The transmission dynamic of different hepatitis B-infected individuals with the effect of hospitalization

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\textbf{ABSTRACT}

We propose an epidemic model for the transmission of hepatitis B virus along with the classification of different infection phases and hospitalized class. We formulate the model and discuss its basic mathematical properties, e.g. existence, positivity, and biological feasibility. Exploiting the next generation matrix approach, we find the basic reproductive number of the model. We perform sensitivity analysis to illustrate the effect of various parameters on the transmission of the disease. We investigate stability of the equilibria of the model in terms of the basic reproduction number. Conditions for the stability of the proposed model are obtained using various approaches. Finally, we perform the numerical simulations to discuss sensitivity analysis and to support our analytical work.

\textbf{1. Introduction}

Hepatitis (inflammation of the liver) was first described by Hippocrates over 2000 years ago. Hepatitis B infection is caused by the hepatitis B virus which is among the most serious viral infections. Hepatitis B is a global health problem and one of the major causes of death around the globe. Approximately 2 billion people are infected with hepatitis B, among which 360 million individuals are chronically infected\textsuperscript{[8,10,15]}. Nearly 780,000 individuals die from hepatitis B infection every year\textsuperscript{[15]}. Hepatitis B virus's infection plays a vital role in the development of primary liver cancer. This virus can be transmitted from one individual to another by different ways, e.g. through blood (sharing of razors, blades, or toothbrushes), semen, and vaginal secretions (unprotected sexual contact)\textsuperscript{[2,6,7,9]}. Vertical transmission, e.g. from infected mother to her child during the time of birth, is another major route of transmission of the hepatitis B virus\textsuperscript{[2,11]}.

Hepatitis B infection has two phases, i.e. acute and chronic carries. Acute hepatitis B refers to the first six months after exposure of an individual to the hepatitis B. In this stage, the immune system is usually able to clear the virus from the body and, eventually, one completely recovers within few months. Symptoms of such hepatitis B include feeling sick, tummy pains, high temperature, etc., which usually vanish after a few weeks, as the immune...
system either clears the virus or controls them. Sometimes an individual may not be aware of the infection of the hepatitis B, particularly, the babies. There is no specific treatment in this stage; however, the hospital care, drinking plenty of fluids, etc., can help.

Having no proper care in the acute stage, the infection leads to a most serious stage, called the chronic stage. This causes serious health problems, such as liver scarring that becomes the cause of liver failure and may also develop liver cancer [8]. Treatment for hepatitis B does not preserve hepatitis B infection; however, it is useful for the deferral or even to inhibit complications from developing liver damage. Individuals with chronic hepatitis B usually need hospitalization (treatment), which may be continued for many years to break or to shrink the bustle of the virus. The treatment of hepatitis B is a developing zone of medicine.

Mathematical modelling is a powerful tool to describe real-world phenomena of different diseases [16,17]. Mathematicians and biologists use epidemic models to understand and control the transmission of different diseases. In the fast couple of decades, mathematical modelling has been frequently used to study the transmission dynamic of hepatitis B infection. Medley et al. used a mathematical model for eliminating the hepatitis B virus in New Zealand [8,11]. In 1991, Andeson et al. described the effect of carries on the transmission of the hepatitis B virus using a simple deterministic model [1]. Zhao et al. [18] and Zou et al. [19] presented models for the transmission and control of the hepatitis B virus in China. Khan et al. [4] developed a model for the hepatitis B virus by classification of different hepatitis B-infected individuals with saturated incidence rate. More recently, a mathematical model for the transmission dynamic and optimal control of hepatitis B has been presented in [5].

The various phases of hepatitis B along with the effect of hospitalization play a very important role in the transmission and control of hepatitis B infection. This has not been investigated collectively yet for their potential role in generating the hepatitis B epidemic model. We consider a model for hepatitis B by identifying the different phases with its hospitalization, i.e. acute, chronic, hospitalization, and develop a hepatitis B virus transmission model. In this report, we develop a model with these new features in Section 2. For the biological feasibility and well-posedness, we discuss the basic mathematical properties of the proposed model in Section 3. In Section 4, we find the basic reproduction number and discuss its sensitivity analysis. Moreover, we investigate the stability in Section 5. Finally, we perform the numerical simulations in Section 6. Section 7 is devoted to conclusion.

2. Formulation of mathematical model

In this section, we present a mathematical model based on the characteristic of hepatitis B virus transmission. We divide the total population into seven different epidemiological classes, namely, the susceptible \( S(t) \), the latent \( L(t) \), the acutely infected \( A(t) \), the chronically infected \( C(t) \), the hospitalized \( H(t) \), the recovered with permanent immunity \( R(t) \), and the vaccinated \( V(t) \).

We also impose the following assumptions on the model:

\[ A_1. \] The initial populations \( S(0), L(0), A(0), C(0), H(0), R(0), \) and \( V(0) \) are all known and non-negative.
A2. Recovered individuals have permanent immunity.
A3. The inflow of new-born with successful vaccination goes to the vaccination compartment.
A4. The inflow of new-born with parental infection goes to the carrier compartment.
A5. The inflow of new-born without parental infection goes to the susceptible compartment.
A6. The hospitalized class contain those individuals who cannot be recovered in acute and chronic carrier stages.
A7. The population with successful vaccination goes to the vaccinated compartment.

The compartmental mathematical model with the above assumptions $A_1 - A_7$ is given by the following system of seven ordinary differential equations:

$$\frac{dS(t)}{dt} = b \xi (1 - \eta C(t)) + \phi V(t) - \beta S(t)A(t) - \gamma \beta S(t)C(t) - (\gamma_3 + d_0)S(t),$$

$$\frac{dL(t)}{dt} = \beta S(t)A(t) + \gamma \beta S(t)C(t) - (\sigma + d_0)L(t),$$

$$\frac{dA(t)}{dt} = \sigma L(t) - (\gamma_1 + \vartheta_1 + d_0)A(t),$$

$$\frac{dC(t)}{dt} = b \xi \eta C(t) + p \gamma_1 A(t) - (\gamma_2 + \vartheta_2 + d_0 + d_1)C(t),$$

$$\frac{dH(t)}{dt} = \vartheta_1 A(t) + \vartheta_2 C(t) - (\vartheta_3 + d_0 + d_2)H(t),$$

$$\frac{dR(t)}{dt} = (1 - p) \gamma_1 A(t) + \gamma_2 C(t) + \vartheta_3 H(t) - d_0 R(t),$$

$$\frac{dV(t)}{dt} = b(1 - \xi) + \gamma_3 S(t) - (\phi + d_0) V(t),$$

with initial conditions

$$S(0) > 0, \quad L(0) \geq 0, \quad A(0) \geq 0, \quad B(0) \geq 0, \quad R(0) \geq 0, \quad V(0) > 0. \quad (2)$$

In models (1)–(2), $b$ represents the birth rate and $\xi$ represents the birth rate without successful vaccination. The parentally infected individuals’ rate is denoted by $\eta$. $\phi$ is to be considered the rate of waning vaccine-induced immunity. $\beta$ and $\gamma$, respectively, represent the transmission and reduced transmission rate of hepatitis B. $d_0, d_1,$ and $d_2$ represent the natural mortality rate and hepatitis B virus-related mortality rates, respectively. Vaccination rate of hepatitis B is represented by $\gamma_3$, while the moving rate of latent to acute hepatitis B is denoted by $\sigma$. $\gamma_1$ and $\gamma_2$ represent the moving rate from acute to chronic carrier and chronic carrier to immune, respectively. $\vartheta_1$ and $\vartheta_2$ represent the hospitalization rates of acutely and chronically infected individuals, respectively. $\vartheta_3$ denotes the recovery rate of hospitalized individuals. The probability of those individuals who fail to recover in acute class is denoted by $p$. 
3. Basic mathematical analysis

Let us consider the Banach space

\[ X = H^1(0, t_+) \times H^1(0, t_+) \times H^1(0, t_+) \times H^1(0, t_+) \]
\[ \times H^1(0, t_+) \times H^1(0, t_+) \times H^1(0, t_+), \quad t_+ > 0. \]

The norm on \( X \) is defined by

\[ \| \varphi \| = \sum_{i=1}^{7} \| \varphi_i \| \quad \text{for} \quad \varphi(t) = (\varphi_1(t), \varphi_2(t), \varphi_3(t), \varphi_4(t), \varphi_5(t), \varphi_6(t), \varphi_7(t))^T \in X, \]

where \( \| . \| \) is the norm of \( H^1(0, t_+) \). The state space of system (1) is given by

\[ \Delta := \{(S, L, A, C, H, R, V) \in X_+ \text{ such that } 0 \leq N \leq 1 \}. \] (3)

In Equation (3), \( N \) represents the total population, i.e. \( N = S + L + A + C + H + R + V \) and \( X_+ = H^1_+(0, t_+) \times H^1_+(0, t_+) \times H^1_+(0, t_+) \times H^1_+(0, t_+) \times H^1_+(0, t_+) \times H^1_+(0, t_+) \times H^1_+(0, t_+) \) is the positive cone of \( H^1(0, t_+) \).

Let \( M \) be a linear operator and assume that \((\varphi_1, \varphi_2, \varphi_3, \varphi_4, \varphi_5, \varphi_6, \varphi_7) = (S, L, A, C, H, R, V)\), then \( M \) becomes

\[ (M\varphi)(t) = (M_1, M_2, M_3, M_4, M_5, M_6, M_7)^T, \] (4)

where

\[ M_1 = \left(-\frac{d\varphi_1}{dt} - (\gamma_3 + d_0)\varphi_1, 0, 0, -b\xi \eta \varphi_4, 0, 0, \phi \varphi_7\right), \]
\[ M_2 = \left(0, -\frac{d\varphi_2}{dt} - (\sigma + d_0)\varphi_2, 0, 0, 0, 0\right), \]
\[ M_3 = \left(0, \sigma \varphi_2, -\frac{d\varphi_3}{dt} - (\gamma_1 + \vartheta_1 + d_0)\varphi_3, 0, 0, 0\right), \]
\[ M_4 = \left(0, 0, p\gamma_1 \varphi_3, -\frac{d\varphi_4}{dt} + b\xi \eta \varphi_4 - (\gamma_2 + \vartheta_2 + d_0 + d_1)\varphi_4, 0, 0, 0\right), \]
\[ M_5 = \left(0, 0, \vartheta_1 \varphi_3, \vartheta_2 \varphi_4, -\frac{d\varphi_5}{dt} - (\vartheta_3 + d_1 + d_2)\varphi_5, 0, 0\right), \]
\[ M_6 = \left(0, 0, (1 - p)\gamma_1 \varphi_3, \gamma_2 \varphi_4, \vartheta_3 \varphi_5, -\frac{d\varphi_6}{dt} - d_0 \varphi_6, 0\right), \]
\[ M_7 = \left(\gamma_3 \varphi_1, 0, 0, 0, 0, 0, -\frac{d\varphi_7}{dt} - (\phi + d_0)\varphi_7\right), \]

and the domain \( D(M) \) with \( \varphi_1(0) = S(0), \varphi_2(0) = L(0), \varphi_3(0) = A(0), \varphi_4(0) = C(0), \varphi_5(0) = H(0), \varphi_6(0) = R(0), \varphi_7(0) = V(0) \) is given as

\[ D(M) = \{ \varphi \in X, \text{ such that } \varphi_i \in MC[0, t_+), \varphi(0) = (\varphi_i(0), \text{ for } i = 1, 2, \ldots, 7) \}. \] (5)

In Equation (5), \( MC[0, t_+] \) represents the set of absolutely continuous functions on \([0, t_+).\)
We also define a nonlinear operator \( N : X \to X \) such that

\[
(N\varphi)(t) = \begin{pmatrix}
\beta \varphi_1 \varphi_3 - \gamma \beta \varphi_1 \varphi_4 \\
\beta \varphi_1 \varphi_3 + \gamma \beta \varphi_1 \varphi_4 \\
0 \\
0 \\
0 \\
b(1 - \xi)
\end{pmatrix}.
\]

(6)

Let \( u(t) = (S(. , t), L(. , t), A(. , t), C(. , t), H(. , t), R(. , t), V(. , t)) \), then we can re-write model (1) as an abstract Cauchy problem

\[
\frac{du(t)}{dt} = M(u(t)) + N(u(t)), \quad u(0) = u_0 \in X,
\]

(7)

where \( u_0(t) = (S(0), L(0), A(0), C(0), H(0), R(0), V(0))^T \).

For \( M \) and \( N \), we follow Inaba and Webb [3,14] to get the following results.

**Lemma 3.1 ([3,14]):** The operator \( M \) generates a \( C_0 \) semi-group \( e^{Mt} \) and the space \( \Delta \) is positively invariant with respect to the semi-flow defined by \( e^{Mt} \).

**Lemma 3.2 ([3,14]):** The operator \( N \) is continuously Frechet differentiable on \( X \).

**Theorem 3.3:** For each \( u_0 \in X_+ \), there exist a maximal interval of existence \( 0, t_0 \) and a unique continues mild solution \( u(t, u_0) \in X_+, t \in 0, t_0 \) for Equation (7), such that

\[
u(t) = e^{Mt}u_0 + \int_0^t e^{M(t-\tau)}N(u(\tau)) \, d\tau.
\]

(8)

**Proposition 3.4:** For the initial data \( S(0) > 0, L(0) \geq 0, A(0) \geq 0, C(0) \geq 0, H(0) \geq 0, R(0) \geq 0 \) and \( V(0) > 0 \), the solution \( (S(t), L(t), A(t), C(t), H(t), R(t), V(t)) \) of model (1) are positive for all \( t > 0 \), whenever they exist.

**Proof:** Let \( \varphi_1 = 1 - \eta C(t), \varphi_2 = \beta A(t) + \gamma \beta C(t), \) and \( I \subset 0, +\infty \). We assume that the solution of system (1) exist in \( I \), then for all \( t \in I \), the solution of the first equation of system (1) looks like

\[
S(t) = S(0)\exp \{- (d_0 + \gamma_3)t + \int_0^t \varphi_2(x) \, dx \}
+ \exp \{- (d_0 + \gamma_3)t + \int_0^t \varphi_2(x) \, dx \}
\times \int_0^t (b\xi \varphi_1 + \phi V(t)) \exp \{ (d_0 + \gamma_3)y + \int_0^y \varphi_2(u) \, du \} \, dy > 0.
\]

\[\blacksquare\]
Hence \( S(t) > 0 \) for all \( t \in I \). The solution of the second equation of system (1) yields

\[
L(t) = L(0)\exp(-(\sigma + d_0)t) + \exp(-(\sigma + d_0)t) \times \int_0^t \varphi_2(y)\exp(\sigma + d_0)y \, dy \geq 0. \tag{10}
\]

Similarly, it can be shown that \( A(t) \geq 0, C(t) \geq 0, H(t) \geq 0, R(t) \geq 0, \) and \( V(t) > 0 \). Hence the solution \((S(t), L(t), A(t), C(t), H(t), R(t), V(t))\) of model (1) is positive for all \( t \).

**Proposition 3.5:** System (1) is a dynamical system in the biological feasible region given by

\[
\Delta = \left\{ (S, L, A, C, H, R, V) \in \mathbb{R}_+^7 : N \leq \frac{b_2}{d_0} \right\}. \tag{11}
\]

**Proof:** The differentiability of the right-hand side of system (1) ensures the existence of the unique maximal solution for any associated Cauchy problem. Consequently, initial value problem (1) is well-posed and biologically feasible, because all the state variables are non-negative. So for the required result, it is sufficient to study the dynamics of the flow generated by model (1). Since the solutions of system (1) are positive and bounded, therefore, it remains to show that the vector field defined by this system is transversal to the boundary of \( \Delta \) on all its faces. The face corresponding to \( S = b/(d_0 + \gamma_3) \) has direction \((1, 0, 0, 0, 0, 0, 0)\) and the inner product with the vector field is \( b_2 \varphi_1 + \beta_1 V(t) - \beta_2 S(t) - (d_0 + \gamma_3)S(t) \leq b_2 - (d_0 + \gamma_3)S(t) \). Similarly, we can check for the faces \( LA, C, H, R, V \). At last, the face corresponding to \( N = b_2/d_0 \) has a direction \((1, 1, 1, 1, 1, 1)\) and the inner product with the vector field is \( b - d_0 N(t) - d_1 C(t) - d_2 H(t) \leq b - dN \). Thus the vector field on these faces points toward the region \( \Delta \). \( \blacksquare \)

### 4. The analysis of reproduction number

#### 4.1. Reproduction number

In epidemiological models, the role of threshold quantity (basic reproduction number) is very important. It represents the expected average number of new infections produced directly and indirectly by a single infective, when introduced into a completely susceptible population [12,13]. We find the basic reproduction number for model (1) by following Driessche and Watmough [13]. Let \( \chi = (L(t), A(t), C(t))^T \), so from model (1), we have

\[
\frac{d\chi}{dt} = F - V, \tag{12}
\]

where \( F \) and \( V \) are defined as

\[
F = \begin{pmatrix} \beta S(t)A(t) + \gamma S(t)C(t) \\ 0 \\ 0 \end{pmatrix}, \quad V = \begin{pmatrix} q_2 L(t) \\ q_3 A(t) - \sigma L(t) \\ (q_4 - b_2 \gamma_2) C(t) - p \gamma_1 A(t) \end{pmatrix}. \tag{13}
\]

In Equation (13), \( q_1 = d_0 + \gamma_3, q_2 = \sigma + d_0, q_3 = d_0 + \gamma_1 + \vartheta_1, q_4 = d_0 + d_1 + \gamma_2 + \vartheta_2, q_5 = d_0 + d_2 + \vartheta_2, \) and \( q_6 = d_0 + \phi \). Taking the Jacobian of \( F \) and \( V \) at disease-free
equilibrium $E_0 = (S_0, 0, 0, 0, 0, V_0)$, we get
\[
F = \begin{pmatrix}
0 & \beta S_0 & \gamma \beta S_0 \\
0 & 0 & 0 \\
0 & 0 & 0
\end{pmatrix}, \quad V = \begin{pmatrix}
q_2 & 0 & 0 \\
-\sigma & q_3 & 0 \\
0 & -p \gamma_1 & q_4 - b \xi \eta
\end{pmatrix}.
\]

The basic reproduction number $R_0$ is the spectral radius of the next generation matrix $\bar{K} = FV^{-1}$, i.e. $R_0 = \rho(FV^{-1}) = \max(|\lambda_1|, \ldots, |\lambda_3|)$, where $\lambda_i$ for $i = 1, 2, 3$ are the eigenvalues of $\bar{K}$. The basic reproduction number $R_0$ for the proposed model (1) becomes $R_0 = \gamma_01 + \gamma_02$, where
\[
\gamma_01 = \frac{\sigma \beta S_0}{(d_0 + \gamma_1 + \vartheta_1)(d_0 + \sigma)} \quad \text{and} \quad \gamma_02 = \frac{p \gamma \gamma_01}{d_0 + d_1 + \gamma_2 + \vartheta_2 - b \xi \eta}.
\] (14)

### 4.2. Sensitivity analysis

Usually uncertainties in data collection and estimated values significantly affect the basic reproduction number. We perform sensitivity analysis to define the relative significance of epidemic parameters to the disease transmission and its control.

**Definition 4.1:** The normalized forward sensitivity index of the basic reproduction number $R_0$ that depends differentiably on a parameter $\varphi$ is defined as
\[
S_{\varphi} = \frac{\Phi \frac{\partial R_0}{\partial \varphi}}{R_0}. \tag{15}
\]

We perform sensitivity analysis by calculating the sensitivity indices of the basic reproduction number to the epidemic parameters which are involved. These indices allow us the importance of different factors involved in disease transmission and also to measure the relative change in the reproduction number with the change in a parameter. Using these indices, we find the parameters that highly affect the reproduction number and are essential to develop control strategies.

Table 1 shows that the parameters $\beta$, $\sigma$, $\gamma$, $\xi$, $\eta$, and $\phi$ have a positive influence on the reproduction number $R_0$, which describe that the growth or decay of these parameters say by 10 per cent will increase or decrease the reproduction number by 10 per cent, 0.025 per cent, 0.2 per cent, 0.000183 per cent and 8.135 per cent, respectively. But on the other hand, the index for parameters $\gamma_1$, $\gamma_3$, $\vartheta_1$, and $\vartheta_2$ illustrates that increasing

| Parameter | S.Index | Value | Parameter | S.Index | Value |
|-----------|---------|-------|-----------|---------|-------|
| $\beta$   | $S_{\beta}$ | +1 | $\eta$    | $S_{\eta}$ | 0.183 $\times 10^{-5}$ |
| $\sigma$  | $S_{\sigma}$ | +0.302 | $\xi$    | $S_{\xi}$ | 0.021 |
| $\gamma_1$ | $S_{\gamma_1}$ | -0.0263 | $\phi$   | $S_{\phi}$ | 0.8135 |
| $\gamma_2$ | $S_{\gamma_2}$ | -0.646 | $\vartheta_1$ | $S_{\vartheta_1}$ | -0.264 |
| $\gamma_3$ | $S_{\gamma_3}$ | -0.823 | $\vartheta_2$ | $S_{\vartheta_2}$ | -0.0025 |
| $\gamma$  | $S_{\gamma}$ | 0.25 $\times 10^{-2}$ |
their values by 10 per cent will decrease the values of reproduction number $R_0$ by 0.26 per cent, 8.23 per cent, 2.264 per cent, and 0.025 per cent, respectively.

In order to control the infection of hepatitis B, we focus to control hepatitis B transmission rate $\beta$, which has got highest sensitivity index 1. This means that a decrease in transmission rate $\beta$ by 10 per cent would decrease basic reproduction by 10 per cent. The second highest sensitivity index $-0.823$ is that of vaccination rate $\gamma_3$, i.e. increasing $\gamma_3$ by 10 per cent will decrease $R_0$ by 8.23 per cent. The parameters $\sigma, \gamma, \eta, \xi, \phi$ collectively have got the sensitivity index $1.328$. So decreasing these parameters by 10 per cent collectively decreases $R_0$ by 13.28 per cent. Similarly the parameters $\gamma_1, \gamma_2, \vartheta_1, \vartheta_2$ have got the sensitivity index $0.93$. So increasing the treatment of hepatitis B-infected individuals (acutely and chronically) will decrease $R_0$ by 9.3 per cent. Therefore, it is easy to develop a control strategy.

5. Steady state analysis

In order to study the qualitative behaviour of the proposed problem, we find the disease-free and endemic equilibrium. The disease-free equilibrium of model (1) is denoted by $E_0$ and defined as $E_0 = (S_0, 0, 0, 0, 0, 0, V_0)$, where

$$S_0 = \frac{b(\phi + \xi d_0)}{d_0(d_0 + \gamma_3 + \phi)}, \quad V_0 = \frac{b(d_0 + \gamma_3 - d_0 \xi)}{d_0(d_0 + \gamma_3 + \phi)}. \quad (16)$$

Similarly the disease endemic state is denoted by $E_*$ and defined as $E_* = (S_*, L_*, A_*, C_*, H_*, R_*, V_*)$ for $R_0 > 1$, where

$$S_* = \frac{q_2 q_3 q_4 - q_2 q_3 b \xi \eta}{\sigma \beta (q_4 + p \gamma \gamma_1 - b \xi \eta)}, \quad L_* = \frac{d_0 (d_0 + \gamma_3 + \phi) q_3 q_4 S_* (R_0 - 1)}{\sigma q_6 (\beta S_* (q_4 + p \gamma \gamma_1 - b \xi \eta) + p \gamma \gamma_1 b \eta)},$$

$$A_* = \frac{d_0 (d_0 + \gamma_3 + \phi)(q_4 - b \xi \eta) S_* (R_0 - 1)}{q_6 (\beta (q_4 + p \gamma \gamma_1 - b \xi \eta) S_* + p \gamma \gamma_1 b \eta)},$$

$$C_* = \frac{d_0 (d_0 + \gamma_3 + \phi) \beta p \gamma \gamma_1 d_0 q_3 S_*^2 (R_0 - 1)}{q_6 (\beta (q_4 + p \gamma \gamma_1 - b \xi \eta) S_* + p \gamma \gamma_1 b \eta)},$$

$$H_* = \frac{1}{q_5} (\vartheta_1 A_* + \vartheta_2 C_*), \quad R_* = \frac{1}{d_0} ((1 - p) \gamma_1 A_* + \gamma_2 C_* + \vartheta_3 H_*),$$

$$V_* = \frac{1}{q_6} (b(1 - \xi) + v S_*). \quad (17)$$

5.1. Local stability analysis

To investigate the local stability, we make use of the following results.

**Theorem 5.1:** The disease-free equilibrium point $E_0 = (S_0, 0, 0, 0, 0, V_0)$ of model (1) is locally asymptotically stable, if $R_0 < 1$. 
**Proof:** The Jacobian matrix of model (1) around the disease-free equilibrium point $E_0$ becomes

$$J_0 = \begin{pmatrix}
-q_1 & 0 & -\beta S_0 & -(b \xi \eta + \gamma \beta S_0) & 0 & 0 & \phi \\
0 & -q_2 & \beta S_0 & \gamma \beta S_0 & 0 & 0 & 0 \\
0 & \sigma & -q_3 & 0 & 0 & 0 & 0 \\
0 & 0 & p \gamma_1 & b \xi \eta - q_4 & 0 & 0 & 0 \\
0 & 0 & (1 - p) \gamma_1 & \gamma_2 & \vartheta_2 & -q_5 & 0 \\
\gamma_3 & 0 & 0 & 0 & \vartheta_3 & -d_0 & 0 \\
\end{pmatrix}. \quad (18)$$

The characteristic equation of $J_0$ has the form

$$(\zeta + d_0)(\zeta + q_5)(\zeta^5 + a_4 \zeta^4 + a_3 \zeta^3 + a_2 \zeta^2 + a_1 \zeta + a_0) = 0, \quad (19)$$

where

$$a_0 = q_1 q_2 q_3 q_6 (q_4 - b \xi \eta)(1 - R_0) + (\phi \gamma_3 q_2 q_3 + \sigma \beta S_0 \phi \gamma_3)(q_4 - b \xi \eta) + \sigma \beta S_0 p \gamma_1 \phi \gamma_3, \quad a_1 = d_0 (d_0 + \gamma_3 + \phi) q_3 q_4 + (q_2 q_3 q_6 + q_1 q_2 q_3)(q_4 - b \xi \eta)(1 - R_0) + \sigma \beta S_0 b \xi \eta q_1$$

$$+ (q_1 q_6 + q_1 q_2 q_6)(q_4 - b \xi \eta) + q_1 q_6 (1 - \gamma_0) + \phi \gamma_3 (b \xi \eta q_2 + b \xi \eta q_3 + \sigma \beta S_0$$

$$- q_2 (q_3 + q_4)),$$

$$a_2 = (q_4 - b \xi \eta)(q_1 q_2 + q_1 q_3 + q_1 q_6 + q_2 q_6 + q_3 q_6 + q_2 q_3 (1 - R_0))$$

$$+ (q_1 q_2 q_3 + q_2 q_3 q_6)(1 - \gamma_0) + d_0 (d_0 + \gamma_3 + \phi)(q_2 + q_3 + q_4) + \gamma_3 \phi b \xi \eta,$$

$$a_3 = q_1 q_2 + q_1 q_3 + d_0 (d_0 + \gamma_3 + \phi) + q_2 q_6 + q_3 q_6$$

$$+ (q_1 + q_2 + q_3 + q_6)(q_4 - b \xi \eta) + q_2 q_3 (1 - \gamma_0),$$

$$a_4 = q_1 + q_2 + q_3 + q_4 + q_6 - b \xi \eta.$$

The fundamental theorem of algebra reveals that there are seven roots of Equation (19). Hence, the Jacobian matrix $J_0$ (18) has seven eigenvalues. Two eigenvalues $\zeta_1 = -q_5$ and $\zeta_2 = -d_0$ among them have negative real parts. The remaining five eigenvalues are obtained by solving

$$P(\zeta) = \zeta^5 + a_4 \zeta^4 + a_3 \zeta^3 + a_2 \zeta^2 + a_1 \zeta + a_0. \quad (20)$$

Roots of Equation (25) have negative real parts, if the Routh–Hewritt criterion ($H_1$): $a_i > 0$ for $i = 1 \ldots 5$, $a_2 a_3 a_4 > a_2^2 + a_1 a_4^2$ and $(a_1 a_4 - a_0)(a_2 a_3 a_4 - a_2^2 - a_1 a_4^2) > a_0 (a_3 a_4 - a_2^2 + a_0^2 a_4)$ hold. It can be noted that ($H_1$) satisfied if and only if $R_0 < 1$. Thus, we conclude that all the eigenvalues have negative real parts if and only if $R_0 < 1$.

**Theorem 5.2:** The disease endemic state $E_* = (S_*, L_*, A_*, C_*, H_*, R_*, V_*)$ of model (1) is locally asymptotically stable, if $R_0 > 1$ and $q_4 > b \xi \eta$. 
**Proof:** The Jacobian matrix of model (1) around the disease endemic equilibrium point \( E^* \) is

\[
J^* = \begin{pmatrix}
-\beta A^* - \gamma \beta C^* - q_1 & 0 & -\beta S^* & -(b\xi \eta + \gamma \beta S^*) & 0 & 0 & \phi \\
\beta A^* + \gamma \beta C^* & -q_2 & \beta S^* & \gamma \beta S^* & 0 & 0 & 0 \\
0 & \sigma & -q_3 & 0 & 0 & 0 & 0 \\
0 & 0 & \nu_1 p\gamma_1 & b\xi \eta - q_4 & 0 & 0 & 0 \\
0 & 0 & 0 & (1 - p)\gamma_1 & \nu_2 & -d_0 & 0 \\
\gamma_3 & 0 & 0 & 0 & 0 & 0 & -q_6 \\
\end{pmatrix} \tag{21}
\]

Clearly two eigenvalues of the Jacobian matrix \( J^* \) at Equation (21) of model (1) around the disease endemic equilibrium \( E^* \) are negative, i.e. \( \lambda_1 = -d_0 \) and \( \lambda_2 = -q_5 \). For the remaining, we taking the following reduced matrix:

\[
J^* = \begin{pmatrix}
-\beta A^* - \gamma \beta C^* - q_1 & 0 & -\beta S^* & -(b\xi \eta + \gamma \beta S^*) & \phi \\
\beta A^* + \gamma \beta C^* & -q_2 & \beta S^* & \gamma \beta S^* & 0 \\
0 & \sigma & -q_3 & 0 & 0 \\
0 & 0 & \nu_1 p\gamma_1 & b\xi \eta - q_4 & 0 \\
\gamma_3 & 0 & 0 & 0 & -q_6 \\
\end{pmatrix} \tag{22}
\]

Using the elementary row operation, Equation (22) \( J^* \) takes the following form:

\[
J^* = \begin{pmatrix}
-\beta A^* - \gamma \beta C^* - q_1 & 0 & -\beta S^* & -(b\xi \eta + \gamma \beta S^*) & \phi \\
0 & -q_2 & \frac{K_1}{q_1} & \gamma K_1 - b\xi \eta K_2 & \frac{\phi K_2}{q_1} \\
0 & 0 & -q_3 + \frac{\sigma K_1}{q_2} & \frac{\gamma K_1 - b\xi \eta \sigma}{q_2} & \frac{\sigma \phi K_2}{q_2} \\
0 & 0 & 0 & K_3 - b\xi \eta K_4 & \phi K_4 \\
0 & 0 & 0 & 0 & K_5 \\
\end{pmatrix} \tag{23}
\]

The values of \( K_1, K_2, K_3, K_4, \) and \( K_5 \) in the above matrix \( J^* \) at Equation (23) are given by

\[
K_1 = \frac{q_1 \beta S^*}{\beta A^* + \gamma \beta C^* + q_1}, \quad K_2 = \frac{\beta A^* + \gamma \beta C^*}{\beta A^* + \gamma \beta C^* + q_1},
\]

\[
K_3 = b\xi \eta - q_4 - \frac{\sigma \beta p\gamma_1 q_1 S^*}{\sigma \beta S^* q_1 - q_2 q_3 (\beta A^* + \gamma \beta C^* + q_1)},
\]

\[
K_4 = \frac{\sigma q_2 q_3 (\beta A^* + \gamma \beta C^* + q_1) - \sigma \beta q_1 S^*}{q_2 q_3 (\beta A^* + \gamma \beta C^* + q_1)},
\]

\[
K_5 = \frac{\phi \gamma_3 p\gamma_1 (b\xi \eta + \gamma \beta S^*) - \beta S^* (b\xi \eta - q_4))}{p\gamma_1 (\beta A^* + \gamma \beta C^* + q_1) (K_3 - b\xi \eta K_4)} - \frac{q_6 (\beta A^* + \gamma \beta C^* + d_1) + d_0 \gamma_3}{\beta A^* + \gamma \beta C^* + \gamma_3 + \nu_1 + d_1}.
\]

The eigenvalues of \( J^* \) at Equation (23) takes the following form:

\[
\lambda_3 = -\beta A^* - \gamma \beta C^* - q_1 < 0, \quad \lambda_4 = -q_2 < 0, \quad \lambda_5 = -q_3 + \frac{\sigma K_1}{q_2},
\]

\[
\lambda_6 = K_3 - b\xi \eta K_4, \quad \lambda_7 = K_5.
\]
Clearly two eigenvalues of matrix $J_*$ at Equation (23) have negative real parts, i.e. $\lambda_3 < 0$ and $\lambda_4 < 0$, while $\lambda_5, \lambda_6,$ and $\lambda_7$ have negative real parts if and only if

\[
\frac{\beta p y \gamma}{q_2 q_4 (\beta A_* + \gamma \beta C_* + q_1)} - \gamma \beta S_* < 1,
\]

which holds as $E_*$ exist. Therefore, all eigenvalues contain negative real parts, and we have the conclusion that the disease endemic equilibrium point $E_*$ is locally asymptotically stable if $R_0 > 1$.

5.2. Global stability analysis

To investigate the global stability, we exploit the following results.

**Theorem 5.3:** For $R_0 \leq 1$, the disease-free equilibrium point $E_0 = (S_0, 0, 0, 0, 0, V_0)$ of the proposed model (1) is globally asymptotically stable if

(a) $S \geq S_0, V \geq V_0$

and unstable, otherwise.

**Proof:** Let us construct the Lyapunov function

\[
F(t) = \frac{1}{2} ((S - S_0) + L(t) + A(t) + C(t) + H(t) + R(t) + (V - V_0))^2
+ k_1 (S - S_0) + k_2 L(t) + k_3 A(t) + k_4 (V - V_0),
\]

where $k_i, i = 1, 2, \ldots, 4,$ are positive constants to be determined latter. Differentiating Equation (25) with respect to $t$, we obtain

\[
\frac{dF(t)}{dt} = ((S - S_0) + L(t) + A(t) + C(t) + H(t) + R(t) + (V - V_0))(b - d_0 N(t)
- d_1 C(t) - d_2 H(t)) + k_1 \frac{dS}{dt} + k_2 \frac{dL}{dt} + k_3 \frac{dA}{dt} + k_4 \frac{dV}{dt}.
\]

Choosing $k_1 = k_2 = k_4 = q_3$ and $k_3 = \beta S_0$, then Equation (26) reduces to

\[
\frac{dF(t)}{dt} = -((S - S_0) + L(t) + A(t) + C(t) + H(t) + R(t) + (V - V_0))(d_0 (S - S_0)
+ d_0 (L(t) + A(t) + C(t) + H(t) + R(t)) + d_0 (V - V_0) + d_1 C(t) + d_2 H(t))
- d_0 q_3 (S - S_0) - q_2 q_3 (1 - \gamma_{01}) L(t) - \sigma \beta S_0 q_3 A(t) - d_0 q_3 (V - V_0).
\]

If $R_0 < 1$, we have $0 < \gamma_{01} < 1$, therefore $dF(t)/dt$ is negative. Also $dF(t)/dt = 0$ at $E_0 = (S_0, 0, 0, 0, 0, V_0)$, thus the largest compact invariant set is the singleton set $\{E_0\}$, so LaSalle’s invariant principle implies that the disease-free equilibrium point $E_0 = (S_0, 0, 0, 0, 0, V_0)$ is globally asymptotically stable.
Theorem 5.4: If $R_0 > 1$, then model (1) is globally asymptotically stable at endemic equilibrium $E_\ast$.

**Proof:** Let $J$ and $J^{[3]}$ be the Jacobian matrix and third additive compound matrix of the subsystem containing only the first four equations of model (1) given by

\[
J = \begin{pmatrix}
-A_{11} & A_{12} & -A_{13} & -A_{14} \\
A_{21} & -A_{22} & A_{23} & A_{24} \\
A_{31} & A_{32} & -A_{33} & A_{34} \\
A_{41} & A_{42} & A_{43} & -A_{44}
\end{pmatrix},
\]

\[
J^{[3]} = \begin{pmatrix}
-(A_{11} + A_{22} + A_{33}) & A_{34} & A_{43} & -A_{42} \\
-A_{41} & -(A_{11} + A_{22} + A_{44}) & A_{32} & -A_{13} \\
-A_{24} & A_{14} & A_{12} & A_{23} \\
-(A_{11} + A_{33} + A_{44}) & -(A_{22} + A_{33} + A_{44}) & A_{21} & 0
\end{pmatrix},
\]

where

\[
A_{11} = \beta A + \gamma \beta C + q_1, \quad A_{12} = A_{31} = A_{34} = A_{41} = A_{42} = 0, \quad A_{13} = \beta S, \\
A_{14} = \gamma \beta S, \\
A_{21} = \beta A + \gamma \beta C, \quad A_{22} = q_2, \quad A_{23} = \beta S, \quad A_{34} = \gamma \beta S, \quad A_{32} = \sigma, \quad A_{33} = q_3, \\
A_{43} = p \gamma_1, \\
A_{44} = q_4.
\]

Let us define a function $P(\chi) = P(S(t), L(t), A(t), C(t)) = \text{diag}[S(t), L(t), A(t), C(t)]$, which implies that $P^{-1}(\chi) = \text{diag}[1/S(t), 1/L(t), 1/A(t), 1/C(t)]$. The time derivative of $P(\chi)$ yields that $P_f(\chi) = \text{diag}[\dot{S}(t), \dot{L}(t), \dot{A}(t), \dot{C}(t)]$. A direct computation shows that $B = P_f P^{-1} + J^{[3]} P^{-1}$, which becomes

\[
B = \begin{pmatrix}
a_{11} & 0 & a_{13} & -a_{14} \\
a_{21} & a_{22} & a_{23} & a_{24} \\
0 & a_{32} & a_{33} & 0 \\
0 & 0 & a_{43} & a_{44}
\end{pmatrix},
\]

with

\[
a_{11} = \frac{\dot{S}(t)}{S(t)} - \beta A(t) - \gamma \beta C(t) - q_1 - q_2 - q_3 + \frac{\gamma \beta S^2(t)}{A(t)} - \frac{\gamma \beta S^2(t)}{C(t)}, \\
a_{13} = \frac{\gamma \beta S^2(t)}{A(t)}, \quad a_{14} = -\frac{\gamma \beta S^2(t)}{C(t)}, \quad a_{21} = p \gamma_1 S(t) L(t), \\
a_{22} = \frac{\dot{L}(t)}{L(t)} - \beta A(t) - \gamma \beta C(t) - q_1 - q_2 - q_4, \quad a_{23} = \frac{\beta S(t) L(t)}{A(t)},
\]
Table 2. Parameter values used in the numerical simulation of model (1).

| Notation | Parameter description                      | Value     |
|----------|--------------------------------------------|-----------|
| b        | Birth rate                                 | 0.0121000 |
| \( \gamma_3 \) | Vaccination rate                         | 0.5000000 |
| \( d_0 \) | Natural mortality rate                     | 0.0069300 |
| \( \gamma \) | Reduced transmission rate                 | 0.1600000 |
| \( d_1, d_2 \) | Hepatitis B-related death rate           | 0.0020000 |
| \( \sigma \) | Moving rate from latent to acute         | 0.0160000 |
| \( \vartheta_1 \) | Hospitalization of acutely infected      | 0.3600000 |
| \( \eta \) | Perinatally infected individuals rate     | 0.1100000 |
| \( \vartheta_2 \) | Recovery of hospitalized individuals     | 0.3400000 |
| \( \vartheta_3 \) | Hospitalization of chronically infected   | 0.5900000 |
| \( \xi \) | Birth rate without successful vaccination | 0.3200000 |
| \( \phi \) | Waning vaccine-induced immunity rate       | 0.1000000 |
| \( \gamma_1 \) | Moving rate from acute to chronic carrier | 0.0109500 |
| \( \gamma_2 \) | Moving rate from chronic carrier to immune| 0.0000684 |
| \( \beta \) | Transmission rate from susceptible to infected | 0.9500000 |
| \( p \) | Probability of those individuals who fail to recover in acute class | 0.8850000 |

Figure 1. The dynamics of the basic reproduction number \( R_0 \) versus sensitive parameters \( \beta, \gamma_1, \gamma_2, \) and \( \gamma_3 \). (a) \( R_0 \) versus \( \gamma_1 \) and \( \beta \). (b) \( R_0 \) versus \( \gamma_2 \) and \( \beta \). (c) \( R_0 \) versus \( \gamma_3 \) and \( \beta \).
\[ a_{24} = \frac{\beta S(t)L(t)}{C(t)}, \quad a_{32} = \frac{\sigma A(t)}{L(t)}, \]
\[ a_{33} = \frac{\dot{A}(t)}{A(t)} - \beta A(t) - \gamma \beta C(t) - q_1 - q_3 - q_4, \]
\[ a_{43} = \frac{\beta A(t)C(t) + \gamma \beta C^2(t)}{A(t)}, \]
\[ a_{44} = \frac{\dot{C}(t)}{C(t)} - q_2 - q_3 - q_4. \]  

(29)

Consequently,

\[ h_1(t) = a_{11} + \sum_{j=2}^{4} |a_{1j}|, \]

Figure 2. The dynamics of the basic reproduction number $R_0$ versus sensitive parameters $\sigma$, $\gamma_1$, $\gamma_2$, and $\gamma_3$. (a) $R_0$ versus $\sigma$ and $\gamma_1$. (b) $R_0$ versus $\sigma$ and $\gamma_2$. (c) $R_0$ versus $\sigma$ and $\gamma_3$. 
\begin{align*}
\frac{\dot{S}(t)}{S(t)} &= -\beta A(t) - \gamma \beta C(t) - q_1 - q_2 - q_3 + \frac{\gamma \beta S^2(t)}{A(t)} + \frac{\gamma \beta S^2(t)}{C(t)}, \\
\leq \frac{\dot{S}(t)}{S(t)} &= -\beta A(t) - q_1 - q_2 - q_3,
\end{align*}

\begin{align*}
\dot{h}_2(t) &= a_{22} + \sum_{j=1 \text{ and } j \neq 2}^{4} |a_{2j}|, \\
\frac{\dot{L}(t)}{L(t)} &= -\beta A(t) - \gamma \beta C(t) - q_1 - q_2 - q_4 + p \gamma_1 S(t)L(t) + \frac{\beta S(t)L(t)}{A(t)} + \frac{\beta S(t)}{C(t)}, \\
\leq \frac{\dot{L}(t)}{L(t)} &= -\beta A(t) - \gamma \beta C(t) - q_1 - q_2 - q_4,
\end{align*}

\begin{align*}
\dot{h}_3(t) &= a_{33} + \sum_{j=1 \text{ and } j \neq 3}^{4} |a_{3j}|,
\end{align*}

Figure 3. The dynamics of the basic reproduction number $R_0$ versus sensitive parameters $\sigma$, $\eta$, $\vartheta_1$, and $\vartheta_2$. (a) $R_0$ versus $\sigma$ and $\eta$. (b) $R_0$ versus $\vartheta_1$ and $\sigma$. (c) $R_0$ versus $\vartheta_2$ and $\sigma$. 
\[
\begin{align*}
\frac{\dot{A}(t)}{A(t)} - \beta A(t) - \gamma \beta C(t) - q_1 - q_3 - q_4 + \frac{\sigma A(t)}{L(t)}, \\
\leq \frac{\dot{A}(t)}{A(t)} - \beta A(t) - \gamma \beta C(t) - q_1 - q_3 - q_4,
\end{align*}
\]

\[
\begin{align*}
h_4(t) &= a_{44} + \sum_{j=1 \text{ and } j \neq 4}^{4} |a_{4j}|, \\
= \frac{\dot{C}(t)}{C(t)} - q_2 - q_3 - q_4 + \frac{\beta A(t)C(t) + \gamma \beta C^2(t)}{A(t)}, \\
\leq \frac{\dot{C}(t)}{C(t)} - q_2 - q_3 - q_4.
\end{align*}
\]

Let \((b_1, b_2, b_3, b_4)\) be a vector in \(\mathbb{R}^4\) and the Lozinski measure \(\ell(B)\) of \(B\) is defined as \(\ell(B) = h_i(t), i = 1,2,3,4\). The integration of the Lozinski measure \(\ell(B)\) and by taking limit

**Figure 4.** The dynamics of the basic reproduction number \(R_0\) versus sensitive parameters \(\gamma_1, \gamma_2, \gamma_3,\) and \(\vartheta_3\). (a) \(R_0\) versus \(\gamma_1\) and \(\gamma_2\). (b) \(R_0\) versus \(\gamma_1\) and \(\gamma_3\). (c) \(R_0\) versus \(\vartheta_3\) and \(\gamma_3\).
as \( t \to \infty \) leads to the following equation:

\[
\bar{q} = \lim_{t \to \infty} \sup \sup \frac{1}{t} \int_0^t \ell(B) \, dt < 0.
\]

The system containing the first four equations of model (1) is globally asymptotically stable around its interior equilibrium \((S^*, L^*, A^*, C^*)\). The solution of the limiting system of the remaining three equations of model (1) gives that \( H(t) \to H^* \), \( R(t) \to R^* \), and \( V(t) \to V^* \) as \( t \to \infty \). Hence the disease endemic equilibrium point \( E_0 \) is globally asymptotically stable.

6. Numerical simulation and discussion

To verify our analytical results, we perform numerical simulations of model (1). Our simulations are based on a qualitative point of view and the parameters are taken in a biologically

![Figure 5](image-url)

**Figure 5.** The plot represents the stability results of the compartmental population (susceptible, latent, acute and chronic) model (1). (a) Susceptible population. (b) Latent population. (c) Acutely infected population. (d) Chronically infected population.
feasible way. The numerical results are obtained by using the Runge–Kutta method of fourth order. Moreover, the parameter values taken are presented in Table 2. The time interval is taken as 0–200 units, while the different initial population sizes for the compartmental population susceptible $S(t)$, latent $L(t)$, acutely infected $A(t)$, chronic carries $C(t)$, hospitalized $H(t)$, recovered $R(t)$, and vaccinated individuals $V(t)$ are presented in Table 2. By using the parameters values, initial population sizes, and the time interval 0–200, we obtain the simulation as shown in Figures 5 and 6. The simulation presented in Figures 1–4 shows that there are always susceptible and vaccinated population, while the infected individuals vanish. The trajectories of susceptible $S(t)$, latent $L(t)$, acutely infected $A(t)$, chronically infected $C(t)$, hospitalized $H(t)$, recovered $R(t)$, and vaccinated $V(t)$ converge to the disease-free equilibrium point. Which ensure the stability of the proposed

![Graphs](image)

**Figure 6.** The plot represents the stability results of the compartmental population (hospitalized, recovered and vaccination) model (1). (a) Hospitalized population. (b) Recovered population. (c) Vaccinated population.
model (1) at the disease-free equilibrium point. Similarly the proposed model is stable at disease endemic equilibrium.

### 6.1. Impact of hospitalization and vaccination

In the prevention of hepatitis B, the role of hospitalization and vaccination is very important. Figures 7 and 8 represent the simulation of model (1) with the effect of hospitalization and vaccination, respectively. Figure 7 shows the dynamic of model (1) with and without hospitalization. Similarly, Figure 8 shows the dynamic of model (1) with and without vaccination. We see that the hospitalization and vaccination have a high effectiveness on the hepatitis B transmission and its control. These numerical simulations show that the effective hospitalization and vaccination is one of the better control measures of the hepatitis B infection.

**Figure 7.** The plot represents the dynamic of the compartmental population (acute, chronic, hospitalized, and recovered) model under the effect of hospitalization and without hospitalization. (a) Susceptible population; (b) latent population; (c) acutely infected population; (d) chronically infected population.
7. Concluding remarks

We developed an epidemic model for the transmission dynamic of hepatitis B virus. The different infection phases (acute and chronic) of hepatitis B are classified with the effect of hospitalization. We discuss the existence, the positive solutions, and the biological feasibility of the proposed model. We find the basic reproduction number and performed its sensitivity analysis using the next generation matrix approach and normalized forward sensitivity index method, respectively. We also discussed the stability analysis of the model at both disease-free and disease endemic equilibria. For the local stability linearization, Routh–Hurwitz criteria were used. While for the global stability analysis, the Lyapunov function theory and the geometrical approach were utilized. Finally, we performed the numerical simulation and verified our analytical findings. The simulation ensured that the hospitalization and vaccination are one of the effective control mechanisms to control the hepatitis B infection.

In future, we will use the optimal control theory to design a mechanism for the minimization of hepatitis B infection on the basis of the normalized forward sensitivity index. Work on such issues are in progress and will be reported in a near future publication.

Disclosure statement

No potential conflict of interest was reported by the authors.

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