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Research Article

Stability analysis of the transmission dynamics of an HBV model

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Abstract

Hepatitis B virus (HBV) infection is a major public health problem in the world today. A mathematical model is formulated to describe the spread of hepatitis B, which can be controlled by vaccination as well as treatment. We study the dynamical behavior of the system with fixed control for both vaccination and treatment. The results shows that the dynamics of the model is completely determined by the basic reproductive number R_0. if $R_0 < 1$, the disease-free equilibrium is globally asymptotically stable by using approach that given by Kamgang and Sallet. Then the authors prove that if $R_0 > 1$, the disease-free equilibrium is unstable and the disease is uniformly persistent. Furthermore, If $R_0 > 1$, the unique endemic equilibrium is globally asymptotically stable by using a generalization of the Poincar e-Bendixson criterion.

Keywords : Hepatitis B virus (HBV); Basic reproduction number (R_0); Gompound matrices; Global stability.

1 Introduction

Hepatitis B is a potentially life-threatening liver infection caused by the hepatitis B virus. It is a major global health problem. It can cause chronic liver disease, chronic infection and death from cirrhosis and cancer [34]. Infections of hepatitis B occur only if the virus is able to enter the blood stream and reach the liver. Once in the liver, the virus reproduces and releases large numbers of new viruses into the blood stream [6].

In an study [31], the authers presented an epidemic model of S-E-I-C-R-S type that is described by the following system of ordinary differential equations. A flow chart of this compartmental model is shown in figure 1.

$$\begin{aligned}
\dot{S}(t) =& \nu - \nu p_1 C - \nu p_2 R - \rho(I + \theta C)S \\
& - \nu S - u_1 S + \lambda_4 R \\
\dot{E}(t) =& \rho(I + \theta C)S - (\nu + \lambda_1)E \\
\dot{I}(t) =& \lambda_1 E - (\nu + \lambda_2)I \\
\dot{C}(t) =& \nu p_1 C + p_3 \lambda_2 I - (\nu + \lambda_3)C - u_2 C \\
\dot{R}(t) =& \nu p_2 R + (1 - p_3)\lambda_2 I + \lambda_3 C - \nu R \\
& - \lambda_4 R + u_1 S + u_2 C
\end{aligned} \tag{1.1}$$

A community affected by HBV infection is divided into five compartments, namely: the susceptible individuals S(t); infected but not yet infectious individuals (exposed) E(t); acute infected individuals I(t); chronic HBV carriers C(t); and recovered R(t) for hepatitis B virus (HBV) infection that propagates through contact between infected and the susceptible individuals and also through of infected parents.

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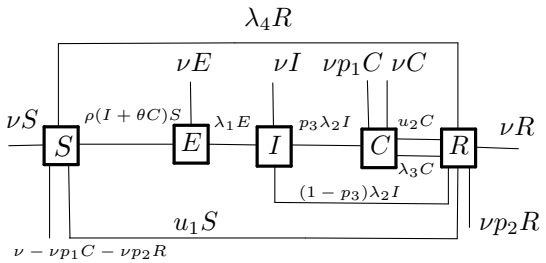

Figure 1: Diagram for the HBV dynamics with two controls

In these equations, all the parameters are non-negative. We assume stable population with equal per capital birth and death ν (as disease induced death rate is not considered in system). The main parameter listed in table 1.[31]

Table 1. Definition of parameters used in model (2.1)

Parameter	Description
ν	Birth(and death) rate
ρ	Transmission rate
θ	Infectiousness of darriers relative to acute infections
λ_1	Rate moving from exposed to acute
λ_2	Rate at which individuals leave the acute infection class
λ_3	Rate moving from carrier to recovery
λ_4	Loss of recovery rate
p_1	Probability of infected newborns
p_2	Probability of immune newborns
p_3	Proportion of acute infection individuals become carriers
u_1	Proportion of the susceptible that is vaccinated per unit time
u_2	Proportion of the chronic HBV carriers that is treated per unit time

For simplicity, we normalize the population size to 1; i.e. now S,E,I,C and R are, respectively, the fraction of the susceptible, the exposed, the acute infective, the carriers and the recovered individuals in the population and $S+E+I+C+R=1$ holds [28, 31]. Hence, the fifth equation may be omitted, and the Eq. (1.1) becomes:

$$\begin{aligned}
\dot{S}(t) &= \nu - \nu p_1 C - \rho(I+\theta C)S - \nu S - u_1 S \\
&\quad + (\lambda_4 - \nu p_2)(1-S-E-I-C) \\
\dot{E}(t) &= \rho(I+\theta C)S - (\nu+\lambda_1)E \\
\dot{I}(t) &= \lambda_1 E - (\nu+\lambda_2)I \qquad (1.2) \\
\dot{C}(t) &= \nu p_1 C + p_3\lambda_2 I - (\nu+\lambda_3)C - u_2 C
\end{aligned}$$

Moreover, under the dynamics described by Eq (1.2) , the region

$$\Pi = \Big\{(S,E,I,C) \in \mathbb{R}^4_+ \mid S \le \frac{\nu+\lambda_4-\nu p_2}{\nu+u_1+\lambda_4-\nu p_2},$$
$$S+E+I+C \le \frac{\nu+\lambda_4}{\nu+\lambda_4-\nu p_2}\Big\}$$

is positively invariant [31]. Hence, the system is mathematically well-posed. There, for initial starting point $x_0 \in \mathbb{R}^4_+$, the trajectory lies in Π. Therefore, in the rest of the paper we will study the system (1.2) in the feasible region Π.

In this work, we present a complete mathematical analysis for the global stability problem at the disease-free equilibrium and endemic equilibrium of an mathematical model for hepatitis B virus infection with tow controls: vaccination and treatment, we assume that the control parameters $u_1(t)$ and $u_2(t)$ are constant functions. In order to study the global stability of the disease-free equilibrium and endemic equilibrium we apply the approach in Kamgang and Sallet [13, 28] and geometrical approach of Li and Muldowney in [3, 4, 10, 14, 16, 18, 21, 23, 30]. We obtain simple sufficient conditions that the disease free equilibrium and endemic equilibrium of Eq (1.2) are globally asymptotically stable.

The rest of the paper is organized as follows: In Section 2, the Kamgang and Sallet approach is used to study the global stability of the disease-free equilibrium. in Section 3, the Li-Muldowney geometric approach is used to study the global stability of the endemic equilibrium. Finally, the conclusions are summarized in Section 4.

2 The disease-free equilibrium

In this section, we study the stability of the disease-free equilibrium.

2.1 Existence and local stability of the disease-free equilibrium

Firstly, we analyze the local stability of the disease-free equilibrium. Model given by system (1.2) has a unique disease-free equilibrium, obtained by setting the right-hand sides of system (1.2) to zero, given by [31]

$$P_0 = (S_0, E_0, I_0, C_0) = \left(\frac{\nu-\nu p_2+\lambda_4}{u_1+\nu+\lambda_4-\nu p_2}, 0, 0, 0\right)$$

The basic reproduction number R_0, gives the total number of secondary infections that an average infectious individual will induce given that the rest of the populations susceptible. Using the notationin Van den Driessche and Watmough [32], we have

$$\mathbf{F} = \begin{bmatrix} 0 & \rho S_0 & \rho\theta S_0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

$$\mathbf{V} = \begin{bmatrix} \nu+\lambda_1 & 0 & 0 \\ -\lambda_1 & \nu+\lambda 2 & 0 \\ 0 & -p_3\lambda_2 & \nu+\lambda_3+u_2-\nu p_1 \end{bmatrix}$$

The basic reproduction number is given by [31]

$$R_0 = \rho(FV^{-1}) = \frac{\rho\lambda_1(\nu+\lambda_3+u_2-p_1\nu+\theta p_3\lambda_2)}{(\nu+\lambda_1)(\nu+\lambda_2)(\nu+\lambda_3+u_2-p_1\nu)}S_0 \quad (2.3)$$

The disease free equilibrium P_0 is locally asymptotically stable when $R_0 < 1$, and unstable for $R_0 > 1$. **Proof.** see [31] pp 6.

2.2 Global stability of the disease-free equilibrium

In this section, we study the global properties of the disease-free equilibrium. The following theorem provides the global property of the disease-free equilibrium. In order to study the global stability of the disease-free equilibrium, we apply the novel approach in Kamgang and Sallet .[13, 28]

Definition 2.1. *We call any real square matrix with nonnegative off-diagonal entries a Metzler matrix.[13]*

Lemma 2.1. *Let M be a Metzler matrix, which is block decomposed:*

$$\mathbf{M} = \begin{bmatrix} A & B \\ C & D \end{bmatrix}$$

where A and D are square matrices. Then M is Metzler stable if and only if A and $D - CA^{-1}B$ are Metzler stable.

Proof. see [13] pp 3.

Definition 2.2. *(Regular splitting). For a real Metzler matrix M, $M = K + N$ is a regular splitting if K is a Metzler stable matrix and $N \geq 0$ is a nonnegative matrix.[13]*

Lemma 2.2. *Let $M = K + N$ be a regular splitting of a real Metzler matrix M, then M is Metzler stable if and only if $\rho(-NA^{-1}) < 1$.[13]*

Proof. see [13] pp 4.

Lemma 2.3. *. If the following hypothesis $(i-v)$ are satisfied, the disease-free equilibrium (DFE) is globally asymptotically stable for system*

$$\begin{cases} \dot{X}_1 = A_1(X)(X_1 - X_1^*) + A_{12}(X)X_2 \\ \dot{X}_2 = A_2(X)X_2 \end{cases} \quad (2.4)$$

on the positively invariant set $\Omega \in R_+^{n_1+n_2}$ where $X_1 \in R_+^{n_1}$, $X_2 \in R_+^{n_2}$, $X = (X_1, X_2)$, and $X^* = (X_1^*, 0)$ denotes a disease-free equilibrium (DFE) of the system (2.4). The variable X_1 denotes the numbers (or densities) in the different compartments of susceptibles, immunes, recovered individuals etc., in other words all the individuals who are not infected and who are not transmitting the disease (e.g, quarantined). The variable X_2 denotes the numbers (or densities) of infected individuals; i.e., latent, infectious, carrying individuals and so on.

(i) The system is defined on a positively invariant set Ω of the nonnegative orthant. The system is dissipative on Ω.

(ii) The sub-system $\dot{X}_1 = A_1(X_1, 0)(X_1 - X_1^*)$ is globally asymptotically stable at the equilibrium X_1^* on the canonical projection of Ω on $R_+^{n_1}$.

(iii) The matrix $A_2(X)$ is Metzler and irreducible for any given $X \in \Omega$.

(iv) There exists an upper-bound matrix $\overline{A_2}$ for $\Lambda = \{A_2(X) : X \in \Omega\}$ with the property that either $\overline{A_2} \notin \Lambda$ or if $\overline{A_2} \in \Lambda$ (i.e.,$\overline{A_2} = \max_\Omega \Lambda$) then for any $\overline{X} \in \Omega$, such that $\overline{A_2} = A_2(\overline{X})$, $\overline{X} \in R_+^{n_1} \times \{0\}$ (i.e. the points where the maximum is realized are contained in the disease-free sub-manifold).

(v) $\alpha(\overline{A_2}) \leq 0$, where $\alpha(\overline{A_2})$ is spectral bound of $\overline{A_2}$.

Proof. see [13] pp 5.

Now, we have the following theorem for the global stability of the disease-free equilibrium of system (1.2).

Theorem 2.1. *For the model (1.2), the disease-free equilibrium is globally asymptotically stable if $R_0 \leq 1$.*

Proof. In order to proof the Theorem and get the global asymptotic stability when the $R_0 \leq 1$, we apply the lemma (2.3) and we have:

(i) There $X_1 = S$, $X_2 = (E, I, C)$ and $X = (S, E, I, C) = (X_1, X_2)$ according to [31]. The invariant domain Π is obviously positively compact set.

(ii) We put $P_0 = X^* = (X_1^*, 0)$, then

$$A_1(X) = -(\nu + u_1 + \lambda_4 - \nu p_2)$$

$$A_{12}(X) = \begin{bmatrix} -\lambda_4 + \nu p_2 \\ -\rho S - \lambda_4 + \nu p_2 \\ -\rho\theta S - \lambda_4 - \nu p_1 + \nu p_2 \end{bmatrix}^T$$

then

$$\dot{S}(t) = A_1(X)(S - \frac{\nu + \lambda_4 - \nu p_2}{\nu + u_1 + \lambda_4 - \nu p_2})$$

hence

$$\dot{X}_1 = A_1(X)(X_1 - X_1^*)$$

This is a linear system which is globally asymptotically stable at

$$X_1^* = \frac{\nu + \lambda_4 - \nu p_2}{\nu + u_1 + \lambda_4 - \nu p_2}$$

(iii) The matrix $A_2(X)$ is given by

$$A_2(X) = \begin{bmatrix} -(\nu+\lambda_1) & \rho S & \rho\theta S \\ \lambda_1 & -(\nu+\lambda_2) & 0 \\ 0 & p_3\lambda_2 & -(\nu+\lambda_3-u_2-\nu p_1) \end{bmatrix}$$

for any $X \in \Pi$ the matrix $A_2(X)$ is Metzler and irreducible.

(iv) This maximum $A_2(\overline{X})$ is given by

$$A_2(\overline{X}) = \begin{bmatrix} -(\nu+\lambda_1) & \rho\frac{\nu+\lambda_4-\nu p_2}{\nu+u_1+\lambda_4-\nu p_2} & \rho\theta\frac{\nu+\lambda_4-\nu p_2}{\nu+u_1+\lambda_4-\nu p_2} \\ \lambda_1 & -(\nu+\lambda_2) & 0 \\ 0 & p_3\lambda_2 & -(\nu+\lambda_3-u_2-\nu p_1) \end{bmatrix}$$

(v) The hypothesis (v) requires that $\alpha(\overline{A_2}) \leq 0$. Writing $\overline{A_2}$ as a block matrix

$$\overline{\mathbf{A_2}} = \begin{bmatrix} A & B \\ C & D \end{bmatrix}$$

where

$$A = -(\nu + \lambda_1)$$

$$B = \begin{bmatrix} \rho\frac{\nu+\lambda_4-\nu p_2}{\nu+u_1+\lambda_4-\nu p_2} & \rho\theta\frac{\nu+\lambda_4-\nu p_2}{\nu+u_1+\lambda_4-\nu p_2} \end{bmatrix}$$

$$C = \begin{bmatrix} \lambda_1 \\ 0 \end{bmatrix}$$

$$D = \begin{bmatrix} -(\nu+\lambda_2) & 0 \\ p_3\lambda_2 & -(\nu+\lambda_3-u_2-\nu p_1) \end{bmatrix}$$

according to lemmas 2.1 and 2.2

$$\overline{\mathbf{A_2}} = D - CA^{-1}B = \begin{bmatrix} -(\nu+\lambda_2) + \frac{\rho\lambda_1 S_0}{\nu+\lambda_1} & \frac{\rho\theta\lambda_1 S_0}{\nu+\lambda_1} \\ p_3\lambda_2 & -(\nu+\lambda_3-u_2-\nu p_1) \end{bmatrix}$$

The characteristic equation of $\overline{A_2}$ is given by

$$\begin{aligned} &\det(\lambda I - (D - CA^{-1}B)) \\ &= \lambda^2 + (\nu + \lambda_2 + \nu + \lambda_3 + u_2 - \nu p_1 \\ &- \frac{\rho\lambda_1 S_0}{\nu+\lambda_1}\Big)\lambda + \Big((\nu + \lambda_2 - \frac{\rho\lambda_1 S_0}{\nu+\lambda_1}) \\ &(\nu + \lambda_3 + u_2 - \nu p_1) - \frac{p_3\lambda_1\theta\rho\lambda_2 S_0}{\nu+\lambda_1}\Big) \\ &= 0 \end{aligned}$$

It follows from the Routh Hurwitz criterion that the two eigenvalues have negative real parts if and only if $R_0 < 1$. When $R_0 = 1$, one eigenvalues zero and another is negative real root. Hence, $\overline{A_2}$ is a stable Metzler matrix if and only if $R_0 \leq 1$, that is $\alpha(\overline{A_2}) \leq 0$ if and only if $R_0 \leq 1$.

Then hypotheses $(i - v)$ of lemma 2.3 are satisfied. Then by lemma 2.3 we have shown that the disease-free equilibrium is globally asymptotically stable if $R_0 \leq 1$.

3 Endemic equilibrium

In this section, we study the stability of the endemic equilibrium.

3.1 Existence and uniqueness and local stability of endemic equilibrium

Here, the condition for the existence and uniqueness of the endemic equilibrium of the system (1.2) is determined. Let $P^* = (S^*, E^*, I^*, C^*)$ be the endemic equilibrium. To find the endemic equilibrium, we equate all equations in the system (1.2) to zero and rewrite it as follows:[31]

$$\begin{aligned} S^* &= \frac{(\nu+\lambda_1)(\nu+\lambda_2)(\nu+\lambda_3-p_1\nu+u_2)}{\rho\lambda_1(\nu+\lambda_3+\theta\lambda_2 p_3-p_1\nu+u_2)} \\ E^* &= \frac{\rho\theta(\nu+\lambda_2)C^*S^*}{(\nu+\lambda_1)(\nu+\lambda_2)-\rho\lambda_1 S^*} \\ I^* &= \frac{\theta\rho\lambda_1 C^*S^*}{(\nu+\lambda_1)(\nu+\lambda_2)-\rho\lambda_1 S^*} \\ C^* &= \Big[\lambda_1\lambda_2 p_3(\nu+\lambda_4-\nu p_2+u_1)S^*(R_0-1)\Big]/ \\ &\Big[(\nu+\lambda_3-p_1\nu+u_2)[(\nu+\lambda_4-\nu p_2)(\nu+\lambda_2 \\ &+\lambda_1)+\lambda_1\lambda_2]+\lambda_1\lambda_2 p_3(\nu p_1-\nu p_2+\lambda_4)\Big] \end{aligned}$$

Lemma 3.1. *(i) If $R_0 < 1$, then the system (1.2) has only one equilibrium, which is disease free equilibrium.*

(ii) If $R_0 > 1$, then the system (1.2) has two equilibria: one is disease free and the other is endemic equilibrium.

(iii) If $R_0 = 1$, then the endemic equilibrium reduces to the disease free equilibrium.

Proof. see [31] pp 5.

Theorem 3.1. *If $R_0 > 1$, then the endemic equilibrium is locally asymptotically stable.*

Proof. see [31] pp 6.

3.2 Global stability of the endemic equilibrium

Here, we study the global behavior of the endemic equilibrium $P^* = (S^*, E^*, I^*, C^*)$ for system (1.2). In the following, using the geometrical approach of Li and Muldowney in [21], we obtain simple sufficient conditions that the endemic equilibrium $P^* = (S^*, E^*, I^*, C^*)$ is globally asymptotically stable. A brief outline of this geometrical approach can be found in [3, 4, 10, 14, 16, 18, 21, 23, 30].
Consider the autonomous dynamical system:

$$\dot{x} = f(x) \tag{3.5}$$

where $f : D \to \mathbb{R}^n$, $D \subset \mathbb{R}^n$ is open set. Let $\|.\|$ denote a vector norm in $\mathbb{R}^n$ as well as the matrix norm which it induces for $n \times n$ matrices. The Lozinski measure $\mu(A)$ of $n \times n$ matrix A with respect to the norm $\|.\|$ is defined as:

$$\mu(A) = \lim_{h \to 0^+} \frac{\|I + hA\| - 1}{h}$$

[4, 10, 21]. Lozinski measure have been used for estimation of eigenvalues of matrices. Consider a nonsingular $P(x)$ be $\binom{n}{2} \times \binom{n}{2}$ matrix-valued function that is C^1 on D and a vector norm $\|.\|$ on $\mathbb{R}^{\binom{n}{2}}$. Consider

$$B = P_f P^{-1} + P J^{[2]} P^{-1}$$

Here the matrix $P_f = (DP)(f)$ or, equivalently, P_f is matrix obtained by replacing each entry p_{ij} in P by its direction derivative in the direction of f ,

$$(p_{ij})_f = \left(\frac{\partial p_{ij}}{\partial x}\right)^T .f(x)$$

and $J^{[2]}$ is second additive compound matrix of the jacobian matrix J.

Theorem 3.2. *Under the following assumptions:*

(i) D is simply connected;

(ii) there is a compact absorbing set $K \subset D$;

(iii) $\overline{x}$ is only equilibrium of (3.5) in D.

$\overline{x}$ is globally asymptotically stable in D, if there exist a $\delta > 0$ and

$$\mu(P_f P^{-1} + P J^{[2]} P^{-1}) \leq -\delta < 0$$

for all $x \in K$.

Proof. see [21, 4, 10].

Definition 3.1. *[16, 23, 30]. The system (1.2) is said to be uniformly persistent in Π, if there exists a constant $\epsilon > 0$ such that any solution $(S(t), E(t), I(t), C(t))$ of system (1.2) with initial value $(S_0, E_0, I_0, C_0) \in \dot{\Pi}$ satisfies*

$$\min\Big\{\liminf_{t\to\infty} S(t), \liminf_{t\to\infty} E(t), \liminf_{t\to\infty} I(t), \liminf_{t\to\infty} C(t)\Big\} \geq \epsilon$$

Lemma 3.2. *If $R_0 > 1$, then system (1.2) is uniformly persistent.*

The proof is similar to that given by [4, 21] so we omit it.

Remark 3.1. *The uniform persistence of system (1.2) in the bounded set Π is equivalent to the existence of a compact $K \subset \dot{\Pi}$ that is absorbing for (1.2).[4, 16, 30]*

Lemma (3.1) shows the existence of a unique endemic equilibrium if $R_0 > 1$. We now claim the following:

Theorem 3.3. *For $R_0 > 1$, the unique endemic equilibrium of the system (1.2) is globally asymptotically stable if*

$$\max\Big\{-\nu + \lambda_1 + 2\rho(1+\theta) + \frac{1}{\varepsilon_0}(5\lambda_4 + 3\nu p_1 + 2\nu p_2), -\nu + \lambda_1 + \frac{2}{\varepsilon_0}(\rho(1+\theta) + p_3\lambda_2)\Big\} < -k$$

for some positive constant $k > 0$.

Proof. The proof of theorem is based on the method of Theorem (3.2). Hence in order to apply Theorem (3.2) and get the global asymptotic stability when the $R_0 > 1$, it is necessary to find a norm $\|.\|$ on R^6 such that $\mu(B) < 0$ for all $x \in \dot{\Pi}$. The Jacobian matrix of system (1.2) at endemic equilibrium:[31]

$$J = [a_{ij}]_{4\times 4}$$

where

$$\begin{aligned}
a_{11} &= -(\nu + \lambda_4 - \nu p_2 + u_1 + \rho(I + \theta C))\\
a_{12} &= -(\lambda_4 - \nu p_2)\\
a_{13} &= -(\rho S + \lambda_4 - \nu p_2)\\
a_{14} &= -(\nu p_1 + \lambda_4 - \nu p_2 + \rho\theta S)\\
a_{21} &= \rho(I + \theta C)\\
a_{22} &= -(\nu + \lambda_1)\\
a_{23} &= \rho S\\
a_{24} &= \rho\theta S
\end{aligned}$$

$$\begin{aligned}
a_{31} &= 0\\
a_{32} &= \lambda_1\\
a_{33} &= -(\nu + \lambda_2)\\
a_{34} &= 0\\
a_{41} &= 0\\
a_{42} &= 0\\
a_{43} &= p_3\lambda_2\\
a_{44} &= \nu p_1 - \nu - \lambda_3 - u_2
\end{aligned}$$

its second additive compound matrix $J^{[2]}$ is:

$$J^{[2]} = [m_{ij}]_{6\times 6}$$

where

$$\begin{aligned}
m_{11} &= -(\rho(I + \theta C) + \nu + u_1 + \lambda_4 - \nu p_2)\\
&\quad -(\nu + \lambda_1)\\
m_{12} &= \rho S\\
m_{13} &= \rho\theta S\\
m_{14} &= \rho S + \lambda_4 - \nu p_2\\
m_{15} &= \rho\theta S + \lambda_4 + \nu p_1 - \nu p_2\\
m_{16} &= 0\\
m_{21} &= \lambda_1\\
m_{22} &= -(\rho(I + \theta C) + \nu + u_1 + \lambda_4 - \nu p_2)\\
&\quad -(\nu + \lambda_1)\\
m_{23} &= 0\\
m_{24} &= -(\lambda_4 - \nu p_2)\\
m_{25} &= 40\\
m_{26} &= \rho\theta S + \lambda_4 + \nu p_1 - \nu p_2
\end{aligned}$$

$$\begin{aligned}
m_{31} &= 0\\
m_{32} &= p_3\lambda_2\\
m_{33} &= -(\rho(I + \theta C) + \nu + u_1 + \lambda_4 - \nu p_2)\\
&\quad -(\nu + \lambda_3 + u_2 - \nu p_1)\\
m_{34} &= 0\\
m_{35} &= -(\lambda_4 - \nu p_2)\\
m_{36} &= -(\rho S + \lambda_4 - \nu p_2)\\
m_{41} &= 0\\
m_{42} &= \rho(I + \theta C)\\
m_{43} &= 0\\
m_{44} &= -(\nu + \lambda_1) - (\nu + \lambda_2)\\
m_{45} &= 0\\
m_{46} &= -\rho\theta S
\end{aligned}$$

$$\begin{aligned}
m_{51} &= 0\\
m_{52} &= 0\\
m_{53} &= \rho(I + \theta C)\\
m_{54} &= p_3\lambda_2\\
m_{55} &= -(\nu + \lambda_1) - (\nu + \lambda_3 + u_2 - \nu p_1)\\
m_{56} &= \rho S\\
m_{61} &= 0\\
m_{62} &= 0\\
m_{63} &= 0\\
m_{64} &= 0\\
m_{65} &= 0\\
m_{66} &= -(\nu + \lambda_2) - (\nu + \lambda_3 + u_2 - \nu p_1)
\end{aligned}$$

Set the function

$$P(S, E, C) = \begin{bmatrix}
\frac{1}{S} & 0 & 0 & 0 & 0 & 0\\
0 & \frac{1}{S} & 0 & 0 & 0 & 0\\
0 & 0 & \frac{1}{S} & 0 & 0 & 0\\
0 & 0 & 0 & \frac{1}{E} & 0 & 0\\
0 & 0 & 0 & 0 & \frac{1}{C} & 0\\
0 & 0 & 0 & 0 & 0 & \frac{1}{C}
\end{bmatrix}$$

then

$$P_f P^{-1} = \begin{bmatrix}
-\frac{\dot{S}}{S} & 0 & 0 & 0 & 0 & 0\\
0 & -\frac{\dot{S}}{S} & 0 & 0 & 0 & 0\\
0 & 0 & -\frac{\dot{S}}{S} & 0 & 0 & 0\\
0 & 0 & 0 & -\frac{\dot{E}}{E} & 0 & 0\\
0 & 0 & 0 & 0 & -\frac{\dot{C}}{C} & 0\\
0 & 0 & 0 & 0 & 0 & -\frac{\dot{C}}{C}
\end{bmatrix}$$

therefor

$$B = P_f P^{-1} + P J^{[2]} P^{-1} = [b_{ij}]_{6\times 6}$$

where

$$
\begin{aligned}
b_{11} &= -\tfrac{\dot{S}}{S} - (\rho(I+\theta C) + \nu + u_1 + \lambda_4 - \nu p_2) \\
&\quad -(\nu + \lambda_1) \\
b_{12} &= \rho S \\
b_{13} &= \rho\theta S \\
b_{14} &= (\rho S + \lambda_4 - \nu p_2)\tfrac{E}{S} \\
b_{15} &= (\rho\theta S + \lambda_4 + \nu p_1 - \nu p_2)\tfrac{C}{S} \\
b_{16} &= 0 \\
b_{21} &= \lambda_1 \\
b_{22} &= -\tfrac{\dot{S}}{S} - (\rho(I+\theta C) + \nu + u_1 + \lambda_4 - \nu p_2) \\
&\quad -(\nu + \lambda_2) \\
b_{23} &= 0 \\
b_{24} &= -(\lambda_4 - \nu p_2)\tfrac{E}{S} \\
b_{25} &= 0 \\
b_{26} &= (\rho\theta S + \lambda_4 + \nu p_1 - \nu p_2)\tfrac{C}{S}
\end{aligned}
$$

$$
\begin{aligned}
b_{31} &= 0 \\
b_{32} &= p_3\lambda_2 \\
b_{33} &= -\tfrac{\dot{S}}{S} - (\rho(I+\theta C) + \nu + u_1 + \lambda_4 - \nu p_2) \\
&\quad -(\nu + \lambda_3 + u_2 - \nu p_1) \\
b_{34} &= 0 \\
b_{35} &= -(\lambda_4 - \nu p_2)\tfrac{C}{S} \\
b_{36} &= (\rho S + \lambda_4 - \nu p_2)\tfrac{C}{S} \\
b_{41} &= 0 \\
b_{42} &= \rho(I+\theta C)\tfrac{E}{S} \\
b_{43} &= 0 \\
b_{44} &= -\tfrac{\dot{E}}{E} - (\nu + \lambda_1) - (\nu + \lambda_2) \\
b_{45} &= 0 \\
b_{46} &= -\rho\theta S\tfrac{C}{E}
\end{aligned}
$$

$$
\begin{aligned}
b_{51} &= 0 \\
b_{52} &= 0 \\
b_{53} &= \rho(I+\theta C)\tfrac{S}{C} \\
b_{54} &= p_3\lambda_2\tfrac{E}{C} \\
b_{55} &= -\tfrac{\dot{C}}{C} - (\nu + \lambda_1) - (\nu + \lambda_3 + u_2 - \nu p_1) \\
b_{56} &= \rho S \\
b_{61} &= 0 \\
b_{62} &= 0 \\
b_{63} &= 0 \\
b_{64} &= 0 \\
b_{65} &= \lambda_1 \\
b_{66} &= -\tfrac{\dot{C}}{C} - (\nu + \lambda_2) - (\nu + \lambda_3 + u_2 - \nu p_1)
\end{aligned}
$$

From the system (1.2), we have

$$
\begin{aligned}
\frac{\dot{S}}{S} &= \frac{1}{S}\nu - (\rho(I+\theta C) + \nu + u_1 + \lambda_4 - \nu p_2) - (\lambda_4 - \nu p_2)\frac{E}{S} \\
&\quad - (\lambda_4 - \nu p_2)\frac{I}{S} - (\lambda_4 + \nu p_1 - \nu p_2)\frac{C}{S} \\
\frac{\dot{E}}{E} &= \rho(I+\theta C)\frac{E}{S} - (\nu + \lambda_1) \\
\frac{\dot{C}}{C} &= p_3\lambda_2\frac{I}{C} - (\nu + \lambda_3 + u_2 - \nu p_1)
\end{aligned}
$$

According to [4, 10], for a norm $\|.\|$ on R^n, the Lozinskii measure μ associated with $\|.\|$ can be evaluated for a $n \times n$ matrix B as follow:

$$
\mu(B) = \inf\Big\{k : D_+\|z\| \le k\|z\|, \text{ for all solutions of } \dot{z} = Bz\Big\} \tag{3.6}
$$

Where D_+ is the right-hand derivative [24]. As in [4, 10], we consider the following norm on R^6:

$$
\|z\| = \max\{U_1, U_2\}
$$

Where $z \in R^6$, with components z_i, $i = 1, \ldots, 6$ and

$$
U_1(z_1, z_2, z_3) = \begin{cases} \max\{|z_1|, |z_2| + |z_3|\} & \operatorname{sgn}(z_1) = \operatorname{sgn}(z_2) = \operatorname{sgn}(z_3) \\ \max\{|z_1|, |z_1| + |z_3|\} & \operatorname{sgn}(z_1) = \operatorname{sgn}(z_2) = -\operatorname{sgn}(z_3) \\ \max\{|z_1|, |z_2|, |z_3|\} & \operatorname{sgn}(z_1) = -\operatorname{sgn}(z_2) = \operatorname{sgn}(z_3) \\ \max\{|z_1| + |z_3|, |z_2| + |z_3|\} & -\operatorname{sgn}(z_1) = \operatorname{sgn}(z_2) = \operatorname{sgn}(z_3) \end{cases}
$$

$$
U_2(z_4, z_5, z_6) = \begin{cases} |z_4| + |z_5| + |z_6| & \operatorname{sgn}(z_4) = \operatorname{sgn}(z_5) = \operatorname{sgn}(z_6) \\ \max\{|z_4| + |z_5|, |z_4| + |z_6|\} & \operatorname{sgn}(z_4) = \operatorname{sgn}(z_5) = -\operatorname{sgn}(z_6) \\ \max\{|z_5|, |z_4| + |z_6|\} & \operatorname{sgn}(z_4) = -\operatorname{sgn}(z_5) = \operatorname{sgn}(z_6) \\ \max\{|z_4| + |z_6|, |z_5| + |z_6|\} & -\operatorname{sgn}(z_4) = \operatorname{sgn}(z_5) = \operatorname{sgn}(z_6) \end{cases}
$$

We now study solutions to

$$
\dot{z}(t) = B(t)z(t).
$$

case A. $U_1 > U_2$

case A1. $z_1, z_2, z_3 > 0$ and $|z_1| > |z_2| + |z_3|$. Then:

$$
\|z\| = |z_1|
$$

so

$$
D_+\|z\| = \dot{z_1} \Longrightarrow D_+\|z\| \le (-(\nu + \lambda_1) + 2\rho(1+\theta) + \frac{2}{\epsilon}(\lambda_4 + \nu p_1))\|z\| \tag{3.7}
$$

case A2. $z_1, z_2, z_3 > 0$ and $|z_1| < |z_2| + |z_3|$. Then:

$$
\|z\| = |z_2| + |z_3|
$$

so

$$
D_+\|z\| = \dot{z_2} + \dot{z_3} \Longrightarrow D_+\|z\| \le (-\nu + \lambda_1 + \rho(1+\theta) + \frac{3}{\epsilon}(\lambda_4 + \nu p_1))\|z\| \tag{3.8}
$$

case A3. $z_1 < 0$, $z_2, z_3 > 0$ and $|z_1| > |z_2|$. Then:

$$
\|z\| = |z_1| + |z_3|
$$

so

$$
D_+\|z\| = -\dot{z_1} + \dot{z_3} \Longrightarrow D_+\|z\| \le (-\nu + 2\rho(1+\theta) + \frac{1}{\epsilon}(5\lambda_4 + 3\nu p_1 + 2\nu p_2))\|z\| \tag{3.9}
$$

case A4. $z_1 < 0$, $z_2, z_3 > 0$ and $|z_1| < |z_2|$. Then:

$$
\|z\| = |z_2| + |z_3|
$$

so

$$D_+\|z\|= \dot{z_2} + \dot{z_3} \Longrightarrow D_+\|z\| \leq (-\nu + \rho(1+\theta) + \frac{1}{\epsilon}(2\lambda_4 + 3\nu p_1))\|z\| \quad (3.10)$$

case A5. $z_3 < 0$, $z_1, z_2 > 0$ and $|z_1|+|z_3|< |z_2|$.

Then:

$$\|z\|= |z_2|$$

so

$$D_+\|z\| = \dot{z_2} \Longrightarrow D_+\|z\| \leq (-\nu - \lambda_2 + \lambda_1 + \rho\theta + \frac{2}{\epsilon}(\lambda_4 + \nu p_1))\|z\| \quad (3.11)$$

case A6. $z_3 < 0$, $z_1, z_2 > 0$ and $|z_1|+|z_3|> |z_2|$.

Then:

$$\|z\|= |z_1|+|z_3|$$

so

$$D_+\|z\|= \dot{z_1} + \dot{z_3} \Longrightarrow D_+\|z\| \leq (-\nu + \rho(1+\theta) + \frac{1}{\epsilon}(4\lambda_4 + 3\nu p_1 + 2\nu p_2))\|z\| \quad (3.12)$$

case A7. $z_2 < 0$, $z_1, z_3 > 0$ and $|z_1|> \max\{|z_2|, |z_3|\}$.

Then:

$$\|z\|= |z_1|$$

so

$$D_+\|z\|= \dot{z_1} \Longrightarrow D_+\|z\| \leq (-\nu - \lambda_1 + \rho\theta + \frac{2}{\epsilon}(\lambda_4 + \nu p_1))\|z\| \quad (3.13)$$

case A8. $z_2 < 0$, $z_1, z_3 > 0$ and $|z_2|> \max\{|z_1|, |z_3|\}$.

Then:

$$\|z\|= |z_2|$$

so

$$D_+\|z\|= -\dot{z_2} \Longrightarrow D_+\|z\| \leq (-\nu - \lambda_2 + \rho\theta + \frac{2}{\epsilon}(\lambda_4 + \nu p_1))\|z\| \quad (3.14)$$

case A9. $z_2 < 0$, $z_1, z_3 > 0$ and $|z_3|> \max\{|z_1|, |z_2|\}$.

Then:

$$\|z\|= |z_3|$$

so

$$D_+\|z\|= \dot{z_3} \Longrightarrow D_+\|z\| \leq (-\nu - \lambda_3 - u_2 + \frac{1}{\epsilon}(3\lambda_4 + \nu p_1 + \nu p_2))\|z\| \quad (3.15)$$

case B. $U_1 > U_2$

case B1. $z_4, z_5, z_6 > 0$.

Then:

$$\|z\|= |z_4|+|z_5|+|z_6|$$

so

$$D_+\|z\|= \dot{z_4} + \dot{z_5} + \dot{z_6} \Longrightarrow D_+\|z\| \leq (-\nu + \frac{1}{\epsilon}(p_3\lambda_2 + 2\rho(1+\theta)))\|z\| \quad (3.16)$$

case B2. $z_4, z_5 > 0$,$z_6 < 0$.

Then:

$$\|z\|= |z_4|+|z_5|$$

so

$$D_+\|z\|= \dot{z_4} + \dot{z_5} \Longrightarrow D_+\|z\| \leq (-\nu + \frac{1}{\epsilon}(p_3\lambda_2 + 2\rho(1+\theta)))\|z\| \quad (3.17)$$

case B3. $z_4, z_5 > 0$,$z_6 < 0$,$|z_5|< |z_6|$.

Then:

$$\|z\|= |z_4|+|z_6|$$

so

$$D_+\|z\|= \dot{z_4} + \dot{z_6} \Longrightarrow D_+\|z\| \leq (-\nu + \lambda_2 + \frac{2}{\epsilon}\rho(1+\theta))\|z\| \quad (3.18)$$

case B4. $z_4, z_6 > 0$,$z_5 < 0$,$|z_5|> |z_4|+|z_6|$.

Then:

$$\|z\|= |z_5|$$

so

$$D_+\|z\|= -\dot{z_5} \Longrightarrow D_+\|z\| \leq (-\nu - \lambda_1 - \frac{1}{\epsilon}(p_3\lambda_2 - \rho(1+\theta)))\|z\| \quad (3.19)$$

case B5. $z_4, z_6 > 0$,$z_5 < 0$,$|z_5|< |z_4|+|z_6|$.

Then:

$$\|z\|= |z_4|+|z_6|$$

so

$$D_+\|z\|= \dot{z_4} + \dot{z_6} \Longrightarrow D_+\|z\| \leq (-\nu - \lambda_2 + \lambda_1 + \frac{1}{\epsilon}(\rho(1+\theta)))\|z\| \quad (3.20)$$

case B6. $z_5, z_6 > 0$,$z_4 < 0$,$|z_5|< |z_4|$.

Then:

$$\|z\|= |z_4|+|z_6|$$

so

$$D_+\|z\| = -\dot{z_4} + \dot{z_6} \Longrightarrow D_+\|z\| \leq (-\nu - \lambda_2 + \lambda_1 + \frac{2}{\epsilon}(\rho(1+\theta)))\|z\| \quad (3.21)$$

case B7. $z_5, z_6 > 0, z_4 < 0$,$|z_5| > |z_4|$.

Then:

$$\|z\| = |z_5| + |z_6|$$

so

$$D_+\|z\| = \dot{z_5} + \dot{z_6} \Longrightarrow D_+\|z\| \leq (-\nu + \frac{2}{\epsilon}(\rho(1+\theta)))\|z\| \quad (3.22)$$

Combining the results of the sixteen cases presented here in Equations (3.7)-(3.22), we obtain the result

$$D_+\|z\| \leq \max\Big\{ -\nu + \lambda_1 + 2\rho(1+\theta) + \frac{1}{\epsilon}(5\lambda_4 + 3\nu p_1 + 2\nu p_2), -\nu + \lambda_1 + \frac{2}{\epsilon}(\rho(1+\theta) + p_3\lambda_2)\Big\}\|z\|$$

then, by Equation (3.6)

$$\mu(B) \leq \max\Big\{ -\nu + \lambda_1 + 2\rho(1+\theta) + \frac{1}{\epsilon}(5\lambda_4 + 3\nu p_1 + 2\nu p_2), -\nu + \lambda_1 + \frac{2}{\epsilon}(\rho(1+\theta) + p_3\lambda_2)\Big\}$$

Therefore, if there is a positive number $k > 0$ such that

$$\max\Big\{ -\nu + \lambda_1 + 2\rho(1+\theta) + \frac{1}{\epsilon}(5\lambda_4 + 3\nu p_1 + 2\nu p_2), -\nu + \lambda_1 + \frac{2}{\epsilon}(\rho(1+\theta) + p_3\lambda_2)\Big\} \leq -k$$

then $\mu(B) < 0$ on $\dot{\Pi}$. Thus, the endemic equilibrium is globally asymptotically stable amongst all solutions which intersect the interior of Π, completing the proof of Theorem (3.3).

Theorem (3.3) gives a sufficient condition for the endemic equilibrium to be globally asymptotically stable.

4 Conclusion

Approximately 350 to 400 million people worldwide have chronic hepatitis B virus (HBV) infection, and HBV control is a major public health concern. Mathematical models can be a useful tools in this approach which help us to optimize the use of finite sources or simply to goal control measures more impressively. In the present paper we examine the dynamic behavior of a S-E-I-C-R-S model of hepatitis B virus infection with two controls: vaccination and treatment. This paper has proved to be very useful: determining the conditions for both the disease free equilibrium and endemic equilibrium and their stability. It is rigorously established in Theorems (2.1) and (3.3) that the basic reproduction number R_0 is a sharp threshold parameter and completely determines the global dynamics of (1.2) in the feasible region Π. If $R_0 < 1$, the disease-free equilibrium is globally asymptotically stable in Π, and the disease always dies out. If $R_0 > 1$, a unique endemic equilibrium is globally asymptotically stable in Π and the disease persist. The proof of the globally asymptotically stability of P_0 (disease-free equilibrium) when $R_0 < 1$, utilizes a new approach of [Kamgang and Sallet] to global stability problems in R^n and the proof of the global stability of P^* (endemic equilibrium) when $R_0 > 1$, utilizes a new approach of [Li and Muldowney] to global stability problems in R^n.

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