METHOD ARTICLE

Mathematical model and analysis of hepatitis B virus transmission dynamics [version 1; peer review: 1 not approved]

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Abstract

Hepatitis B is a liver infection induced by the hepatitis B virus (HBV). In this paper, the dynamics involved in the transmission of HBV is mathematically formulated with considerations of different populations of individuals. The role of HBV vaccination of new born babies and the treatment of infected individuals in controlling the transmission are factored into the model. The model in this study is based on the standard SEIR model.

Keywords

Hepatitis B virus (HBV); Disease-free equilibrium; Endemic equilibrium state; Stability analysis

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Any reports and responses or comments on the article can be found at the end of the article.

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Introduction

Hepatitis B (HB) is a potentially life-threatening liver infection caused by the hepatitis B virus (HBV), which is a DNA virus classified in the virus family of Hepadnaviridae. The World Health Organization (WHO) in 1 reported that more than 0.25 billion people are living with HBV infection, most of which resulted in several deaths.

A vaccine against HB has been available since 1982, nevertheless there is still an increase in its transmission and spread. Key facts from 1 reveal that HBV can survive outside the human body for at least 7 days, and during this period HBV can still cause infection if it enters any unimmunized human body. Most HB carriers are asymptomatic during the acute infection phase, nonetheless some people experience acute illness that can last for several days with variations in the progression.

The use of mathematical models in scientific research has improved our understanding of contributing factors. Mathematical model of HBV has ranged from simple models^{2,3} to more complex models involving the contributions of controls (e.g. vaccines)⁴, and analysis of the impact of immigrant⁵.

Motivated by other HB studies, we use an infectious disease model to understand the impact of HB vaccination and treatment on the dynamics of HBV transmission and prevalence using an SEIR format.

Methods

Mathematical model

A variety of mathematical models exist, such as the SIR, SIS, SIRS, and their variations; where S=Susceptible class, I=Infective class, and R=Recovered class. The model used in this study takes the form of SEIR based on ordinary differential equations, which shall be solved to obtain the disease-free equilibrium (DFE) state.

Governing equations

Table 1 lists the parameters used. Figure 1 shows a schematic presentation of the model.

Table 1. Parameter table.

Par.	Description
ϕ	rate of expiration of vaccine efficacy
k	rate of conversion from S to L
μ	rate of conversion from L to I
ψ	rate of conversion from I to R
π	rate of conversion from R to S
η	HB-induced mortality
β	natural mortality
P	population of new births
cP	immunized new births
N	total population size

Figure 1. Schematic presentation of the model.

We formulate the HB transmission model as follows:

$$\frac{dM(t)}{dt} = cP - \phi M(t) - \beta M(t) \quad (1)$$

$$\frac{dS(t)}{dt} = (1-c)P + \phi M(t) + \pi R(t) - (kI(t) + \beta)S(t) \quad (2)$$

$$\frac{dL(t)}{dt} = kS(t)I(t) - qL(t) - \mu L(t) - \beta L(t) \quad (3)$$

$$\frac{dI(t)}{dt} = \mu L(t) - \psi I(t) - \eta I(t) - \beta I(t) \quad (4)$$

$$\frac{dR(t)}{dt} = qL(t) - \psi I(t) - \pi R(t) - \beta R(t) \quad (5)$$

$$N(t) = M(t) + S(t) + L(t) + I(t) + R(t) \quad (6)$$

where M = immunized individuals, S = susceptible, L = latently infected/exposed, I = infectious individuals, and R = recovered.

Equilibrium solutions

Let $E(M, S, L, I, R)$ be the equilibrium point of the system described by (1)–(6). At the equilibrium state, we have

$$\frac{dM}{dt} = \frac{dS}{dt} = \frac{dL}{dt} = \frac{dI}{dt} = \frac{dR}{dt} = 0.$$

i.e.,

$$cP - \phi M - \beta M = 0 \quad (7)$$

$$cP - (\phi + \beta)M = 0 \quad (8)$$

$$(1-c)P + \phi M + \pi R - kSI - \beta S = 0 \quad (9)$$

$$(1-c)P + \phi M + \pi R - (kI + \beta)S = 0 \quad (10)$$

$$kSI - qL - \mu L - \beta L = 0 \quad (11)$$

$$kSI - (q + \mu + \beta)L = 0 \quad (12)$$

$$\mu L - \psi I - \eta I - \beta I = 0 \quad (13)$$

$$\mu L - (\psi + \eta + \beta)I = 0 \quad (14)$$

$$qL - \psi I - \pi R - \beta R = 0 \quad (15)$$

$$qL + \psi I - (\pi + \beta)R = 0 \quad (16)$$

In order to obtain the DFE state we solve equation (7)–equation (15) simultaneously.

Existence of a trivial equilibrium state (TES)

Let $E_o (M_o, S_o, L_o, I_o, R_o)$ be TES of (1)–(6) of the model, $\exists$ no TES since the population cannot be extinct, so long as new babies are born into the population (i.e. $cP \neq 0$ and $(1 - c)P \neq 0$).

That is, $E_o (M_o, S_o, L_o, I_o, R_o) \neq (0, 0, 0, 0, 0)$

DFE state

DFE state is the state of total eradication of disease. Let $E^o (M^o, S^o, L^o, I^o, R^o)$ be the DFE state. Suppose, both I and L must be zero. That is, for DFE state:

$$I^o = L^o = 0 \quad (17)$$

Substituting $I - L = 0$ into equation (7)–equation (11) and solving simultaneously we have:

From Equation (7):

$$\begin{aligned} cP - (\phi + \beta)M &= 0 \\ M^o &= \frac{cP}{\phi + \beta} \end{aligned} \quad (18)$$

From Equation (9)

$$(1 - c)P + \frac{\phi cP}{\phi + \beta} + \pi R - \beta S = 0 \quad (19)$$

From Equation (11)

$$\begin{aligned} qL + \psi I - (\pi + \beta)R &= 0 \\ \Rightarrow (\pi + \beta)R &= 0 \text{ (since } L = I = 0) \\ \Rightarrow \text{Either } (\pi + \beta) &= 0 \text{ Or } R = 0 \end{aligned} \quad (20)$$

Since π and β are positive constants, $(\pi + \beta) \neq 0$.

Therefore, $R^o = 0$.

If $R = 0$, Equation (9) becomes

$$\begin{aligned} (1 - c)P + \frac{\phi cP}{\phi + \beta} - \beta S &= 0 \\ \Rightarrow S^o &= \frac{(\phi + \beta)(1 - c)P + \phi cP}{\beta(\phi + \beta)} \end{aligned}$$

or

$$S^o = \frac{\phi + \beta - c\beta)P}{\beta(\phi + \beta)} \quad (22)$$

Therefore the DFE state of the model is

$$E^o (M^o, S^o, L^o, I^o, R^o) = \left(\frac{cP}{\phi + \beta}, \frac{(\phi + \beta - c\beta)P}{\beta(\phi + \beta)}, 0, 0, 0 \right)$$

Stability analysis of the DFE state

To determine the stability of the DFE state E^o , we examine the behavior of the model population near this equilibrium solution. Here, we determine condition(s) that must be met if the disease is to be totally eradicated.

Recall that the system of equations in this model at equilibrium state is:

$$cP - (\phi + \beta)M = 0$$

$$\begin{aligned} (1 - c)P + \phi M + \pi R - (kI + \beta)S &= 0 \\ kSI - (q + \mu + \beta)L &= 0 \\ \mu L - (\psi + \beta + \eta)I &= 0 \\ qL + \psi I - (\pi + \beta)R &= 0 \end{aligned} \quad (23)$$

We now linearize the system of equations to get the Jacobian matrix J .

$$J = \begin{bmatrix} \omega_1 & 0 & 0 & 0 & 0 \\ \phi & \omega_2 & 0 & -kS^o & \pi \\ 0 & kI^o & \omega_3 & kS^o & 0 \\ 0 & 0 & \mu & \omega_4 & 0 \\ 0 & 0 & q & \psi & \omega_5 \end{bmatrix} \quad (24)$$

where

$$\begin{aligned} \omega_1 &= -(\phi + \beta), \omega_2 = -(kI^o + \beta), \omega_3 = -(q + \mu + \beta), \omega_4 = -(\psi + \beta + \eta), \\ \omega_5 &= -(\pi + \beta) \end{aligned}$$

At the disease-free equilibrium, $E^o (M^o, S^o, L^o, I^o, R^o)$, the Jacobian Matrix becomes

$$J = \begin{bmatrix} \omega_6 & 0 & 0 & 0 & 0 \\ \phi & -\beta & 0 & \omega_7 & \pi \\ 0 & kI^o & \omega_8 & \omega_9 & 0 \\ 0 & 0 & \mu & \omega_{10} & 0 \\ 0 & 0 & q & \psi & \omega_{11} \end{bmatrix} \quad (25)$$

where

$$\begin{aligned} \omega_6 &= -(\phi + \beta), \omega_7 = -k \frac{(\phi + \beta - c\beta)P}{\beta(\phi + \beta)}, \omega_8 = -(q + \mu + \beta), \\ \omega_9 &= k \frac{(\phi + \beta - c\beta)P}{\beta(\phi + \beta)}, \omega_{10} = -(\psi + \beta + \eta), \omega_{11} = (q + \mu + \beta + \lambda) > \\ &= -(\pi + \beta) \end{aligned}$$

The characteristic equation $|J_o - I\lambda| = 0$ is obtained from the Jacobian determinant with the Eigen values λ_i ($i = 1, 2, 3, 4, 5$)

$$= (\lambda^2 + (\phi + 2\beta)\lambda + (\phi\beta + \beta^2))(-\pi - \beta - \lambda)[X] = 0 \quad (26)$$

where

$$[X] = \begin{bmatrix} -(q + \mu + \beta) - \lambda & -k \frac{(\phi + \beta - c\beta)P}{\beta(\phi + \beta)} \\ \mu & -(\psi + \beta + \eta) - \lambda \end{bmatrix}$$

From Equation (26), either

$$(\lambda^2 + (\phi + 2\beta)\lambda + (\phi\beta + \beta^2))(-\pi - \beta - \lambda) = 0 \quad (27)$$

or

$$\begin{bmatrix} -(q + \mu + \beta) - \lambda & -k \frac{(\phi + \beta - c\beta)P}{\beta(\phi + \beta)} \\ \mu & -(\psi + \beta + \eta) - \lambda \end{bmatrix} = 0 \quad (28)$$

From Equation (27), we deduce

$$\lambda_1 = -(\pi + \beta) \quad (29)$$

$$\lambda_2 = -\beta \quad (30)$$

and

$$\lambda_3 = -(\phi + \beta) \quad (31)$$

Let

$$A = \begin{bmatrix} -(q + \mu + \beta) - \lambda & -k \frac{(\phi + \beta - c\beta)P}{\beta(\phi + \beta)} \\ \mu & -(\psi + \beta + \eta) - \lambda \end{bmatrix} = 0$$

For the DFE to be asymptotically stable, $\text{trace}(A) < 0$ and $\det A > 0$.

$$\det A = (q + \mu + \beta + \lambda)(\psi + \beta + \eta + \lambda) - k\mu \frac{(\phi + \beta - c\beta)P}{\beta(\phi + \beta)}$$

And the trace of A is

$$\text{Trace}(A) = -(q + \mu + \beta + \lambda) - (\psi + \beta + \eta + \lambda)$$

Obviously, $\text{trace}(A) < 0$ since all the parameters q, t, β, ψ, β and η are positive.

For the determinant of A to be positive, we must have

$$(q + \mu + \beta + \lambda)(\psi + \beta + \eta) - k\mu \frac{(\phi + \beta - c\beta)P}{\beta(\phi + \beta)} > 0$$

or

$$(q + \mu + \beta + \lambda)(\psi + \beta + \eta) > k\mu \frac{(\phi + \beta - c\beta)P}{\beta(\phi + \beta)} \quad (32)$$

From equation (29)–equation (31), $\lambda_1, \lambda_2, \lambda_3$ of (25) all have negative real parts. We now establish the necessary and sufficient conditions for the remaining two Eigen values of (25) to have negative real part. The remaining two Eigen values of equation (25) will have negative real part if and only if $\det A > 0$. i.e.

$$(q + \mu + \beta + \lambda)(\psi + \beta + \eta) > k\mu \left(\frac{(\phi + \beta - c\beta)P}{\beta(\phi + \beta)} \right)$$

The Routh-Hurwitz theorem states that the equilibrium state will be asymptotically stable if and only if all the Eigen values of the characteristic equation $|J - I\lambda| = 0$ have negative real part. Using this theorem we see that the DFE of this model will be asymptotically stable if and only if

$$(q + \mu + \beta + \lambda)(\psi + \beta + \eta) > k\mu \left(\frac{(\phi + \beta - c\beta)P}{\beta(\phi + \beta)} \right)$$

or

$$k\mu \left(\frac{(\phi + \beta - c\beta)P}{\beta(\phi + \beta)} \right) < (q + \mu + \beta + \lambda)(\psi + \beta + \eta) \quad (33)$$

The inequality (32) gives the condition, necessary and sufficient for the DFE state of the model to be stable (asymptotically). This means that the product of total contraction and total breakdown of latent class given by $k\mu \left(\frac{(\phi + \beta - c\beta)P}{\beta(\phi + \beta)} \right)$ must be less than the total removal rate from both latent and infectious classes given by $(q + \mu + \beta + \lambda)(\psi + \beta + \eta)$.

Alternatively, the inequality (32) can also be expressed as

$$(q + \mu + \beta + \lambda) > k\mu \left(\frac{(\phi + \beta - c\beta)P}{\beta(\phi + \beta)(\psi + \beta + \eta)} \right) \quad (34)$$

The inequality (33) also gives the condition necessary and sufficient for the stability of DFE state, thus sum of the rate of recovery of latently infected people, the rate at which latently infected individuals progress to active infection and the rate of natural death of individuals (in the population, i.e. total removal rate from the latent class) must have a lower bound given by

$$k\mu \left(\frac{(\phi + \beta - c\beta)P}{\beta(\phi + \beta)(\psi + \beta + \eta)} \right)$$

Conclusion

Presented in this paper is a mathematical model of the role of vaccination and treatment on HB transmission dynamics. The proportion dynamics of the classes is described using five differential equations. We conclude that the trivial equilibrium state $E_o(M_o, S_o, L_o, I_o, R_o)$ is unstable; this is the state where there is no individual in the population. The DFE state, $E^o(M^o, S^o, L^o, I^o, R^o)$, was determined and its stability analysed using Routh-Hurwitz theorem.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

Competing interests

No competing interests were disclosed.

Grant information

The author(s) declared that no grants were involved in supporting this work.

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Summary. Authors proposed a compartmental SEIR model for the spread of Hepatitis B Virus (HBV). Attention is given to formulated with considerations of different populations of individuals the role of HBV vaccination of new born babies and the treatment of infected individuals. The model analysis mainly concerns the local stability of the disease-free equilibrium (DFE).

To the question "Is the rationale for developing the new method (or application) clearly explained?", my answer is "No". Indeed, there is some literature on the subject of HBV where age-structured model for the transmission dynamics of HBV is proposed with a focus on intervention options such as vaccination, prevention of HBV perinatal infections and treatment. See for example Djidjou-Demasse *et al.* (2016)¹, Zhao *et al.* (2000)², Zou *et al.* (2010)^{3,4} and references therein.

To the question "Is the description of the method technically sound?", my answer is "No". Well, authors derived two basic properties of the model dynamics: the existence of a DFE and the local stability. However, the manuscript is suffering from a lack of originality compared to the existing literature on the similar subjects. Moreover, according to the title of the manuscript, "Mathematical model and analysis of hepatitis B virus transmission dynamics", it was expected to have more analysis materials in the manuscript.

To the question "Are the conclusions about the method and its performance adequately supported by the findings presented in the article?", my answer is "No". Authors stated that "we use an infectious disease model to understand the impact of HB vaccination and treatment on the dynamics of HBV transmission and prevalence". However, through authors analysis it is far from clear how they highlight the impact of vaccination and treatment on the HBV dynamics.

As a general comments, it is quite surprising how the authors tackle the question of vaccination of new babies without structuring the host population by age (or by age groups).

As a conclusion I Not Approved this paper for indexing.

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Is the rationale for developing the new method (or application) clearly explained?

No

Is the description of the method technically sound?

No

Are sufficient details provided to allow replication of the method development and its use by others?

Yes

If any results are presented, are all the source data underlying the results available to ensure full reproducibility?

No source data required

Are the conclusions about the method and its performance adequately supported by the findings presented in the article?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Differential Equations, Dynamical Systems, and Mathematical Biology.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

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