B A_3^B)} A_3^B F \left(\frac{A^B}{A_3^B} \right) + \frac{\gamma_C \beta_C H_3}{\rho_C \phi_C} A^C. \end{aligned}$$

We calculate $\frac{d\Lambda_3}{dt}$ as follows:

$$\begin{aligned} \frac{d\Lambda_3}{dt} &= \left(1 - \frac{H_3}{H} \right) [\phi - \sigma H - \beta_B H V^B - \alpha_B H Y^B - \beta_C H V^C - \alpha_C H Y^C] \\ &\quad + \left(1 - \frac{Y_3^B}{Y^B} \right) [\beta_B H V^B + \alpha_B H Y^B - \delta_B Y^B] + \beta_C H V^C + \alpha_C H Y^C - \delta_C Y^C \\ &\quad + \frac{\beta_B H_3}{\phi_B + \gamma_B A_3^B} \left(1 - \frac{V_3^B}{V^B} \right) [\theta_B Y^B - \phi_B V^B - \gamma_B A^B V^B] + \frac{\beta_C H_3}{\phi_C} [\theta_C Y^C - \phi_C V^C - \gamma_C A^C V^C] \\ &\quad + \frac{\gamma_B \beta_B H_3}{\rho_B (\phi_B + \gamma_B A_3^B)} \left(1 - \frac{A_3^B}{A^B} \right) [\rho_B A^B V^B - \lambda_B A^B] + \frac{\gamma_C \beta_C H_3}{\rho_C \phi_C} [\rho_C A^C V^C - \lambda_C A^C]. \end{aligned} \quad (5.21)$$

Then simplifying Eq (5.21), we get:

$$\begin{aligned} \frac{d\Lambda_3}{dt} = & \left(1 - \frac{H_3}{H}\right)(\phi - \sigma H) + \alpha_B H_3 Y^B - \delta_B Y^B - (\beta_B H V^B + \alpha_B H Y^B) \frac{Y_3^B}{Y^B} + \delta_B Y_3^B + \frac{\beta_B H_3 \theta_B}{\phi_B + \gamma_B A_3^B} Y^B \\ & - \frac{\beta_B H_3 \theta_B}{\phi_B + \gamma_B A_3^B} Y^B \frac{V_3^B}{V^B} + \frac{\beta_B H_3 \phi_B}{\phi_B + \gamma_B A_3^B} V_3^B + \frac{\beta_B H_3 \gamma_B}{\phi_B + \gamma_B A_3^B} A^B V_3^B + \left(\alpha_C H_3 + \frac{\beta_C H_3 \theta_C}{\phi_C} - \delta_C\right) Y^C \\ & - \frac{\gamma_B \beta_B H_3 \lambda_B}{\rho_B (\phi_B + \gamma_B A_3^B)} A^B + \frac{\gamma_B \beta_B H_3 \lambda_B}{\rho_B (\phi_B + \gamma_B A_3^B)} A_3^B - \frac{\gamma_C \beta_C H_3 \lambda_C}{\rho_C \phi_C} A^C. \end{aligned}$$

Using the equilibrium conditions for Ξ_3 :

$$\begin{aligned} \phi &= \sigma H_3 + \beta_B H_3 V_3^B + \alpha_B H_3 Y_3^B, \quad \beta_B H_3 V_3^B + \alpha_B H_3 Y_3^B = \delta_B Y_3^B, \\ \theta_B Y_3^B &= (\phi_B + \gamma_B A_3^B) V_3^B, \quad V_3^B = \frac{\lambda_B}{\rho_B}, \end{aligned}$$

we obtain

$$\left(\alpha_B H_3 - \delta_B + \frac{\beta_B H_3 \theta_B}{\phi_B + \gamma_B A_3^B}\right) Y^B = \left(\alpha_B H_3 Y_3^B - \delta_B Y_3^B + \frac{\beta_B H_3 \theta_B}{\phi_B + \gamma_B A_3^B} Y_3^B\right) \frac{Y^B}{Y_3^B} = 0,$$

and

$$\begin{aligned} \frac{d\Lambda_3}{dt} &= \left(1 - \frac{H_3}{H}\right)(\sigma H_3 - \sigma H) + \left(1 - \frac{H_3}{H}\right)(\beta_B H_3 V_3^B + \alpha_B H_3 Y_3^B) \\ &\quad - \beta_B H_3 V_3^B \frac{H V^B Y_3^B}{H_3 V_3^B Y^B} - \alpha_B H Y_3^B + 2\beta_B H_3 V_3^B + \alpha_B H_3 Y_3^B - \beta_B H_3 V_3^B \frac{Y^B V_3^B}{Y_3^B V^B} \\ &\quad + \frac{\beta_C \theta_C + \alpha_C \phi_C}{\phi_C} \left(H_3 - \frac{\delta_C \phi_C}{\beta_C \theta_C + \alpha_C \phi_C}\right) Y^C - \frac{\gamma_C \beta_C H_3 \lambda_C}{\rho_C \phi_C} A^C \\ &= -\left(\frac{\sigma + \alpha_B Y_3^B}{H}\right)(H - H_3)^2 + \beta_B H_3 V_3^B \left[3 - \frac{H_3}{H} - \frac{H V^B Y_3^B}{H_3 V_3^B Y^B} - \frac{Y^B V_3^B}{Y_3^B V^B}\right] \\ &\quad + \frac{\beta_C \theta_C + \alpha_C \phi_C}{\phi_C} (H_3 - H_5) Y^C - \frac{\gamma_C \beta_C H_3 \lambda_C}{\rho_C \phi_C} A^C. \end{aligned}$$

Hence, if $\Re_2^B \leq 1$, then Ξ_5 does not exist, since $V_5^C \leq 0$ and $Y_5^C \leq 0$. In this case, we have

$$\begin{aligned} \dot{Y}^C &= \beta_C H V^C + \alpha_C H Y^C - \delta_C Y^C \leq 0, \\ \dot{V}^C &= \theta_C Y^C - \phi_C V^C - \gamma_C A^C V^C \leq 0. \end{aligned}$$

It folloes that:

$$\dot{Y}^C + \frac{\beta_C H}{\phi_C} \dot{V}^C = \frac{\beta_C \theta_C + \alpha_C \phi_C}{\phi_C} \left(H - \frac{\delta_C \phi_C}{\beta_C \theta_C + \alpha_C \phi_C}\right) Y^C - \frac{\beta_C H \gamma_C}{\phi_C} A^C V^C \leq 0 \text{ for all } Y^C, A^C, V^C > 0.$$

This happens when $H_3 \leq \frac{\delta_C \phi_C}{\beta_C \theta_C + \alpha_C \phi_C} = H_5$. Then using inequality (5.1) and $\Re_2^B \leq 1$, we get $\frac{d\Lambda_3}{dt} \leq 0$ for all $H, Y^B, Y^C, V^B, A^C > 0$. Further, $\frac{d\Lambda_3}{dt} = 0$ when $H = H_3$, $Y^B = Y_3^B$, $V^B = V_3^B$, $A^C = 0$, and

$(H_3 - H_5)Y^C = 0$. Furthermore, every trajectory of system (2.1) converges to $\tilde{\Omega}_3$ whose elements satisfy $V^B = V_3^B$. Then $\dot{V}^B = 0$. Using the fourth part of Eq (2.1), gives

$$\begin{aligned} 0 = \dot{V}^B &= \theta_B Y_3^B - \phi_B V_3^B - \gamma_B A^B V_3^B \implies A^B(t) = A_3^B, \text{ for all } t, \\ (H_3 - H_5)Y^C &= 0. \end{aligned} \quad (5.22)$$

We have two cases:

Case 1 If $H_3 < H_5$: From Eq (5.22) leads to $Y^C = 0$. Then $\dot{Y}^C = 0$ and by using the third part of Eq (2.1), implies

$$0 = \dot{Y}^C = \beta_C H_3 V^C \implies V^C(t) = 0, \text{ for all } t. \quad (5.23)$$

Hence, the set $\tilde{\Omega}_3$ reduces to $\{\Xi_3\}$.

Case 2 If $H_3 = H_5$: From the first part of Eq (2.1), we have

$$\begin{aligned} 0 &= \phi - \sigma H_3 - \beta_B H_3 V_3^B - \alpha_B H_3 Y_3^B - \beta_C H_3 V^C - \alpha_C H_3 Y^C, \\ \implies 0 &= \beta_C H_3 V^C + \alpha_C H_3 Y^C, \\ \implies V^C &= Y^C = 0. \end{aligned} \quad (5.24)$$

Hence, the set $\tilde{\Omega}_3$ reduces to $\{\Xi_3\}$.

Therefore, $\tilde{\Omega}_3 = \{\Xi_3\}$. By applying L-LAST, we conclude that Ξ_3 is GAS. $\square$

Theorem 5. Let $\mathfrak{R}_1^C > 1$ and $\mathfrak{R}_2^C \leq 1$, then Ξ_4 is GAS in Γ_4 .

Proof. Define

$$\begin{aligned} \Lambda_4 &= H_4 F\left(\frac{H}{H_4}\right) + Y^B + Y_4^C F\left(\frac{Y^C}{Y_4^C}\right) + \frac{\beta_B H_4}{\phi_B} V^B + \frac{\beta_C H_4}{\phi_C + \gamma_C A_4^C} V_4^C F\left(\frac{V^C}{V_4^C}\right) \\ &\quad + \frac{\gamma_B \beta_B H_4}{\rho_B \phi_B} A^B + \frac{\gamma_C \beta_C H_4}{\rho_C (\phi_C + \gamma_C A_4^C)} A_4^C F\left(\frac{A^C}{A_4^C}\right). \end{aligned}$$

We calculate $\frac{d\Lambda_4}{dt}$ as follows:

$$\begin{aligned} \frac{d\Lambda_4}{dt} &= \left(1 - \frac{H_4}{H}\right) [\phi - \sigma H - \beta_B H V^B - \alpha_B H Y^B - \beta_C H V^C - \alpha_C H Y^C] + \beta_B H V^B + \alpha_B H Y^B \\ &\quad - \delta_B Y^B + \left(1 - \frac{Y_4^C}{Y^C}\right) [\beta_C H V^C + \alpha_C H Y^C - \delta_C Y^C] + \frac{\beta_B H_4}{\phi_B} [\theta_B Y^B - \phi_B V^B - \gamma_B A^B V^B] \\ &\quad + \frac{\beta_C H_4}{\phi_C + \gamma_C A_4^C} \left(1 - \frac{V_4^C}{V^C}\right) [\theta_C Y^C - \phi_C V^C - \gamma_C A^C V^C] + \frac{\gamma_B \beta_B H_4}{\rho_B \phi_B} [\rho_B A^B V^B - \lambda_B A^B] \\ &\quad + \frac{\gamma_C \beta_C H_4}{\rho_C (\phi_C + \gamma_C A_4^C)} \left(1 - \frac{A_4^C}{A^C}\right) [\rho_C A^C V^C - \lambda_C A^C]. \end{aligned} \quad (5.25)$$

Then by simplifying Eq (5.25), we get:

$$\frac{d\Lambda_4}{dt} = \left(1 - \frac{H_4}{H}\right) (\phi - \sigma H) + \alpha_B H_4 Y^B + \alpha_C H_4 Y^C - \delta_B Y^B - \delta_C Y^C - \beta_C H V^C \frac{Y_4^C}{Y^C}$$

$$\begin{aligned}
& -\alpha_C H Y_4^C + \delta_C Y_4^C + \frac{\beta_B H_4 \theta_B}{\phi_B} Y^B + \frac{\beta_C H_4 \theta_C}{\phi_C + \gamma_C A_4^C} Y^C - \frac{\beta_C H_4 \theta_C}{\phi_C + \gamma_C A_4^C} Y^C \frac{V_4^C}{V^C} \\
& + \frac{\beta_C H_4 \phi_C}{\phi_C + \gamma_C A_4^C} V_4^C + \frac{\beta_C H_4 \gamma_C}{\phi_C + \gamma_C A_4^C} A^C V_4^C - \frac{\lambda_B \gamma_B \beta_B H_4}{\rho_B \phi_B} A^B - \frac{\lambda_C \gamma_C \beta_C H_4}{\rho_C (\phi_C + \gamma_C A_4^C)} A^C \\
& + \frac{\lambda_C \gamma_C \beta_C H_4}{\rho_C (\phi_C + \gamma_C A_4^C)} A_4^C.
\end{aligned}$$

Using the equilibrium conditions for Ξ_4 :

$$\begin{aligned}
\phi &= \sigma H_4 + \beta_C H_4 V_4^C + \alpha_C H_4 Y_4^C, \quad \beta_C H_4 V_4^C + \alpha_C H_4 Y_4^C = \delta_C Y_4^C, \\
\theta_C Y_4^C &= (\phi_C + \gamma_C A_4^C) V_4^C, \quad V_4^C = \frac{\lambda_C}{\rho_C},
\end{aligned}$$

we obtain

$$\left(\alpha_C H_4 - \delta_C + \frac{\beta_C H_4 \theta_C}{\phi_C + \gamma_C A_4^C} \right) Y^C = \left(\alpha_C H_4 Y_4^C - \delta_C Y_4^C + \frac{\beta_C H_4 \theta_C}{\phi_C + \gamma_C A_4^C} Y_4^C \right) \frac{Y^C}{Y_4^C} = 0,$$

and

$$\begin{aligned}
\frac{d\Lambda_4}{dt} &= \left(1 - \frac{H_4}{H} \right) (\sigma H_4 - \sigma H) + \left(1 - \frac{H_4}{H} \right) (\beta_C H_4 V_4^C + \alpha_C H_4 Y_4^C) \\
&\quad - \beta_C H_4 V_4^C \frac{H V^C Y_4^C}{H_4 V_4^C Y^C} - \alpha_C H Y_4^C + 2\beta_C H_4 V_4^C + \alpha_C H_4 Y_4^C - \beta_C H_4 V_4^C \frac{Y^C V_4^C}{Y_4^C V^C} \\
&\quad - \frac{\lambda_B \gamma_B \beta_B H_4}{\rho_B \phi_B} A^B + \left(\alpha_B H_4 + \frac{\beta_B H_4 \theta_B}{\phi_B} - \delta_B \right) Y^B \\
&= - \left(\frac{\sigma + \alpha_C Y_4^C}{H} \right) (H - H_4)^2 + \beta_C H_4 V_4^C \left[3 - \frac{H_4}{H} - \frac{H V^C Y_4^C}{H_4 V_4^C Y^C} - \frac{Y^C V_4^C}{Y_4^C V^C} \right] \\
&\quad + \frac{\alpha_B \phi_B + \beta_B \theta_B}{\phi_B} (H_4 - H_6) Y^B - \frac{\lambda_B \gamma_B \beta_B H_4}{\rho_B \phi_B} A^B.
\end{aligned}$$

Hence, if $\mathfrak{R}_2^C \leq 1$, then Ξ_6 does not exist since $V_6^B \leq 0$ and $Y_6^B \leq 0$. In this case

$$\begin{aligned}
\dot{Y}^B &= \beta_B H V^B + \alpha_B H Y^B - \delta_B Y^B \leq 0, \\
\dot{V}^B &= \theta_B Y^B - \phi_B V^B - \gamma_B A^B V^B \leq 0.
\end{aligned}$$

It follows that,

$$\dot{Y}^B + \frac{\beta_B H}{\phi_B} \dot{V}^B = \frac{\alpha_B \phi_B + \beta_B \theta_B}{\phi_B} \left(H - \frac{\delta_B \phi_B}{\alpha_B \phi_B + \beta_B \theta_B} \right) Y^B - \frac{\beta_B H \gamma_B}{\phi_B} A^B V^B \leq 0 \text{ for all } Y^B, A^B, V^B > 0.$$

This happens when $H_4 \leq \frac{\delta_B \phi_B}{\alpha_B \phi_B + \beta_B \theta_B} = H_6$. Then by using inequality (5.1) and $\mathfrak{R}_2^C \leq 1$, we get $\frac{d\Lambda_4}{dt} \leq 0$ for all $H, Y^B, Y^C, V^C, A^B > 0$. Further, $\frac{d\Lambda_4}{dt} = 0$ when $H = H_4$, $Y^C = Y_4^C$, $V^C = V_4^C$, and $(H_4 - H_6) Y^B = A^B = 0$. Furthermore, every trajectory of system (2.1) converges to $\tilde{\Omega}_4$ such that its elements satisfy $V^C = V_4^C$. Then $\dot{V}^C = 0$, by using the fifth part of Eq (2.1), we get

$$0 = \dot{V}^C = \theta_C Y_4^C - \phi_C V_4^C - \gamma_C A^C V_4^C \implies A^C(t) = A_4^C, \text{ for all } t,$$

$$(H_4 - H_6) Y^B = 0. \quad (5.26)$$

We have two cases :

Case 1 If $H_4 < H_6$: From Eq (5.26) leads to $Y^B = 0$. Then, $\dot{Y}^B = 0$. Through the second part of Eq (2.1), we obtain

$$0 = \dot{Y}^B = \beta_B H_4 V^B \implies V^B(t) = 0, \text{ for all } t. \quad (5.27)$$

Hence, the set $\tilde{\Omega}_4$ reduces to $\{\Xi_4\}$.

Case 2 If $H_4 = H_6$: From the first part of Eq (2.1), we have

$$\begin{aligned} 0 &= \phi - \sigma H_4 - \beta_B H_4 V^B - \alpha_B H_4 Y^B - \beta_C H_4 V_4^C - \alpha_C H_4 Y_4^C, \\ &\implies 0 = \beta_B H_4 V^B + \alpha_B H_4 Y^B, \\ &\implies V^B = Y^B = 0. \end{aligned} \quad (5.28)$$

Hence, the set $\tilde{\Omega}_4$ reduces to $\{\Xi_4\}$.

Consequently, $\tilde{\Omega}_4 = \{\Xi_4\}$. By applying L-LAST, we find that Ξ_4 is GAS. $\square$

Theorem 6. Let $\mathfrak{R}_2^B > 1$, $\tilde{\mathfrak{R}}_2^B > 1$, $\mathfrak{R}_0^B/\mathfrak{R}_0^C > 1$ and $\mathfrak{R}_3^C \leq 1$, then Ξ_5 is GAS in Γ_5 .

Proof. Define

$$\begin{aligned} \Lambda_5 &= H_5 F\left(\frac{H}{H_5}\right) + Y_5^B F\left(\frac{Y^B}{Y_5^B}\right) + Y_5^C F\left(\frac{Y^C}{Y_5^C}\right) + \frac{\beta_B H_5}{\phi_B + \gamma_B A_5^B} V_5^B F\left(\frac{V^B}{V_5^B}\right) \\ &\quad + \frac{\beta_C H_5}{\phi_C} V_5^C F\left(\frac{V^C}{V_5^C}\right) + \frac{\gamma_B \beta_B H_5}{\rho_B (\phi_B + \gamma_B A_5^B)} A_5^B F\left(\frac{A^B}{A_5^B}\right) + \frac{\gamma_C \beta_C H_5}{\rho_C \phi_C} A^C. \end{aligned}$$

We calculate $\frac{d\Lambda_5}{dt}$ as

$$\begin{aligned} \frac{d\Lambda_5}{dt} &= \left(1 - \frac{H_5}{H}\right) [\phi - \sigma H - \beta_B H V^B - \alpha_B H Y^B - \beta_C H V^C - \alpha_C H Y^C] \\ &\quad + \left(1 - \frac{Y_5^B}{Y^B}\right) [\beta_B H V^B + \alpha_B H Y^B - \delta_B Y^B] + \left(1 - \frac{Y_5^C}{Y^C}\right) [\beta_C H V^C + \alpha_C H Y^C - \delta_C Y^C] \\ &\quad + \frac{\beta_B H_5}{\phi_B + \gamma_B A_5^B} \left(1 - \frac{V_5^B}{V^B}\right) [\theta_B Y^B - \phi_B V^B - \gamma_B A^B V^B] \\ &\quad + \frac{\beta_C H_5}{\phi_C} \left(1 - \frac{V_5^C}{V^C}\right) [\theta_C Y^C - \phi_C V^C - \gamma_C A^C V^C] + \frac{\gamma_B \beta_B H_5}{\rho_B (\phi_B + \gamma_B A_5^B)} \left(1 - \frac{A_5^B}{A^B}\right) [\rho_B A^B V^B - \lambda_B A^B] \\ &\quad + \frac{\gamma_C \beta_C H_5}{\rho_C \phi_C} [\rho_C A^C V^C - \lambda_C A^C]. \end{aligned} \quad (5.29)$$

Then by simplifying Eq (5.29), we obtain

$$\frac{d\Lambda_5}{dt} = \left(1 - \frac{H_5}{H}\right) (\phi - \sigma H) + \alpha_B H_5 Y^B + \alpha_C H_5 Y^C - \delta_B Y^B - (\beta_B H V^B + \alpha_B H Y^B) \frac{Y_5^B}{Y^B}$$

$$\begin{aligned}
& + \delta_B Y_5^B - \delta_C Y^C - (\beta_C H V^C + \alpha_C H Y^C) \frac{Y_5^C}{Y^C} + \delta_C Y_5^C + \frac{\beta_B H_5 \theta_B}{\phi_B + \gamma_B A_5^B} Y^B \\
& - \frac{\beta_B H_5 \theta_B}{\phi_B + \gamma_B A_5^B} Y^B \frac{V_5^B}{V^B} + \frac{\beta_B H_5 \phi_B}{\phi_B + \gamma_B A_5^B} V_5^B + \frac{\gamma_B \beta_B H_5}{\phi_B + \gamma_B A_5^B} A^B V_5^B + \frac{\beta_C H_5 \theta_C}{\phi_C} Y^C \\
& - \frac{\beta_C H_5 \theta_C}{\phi_C} Y^C \frac{V_5^C}{V^C} + \beta_C H_5 V_5^C + \frac{\gamma_C \beta_C H_5}{\phi_C} A^C V_5^C - \frac{\lambda_B \gamma_B \beta_B H_5}{\rho_B (\phi_B + \gamma_B A_5^B)} A^B \\
& + \frac{\lambda_B \gamma_B \beta_B H_5}{\rho_B (\phi_B + \gamma_B A_5^B)} A_5^B - \frac{\lambda_C \gamma_C \beta_C H_5}{\rho_C \phi_C} A^C.
\end{aligned}$$

Using the equilibrium conditions for Ξ_5 :

$$\begin{aligned}
\phi &= \sigma H_5 + \beta_B H_5 V_5^B + \alpha_B H_5 Y_5^B + \beta_C H_5 V_5^C + \alpha_C H_5 Y_5^C, \\
\beta_B H_5 V_5^B + \alpha_B H_5 Y_5^B &= \delta_B Y_5^B, \quad \theta_B Y_5^B = (\phi_B + \gamma_B A_5^B) V_5^B, \quad V_5^B = \frac{\lambda_B}{\rho_B}, \\
\beta_C H_5 V_5^C + \alpha_C H_5 Y_5^C &= \delta_C Y_5^C, \quad \theta_C Y_5^C = \phi_C V_5^C,
\end{aligned}$$

we obtain

$$\begin{aligned}
\left(\alpha_C H_5 - \delta_C + \frac{\beta_C H_5 \theta_C}{\phi_C} \right) Y^C &= \left(\alpha_C H_5 Y_5^C + \frac{\beta_C H_5 \theta_C}{\phi_C} Y_5^C - \delta_C Y_5^C \right) \frac{Y^C}{Y_5^C} = 0, \\
\left(\alpha_B H_5 - \delta_B + \frac{\beta_B H_5 \theta_B}{\phi_B + \gamma_B A_5^B} \right) Y^B &= \left(\alpha_B H_5 Y_5^B + \frac{\beta_B H_5 \theta_B}{\phi_B + \gamma_B A_5^B} Y_5^B - \delta_B Y_5^B \right) \frac{Y^B}{Y_5^B} = 0,
\end{aligned}$$

and

$$\begin{aligned}
\frac{d\Lambda_5}{dt} &= \left(1 - \frac{H_5}{H} \right) (\sigma H_5 - \sigma H) + \left(1 - \frac{H_5}{H} \right) (\beta_B H_5 V_5^B + \alpha_B H_5 Y_5^B + \beta_C H_5 V_5^C + \alpha_C H_5 Y_5^C) \\
&- \beta_B H_5 V_5^B \frac{H V^B Y_5^B}{H_5 V_5^B Y^B} - \alpha_B H Y_5^B + 2\beta_B H_5 V_5^B + \alpha_B H_5 Y_5^B - \beta_C H_5 V_5^C \frac{H V^C Y_5^C}{H_5 V_5^C Y^C} - \alpha_C H Y_5^C \\
&+ 2\beta_C H_5 V_5^C + \alpha_C H_5 Y_5^C - \beta_B H_5 V_5^B \frac{Y^B V_5^B}{Y_5^B V^B} - \beta_C H_5 V_5^C \frac{Y^C V_5^C}{Y_5^C V^C} + \frac{\gamma_C \beta_C H_5}{\phi_C} \left(V_5^C - \frac{\lambda_C}{\rho_C} \right) A^C \\
&= - \left(\frac{\sigma + \alpha_B Y_5^B + \alpha_C Y_5^C}{H} \right) (H - H_5)^2 + \beta_B H_5 V_5^B \left[3 - \frac{H_5}{H} - \frac{H V^B Y_5^B}{H_5 V_5^B Y^B} - \frac{Y^B V_5^B}{Y_5^B V^B} \right] \\
&+ \beta_C H_5 V_5^C \left[3 - \frac{H_5}{H} - \frac{H V^C Y_5^C}{H_5 V_5^C Y^C} - \frac{Y^C V_5^C}{Y_5^C V^C} \right] + \frac{\gamma_C \beta_C H_5}{\phi_C} (V_5^C - V_7^C) A^C.
\end{aligned}$$

Hence, if $\mathfrak{R}_3^C \leq 1$, then Ξ_7 does not exist, since $A_7^C \leq 0$.

$$\dot{A}^C = \rho_C \left(V^C - \frac{\lambda_C}{\rho_C} \right) A^C \leq 0 \text{ for all } A^C > 0.$$

Thus, happens when $V_5^C \leq \frac{\lambda_C}{\rho_C} = V_7^C$. Then by using inequality (5.1) and $\mathfrak{R}_3^C \leq 1$, we get $\frac{d\Lambda_5}{dt} \leq 0$ for all $H, Y^B, Y^C, V^B, V^C, A^C > 0$. Further, $\frac{d\Lambda_5}{dt} = 0$ when $H = H_5, Y^B = Y_5^B, Y^C = Y_5^C, V^B = V_5^B, V^C = V_5^C$,

and $(V_5^C - V_7^C)A^C = 0$. Additionally, every trajectory of system (2.1) tends to $\tilde{\Omega}_5$ where the elements satisfy $V^B = V_5^B$. Then $\dot{V}^B = 0$. By the fourth part of Eq (2.1), we have

$$\begin{aligned} 0 = \dot{V}^B &= \theta_B Y_5^B - \phi_B V_5^B - \gamma_B A^B V_5^B \implies A^B(t) = A_5^B, \text{ for all } t, \\ (V_5^C - V_7^C)A^C &= 0. \end{aligned} \quad (5.30)$$

We have two cases:

Case 1 If $V_5^C < V_7^C$: From Eq (5.30) leads to $A^C = 0$. Hence, the set $\tilde{\Omega}_5$ reduces to $\{\Xi_5\}$.

Case 2 If $V_5^C = V_7^C$: From the five part of Eq (2.1), we have

$$\begin{aligned} 0 &= \theta_C Y_5^C - \phi_C V_5^C - \gamma_C A^C V_5^C, \\ \implies 0 &= \gamma_C A^C V_5^C, \\ \implies A^C &= 0. \end{aligned}$$

Hence, the set $\tilde{\Omega}_5$ reduces to $\{\Xi_5\}$.

Consequently, $\tilde{\Omega}_5 = \{\Xi_5\}$. Based on L-LAST, we find that Ξ_5 is GAS. □

Theorem 7. Let $\mathfrak{R}_2^C > 1$, $\tilde{\mathfrak{R}}_2^C > 1$, $\mathfrak{R}_0^C/\mathfrak{R}_0^B > 1$ and $\mathfrak{R}_3^B \leq 1$, then Ξ_6 is GAS in Γ_6 .

Proof. Define

$$\begin{aligned} \Lambda_6 &= H_6 F\left(\frac{H}{H_6}\right) + Y_6^B F\left(\frac{Y^B}{Y_6^B}\right) + Y_6^C F\left(\frac{Y^C}{Y_6^C}\right) + \frac{\beta_B H_6}{\phi_B} V_6^B F\left(\frac{V^B}{V_6^B}\right) \\ &+ \frac{\beta_C H_6}{\phi_C + \gamma_C A_6^C} V_6^C F\left(\frac{V^C}{V_6^C}\right) + \frac{\gamma_B \beta_B H_6}{\rho_B \phi_B} A^B + \frac{\gamma_C \beta_C H_6}{\rho_C (\phi_C + \gamma_C A_6^C)} A_6^C F\left(\frac{A^C}{A_6^C}\right). \end{aligned}$$

We calculate $\frac{d\Lambda_6}{dt}$ as follows:

$$\begin{aligned} \frac{d\Lambda_6}{dt} &= \left(1 - \frac{H_6}{H}\right) [\phi - \sigma H - \beta_B H V^B - \alpha_B H Y^B - \beta_C H V^C - \alpha_C H Y^C] \\ &+ \left(1 - \frac{Y_6^B}{Y^B}\right) [\beta_B H V^B + \alpha_B H Y^B - \delta_B Y^B] + \left(1 - \frac{Y_6^C}{Y^C}\right) [\beta_C H V^C + \alpha_C H Y^C - \delta_C Y^C] \\ &+ \frac{\beta_B H_6}{\phi_B} \left(1 - \frac{V_6^B}{V^B}\right) [\theta_B Y^B - \phi_B V^B - \gamma_B A^B V^B] \\ &+ \frac{\beta_C H_6}{\phi_C + \gamma_C A_6^C} \left(1 - \frac{V_6^C}{V^C}\right) [\theta_C Y^C - \phi_C V^C - \gamma_C A^C V^C] \\ &+ \frac{\gamma_B \beta_B H_6}{\rho_B \phi_B} [\rho_B A^B V^B - \lambda_B A^B] + \frac{\gamma_C \beta_C H_6}{\rho_C (\phi_C + \gamma_C A_6^C)} \left(1 - \frac{A_6^C}{A^C}\right) [\rho_C A^C V^C - \lambda_C A^C]. \end{aligned} \quad (5.31)$$

Then by simplifying Eq (5.31), we get:

$$\frac{d\Lambda_6}{dt} = \left(1 - \frac{H_6}{H}\right) (\phi - \sigma H) + \alpha_B H_6 Y^B + \alpha_C H_6 Y^C - \delta_B Y^B - \beta_B H V^B \frac{Y_6^B}{Y^B} - \alpha_B H Y_6^B$$

$$\begin{aligned}
& + \delta_B Y_6^B - \delta_C Y_6^C - \beta_C H V_6^C \frac{Y_6^C}{Y_6^C} - \alpha_C H Y_6^C + \delta_C Y_6^C + \frac{\beta_B H_6 \theta_B}{\phi_B} Y_6^B - \frac{\beta_B H_6 \theta_B}{\phi_B} Y_6^B \frac{V_6^B}{V_6^B} \\
& + \beta_B H_6 V_6^B + \frac{\gamma_B \beta_B H_6}{\phi_B} A^B V_6^B + \frac{\beta_C H_6 \theta_C}{\phi_C + \gamma_C A_6^C} Y_6^C - \frac{\beta_C H_6 \theta_C}{\phi_C + \gamma_C A_6^C} Y_6^C \frac{V_6^C}{V_6^C} + \frac{\beta_C H_6 \phi_C}{\phi_C + \gamma_C A_6^C} V_6^C \\
& + \frac{\gamma_C \beta_C H_6}{\phi_C + \gamma_C A_6^C} A^C V_6^C - \frac{\lambda_B \gamma_B \beta_B H_6}{\rho_B \phi_B} A^B - \frac{\lambda_C \gamma_C \beta_C H_6}{\rho_C (\phi_C + \gamma_C A_6^C)} A^C + \frac{\lambda_C \gamma_C \beta_C H_6}{\rho_C (\phi_C + \gamma_C A_6^C)} A_6^C.
\end{aligned}$$

Using the equilibrium conditions for Ξ_6 :

$$\begin{aligned}
\phi &= \sigma H_6 + \beta_B H_6 V_6^B + \alpha_B H_6 Y_6^B + \beta_C H_6 V_6^C + \alpha_C H_6 Y_6^C, \\
\beta_B H_6 V_6^B + \alpha_B H_6 Y_6^B &= \delta_B Y_6^B, \quad \theta_B Y_6^B = \phi_B V_6^B, \\
\beta_C H_6 V_6^C + \alpha_C H_6 Y_6^C &= \delta_C Y_6^C, \quad \theta_C Y_6^C = (\phi_C + \gamma_C A_6^C) V_6^C, \quad V_6^C = \frac{\lambda_C}{\rho_C},
\end{aligned}$$

we obtain

$$\begin{aligned}
\left(\alpha_B H_6 - \delta_B + \frac{\beta_B H_6 \theta_B}{\phi_B} \right) Y_6^B &= \left(\alpha_B H_6 Y_6^B + \frac{\beta_B H_6 \theta_B}{\phi_B} Y_6^B - \delta_B Y_6^B \right) \frac{Y_6^B}{Y_6^B} = 0, \\
\left(\alpha_C H_6 - \delta_C + \frac{\beta_C H_6 \theta_C}{\phi_C + \gamma_C A_6^C} \right) Y_6^C &= \left(\alpha_C H_6 Y_6^C + \frac{\beta_C H_6 \theta_C}{\phi_C + \gamma_C A_6^C} Y_6^C - \delta_C Y_6^C \right) \frac{Y_6^C}{Y_6^C} = 0,
\end{aligned}$$

and

$$\begin{aligned}
\frac{d\Lambda_6}{dt} &= \left(1 - \frac{H_6}{H} \right) (\sigma H_6 - \sigma H) + \left(1 - \frac{H_6}{H} \right) (\beta_B H_6 V_6^B + \alpha_B H_6 Y_6^B + \beta_C H_6 V_6^C + \alpha_C H_6 Y_6^C) \\
&- \beta_B H_6 V_6^B \frac{H V_6^B Y_6^B}{H_6 V_6^B Y_6^B} - \alpha_B H Y_6^B + 2\beta_B H_6 V_6^B + \alpha_B H_6 Y_6^B - \beta_C H_6 V_6^C \frac{H V_6^C Y_6^C}{H_6 V_6^C Y_6^C} - \alpha_C H Y_6^C \\
&+ 2\beta_C H_6 V_6^C + \alpha_C H_6 Y_6^C - \beta_B H_6 V_6^B \frac{Y_6^B V_6^B}{Y_6^B V_6^B} + \frac{\gamma_B \beta_B H_6}{\phi_B} \left(V_6^B - \frac{\lambda_B}{\rho_B} \right) A^B - \beta_C H_6 V_6^C \frac{Y_6^C V_6^C}{Y_6^C V_6^C} \\
&= - \left(\frac{\sigma + \alpha_B Y_6^B + \alpha_C Y_6^C}{H} \right) (H - H_6)^2 + \beta_B H_6 V_6^B \left[3 - \frac{H_6}{H} - \frac{H V_6^B Y_6^B}{H_6 V_6^B Y_6^B} - \frac{Y_6^B V_6^B}{Y_6^B V_6^B} \right] \\
&+ \beta_C H_6 V_6^C \left[3 - \frac{H_6}{H} - \frac{H V_6^C Y_6^C}{H_6 V_6^C Y_6^C} - \frac{Y_6^C V_6^C}{Y_6^C V_6^C} \right] + \frac{\gamma_B \beta_B H_6}{\phi_B} (V_6^B - V_7^B) A^B.
\end{aligned}$$

Hence, if $\mathfrak{R}_3^B \leq 1$, then Ξ_7 does not exist, since $A_7^B \leq 0$.

$$A^B = \rho_B \left(V_6^B - \frac{\lambda_B}{\rho_B} \right) A^B \leq 0 \text{ for all } A^B > 0.$$

This happens when $V_6^B \leq \frac{\lambda_B}{\rho_B} = V_7^B$. Then by using inequality (5.1) and $\mathfrak{R}_3^B \leq 1$, we get $\frac{d\Lambda_6}{dt} \leq 0$ for all $H, Y^B, Y^C, V^B, V^C, A^B > 0$. Further, $\frac{d\Lambda_6}{dt} = 0$ when $H = H_6, Y^B = Y_6^B, Y^C = Y_6^C, V^B = V_6^B, V^C = V_6^C$, and $(V_6^B - V_7^B) A^B = 0$. Additionally, every trajectory of system (2.1) converges to $\tilde{\Omega}_6$ with the elements satisfying $V^C = V_6^C$. Then $\dot{V}^C = 0$. The fifth equation of system (2.1) provides

$$0 = \dot{V}^C = \theta_C Y_6^C - \phi_C V_6^C - \gamma_C A^C V_6^C \implies A^C(t) = A_6^C, \text{ for all } t.$$

$$(V_6^B - V_7^B)A^B = 0. \quad (5.32)$$

We have two cases:

Case 1 If $V_6^B < V_7^B$: From Eq (5.32) leads to $A^B = 0$. Hence, the set $\tilde{\Omega}_6$ reduces to $\{\Xi_6\}$.

Case 2 If $V_6^B = V_7^B$: From the fourth part of Eq (2.1), we have

$$\begin{aligned} 0 &= \theta_B Y_6^B - \phi_B V_6^B - \gamma_B A^B V_6^B, \\ \implies 0 &= \gamma_B A^B V_6^B, \\ \implies A^B &= 0. \end{aligned}$$

Hence, the set $\tilde{\Omega}_6$ reduces to $\{\Xi_6\}$.

Consequently, $\tilde{\Omega}_6 = \{\Xi_6\}$. Based on L-LAST, we find that Ξ_6 is GAS. $\square$

Theorem 8. Let $\mathfrak{R}_3^B > 1$ and $\mathfrak{R}_3^C > 1$, then Ξ_7 is GAS in Γ_7 .

Proof. Define

$$\begin{aligned} \Lambda_7 &= H_7 F\left(\frac{H}{H_7}\right) + Y_7^B F\left(\frac{Y^B}{Y_7^B}\right) + Y_7^C F\left(\frac{Y^C}{Y_7^C}\right) + \frac{\beta_B H_7}{\phi_B + \gamma_B A_7^B} V_7^B F\left(\frac{V^B}{V_7^B}\right) \\ &+ \frac{\beta_C H_7}{\phi_C + \gamma_C A_7^C} V_7^C F\left(\frac{V^C}{V_7^C}\right) + \frac{\gamma_B \beta_B H_7}{\rho_B (\phi_B + \gamma_B A_7^B)} A_7^B F\left(\frac{A^B}{A_7^B}\right) + \frac{\gamma_C \beta_C H_7}{\rho_C (\phi_C + \gamma_C A_7^C)} A_7^C F\left(\frac{A^C}{A_7^C}\right). \end{aligned}$$

We calculate $\frac{d\Lambda_7}{dt}$ as:

$$\begin{aligned} \frac{d\Lambda_7}{dt} &= \left(1 - \frac{H_7}{H}\right) [\phi - \sigma H - \beta_B H V^B - \alpha_B H Y^B - \beta_C H V^C - \alpha_C H Y^C] \\ &+ \left(1 - \frac{Y_7^B}{Y^B}\right) [\beta_B H V^B + \alpha_B H Y^B - \delta_B Y^B] + \left(1 - \frac{Y_7^C}{Y^C}\right) [\beta_C H V^C + \alpha_C H Y^C - \delta_C Y^C] \\ &+ \frac{\beta_B H_7}{\phi_B + \gamma_B A_7^B} \left(1 - \frac{V_7^B}{V^B}\right) [\theta_B Y^B - \phi_B V^B - \gamma_B A^B V^B] \\ &+ \frac{\beta_C H_7}{\phi_C + \gamma_C A_7^C} \left(1 - \frac{V_7^C}{V^C}\right) [\theta_C Y^C - \phi_C V^C - \gamma_C A^C V^C] \\ &+ \frac{\gamma_B \beta_B H_7}{\rho_B (\phi_B + \gamma_B A_7^B)} \left(1 - \frac{A_7^B}{A^B}\right) [\rho_B A^B V^B - \lambda_B A^B] \\ &+ \frac{\gamma_C \beta_C H_7}{\rho_C (\phi_C + \gamma_C A_7^C)} \left(1 - \frac{A_7^C}{A^C}\right) [\rho_C A^C V^C - \lambda_C A^C]. \end{aligned} \quad (5.33)$$

Then by simplifying Eq (5.33), we get:

$$\begin{aligned} \frac{d\Lambda_7}{dt} &= \left(1 - \frac{H_7}{H}\right) (\phi - \sigma H) + \alpha_B H_7 Y^B + \alpha_C H_7 Y^C - \delta_B Y^B \\ &- \beta_B H V^B \frac{Y_7^B}{Y^B} - \alpha_B H Y_7^B + \delta_B Y_7^B - \delta_C Y^C - \beta_C H V^C \frac{Y_7^C}{Y^C} - \alpha_C H Y_7^C \end{aligned}$$

$$\begin{aligned}
& + \delta_C Y_7^C + \frac{\beta_B H_7 \theta_B}{\phi_B + \gamma_B A_7^B} Y^B - \frac{\beta_B H_7 \theta_B}{\phi_B + \gamma_B A_7^B} Y^B \frac{V_7^B}{V^B} + \frac{\beta_B H_7 \phi_B}{\phi_B + \gamma_B A_7^B} V_7^B \\
& + \frac{\gamma_B \beta_B H_7}{\phi_B + \gamma_B A_7^B} A^B V_7^B + \frac{\beta_C H_7 \theta_C}{\phi_C + \gamma_C A_7^C} Y^C - \frac{\beta_C H_7 \theta_C}{\phi_C + \gamma_C A_7^C} Y^C \frac{V_7^C}{V^C} \\
& + \frac{\beta_C H_7 \phi_C}{\phi_C + \gamma_C A_7^C} V_7^C + \frac{\gamma_C \beta_C H_7}{\phi_C + \gamma_C A_7^C} A^C V_7^C - \frac{\lambda_B \gamma_B \beta_B H_7}{\rho_B (\phi_B + \gamma_B A_7^B)} A^B \\
& + \frac{\lambda_B \gamma_B \beta_B H_7}{\rho_B (\phi_B + \gamma_B A_7^B)} A_7^B - \frac{\lambda_C \gamma_C \beta_C H_7}{\rho_C (\phi_C + \gamma_C A_7^C)} A^C \\
& + \frac{\lambda_C \gamma_C \beta_C H_7}{\rho_C (\phi_C + \gamma_C A_7^C)} A_7^C.
\end{aligned}$$

Using the equilibrium conditions for Ξ_6 :

$$\begin{aligned}
\phi &= \sigma H_7 + \beta_B H_7 V_7^B + \alpha_B H_7 Y_7^B + \beta_C H_7 V_7^C + \alpha_C H_7 Y_7^C, \\
\beta_B H_7 V_7^B + \alpha_B H_7 Y_7^B &= \delta_B Y_7^B, \quad \theta_B Y_7^B = (\phi_B + \gamma_B A_7^B) V_7^B, \quad V_7^B = \frac{\lambda_B}{\rho_B}, \\
\beta_C H_7 V_7^C + \alpha_C H_7 Y_7^C &= \delta_C Y_7^C, \quad \theta_C Y_7^C = (\phi_C + \gamma_C A_7^C) V_7^C, \quad V_7^C = \frac{\lambda_C}{\rho_C},
\end{aligned}$$

we obtain

$$\begin{aligned}
\left(\alpha_B H_7 - \delta_B + \frac{\beta_B H_7 \theta_B}{\phi_B + \gamma_B A_7^B} \right) Y^B &= \left(\alpha_B H_7 Y_7^B + \frac{\beta_B H_7 \theta_B}{\phi_B + \gamma_B A_7^B} Y_7^B - \delta_B Y_7^B \right) \frac{Y^B}{Y_7^B} = 0, \\
\left(\alpha_C H_7 - \delta_C + \frac{\beta_C H_7 \theta_C}{\phi_C + \gamma_C A_7^C} \right) Y^C &= \left(\alpha_C H_7 Y_7^C + \frac{\beta_C H_7 \theta_C}{\phi_C + \gamma_C A_7^C} Y_7^C - \delta_C Y_7^C \right) \frac{Y^C}{Y_7^C} = 0,
\end{aligned}$$

and

$$\begin{aligned}
\frac{d\Lambda_7}{dt} &= \left(1 - \frac{H_7}{H} \right) (\sigma H_7 - \sigma H) + \left(1 - \frac{H_7}{H} \right) (\beta_B H_7 V_7^B + \alpha_B H_7 Y_7^B + \beta_C H_7 V_7^C + \alpha_C H_7 Y_7^C) \\
&\quad - \beta_B H V^B \frac{Y_7^B}{Y^B} - \alpha_B H Y_7^B + 2\beta_B H_7 V_7^B + \alpha_B H_7 Y_7^B - \beta_C H V^C \frac{Y_7^C}{Y^C} - \alpha_C H Y_7^C + 2\beta_C H_7 V_7^C \\
&\quad + \alpha_C H_7 Y_7^C - \beta_B H_7 V_7^B \frac{Y^B V_7^B}{Y_7^B V^B} - \beta_C H_7 V_7^C \frac{Y^C V_7^C}{Y_7^C V^C} \\
&= - \left(\frac{\sigma + \alpha_B Y_7^B + \alpha_C Y_7^C}{H} \right) (H - H_7)^2 + \beta_B H_7 V_7^B \left[3 - \frac{H_7}{H} - \frac{H V^B Y_7^B}{H_7 V_7^B Y^B} - \frac{Y^B V_7^B}{Y_7^B V^B} \right] \\
&\quad + \beta_C H_7 V_7^C \left[3 - \frac{H_7}{H} - \frac{H V^C Y_7^C}{H_7 V_7^C Y^C} - \frac{Y^C V_7^C}{Y_7^C V^C} \right].
\end{aligned}$$

Utilizing inequality (5.1), we obtain $\frac{d\Lambda_7}{dt} \leq 0$ for all $H, Y^B, Y^C, V^B, V^C > 0$. Further, $\frac{d\Lambda_7}{dt} = 0$ when $H = H_7, Y^B = Y_7^B, Y^C = Y_7^C, V^B = V_7^B$ and $V^C = V_7^C$. Furthermore, every trajectory of system (2.1) leads to $\tilde{\Omega}_7$ which has elements including $V^B = V_7^B$ and $V^C = V_7^C$. Then $\dot{V}^B = \dot{V}^C = 0$. Thus, the fourth and fifth parts of Eq (2.1), imply that

$$0 = \dot{V}^B = \theta_B Y_7^B - \phi_B V_7^B - \gamma_B A^B V_7^B \implies A^B(t) = A_7^B, \text{ for all } t,$$

$$0 = \dot{V}^C = \theta_C Y_7^C - \phi_C V_7^C - \gamma_C A^C V_7^C \implies A^C(t) = A_7^C, \text{ for all } t.$$

Therefore, $\tilde{\Omega}_7 = \{\Xi_7\}$. By utilizing L-LAST, we find that Ξ_7 is GAS. $\square$

The criteria for the existence and global stability of the equilibrium points are summarized in Table 2.

Table 2. Existence and global stability criteria for the system's equilibria.

Equilibrium point	Existence criteria	Global stability criteria
$\Xi_0 = (H_0, 0, 0, 0, 0, 0)$	None	$\mathfrak{R}_0^B \leq 1$ and $\mathfrak{R}_0^C \leq 1$
$\Xi_1 = (H_1, Y_1^B, 0, V_1^B, 0, 0)$	$\mathfrak{R}_0^B > 1$	$\mathfrak{R}_0^B > 1$, $\mathfrak{R}_0^C/\mathfrak{R}_0^B \leq 1$ and $\mathfrak{R}_1^B \leq 1$
$\Xi_2 = (H_2, 0, Y_2^C, 0, V_2^C, 0)$	$\mathfrak{R}_0^C > 1$	$\mathfrak{R}_0^C > 1$, $\mathfrak{R}_0^B/\mathfrak{R}_0^C \leq 1$ and $\mathfrak{R}_1^C \leq 1$
$\Xi_3 = (H_3, Y_3^B, 0, V_3^B, 0, A_3^B)$	$\mathfrak{R}_1^B > 1$	$\mathfrak{R}_1^B > 1$ and $\mathfrak{R}_2^B \leq 1$
$\Xi_4 = (H_4, 0, Y_4^C, 0, V_4^C, A_4^C)$	$\mathfrak{R}_1^C > 1$	$\mathfrak{R}_1^C > 1$ and $\mathfrak{R}_2^C \leq 1$
$\Xi_5 = (H_5, Y_5^B, Y_5^C, V_5^B, V_5^C, A_5^B)$	$\mathfrak{R}_2^B > 1$, $\tilde{\mathfrak{R}}_2^B > 1$ and $\mathfrak{R}_0^B/\mathfrak{R}_0^C > 1$	$\mathfrak{R}_2^B > 1$, $\tilde{\mathfrak{R}}_2^B > 1$, $\mathfrak{R}_3^C \leq 1$ and $\mathfrak{R}_0^B/\mathfrak{R}_0^C > 1$
$\Xi_6 = (H_6, Y_6^B, Y_6^C, V_6^B, V_6^C, 0, A_6^C)$	$\mathfrak{R}_2^C > 1$, $\tilde{\mathfrak{R}}_2^C > 1$ and $\mathfrak{R}_0^C/\mathfrak{R}_0^B > 1$	$\mathfrak{R}_2^C > 1$, $\tilde{\mathfrak{R}}_2^C > 1$, $\mathfrak{R}_3^B \leq 1$ and $\mathfrak{R}_0^C/\mathfrak{R}_0^B > 1$
$\Xi_7 = (H_7, Y_7^B, Y_7^C, V_7^B, V_7^C, A_7^B, A_7^C)$	$\mathfrak{R}_3^B > 1$ and $\mathfrak{R}_3^C > 1$	$\mathfrak{R}_3^B > 1$ and $\mathfrak{R}_3^C > 1$

6. HBV/HCV co-infection model under the impact of antiviral treatments

In this section, we reformulate the HBV/HCV coinfection model by incorporating the efficacy of therapeutic interventions in reducing viral transmission. Experimental studies have provided evidence for cell-to-cell transmission in HBV and HCV [64, 65]. Consequently, this study investigates the potential effects of interventions targeting two transmission routes: virus-to-cell transmission and cell-to-cell transmission. The control variables are interpreted as mechanism-specific intervention efficacies rather than as representations of particular approved drugs. They are defined as: η_1 for blocking HBV infection via virus-to-cell transmission, η_2 for blocking HBV infection via cell-to-cell transmission, η_3 for blocking HCV infection via virus-to-cell transmission, and η_4 for blocking HCV infection via cell-to-cell transmission. Thus, the modified version of model (2.1) becomes:

$$\begin{cases} \dot{H} = \phi - \sigma H - (1 - \eta_1(t))\beta_B H V^B - (1 - \eta_2(t))\alpha_B H Y^B \\ \quad - (1 - \eta_3(t))\beta_C H V^C - (1 - \eta_4(t))\alpha_C H Y^C, \\ \dot{Y}^B = (1 - \eta_1(t))\beta_B H V^B + (1 - \eta_2(t))\alpha_B H Y^B - \delta_B Y^B, \\ \dot{Y}^C = (1 - \eta_3(t))\beta_C H V^C + (1 - \eta_4(t))\alpha_C H Y^C - \delta_C Y^C, \\ \dot{V}^B = \theta_B Y^B - \phi_B V^B - \gamma_B A^B V^B, \\ \dot{V}^C = \theta_C Y^C - \phi_C V^C - \gamma_C A^C V^C, \\ \dot{A}^B = \rho_B A^B V^B - \lambda_B A^B, \\ \dot{A}^C = \rho_C A^C V^C - \lambda_C A^C, \end{cases} \quad (6.1)$$

where, $\eta_i(t) \in [0, 1]$.

6.1. Effect of cell-to-cell transmission on the HBV and HCV co-dynamics

In this subsection, we evaluate the contribution of cell-to-cell transmission to HBV/HCV co-dynamics by comparing model with and without cell-to-cell transmission. First, we assume that

all $\eta_i(t)$, $i = 1, \dots, 4$ are constant, and $\eta = \eta_1 = \eta_2 = \eta_3 = \eta_4$. The model will become

$$\begin{cases} \dot{H} = \phi - \sigma H - (1 - \eta)\beta_B HV^B - (1 - \eta)\alpha_B HY^B - (1 - \eta)\beta_C HV^C - (1 - \eta)\alpha_C HY^C, \\ \dot{Y}^B = (1 - \eta)\beta_B HV^B + (1 - \eta)\alpha_B HY^B - \delta_B Y^B, \\ \dot{Y}^C = (1 - \eta)\beta_C HV^C + (1 - \eta)\alpha_C HY^C - \delta_C Y^C, \\ \dot{V}^B = \theta_B Y^B - \phi_B V^B - \gamma_B A^B V^B, \\ \dot{V}^C = \theta_C Y^C - \phi_C V^C - \gamma_C A^C V^C, \\ \dot{A}^B = \rho_B A^B V^B - \lambda_B A^B, \\ \dot{A}^C = \rho_C A^C V^C - \lambda_C A^C. \end{cases} \quad (6.2)$$

Therefore, the basic reproduction number is derived using the same next-generation matrix approach, with the substitutions β_B by $(1 - \eta)\beta_B$, α_B by $(1 - \eta)\alpha_B$, β_C by $(1 - \eta)\beta_C$, and α_C by $(1 - \eta)\alpha_C$. Consequently, we obtain:

$$\begin{aligned} \mathfrak{R}_0 &= \rho(FV^{-1}) = \max \left\{ \frac{H_0(1 - \eta)(\alpha_B \phi_B + \beta_B \theta_B)}{\delta_B \phi_B}, \frac{H_0(1 - \eta)(\alpha_C \phi_C + \beta_C \theta_C)}{\delta_C \phi_C} \right\} \\ &= \max \{ \mathfrak{R}_0^B, \mathfrak{R}_0^C \}. \end{aligned}$$

We define the reproduction number associated with the combined cell-to-cell and virus-to-cell transmission system (6.2) by $\mathfrak{R}_0^{comb}$, where

$$\begin{aligned} \mathfrak{R}_0^{B,comb}(\eta) &= \frac{H_0(1 - \eta)(\alpha_B \phi_B + \beta_B \theta_B)}{\delta_B \phi_B} = \frac{(1 - \eta)H_0\alpha_B}{\delta_B} + \frac{(1 - \eta)H_0\beta_B\theta_B}{\delta_B \phi_B} \\ &= \mathfrak{R}_0^{B,c}(\eta) + \mathfrak{R}_0^{B,v}(\eta), \\ \mathfrak{R}_0^{C,comb}(\eta) &= \frac{H_0(1 - \eta)(\alpha_C \phi_C + \beta_C \theta_C)}{\delta_C \phi_C} = \frac{(1 - \eta)H_0\alpha_C}{\delta_C} + \frac{(1 - \eta)H_0\beta_C\theta_C}{\delta_C \phi_C} \\ &= \mathfrak{R}_0^{C,c}(\eta) + \mathfrak{R}_0^{C,v}(\eta), \end{aligned}$$

where

$$\begin{aligned} \mathfrak{R}_0^{B,c}(\eta) &= \frac{(1 - \eta)H_0\alpha_B}{\delta_B}, \quad \mathfrak{R}_0^{B,v}(\eta) = \frac{(1 - \eta)H_0\beta_B\theta_B}{\delta_B \phi_B}, \\ \mathfrak{R}_0^{C,c}(\eta) &= \frac{(1 - \eta)H_0\alpha_C}{\delta_C}, \quad \mathfrak{R}_0^{C,v}(\eta) = \frac{(1 - \eta)H_0\beta_C\theta_C}{\delta_C \phi_C}. \end{aligned}$$

Here, $\mathfrak{R}_0^{B,v}(\eta)$ and $\mathfrak{R}_0^{C,v}(\eta)$ is the reproduction number for the following HBV/HCV model with only virus-to-cell transmission:

$$\begin{aligned} \dot{H} &= \phi - \sigma H - (1 - \eta)\beta_B HV^B - (1 - \eta)\beta_C HV^C, \\ \dot{Y}^B &= (1 - \eta)\beta_B HV^B - \delta_B Y^B, \\ \dot{Y}^C &= (1 - \eta)\beta_C HV^C - \delta_C Y^C, \\ \dot{V}^B &= \theta_B Y^B - \phi_B V^B - \gamma_B A^B V^B, \\ \dot{V}^C &= \theta_C Y^C - \phi_C V^C - \gamma_C A^C V^C, \\ \dot{A}^B &= \rho_B A^B V^B - \lambda_B A^B, \end{aligned}$$

$$\dot{A}^C = \rho_C A^C V^C - \lambda_C A^C. \quad (6.3)$$

We have

$$\begin{aligned} \mathfrak{R}_0^{B,comb}(\eta) &= \mathfrak{R}_0^{B,v}(\eta) + \mathfrak{R}_0^{B,c}(\eta), \\ &= (1 - \eta) \mathfrak{R}_0^{B,v}(0) + (1 - \eta) \mathfrak{R}_0^{B,c}(0), \\ &= (1 - \eta) \mathfrak{R}_0^{B,comb}(0). \\ \mathfrak{R}_0^{C,comb}(\eta) &= \mathfrak{R}_0^{C,v}(\eta) + \mathfrak{R}_0^{C,c}(\eta), \\ &= (1 - \eta) \mathfrak{R}_0^{C,v}(0) + (1 - \eta) \mathfrak{R}_0^{C,c}(0), \\ &= (1 - \eta) \mathfrak{R}_0^{C,comb}(0). \end{aligned}$$

We estimate that the efficacy of the drug η by ensuring that $\mathfrak{R}_0^{B,v}(0) \leq 1$, $\mathfrak{R}_0^{C,v}(0) \leq 1$, and $\mathfrak{R}_0^{B,comb}(\eta) \leq 1$, $\mathfrak{R}_0^{C,comb}(\eta) \leq 1$, which ensures a stable for free equilibrium point of model in Eqs (6.2) and (6.3), respectively:

$$\begin{aligned} \mathfrak{R}_0^{B,comb}(\eta) \leq 1 &\iff \eta_{\min}^{B,comb} \leq \eta \leq 1, \quad \eta_{\min}^{B,comb} = \max \left\{ 0, 1 - \frac{1}{\mathfrak{R}_0^{B,comb}(0)} \right\}, \\ \mathfrak{R}_0^{B,v}(\eta) \leq 1 &\iff \eta_{\min}^{B,v} \leq \eta \leq 1, \quad \eta_{\min}^{B,v} = \max \left\{ 0, 1 - \frac{1}{\mathfrak{R}_0^{B,v}(0)} \right\}. \end{aligned} \quad (6.4)$$

And

$$\begin{aligned} \mathfrak{R}_0^{C,comb}(\eta) \leq 1 &\iff \eta_{\min}^{C,comb} \leq \eta \leq 1, \quad \eta_{\min}^{C,comb} = \max \left\{ 0, 1 - \frac{1}{\mathfrak{R}_0^{C,comb}(0)} \right\}, \\ \mathfrak{R}_0^{C,v}(\eta) \leq 1 &\iff \eta_{\min}^{C,v} \leq \eta \leq 1, \quad \eta_{\min}^{C,v} = \max \left\{ 0, 1 - \frac{1}{\mathfrak{R}_0^{C,v}(0)} \right\}. \end{aligned} \quad (6.5)$$

We obtain

$$\begin{aligned} \mathfrak{R}_0^{B,comb}(0) &= \frac{H_0 \alpha_B \phi_B}{\delta_B \phi_B} + \frac{H_0 \beta_B \theta_B}{\delta_B \phi_B} > \frac{H_0 \beta_B \theta_B}{\delta_B \phi_B} = \mathfrak{R}_0^{B,v}(0), \\ \mathfrak{R}_0^{C,comb}(0) &= \frac{H_0 \alpha_C \phi_C}{\delta_C \phi_C} + \frac{H_0 \beta_C \theta_C}{\delta_C \phi_C} > \frac{H_0 \beta_C \theta_C}{\delta_C \phi_C} = \mathfrak{R}_0^{C,v}(0). \end{aligned}$$

These results indicate that $\mathfrak{R}_0^{B,v}(\eta) < \mathfrak{R}_0^{B,comb}(\eta)$ and $\mathfrak{R}_0^{C,v}(\eta) < \mathfrak{R}_0^{C,comb}(\eta)$, demonstrating that neglecting cell-to-cell transmission yields an underestimation of the basic reproduction number. Furthermore, from Eqs (6.4) and (6.5), we observe that $\eta_{\min}^{B,v} < \eta_{\min}^{B,comb}$ and $\eta_{\min}^{C,v} < \eta_{\min}^{C,comb}$. This implies that a treatment strategy based solely on virus-to-cell transmission may predict stability at lower efficacy levels, whereas the combined transmission model may still remain unstable within the interval

$$\eta_{\min}^{B,v} \leq \eta < \eta_{\min}^{B,comb} \quad \text{and} \quad \eta_{\min}^{C,v} \leq \eta < \eta_{\min}^{C,comb}.$$

Overall, these findings highlight that ignoring cell-to-cell transmission can result in underestimating the antiviral efficacy required for viral clearance. Consequently, the model described by Eq (2.1), which incorporates both transmission pathways, provides a more accurate representation of within-host HBV/HCV co-dynamics than models considering only virus-to-cell transmission.

6.2. The optimal control problem

Classical optimization theory has been widely used to develop control mechanisms for various infectious diseases. Our goal is to minimize HBV/HCV coinfection in a community by maximizing the population of uninfected hepatocytes through control variables that represent the efficiency of drug therapy in blocking new infections of HBV and HCV, denoted by $\eta_1(t)$, $\eta_2(t)$, $\eta_3(t)$, and $\eta_4(t)$, respectively. The problem is to maximize the objective functional

$$J(\eta_1, \eta_2, \eta_3, \eta_4) = \int_0^{t_f} \left[H(t) - \left(\frac{A_1}{2} \eta_1^2(t) + \frac{A_2}{2} \eta_2^2(t) + \frac{A_3}{2} \eta_3^2(t) + \frac{A_4}{2} \eta_4^2(t) \right) \right] dt, \quad (6.6)$$

over the admissible controls, subject to model (6.1) and the following specified initial conditions:

$$\begin{aligned} H(0) &= H_0, \quad Y^B(0) = Y_0^B, \quad Y^C(0) = Y_0^C, \quad V^B(0) = V_0^B, \\ V^C(0) &= V_0^C, \quad A^B(0) = A_0^B, \quad A^C(0) = A_0^C. \end{aligned}$$

The parameters A_1 , A_2 , A_3 , and A_4 are non-negative weighting coefficients reflecting the relative benefits and costs associated with the treatment strategy. Our objective is to maximize the functional defined in Eq (6.6) by increasing the population of uninfected hepatocytes. Accordingly, we aim to determine an optimal control quadruple $(\tilde{\eta}_1, \tilde{\eta}_2, \tilde{\eta}_3, \tilde{\eta}_4)$ such that

$$\tilde{J}(\tilde{\eta}_1, \tilde{\eta}_2, \tilde{\eta}_3, \tilde{\eta}_4) = \max\{J(\eta_1, \eta_2, \eta_3, \eta_4) : (\eta_1, \eta_2, \eta_3, \eta_4) \in E\}, \quad (6.7)$$

where E is the control set defined by

$$E = \{\eta = (\eta_1, \eta_2, \eta_3, \eta_4) : \eta_i \text{ measurable}, 0 \leq \eta_i(t) \leq 1, t \in [0, t_f], i = 1, 2, 3, 4\}.$$

Pontryagin's Maximum Principle [66] provides necessary conditions for an optimal control problem. This principle converts Eqs (6.1), (6.6), and (6.7) into a problem of maximizing an Hamiltonian H , pointwisely with respect to η_1, η_2, η_3 , and η_4 :

$$\mathcal{H} = H - \left(\frac{A_1}{2} \eta_1^2(t) + \frac{A_2}{2} \eta_2^2(t) + \frac{A_3}{2} \eta_3^2(t) + \frac{A_4}{2} \eta_4^2(t) \right) + \sum_{i=1}^7 \kappa_i f_i, \quad (6.8)$$

where f_i is the right-hand side of the differential equation of i -th state variable. By applying Pontryagin's Maximum Principle [66] and the existence result for the optimal control from [67], we obtain the following theorem.

Theorem 9. *There exists an optimal control $\tilde{\eta} = (\tilde{\eta}_1, \tilde{\eta}_2, \tilde{\eta}_3, \tilde{\eta}_4)$ and corresponding solution $\tilde{H}, \tilde{Y}^B, \tilde{Y}^C, \tilde{V}^B, \tilde{V}^C, \tilde{A}^B$, and $\tilde{A}^C$, that maximizes $J(\eta_1, \eta_2, \eta_3, \eta_4)$ over E . Furthermore, there exists adjoint functions, $\kappa_1, \kappa_2, \kappa_3, \kappa_4, \kappa_5, \kappa_6$ and κ_7 satisfying the equations.*

$$\begin{aligned} \dot{\kappa}_1 &= -1 + \sigma \kappa_1 + (1 - \tilde{\eta}_1)(\kappa_1 - \kappa_2) \beta_B \tilde{V}^B + (1 - \tilde{\eta}_2)(\kappa_1 - \kappa_2) \alpha_B \tilde{Y}^B \\ &\quad + (1 - \tilde{\eta}_3)(\kappa_1 - \kappa_3) \beta_C \tilde{V}^C + (1 - \tilde{\eta}_4)(\kappa_1 - \kappa_3) \alpha_C \tilde{Y}^C, \\ \dot{\kappa}_2 &= (1 - \tilde{\eta}_2)(\kappa_1 - \kappa_2) \alpha_B \tilde{H} + \delta_B \kappa_2 - \theta_B \kappa_4, \\ \dot{\kappa}_3 &= (1 - \tilde{\eta}_4)(\kappa_1 - \kappa_3) \alpha_C \tilde{H} + \delta_C \kappa_3 - \theta_C \kappa_5, \end{aligned}$$

$$\begin{aligned}
\dot{\kappa}_4 &= (1 - \tilde{\eta}_1)(\kappa_1 - \kappa_2)\beta_B\tilde{H} + \kappa_4(\phi_B + \gamma_B\tilde{A}^B) - \rho_B\tilde{A}^B\kappa_6, \\
\dot{\kappa}_5 &= (1 - \tilde{\eta}_3)(\kappa_1 - \kappa_3)\beta_C\tilde{H} + \kappa_5(\phi_C + \gamma_C\tilde{A}^C) - \rho_C\tilde{A}^C\kappa_7, \\
\dot{\kappa}_6 &= \tilde{V}^B(\gamma_B\kappa_4 - \rho_B\kappa_6) + \lambda_B\kappa_6, \\
\dot{\kappa}_7 &= \tilde{V}^C(\gamma_C\kappa_5 - \rho_C\kappa_7) + \lambda_C\kappa_7,
\end{aligned}$$

with the transversality conditions

$$\kappa_i(t_f) = 0, \quad i = 1, \dots, 7.$$

Moreover, the optimal control is given by

$$\tilde{\eta}_1 = \min\left(1, \max\left(0, \frac{1}{A_1}(\kappa_1 - \kappa_2)\beta_B\tilde{H}\tilde{V}^B\right)\right), \quad (6.9)$$

$$\tilde{\eta}_2 = \min\left(1, \max\left(0, \frac{1}{A_2}(\kappa_1 - \kappa_2)\alpha_B\tilde{H}\tilde{Y}^B\right)\right), \quad (6.10)$$

$$\tilde{\eta}_3 = \min\left(1, \max\left(0, \frac{1}{A_3}(\kappa_1 - \kappa_3)\beta_C\tilde{H}\tilde{V}^C\right)\right), \quad (6.11)$$

$$\tilde{\eta}_4 = \min\left(1, \max\left(0, \frac{1}{A_4}(\kappa_1 - \kappa_3)\alpha_C\tilde{H}\tilde{Y}^C\right)\right), \quad (6.12)$$

is control of HBV/HCV model.

Proof. The existence of an optimal control follows from the sufficient conditions given by Fleming and Rishel [67]. We verify the required assumptions as follows:

- H_1 The admissible control set E is nonempty, and every control component is non-negative and Lebesgue-integrable over the interval $[0, t_f]$.
- H_2 The right-hand side of the controlled system (6.1) is bounded by a linear function of the state and control variables. Consequently, the corresponding state system admits a solution. By definition, each component right-hand side is continuous and can be expressed in the form:

$$\dot{X} = AX + B(X), \quad (6.13)$$

where X denotes the vector of state variables. Since the state and control variables H , Y^B , Y^C , V^B , V^C , A^B , A^C , η_1 , η_2 , η_3 , and η_4 remain bounded on $[0, t_f]$, the matrix A and the vector $B(X)$ are bounded. In particular, considering the control system (6.1) with initial conditions H_0 , Y_0^B , Y_0^C , V_0^B , V_0^C , A_0^B , and A_0^C , the state vector can be written as

$$X = \begin{pmatrix} H \\ Y^B \\ Y^C \\ V^B \\ V^C \\ A^B \\ A^C \end{pmatrix}.$$

The matrix A and the vector $B(X)$ are defined in Eqs (6.14) and (6.15), respectively:

$$A = \begin{pmatrix} -\sigma & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -\delta_B & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -\delta_C & 0 & 0 & 0 & 0 \\ 0 & \theta_B & 0 & -\phi_B & 0 & 0 & 0 \\ 0 & 0 & \theta_C & 0 & -\phi_C & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -\lambda_B & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -\lambda_C \end{pmatrix}, \quad (6.14)$$

and

$$B(X) = \begin{pmatrix} \phi - (1 - \eta_1)\beta_B HV^B - (1 - \eta_2)\alpha_B HY^B - (1 - \eta_3)\beta_C HV^C - (1 - \eta_4)\alpha_C HY^C \\ (1 - \eta_1)\beta_B HV^B + (1 - \eta_2)\alpha_B HY^B \\ (1 - \eta_3)\beta_C HV^C + (1 - \eta_4)\alpha_C HY^C \\ -\gamma_B A^B V^B \\ -\gamma_C A^C V^C \\ \rho_B A^B V^B \\ \rho_C A^C V^C \end{pmatrix}. \quad (6.15)$$

Thus, the system (6.13) is a nonlinear, with bounded coefficients. Let

$$S(X) = AX + B(X). \quad (6.16)$$

For any two state vectors X_1 and X_2 , the nonlinear part satisfies

$$\begin{aligned} |B(X_1) - B(X_2)| &= |(1 - \eta_1)\beta_B H_1 V_1^B - (1 - \eta_2)\alpha_B H_1 Y_1^B - (1 - \eta_3)\beta_C H_1 V_1^C \\ &\quad - (1 - \eta_4)\alpha_C H_1 Y_1^C + (1 - \eta_1)\beta_B H_2 V_2^B + (1 - \eta_2)\alpha_B H_2 Y_2^B \\ &\quad + (1 - \eta_3)\beta_C H_2 V_2^C + (1 - \eta_4)\alpha_C H_2 Y_2^C| \\ &\quad + |(1 - \eta_1)\beta_B H_1 V_1^B + (1 - \eta_2)\alpha_B H_1 Y_1^B - (1 - \eta_1)\beta_B H_2 V_2^B \\ &\quad - (1 - \eta_2)\alpha_B H_2 Y_2^B| + |(1 - \eta_3)\beta_C H_1 V_1^C + (1 - \eta_4)\alpha_C H_1 Y_1^C - (1 - \eta_3)\beta_C H_2 V_2^C \\ &\quad - (1 - \eta_4)\alpha_C H_2 Y_2^C| + \gamma_B |A_1^B V_1^B - A_2^B V_2^B| + \gamma_C |A_1^C V_1^C - A_2^C V_2^C| \\ &\quad + \rho_B |A_1^B V_1^B - A_2^B V_2^B| + \rho_C |A_1^C V_1^C - A_2^C V_2^C| \\ &\leq 2|(1 - \eta_1)\beta_B H_1 V_1^B + (1 - \eta_2)\alpha_B H_1 Y_1^B - (1 - \eta_1)\beta_B H_2 V_2^B - (1 - \eta_2)\alpha_B H_2 Y_2^B| \\ &\quad + 2|(1 - \eta_3)\beta_C H_1 V_1^C + (1 - \eta_4)\alpha_C H_1 Y_1^C - (1 - \eta_3)\beta_C H_2 V_2^C \\ &\quad - (1 - \eta_4)\alpha_C H_2 Y_2^C| + \gamma_B |A_1^B V_1^B - A_2^B V_2^B| + \gamma_C |A_1^C V_1^C - A_2^C V_2^C| \\ &\quad + \rho_B |A_1^B V_1^B - A_2^B V_2^B| + \rho_C |A_1^C V_1^C - A_2^C V_2^C| \\ &\leq 2\beta_B (1 - \eta_1) |H_1| |V_1^B - V_2^B| + 2\beta_B (1 - \eta_1) |V_2^B| |H_1 - H_2| \\ &\quad + 2\alpha_B (1 - \eta_2) |H_1| |Y_1^B - Y_2^B| + 2\alpha_B (1 - \eta_2) |Y_2^B| |H_1 - H_2| \\ &\quad + 2\beta_C (1 - \eta_3) |H_1| |V_1^C - V_2^C| + 2\beta_C (1 - \eta_3) |V_2^C| |H_1 - H_2| \\ &\quad + 2\alpha_C (1 - \eta_4) |H_1| |Y_1^C - Y_2^C| + 2\alpha_C (1 - \eta_4) |Y_2^C| |H_1 - H_2| \\ &\quad + \gamma_B |A_1^B| |V_1^B - V_2^B| + \gamma_B |V_2^B| |A_1^B - A_2^B| + \gamma_C |A_1^C| |V_1^C - V_2^C| \end{aligned}$$

$$\begin{aligned}
& + \gamma_C |V_2^C| |A_1^C - A_2^C| + \rho_B |A_1^B| |V_1^B - V_2^B| + \rho_B |V_2^B| |A_1^B - A_2^B| \\
& + \rho_C |A_1^C| |V_1^C - V_2^C| + \rho_C |V_2^C| |A_1^C - A_2^C|.
\end{aligned}$$

The boundedness of the system has been established in Appendix B. Using the established bounds for each function, we obtain:

$$\begin{aligned}
|B(X_1) - B(X_2)| & \leq M_1 |H_1 - H_2| + M_2 |Y_1^B - Y_2^B| + M_3 |Y_1^C - Y_2^C| + M_4 |V_1^B - V_2^B| \\
& + M_5 |V_1^C - V_2^C| + M_6 |A_1^B - A_2^B| + M_7 |A_1^C - A_2^C|,
\end{aligned}$$

where

$$\begin{aligned}
M_1 &= 2\beta_B (1 - \eta_1) \frac{2\theta_B \phi}{\delta_{BQ}} + 2\alpha_C (1 - \eta_2) \frac{\phi}{\varrho} + 2\alpha_B (1 - \eta_2) \frac{\phi}{\varrho} + 2\beta_C (1 - \eta_3) \frac{2\theta_C \phi}{\delta_{CQ}}, \\
M_2 &= 2\alpha_B (1 - \eta_2) \frac{\phi}{\varrho}, \\
M_3 &= 2\alpha_C (1 - \eta_4) \frac{\phi}{\varrho}, \\
M_4 &= (\gamma_B + \rho_B) \frac{2\theta_B \rho_B \phi}{\delta_B \gamma_{BQ}} + 2\beta_B (1 - \eta_1) \frac{\phi}{\varrho}, \\
M_5 &= (\gamma_C + \rho_C) \frac{2\theta_C \rho_C \phi}{\delta_C \gamma_{CQ}} + 2\beta_C (1 - \eta_3) \frac{\phi}{\varrho}, \\
M_6 &= (\gamma_B + \rho_B) \frac{2\theta_B \phi}{\delta_{BQ}}, \\
M_7 &= (\gamma_C + \rho_C) \frac{2\theta_C \phi}{\delta_{CQ}}.
\end{aligned}$$

Therefore, we have

$$\begin{aligned}
|B(X_1) - B(X_2)| & \leq M[|H_1 - H_2| + |Y_1^B - Y_2^B| + |Y_1^C - Y_2^C| + |V_1^B - V_2^B| + |V_1^C - V_2^C| \\
& + |A_1^B - A_2^B| + |A_1^C - A_2^C|],
\end{aligned}$$

where, $M = \max\{M_1, M_2, M_3, M_4, M_5, M_6, M_7\}$ is independent of the state variables. Since the matrix A is bounded, the linear term AX is Lipschitz-continuous with respect to the state variables. Therefore, combining this property with the Lipschitz continuity of $B(X)$, we conclude that $S(X)$ is uniformly Lipschitz continuous. Therefore, since the control functions η_1, η_2, η_3 , and η_4 are bounded and the state variables remain non-negative and bounded, the right-hand side of the controlled system is continuous and uniformly Lipschitz continuous. Thus, by the standard existence and uniqueness theorem for ODEs, the controlled system (6.1) admits a unique solution.

H_3 The control set E is convex and closed. Recall that a set E is convex if, for any $\eta, \eta^* \in E$ and every $v \in [0, 1]$, then $v\eta + (1 - v)\eta^* \in E$.

Let $\eta = (\eta_1, \eta_2, \eta_3, \eta_4) \in E$ and $\eta^* = (\eta_1^*, \eta_2^*, \eta_3^*, \eta_4^*) \in E$. For an arbitrary $v \in [0, 1]$, by the definition of E , each control satisfies $0 \leq \eta_i, \eta_i^* \leq 1, i = 1, 2, 3, 4$. Thus,

$$0 \leq v\eta_i + (1 - v)\eta_i^* \leq v + (1 - v) = 1, i = 1, 2, 3, 4.$$

Hence, $0 \leq v\eta_i + (1-v)\eta_i^* \leq 1$, $i = 1, 2, 3, 4$, which implies that $v\eta + (1-v)\eta^* \in E$. Therefore, E is convex. Furthermore, the control set E is closed by its definition. Consequently, E is a convex and closed set.

H_4 The integrand of the objective functional, $H(t) - \frac{A_1}{2}\eta_1^2(t) - \frac{A_2}{2}\eta_2^2(t) - \frac{A_3}{2}\eta_3^2(t) - \frac{A_4}{2}\eta_4^2(t)$, is concave with respect to the control variables on E . To establish this, we recall the a multivariable function as $G(x_1, \dots, x_n)$ is concave if and only if the Hessian matrix

$$H(x) = \left(\frac{\partial^2 G(x)}{\partial x_i \partial x_j} \right),$$

is negative semidefinite. The Hessian matrix of G with respect to the control variables is given by

$$H(\eta) = \begin{pmatrix} \frac{\partial^2 G(x)}{\partial \eta_1^2} & \frac{\partial^2 G(x)}{\partial \eta_1 \partial \eta_2} & \frac{\partial^2 G(x)}{\partial \eta_1 \partial \eta_3} & \frac{\partial^2 G(x)}{\partial \eta_1 \partial \eta_4} \\ \frac{\partial^2 G(x)}{\partial \eta_2 \partial \eta_1} & \frac{\partial^2 G(x)}{\partial \eta_2^2} & \frac{\partial^2 G(x)}{\partial \eta_2 \partial \eta_3} & \frac{\partial^2 G(x)}{\partial \eta_2 \partial \eta_4} \\ \frac{\partial^2 G(x)}{\partial \eta_3 \partial \eta_1} & \frac{\partial^2 G(x)}{\partial \eta_3 \partial \eta_2} & \frac{\partial^2 G(x)}{\partial \eta_3^2} & \frac{\partial^2 G(x)}{\partial \eta_3 \partial \eta_4} \\ \frac{\partial^2 G(x)}{\partial \eta_4 \partial \eta_1} & \frac{\partial^2 G(x)}{\partial \eta_4 \partial \eta_2} & \frac{\partial^2 G(x)}{\partial \eta_4 \partial \eta_3} & \frac{\partial^2 G(x)}{\partial \eta_4^2} \end{pmatrix} = \begin{pmatrix} -A_1 & 0 & 0 & 0 \\ 0 & -A_2 & 0 & 0 \\ 0 & 0 & -A_3 & 0 \\ 0 & 0 & 0 & -A_4 \end{pmatrix}.$$

Since $A_i \geq 0$, $i = 1, 2, 3, 4$. Hence, $H(\eta)$ is negative semidefinite, which implies that G is concave with respect to η_1, η_2, η_3 , and η_4 . Therefore, the integrand of the objective functional is concave on E .

H_5 There exist positive constants κ_1, κ_2 , and a constant $\lambda > 1$ such that the integrand of the objective functional satisfies the required growth condition

$$L(t, H, \eta_1, \eta_2, \eta_3, \eta_4) \leq \kappa_2 - \kappa_1 \left(|\eta_1(t)|^2 + |\eta_2(t)|^2 + |\eta_3(t)|^2 + |\eta_4(t)|^2 \right)^{\lambda/2}. \quad (6.17)$$

From Eq (6.6), we have

$$L(t, H, \eta_1, \eta_2, \eta_3, \eta_4) = H(t) - \frac{A_1}{2}\eta_1^2(t) - \frac{A_2}{2}\eta_2^2(t) - \frac{A_3}{2}\eta_3^2(t) - \frac{A_4}{2}\eta_4^2(t).$$

Let $A = \min \{A_1, A_2, A_3, A_4\}$, then

$$L(t, H, \eta_1, \eta_2, \eta_3, \eta_4) \leq \frac{\phi}{\varrho} - \frac{A}{2} \left(\eta_1^2(t) + \eta_2^2(t) + \eta_3^2(t) + \eta_4^2(t) \right).$$

Thus, by setting $\kappa_2 = \frac{\phi}{\varrho} > 0$, $\kappa_1 = \frac{A}{2} > 0$, we obtain

$$L(t, H, \eta_1, \eta_2, \eta_3, \eta_4) \leq \kappa_2 - \kappa_1 \left(\eta_1^2(t) + \eta_2^2(t) + \eta_3^2(t) + \eta_4^2(t) \right).$$

Hence, the required growth condition is satisfied Eq (6.17) by taking $\lambda = 2 > 1$.

Therefore, all the assumptions required for the existence of an optimal control are satisfied. Consequently, an optimal control $(\tilde{\eta}_1, \tilde{\eta}_2, \tilde{\eta}_3, \tilde{\eta}_4) \in E$ exists.

The adjoint equations and transversality conditions can be obtained by using Pontryagin's Maximum Principle such that

$$\begin{aligned}\mathcal{H} = & H - \left(\frac{A_1}{2} \eta_1^2(t) + \frac{A_2}{2} \eta_2^2(t) + \frac{A_3}{2} \eta_3^2(t) + \frac{A_4}{2} \eta_4^2(t) \right) \\ & + \kappa_1 \left[\phi - \sigma H - (1 - \eta_1(t)) \beta_B H V^B - (1 - \eta_2(t)) \alpha_B H Y^B - (1 - \eta_3(t)) \beta_C H V^C - (1 - \eta_4(t)) \alpha_C H Y^C \right] \\ & + \kappa_2 \left[(1 - \eta_1(t)) \beta_B H V^B + (1 - \eta_2(t)) \alpha_B H Y^B - \delta_B Y^B \right] \\ & + \kappa_3 \left[(1 - \eta_3(t)) \beta_C H V^C + (1 - \eta_4(t)) \alpha_C H Y^C - \delta_C Y^C \right] \\ & + \kappa_4 \left[\theta_B Y^B - \phi_B V^B - \gamma_B A^B V^B \right] + \kappa_5 \left[\theta_C Y^C - \phi_C V^C - \gamma_C A^C V^C \right] \\ & + \kappa_6 \left[\rho_B A^B V^B - \lambda_B A^B \right] + \kappa_7 \left[\rho_C A^C V^C - \lambda_C A^C \right].\end{aligned}$$

Then,

$$\begin{aligned}\dot{\kappa}_1 &= -\frac{\partial \mathcal{H}}{\partial H} = -1 + \sigma \kappa_1 + (1 - \eta_1)(\kappa_1 - \kappa_2) \beta_B V^B + (1 - \eta_2)(\kappa_1 - \kappa_2) \alpha_B Y^B \\ &\quad + (1 - \eta_3)(\kappa_1 - \kappa_3) \beta_C V^C + (1 - \eta_4)(\kappa_1 - \kappa_3) \alpha_C Y^C, \\ \dot{\kappa}_2 &= -\frac{\partial \mathcal{H}}{\partial Y^B} = (1 - \eta_2)(\kappa_1 - \kappa_2) \alpha_B H + \delta_B \kappa_2 - \theta_B \kappa_4, \\ \dot{\kappa}_3 &= -\frac{\partial \mathcal{H}}{\partial Y^C} = (1 - \eta_4)(\kappa_1 - \kappa_3) \alpha_C H + \delta_C \kappa_3 - \theta_C \kappa_5, \\ \dot{\kappa}_4 &= -\frac{\partial \mathcal{H}}{\partial V^B} = (1 - \eta_1)(\kappa_1 - \kappa_2) \beta_B H + \kappa_4 (\phi_B + \gamma_B A^B) - \rho_B A^B \kappa_6, \\ \dot{\kappa}_5 &= -\frac{\partial \mathcal{H}}{\partial V^C} = (1 - \eta_3)(\kappa_1 - \kappa_3) \beta_C H + \kappa_5 (\phi_C + \gamma_C A^C) - \rho_C A^C \kappa_7, \\ \dot{\kappa}_6 &= -\frac{\partial \mathcal{H}}{\partial A^B} = V^B (\gamma_B \kappa_4 - \rho_B \kappa_6) + \lambda_B \kappa_6, \\ \dot{\kappa}_7 &= -\frac{\partial \mathcal{H}}{\partial A^C} = V^C (\gamma_C \kappa_5 - \rho_C \kappa_7) + \lambda_C \kappa_7,\end{aligned}$$

where $\kappa_i(t_f) = 0$, $i = 1, \dots, 7$. The optimal control $\tilde{\eta}_1, \tilde{\eta}_2, \tilde{\eta}_3$, and $\tilde{\eta}_4$ can be solved from the optimality conditions,

$$\begin{aligned}\frac{\partial \mathcal{H}}{\partial \eta_1} = 0 &\implies -A_1 \eta_1 + (\kappa_1 - \kappa_2) \beta_B H V^B = 0 \implies \eta_1 = \frac{1}{A_1} (\kappa_1 - \kappa_2) \beta_B H V^B, \\ \frac{\partial \mathcal{H}}{\partial \eta_2} = 0 &\implies -A_2 \eta_2 + (\kappa_1 - \kappa_2) \alpha_B H Y^B = 0 \implies \eta_2 = \frac{1}{A_2} (\kappa_1 - \kappa_2) \alpha_B H Y^B, \\ \frac{\partial \mathcal{H}}{\partial \eta_3} = 0 &\implies -A_3 \eta_3 + (\kappa_1 - \kappa_3) \beta_C H V^C = 0 \implies \eta_3 = \frac{1}{A_3} (\kappa_1 - \kappa_3) \beta_C H V^C, \\ \frac{\partial \mathcal{H}}{\partial \eta_4} = 0 &\implies -A_4 \eta_4 + (\kappa_1 - \kappa_3) \alpha_C H Y^C = 0 \implies \eta_4 = \frac{1}{A_4} (\kappa_1 - \kappa_3) \alpha_C H Y^C.\end{aligned}$$

By the bounds in E of the controls, it is easy to obtain $\tilde{\eta}_1, \tilde{\eta}_2, \tilde{\eta}_3$, and $\tilde{\eta}_4$ in the form of Eqs (6.9)–(6.12), respectively. $\square$

7. Numerical simulations

The global stability properties of the system's equilibrium points are demonstrated through numerical simulations. The parameter values used in the simulations are listed in Table 3. Some of these parameters are adopted from existing studies on HBV-only and HCV-only infections for the purpose of carrying out the simulations. To the best of our knowledge, there is currently no available experimental or clinical dataset (such as measurements of HBV, HCV, or antibody levels) for patients with HBV–HCV coinfection.

The parameters β_B , α_B , β_C , α_C , ρ_B , and ρ_C are varied across the numerical scenarios to illustrate different transmission and immune-response regimes. In particular, the relative magnitudes of the cell-to-cell transmission coefficients α_B , α_C compared with the corresponding virus-to-cell transmission coefficients β_B , β_C are selected for numerical purposes and are not intended to represent experimentally estimated or patient-specific values. Accordingly, Scenarios 1–8 are illustrative numerical experiments designed to demonstrate the theoretical stability results and to examine the effects of different transmission and antibody response regimes, rather than clinical or predictive scenarios. Parameter estimation using experimental or patient viral-load data would be an important direction for future work.

Table 3. Model parameters.

Parameter	Value	Unit	Source
ϕ	10	cell mm ⁻³ day ⁻¹	[41, 68–70]
σ	0.01	day ⁻¹	[30, 39, 71, 72]
β_B	Varied	mm ³ virus ⁻¹ day ⁻¹	-
α_B	Varied	mm ³ cells ⁻¹ day ⁻¹	-
β_C	Varied	mm ³ virus ⁻¹ day ⁻¹	-
α_C	Varied	mm ³ cells ⁻¹ day ⁻¹	-
δ_B	0.0693	day ⁻¹	[23, 69]
δ_C	0.14	day ⁻¹	[73–75]
θ_B	0.87	viruses cells ⁻¹ day ⁻¹	[30, 76, 77]
ϕ_B	0.67	day ⁻¹	[23, 78, 79]
γ_B	0.01	mm ³ μ g ⁻¹ day ⁻¹	[50, 80]
θ_C	2.9	viruses cells ⁻¹ day ⁻¹	[39, 44, 49]
ϕ_C	6	day ⁻¹	[39, 49, 81]
γ_C	0.006	mm ³ μ g ⁻¹ day ⁻¹	[49, 82]
ρ_B	Varied	mm ³ virus ⁻¹ day ⁻¹	-
λ_B	0.15	day ⁻¹	[49, 50, 80]
ρ_C	Varied	mm ³ virus ⁻¹ day ⁻¹	-
λ_C	0.01	day ⁻¹	[73, 75]

7.1. Stability analysis of the equilibrium

In this following subsection, we numerically validate the global stability results established in Theorems 1–8. Specifically, we show that the solutions of system (2.1), starting from various initial

conditions corresponding to different stages of HBV/HCV coinfection, converge to one of the eight equilibrium states. To this end, the system (2.1) is solved under multiple sets of initial conditions as follows:

$$\begin{aligned} H(0) &= 10 + 50k, & Y^B(0) &= 0.5 + 2k, \\ Y^C(0) &= 0.1 + 2k, & V^B(0) &= 0.1 + 0.1k, \\ V^C(0) &= 0.1 + 0.1k, & A^B(0) &= 5 + 10k, \\ A^C(0) &= 10 + 5k, & k &= 1, 2, \dots, 5. \end{aligned}$$

Selecting the values of $\beta_B, \alpha_B, \beta_C, \alpha_C, \rho_B$, and ρ_C gives rise to the following scenarios:

- Scenario 1** Stability of Ξ_0 : $\beta_B = 0.000001, \alpha_B = \beta_C = 0.00001, \alpha_C = 0.0001$, and $\rho_B = \rho_C = 0.001$. For these parameter values, we have $\mathfrak{R}_0^B = 0.163 < 1$ and $\mathfrak{R}_0^C = 0.749 < 1$. Figure 2 shows that the trajectories converge to the equilibrium $\Xi_0 = (1000, 0, 0, 0, 0, 0, 0)$ for different initial conditions. This indicates that both HBV and HCV are eliminated in this scenario. These results confirm that Ξ_0 is GAS in accordance with Theorem 1.
- Scenario 2** Stability of Ξ_1 : $\beta_B = \alpha_B = 0.0001, \beta_C = 0.00001, \alpha_C = 0.0001$, and $\rho_B = \rho_C = 0.001$. For these parameter values, we obtain $\mathfrak{R}_0^B = 3.317 > 1, \mathfrak{R}_1^B = 0.896 < 1$, and hence $\mathfrak{R}_0^C/\mathfrak{R}_0^B = 0.226 < 1$. The equilibrium point Ξ_1 exists with $\Xi_1 = (301.5, 100.794, 0, 130.88, 0, 0, 0)$. Figure 3 clearly shows that the trajectories converge to Ξ_1 for all initial values. This indicates that HBV monoinfection without an active antibody response is established. This result indicates that HBV outcompetes HCV under the assumed parameter regime. These numerical results agrees with Theorem 2.
- Scenario 3** Stability of Ξ_2 : $\beta_B = \alpha_B = 0.00001, \beta_C = 0.0001, \alpha_C = 0.001, \rho_B = 0.001$, and $\rho_C = 0.0001$. This gives $\mathfrak{R}_0^C = 7.488 > 1, \mathfrak{R}_1^C = 0.304 < 1$, and then $\mathfrak{R}_0^B/\mathfrak{R}_0^C = 0.044 < 1$. Figure 4 shows that the trajectories converge to the equilibrium $\Xi_2 = (133.545, 0, 61.89, 0, 29.913, 0, 0)$ for different initial conditions. HCV outcompetes HBV under the assumed parameter regime. These results confirm that, Ξ_2 is GAS in accordance with Theorem 3.
- Scenario 4** Stability of Ξ_3 : $\beta_B = \alpha_B = 0.0001, \beta_C = 0.00001, \alpha_C = 0.0001, \rho_B = 0.01$, and $\rho_C = 0.001$. This yields $\mathfrak{R}_1^B = 5.491 > 1$ and $\mathfrak{R}_2^B = 0.893 < 1$. Figure 5 shows that the trajectories converge to the equilibrium $\Xi_3 = (560.455, 63.426, 0, 15, 0, 300.873, 0)$ for different initial conditions. Consequently, an HBV monoinfection accompanied by a stimulated HBV-specific antibody response is established. Although the model includes an HBV-specific antibody response, HBV suppresses HCV growth and reduces the establishment of HCV infection. These results confirm that, Ξ_3 is G.A.S in accordance with Theorem 4.
- Scenario 5** Stability of Ξ_4 : Let $\beta_B = \alpha_B = 0.00001, \beta_C = 0.0001, \alpha_C = 0.001, \rho_B = 0.001$, and $\rho_C = 0.005$. The values of $\mathfrak{R}_1^C$ and $\mathfrak{R}_2^C$ are computed as $\mathfrak{R}_1^C = 14.853 > 1$ and $\mathfrak{R}_2^C = 0.326 < 1$. Figure 6 shows that the trajectories converge to the equilibrium $\Xi_4 = (139.546, 0, 61.461, 0, 2, 0, 13853.077)$ for different initial conditions. Consequently, HCV

monoinfection accompanied by an elevated HCV-specific humoral response is established under the assumed parameter regime. The large value of A^C should be interpreted as an enhanced modeled humoral response rather than as evidence of complete protective immunity or HCV clearance. In this scenario, HCV remains present despite the elevated A^C , illustrating that the modeled humoral response does not necessarily eliminate the virus. HCV also suppresses HBV growth and inhibits the establishment of HBV infection. This numerical result is consistent with Theorem 5.

Scenario 6 Stability of Ξ_5 : $\beta_B = 0.001$, $\alpha_B = \beta_C = 0.0001$, $\alpha_C = 0.001$, $\rho_B = 0.02$, and $\rho_C = 0.0001$. Then, we calculate $\mathfrak{R}_2^B = 3.882 > 1$, $\tilde{\mathfrak{R}}_2^B = 5.189$, $V_5^C = 25.63 < V_7^C = 100$, and $\mathfrak{R}_0^B/\mathfrak{R}_0^C = 2.695 > 1$. Figure 7 shows that the trajectories converge to the equilibrium $\Xi_5 = (133.545, 17.903, 53.028, 7.5, 25.63, 140.674, 0)$ for different initial conditions. As a result, HBV/HCV coinfection is established, with only the HBV-specific antibody response being stimulated. In this case, the activity of HBV-specific antibodies reduces HBV replication, thereby allowing the two viruses to coexist.

Scenario 7 Stability of Ξ_6 : $\beta_B = 0.00025$, $\alpha_B = 0.00045$, $\beta_C = 0.004$, $\alpha_C = 0.001$, $\rho_B = 0.001$, and $\rho_C = 0.0025$. We compute $\mathfrak{R}_2^C = 3.83 > 1$, $\tilde{\mathfrak{R}}_2^C = 1.565 > 1$, $V_6^B = 138.45 < V_7^B = 150$, and $\mathfrak{R}_0^C/\mathfrak{R}_0^B = 1.874 > 1$. Figure 8 shows that the trajectories converge to the equilibrium $\Xi_6 = (89.462, 74.172, 28.323, 96.312, 4, 0, 2422.418)$ for different initial conditions. As a result, HBV/HCV coinfection is established, with only the HCV-specific antibody response being stimulated. In this case, the activity of HCV-specific antibodies reduces HCV replication, thereby allowing the two viruses to coexist.

Scenario 8 Stability of Ξ_7 : $\beta_B = 0.001$, $\alpha_B = 0.0001$, $\beta_C = 0.001$, $\alpha_C = 0.002$, $\rho_B = 0.01$, and $\rho_C = 0.001$. This selection yields $\mathfrak{R}_3^B = 1.333 > 1$ and $\mathfrak{R}_3^C = 2.853 > 1$. Figure 9 shows that the trajectories lead to the equilibrium $\Xi_7 = (64.533, 15.402, 59.018, 15, 10, 22.334, 1852.544)$ for different initial conditions. In this scenario, HBV/HCV coinfection is established for all considered initial conditions. Both HBV-specific and HCV-specific antibody responses are activated, and their combined activity permits the coexistence of the two viruses.

To further assess the local stability of the equilibrium points, we evaluate the Jacobian matrix $J = J(H, Y^B, Y^C, V^B, V^C, A^B, A^C)$ corresponding to system (2.1), as given in Eq (5.7). At each equilibrium point, the eigenvalues ξ_j , $j = 1, 2, \dots, 7$, of the Jacobian matrix are computed. An equilibrium point is locally asymptotically stable if $\text{Re}(\xi_j) < 0$, $j = 1, 2, \dots, 7$. The parameter values $\beta_B, \alpha_B, \beta_C, \alpha_C, \rho_B$, and ρ_C are selected according to Scenarios 1–8, and the corresponding non-negative equilibrium points and their eigenvalues are evaluated. Table 4 summarizes the non-negative equilibria, the real parts of their eigenvalues, and the corresponding stability classifications. The numerical eigenvalue calculations are consistent with the analytical local stability result established for Ξ_0 and the analytical local instability results established for Ξ_1 and Ξ_2 . Moreover, for the equilibria covered by Theorems 1–8, the established global asymptotic stability results also imply local asymptotic stability. Therefore, the Jacobian-based calculations in Table 4 are presented as a supplementary numerical verification of the analytical results and, where applicable, as a check of the stability behavior under the parameter regimes considered in the numerical simulations.

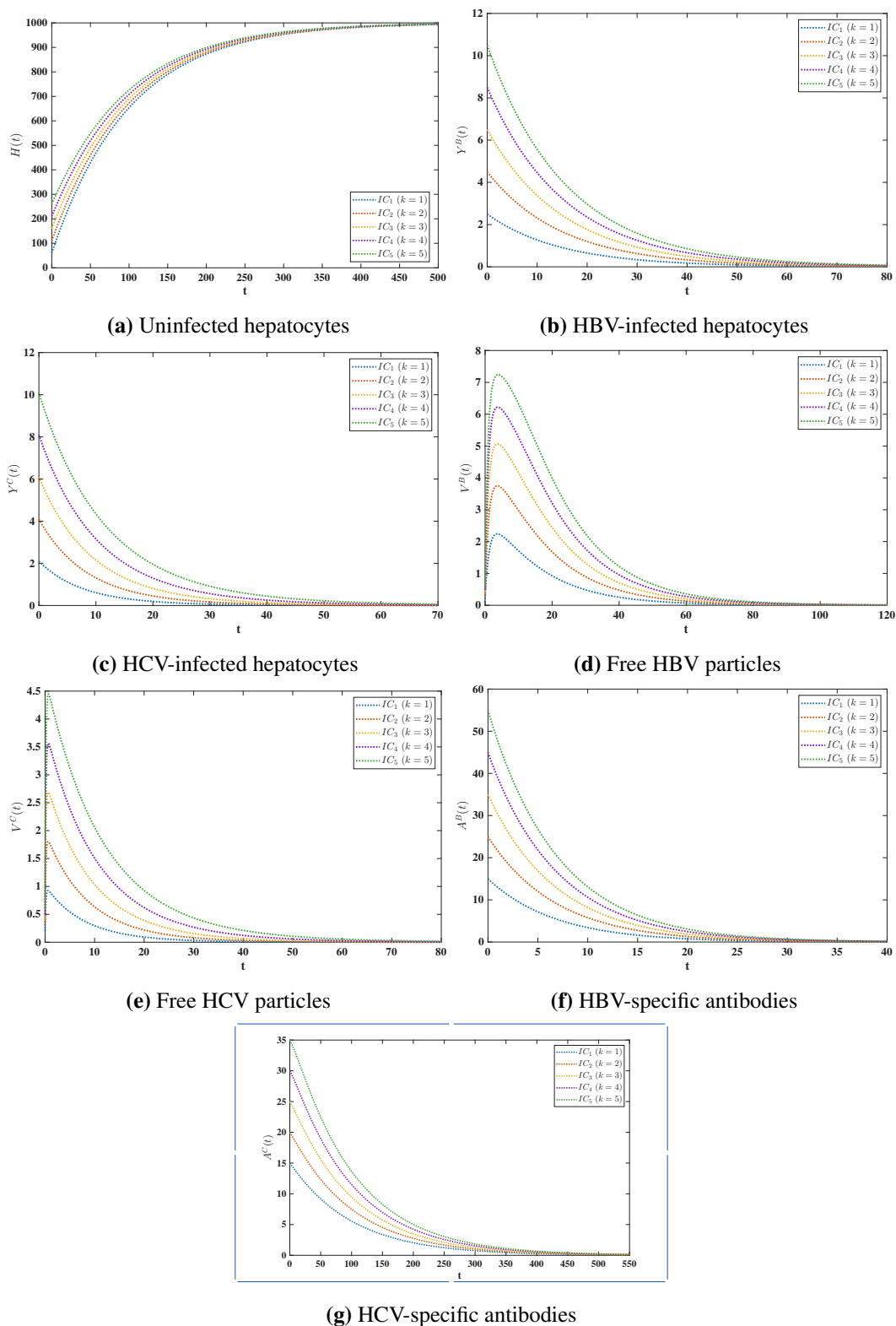


Figure 2. Solutions of system (2.1) tend to $\Xi_0 = (1000, 0, 0, 0, 0, 0, 0)$ for different initial conditions, with $\mathfrak{R}_0^B = 0.163 < 1$ and $\mathfrak{R}_0^C = 0.749 < 1$ (**Scenario 1**).

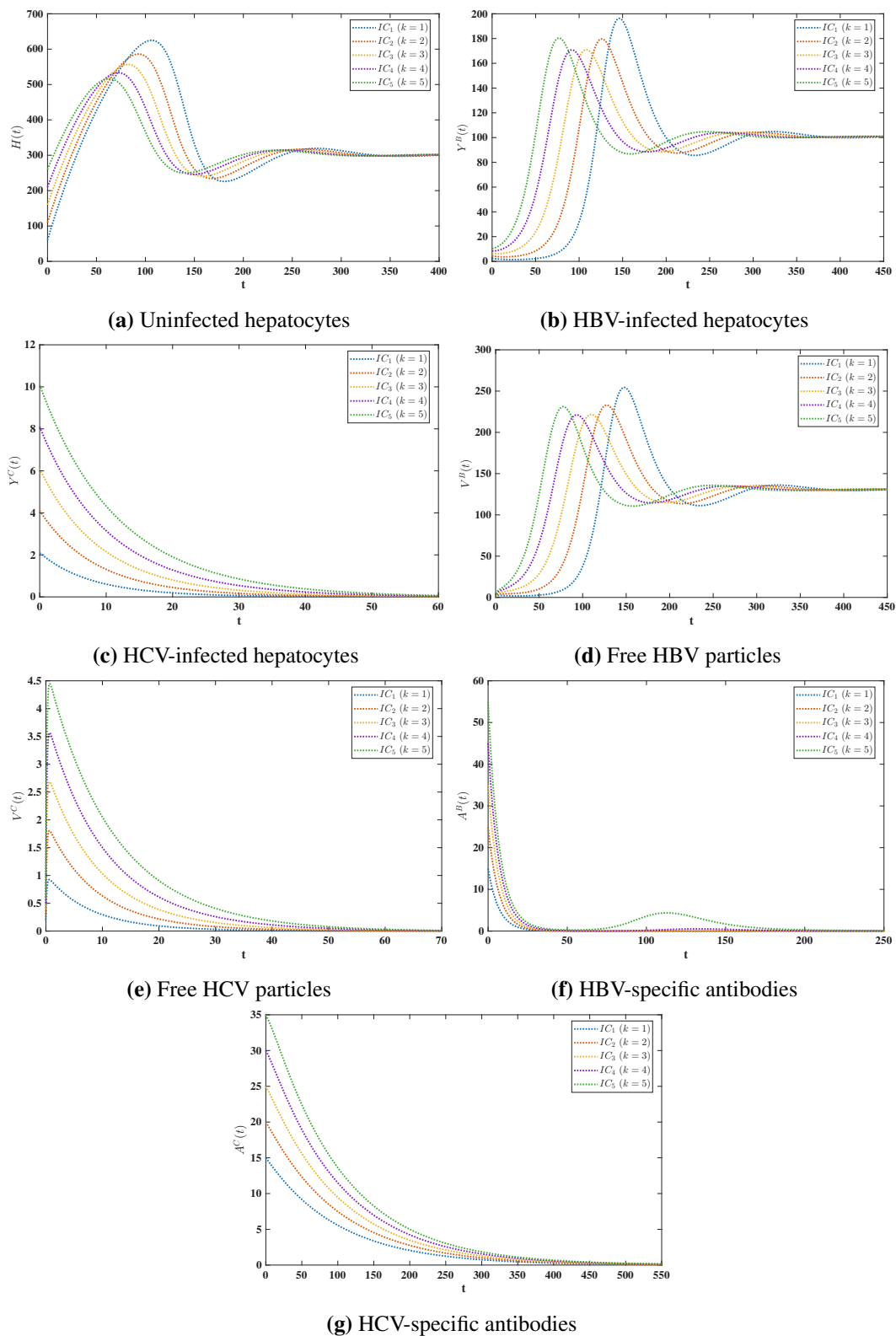


Figure 3. Solutions of system (2.1) tend to $\Xi_1 = (301.5, 100.79, 0, 130.88, 0, 0, 0)$ for different initial conditions, with $\mathfrak{R}_0^B = 3.317 > 1$, $\mathfrak{R}_0^C/\mathfrak{R}_0^B = 0.226 < 1$ and $\mathfrak{R}_1^B = 0.896 < 1$ (**Scenario 2**).

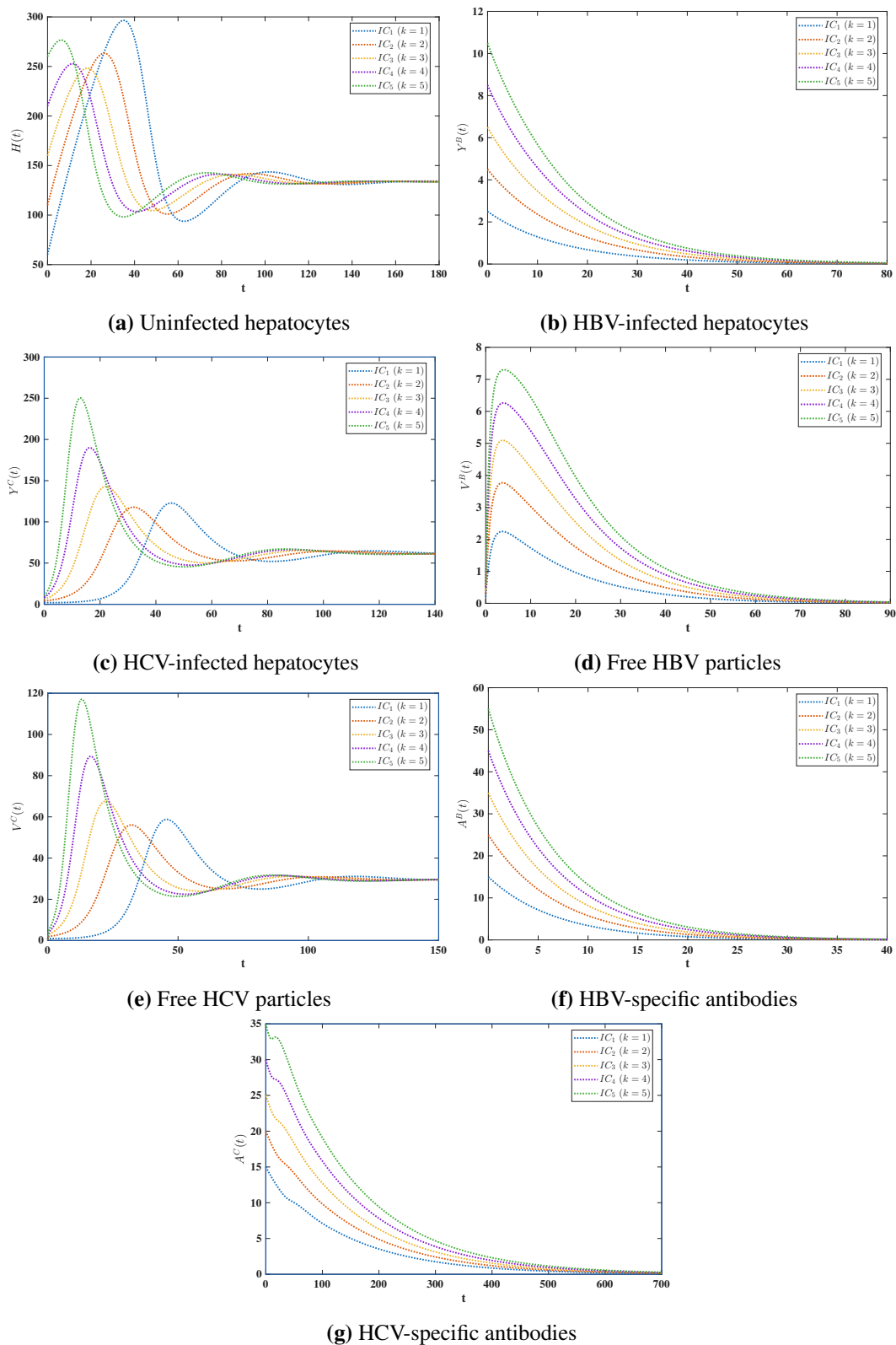


Figure 4. Solutions of system (2.1) tend to $\Xi_2 = (133.546, 0, 61.89, 0, 29.91, 0, 0)$ for different initial conditions, with $\mathfrak{R}_0^C = 7.488 > 1$, $\mathfrak{R}_0^B/\mathfrak{R}_0^C = 0.044 < 1$ and $\mathfrak{R}_1^C = 0.304 < 1$ (**Scenario 3**).

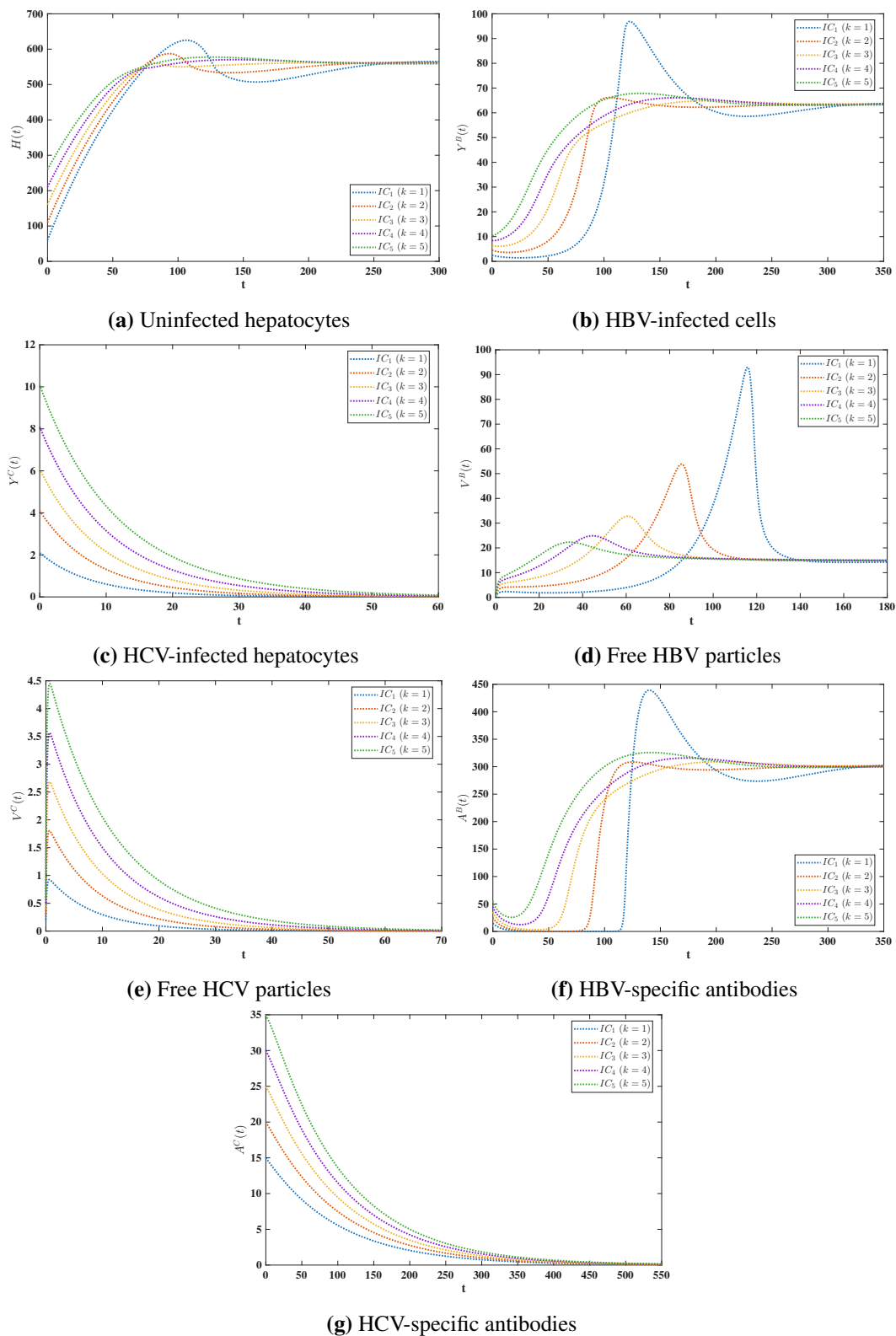


Figure 5. Solutions of system (2.1) tend to $\Xi_3 = (560.455, 63.426, 0, 15, 0, 300.87, 0)$ for different initial conditions, with $\mathfrak{R}_1^B = 5.491 > 1$ and $\mathfrak{R}_2^B = 0.893 < 1$ (**Scenario 4**).

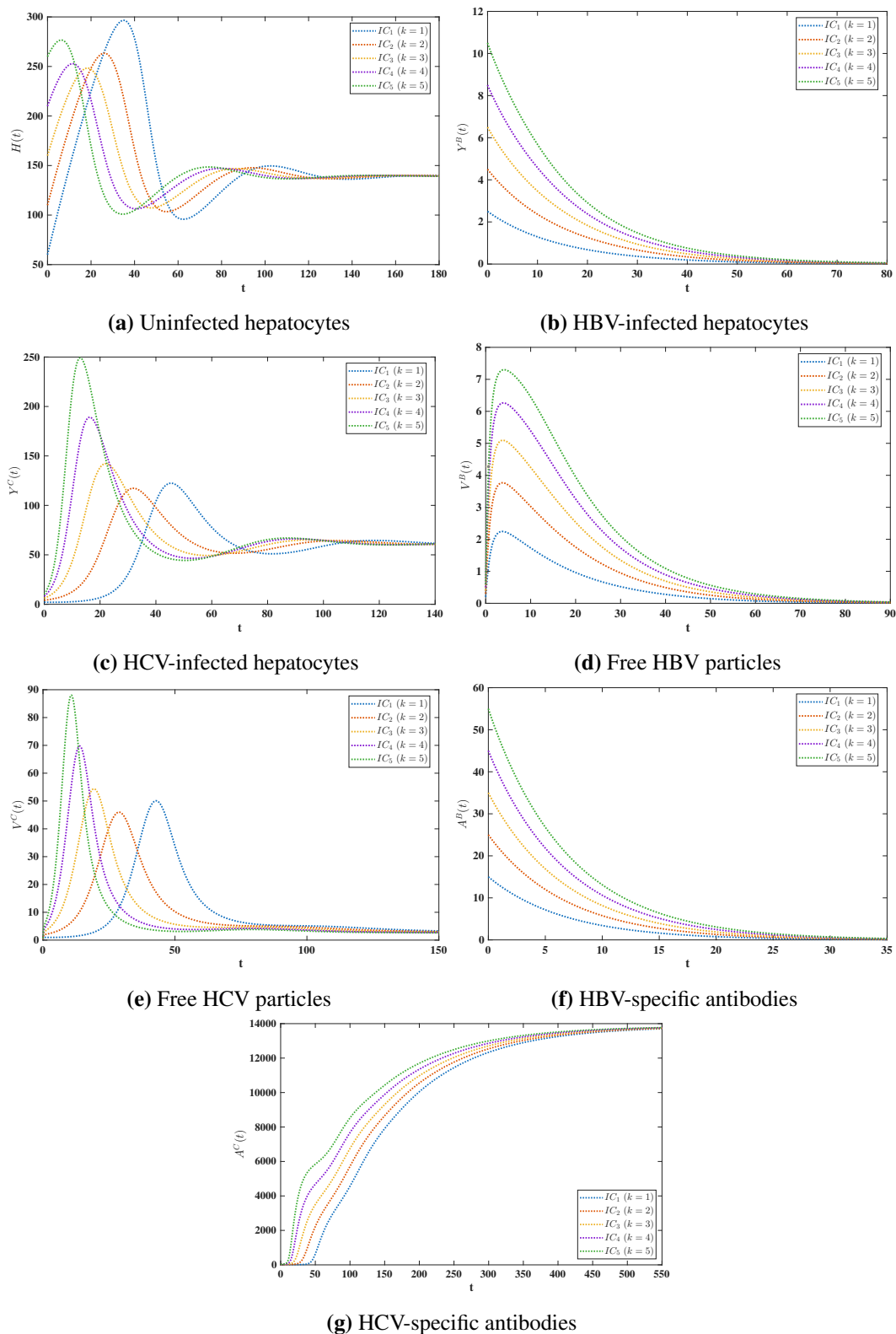


Figure 6. Solutions of system (2.1) tend to $\Xi_4 = (139.546, 0, 61.46, 0, 2, 0, 13853.07)$ for different initial conditions, with $\mathfrak{R}_1^C = 14.853 > 1$ and $\mathfrak{R}_2^C = 0.326 < 1$ (**Scenario 5**).

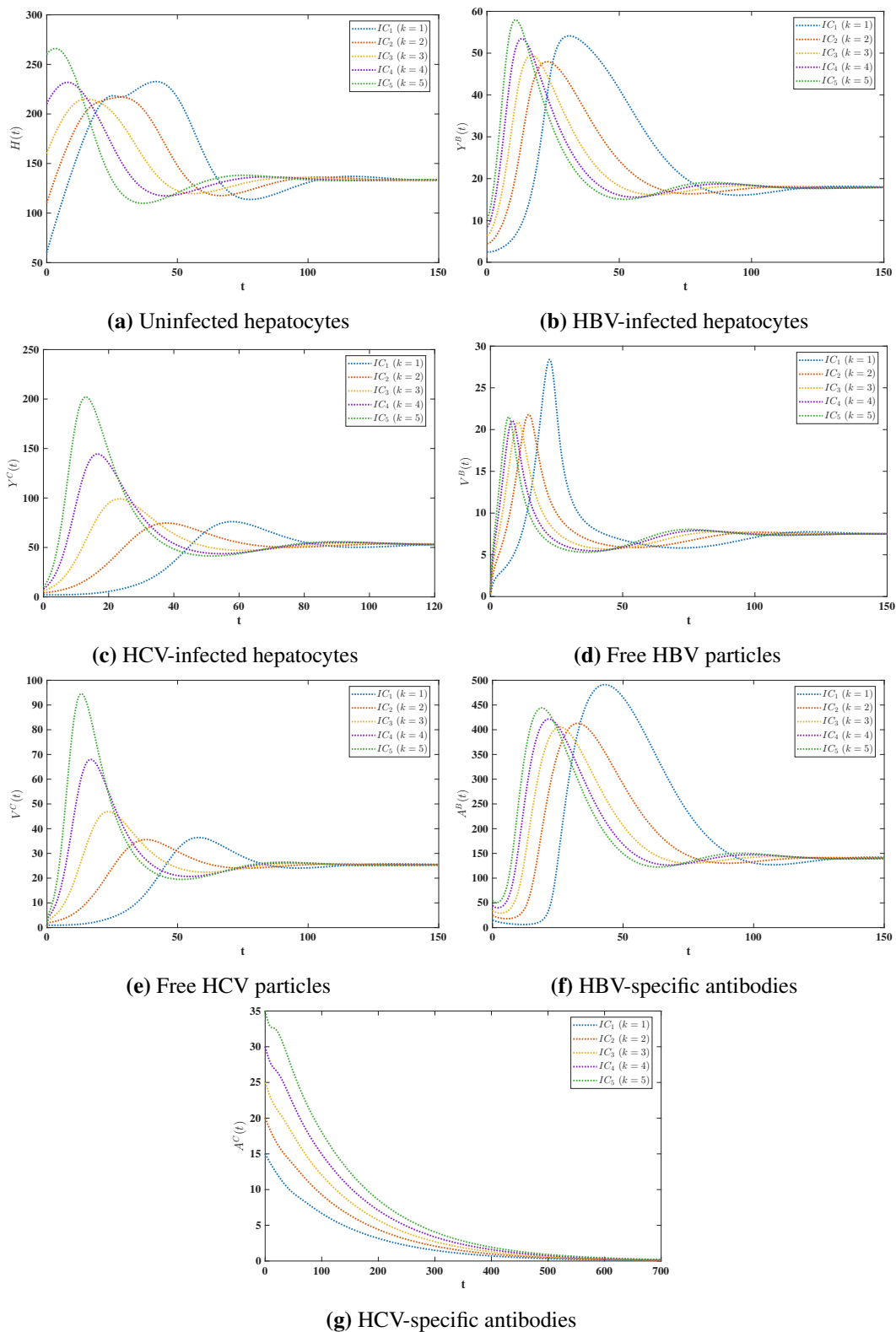


Figure 7. Solutions of system (2.1) tend to $\Xi_5 = (133.54, 17.9, 53.027, 7.5, 25.63, 140.67, 0)$ for different initial conditions, with $\mathfrak{R}_2^B = 3.882 > 1$, $\tilde{\mathfrak{R}}_2^B = 5.189 > 1$, $\mathfrak{R}_3^C = 0.0413 < 1$ and $\mathfrak{R}_0^B/\mathfrak{R}_0^C = 2.695 > 1$ (**Scenario 6**).

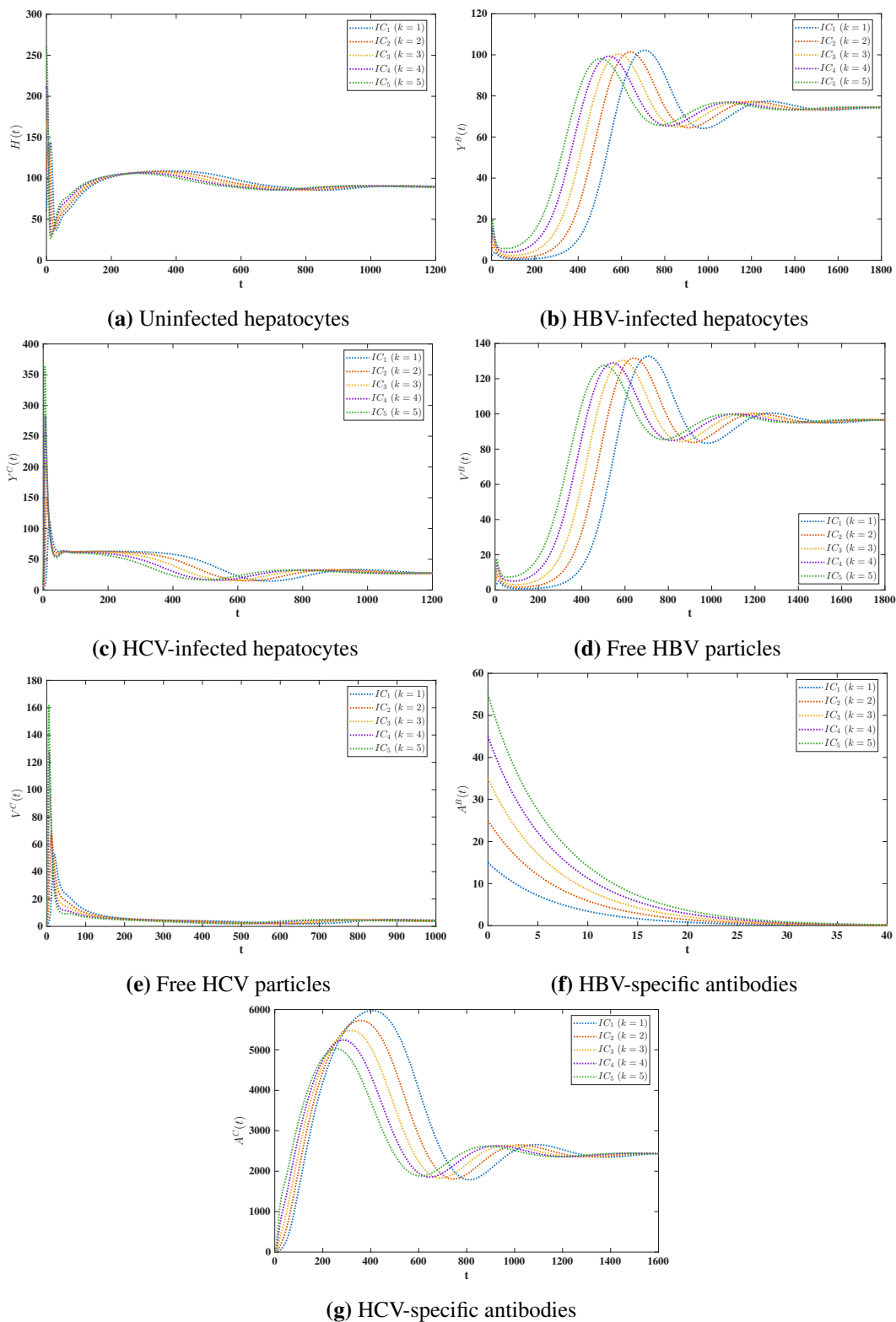


Figure 8. Solutions of system (2.1) tend to $\Xi_6 = (89.46, 74.17, 28.32, 96.31, 4, 0, 2422.4)$ for different initial conditions, with $\mathfrak{R}_2^C = 3.83 > 1$, $\tilde{\mathfrak{R}}_2^C = 1.565 > 1$, $\mathfrak{R}_0^C / \mathfrak{R}_0^B = 1.874 > 1$ and $\mathfrak{R}_3^B = 0.5203 < 1$ (**Scenario 7**).

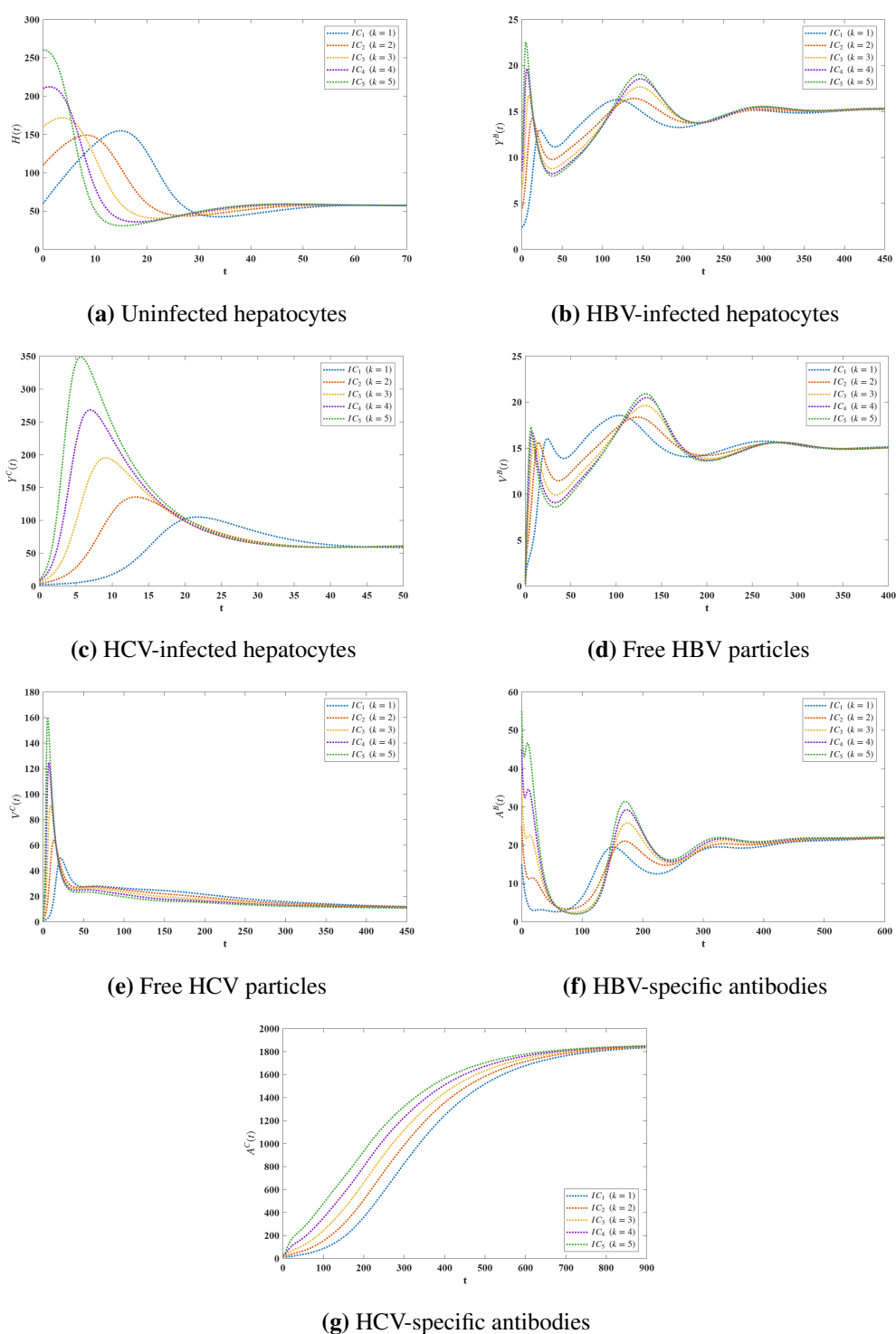


Figure 9. Solutions of system (2.1) tend to $\Xi_7 = (64.533, 15.4, 59.02, 15, 10, 22.33, 1852.54)$ for different initial conditions, with $\mathfrak{R}_3^B = 1.333 > 1$ and $\mathfrak{R}_3^C = 2.853 > 1$ (**Scenario 8**).

Table 4. Local stability of non-negative equilibria Ξ_i , $i = 0, 1, \dots, 7$.

Scenario	The equilibria	$\text{Re}(\xi_j)$, $j = 1, 2, \dots, 7$	Stability
1	$\Xi_0 = (1000, 0, 0, 0, 0, 0, 0, 0)$	$(-0.150, -0.010, -0.010, -0.684, -0.045, -6.005, -0.035)$	Stable
2	$\Xi_0 = (1000, 0, 0, 0, 0, 0, 0, 0)$	$(-0.150, -0.010, -0.010, -0.778, 0.138, -6.005, -0.035)$	Unstable
	$\Xi_1 = (301.5, 100.794, 0, 130.881, 0, 0, 0, 0)$	$(-0.019, -0.010, -6.001, -0.108, -0.710, -0.016, -0.016)$	Stable
3	$\Xi_0 = (1000, 0, 0, 0, 0, 0, 0, 0)$	$(-0.150, -0.010, -0.010, -6.042, 0.902, -0.684, -0.045)$	Unstable
	$\Xi_2 = (133.545, 0, 61.890, 0, 29.913, 0, 0, 0)$	$(-0.150, -0.007, -0.672, -0.066, -6.007, -0.037, -0.037)$	Stable
	$\Xi_0 = (1000, 0, 0, 0, 0, 0, 0, 0)$	$(-0.150, -0.010, -0.010, -0.778, 0.138, -6.005, -0.035)$	Unstable
4	$\Xi_1 = (301.500, 100.794, 0, 130.881, 0, 0, 0, 0)$	$(-0.010, 1.159, -6.001, -0.108, -0.710, -0.016, -0.016)$	Unstable
	$\Xi_3 = (560.455, 63.426, 0, 15, 0, 300.873, 0, 0)$	$(-0.010, -6.003, -0.081, -3.566, -0.110, -0.017, -0.017)$	Stable
	$\Xi_0 = (1000, 0, 0, 0, 0, 0, 0, 0)$	$(-0.15, -0.01, -0.01, -6.042, 0.902, -0.684, -0.045)$	Unstable
5	$\Xi_2 = (133.545, 0, 61.89, 0, 29.913, 0, 0, 0)$	$(-0.150, 0.14, -0.672, -0.066, -6.007, -0.037, -0.037)$	Unstable
	$\Xi_4 = (139.546, 0, 61.461, 0, 2, 0, 13853.077)$	$(-0.15, -0.009, -0.066, -0.036, -0.036, -0.672, -89.11)$	Stable
	$\Xi_0 = (1000, 0, 0, 0, 0, 0, 0, 0)$	$(-0.150, -0.010, -0.010, -6.042, 0.902, -1.316, 0.677)$	Unstable
	$\Xi_1 = (49.553, 137.150, 0, 178.09, 0, 0, 0, 0)$	$(-0.010, 3.412, -6.002, -0.088, -0.754, -0.091, -0.091)$	Unstable
6	$\Xi_2 = (133.545, 0, 61.890, 0, 29.913, 0, 0, 0)$	$(-0.150, -0.007, -0.822, 0.096, -6.007, -0.037, -0.037)$	Unstable
	$\Xi_3 = (377.632, 89.808, 0, 7.500, 0, 974.770, 0, 0)$	$(-0.010, -6.018, 0.255, -10.308, -0.088, -0.040, -0.040)$	Unstable
	$\Xi_5 = (133.545, 17.903, 53.028, 7.500, 25.630, 140.674, 0, 0)$	$(-0.007, -0.043, -0.043, -0.044, -2.032, -6.007)$	Stable
	$\Xi_0 = (1000, 0, 0, 0, 0, 0, 0, 0)$	$(-0.150, -0.010, -0.010, -7.404, 2.264, -0.847, 0.558)$	Unstable
	$\Xi_1 = (89.462, 131.391, 0, 170.612, 0, 0, 0, 0)$	$(-0.010, 0.021, -6.170, 0.119, -0.703, -0.054, -0.054)$	Unstable
	$\Xi_2 = (47.727, 0, 68.019, 0, 32.876, 0, 0, 0)$	$(-0.150, 0.072, -0.686, -0.032, -6.095, -0.103, -0.103)$	Unstable
7	$\Xi_3 = (94.049, 130.729, 0, 150, 0, 8.823, 0, 0)$	$(-0.010, -6.178, 0.132, -0.772, -0.017, -0.051, -0.051)$	Unstable
	$\Xi_4 = (111.804, 0, 63.443, 0, 4, 0, 6665.981)$	$(-0.150, -0.705, 0.016, -46.015, -0.009, -0.045, -0.045)$	Unstable
	$\Xi_6 = (89.462, 74.172, 28.323, 96.312, 4, 0, 2422.418)$	$(-0.054, -0.004, -0.004, -0.054, -0.054, -0.702, -20.578)$	Stable
	$\Xi_0 = (1000, 0, 0, 0, 0, 0, 0, 0)$	$(-0.150, -0.010, -0.010, -6.037, 1.897, -1.316, 0.677)$	Unstable
	$\Xi_1 = (49.553, 137.150, 0, 178.090, 0, 0, 0, 0)$	$(-0.010, 88.895, -6.002, -0.038, -0.754, -0.091, -0.091)$	Unstable
	$\Xi_2 = (56.376, 0, 67.402, 0, 32.578, 0, 0, 0)$	$(-0.150, 0.023, -0.742, 0.009, -6.028, -0.088, -0.088)$	Unstable
8	$\Xi_3 = (282.904, 103.477, 0, 15.000, 0, 533.167, 0, 0)$	$(-0.010, -6.125, 0.551, -5.908, -0.046, -0.062, -0.062)$	Unstable
	$\Xi_4 = (65.124, 0, 66.777, 0, 10, 0, 2227.549)$	$(-0.150, -0.752, 0.019, -19.368, -0.007, -0.077, -0.077)$	Unstable
	$\Xi_5 = (56.376, 13.283, 60.827, 15, 29.400, 10.042, 0, 0)$	$(0.019, -0.008, -0.008, -0.088, -0.088, -0.819, -6.028)$	Unstable
	$\Xi_7 = (64.533, 15.402, 59.018, 15, 10, 22.334, 1852.544)$	$(-0.007, -0.016, -0.016, -0.077, -0.077, -0.924, -17.120)$	Stable

7.2. Numerical simulations of optimal control

The impact of the optimal control is demonstrated through numerical simulations. Using the parameter values presented in Table 3, together with those defined in Scenario 8, Figures 10 and 11 illustrates that the equilibrium point Ξ_7 shifts to Ξ_0 when the control is applied, thereby satisfying the objective function. This analysis was carried out using the forward-backward sweep method [83, 84]. The fourth-order Runge–Kutta (RK4) method is first used to solve the state system forward in time. The adjoint system is then solved backward in time using the transversality conditions and the computed state trajectories. The control functions are subsequently updated according to the control characterization in Eqs (6.9)–(6.12). To enhance numerical stability and convergence, an optional relaxation step is used, in which the updated control is defined as a convex combination of the newly computed and previous control functions, as follows:

$$\eta = (1 - \omega^{relax}) \eta^{old} + \omega^{relax} \eta^{new},$$

where $\omega^{relax} \in (0, 1]$ is the relaxation parameter. Using the initial condition specified at the beginning of this section, together with the parameter values $A_1 = 50$, $A_2 = 50$, $A_3 = 30$, and $A_4 = 50$, we compute the solution over the time interval $[0, 500]$. The relaxation parameter is chosen as $\omega^{relax} = 0.3$, and the convergence tolerance is taken to be 10^{-6} .

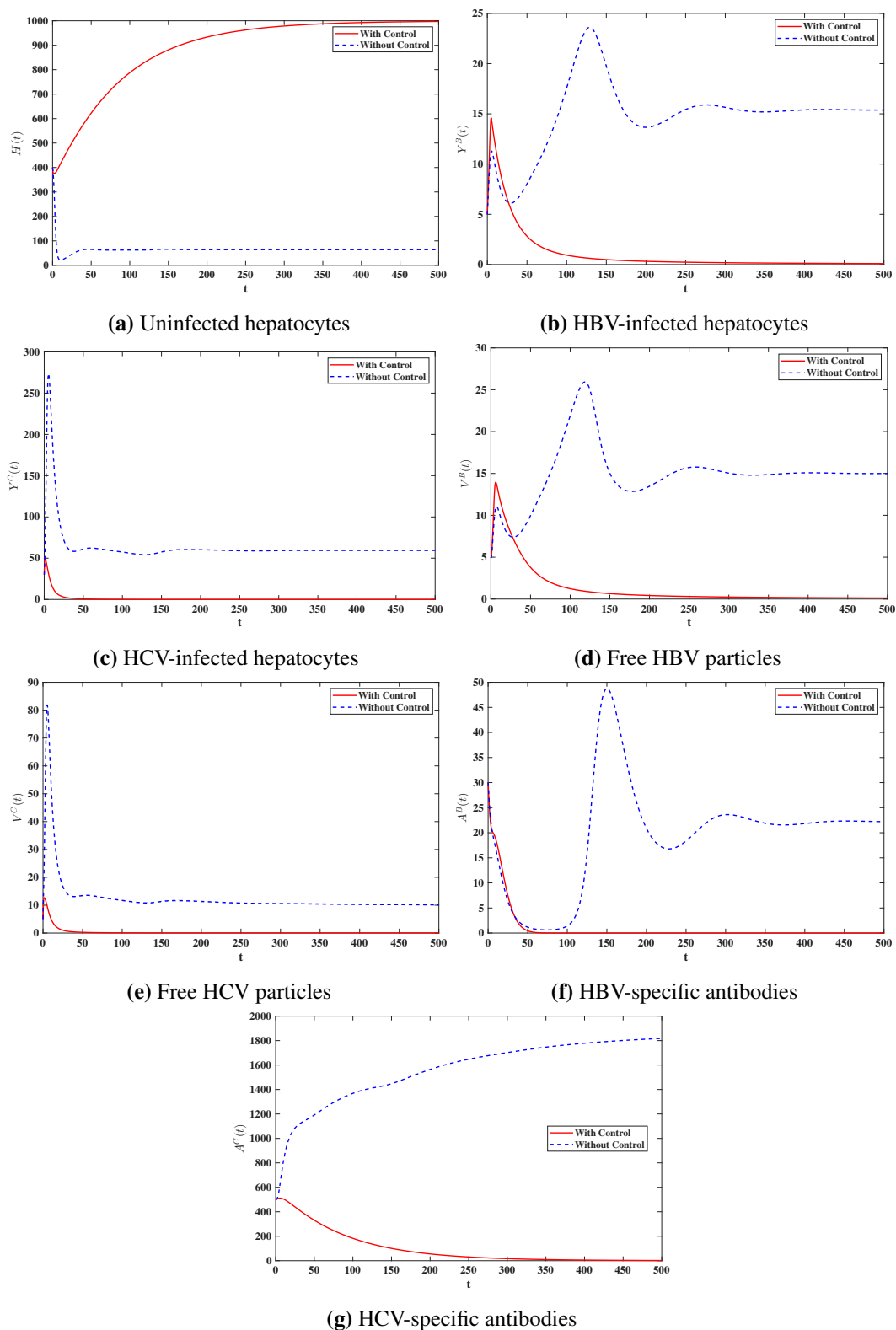


Figure 10. The compartment (uninfected hepatocytes, HBV-infected cells, HCV-infected cells, Free HBV particles, Free HCV particles, HBV-specific antibodies, and HCV-specific antibodies), with and without optimal control, are illustrated over the time interval $[0, 500]$ using the forward-backward sweep method.

Figure 10(a) illustrates that the population of uninfected hepatocytes is higher in the presence of control compared with the case without control. From Figure 10(b),(c), it can be seen that the numbers of HBV-infected and HCV-infected hepatocytes under control decreases and approaches zero, while in the absence of control, they stabilize at approximately 15.37 and 59.21, respectively. This indicates that appropriate therapeutic intervention can significantly reduce the number of infected hepatocytes.

The effect of therapy is also evident in Figure 10(d),(e), where the populations of HBV and HCV virions diminish to zero under control. In contrast, without control, they persist at levels of approximately 14.99 and 10.16, respectively. This highlights the role of treatment in suppressing viral replication. Additionally, the impact of control on HBV-specific and HCV-specific antibodies is demonstrated in Figure 10(f),(g). With control, the levels of these antibodies decrease to zero, whereas without control they approach 22.21 and 1817.71, respectively.

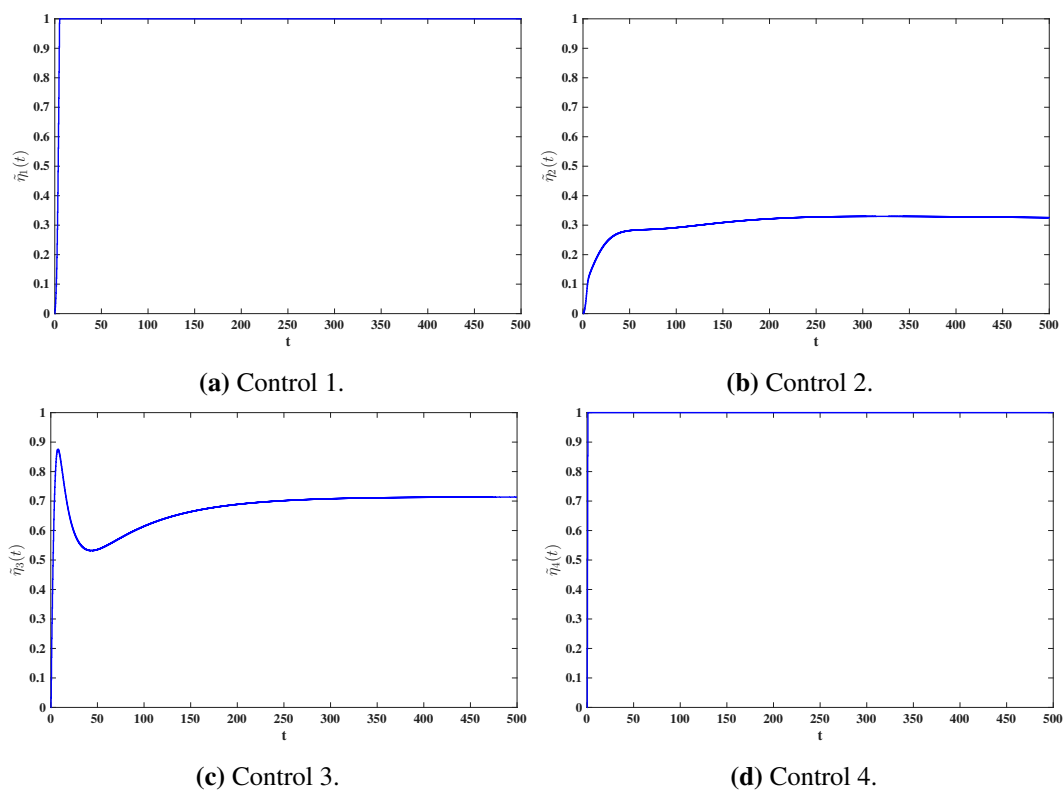


Figure 11. The controls state $\tilde{\eta}_1(t)$, $\tilde{\eta}_2(t)$, $\tilde{\eta}_3(t)$, and $\tilde{\eta}_4(t)$.

The four optimal controls $\tilde{\eta}_1$, $\tilde{\eta}_2$, $\tilde{\eta}_3$, and $\tilde{\eta}_4$, which correspond to blocking new infections of HBV and HCV, are illustrated in Figure 11. The four curves describe the drug administration schedule over the treatment period. The control functions are initially set to zero, to provide an initial guess for the forward-backward sweep algorithm. This initial choice represents the uncontrolled situation and does not imply that the optimal intervention is zero at the beginning of the simulation. The control functions are subsequently updated iteratively based on the state and adjoint trajectories until the convergence criterion is satisfied. Based on the numerical results obtained using the forward-backward sweep method, the objective functional was evaluated from the computed state and control trajectories, with the integral approximated using the trapezoidal rule. The value of the

objective functional without control is $J_0 = 442170.67$, whereas its value under the optimal control strategy is $J^* = 412616.51$. Thus, the optimal control strategy results in an approximate reduction of 6.684% in the objective functional.

7.3. Parameter sensitivity analysis

Sensitivity analysis is a fundamental technique in biological modeling, as it provides insight into how variations in the model parameters influence system behavior, thereby improving understanding of the model structure. It is particularly effective for determining the parameters that most strongly govern the dynamics of the system. Several methods exist for investigating parameter influence in biological systems, including direct differentiation, Latin hypercube sampling (LHS), and approaches based on system linearization followed by solution of the resulting equations [85].

In this work, a derivative-based sensitivity analysis is used for system (2.1). Sensitivities are computed analytically using partial derivatives with respect to the model parameters. The analysis focuses on the threshold quantities $\mathfrak{R}_0^B$ and $\mathfrak{R}_0^C$, as they play a key role in identifying the stability of the disease-free equilibrium Ξ_0 . We define the normalized forward sensitivity index as

$$\Lambda_{\alpha}^{\mathfrak{R}_0^i} = \frac{\partial \mathfrak{R}_0^i}{\partial \alpha} \cdot \frac{\alpha}{\mathfrak{R}_0^i}, \quad i = B, C, \quad (7.1)$$

where α represents a model parameter. The resulting sensitivity indices for $\mathfrak{R}_0^B$ and $\mathfrak{R}_0^C$, computed using Eq (7.1), are summarized in Table 5 and illustrated in Figure 12.

Table 5. Sensitivity index of $\mathfrak{R}_0^B$ and $\mathfrak{R}_0^C$.

Parameter α	Sensitivity index $\Lambda_{\alpha}^{\mathfrak{R}_0^B}$	Parameter α	Sensitivity index $\Lambda_{\alpha}^{\mathfrak{R}_0^C}$
ϕ	1	ϕ	1
β_B	0.114927	β_C	0.0461049
θ_B	0.114927	θ_C	0.0461049
α_B	0.885073	α_C	0.953895
ϕ_B	-0.114927	ϕ_C	-0.0461049
σ	-1	σ	-1
δ_B	-1	δ_C	-1

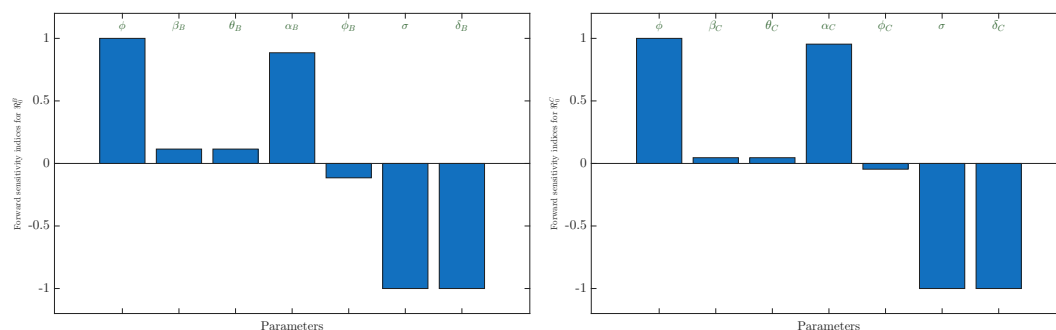


Figure 12. Forward sensitivity analysis of the parameters on $\mathfrak{R}_0^B$ and $\mathfrak{R}_0^C$.

The present sensitivity analysis is intended to quantify the direct relative influence of individual parameters on the threshold quantities $\mathfrak{R}_0^B$ and $\mathfrak{R}_0^C$. Since these threshold quantities have explicit analytical expressions, the normalized forward sensitivity indices can be obtained directly by differentiation, providing a transparent interpretation of how each parameter affects viral invasion. Thus, the sensitivity analysis complements the analytical threshold and stability results established in this study. A global uncertainty analysis, such as LHS combined with partial rank correlation coefficients (LHS/PRCC), could provide additional information about the parameter uncertainty and its effects on the full model dynamics or equilibrium levels; however, such an analysis is beyond the scope of the present study.

7.3.1. Sensitivity indices $\Lambda_\alpha^{\mathfrak{R}_0^B}$

The computed sensitivity indices yield the following observations:

- The parameters ϕ , β_B , θ_B , and α_B all have positive sensitivity indices, indicating that increasing their values leads to higher $\mathfrak{R}_0^B$ and thus enhances the potential for HBV invasion. Among these, ϕ has the strongest positive effect, followed by α_B , while β_B and θ_B has a relatively smaller impact. For instance, a 10% increase in ϕ leads to an approximate 10% rise in $\mathfrak{R}_0^B$, whereas a similar increase in α_B results in about 8.85%. In comparison, β_B and θ_B produces a smaller effect of approximately 1.149%.
- Conversely, the parameters ϕ_B , σ , and δ_B have negative sensitivity indices, implying that increasing these parameters reduces $\mathfrak{R}_0^B$ and suppresses the potential for HBV invasion. Among them, σ and δ_B exert the strongest negative influence, while ϕ_B has a comparatively weaker effect. For example, a 10% increase in σ and δ_B leads to an approximate 10% decrease in $\mathfrak{R}_0^B$, whereas a similar increase in ϕ_B results in a reduction of about 1.149%.

7.3.2. Sensitivity indices $\Lambda_\alpha^{\mathfrak{R}_0^C}$

The computed sensitivity indices yield the following observations:

- The parameters ϕ , β_C , θ_C , and α_C all have positive sensitivity indices, indicating that increasing their values leads to higher $\mathfrak{R}_0^C$ and thus enhances the potential for HCV invasion. Among these, ϕ has the strongest positive effect, followed by α_C , while β_C and θ_C have relatively smaller impacts. For instance, a 10% increase in ϕ leads to an approximate 10% rise in $\mathfrak{R}_0^C$, whereas a similar increase in α_C results in about 9.54%. In comparison, β_C and θ_C produces a smaller effects of approximately 0.461%.
- Conversely, the parameters ϕ_C , σ , and δ_C have negative sensitivity indices, implying that increasing these parameters reduces $\mathfrak{R}_0^C$ and suppresses the potential for HCV invasion. Among them, σ and δ_C exert the strongest negative influence, while ϕ_C has a comparatively weaker effect. For example, a 10% increase in σ and δ_C leads to an approximate 10% decrease in $\mathfrak{R}_0^C$, whereas a similar increase in ϕ_C results in a reduction of about 0.461%.

8. Discussion

HBV and HCV primarily infect hepatocytes and can lead to severe liver complications, such as cirrhosis and hepatocellular carcinoma. Numerous studies have reported HBV/HCV coinfection in clinical settings. To enhance treatment approaches for such coinfections, mathematical models have been developed to better understand the interactions among HBV, HCV, and the host immune response. These models provide a framework for investigating disease progression and evaluating potential therapeutic strategies. In this study, we propose a coinfection model to investigate the within-host dynamics of HBV and HCV, incorporating both virus-to-cell and cell-to-cell transmission pathways, as well as virus-specific humoral responses. We analyzed the fundamental qualitative properties of the model and identified eight possible equilibria whose existence and stability are characterized by threshold parameters. The main findings can be summarized as follows:

- The disease-free equilibrium Ξ_0 always exists for all parameter values. It is GAS once $\mathcal{R}_0^B \leq 1$ and $\mathcal{R}_0^C \leq 1$. Under these conditions, both HBV and HCV are eliminated from the modeled host population. Thus, parameter regimes satisfying these threshold conditions are associated with viral clearance in the model.
- The HBV monoinfection equilibrium point without a positive antibody response Ξ_1 exists when $\mathcal{R}_0^B > 1$. It is GAS if $\mathcal{R}_0^B > 1$, $\mathcal{R}_0^C/\mathcal{R}_0^B \leq 1$ and $\mathcal{R}_1^B \leq 1$. Under these conditions, HBV persists whereas HCV is eliminated, without a positive HBV-specific antibody response. The relative values of the reproduction thresholds indicate that, within the model, the persistence of HBV can lead to the exclusion of HCV under these parameter conditions.
- The HCV monoinfection equilibrium point without a positive antibody response Ξ_2 exists when $\mathcal{R}_0^C > 1$. It is GAS if $\mathcal{R}_0^C > 1$, $\mathcal{R}_0^B/\mathcal{R}_0^C \leq 1$, and $\mathcal{R}_1^C \leq 1$. Under these conditions, HCV persists whereas HBV is eliminated, without a positive HCV-specific antibody response. Similarly, the threshold conditions indicate that the persistence of HCV can lead to exclusion of HBV under these parameter conditions.
- The HBV monoinfection equilibrium point with a positive HBV-specific antibody response, Ξ_3 exists when $\mathcal{R}_1^B > 1$. It is GAS if $\mathcal{R}_1^B > 1$ and $\mathcal{R}_2^B \leq 1$. Under these conditions, HBV persists together with a positive modeled HBV-specific humoral response, while HCV is eliminated.
- The HCV monoinfection equilibrium point with a positive HCV-specific antibody response, Ξ_4 exists when $\mathcal{R}_1^C > 1$. It is GAS if $\mathcal{R}_1^C > 1$ and $\mathcal{R}_2^C \leq 1$. Under these conditions, HCV persists together with a positive modeled HCV-specific humoral response, while HBV is eliminated. The HCV-specific antibody compartment should be interpreted as an aggregate humoral response rather than as evidence of complete protective immunity.
- The HBV/HCV coexistence equilibrium with a positive HBV-specific antibody response and no positive HCV-specific antibody response, Ξ_5 exists when $\mathcal{R}_2^B > 1$, $\tilde{\mathcal{R}}_2^B > 1$, and $\mathcal{R}_0^B/\mathcal{R}_0^C > 1$. It is GAS under the condition that $\mathcal{R}_2^B > 1$, $\tilde{\mathcal{R}}_2^B > 1$, $\mathcal{R}_0^B/\mathcal{R}_0^C > 1$, and $\mathcal{R}_3^C \leq 1$. Thus, both viruses persist, with a positive modeled HBV-specific humoral response.
- The HBV/HCV coexistence equilibrium with a positive HCV-specific antibody response and no positive HBV-specific antibody response, Ξ_6 exists if $\mathcal{R}_2^C > 1$, $\tilde{\mathcal{R}}_2^C > 1$ and $\mathcal{R}_0^C/\mathcal{R}_0^B > 1$. It is

GAS under the condition that $\mathcal{R}_2^C > 1$, $\tilde{\mathcal{R}}_2^C > 1$, $\mathcal{R}_0^C/\mathcal{R}_0^B > 1$ and $\mathcal{R}_3^B \leq 1$. Thus, both viruses persist, with a positive modeled HCV-specific humoral response.

- The HBV/HCV coexistence equilibrium with positive HBV- and HCV-specific antibody responses, Ξ_7 , exists and is GAS when $\mathcal{R}_3^B > 1$ and $\mathcal{R}_3^C > 1$. This equilibrium represents persistent coinfection in the presence of positive modeled humoral responses against both viruses.

From a biological perspective, the threshold quantities describe different aspects of viral invasion, persistence, competition, and modeled humoral responses. The basic reproduction numbers $\mathcal{R}_0^B$ and $\mathcal{R}_0^C$ determine whether HBV or HCV can invade a virus-free hepatocyte population. The thresholds $\mathcal{R}_1^B$ and $\mathcal{R}_1^C$ characterize the persistence of the corresponding virus in the presence of the competing infection, whereas $\mathcal{R}_2^B$ and $\mathcal{R}_2^C$ are associated with the emergence of coexistence states. The thresholds $\mathcal{R}_3^B$ and $\mathcal{R}_3^C$ determine whether a positive modeled virus-specific humoral response can be maintained. Accordingly, the different equilibria distinguish between competitive exclusion, in which one virus persists while the other is eliminated, and coexistence, in which both viruses persist under the corresponding threshold conditions. These interpretations are specific to the mechanisms included in the present within-host model and should not be regarded as direct evidence of biological suppression of one virus by the other.

The inclusion of both virus-to-cell and cell-to-cell transmission provides an additional mechanistic feature of the model. These pathways offer alternative routes for maintaining infection and therefore can influence the persistence conditions and the treatment effort required for viral clearance. In contrast to models that consider only virus-to-cell transmission or single-virus dynamics, the present framework allows HBV and HCV to compete for uninfected hepatocytes while simultaneously accounting for two transmission pathways and virus-specific modeled humoral responses. This provides a qualitative framework for examining how transmission mechanisms and viral competition may jointly shape HBV/HCV coinfection dynamics.

We also investigated the HBV/HCV coinfection model under antiviral treatment by incorporating four control functions: η_1 to inhibit HBV infection through virus-to-cell transmission, η_2 to inhibit HBV infection through cell-to-cell transmission, η_3 to inhibit HCV infection through virus-to-cell transmission, and η_4 to inhibit HCV infection through cell-to-cell transmission. First, we investigated the effect of cell-to-cell transmission on HBV/HCV coinfection dynamics. The results indicate that neglecting cell-to-cell transmission may underestimate the treatment effort required to achieve viral clearance. Thus, incorporating both transmission pathways provides a more comprehensive representation of within-host HBV/HCV dynamics than models considering only virus-to-cell transmission. We then formulated an optimal control problem to determine treatment strategies that increase the population of uninfected hepatocytes while accounting for treatment costs.

An important limitation of the present model is the assumption that HBV- and HCV-infected hepatocytes are mutually exclusive. This assumption provides a mathematically tractable framework for studying the interaction between the two viruses through their competition for uninfected hepatocytes. However, experimental studies have shown that HBV and HCV can coexist within the same hepatocyte and that HCV replication may suppress HBV replication [55, 56]. Thus, the present model should be viewed as an effective approximation of viral competition and interference rather than a complete representation of cellular coinfection. Future work could incorporate a doubly infected hepatocyte compartment and explicit intracellular HBV-HCV interactions to provide a more detailed

description of coinfection dynamics.

Another limitation concerns the availability of experimental or clinical data for HBV/HCV coinfection. The values of the cell-to-cell transmission coefficients α_B , α_C , relative to the corresponding virus-to-cell transmission coefficients β_B , β_C , were selected for illustrative numerical investigations of different transmission regimes. Therefore, the parameter sets used in Scenarios 1–8 should be interpreted as illustrative rather than patient-specific or predictive. Future studies incorporating experimental measurements or patient viral-load data could provide parameter estimates and enable model calibration and validation, thereby improving the predictive capability of the model.

Several additional limitations of the present model should also be acknowledged. First, the model does not explicitly incorporate intracellular HBV dynamics, such as intracellular delays or the covalently closed circular DNA (cccDNA) compartment, which plays an important role in HBV persistence. Second, the antiviral treatment terms are assumed to affect viral transmission only and do not explicitly account for treatment effects on viral production or the death rate of infected hepatocytes. Third, infection is described using bilinear mass-action incidence, which may not fully capture saturation effects at high viral or infected cell densities. Fourth, the recruitment of uninfected hepatocytes is assumed to be constant, and therefore possible feedback mechanisms associated with liver regeneration are not represented. Fifth, the model does not include CTL-mediated killing of infected hepatocytes, although cellular immune responses play an important role in the control of HBV and HCV infections. Finally, the optimal control formulation is deterministic and open-loop and does not explicitly incorporate treatment adherence, pharmacokinetic/pharmacodynamic constraints, or other clinically relevant treatment limitations. Addressing these biological and clinical factors in future extensions could provide a more comprehensive representation of HBV/HCV coinfection dynamics and treatment.

9. Conclusions

Mathematical models provide useful frameworks for investigating the complex dynamics of infectious diseases and evaluating potential intervention strategies. In this paper, we developed an optimal control model for HBV/HCV coinfection that incorporates humoral immunity and cell-to-cell transmission. The model consists of seven differential equations describing the interactions among uninfected hepatocytes, HBV-infected cells, HCV-infected cells, free HBV particles, free HCV particles, HBV-specific antibodies, and HCV-specific antibodies. We first established the non-negativity and boundedness of the model solutions. Subsequently, we identified the equilibria and established their existence conditions in terms of ten threshold parameters. The global asymptotic stability of the equilibria was established by constructing suitable Lyapunov functions and applying the Lyapunov–LaSalle invariance principle.

We also investigated the role of cell-to-cell transmission and demonstrated that this transmission mechanism can substantially influence the infection dynamics and the conditions for infection persistence. Numerical simulations were performed to illustrate the theoretical results, and the numerical observations were consistent with the analytical stability results. Sensitivity analysis was further conducted to examine the effects of model parameters on the basic reproduction numbers, $\mathcal{R}_0^B$ and $\mathcal{R}_0^C$.

Finally, an optimal control problem was formulated to determine four time-dependent control

functions aimed at increasing the population of uninfected hepatocytes while reducing viral transmission and accounting for treatment costs. The four controls represent the effectiveness of therapeutic interventions in reducing HBV and HCV transmission through the virus-to-cell and cell-to-cell pathways. The resulting optimality system was solved numerically using the fourth-order Runge-Kutta method. The numerical results demonstrate that the proposed control strategy can reduce viral infection and increase the population of uninfected hepatocytes under the considered parameter scenarios. Overall, the model provides a mathematical framework for examining the combined effects of cell-to-cell transmission, humoral immunity, and therapeutic intervention in HBV/HCV coinfection.

Use of AI tools declaration

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

Conflict of interest

The authors declare there is no conflict of interest.

Author contributions

Conceptualization, RA, AE and AH; methodology, RA, AE and AA; formal analysis, RA, AE and AH; investigation, RA and AA; writing—original draft preparation, RA and AE; writing—review and editing, AE, AA and AH. All authors have read and agreed to the published version of the manuscript.

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A. Basic reproduction numbers

The basic reproduction numbers for HBV monoinfection, HCV monoinfection, and HBV/HCV co-infection are derived using the next-generation matrix approach of [86].

A.1. The basic reproduction number for HBV monoinfection

The HBV monoinfection model is given by:

$$\begin{aligned}\dot{H} &= \phi - \sigma H - \beta_B H V^B - \alpha_B H Y^B, \\ \dot{Y}^B &= \beta_B H V^B + \alpha_B H Y^B - \delta_B Y^B, \\ \dot{V}^B &= \theta_B Y^B - \phi_B V^B - \gamma_B A^B V^B, \\ \dot{A}^B &= \rho_B A^B V^B - \lambda_B A^B.\end{aligned}\tag{A.1}$$

The infection-free equilibrium of system (A.1) is given is $\Xi_0 = (H_0, 0, 0, 0)$, where $H_0 = \phi/\sigma$. Define

$$F_B = \begin{bmatrix} \beta_B H V^B + \alpha_B H Y^B \\ 0 \end{bmatrix}, \quad V_B = \begin{bmatrix} \delta_B Y^B \\ -\theta_B Y^B + \phi_B V^B + \gamma_B A^B V^B \end{bmatrix}.$$

Linearization of the system around the infection-free equilibrium produces the Jacobian matrices

$$\mathcal{F}_B = \begin{bmatrix} \alpha_B H_0 & \beta_B H_0 \\ 0 & 0 \end{bmatrix}, \quad \mathcal{V}_B = \begin{bmatrix} \delta_B & 0 \\ -\theta_B & \phi_B \end{bmatrix}.$$

The basic reproduction number for HBV monoinfection is given by:

$$\mathfrak{R}_0^B = \rho(\mathcal{F}_B \mathcal{V}_B^{-1}) = \frac{H_0 (\beta_B \theta_B + \alpha_B \phi_B)}{\delta_B \phi_B}.$$

A.2. The basic reproduction number for HCV monoinfection

The HCV monoinfection model is given by:

$$\begin{aligned}\dot{H} &= \phi - \sigma H - \beta_C H V^C - \alpha_C H Y^C, \\ \dot{Y}^C &= \beta_C H V^C + \alpha_C H Y^C - \delta_C Y^C, \\ \dot{V}^C &= \theta_C Y^C - \phi_C V^C - \gamma_C A^C V^C, \\ \dot{A}^C &= \rho_C A^C V^C - \lambda_C A^C.\end{aligned}\tag{A.2}$$

The infection-free equilibrium of system (A.2) is given is $\Xi_0 = (H_0, 0, 0, 0)$, where $H_0 = \phi/\sigma$. Let us define

$$F_C = \begin{bmatrix} \beta_C H V^C + \alpha_C H Y^C \\ 0 \end{bmatrix}, \quad V_C = \begin{bmatrix} \delta_C Y^C \\ -\theta_C Y^C + \phi_C V^C + \gamma_C A^C V^C \end{bmatrix}.$$

Linearization of the system around the infection-free equilibrium produces the Jacobian matrices

$$\mathcal{F}_C = \begin{bmatrix} \alpha_C H_0 & \beta_C H_0 \\ 0 & 0 \end{bmatrix}, \quad \mathcal{V}_C = \begin{bmatrix} \delta_C & 0 \\ -\theta_C & \phi_C \end{bmatrix}.$$

The basic reproduction number for HCV monoinfection is given by:

$$\mathfrak{R}_0^C = \rho(\mathcal{F}_C \mathcal{V}_C^{-1}) = \frac{H_0 (\alpha_C \phi_C + \beta_C \theta_C)}{\delta_C \phi_C}.$$

A.3. The basic reproduction number for HBV/HCV coinfection

Similarly, the basic reproduction number for the HBV/HCV co-infection model (2.1) can be obtained as the spectral radius of the next-generation matrix, namely $\rho(\mathcal{F}_0\mathcal{V}_0^{-1})$, where

$$\mathcal{F}_0 = \begin{bmatrix} \alpha_B H_0 & 0 & \beta_B H_0 & 0 \\ 0 & \alpha_C H_0 & 0 & \beta_C H_0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}, \text{ and } \mathcal{V}_0 = \begin{bmatrix} \delta_B & 0 & 0 & 0 \\ 0 & \delta_C & 0 & 0 \\ -\theta_B & 0 & \phi_B & 0 \\ 0 & -\theta_C & 0 & \phi_C \end{bmatrix}.$$

The basic reproduction number for the HBV/HCV co-infection model is given by:

$$\mathfrak{R}_0 = \rho(\mathcal{F}_0\mathcal{V}_0^{-1}) = \max \left\{ \frac{H_0(\alpha_B\phi_B + \beta_B\theta_B)}{\delta_B\phi_B}, \frac{H_0(\alpha_C\phi_C + \beta_C\theta_C)}{\delta_C\phi_C} \right\} = \max \{ \mathfrak{R}_0^B, \mathfrak{R}_0^C \}.$$

B. Non-negativity and boundedness of the solutions of system (6.1)

We investigate the fundamental properties of system (6.1). In particular, we establish the non-negativity and boundedness of its solutions.

Lemma 4. *The solutions of system (6.1) are non-negative and bounded.*

Proof. We have that

$$\begin{aligned} \dot{H} \big|_{(H=0)} &= \phi > 0, \\ \dot{Y}^B \big|_{(Y^B=0, H \geq 0, V^B \geq 0, \eta_1 \in [0,1])} &= (1 - \eta_1(t))\beta_B H V^B \geq 0, \\ \dot{Y}^C \big|_{(Y^C=0, H \geq 0, V^C \geq 0, \eta_3 \in [0,1])} &= (1 - \eta_3(t))\beta_C H V^C \geq 0, \\ \dot{V}^B \big|_{(V^B=0, Y^B \geq 0)} &= \theta_B Y^B \geq 0, \\ \dot{V}^C \big|_{(V^C=0, Y^C \geq 0)} &= \theta_C Y^C \geq 0, \\ \dot{A}^B \big|_{(A^B=0)} &= 0, \\ \dot{A}^C \big|_{(A^C=0)} &= 0. \end{aligned}$$

This ensures that $(H(t), Y^B(t), Y^C(t), V^B(t), V^C(t), A^B(t), A^C(t)) \in R_{\geq 0}^7$ for all $t \geq 0$ when $(H(0), Y^B(0), Y^C(0), V^B(0), V^C(0), A^B(0), A^C(0)) \in R_{\geq 0}^7$.

Let us define

$$\Theta = H + Y^B + Y^C + \frac{\delta_B}{2\theta_B} V^B + \frac{\delta_C}{2\theta_C} V^C + \frac{\delta_B \gamma_B}{2\theta_B \rho_B} A^B + \frac{\delta_C \gamma_C}{2\theta_C \rho_C} A^C.$$

Then

$$\begin{aligned} \dot{\Theta} &= \phi - \sigma H - \frac{\delta_B}{2} Y^B - \frac{\delta_C}{2} Y^C - \frac{\delta_B \phi_B}{2\theta_B} V^B - \frac{\delta_C \phi_C}{2\theta_C} V^C - \frac{\delta_B \gamma_B \lambda_B}{2\theta_B \rho_B} A^B - \frac{\delta_C \gamma_C \lambda_C}{2\theta_C \rho_C} A^C, \\ &\leq \phi - \kappa \left[H + Y^B + Y^C + \frac{\delta_B}{2\theta_B} V^B + \frac{\delta_C}{2\theta_C} V^C + \frac{\delta_B \gamma_B}{2\theta_B \rho_B} A^B + \frac{\delta_C \gamma_C}{2\theta_C \rho_C} A^C \right] = \phi - \kappa \Theta, \end{aligned}$$

where $\kappa = \min \left\{ \sigma, \frac{\delta_B}{2}, \frac{\delta_C}{2}, \phi_B, \phi_C, \lambda_B, \lambda_C \right\}$. Thus, $0 \leq \Theta(t) \leq \frac{\phi}{\kappa}$ if $\Theta(0) \leq \frac{\phi}{\kappa}$ for $t \geq 0$. Since $H, Y^B, Y^C, V^B, V^C, A^B$ and A^C are all non-negative, then $0 \leq H(t), Y^B(t), Y^C(t) \leq \frac{\phi}{\kappa}, 0 \leq V^B(t) \leq \frac{2\theta_B\phi}{\delta_B\kappa}, 0 \leq V^C(t) \leq \frac{2\theta_C\phi}{\delta_C\kappa}, 0 \leq A^B(t) \leq \frac{2\theta_B\rho_B\phi}{\delta_B\gamma_B\kappa}, 0 \leq A^C(t) \leq \frac{2\theta_C\rho_C\phi}{\delta_C\gamma_C\kappa}$ if $H(0) + Y^B(0) + Y^C(0) + \frac{\delta_B}{2\theta_B}V^B(0) + \frac{\delta_C}{2\theta_C}V^C(0) + \frac{\delta_B\gamma_B}{2\theta_B\rho_B}A^B(0) + \frac{\delta_C\gamma_C}{2\theta_C\rho_C}A^C(0) \leq \frac{\phi}{\kappa}$. This establishes that the solutions remain bounded. $\square$



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