J. Math. Computer Sci., 38 (2025), 371–378

Online: ISSN 2008-949X

Journal of Mathematics and Computer Science

Journal Homepage: www.isr-publications.com/jmcs

Study the modified mathematical model of hepatitis B virus infection with immune response

Entissar M. Ahmed*, Noufe H. Aljahdaly

Department of Mathematics, Faculty of Sciences and Arts, King Abdulaziz University, Rabigh, Saudi Arabia.

Abstract

Hepatitis B is a viral infection caused by the hepatitis B virus (HBV), which primarily targets liver cells. Numerous studies in the literature have employed mathematical modeling to investigate the dynamics of HBV infection. This article develops a mathematical model that captures that captures the effects of the immune system response on uninfected cells as well as free viruses. The analysis of the model focuses on key mathematical properties, including positivity, boundedness, equilibrium points, the basic reproduction number (R_0), and local stability. Numerical simulations and sensitivity analyses are performed to further understand the model's behavior under various parameter settings. The results demonstrate that while the parameter representing the immune response's effect on viral clearance does not alter (R_0), it has a significant impact on improving numerical outcomes. Sensitivity analysis reveals that an HBV outbreak can become widespread if certain parameters change. Specifically, a reduction in the rate of viral production by infected cells, the natural death rate of uninfected cells, and the natural death rate of free viruses increases the risk of the infection becoming a pandemic. Conversely, an increase in the growth rate of uninfected cells, the natural death rate of free viruses, and the probability of the virus successfully infecting uninfected cells and producing new infected cells, also contributes to the spread of the infection. These findings highlight the factors that influence the dynamics of HBV transmission.

Keywords: Mathematical model, theoretical analysis, numerical solutions, Hepatitis B.

2020 MSC: 92C50, 34D20, 92D30, 37N25, 65L07.

1. Introduction

Hepatitis B (HB) infection is one of the most serious viral infections globally, affecting approximately two billion individuals, particularly those of African, Asian, and Pacific Island descent. The Hepatitis B virus (HBV) is transmitted through bodily fluids and primarily causes inflammation of the liver. Modes of transmission include childbirth, sharing needles, toothbrushes, razors, syringes, or any contaminated sharp instrument, contact with open wounds, and sexual contact. While HBV is preventable through vaccination, it is not curable. HBV infection can present as either an acute or chronic condition. The acute phase represents the initial stage of infection when the immune system recognizes and mounts a response against the virus. Symptoms of the acute phase, which may include fever, nausea, and vomiting, are typically due to the body's immune response. Most individuals are able to clear the virus during this

*Corresponding author

Email addresses: entissar730@gmail.com (Entissar M. Ahmed), Nhaljahdaly@kau.edu.sa (Noufe H. Aljahdaly)

doi: 10.22436/jmcs.038.03.06

Received: 2024-07-27 *Revised:* 2024-10-08 *Accepted:* 2024-12-02

phase, which only occurs once. However, if the immune response is insufficient to eliminate the virus, the infection progresses to a chronic phase. Chronic hepatitis B is associated with severe long-term liver damage. Potential complications include co-infection with hepatitis D, cirrhosis, chronic liver failure, and hepatocellular carcinoma (liver cancer) [2, 6, 7].

A mathematical model is a powerful tool for describing various problems across multiple fields, including science, environmental studies, industry, and social sciences. Hepatitis B (HB) infection has been extensively studied through mathematical modeling in the literature. Several researchers [1, 4, 9, 12] have examined the basic model, which consists of three components: uninfected cells (s), infected cells (I), and free virus particles (v). The basic model is represented by the following system of differential equations

$$\frac{ds}{dt} = \tau - ds - \beta sv, \quad \frac{dI}{dt} = \beta sv - \delta I, \quad \frac{dv}{dt} = kI - uv,$$

where τ represents the growth rate of uninfected cells (s), and d, δ, and u are the natural death rates of uninfected cells (s), infected cells (I), and virus particles (v), respectively. β denotes the rate at which the virus infects uninfected cells, converting them into infected cells (I), while k represents the rate at which infected cells produce new virus particles. The delay in viral dynamics was incorporated into the basic model in [10]. Both acute HBV infection [8] and chronic HBV infection [3] have been studied through similar mathematical frameworks.The effects of vaccination strategies have been investigated in [14], while optimal treatment approaches for HBV infection were explored in [5]. Additionally, [13] considered the combined effects of vaccination, treatment, migration, and screening. The co-infection of HBV and COVID-19 has been analyzed in [11]. The dimensionless mathematical model for chronic HBV infection, including the immune response [3], is described by the following system:

$$\frac{ds}{dt} = \tau - ds - \beta sv, \quad \frac{dI}{dt} = \beta sv - \delta I - pIz, \quad \frac{dv}{dt} = kI - uv, \quad \frac{dz}{dt} = cIz - \mu z, \tag{1.1}$$

where p is the rate of I death by immune system cell. The novelty in this article is to modify the system (1.1) to account for the impact of the immune response not only on infected cells but also on uninfected cells (s) and the virus particles (v). The modified system of equations is as follows:

$$\frac{ds}{dt} = \tau - ds - \beta sv, \tag{1.2}$$

$$\frac{dI}{dt} = \beta sv - \delta I - p_1 Iz, \tag{1.3}$$

$$\frac{dv}{dt} = kI - uv - \beta sv - p_2 vz, \tag{1.4}$$

$$\frac{dz}{dt} = cIz - \mu z, \tag{1.5}$$

where p_1 and p_2 are the rate of I death and v death respectively by immune system cell. The structure of this article is as follows. Section 2 presents the theoretical analysis of the modified system, which includes positivity and boundedness, equilibrium points, and local stability. Section 3 discusses the results, and Section 4 provides the conclusion.

2. Theoretical analysis

This section is a study the aforementioned model theoretically to prove the validation of the model.

2.1. Positivity

Theorem 2.1. *All solutions with positive initial conditions remain non-negative in the region* R^4.

Proof. We note in Eq. (1.2) that $\frac{ds}{s} \geqslant Q_1(s, I, \nu, z)$, where $Q_1(s, I, \nu, z) = -(d + \beta\nu)$. Thus,

$$\frac{ds}{s} \geqslant -(d + \beta\nu). \tag{2.1}$$

By integrating Eq. (2.1) over the interval $[0, 1]$ and assuming $s(0) \leqslant 0$, we obtain

$$s(t) \geqslant s(0) \exp \int_0^t Q_1(s, I, \nu, z) dw \geqslant 0,$$

which implies that $s(t) \geqslant 0$ for all t, provided that $I(0) \geqslant 0$. Similarly, by Eq. (1.3), we have

$$\frac{dI}{dt} \geqslant -(\delta + p_1 z)I, \quad \frac{dI}{I} \geqslant -(\delta + p_1 z)dt, \quad \frac{dI}{I} \geqslant Q_2(I, z), \tag{2.2}$$

where $Q_2(I, z) = -(\delta + p_1 z)$. After integrating Eq. (2.2) over the interval $[0, t]$, we obtain $\ln I(t) = \int_0^t Q_2(I, z) dw$, and thus,

$$I(t) \geqslant I(0)) \exp \int_0^t Q_2(I, z) dw \geqslant 0.$$

Therefore, $I(t) \geqslant 0$, $\forall t$. For (1.4), we have $\frac{d\nu}{\nu} \geqslant Q_3(s, z)$, where $Q_3 = -(p_2 z + u)$. Hence, $\nu(t) \geqslant \nu(0) \exp \int_0^t Q_3(s, z) dw \geqslant 0$ provided that $\nu(0) \geqslant 0$. Therefore, $\nu(t) \geqslant 0$, $\forall t$. Finally, for Eq. (1.5) we have $\frac{dz}{z} \geqslant Q_4(I, z)$, where $Q_4(I, z) = -\mu$. Hence, $z(t) \geqslant z(0) \exp \int_0^t Q_4(I, z) dw$, provided that $z(0) \geqslant 0$. Therefore, $z(t) \geqslant 0$, $\forall t$. Thus, the solution $(s(t), I(t), \nu(t), z(t))$ remains non negative for all initial conditions. □

2.2. Boundedness

Theorem 2.2. *All solutions subject to the initial conditions are bounded in the region* Γ*:*

$$\Gamma \left[(s, I, \nu, z) \in R^4, \ s \leqslant \tau, \ s + I \leqslant \tau\sigma, \ \nu \leqslant \frac{k\tau}{\sigma u}, \ \frac{s}{p_1} + \frac{I}{p_1} + \frac{z}{C} \leqslant \frac{\tau}{p_1 \sigma} \right].$$

Proof. In Eq. (1.2), we note that $\frac{ds}{dt} \geqslant \tau$ and $\tau \geqslant 0$, thus $\lim_{t\to\infty} \sup S(t) \leqslant \tau$. Rewriting Eq. (1.3), we have

$$\frac{ds}{dt} + \frac{dI}{dt} = \tau - ds - \beta s\nu - \delta I - p_1 Iz \leqslant \tau - ds - \delta I,$$

which leads to

$$\frac{d}{dt}(s + I) \leqslant \tau - \sigma(s + I),$$

where $\sigma = \min(d, \delta)$. Hence,

$$\lim_{t\to\infty} \sup(s(t) + I(t)) \leqslant \frac{\tau}{\sigma}.$$

Next, Eq. (1.4) can be rewritten as

$$\frac{d\nu}{dt} = kI - u\nu - \beta S\nu - p_2 \nu z \leqslant kI - u\nu.$$

Substituting $I \leqslant \frac{\tau}{\sigma}$, we get $\frac{d\nu}{dt} \leqslant k\frac{\tau}{\sigma} - u\nu \leqslant k\frac{\tau}{\sigma} - u\nu$, which implies

$$\lim_{t\to\infty} \sup \nu(t) \leqslant \frac{k\tau}{\sigma u}.$$

Now, we have:

$$\frac{dW}{dt} = \frac{1}{p_1}\frac{ds}{dt} + \frac{1}{p_1}\frac{dI}{dt} + \frac{1}{c}\frac{dz}{dt},$$

where

$$\frac{1}{p_1}\frac{ds}{dt} = \frac{\tau}{p_1} - \frac{ds}{p_1} - \frac{1}{p_1}\beta s\nu, \quad \frac{1}{p_1}\frac{dI}{dt} = \frac{1}{p_1}\beta SV - \frac{1}{p_1}\delta I - \frac{p_1}{p_1}Iz, \quad \frac{1}{p_1}\frac{dz}{dt} = \frac{c}{c}Iz - \frac{\mu}{c}z.$$

Therefore,

$$\frac{dW}{dt} = \frac{d}{dt}(\frac{s}{p_1} + \frac{I}{p_1} + \frac{z}{p_1}) \leqslant \frac{\tau}{p_1} - \frac{ds}{p_1} - \frac{\delta}{p_1}I - \frac{\mu}{c}z \leqslant \frac{\tau}{p_1} - \sigma(\frac{s}{p_1} + \frac{1}{p_1} + \frac{z}{c}),$$

where $\sigma = \min(d, s, \mu)$. Hence,

$$\lim_{t\to\infty} \sup W(t) \leqslant \frac{\tau}{p_1\sigma}.$$

Therefore, all solutions of the studied mathematical model are bounded in the region Γ, where

$$\Gamma\left[(s, I, \nu, z) \in R^4,\ s \leqslant \tau,\ s + I \leqslant \frac{\tau}{\sigma},\ \nu \leqslant \frac{k\tau}{\sigma u}, \frac{s}{p_1} + \frac{I}{p_1} + \frac{z}{c} \leqslant \frac{\tau}{p_1\sigma}\right].$$

□

2.3. Equilibrium points

The equilibrium points of our system of equations represent stable solutions obtained by setting the rates of change in the model to zero. These four equilibrium points are denoted as $E_i = (s_i, I_i, \nu_i, z_i)$ for $i = 1, 2, 3$,

$$E_1 = (\frac{\tau}{d}, 0, 0, 0), \quad E_2 = (\frac{us}{k\beta - \beta\delta}, \frac{-du}{k\beta - \beta\delta} + \frac{\tau}{\delta}, \frac{-d}{\beta} + \frac{(k-\delta)\tau}{u\delta}, 0), \quad E_3 = (k_3, I_3, \nu_3, z_3).$$

The point E_3 satisfies the following equations:

$$s_3 = \frac{\tau}{(d + \beta\nu u)}, \quad I_4 = \frac{\beta s\nu_3}{(\delta + \beta z_3)}, \quad \nu_4 = \frac{kI_3}{(u + \beta s_3 + p_2 z_4)}, \quad cI - \mu = 0.$$

2.4. Reproduction number

In this paper, we define the basic reproduction number, denoted as R_0 as the average number of secondary infection cases generated by a single infected individual in a completely susceptible population. Let $P = (I, s, \nu, z)$ the studied model can be rewritten as $P' = f(P) - V(P)$,

$$f(P) = \begin{pmatrix} S\nu\beta \\ 0 \\ 0 \\ 0 \end{pmatrix}, \quad V(P) = \begin{pmatrix} \dot{I} + p_1 Iz\nu \\ -\tau + ds + \beta s\nu \\ -kI + ku + \beta s\nu + p_2\nu z \\ -cIz + \mu z \end{pmatrix}.$$

Now, evaluating the Jacobian of f and V at E_1, we have

$$D(f)(E_1) = \begin{pmatrix} 0 & 0 & \frac{\beta\tau}{d} & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}.$$

Additionally, we have

$$D(V)(E_1) = \begin{pmatrix} \delta & 0 & \frac{\beta\tau}{d} & 0 \\ 0 & d & \frac{\beta\tau}{d} & 0 \\ -K & 0 & u + \frac{\beta\tau}{d} & 0 \\ 0 & 0 & 0 & \mu \end{pmatrix}, \quad (D(V)(E_1))^{-1} = \begin{pmatrix} \frac{1}{\delta} & 0 & \frac{\beta\tau}{d} & 0 \\ \frac{-K\beta\tau}{d^2u\delta + d\beta\tau\delta} & \frac{1}{d} & \frac{-\beta\tau}{d^2u + d\beta\ tau} & 0 \\ \frac{d}{du\delta + \beta\tau\delta} & 0 & \frac{d}{du + \beta\tau} & 0 \\ 0 & 0 & 0 & \frac{1}{\mu} \end{pmatrix}.$$

This leads to the generation matrix:

$$D(f)(E_1).(D(V)(E_1))^{-1} = \begin{pmatrix} \frac{K\beta\tau}{du\delta + \beta\tau\delta} & 0 & \frac{\beta\tau}{du + \beta\ tau} & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}.$$

Then the basic reproduction number R_0 is given by finding the spectrum of $(D(f)(E_1).(D(V)(E_1))^{-1})$ (the largest eigenvalue of the matrix $(D(f)(E_1).(D(V)(E_1))^{-1})$) as follows:

$$R_0 = \rho[D(f)(E_1).(D(V)(E_1))^{-1}] = \frac{K\beta\tau}{du\delta + \beta\tau\delta}.$$

The infection becomes pandemic if $R_0 > 1$. In next theorems, we aim to study the local stability of the equilibrium points.

Theorem 2.3. *The equilibrium point* E_1 *is locally asymptotically stable if* $R_0 \leqslant 0$.

Proof. By evaluating the Jacobian matrix of the studied mathematical model at E_1, we obtain

$$\begin{pmatrix} -d & 0 & \frac{-\beta\tau}{d} & 0 \\ 0 & -\delta & \frac{\beta\tau}{d} & 0 \\ 0 & K & \frac{-du + \beta\tau}{d} & 0 \\ 0 & 0 & 0 & -\mu \end{pmatrix}.$$

By solving the characteristic polynomial $|J(E_1 - \lambda I)| = 0$, we find that the eigenvalues are given by $\lambda_1 = -d$, $\lambda = -\mu$, and $\lambda_{3,4}$ satisfy the quadratic equation

$$\lambda^2 + a_1\lambda + a_2 = 0,$$

where

$$a_1 = \delta + \ mu + \frac{\beta\tau}{d}, \quad a_2 = u\delta + \frac{\beta\tau}{d}(\delta - k).$$

It is evident that λ_1 and λ_2 are negative. Using the Routh-Hurwitz criteria, the eigenvalues λ_3 and λ_4 will also be negative if $a_1 > 0$ and $a_2 > 0$. Clearly $a_1 > 0$, when $R_0 < 0$. □

Theorem 2.4. *The equilibrium point* E_2 *is locally asymptotically stable if* $k \geqslant \delta$, $R_0 \leqslant 1$, *and* $\tau \geqslant \frac{du\delta}{\beta(k-\delta)} + \frac{\mu s}{c}$.

Proof. The Jacobian matrix of the studied system at E_2 is given by:

$$J(f(E_2)) = \begin{pmatrix} \frac{\beta(-K+\delta)\tau}{u\delta} & 0 & \frac{u\delta}{K-\delta} \\ \frac{-d+(K-\delta)\tau}{u\delta} & -\delta & \frac{u\delta}{K-\delta} \\ \frac{d+(-K+\delta)\tau}{u\delta} & K & \frac{Ku}{-K+\delta} \end{pmatrix}.$$

By solving the equation $|J(E_2 - \lambda I)| = 0$, we obtain $\lambda_1 = \frac{ku}{-k+\delta}$, while the other eigenvalues $\lambda_2, \lambda_3, \lambda_4$ satisfy the cubic equation $\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0$, where,

$$a_1 = \frac{ku}{K-u} + \delta + \frac{\beta(K-\delta)\tau}{u\delta}, \quad a_2 = \frac{du\delta}{K-\delta} + \frac{\beta(K-\delta)(u+\delta)\tau}{u\delta}, \quad a_3 = -du\delta + \beta(K-\delta)\tau.$$

It is clear that $a_1 > 0$ and $a_2 > 0$ if $k > \delta$. To demonstrate that the eigenvalues $\lambda_2, \lambda_3, \lambda_4$ are negative, we must show that $a_1a_2 > a_3$ using Routh-Hurwize criteria, where

$$a_1a_2 - a_3 = du\delta - \beta(K-\delta)\tau + (\frac{ku}{k-\delta} + \delta + \frac{\beta(k-\delta)\tau}{u\delta})(\frac{du\delta}{k-\delta} + \frac{\beta(k-\delta)(u+\delta)\tau}{u\delta}).$$

We conclude that $a_1a_2 - a_3$ is positive if $k > \delta$, $R_0 < 0$, and $\tau > \frac{du\delta}{\beta(k-\delta)} + \frac{\mu\delta}{c}$. □

Theorem 2.5. *The equilibrium point* E_3 *is locally asymptotically stable if* $\delta > k$.

Proof. By calculating the Jacobian matrix of our mathematical model at E_3 and solving the characteristic $|J(E_3 - \lambda I)| = 0$, we derive the equation $\lambda^4 + a_3\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0$, where

$$\begin{aligned}
a_0 &= cdp_2s_3v_3z_3\beta + v_3\beta\mu p_1z_3 + v_3\beta\mu p_1p_2z_3^2 + d\mu p_1z_3u + d\mu p_1z_3^2p_2 + d\mu p_1z_3s_3\beta,\\
a_1 &= p_1uv_3z_3\beta + v_3\beta p_1p_2z_3^2 + uv_3\beta\delta + p_2v_3z_3\beta\delta + cp_2s_3v_3z_3\beta + p_1uz_3\mu + p_1p_2z_3^2\mu + p_1s_3z_3\beta\mu\\
&\quad + p_1v_3z_3\beta\mu - dks_3\beta + du\delta + dp_2z_3\delta + ds_3\beta\delta + dp_1z_3u + dp_1z_3^2p_2 + dp_1z_3s_3p_2 + dp_1z_3s_3\beta + dp_1z_3\mu,\\
a_2 &= p_1uz_3 + p_1p_2z_3^2 - ks_3\beta + uv_3\beta + p_1s_3z_3\beta + p_1v_3z_3\beta + p_2v_3z_3\beta + u\delta\\
&\quad + p_2z_3\delta + s_3\beta\delta + v_3\beta\delta + p_1z_3\mu + v_3\beta\mu + d\mu + dp_1z_3 + dp_1z_3 + dp_2z_3 + ds_3\beta + d\delta,\\
a_3 &= d + u + p_1z_3 + p_2z_3 + s_3\beta + v_3\beta.
\end{aligned}$$

Clearly $a_0 > 0$, ($a_1 > 0$, and $a_2 > 0$ if $\delta > k$) and $a_3 > 0$. Applying Descartes' rule of signs, we observe that there are zero sign changes for positive zeros and four sign changes for negative zeros in the equation. Consequently, all roots of the characteristic equation possess a negative real part, indicating that all eigenvalues of the Jacobian matrix exhibit negative real parts, thus demonstrating the local asymptotic stability of the positive equilibrium point E_3. □

3. Discussion of the results

In this section of the article, we analyze the studied system of equations using the parameter values provided in Table 1. Figure 1 illustrates the system's behavior, showing that the population of uninfected cells decreases as the values of infected cells and viruses increase. The immune response becomes more pronounced when the levels of viruses and infected cells are high. The introduction of the new term p_2 does not affect the basic reproduction number R_0, which is given by

$$R_0 = \frac{k\beta\tau}{du\delta + \beta\tau\delta}.$$

In reference [3], the reproduction number is expressed as $R_0 = \frac{k\beta\tau}{du\delta}$, with the difference arising from modifications made to the equation governing the free virus dynamics. Moreover, the sensitivity analysis presented in Figure 3 indicates that the parameter k positively influences R_0 more than the other parameters, while δ has a negative impact on the value of R_0 compared to the other parameters.

Table 1: The value of parameters.

τ	d	β	δ	p_1	k	u	p_2	c	μ
6.9	0.04	0.8	0.2	0.3	0.01	0.24	0.1	0.01	0.2

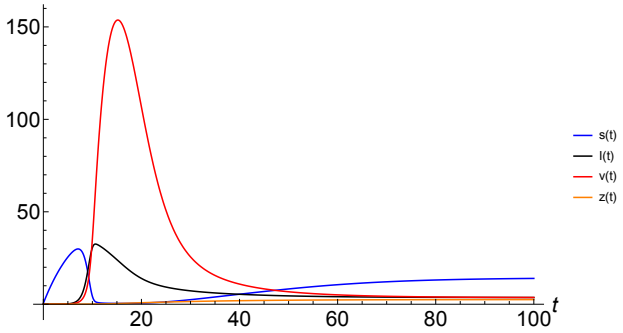

Figure 1: Numerical solution of the model (1.5). The numerical solution of the model illustrates that as the viral load increases, the number of infected cells correspondingly rises, while the population of uninfected cells declines. Over time, the immune response becomes activated, resulting in the generation of immune cells (z), which target both the virus (v) and the infected cells (I).

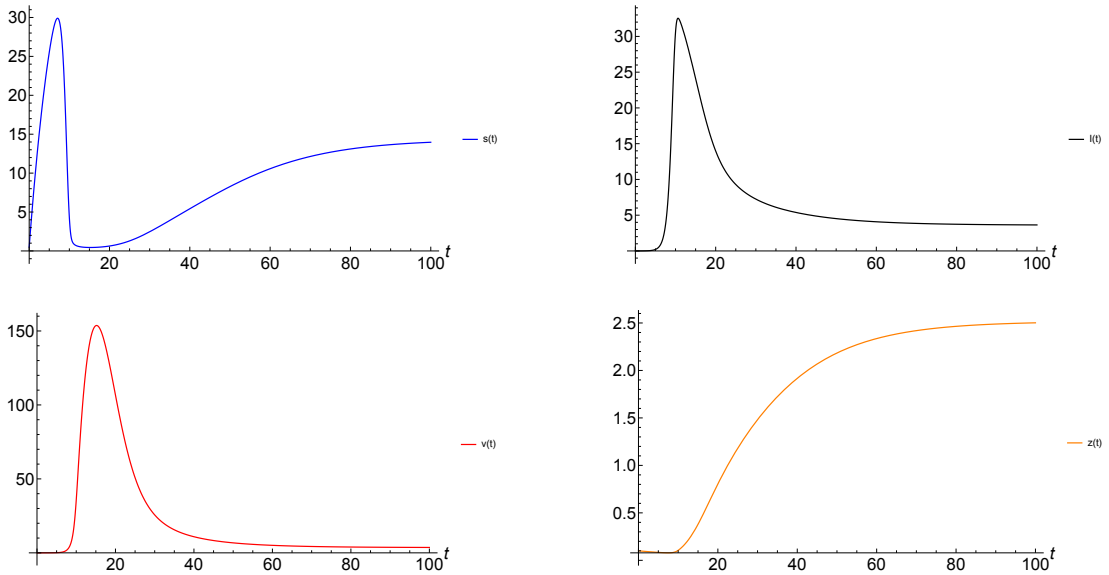

Figure 2: Numerical solutions for each component in the studied model (1.5).

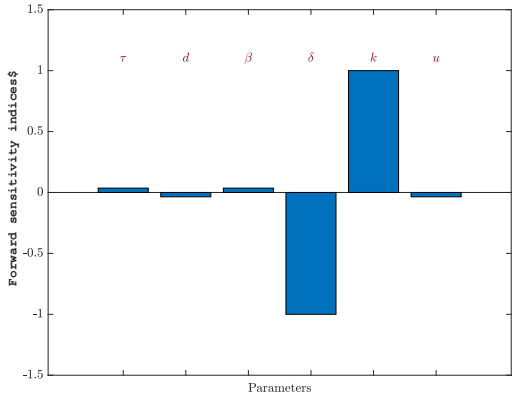

Figure 3: Sensitivity analysis.

4. Conclusion

In this article, we modified the model presented in reference [3] by incorporating the effects of the immune response into the virus equation. This modification allows for a more comprehensive understanding of the dynamics of viral infections, particularly in the context of hepatitis B. Our analysis revealed that the basic reproduction number R_0 increases primarily due to the rate of virus production by infected cells, highlighting the critical role that viral replication plays in disease transmission. Conversely, R_0 is negatively influenced by the natural death rate of the virus, indicating that higher mortality rates among viral particles can effectively reduce the potential for widespread infection.

The findings underscore the importance of the immune response in shaping the dynamics of HBV infection. By integrating immune response dynamics into the model, we provide a more accurate representation of how the immune system interacts with the virus and infected cells over time. This approach may facilitate the development of more effective vaccination and treatment strategies, ultimately leading to better patient outcomes.

Future work can enhance the studied model by examining the effects of various therapeutic interventions, such as antiviral treatments and vaccination strategies. Additionally, exploring the role of co-infections and the impact of different immune cell types could further enrich the model's predictive capabilities. Further refinement of the parameters and inclusion of real-world epidemiological data will help validate the model, ensuring it reflects the complexities of viral infections in diverse populations.

Ultimately, this research contributes to understanding the effect of the immune system's response on hepatitis B dynamics and determines the most effective component in spreading the function.

Acknowledgment

This Project was funded by the Deanship of Scientific Research (DSR) at King Abdulaziz University, Jeddah, under grant no. (GPIP:127-665-2024). The authors, therefore, acknowledge with thanks DSR for technical and financial support.

References

[1] L. G. Guidotti, R. Rochford, J. Chung, M. Shapiro, R. Purcell, F. V. Chisari, *Viral clearance without destruction of infected cells during acute HBV infection*, Science, **284** (1999), 825–829. 1
[2] J. H. Hoofnagle, E. Doo, T. J. Liang, R. Fleischer, A. S. F. Lok, *Management of hepatitis b: summary of a clinical research workshop*, Hepatology, **45** (2007), 1056–1075. 1
[3] Z. Khatun, M. S. Islam, U. Ghosh, *Mathematical modeling of hepatitis b virus infection incorporating immune responses*, Sens. Int., **1** (2020), 8 pages. 1, 3, 4
[4] S. R. Lewin, R. M. Ribeiro, T. Walters, G. K. Lau, S. Bowden, S. Locarnini, A. S. Perelson, *Analysis of hepatitis b viral load decline under potent therapy: complex decay profiles observed*, Hepatology, **34** (2001), 1012–1020. 1
[5] L. Liu, X. Ma, Y. Li, X. Liu, *Mathematical analysis of global dynamics and optimal control of treatment for an age-structured hbv infection model*, Chaos Solitons Fractals, **177** (2023). 1
[6] A. S Lok, E. J. Heathcote, J. H. Hoofnaglel, *Management of hepatitis b: 2000—summary of a workshop*, Gastroenterology, **120** (2001), 1828–1853. 1
[7] A. S. F. Lok, B. J. McMahon, *Chronic hepatitis b*, Hepatology, **45** (2007), 507–539. 1
[8] E. C. Manda, F. Chirove, *Acute hepatitis B virus infection model within the host incorporating immune cells and cytokine responses*, Theory Biosci., **139** (2020), 153–169. 1
[9] M. A. Nowak, S. Bonhoeffer, A. M. Hill, R. Boehme, H. C. Thomas, H. McDade, *Viral dynamics in hepatitis b virus infection*, Proc. Natl. Acad. Sci. USA, **93** (1996), 4398–4402. 1
[10] R. M. Ribeiro, A. Lo, A. S. Perelson, *Dynamics of hepatitis b virus infection*, Microbes Infect., **4** (2002), 829–835. 1
[11] S. W. Teklu, *Analysis of hbv and covid-19 coinfection model with intervention strategies*, Comput. Math. Methods Med., **2023** (2023), 17 pages. 1
[12] M .Tsiang, J. F. Rooney, J. J. Toole, C. S. Gibbs, *Biphasic clearance kinetics of hepatitis b virus from patients during adefovir dipivoxil therapy*, Hepatology, **29** (1999), 1863–1869. 1
[13] F. A. Wodajo, D. M. Gebru, H. T. Alemneh, *Mathematical model analysis of effective intervention strategies on transmission dynamics of hepatitis b virus*, Sci. Rep., **13** (2023), 21 pages. 1
[14] C. Xu, Y. Wang, K. Cheng, X. Yang, X. Wang, S. Guo, M. Liu, X. Liu, *A mathematical model to study the potential hepatitis b virus infections and effects of vaccination strategies in china*, Vaccines, **11** (2023), 20 pages. 1