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Research article

Impact of vaccination and immune response in reducing Hepatitis B-related liver disease model

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Abstract: Hepatitis B virus (HBV) infection can progress from acute infection to chronic liver disease, posing a major public health concern. In this work, a mathematical model incorporating immune response and vaccination is developed using susceptible, infected, chronic, and recovered populations. Positivity and boundedness of solutions are established, and disease-free and endemic equilibria are analyzed. The basic reproduction numbers and stability conditions are derived using the next-generation matrix and Jacobian methods. Critical thresholds are obtained as $\Upsilon^* = 0.2237$ for immune response and $\Gamma^* = 0.7466$ for vaccination. Numerical simulations using the fourth-order Runge–Kutta method demonstrate that enhanced immune response and vaccination can reduce HBV infection and chronic cases. The findings provide quantitative evidence on the role of immune response and vaccination in controlling HBV transmission and disease progression.

Keywords: vaccination; disease progression; liver disease; chronic infection

1. Introduction

Hepatitis B virus (HBV) is a widespread infectious disease, contributing to a significant global burden of liver-related morbidity and mortality. Around 296 million individuals worldwide are affected by chronic Hepatitis B infections. Without proper treatment, the infection can lead to life-threatening liver issues. One major complication is cirrhosis, which involves permanent liver damage. It can also result in hepatocellular carcinoma, a type of liver cancer. Preventive measures like vaccination and early treatment are essential for control [1]. As a result, HBV is responsible for around 820,000 deaths annually, making it a leading cause of liver disease. Vaccination has proven to be the most effective public health intervention for preventing HBV transmission and controlling the disease [2, 3]. The World Health Organization has recommended universal HBV vaccination since 1992, leading to its widespread inclusion in national immunization programs [4]. Countries that have implemented routine vaccination have seen significant reductions in HBV prevalence, particularly among children and young adults [5]. However, the long-term impact of vaccination on reducing HBV-related liver disease at the population level requires further quantitative analysis. The Hepatitis B vaccine is designed to protect against HBV by using a non-infected part of the virus known as the surface antigen (HBsAg). This antigen is synthesized through recombinant DNA technology, a technique that enables genetic manipulation. This involves introducing the gene that encodes for HBsAg into mammalian cells or yeast [6–8]. These cells then produce the antigen, which is used in the vaccine. The vaccine exhibits high efficacy, successfully preventing over 89 percent of infections. Moreover, it plays a crucial role in reducing the risk of developing chronic HBV infections and serious complications associated with the virus, such as liver cirrhosis and liver cancer [9]. The standard vaccination schedule for the Hepatitis B vaccine consists of three doses:

- The first Hepatitis B vaccine dose is ideally given at birth or shortly thereafter.
- The second dose follows within one to two months of the initial shot.
- The third dose is administered six months following the initial vaccination.

In some cases, alternative vaccination schedules may be recommended for specific groups, such as adults or individuals at higher risk of infection [10, 11]. The vaccine is recommended for all infants, children, and adolescents, as well as adults who are at increased risk of HBV infection. This includes healthcare workers, individuals with multiple sexual partners, and those with chronic liver disease [12–14]. Mathematical modeling is a powerful tool for evaluating the long-term effects of vaccination programs. By simulating the dynamics of disease transmission and progression, models can estimate the potential reduction in chronic liver disease cases, cirrhosis, and liver cancer [15, 16]. This article develops a mathematical model to assess the impact of HBV vaccination on reducing liver disease and mortality. By incorporating vaccination coverage, efficacy, and immunity into the model, this research aims to provide critical insights into the broader public health benefits of vaccination and offer evidence to inform future strategies for HBV control. Shulgin et al. [17] investigated a pulse vaccination strategy within the susceptible, infected, recovered (SIR) epidemic model and demonstrated its role in controlling disease transmission.

Guedj et al. [18] investigated the dynamics of Hepatitis C virus (HCV) during interferon-based therapies, focusing on essential parameters such as the production and clearance rates of the virus and the depletion of infected cells. They noted complex viral behaviors, including the triphasic decline in HCV RNA levels followed by rebounds in patients undergoing treatment with pegylated interferon

and ribavirin. Furthermore, they explored innovative modeling strategies to analyze the effects of direct-acting antiviral agents that rapidly reduce the wild-type virus but may contribute to the emergence of drug-resistant strains. The study also emphasized the importance of in vitro systems for improving the understanding of the virus lifecycle in dynamic modeling processes. Megala et al. [19] developed a new epidemiological model for HBV that includes re-infection dynamics, demonstrating globally asymptotic stability of the HBV-free equilibrium. They identified a transcritical bifurcation and showed that the endemic equilibrium is globally stable. The model's effectiveness was validated through numerical simulations using the nonstandard finite difference method, highlighting the importance of vaccination and prevention strategies in controlling HBV transmission. Beddington [20] and DeAngelis [21] introduced the Beddington–DeAngelis (BD) form of non-linear incidence rate, expressed as

$$f(S_H,\ I_H) = \frac{\xi S_H I_H}{(1 + \gamma_1 S_H + \gamma_2 I_H)}. \tag{1.1}$$

This formulation combines the effects of both susceptible and infected individuals on the transmission dynamics, allowing for a more comprehensive understanding of how interactions between these groups influence the spread of disease. The BD incidence rate has been widely adopted in subsequent epidemiological research due to its ability to capture the complexities of disease transmission in real-world scenarios [22]. Kaddar [23, 24] further advanced this field by introducing a delayed model that incorporates the BD incidence rate. This model demonstrated significant values for the inhibitory effects, indicating that delays in the response of susceptible individuals to infection or control measures can have substantial impacts on the dynamics of disease spread. By framing the model in this way, Kaddar highlighted the importance of considering time delays in epidemiological models, which can lead to more accurate predictions and better-informed public health strategies. They formulated the following system of equations:

$$\begin{cases} \dfrac{dS_H}{dt} = \pi - \epsilon S_H - \dfrac{\Phi S_H I_H}{1 + \alpha_1 S_H + \alpha_2 I_H}, \\ \dfrac{dI_H}{dt} = \dfrac{\Phi S_H I_H}{1 + \alpha_1 S_H + \alpha_2 I_H} - (\epsilon + \theta + \sigma) I_H, \\ \dfrac{dR_H}{dt} = \theta I_H - \epsilon R_H. \end{cases} \tag{1.2}$$

The model parameters are defined as follows: π is the recruitment rate, Φ is the transmission coefficient, and ϵ represents the natural mortality rate. The parameter θ indicates the rate at which infected individuals receive treatment, while σ accounts for mortality due to the disease. Although Kaddar [23, 24] explored the behavior of this model, the analysis did not differentiate between stages of infection such as acute, chronic, or cirrhosis. Additionally, vaccination strategies were not included in the framework.

Farhan et al. [25–27] developed and analyzed an HBV infection model incorporating asymptomatic carriers, vaccination, and treatment effects, confirming global stability via Lyapunov functions. They also used deep neural networks to enhance model accuracy and validate predictions against benchmark data. Also, they developed a novel HBV model incorporating asymptomatic carriers, vaccination, and treatment to analyze disease dynamics, stability, and control strategies using

mathematical and numerical methods. They worked on a novel deep neural network framework using Levenberg–Marquardt optimization to accurately model the susceptible, infected, vaccinated, recovered (SIVR) epidemic with a saturated incidence rate. Lengiteng'i et al. [28] investigated the impact of dual stigma and treatment and control strategies on humen immunodeficiency virus–tuberculosis (HIV–TB) coinfection dynamics using a deterministic mathematical model. They analyzed HIV-only, TB-only, and coinfection sub-models, using sensitivity analysis and numerical simulations to identify effective treatment and stigma-reduction interventions. Yavuz et al. [29] formulated an HBV transmission model incorporating vertical transmission and investigated its positivity, disease-free equilibrium, and numerical dynamics. In a subsequent study, Yavuz et al. [30] developed a fractional-order HBV model incorporating vertical transmission, migration, and memory effects, supported by real USA data and parameter calibration. Naik et al. [31] developed a fractional-order HCV model incorporating partial immunity and memory effects and analyzed its global dynamics using the basic reproduction number and Lyapunov methods.

Kiemtore et al. [32] examined the impact of vaccination, treatment of chronic carriers, and media awareness on vertically transmitted HBV. Their simulations showed that these combined control measures can substantially reduce HBV prevalence over time. Mustapha et al. [33] investigated an age-structured HBV transmission model exhibiting backward bifurcation and estimated its parameters using real data from South Africa. They also identified sensitive parameters and showed that reducing the progression of chronically infected children through treatment is crucial for HBV control.

Although these studies have incorporated different factors such as vertical transmission, age structure, migration, memory effects, vaccination, and treatment, few studies have considered the combined role of immune response and vaccination in the dynamics of HBV-related liver disease. Motivated by this gap, the present work develops an HBV liver disease model incorporating the Crowley–Martin (CM) incidence function [34], immune response, and vaccination. The CM incidence function

$$f(S_H,\ I_H) = \frac{\Phi S_H I_H}{(1+\eta_1 S_H)(1+\eta_2 I_H)} \tag{1.3}$$

accounts for nonlinear effects associated with interactions between susceptible and infected populations and has been widely used in epidemiological modeling [35–40]. The proposed model further derives explicit threshold conditions for both immune response and vaccination and is analyzed through positivity, boundedness, equilibrium analysis, reproduction numbers, local stability, and numerical simulations.

This paper is organized into several sections, each addressing a specific aspect of the HBV-related liver disease model. Section 2 presents the mathematical formulation of the model and describes the assumptions underlying the system. In Section 3, the well-posedness of the model is established by verifying the non-negativity and boundedness of the solutions. Section 4 investigates the immune response model without vaccination, including the hepatitis-free and endemic equilibria, the basic reproduction number, and their stability properties. Section 5 extends the analysis by incorporating vaccination and examines the corresponding equilibria, reproduction number, and stability properties. Section 6 derives the critical immune response and vaccination thresholds required for disease control. Section 7 presents the numerical computation of the equilibrium points and numerical simulations to illustrate the model dynamics under vaccination and non-vaccination scenarios. Finally, Section 8

summarizes the main findings of the study, discusses the limitations, and outlines possible directions for future work.

2. Model formulation

The dynamics of the HBV transmission system are governed by the following system of nonlinear differential equations:

$$\begin{cases} \dfrac{d\mathcal{S}}{dt} = r_{in} + \sigma\mathcal{R} - (\kappa + \Gamma)\mathcal{S} - \dfrac{\alpha\mathcal{S}\mathcal{I}}{(1+\eta_1\mathcal{S})(1+\eta_2\mathcal{I})}, \\ \dfrac{d\mathcal{I}}{dt} = \dfrac{\alpha\mathcal{S}\mathcal{I}}{(1+\eta_1\mathcal{S})(1+\eta_2\mathcal{I})} - (\xi + \kappa + \Upsilon + \tau + \gamma)\mathcal{I}, \\ \dfrac{d\mathcal{C}}{dt} = (\xi + \gamma)\mathcal{I} - (\kappa + \tau)\mathcal{C}, \\ \dfrac{d\mathcal{R}}{dt} = -(\kappa + \sigma)\mathcal{R} + \Gamma\mathcal{S} + \Upsilon\mathcal{I}. \end{cases} \tag{2.1}$$

The initial conditions are given by

$$\mathcal{S}(0) = \mathcal{S}_0 \geq 0, \qquad \mathcal{I}(0) = \mathcal{I}_0 \geq 0, \qquad \mathcal{C}(0) = \mathcal{C}_0 \geq 0, \qquad \mathcal{R}(0) = \mathcal{R}_0 \geq 0.$$

The biological interpretation of the state variables and model parameters is provided in Table 1. A schematic representation of the proposed HBV transmission model is presented in Figure 1.

Table 1. Interpretation of the variables and parameters of the HBV model.

Parameters	Interpretation	Units
$\mathcal{S}$	Number of susceptible individuals	individuals
$\mathcal{I}$	Number of individuals with acute HBV infection	individuals
$\mathcal{C}$	Number of individuals with chronic HBV infection	individuals
$\mathcal{R}$	Number of recovered and immune individuals	individuals
r_{in}	Recruitment rate of susceptible individuals into the population	individuals/year
α	HBV transmission rate	person^{-1}year^{-1}
η_1	Saturation parameter associated with the susceptible population	person^{-1}
η_2	Saturation parameter associated with the infected population	person^{-1}
σ	Transition rate from the recovered to the susceptible due to waning immunity	year^{-1}
Γ	Vaccination rate of susceptible individuals	year^{-1}
ξ	Rate of progression from acute to chronic HBV infection	year^{-1}
κ	Natural mortality rate	year^{-1}
Υ	Rate of treatment-induced recovery of infected individuals	year^{-1}
τ	Disease-induced mortality rate	year^{-1}
γ	Additional progression rate due to repeated exposure	year^{-1}

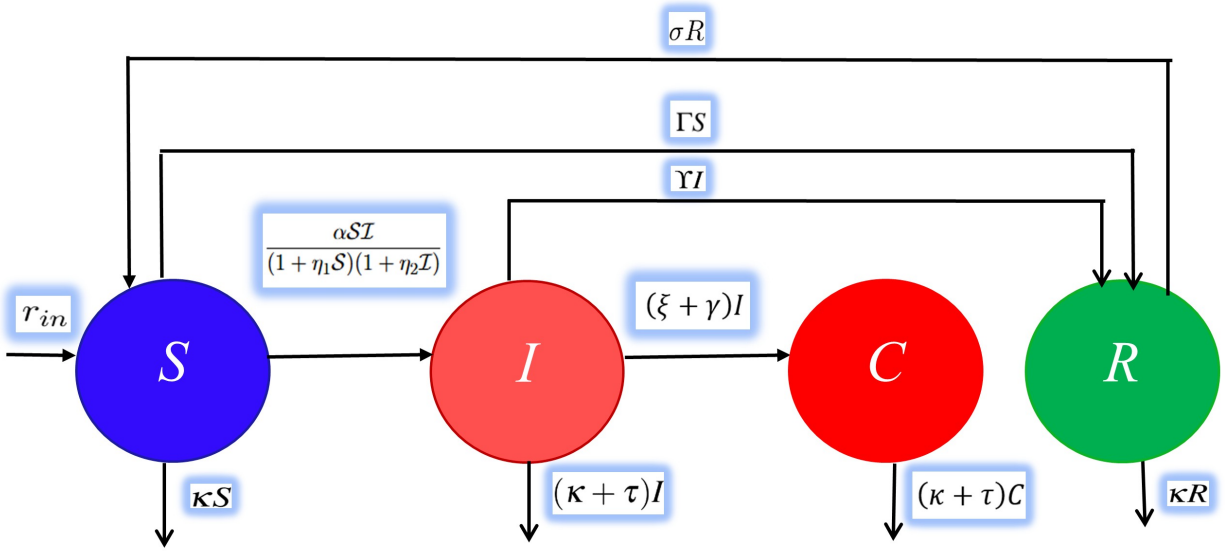


Figure 1. Flowchart of the HBV transmission model incorporating acute and chronic infection.

3. Well-posedness

To ensure biological feasibility, we show that all state variables of system (2.1) remain non-negative for all $t \geq 0$, given non-negative initial conditions. Each equation in the system has non-negative inflow terms and linear or nonlinear loss terms, ensuring that the solutions $\mathcal{S}(t), \mathcal{I}(t), C(t)$, *and* $\mathcal{R}(t)$ cannot become negative. Therefore, the model is positively invariant in the region $\mathbb{R}^4_+$. HBV model (2.1) exhibits boundedness for all its solutions. By summing all the differential equations, we get:

$$\frac{d}{dt}(\mathcal{S}+\mathcal{I}+C+\mathcal{R}) = r_{in} - \kappa(\mathcal{S}+\mathcal{I}+C+\mathcal{R}) - \tau(\mathcal{I}+C).$$

Let

$$N(t) = \mathcal{S}(t) + \mathcal{I}(t) + C(t) + \mathcal{R}(t),$$

then

$$\frac{dN}{dt} = r_{in} - \kappa N - \tau(\mathcal{I}+C).$$

Clearly,

$$\frac{dN}{dt} \leq r_{in} - \kappa N,$$

which means that $N(t)$ is bounded above. The solution of the inequality

$$\frac{dN}{dt} \leq r_{in} - \kappa N$$

implies that as $t \to \infty$, $N(t)$ tends toward a finite upper bound:

$$N(t) \leq \frac{r_{in}}{\kappa}.$$

Thus, the total HBV population $N(t)$ is bounded by $\frac{r_{in}}{\kappa}$ as $t \to \infty$, which means the model is biologically realistic since the population cannot grow indefinitely.

$$\Psi = \left\{(\mathcal{S}, \mathcal{I}, C, \mathcal{R}) \in \mathbb{R}^4_+ : \mathcal{S} + \mathcal{I} + C + \mathcal{R} \leq \frac{r_{in}}{\kappa}\right\}. \tag{3.1}$$

4. Immune response without vaccination

4.1. Hepatitis-free equilibrium E^0

The hepatitis-free equilibrium (HFE) of system (2.1) corresponds to the state in which no infection persists in the population, i.e.,

$$\mathcal{I} = 0, \qquad C = 0.$$

In the absence of vaccination, we set $\Gamma = 0$. Setting the right-hand sides of system (2.1) equal to zero and solving under these conditions yields

$$\mathcal{S}^0 = \frac{r_{in}}{\kappa}, \qquad \mathcal{R}^0 = 0.$$

Hence, the HFE of the model is given by

$$\begin{aligned} E^0 &= (\mathcal{S}^0,\ \mathcal{I}^0,\ C^0,\ \mathcal{R}^0) \\ &= \left(\frac{r_{in}}{\kappa},\ 0,\ 0,\ 0\right). \end{aligned} \tag{4.1}$$

4.2. Basic reproduction number $\mathfrak{R}_0$

$\mathfrak{R}_0$ is computed using the next-generation matrix (NGM) method of van den Driessche and Watmough [41]. Evaluating the corresponding matrices at E^0, we obtain

$$\mathfrak{R}_0 = \frac{\alpha r_{in}}{(\kappa + \eta_1 r_{in})(\xi + \kappa + \Upsilon + \tau + \gamma)}. \tag{4.2}$$

The Jacobian matrix of E^0 without vaccination is

$$J(E^0) = \begin{pmatrix} -\kappa & -\dfrac{\alpha\mathcal{S}_0}{1+\eta_1\mathcal{S}_0} & 0 & \sigma \\ 0 & \dfrac{\alpha\mathcal{S}_0}{1+\eta_1\mathcal{S}_0} - (\xi+\kappa+\Upsilon+\tau+\gamma) & 0 & 0 \\ 0 & (\xi+\gamma) & -(\kappa+\tau) & 0 \\ 0 & \Upsilon & 0 & -(\kappa+\sigma) \end{pmatrix}.$$

The characteristic equation corresponding to the Jacobian $J(E^0)$ is

$$(\lambda+\kappa)(\lambda+\kappa+\tau)(\lambda+\kappa+\sigma)\left[\lambda - \left(\frac{\alpha\mathcal{S}_0}{1+\eta_1\mathcal{S}_0} - (\xi+\kappa+\Upsilon+\tau+\gamma)\right)\right] = 0.$$

Thus, the eigenvalues are

$$\lambda_1 = -\kappa, \quad \lambda_2 = -(\kappa+\tau), \quad \lambda_3 = -(\kappa+\sigma), \quad \lambda_4 = \frac{\alpha\mathcal{S}_0}{1+\eta_1\mathcal{S}_0} - (\xi+\kappa+\Upsilon+\tau+\gamma).$$

Substituting the parameter values given in Table 2 into the Jacobian matrix evaluated at the HFE, the corresponding eigenvalues are obtained as

$$\lambda_1 = -0.08, \qquad \lambda_2 = -0.48, \qquad \lambda_3 = -0.09, \qquad \lambda_4 = 0.1437.$$

Since one eigenvalue is positive, E^0 without vaccination is unstable. This indicates that, in the absence of vaccination, HBV infection can invade the population and persist over time.

4.3. Endemic equilibrium point E^*

The endemic equilibrium point, denoted by $E^* = (\mathcal{S}^*, \mathcal{I}^*, C^*, \mathcal{R}^*)$, represents the persistent existence of HBV infection within the population, where all state variables attain strictly positive values. This equilibrium describes a steady-state situation in which infection transmission, immune response, recovery, and natural removal remain in balance. The endemic equilibrium exists only when $\Re_0 > 1$. For the immune response model without vaccination, we set $\Gamma = 0$. At equilibrium, solving the system yields the following relationships:

$$\mathcal{R}^* = \frac{\Upsilon}{\kappa+\sigma}\mathcal{I}^*, \qquad C^* = \frac{\xi+\gamma}{\kappa+\tau}\mathcal{I}^*, \qquad \mathcal{S}^* = \frac{\Lambda(1+\eta_2\mathcal{I}^*)}{\alpha-\Lambda\eta_1(1+\eta_2\mathcal{I}^*)},$$

where $\Lambda = \xi + \kappa + \Upsilon + \tau + \gamma$. Substituting these expressions into the susceptible equation leads to a quadratic equation for $\mathcal{I}^*$ of the form

$$A(\mathcal{I}^*)^2 + B\mathcal{I}^* + C = 0,$$

where

$$A = \Lambda\eta_1\eta_2\Psi, \quad B = \kappa\Lambda\eta_2 + \Lambda\eta_1 r_{in}\eta_2 + \Lambda\eta_1\Psi - \alpha\Psi, \quad C = \kappa\Lambda - \alpha r_{in} + \Lambda\eta_1 r_{in}, \text{ and } \Psi = \frac{\sigma\Upsilon}{\kappa+\sigma} - \Lambda.$$

Hence, E^* of the system is

$$E^* = \left(\frac{\Lambda(1+\eta_2\mathcal{I}^*)}{\alpha-\Lambda\eta_1(1+\eta_2\mathcal{I}^*)}, \quad \mathcal{I}^*, \quad \frac{\xi+\gamma}{\kappa+\tau}\mathcal{I}^*, \quad \frac{\Upsilon}{\kappa+\sigma}\mathcal{I}^*\right).$$

The Jacobian operator corresponding to system (2.1) at $E^* = (\mathcal{S}^*, \mathcal{I}^*, C^*, \mathcal{R}^*)$ without vaccination ($\Gamma = 0$) is given by

$$J(E^*) = \begin{pmatrix} -\kappa - \dfrac{\alpha\mathcal{I}^*}{(1+\eta_1\mathcal{S}^*)^2(1+\eta_2\mathcal{I}^*)} & -\dfrac{\alpha\mathcal{S}^*}{(1+\eta_1\mathcal{S}^*)(1+\eta_2\mathcal{I}^*)^2} & 0 & \sigma \\ \dfrac{\alpha\mathcal{I}^*}{(1+\eta_1\mathcal{S}^*)^2(1+\eta_2\mathcal{I}^*)} & \dfrac{\alpha\mathcal{S}^*}{(1+\eta_1\mathcal{S}^*)(1+\eta_2\mathcal{I}^*)^2} - \Lambda & 0 & 0 \\ 0 & (\xi+\gamma) & -(\kappa+\tau) & 0 \\ 0 & \Upsilon & 0 & -(\kappa+\sigma) \end{pmatrix},$$

where $\Lambda = \xi + \kappa + \Upsilon + \tau + \gamma$. The computed eigenvalues at E^* without vaccination are

$$\lambda_1 = -0.0842, \qquad \lambda_2 = -0.09187, \qquad \lambda_3 = -0.1117, \qquad \lambda_4 = -0.48.$$

Since all the eigenvalues corresponding to E^* are negative, it is locally asymptotically stable (LAS). This indicates that, in the absence of vaccination, HBV infection persists and approaches a stable endemic state over time.

5. Immune response with vaccination

5.1. Hepatitis-free equilibrium E^0_{vacc}

The HFE of system (2.1) corresponds to the state in which no infection persists in the population, i.e.,

$$\mathcal{I} = 0, \qquad C = 0.$$

Setting the right-hand sides of system (2.1) equal to zero and solving under these conditions, we obtain

$$\begin{aligned} E^0_{\text{vacc}} &= \left(\mathcal{S}^0_{\text{vacc}},\ \mathcal{I}^0_{\text{vacc}},\ C^0_{\text{vacc}},\ \mathcal{R}^0_{\text{vacc}}\right) \\ &= \left(\frac{r_{in}(\kappa+\sigma)}{\kappa(\kappa+\Gamma+\sigma)},\ 0,\ 0,\ \frac{\Gamma r_{in}}{\kappa(\kappa+\Gamma+\sigma)}\right). \end{aligned} \tag{5.1}$$

5.2. Basic reproduction number $\mathfrak{R}_0^{\text{vacc}}$

The basic reproduction number $\mathfrak{R}_0^{\text{vacc}}$ is computed using the next-generation matrix (NGM) method of van den Driessche and Watmough [41]. Evaluating the corresponding matrices at E^0_{vacc}, we obtain

$$\mathfrak{R}_0^{\text{vacc}} = \frac{\alpha r_{in}(\kappa+\sigma)}{(\xi+\kappa+\Upsilon+\tau+\gamma)\left[\kappa(\kappa+\Gamma+\sigma)+\eta_1 r_{in}(\kappa+\sigma)\right]}. \tag{5.2}$$

The Jacobian matrix is

$$J(E^0_{\text{vacc}}) = \begin{pmatrix} -(\kappa+\Gamma) & -\dfrac{\alpha\mathcal{S}^0_{\text{vacc}}}{1+\eta_1\mathcal{S}^0_{\text{vacc}}} & 0 & \sigma \\ 0 & \dfrac{\alpha\mathcal{S}^0_{\text{vacc}}}{1+\eta_1\mathcal{S}^0_{\text{vacc}}} - \Lambda & 0 & 0 \\ 0 & (\xi+\gamma) & -(\kappa+\tau) & 0 \\ \Gamma & \Upsilon & 0 & -(\kappa+\sigma) \end{pmatrix}.$$

Substituting Eq (5.1) into the Jacobian of system (2.1), the computed eigenvalues with vaccination are

$$\lambda_1 = -0.29, \qquad \lambda_2 = -0.48, \qquad \lambda_3 = -0.08, \qquad \lambda_4 = 0.099.$$

Since one of the eigenvalues is positive, the vaccination HFE E^0_{vacc} is unstable. This indicates that the considered vaccination rate is insufficient to eradicate HBV infection. Therefore, a critical vaccination threshold is subsequently determined to identify the vaccination rate required to achieve disease elimination.

5.3. Endemic equilibrium point E^*_{vacc}

The endemic equilibrium point of system (2.1), denoted by $E^*_{\text{vacc}} = (\mathcal{S}^*_{\text{vacc}},\ \mathcal{I}^*_{\text{vacc}},\ C^*_{\text{vacc}},\ \mathcal{R}^*_{\text{vacc}})$, represents the persistent existence of HBV infection within the population, where all state variables attain strictly positive values. This equilibrium describes a steady-state situation in which infection transmission, vaccination, immune response, recovery, and natural removal remain in balance. The

endemic equilibrium exists only when $\Re_0^{\text{vacc}}$. At equilibrium, solving the system yields the following relationships:

$$\mathcal{R}^*_{\text{vacc}} = \frac{\Gamma \mathcal{S}^*_{\text{vacc}} + \Upsilon \mathcal{I}^*_{\text{vacc}}}{\kappa + \sigma}, \qquad C^*_{\text{vacc}} = \frac{\xi + \gamma}{\kappa + \tau}\mathcal{I}^*_{\text{vacc}}, \qquad \mathcal{S}^*_{\text{vacc}} = \frac{\Lambda(1 + \eta_2 \mathcal{I}^*_{\text{vacc}})}{\alpha - \Lambda\eta(1 + \eta_2 \mathcal{I}^*_{\text{vacc}})}.$$

Substituting these expressions into the susceptible equation leads to a quadratic equation for $\mathcal{I}^*_{\text{vacc}}$ of the form

$$A(\mathcal{I}^*_{\text{vacc}})^2 + B\mathcal{I}^*_{\text{vacc}} + C = 0,$$

where

$$A = \Lambda\eta_1\eta_2\Psi, \quad B = \Theta\Lambda\eta_2 + \Lambda\eta_1 r_{in}\eta_2 + \Lambda\eta_1\Psi - \alpha\Psi, \quad C = \Theta\Lambda - \alpha r_{in} + \Lambda\eta_1 r_{in},$$
$$\Psi = \frac{\sigma\Upsilon}{\kappa + \sigma} - \Lambda, \qquad \Theta = (\kappa + \Gamma) - \frac{\sigma\Gamma}{\kappa + \sigma}.$$

The endemic infected population $\mathcal{I}^*_{\text{vacc}}$ is given by the unique positive roots of the quadratic equation, and the root is positive. Hence, E^* of the system is

$$E^*_{\text{vacc}} = \left(\frac{\Lambda(1 + \eta_2 \mathcal{I}^*_{\text{vacc}})}{\alpha - \Lambda\eta_1(1 + \eta_2 \mathcal{I}^*_{\text{vacc}})}, \quad \mathcal{I}^*_{\text{vacc}}, \quad \frac{\xi + \gamma}{\kappa + \tau}\mathcal{I}^*_{\text{vacc}}, \quad \frac{\Gamma \mathcal{S}^*_{\text{vacc}} + \Upsilon \mathcal{I}^*_{\text{vacc}}}{\kappa + \sigma}\right). \tag{5.3}$$

The Jacobian matrix corresponding to system (2.1) at the endemic equilibrium point $E^*_{\text{vacc}} = (\mathcal{S}^*_{\text{vacc}}, \mathcal{I}^*_{\text{vacc}}, C^*_{\text{vacc}}, \mathcal{R}^*_{\text{vacc}})$ with vaccination is given by

$$J(E^*_{\text{vacc}}) = \begin{bmatrix} -(\kappa + \Gamma) - \dfrac{\alpha \mathcal{I}^*_{\text{vacc}}}{(1 + \eta_1 \mathcal{S}^*_{\text{vacc}})^2 (1 + \eta_2 \mathcal{I}^*_{\text{vacc}})} & -\dfrac{\alpha \mathcal{S}^*_{\text{vacc}}}{(1 + \eta_1 \mathcal{S}^*_{\text{vacc}})(1 + \eta_2 \mathcal{I}^*_{\text{vacc}})^2} & 0 & \Gamma \\ \dfrac{\alpha \mathcal{I}^*_{\text{vacc}}}{(1 + \eta_1 \mathcal{S}^*_{\text{vacc}})^2 (1 + \eta_2 \mathcal{I}^*_{\text{vacc}})} & \dfrac{\alpha \mathcal{S}^*_{\text{vacc}}}{(1 + \eta_1 \mathcal{S}^*_{\text{vacc}})(1 + \eta_2 \mathcal{I}^*_{\text{vacc}})^2} - \Lambda & (\xi + \gamma) & \Upsilon \\ 0 & 0 & -(\kappa + \tau) & 0 \\ 0 & \sigma & 0 & -(\kappa + \sigma) \end{bmatrix}. \tag{5.4}$$

The computed eigenvalues of $J(E^*_{\text{vacc}})$ with vaccination are

$$\lambda_1^{\text{vacc}} = -0.4800, \qquad \lambda_2^{\text{vacc}} = -0.2864, \qquad \lambda_{3,4}^{\text{vacc}} = -0.0844 \pm 0.0052\, i.$$

Since $\lambda_1^{\text{vacc}}, \lambda_2^{\text{vacc}} < 0$ and $\text{Re}\,(\lambda_{3,4}^{\text{vacc}}) < 0$, all eigenvalues corresponding to $J(E^*_{\text{vacc}})$ have negative real parts. Therefore, the endemic equilibrium E^*_{vacc} is locally asymptotically stable. This indicates that vaccination reduces the infected and chronic populations while increasing the recovered population. However, partial vaccination alone is not sufficient to completely eradicate HBV infection, since the disease persists at an endemic level. Therefore, in the next section, the critical immune response threshold and subsequently the critical vaccination threshold required for disease eradication are determined.

6. Threshold analysis

In this section, threshold conditions associated with immune response and vaccination are derived to identify the critical levels required to ensure elimination of HBV disease from the population. These threshold quantities provide meaningful epidemiological evidence of immune recovery and vaccination in reducing disease transmission.

6.1. Critical immune response threshold

For the model without vaccination ($\Gamma = 0$), with $\Re_0$ defined in Eq (4.2), the HFE becomes locally asymptotically stable (LAS) when $\Re_0 < 1$. The critical immune response threshold is obtained by imposing $\Re_0 = 1$. Thus,

$$\frac{\alpha r_{in}}{(\kappa + \eta_1 r_{in})(\xi + \kappa + \Upsilon + \tau + \gamma)} = 1, \qquad \xi + \kappa + \Upsilon + \tau + \gamma = \frac{\alpha r_{in}}{\kappa + \eta_1 r_{in}}.$$

Solving for the immune recovery parameter Υ, we obtain the critical immune response threshold

$$\Upsilon^* = \frac{\alpha r_{in}}{\kappa + \eta_1 r_{in}} - \xi - \kappa - \tau - \gamma.$$

Therefore, $\Upsilon > \Upsilon^*$ implies $\Re_0 < 1$, which guarantees disease elimination. Biologically, this indicates that a sufficiently strong immune response can effectively suppress HBV across the population. Using the values reported in Table 2, we obtain

$$\Upsilon^* = 0.2237.$$

Table 2. Parameter values used in numerical simulations.

Parameter	Value	Reference	Parameter	Value	Reference
r_{in}	8	Assumed	ξ	0.1	[19]
Γ	0, 0.2	Assumed	γ	0.05	Assumed
κ	0.08	[22]	Υ	0.08	[22]
$\eta_1,\ \tau$	0.4	[40]	σ	0.01	Assumed
η_2	0.15	Assumed	α	0.35	Fitted

Hence, the critical immune response threshold is $\Upsilon^* = 0.2237$. This result indicates that the immune recovery rate must exceed 0.2237 so as to eliminate HBV infection without the use of vaccination.

6.2. Critical vaccination threshold

Considering the model with vaccination, the reproduction number is given by

$$\Re_0^{\text{vacc}} = \frac{\alpha r_{in}(\kappa + \sigma)}{\left[\kappa(\kappa + \Gamma + \sigma) + \eta_1 r_{in}(\kappa + \sigma)\right](\xi + \kappa + \Upsilon + \tau + \gamma)}.$$

The HFE point becomes locally asymptotically stable (LAS) when $\Re_0^{\text{vacc}} < 1$. The critical vaccination threshold is obtained by setting $\Re_0^{\text{vacc}} = 1$. Hence,

$$\alpha r_{in}(\kappa + \sigma) = \left[\kappa(\kappa + \Gamma + \sigma) + \eta_1 r_{in}(\kappa + \sigma)\right](\xi + \kappa + \Upsilon + \tau + \gamma).$$

Solving for Γ, we obtain

$$\Gamma^* = \frac{\alpha r_{in}(\kappa + \sigma)}{\kappa(\xi + \kappa + \Upsilon + \tau + \gamma)} - \frac{\eta_1 r_{in}(\kappa + \sigma)}{\kappa} - \kappa - \sigma.$$

Substituting the parameter values in Table 2, we obtain $\Gamma^* = 0.7466$. Hence, the critical vaccination threshold is $\Gamma^* = 0.7466$. Therefore, $\Gamma > \Gamma^*$ implies $\Re_0^{\text{vacc}} < 1$, which guarantees eradication of HBV infection from the population. This analysis demonstrates that vaccination significantly enhances disease control and reduces the persistence of HBV transmission. Table 3 presents the stability of the hepatitis-free and endemic equilibria for different vaccination rates. For $\Gamma = 0.2 < \Gamma^* = 0.7466$, the HFE is unstable, while the endemic equilibrium is locally asymptotically stable. This indicates that the considered vaccination rate is insufficient to eliminate HBV infection.

Table 3. Stability of hepatitis-free and endemic equilibria for different vaccination rates.

Vaccination rate	HFE	Endemic equilibrium
$\Gamma = 0.2 < \Gamma^* = 0.7466$	Unstable	Locally asymptotically stable
$\Gamma > \Gamma^* = 0.7466$	Locally asymptotically stable	No biologically feasible endemic equilibrium

7. Numerical computation of equilibrium points

Using the values in Table 2, the equilibrium points of the HBV liver disease model are computed for both cases: Without vaccination and with vaccination. The initial conditions for the numerical simulations are taken as $\mathcal{S}(0) = 100$, $\mathcal{I}(0) = 6$, $\mathcal{C}(0) = 2$, *and* $\mathcal{R}(0) = 5$. The nonlinear system of differential equations is solved numerically using the classical fourth-order Runge–Kutta (RK4) method in MATLAB R2017b. The simulations are performed to analyze the dynamics of the model and to verify the analytical results obtained in the previous sections. Table 4 presents a comparative analysis of the endemic equilibrium E^* in the presence and absence of vaccination.

Table 4. Comparison of endemic equilibrium values without and with vaccination.

Population	Without vaccination	With vaccination
Susceptible ($\mathcal{S}^*$)	88.4024	28.6161
Infected ($\mathcal{I}^*$)	1.3233	0.8892
Chronic ($\mathcal{C}^*$)	0.4135	0.2779
Recovered ($\mathcal{R}^*$)	1.1763	64.3817

Case 1: Without vaccination ($\Gamma = 0$). In the absence of vaccination, the HFE is given by

$$E^0 = \left(\frac{r_{in}}{\kappa}, 0, 0, 0\right).$$

Using the parameter values listed in Table 2, we obtain

$$S^0 = 100.$$

Hence, the HFE is

$$E^0 = (100, 0, 0, 0).$$

For the given parameter values, $\Lambda = 0.71$ and $\Psi = -0.7011$. The endemic infected population is obtained from

$$I^* = \frac{-B + \sqrt{B^2 - 4AC}}{2A},$$

which yields

$$\mathcal{I}^* = 1.3233.$$

The corresponding equilibrium values are

$$\mathcal{S}^* = 88.4024, \qquad C^* = 0.4135, \qquad \mathcal{R}^* = 1.1763.$$

Therefore, the endemic equilibrium without vaccination is given by

$$E^* = (88.4024,\ 1.3233,\ 0.4135,\ 1.1763).$$

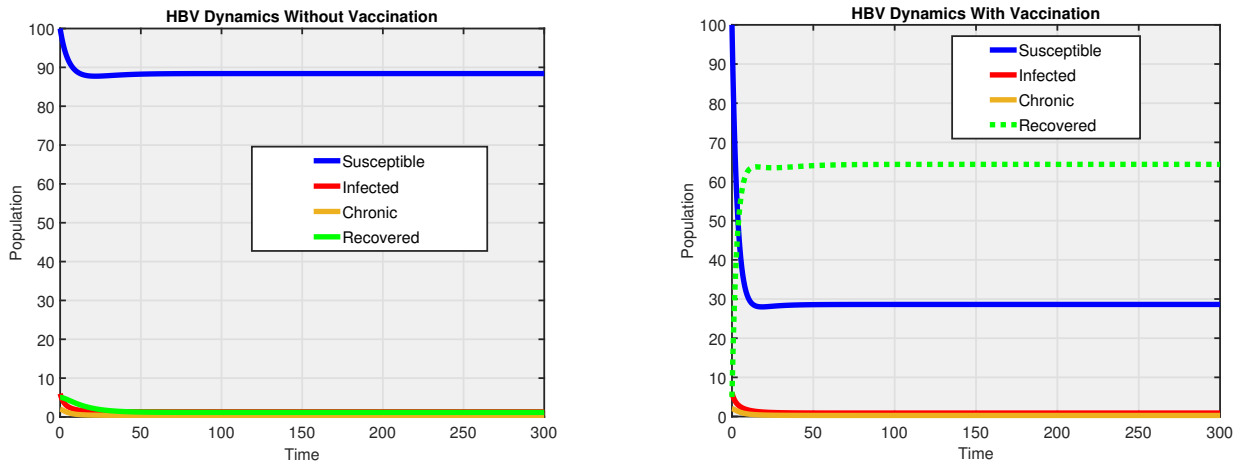
Case 2: With vaccination ($\Gamma = 0.2$). In the presence of vaccination, the HFE is obtained using the parameter values listed in Table 2. Thus, the HFE with vaccination is given by

$$E^0_{\text{vacc}} = (31.0345,\ 0,\ 0,\ 68.9655).$$

The endemic equilibrium with vaccination is denoted by $E^*_{\text{vacc}} = (\mathcal{S}^*_{\text{vacc}}, \mathcal{I}^*_{\text{vacc}}, C^*_{\text{vacc}}, \mathcal{R}^*_{\text{vacc}})$. For the given parameter values, the endemic equilibrium is

$$E^*_{\text{vacc}} = (28.6161,\ 0.8892,\ 0.2779,\ 64.3817).$$

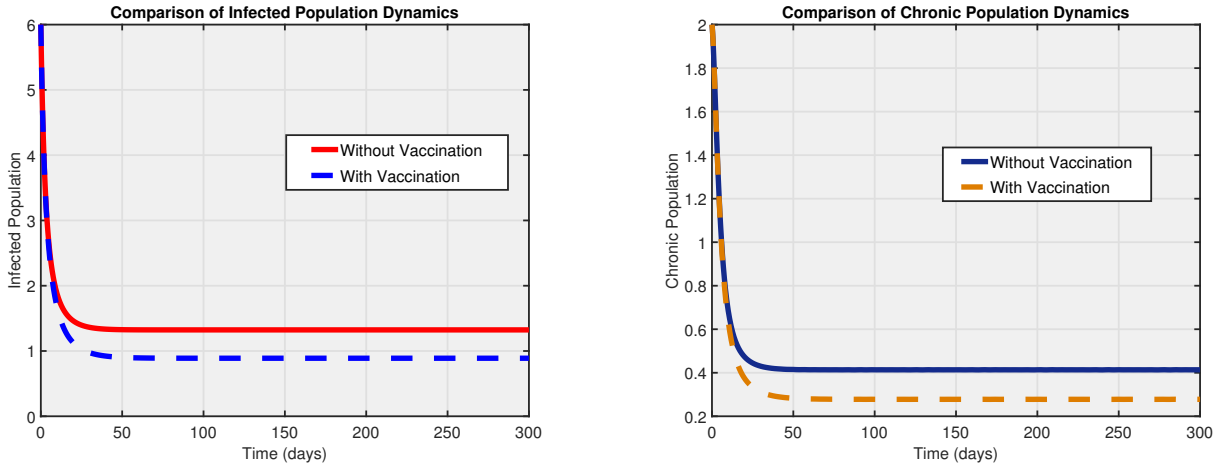
Figure 2 illustrates the comparison of HBV dynamics without and with vaccination. In Figure 2(a), corresponding to the case without vaccination, the infected and chronic populations persist at positive levels, indicating the existence of a stable endemic equilibrium and continuous HBV transmission within the population. The susceptible population remains high, while the recovered population stays comparatively low. In Figure 2(b), vaccination is introduced with $\Gamma = 0.2$. It is observed that the infected and chronic populations decrease significantly, whereas the recovered population increases considerably due to vaccination-induced immunity. Although the disease is not completely eradicated since the reproduction number remains greater than unity, vaccination effectively suppresses HBV transmission and reduces disease persistence in the population.



(a) **(b)**

Figure 2. Comparison of HBV dynamics without and with vaccination. The results demonstrate that vaccination suppresses HBV transmission and reduces disease persistence within the population.

Figure 3 presents the comparison of infected and chronic population dynamics with and without vaccination. Figure 3(a) illustrates that the infected population decreases more rapidly in the presence of vaccination compared to the case without vaccination. Although the infection persists at a low endemic level, vaccination significantly suppresses HBV transmission within the population. Figure 3(b) demonstrates the effect of vaccination on the chronic population. It is observed that the chronic HBV population is substantially reduced under vaccination, indicating that vaccination not only controls disease transmission but also lowers the long-term chronic infection burden. Overall, the results confirm the effectiveness of vaccination in reducing HBV persistence and disease severity.



(a) **(b)**

Figure 3. Comparison of infected and chronic population dynamics with and without vaccination. The vaccination significantly reduces HBV transmission and chronic infection persistence within the population.

Figure 4 illustrates the critical immune response threshold of the HBV model. The reproduction number decreases as the immune response rate increases, indicating the important role of immune recovery in controlling HBV transmission. The horizontal dashed line represents the threshold level at $\Re_0 = 1$, while the vertical dashed line corresponds to the critical immune response threshold $\Upsilon^* = 0.2237$. It is observed that when $\Upsilon < \Upsilon^*$, $\Re_0$ remains greater than unity, and the infection persists in the population. However, for $\Upsilon > \Upsilon^*$, $\Re_0$ becomes less than unity, leading to the elimination of HBV infection.

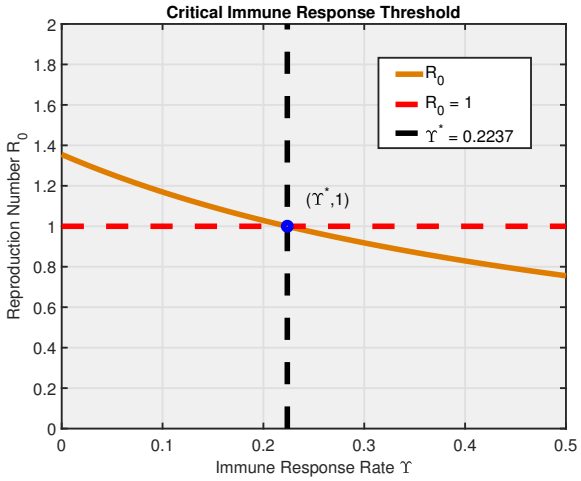


Figure 4. Critical immune response threshold of the HBV model. The threshold value $\Upsilon^* = 0.2237$ represents the critical immune response level required to reduce $\Re_0$ below unity and achieve HBV elimination.

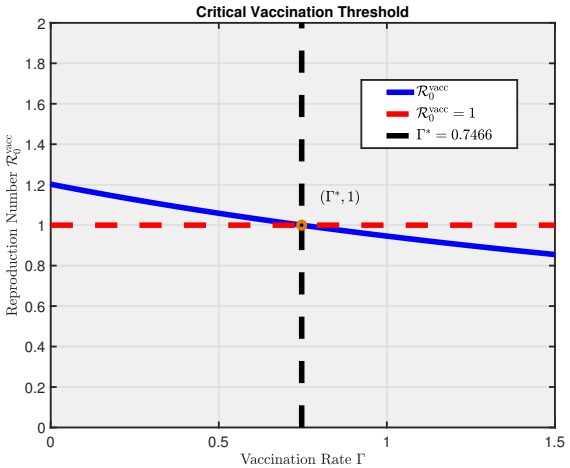


Figure 5. Critical vaccination threshold of the HBV model. The threshold value $\Gamma^* = 0.7466$ represents the critical vaccination level required to reduce $\Re_0^{vacc}$ below unity and achieve HBV eradication.

Figure 5 illustrates the critical vaccination threshold of the HBV model. The reproduction number decreases gradually as the vaccination rate increases, demonstrating the effectiveness of vaccination

in suppressing HBV transmission. The horizontal dashed line represents the threshold level $\Re_0^{vacc} = 1$, while the vertical dashed line indicates the critical vaccination threshold $\Gamma^* = 0.7466$. It is observed that when $\Gamma < \Gamma^*$, $\Re_0$ remains greater than unity, and the disease persists within the population. However, for $\Gamma > \Gamma^*$, $\Re_0$ becomes less than unity, leading to the eradication of HBV infection.

Figure 6 illustrates the contour plot of the reproduction number $\Re_0$ with respect to the vaccination rate Γ and immune response rate Υ. The red threshold curve represents $\Re_0 = 1$, which separates the disease persistence region from the disease eradication region. It is observed that lower vaccination and immune response levels correspond to $\Re_0 > 1$, indicating persistence of HBV infection. As both the vaccination rate and immune response increase, the reproduction number decreases below unity, leading to the elimination of HBV transmission within the population.

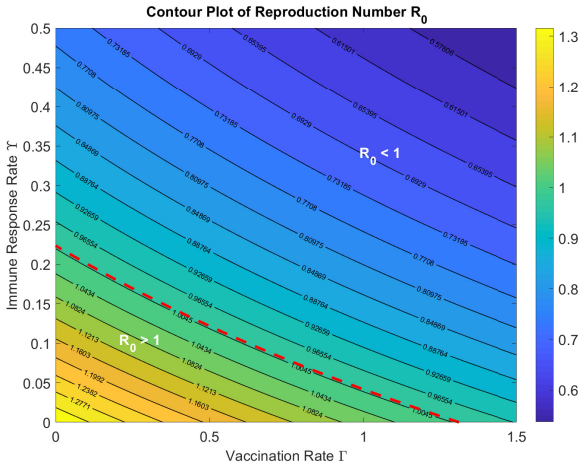


Figure 6. Contour plot of $\Re_0$ versus vaccination rate Γ and immune response rate Υ. The red curve ($\Re_0 = 1$) separates disease persistence from eradication.

8. Conclusions

In this work, a mathematical model was developed to investigate HBV-related liver disease by incorporating immune response and vaccination within a unified framework. The mathematical analysis established the positivity and boundedness of the model solutions and identified the hepatitis-free and endemic equilibria for both vaccination-free and vaccination scenarios. The basic reproduction numbers were derived using the next-generation matrix method, and the local stability of the equilibria was investigated through Jacobian eigenvalue analysis. The analysis further yielded critical threshold values for the immune response and vaccination rates, given by $\Upsilon^* = 0.2237$ and $\Gamma^* = 0.7466$, respectively. The critical immune response threshold indicates that an immune response rate exceeding $\Upsilon^* = 0.2237$ can reduce HBV transmission below the epidemic threshold. Similarly, the critical vaccination threshold $\Gamma^* = 0.7466$ indicates that the vaccination rate must exceed this value to reduce HBV transmission below the epidemic threshold and achieve disease elimination in the model. The numerical simulations further demonstrated that strengthening immune response and increasing vaccination can reduce the infected and chronic populations. However, the model has some limitations, including the use of assumed and fitted parameter values, a constant vaccination rate, and the absence of age-dependent differences and variations in vaccination coverage. Future studies may

incorporate age structure, time-dependent vaccination, vaccine efficacy, and real epidemiological data. Furthermore, optimal intervention strategies combining vaccination and immune response could be investigated to identify more effective approaches for HBV control and elimination.

Use of AI tools declaration

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

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Authors contribution

T. Megala: Conceptualization, model formulation, mathematical analysis, numerical simulations, visualization, and writing—original draft. T. Nandha Gopal: Supervision, methodology, and critical revision of the manuscript. Mehmet Yavuz: Mathematical analysis, validation, and interpretation of results. M. Sivabalan: Numerical validation, visualization, and manuscript revision. M. Siva Pradeep: Validation, literature review, and manuscript editing. All authors have read and approved the final version of the manuscript.

Conflict of interest

The authors declare there is no conflict of interest.

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