Stability Analysis and Optimal Control of a Hepatitis B Virus Transmission Model in the Presence of Vaccination and Treatment Strategy

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Received: 29 April 2021; Revised: 7 June 2021; Accepted: 14 June 2021; Available online: 11 August 2021

Abstract

In this paper, the dynamics of hepatitis B virus (HBV) infection is studied through a mathematical model. The model includes vaccination class of population, vertical transmission of newborns and treatment of both acute HBV infected individuals and chronic HBV carriers. The stability of equilibria both locally and globally is analyzed. The result shows that the basic reproduction number becomes threshold value i.e. the disease-free equilibrium is globally stable when it is less than unity, and the infection is uniformly persistent and the endemic equilibrium is globally stable when it is greater than one. Further, an optimal control model is developed to seek the strategy to minimize the transmission of HBV. There are three control variables within the model which are prevention by vaccination, treatment of acute infected and treatment of chronic HBV carriers. Our numerical results show that among three controls, treatment of acute infected individuals gives the best impact in reducing the HBV infection. However, with three controls together, they give the best strategy in reducing overall HBV infection.

Keywords: hepatitis B virus, HBV chronic carrier, vaccination, vertical transmission, optimal control

Introduction

Hepatitis B virus (HBV) infection is a serious public health problem. The virus is transmitted through contact with the blood or other body fluids of an infected person. It causes liver inflammation and can lead to cirrhosis, primary hepatocellular carcinoma and liver cancer. There are two phases of HBV infection which are acute and chronic. Acute HBV infection lasts less than six months, usually the immune system is able to clear virus from the body and the body will recover within a few months (Hepatitis B Foundation, n.d.), whereas the chronic HBV infection lasts longer than six months. Approximately one-third of chronic HBV infection patients develop an active hepatitis whereas two-thirds of chronic HBV infection patients are chronic carriers who do not develop symptoms but can transmit the virus to other people.

According to World Health Organization, globally in 2015, an estimated 257 million people were living with chronic HBV infection and hepatitis B resulted in 887,000 deaths, mostly from complications including cirrhosis and hepatocellular carcinoma (WHO, 2020). The rate of chronicity is about 90% in infants infected at birth (WHO, 2020; Borgia, Carleo, Gaeta, & Gentile, 2012). Further, researches show that in the top rank endemic countries, mother-to-child transmission occurred in most cases of infection (Borgia et al., 2012; Jonas, 2009; Lavanchy, 2008).

Currently, there is no specific treatment for acute HBV infection, only care is aimed at maintaining comfort and adequate nutritional balance. Chronic HBV infection can be treated with medicines and oral antiviral agents. Despite these drugs available, none of them can clear the infection completely, they can just stop the virus replication and prevent any damage of the liver. In addition, the long period of therapy can be difficult because of three of side effects, compliance and the costs (Nowak et al., 1996). A great deal of HBV infection prevention is an introduction of hepatitis B vaccines. A vaccine against HBV has been available since 1982 and

it has an excellent record of safety and effectiveness. It is now one of the most widely used vaccines in the world. In many countries where between 8-15% of children used to become chronically infected with the hepatitis B virus, vaccination has reduced the rate of chronic infection to less than 1% among immunized children (WHO, 2020).

Even with vaccination campaign, there is still an increase in HBV transmission globally. One of the reasons could be that the HBV can survive outside the body for at least seven days which during this time the virus can cause infection if it enters the body of unvaccinated persons (Emerenini & Inyama, 2017). Therefore, a better understanding of the major contributing factors to the pandemic particularly of the impact of vaccination and other controlling measures for HBV infection is required.

Mathematical modeling becomes one of the powerful tools to explain the dynamical behavior of real-world situations and different diseases including the transmission dynamics of HBV in various regions and countries. Some researchers study the HBV transmission into cell level, they focus on the infection of hepatocytes. Some works include immune response and some others include some drug therapy, e.g. the work by Nowak et al. (1996), Ciupe, Ribeiro, Nelson, Dusheiko, and Perelson (2007), Allali, Meskaf, and Tridane (2018), Chenar, Kyrychko, and Blyuss (2018) and recently Yosyingyong and Viriyapong (2019). Further, some researchers focus on the HBV transmission in human population. Anderson and May (1991) used a simple mathematical model to illustrate the effects of carriers on the transmission of HBV. Zhao, Xu, and Lu (2000) proposed an age structure model to predict the dynamics of HBV transmission and evaluate the long-term effectiveness of the vaccination program in China. Medley, Lindop, Edmunds, and Nokes (2001) gave a model to show that the prevalence of infection is largely determined by a feedback mechanism that relates the rate of transmission, average age at infection and age-related probability of developing carriage following infection. Thornley, Bullen, and Roberts (2008) extended the work of Medley et al. (2001) to seek for strategy for eliminating HBV in New Zealand in 2008. Zou, Zhang, and Ruan (2010) also proposed a mathematical model to understand the transmission dynamics and prevalence of HBV in mainland China. Zhang and Zhou (2012) extended the work of Medley et al. (2001) by adding the moving out term of infected class to carrier and immunized class to study the spread of HBV in China. Kamyad, Akbari, Heydari, and Heydari (2014) proposed a mathematical model involving vertical transmission (hepatitis B virus infection transmits directly from the parents to the offspring) and horizontal transmission (hepatitis B virus infection transmits through contact with infective individuals) with two control variables i.e. vaccination and treatment. Kimbir, Aboiyar, Abu, and Onah (2014) extended the work of Zou et al. (2010) by further assuming that the newborns to carrier mothers infected at birth are latently infected individuals and, therefore, they included them in the latent compartment. Zhang, Wang, and Zhang (2015) proposed a model to understand the transmission dynamics and prevalence of HBV in Xinjiang, China.

Motivated by work mentioned above, in this paper we present the model of transmission dynamics of HBV infection. We extend the work of Zhang and Zhou (2012) and Kimbir et al. (2014) by adding vaccinated class, the factor of being immunized of newborns and some treatments. Three controls which are the percentage of vaccination, the treatment of chronic HBV carrier and the treatment of acute HBV infected individuals will be considered in two scenarios; constant parameters and control variables. Different scenarios of control variables are analyzed within the model to seek for the suitable guideline of vaccination and treatment in reducing the number of HBV infection and eliminating it eventually.

The paper is organized as follows. In section 2, we inform the steps of work in the study and introduce our proposed model. The results begin with model analysis which includes the boundary of solutions, the basic reproduction number and both disease-free and endemic equilibrium points with their stability conditions which are presented in section 3. Next, we propose optimal control model and then discuss some results of numerical simulations towards the end of section 3. Finally, we end this paper with a brief discussion in section 4 and conclusion to our work in section 5.

Materials and Method

In this research, we start by developing a mathematical model describing HBV infection in human population, then we analyze the model starting from determining boundary of model solutions, the disease-free equilibrium point, the basic reproduction number, the local and global stability of disease-free equilibrium point, the endemic equilibrium point including its local and global stability. Further, we then add control variables in our model to seek the best intervention strategies which could help reducing the disease transmission. Finally, we perform numerical simulation to study the dynamics of HBV transmission in different scenarios of control variables. The formulation of our proposed model is described below.

We propose the model which extends the work of Zhang and Zhou (2012) and Kimbir et al. (2014) by adding vaccination class and some treatments. This model includes five classes at time t, S is the number of susceptible individuals, V is the number of vaccinated individuals. I is the number of acute HBV infected individuals, C is the number of chronic HBV carrier individuals and R is the number of immuned individuals. The birth rate of human is b, and k is the proportion of births who are unvaccinated. The susceptible and the vaccinated individuals become acute HBV infected individuals by the infection rate represented by the term $\beta_1 S(I+C)$ and $\beta_2 V(I+C)$, respectively. The parameter u_1 is the percentage of the vaccination of susceptible. The vaccinated move to immuned individuals class at the rate α i.e. when the vaccination for human population works well. But if the vaccine efficacy wanes then vaccinated come back to susceptible individuals class at the rate of ω. The parameter u_2 is the efficiency of treatment of chronic carrier HBV and m is the recovery by gaining natural immunity rate, causing the chronic HBV carrier move to immuned individuals class. The parameter ϕ is the proportion of births vertically infected and μ is the death rate of human. The acute HBV infected individuals leave their class at the rate of γ with proportion of q to the immune class and proportion of $(1-q)$ to the chronic HBV carrier class. σ is the death rate caused by infection. The term $bk\phi C$ represents the number of newborns who become chronic HBV carrier through vertical transmission. Here we let $0<k<1$ and $0<q<1$. The schematic diagram of this model is shown in Figure 1.

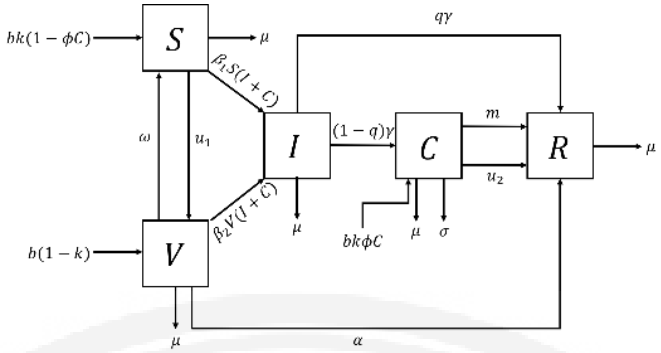

Figure 1 A schematic diagram of hepatitis B virus infection dynamics

From above description, we can write our model into a form of system of equations as follows:

$$\begin{aligned}
\frac{dS}{dt} &= bk(1-\phi C) - \beta_1 S(I+C) + \omega V - (\mu + u_1)S \\
\frac{dV}{dt} &= b(1-k) - \beta_2 V(I+C) + u_1 S - (\omega + \mu + \alpha)V \\
\frac{dI}{dt} &= \beta_1 S(I+C) + \beta_2 V(I+C) - (\mu + \gamma)I \qquad (1) \\
\frac{dC}{dt} &= bk\phi C + (1-q)\gamma I - (\sigma + \mu + m + u_2)C \\
\frac{dR}{dt} &= \alpha V + q\gamma I + (m + u_2)C - \mu R.
\end{aligned}$$

The corresponding differential equations are with initial conditions $S(0) \geq 0, V(0) \geq 0, I(0) \geq 0, C(0) \geq 0, R(0) \geq 0$.

The total population size is N where $N = S + V + I + C + R$.

Results

Boundary of solutions

In this section, the boundary of solutions of (1) is determined.

Since, $N = S + V + I + C + R$, then $\frac{dN}{dt} = \frac{dS}{dt} + \frac{dV}{dt} + \frac{dI}{dt} + \frac{dC}{dt} + \frac{dR}{dt} = b - \mu N - \sigma C \leq b - \mu N.$ (2)

By integration both sides, we have

$$\int_0^t \frac{1}{b - \mu N} dN \leq \int_0^t d$$

$$N_t \leq \frac{b - (b - \mu N_0)e^{-\mu t}}{\mu}.$$

Therefore when $t \to \infty$, then $N_t \to \frac{b}{\mu}$, implies that $0 \leq N_t \leq \frac{b}{\mu}$.

Thus, the considered region for this model is $\Omega = \{(S, V, I, C, R) \in \mathbb{R}_+^5 : N \leq \frac{b}{\mu}\}$.

All solutions of this model are bounded and enter the region Ω. Hence, Ω is a positively invariant. That is every solution of this model remains there for all $t > 0$.

The disease-free equilibrium point (E_0)

The equilibrium point at which the infection is eradicated is calculated. From (1), the disease-free equilibrium point is as follows:

$$E_0 = (S_0, V_0, I_0, C_0, R_0) = \left(\frac{b((\mu+\alpha)k+\omega)}{(\mu+u_1)(\mu+\alpha)+\mu\omega}, \frac{b(1-k)+u_1 S_0}{\omega+\mu+\alpha}, 0, 0, \frac{\alpha V_0}{\mu}\right). \quad (3)$$

The basic reproduction number (R_v)

The basic reproduction number (R_v) is the expected number of secondary cases produced by a typical infective individual. To calculate (R_v), we used the next-generation matrix method by van den Driessche and Watmough (2002) and we obtain

$$\mathcal{F} = \begin{bmatrix} \beta_1 S(I+C) + \beta_2 V(I+C) \\ 0 \end{bmatrix} \quad \text{and} \quad \mathcal{V} = \begin{bmatrix} (\mu+\gamma)I \\ (\sigma+\mu+m+u_2-bk\phi)C - (1-q)\gamma I \end{bmatrix}$$

Then we have

$$F = \begin{bmatrix} \beta_1 S + \beta_2 V & \beta_1 S + \beta_2 V \\ 0 & 0 \end{bmatrix} \text{ and } V = \begin{bmatrix} \mu+\gamma & 0 \\ -(1-q)\gamma & \sigma+\mu+m+u_2-bk\phi \end{bmatrix}.$$

By substituting disease-free equilibrium point (3) in the Jacobian matrices above, we get

$$F(E_0) = \begin{bmatrix} \beta_1 S_0 + \beta_2 V_0 & \beta_1 S_0 + \beta_2 V_0 \\ 0 & 0 \end{bmatrix}, \; V(E_0) = \begin{bmatrix} \mu+\gamma & 0 \\ -(1-q)\gamma & \sigma+\mu+m+u_2-bk\phi \end{bmatrix}.$$

And then

$$V^{-1} = \frac{1}{(\mu+\gamma)(\sigma+\mu+m+u_2-bk\phi)} \begin{bmatrix} \sigma+\mu+m+u_2-bk\phi & 0 \\ (1-q)\gamma & \mu+\gamma \end{bmatrix}.$$

The next generation matrix is $FV^{-1} = \begin{bmatrix} \frac{(\beta_1 S_0 + \beta_2 V_0)(\sigma+\mu+m+u_2+(1-q)\gamma-bk\phi)}{(\mu+\gamma)(\sigma+\mu+m+u_2-bk\phi)} & \frac{\beta_1 S_0 + \beta_2 V_0}{\sigma+\mu+m+u_2-bk\phi} \\ 0 & 0 \end{bmatrix}$.

The basic reproduction number is given by the next generation spectral radius $\rho(FV^{-1})$, which is

$$R_v = \frac{(\beta_1 S_0 + \beta_2 V_0)(\sigma+\mu+m+u_2+(1-q)\gamma-bk\phi)}{(\mu+\gamma)(\sigma+\mu+m+u_2-bk\phi)}, \quad (4)$$

where R_v is the basic reproduction number under vaccination. Without vaccination i.e. when $\omega = 0, u_1 = 0, \alpha = 0$ and $k = 1$, we then have R_0 as follows:

$$R_0 = \frac{\beta_1 b(\sigma+\mu+m+u_2+(1-q)\gamma-b\phi)}{\mu(\mu+\gamma)(\sigma+\mu+m+u_2-b\phi)}. \quad (5)$$

Note here that to have R_v and R_0 to be positive, we then assume $\sigma+\mu+m+u_2 > b\phi$ for this model.

Local stability of disease-free equilibrium point

Theorem 1 (local stability at E_0) If $R_v < 1$, then the disease-free equilibrium point (E_0) is locally asymptotically stable. If $R_v > 1$, then the disease-free equilibrium point (E_0) is unstable.

Proof The Jacobian matrix of (1) is

$$J(E) = \begin{bmatrix} -(\mu+u_1+\beta_1(I+C)) & \omega & -\beta_1 S & -(bk\phi+\beta_1 S) & 0 \\ u_1 & -(\omega+\mu+\alpha+\beta_2(I+C)) & -\beta_2 V & -\beta_2 V & 0 \\ \beta_1(I+C) & \beta_2(I+C) & \beta_1 S+\beta_2 V-\mu-\gamma & \beta_1 S+\beta_2 V & 0 \\ 0 & 0 & (1-q)\gamma & bk\phi-\sigma-\mu-m-u_2 & 0 \\ 0 & \alpha & q\gamma & m+u_2 & -\mu \end{bmatrix}. \quad (6)$$

And at E_0, we have

$$J(E_0)=\begin{bmatrix} -A_1 & \omega & -\beta_1 S_0 & -(bk\phi+\beta_1 S_0) & 0 \\ u_1 & -A_2 & -\beta_2 V_0 & -\beta_2 V_0 & 0 \\ 0 & 0 & A_3 & \beta_1 S_0+\beta_2 V_0 & 0 \\ 0 & 0 & (1-q)\gamma & A_4 & 0 \\ 0 & \alpha & q\gamma & m+u_2 & -\mu \end{bmatrix}, \qquad (7)$$

where $A_1=\mu+u_1, A_2=\omega+\mu+\alpha, A_3=\beta_1 S_0+\beta_2 V_0-\mu-\gamma$ and $A_4=bk\phi-\sigma-\mu-m-u_2$.

From Jacobian matrix above, we set $det(J(E_0)-\lambda I)=0$ to find eigenvalues, then we obtain

$$det(J(E_0)-\lambda I)=(-\mu-\lambda)\left(-(A_1+\lambda)\begin{vmatrix} -(A_2+\lambda) & -\beta_2 V_0 & -\beta_2 V_0 \\ 0 & A_3-\lambda & \beta_1 S_0+\beta_2 V_0 \\ 0 & (1-q)\gamma & A_4-\lambda \end{vmatrix}-u_1\begin{vmatrix} \omega & -\beta_1 S_0 & -(bk\phi+\beta_1 S_0) \\ 0 & A_3-\lambda & \beta_1 S_0+\beta_2 V_0 \\ 0 & (1-q)\gamma & A_4-\lambda \end{vmatrix}\right)$$

$$=(-\mu-\lambda)(\lambda^2+(A_1+A_2)\lambda+A_1A_2-u_1\omega)(\lambda^2-(A_3+A_4)\lambda+A_3A_4-(\beta_1 S_0+\beta_2 V_0)(1-q)\gamma)\ =\ 0.$$

Thus, $\lambda_1=-\mu<0$.

Next, consider $\lambda^2+(A_1+A_2)\lambda+A_1A_2-u_1\omega=0$ and $\lambda^2-(A_3+A_4)\lambda+A_3A_4-(\beta_1 S_0+\beta_2 V_0)(1-q)\gamma=0$, which is considered in the form of $\lambda^2+a_1\lambda+a_2=0.$

For $\lambda^2+(A_1+A_2)\lambda+A_1A_2-u_1\omega=0$, we have $a_1=A_1+A_2$ and $a_2=A_1A_2-u_1\omega$.

So $a_1=2\mu+u_1+\omega+\alpha>0,\ a_2=(\mu+u_1)(\omega+\mu+\alpha)-u_1\omega>0.$ We obtain that $a_1>0$ and $a_2>0$.

Next, consider $\lambda^2-(A_3+A_4)\lambda+A_3A_4-(\beta_1 S_0+\beta_2 V_0)(1-q)\gamma=0$, we have

$a_1=-\beta_1 S_0-\beta_2 V_0+\mu+\gamma-bk\phi+\sigma+\mu+m+u_2,$

$a_2=(\beta_1 S_0+\beta_2 V_0-\mu-\gamma)(bk\phi-\sigma-\mu-m-u_2)-(\beta_1 S_0+\beta_2 V_0)(1-q)\gamma.$

Since, when $R_v<1$, we have $\frac{(\beta_1 S_0+\beta_2 V_0)}{\mu+\gamma}+\frac{(1-q)\gamma(\beta_1 S_0+\beta_2 V_0)}{(\mu+\gamma)(\sigma+\mu+m+u_2-bk\phi)}<1$, i.e. $\frac{(\beta_1 S_0+\beta_2 V_0)}{\mu+\gamma}<1$ and $\frac{(1-q)\gamma(\beta_1 S_0+\beta_2 V_0)}{(\mu+\gamma)(\sigma+\mu+m+u_2-bk\phi)}<1.$

Consider $a_1=-\beta_1 S_0-\beta_2 V_0+\mu+\gamma-bk\phi+\sigma+\mu+m+u_2$, because $\beta_1 S_0+\beta_2 V_0<\mu+\gamma$ and with assumption of R_v being positive i.e. $\sigma+\mu+m+u_2>b\phi>bk\phi$. Therefore, $a_1>0$. Next, we consider

$$a_2=(\beta_1 S_0+\beta_2 V_0-\mu-\gamma)(bk\phi-\sigma-\mu-m-u_2)-(\beta_1 S_0+\beta_2 V_0)(1-q)\gamma$$
$$=-(\beta_1 S_0+\beta_2 V_0)(\sigma+\mu+m+u_2+(1-q)\gamma-bk\phi)+(\mu+\gamma)(\sigma+\mu+m+u_2-bk\phi)$$
$$=(\mu+\gamma)(\sigma+\mu+m+u_2-bk\phi)(1-R_v). \qquad (9)$$

Therefore, $a_2>0$ when $R_v<1$. We obtain that $a_1>0$ and $a_2>0$ when $R_v<1$.

Hence, by the criteria of Routh-Hurwitz, E_0 is locally asymptotically stable when $R_v<1$, and when $R_v>1$, resulting in E_0 being unstable. This completes the proof.

The global stability of the disease-free equilibrium point

Theorem 2 If $R_v<1$, the disease-free equilibrium point (E_0) is globally asymptotically stable.

Proof Here, we use the method of Lyapunov functions.

Let $$L(S,V,I,C,R)=(\sigma+\mu+m+u_2-bk\phi)I+(\beta_1 S+\beta_2 V)C.$$

It can be seen that L is positive definite. Next, calculate the derivative of L along the solutions of the model (1) gives

$$L'(t)=\left((\sigma+\mu+m+u_2-bk\phi)\left(\beta_1 S(I+C)+\beta_2 V(I+C)-(\mu+\gamma)I\right)\right)+(\beta_1 S+\beta_2 V)\left((1-q)\gamma I-(\sigma+\mu+m+u_2-bk\phi)C\right)$$
$$=(\sigma+\mu+m+u_2-bk\phi)(\mu+\gamma)\left(\frac{(\sigma+\mu+m+u_2-bk\phi+(1-q)\gamma)(\beta_1 S+\beta_2 V)}{(\sigma+\mu+m+u_2-bk\phi)(\mu+\gamma)}-1\right)I.$$

Since $I\le\frac{b}{\mu}$, we have $L'(t)\le(\sigma+\mu+m+u_2-bk\phi)(\mu+\gamma)\frac{b}{\mu}\left(\frac{(\sigma+\mu+m+u_2-bk\phi+(1-q)\gamma)(\beta_1 S+\beta_2 V)}{(\sigma+\mu+m+u_2-bk\phi)(\mu+\gamma)}-1\right)$

$$L'(t) \le (\sigma+\mu+m+u_2-bk\phi)(\mu+\gamma)\frac{b}{\mu}\left(\frac{\beta_1 b(\sigma+\mu+m+u_2+(1-q)\gamma-bk\phi)}{\mu(\mu+\gamma)(\sigma+\mu+m+u_2-bk\phi)}-1\right), \left[\because S+V \le \frac{b}{\mu}\right]$$
$$= (\sigma+\mu+m+u_2-bk\phi)(\mu+\gamma)\frac{b}{\mu}\left(\frac{\beta_1 b(\sigma+\mu+m+u_2+(1-q)\gamma-b\phi)}{\mu(\mu+\gamma)(\sigma+\mu+m+u_2-b\phi)}-1\right), [\because k=1]$$
$$= (\sigma+\mu+m+u_2-bk\phi)(\mu+\gamma)\frac{b}{\mu}(R_0-1).$$

Since

$$R_v = \frac{(\beta_1 S_0+\beta_2 V_0)(\sigma+\mu+m+u_2+(1-q)\gamma-bk\phi)}{(\mu+\gamma)(\sigma+\mu+m+u_2-bk\phi)} \le \frac{\beta_1(S_0+V_0)(\sigma+\mu+m+u_2+(1-q)\gamma-bk\phi)}{(\mu+\gamma)(\sigma+\mu+m+u_2-bk\phi)}, [\because \beta_1>\beta_2]$$
$$= \frac{\beta_1 b(\sigma+\mu+m+u_2+(1-q)\gamma-bk\phi)}{\mu(\mu+\gamma)(\sigma+\mu+m+u_2-bk\phi)}, \left[\because S_0+V_0 \le \frac{b}{\mu}\right]$$
$$= \frac{\beta_1 b(\sigma+\mu+m+u_2+(1-q)\gamma-b\phi)}{\mu(\mu+\gamma)(\sigma+\mu+m+u_2-b\phi)}, [\because k=1]$$
$$= R_0.$$

Thus, $R_v \le R_0$. Therefore, E_0 is globally asymptotically stable when $R_0<1$, leads to when $R_v<1$. This completes the proof.

The endemic equilibrium point (E_1^*)

The endemic equilibrium point is denoted by $E_1^* = (S^*, V^*, I^*, C^*, R^*)$, where

$$S^* = \frac{b\omega(1-k)+bk(1-\phi C^*)(\omega+\mu+\alpha+\beta_2(I^*+C^*))}{(\omega+\mu+\alpha+\beta_2(I^*+C^*))(\mu+\beta_1(I^*+C^*))+u_1(\mu+\alpha+\beta_2(I^*+C^*))},$$

$$V^* = \frac{b(1-k)+u_1 S^*}{\omega+\mu+\alpha+\beta_2(I^*+C^*)},\ C^* = \frac{(1-q)\gamma I^*}{\sigma+\mu+m+u_2-bk\phi}, R^* = \frac{(m+u_2)C^*+q\gamma I^*+\alpha V^*}{\mu},$$

I^* is the positive solution of $Z_1(I^*)^2+Z_2 I^*+Z_3=0 \quad (10)$

where $Z_1 = -(bk\phi((1-q)\gamma-A_4)\beta_1\beta_2\omega N_1(N_1+1)+(\mu+\gamma)A_4\omega\beta_1\beta_2(N_1-1)^2) < 0,$

$$Z_2 = b\omega((1-q)\gamma-A_4)\beta_1\beta_2(N_1+1)-bk\phi N_1((1-q)\gamma-A_4)(\beta_1\omega(\omega+\mu+\alpha))-bk\phi((1-q)\gamma-A_4)\beta_2 u_1\omega N_1$$
$$+(\mu+\gamma)A_4\omega\beta_2\mu(N_1+1)+(\mu+\gamma)A_4\omega\beta_1(\omega+\mu+\alpha)(N_1+1)+(\mu+\gamma)A_4\omega\beta_2(N_1+1)u_1,$$

$$Z_3 = \frac{\beta_1 b((\mu+\alpha)k+\omega)+\beta_2 b(\mu(1-k)+u_1))(\sigma+\mu+m+u_2+(1-q)\gamma-bk\phi)}{(\mu+\gamma)(\sigma+\mu+m+u_2-bk\phi)(\mu(\omega+\mu+\alpha)+u_1(\mu+\alpha))}.$$

Local stability of the endemic equilibrium point

Theorem 3 (local stability at E_1^*) When $R_v>1$, the endemic equilibrium point $\left(E_1^*\right)$ exists and is stable if it satisfies the Routh-Hurwitz criteria.

Proof From section3.6, we can see that $S^*>0, V^*>0$, $C^*>0$ and $R^*>0$. Next, consider I^* from (10). By considering the coefficient Z_1, Z_2 and Z_3 above. It can be verified that $Z_1<0$. Next when we calculate $R_v - Z_3$, we obtain that $R_v - Z_3 = 0$. Thus, we have $Z_3 = R_v$, i.e. when $R_v>1$, we have $Z_3>0$. We therefore see that (10) can only be expressed as either $(-ve)\lambda^2+(-ve)\lambda+(+ve)=0$ or $(-ve)\lambda^2+(+ve)\lambda+(+ve)=0$, and by the Descartes' rule of sign changes there is only one positive root of (10) that is, $I^*>0$ (Eigenwillig, 2008), i.e. E_1^* exists.

Next, consider Jacobian matrix of endemic equilibrium point, we have

$$J(E_1^*) = \begin{bmatrix} -\left(\mu+u_1+\beta_1(I^*+C^*)\right) & \omega & -\beta_1 S^* & -(bk\phi+\beta_1 S^*) & 0 \\ u_1 & -\left(\omega+\mu+\alpha+\beta_2(I^*+C^*)\right) & -\beta_2 V^* & -\beta_2 V^* & 0 \\ \beta_1(I^*+C^*) & \beta_2(I^*+C^*) & \beta_1 S^*+\beta_2 V^*-\mu-\gamma & \beta_1 S^*+\beta_2 V^* & 0 \\ 0 & 0 & (1-q)\gamma & bk\phi-\sigma-\mu-m-u_2 & 0 \\ 0 & \alpha & q\gamma & m+u_2 & -\mu \end{bmatrix}.$$

By setting $\det(J(E_1^*)-\lambda I)=0$, we have $\lambda_1 = -\mu'$ and $\lambda^4+a_1\lambda^3+a_2\lambda^2+a_3\lambda+a_4=0$ (11), where

$$a_1 = \mu+\gamma+\sigma+\mu+m+u_2-bk\phi-\beta_1S^*-\beta_2V^*+\mu+\beta_1(I^*+C^*)+\beta_2(I^*+C^*)+\omega+\mu+\alpha+u_2,$$

$$a_2 = (\beta_1S^*+\beta_2V^*)(bk\phi-\sigma-\mu-m-u_2-(1-q)\gamma)+(\mu+\gamma)(\sigma+\mu+m+u_2-bk\phi)-(\beta_1S^*+\beta_2V^*)(\mu+\beta_1(I^*+C^*)$$
$$+\omega+\mu+\alpha+\beta_2(I^*+C^*)+u_1)+(\mu+\gamma+\sigma+\mu+m+u_2-bk\phi)(\mu+\beta_1(I^*+C^*)+\beta_2(I^*+C^*)+\omega+\mu+\alpha+u_2)$$
$$+((\mu+\beta_1(I^*+C^*))(\omega+\mu+\alpha+\beta_2(I^*+C^*))+u_1(\mu+\alpha+\beta_2(I^*+C^*))+((\beta_1^2S^*)+\beta_2^2V^*)(I+C)$$

$$a_3 = (\beta_1S^*+\beta_2V^*)(bk\phi-\sigma-\mu-m-u_2-(1-q)\gamma)(\mu+\beta_1(I^*+C^*)+\beta_2(I^*+C^*)+\omega+\mu+\alpha+u_1)$$
$$+(\mu+\gamma)(\sigma+\mu+m+u_2-bk\phi)(\mu+\beta_1(I^*+C^*)+\beta_2(I^*+C^*)+\omega+\mu+\alpha+u_2)$$
$$-(\beta_1S^*+\beta_2V^*)((\mu+\beta_1(I^*+C^*))(\omega+\mu+\alpha+\beta_2(I^*+C^*))+u_1(\mu+\alpha+\beta_2(I^*+C^*)))$$
$$+(\mu+\gamma+\sigma+mu+m+u_2-bk\phi)((\mu+\beta_1(I^*+C^*))(\omega+\mu+\alpha+\beta_2(I^*+C^*))+u_1(\mu+\alpha+\beta_2(I^*+C^*)))$$
$$+(I^*+C^*)(\beta_1bk\phi(1-q)\gamma+bk\phi(1-q)\gamma(\beta_2u_1+\beta_1(\omega+\mu+\alpha+\beta(I^*+C^*)))$$
$$+\beta_1^2S^*(\sigma+\mu+m+u_2+(1-q)\gamma-bk\phi)+\beta_1S^*(\beta_2u_1+\beta_1(\omega+\mu+\alpha+\beta_2(I^*+C^*))))$$
$$+\beta_2V^*\left(\beta_2(\sigma+\mu+m+u_2+(1-q)\gamma-bk\phi)+\beta_2(\mu+u_1+\beta_1(I^*+C^*))+\beta_1\omega\right)+\beta_1(\omega+\mu+\alpha+\beta_2(I^*+C^*)))$$

$$a_4 = (I^*+C^*)(\beta_1S^*(\sigma+\mu+m+u_2+(1-q)\gamma-bk\phi)(\beta_2u_1+\beta_2V^*(\sigma+\mu+m+u_2+(1-q)\gamma$$
$$-bk\phi)(\beta_2(\mu+u_1+\beta_1(I^*+C^*))+\beta_1\omega)+(\beta_1S^*+\beta_2V^*)(bk\phi-\sigma-\mu-m-u_2-(1-q)\gamma)$$
$$((\mu+\beta_1(I^*+C^*))(\omega+\mu+\alpha+\beta_2(I^*+C^*)+u_1(\mu+\alpha+\beta_2(I^*+C^*))))+(\mu+\gamma)(\sigma+\mu+m$$
$$+u_2-bk\phi)((\mu+\beta_1(I^*+C^*))(\omega+\mu+\alpha+\beta_2(I^*+C^*))+u_1(\mu+\alpha+\beta_2(I^*+C^*))).$$

By using Routh-Hurwitz criteria, E_1^* is stable if $a_1>0, a_3>0, a_4>0$ and $a_1a_2a_3>a_3^2+a_1^2a_4$. This completes the proof.

Global stability of the endemic equilibrium point

In this section, the geometric approach of Li and Muldowney (1993) and Li and Muldowney (1996) is used to analyze the global stability of the endemic equilibrium point. The concept of the geometric approach of Li and Muldowney is briefly explained below. Consider the autonomous dynamical system

$$\dot{x} = f(x), \tag{12}$$

where $f:\Omega\to\mathbb{R}^n, \Omega\subset\mathbb{R}^n$ open set and $f\in C^1(\Omega)$.

The following assumptions are made: (H1) Ω is simply connected; (H2) There exists a compact absorbing set $\Gamma\subset\Omega$; (H3) $\bar{x}$ is a unique equilibrium point of (12) in Ω. Here is the result due to Li and Muldowney (1993) and Li and Muldowney (1996).

Theorem 4 Under the assumptions (H1), (H2) and (H3), the unique equilibrium point $\bar{x}$ of (12) is globally asymptotically stable int Ω provided the quantity $\bar{q}_2<0$, where $\bar{q}_2=\limsup_{t\to\infty}\sup_{x_0\in\Gamma}\frac{1}{t}\int_0^t v(B(x(s,x_0)))ds$. The matrix B is defined as $B=P_fP^{-1}+PJ^{[2]}P^{-1}$, where P_f is obtained by replacing the entry P_{ij} of P by its derivative in the direction of solution of f and $J^{[2]}$ is the second additive compound matrix of Jacobian J of the system (12). Further, the $v(B)$ is the Lozinskii measure with respect to a vector norm $\|\cdot\|$ in $\mathbb{R}^n$, and $v(B)=\lim_{h\to0^+}\frac{\|I+hB\|-1}{h}$.

Lemma 1 The system (1) is uniformly persistent in int Ω when $R_v>1$.

Proof From section 3.5, we see that when $R_v<1$, we have $\frac{dL}{dt}<0$ and when $R_v>1$, $\frac{dL}{dt}>0$ which leads to the instability of E_0. With the result of Freedman, Ruan, and Tang (1994) and Butler, Freedman, and Waltman (1986), we conclude that E_0 is unstable when $R_v>1$ and hence the system is uniformly persistent in the interior Ω i.e. there exists a constant $c>0$ such that

$$\liminf_{t\to\infty}S(t)>c, \liminf_{t\to\infty}V(t)>c, \liminf_{t\to\infty}I(t)>c, \liminf_{t\to\infty}C(t)>c, \liminf_{t\to\infty}R(t)>c$$

provided $(S(0),V(0),I(0),C(0),R(0)) \in \Omega$. The uniformly persistence together with boundedness of Ω is equivalent to the existence of a compact set, which is absorbing for our model (1) in the interior of Ω.

Theorem 5 The endemic equilibrium point E_1^* is globally asymptotically stable in int Ω when $R_v > 1$ and when $\bar{b} > 0$ ($\bar{b}$ is defined in the proof).

Proof Since the system (1) is uniformly persistent in *int* Ω when $R_v > 1$, therefore there exists a compact absorbing set $\Gamma \subset$ *int* Ω (Li and Muldowney, 1996). Now, since the system (1) is uniformly persistent in *int* Ω, then there exists a constant $m > 0$, independent of the initial data in *int* Ω, such that, all solutions $(S(t),V(t),I(t),C(t),R(t))$ of (1) satisfy

$$\liminf_{t\to\infty} S(t) > m, \liminf_{t\to\infty} V(t) > m, \liminf_{t\to\infty} I(t) > m, C(t) > m, \liminf_{t\to\infty} R(t) > m \qquad (13)$$

provided $(S(0),V(0),I(0),C(0),R(0)) \in$ *int* Ω.

The Jacobian matrix of (1) is

$$J(E) = \begin{bmatrix} -(\mu+u_1+\beta_1(I+C)) & \omega & -\beta_1 S & -(bk\phi+\beta_1 S) \\ u_1 & -(\omega+\mu+\alpha+\beta_2(I+C)) & -\beta_2 V & -\beta_2 V \\ \beta_1(I+C) & \beta_2(I+C) & (\beta_1 S+\beta_2 V-\mu-\gamma) & \beta_1 S+\beta_2 V \\ 0 & 0 & (1-q)\gamma & (bk\phi-\sigma-\mu-m-u_2) \\ 0 & \alpha & q\gamma & m+u_2 \end{bmatrix}. \qquad (14)$$

Let $M_{11} = \mu+u_1+\beta_1(I+C), M_{22} = \omega+\mu+\alpha+\beta_2(I+C), M_{33} = \beta_1 S+\beta_2 V-\mu-\gamma,\ M_{44} = bk\phi-\sigma-\mu-m-u_2.$

Its corresponding second compound matrix $J^{[2]}$ is given by,

$$J^{[2]} = \begin{bmatrix} -(M_{11}+M_{22}) & -\beta_2 V & -\beta_2 V & \beta_1 S & (bk\phi+\beta_1 S) & 0 \\ \beta_2(I+C) & -M_{11}+M_{33} & \beta_1 S+\beta_2 V & \omega & 0 & (bk\phi+\beta_1 S) \\ 0 & (1-q)\gamma & -M_{11}+M_{44} & 0 & \omega & -\beta_1 S \\ -\beta_1(I+C) & u_1 & 0 & -M_{22}+M_{33} & \beta_1 S+\beta_2 V & \beta_2 V \\ 0 & 0 & u_1 & (1-q)\gamma & -M_{22}+M_{44} & -\beta_2 V \\ 0 & 0 & \beta_1(I+C) & 0 & \beta_2(I+C) & M_{33}+M_{44} \end{bmatrix}. \qquad (15)$$

We let $Q = Q(S,V,I,C) =$ diag $(1,1,1,1,I,I)$. Then we have $Q_f Q^{-1} = \text{diag}\left(0,0,0,0,\frac{I'}{I},\frac{I'}{I}\right)$. Next, we determine $B = Q_f Q^{-1} + QJ^{[2]}Q^{-1}$, which is

$$B = \begin{bmatrix} -(M_{11}+M_{22}) & -\beta_2 V & -\beta_2 V & \beta_1 S & \frac{(bk\phi+\beta_1 S)}{I} & 0 \\ \beta_2(I+C) & -M_{11}+M_{33} & \beta_1 S+\beta_2 V & \omega & 0 & \frac{(bk\phi+\beta_1 S)}{I} \\ 0 & (1-q)\gamma & -M_{11}+M_{44} & 0 & \frac{\omega}{I} & -\beta_1\frac{S}{I} \\ -\beta_1(I+C) & u_1 & 0 & -M_{22}+M_{33} & \frac{\beta_1 S+\beta_2 V}{I} & \beta_2\frac{V}{I} \\ 0 & 0 & u_1 I & (1-q)\gamma I & (-M_{22}+M_{44})+\frac{I'}{I} & -\beta_2 V \\ 0 & 0 & \beta_1(I+C)I & 0 & \beta_2(I+C) & (M_{33}+M_{44})+\frac{I'}{I} \end{bmatrix} = \begin{bmatrix} B_{11} & B_{12} \\ B_{21} & B_{22} \end{bmatrix},$$

where $B_{11} = [-(M_{11}+M_{22})], B_{12} = \begin{bmatrix} -\beta_2 V & -\beta_2 V & \beta_1 S & \frac{(bk\phi+\beta_1 S)}{I} & 0 \end{bmatrix},$

$$B_{21}=\begin{bmatrix}\beta_2(I+C)\\0\\-\beta_1(I+C)\\0\\0\end{bmatrix} \text{ and } B_{22}=\begin{bmatrix}-M_{11}+M_{33} & \beta_1S+\beta_2V & \omega & 0 & \frac{bk\phi+\beta_1S}{I}\\ (1-q)r & -M_{11}+M_{44} & 0 & \frac{\omega}{I} & -\beta_1\frac{S}{I}\\ u_1 & 0 & -M_{22}+M_{33} & \frac{\beta_1S+\beta_2V}{I} & \beta_2\frac{V}{I}\\ 0 & u_1I & (1-q)\gamma I & -M_{22}+M_{44}+\frac{I'}{I} & -\beta_2V\\ 0 & \beta_1(I+C)I & 0 & \beta_2(I+C) & M_{33}+M_{44}+\frac{I'}{I}\end{bmatrix}.$$

The Lozinskii measure of matrix B is defined as $v(B)\le\max\{g_1,g_2\}$, (16)

where $g_1=v(B_{11})+\|B_{12}\|$ and $g_2=\|B_{21}\|+v(B_{22})$. One can easily compute that

$v(B_{11})=-(M_{11}+M_{22}),\|B_{12}\|=2\beta_2V+\beta_1S+\frac{bk\phi+\beta_1S}{I}$, ,$\|B_{21}\|=(\beta_1+\beta_2)(I+C)$, and $v(B_{22})$ is to be determined. Therefore, we have $g_1=v(B_{11})+\|B_{12}\|=-(M_{11}+M_{22})+2\beta_2V+\beta_1S+\frac{bk\phi+\beta_1S}{I}$, (17)

$g_2=\|B_{21}\|+v(B_{22})=(\beta_1+\beta_2)(I+C)+v(B_{22})$. (18)

The matrix B_{22} is now partitioned as, $B_{22}=C=\begin{bmatrix}C_{11} & C_{12}\\ C_{21} & C_{22}\end{bmatrix}$ where

$$C_{11}=[-M_{11}+M_{33}],\ C_{21}=\begin{bmatrix}\beta_1S+\beta_2V & \omega & 0 & \frac{bk\phi+\beta_1S}{I}\end{bmatrix},\ C_{21}=\begin{bmatrix}(1-q)\gamma & u_1 & 0 & 0\end{bmatrix}^T,$$

$$C_{22}=\begin{bmatrix}-M_{11}+M_{44} & 0 & \frac{\omega}{I} & -\beta_1\frac{S}{I}\\ 0 & -M_{22}+M_{33} & \frac{\beta_1S+\beta_2V}{I} & \beta_2\frac{V}{I}\\ u_1I & (1-q)\gamma I & -M_{22}+M_{44}+\frac{I'}{I} & -\beta_2V\\ \beta_1(I+C)I & 0 & \beta_2(I+C) & M_{33}+M_{44}+\frac{I'}{I}\end{bmatrix}.$$

As above, we define the Lozinskii measure of matrix C as $v(C)\le\max\{g_3,g_4\}$, (19)

where $g_3=v(C_{11})+\|C_{12}\|$ and $g_4=\|G_{21}\|+v(C_{22})$. Then,

$v(C_{11})=-M_{11}+M_{33},\|C_{12}\|=\beta_1S+\beta_2V+\omega+\frac{bk\phi+\beta_1S}{I},\|C_{21}\|=(1-q)\gamma+u_1$, and $v(C_{22})$ is to be determined. Therefore, we have $g_3=v(C_{11})+\|C_{12}\|=-M_{11}+M_{33}+\beta_1S+\beta_2V+\omega+\frac{bk\phi+\beta_1S}{I}$, (20)

$g_4=\|C_{21}\|+v(C_{22})=(1-q)\gamma+u_1+v(C_{22})$. (21)

Next, the matrix C_{22} is partitioned as, $C_{22}=F=\begin{bmatrix}F_{11} & F_{12}\\ F_{21} & F_{22}\end{bmatrix}$ where $F_{11}=[-M_{11}+M_{44}],\ F_{12}=\begin{bmatrix}0 & \frac{\omega}{I} & \frac{-\beta_1S}{I}\end{bmatrix}$,

$$F_{21}=\begin{bmatrix}0 & u_1I & \beta_1(I+C)I\end{bmatrix}^T,\ F_{22}=\begin{bmatrix}-M_{22}+M_{33} & \frac{\beta_1S+\beta_2V}{I} & \frac{\beta_2V}{I}\\ (1-q)\gamma I & -M_{22}+M_{44}+\frac{I'}{I} & -\beta_2V\\ 0 & \beta_2(I+C) & M_{22}+M_{44}+\frac{I'}{I}\end{bmatrix}.$$

Next, we define the Lozinskii measure of matrix F as $v(F)\le\max\{g_5,g_6\}$, (22)

where $g_5=v(F_{11})+\|F_{12}\|$ and $g_6=\|F_{21}\|+v(F_{22})$. Then,

$v(F_{11})=-M_{11}+M_{44},\|F_{12}\|=\frac{\omega}{I}+\frac{\beta_1S}{I},\|F_{21}\|=u_1I+\beta_1(I+C)I$, and $v(F_{22})$ is to be determined. Therefore, we have $g_5=v(F_{11})+\|F_{12}\|=-M_{11}+M_{44}+\frac{\omega}{I}+\frac{\beta_1S}{I}, g_6=\|F_{21}\|+v(F_{22})=u_1I+\beta_1(I+C)I+v(F_{22})$.

Further, the matrix F_{22} is partitioned as $F_{22} = G = \begin{bmatrix} G_{11} & G_{12} \\ G_{21} & G_{22} \end{bmatrix}$ where $G_{11} = [-M_{22} + M_{33}], G_{12} = \begin{bmatrix} \frac{\beta_1 S + \beta_2 V}{I} & \beta_2 \frac{V}{I} \end{bmatrix}$,

$G_{21} = \begin{bmatrix} (1-q)\gamma I & 0 \end{bmatrix}^T$ $G_{22} = \begin{bmatrix} -M_{22} + M_{44} + \frac{I'}{I} & -\beta_2 V \\ \beta_2(I+C) & M_{33} + M_{44} + \frac{I'}{I} \end{bmatrix}$.

Now, we define the Lozinskii measure of matrix G as $v(G) \le \max\{g_7, g_8\}$, (23)

where $g_7 = v(G_{11}) + \| G_{12} \|$ and $g_8 = \| G_{21} \| + v(G_{22})$. Then

$v(G_{11}) = -M_{22} + M_{33}, \| G_{12} \| = \frac{\beta_1 S + \beta_2 V}{I} + \beta_2 \frac{V}{I}, \| G_{12} \| = (1-q)\gamma I.$ Also

$$v(G_{22}) = \max\{-M_{22} + M_{44} + \frac{I'}{I} + \beta_2(I+C), M_{33} + M_{44} + \frac{I'}{I} + \beta_2 V\}$$

$$= \max\{-(\omega + \mu + \alpha) + M_{44} + \frac{I'}{I}, \beta_1 S + \beta_2 V - \mu - \gamma + \beta_2 V + M_{44} + \frac{I^*}{I}\}$$

$$= M_{44} + \frac{I'}{I} + \sup\{-(\omega + \mu + \alpha), \beta_1 S + 2\beta_2 V - \mu - \gamma\}.$$

Thus, we have $g_7 = v(G_{11}) + \| G_{12} \| = -M_{22} + M_{33} + \frac{\beta_1 S + 2\beta_2 V}{I} = \frac{I'}{I} + \frac{(\beta_1 S + 2\beta_2 V) - (\beta_1 S + \beta_2 V)C}{I} - M_{22},$ (24)

$g_8 = \| G_{21} \| + v(G_{22}) = (1-q)\gamma I + M_{44} + \frac{I'}{I} + \sup\{-(\omega + \mu + \alpha), \beta_1 S + 2\beta_2 V - \mu - \gamma\}$. (25)

From the third equation of the system (1), we have

$$\frac{I'}{I} = \beta_1 S + \beta_2 V - \mu - \gamma + (\beta_1 S + \beta_2 V)\frac{C}{I}$$
$$\frac{I'}{I} - (\beta_1 S + \beta_2 V)\frac{C}{I} = \beta_1 S + \beta_2 V - \mu - \gamma. \quad (26)$$

Substituting (26), in (24), we have

$$g_7 = -M_{22} + \frac{I'}{I} - (\beta_1 S + \beta_2 V)\frac{C}{I} + \frac{\beta_1 S + 2\beta_2 V}{I} = \frac{I'}{I} + \frac{(\beta_1 S + 2\beta_2 V) - (\beta_1 S + \beta_2 V)C}{I} - M_{22}. \quad (27)$$

Thus,

$$v(G) \le \max\{g_7, g_8\}$$

$$= \max\{\frac{I'}{I} + \frac{(\beta_1 S + 2\beta_2 V) - (\beta_1 S + \beta_2 V)C}{I} - M_{22}, \frac{I'}{I} + (1-q)\gamma I + M_{44} + \sup\{-(\omega + \mu + \alpha), \beta_1 S + 2\beta_2 V - \mu - \gamma\}\}$$

$$= \frac{I'}{I} + \max\left\{\frac{(\beta_1 S + 2\beta_2 V) - (\beta_1 S + \beta_2 V)C}{I} - M_{22}, (1-q)\gamma I + M_{44} + \sup\{-(\omega + \mu + \alpha), \beta_1 S + 2\beta_2 V - \mu - \gamma\}\right\}. \quad (28)$$

Now from (22), $v(F) \le \max\{g_5, g_6\}$, where $g_5 = M_{44} + \frac{\beta_1 S + \omega}{I} - M_{11}$ and $g_6 = [u_1 + \beta_1(I+C)]I + v(F_{22})$,

we consider $g_5 = M_{44} + \frac{\beta_1 S + \omega}{I} - M_{11} + \frac{I'}{I} - \frac{I'}{I} = \frac{I'}{I} + M_{44} + \frac{\beta_1 S + \omega}{I} - M_{11} - \frac{I'}{I}.$

Therefore,

$$v(F) \le \frac{I'}{I} + \max\left\{M_{44} + \frac{\beta_1 S + \omega}{I} - M_{11} - \frac{I'}{I}, (u_1 + \beta_1(I+C))I + \frac{(\beta_1 S + 2\beta_2 V) - (\beta_1 S + \beta_2 V)C}{I} - M_{22},\right.$$
$$\left.(u_1 + \beta_1(I+C) + (1-q)\gamma)I + M_{44} + \sup\{-(\omega + \mu + \alpha), \beta_1 S + 2\beta_2 V - \mu - \gamma\}\right\}.$$

Now from (19), $v(C) \le \max\{g_3, g_4\}$, where

$g_3 = -M_{11} + M_{33} + \beta_1 S + \beta_2 V + \omega + \frac{bk\phi + \beta_1 S}{I}$, $g_4 = (1-q)\gamma + u_1 + v(C_{22})$,

we consider $g_3 = M_{33} + \beta_1 S + \beta_2 V + \omega + \frac{bk\phi + \beta_1 S}{I} - M_{11} + 0$

$$= \frac{I'}{I} + M_{33} + \beta_1 S + \beta_2 V + \omega + \frac{bk\phi + \beta_1 S}{I} - M_{11} - \frac{I'}{I}.$$

Therefore, $v(C) \le \frac{I'}{I} + \max\left\{M_{33} + \beta_1 S + \beta_2 V + \omega + \frac{bk\phi + \beta_1 S}{I} - M_{11} - \frac{I'}{I},\right.$

$(1-q)\gamma + u_1 + M_{44} + \frac{\beta_1 S + \omega}{I} - M_{11} - \frac{I'}{I}, (1-q)\gamma + u_1 + (u_1 + \beta_1(I+C))I + \frac{(\beta_1 S + 2\beta_2 V) - (\beta_1 S + \beta_2 V)C}{I} - M_{22},$

$\left.(1-q)\gamma + u_1 + (u_1 + \beta_1(I+C) + (1-q)\gamma)I + M_{44} + \sup\{-(\omega+\mu+\alpha), \beta_1 S + 2\beta_2 V - \mu - \gamma\}\right\}.$

Now from (16), $v(B) \le \max\{g_1, g_2\}$, where

$g_1 = -(M_{11} + M_{22}) + 2\beta_2 V + \beta_1 S + \frac{bk\phi + \beta_1 S}{I}, g_2 = (\beta_1 + \beta_2)(I+C) + v(B_{22})$, we consider

$g_1 = 2\beta_2 V + \beta_1 S + \frac{bk\phi + \beta_1 S}{I} - (M_{11} + M_{22}) + 0 = \frac{I'}{I} + 2\beta_2 V + \beta_1 S + \frac{bk\phi + \beta_1 S}{I} - (M_{11} + M_{22}) - \frac{I'}{I}.$

Therefore, $v(B) \le \frac{I'}{I} + \max\{2\beta_2 V + \beta_1 S + \frac{bk\phi + \beta_1 S}{I} - (M_{11} + M_{22}) - \frac{I'}{I},$

$(\beta_1 + \beta_2)(I+C) + M_{33} + \beta_1 S + \beta_2 V + \omega + \frac{bk\phi + \beta_1 S}{I} - M_{11} - \frac{I'}{I},$

$(\beta_1 + \beta_2)(I+C) + (1-q)\gamma + u_1 + M_{44} + \frac{\beta_1 S + \omega}{I} - M_{11} - \frac{I'}{I},$

$(\beta_1 + \beta_2)(I+C) + (1-q)\gamma + u_1 + (u_1 + \beta_1(I+C))I + \frac{(\beta_1 S + 2\beta_2 V) - (\beta_1 S + \beta_2 V)C}{I} - M_{22},$

$(\beta_1 + \beta_2)(I+C) + (1-q)\gamma + u_1 + (u_1 + \beta_1(I+C) + (1-q)\gamma)I + M_{44}$

$+ \sup\{-(\omega+\mu+\alpha), \beta_1 S + 2\beta_2 V - \mu - \gamma\}\}.$

Hence, we obtain $v(B) \le \frac{I'}{I} - \bar{b}$, where

$\bar{b} = \min\{-2\beta_2 V - \beta_1 S - \frac{bk\phi + \beta_1 S}{I} + (M_{11} + M_{22}) + \frac{I'}{I}, -(\beta_1 + \beta_2)(I+C) - M_{33} - \beta_1 S - \beta_2 V - \omega - \frac{bk\phi + \beta_1 S}{I}$

$+ M_{11} + \frac{I'}{I}, -(\beta_1 + \beta_2)(I+C) - (1-q)\gamma - u_1 - M_{44} - \frac{\beta_1 S + \omega}{I} + M_{11} + \frac{I'}{I}, -(\beta_1 + \beta_2)(I+C) - (1-q)\gamma - u_1$

$-(u_1 + \beta_1(I+C))I - \frac{(\beta_1 S + 2\beta_2 V) + (\beta_1 S + \beta_2 V)C}{I} + M_{22}, -(\beta_1 + \beta_2)(I+C) - (1-q)\gamma - u_1 - (u_1 + \beta_1(I+C)$

$+ (1-q)\gamma)I - M_{44} - \inf\{(\omega+\mu+\alpha), -\beta_1 S + 2\beta_2 V + \mu + \gamma\}\}.$

Let us consider any solution $S(t), V(t), I(t), C(t)$ emanating from the compact absorbing set $\Gamma \subset \Omega$. Let $\bar{t}$ be large enough such that the system is persistent and $(S(t), V(t), I(t), C(t)) \subset \Gamma$ for all $t \ge \bar{t}$. Then along each solution $S(t), V(t), I(t), C(t)$ such that $(S(0), V(0), I(0), C(0)) \in \Gamma$, for $t > \bar{t}$, $\frac{1}{t}[\ln I(t) - \ln I(0)] < \frac{\bar{b}}{2}$.

As a result, $\frac{1}{t}\int_0^t v(B)ds \le \frac{1}{t}\int_0^t (\frac{I'}{I} - \bar{b})ds = \frac{1}{t}((\ln I(t) - \ln I(0)) - \bar{b}t) = \frac{\ln I(t) - \ln I(0)}{t} - \bar{b} < -\frac{\bar{b}}{2}$, which implies $\overline{q_2} \le -\frac{\bar{b}}{2} < 0$. Hence, by Theorem 4, E_1^* is globally asymptotically stable in $\text{int}\,\Omega$ when $R_v > 1$ and $\bar{b} > 0$. This completes the proof.

Extension of the model into an optimal control model

In this section, we extend model (1) by applying optimal control variables in the model, this is to determine the best intervention strategies that help eradicating the disease in the specified time. The optimal control model includes three control variables defined as (i) $u_1(t)$ is the prevention by vaccination, (ii) $u_2(t)$ is a treatment effort of chronic HBV carrier individuals, and (iii) $u_3(t)$ is a treatment effort of acute infected individuals. The model is written as follows:

$$\begin{aligned}
\frac{dS}{dt} &= bk(1-\phi C) - \beta_1 S(I+C) + \omega V - (\mu + u_1(t))S \\
\frac{dV}{dt} &= b(1-k) - \beta_2 V(I+C) + u_1(t)S - (\omega + \mu + \alpha)V \\
\frac{dI}{dt} &= \beta_1 S(I+C) + \beta_2 V(I+C) - (\mu + \gamma)I \\
\frac{dC}{dt} &= bk\phi C + (1-u_3(t))\gamma I - (\sigma + \mu + m + u_2(t))C \\
\frac{dR}{dt} &= \alpha V + u_3(t)\gamma I + (m + u_2(t))C - \mu R.
\end{aligned} \tag{29}$$

The control set U is Lebesgue measurable and it is defined as $U = \{(u_1(t), u_2(t), u_3(t)) : 0 \le u_1(t) \le u_{1max}(t) \le 1, 0 \le u_2(t) \le u_{2max}(t) \le 1, 0 \le u_3(t) \le u_{3max}(t) \le 1, 0 \le t \le T\}$. The goal is to reduce the population number of acute infected individuals and the population number of chronic HBV carrier individuals. The objective function is constructed as

$$J = \int_0^T [I(t) + C(t) + M_1 u_1(t) S(t) + M_2 u_1^2(t) + M_3 u_2(t) C(t) + M_4 u_2^2(t) + M_5 u_3(t) I(t) + M_6 u_3^2(t))]dt, \tag{30}$$

where M_1, M_2, M_3, M_4, M_5 and M_6 are positive constants. The expression $M_1 u_1(t) S(t) + M_2 u_1^2(t)$ represents costs associated with u_1 and $M_3 u_2(t) C(t) + M_4 u_2^2(t)$ represents cost associated with u_2 and $M_5 u_3(t) I(t) + M_6 u_3^2(t)$ represents cost associated with u_3.

All parameters' definitions are the same as stated in section 2. The model is analyzed basing on the theory of Pontryagin, Boltyanskii, Gamkrelidze, and Mishchenko (1986). For the optimal control model, the objective of the model is given by:

$$J(u_1^*, u_2^*, u_3^*) = min \int_0^T \left(I(t) + C(t) + M_1 u_1(t) S(t) + M_2 u_1^2(t) + M_3 u_2(t) C(t) + M_4 u_2^2(t) + M_5 u_3(t) I(t) + M_6 u_3^2(t) \right) dt. \tag{31}$$

Next, by applying Pontryagin's Maximum Principle (PMP), we give the necessary conditions for an optimal control problem. Therefore, we obtained a Hamiltonian (H) function defined as:

$$H = L(I, C, u_1, u_2, u_3) + \lambda_S \frac{dS}{dt} + \lambda_V \frac{dV}{dt} + \lambda_I \frac{dI}{dt} + \lambda_C \frac{dC}{dt} + \lambda_R \frac{dR}{dt}, \text{ where}$$

$$L(y, u_1, u_2) = \left[I(t) + C(t) + M_1 u_1(t) S(t) + M_2 u_1^2(t) + M_3 u_2(t) C(t) + M_4 u_2^2(t) + M_5 u_3(t) I(t) + M_6 u_3^2(t) \right]. \tag{32}$$

Thus, we obtain a Hamiltonian function as follows

$$\begin{aligned}
H = {} & I(t) + C(t) + M_1 u_1(t) S(t) + M_2 u_1^2(t) + M_3 u_2(t) C(t) + M_4 u_2^2(t) + M_5 u_3(t) I(t) + M_6 u_3^2(t) \\
& + \lambda_S \left(bk(1-\phi C(t)) - \beta_1 S(t)(I(t)+C(t)) + \omega V(t) - (\mu + u_1(t))S(t) \right) \\
& + \lambda_V \left(b(1-k) - \beta_2 V(t)(I(t)+C(t)) + u_1(t)S(t) - (\omega + \mu + \alpha)V(t) \right) \\
& + \lambda_I \left(\beta_1 S(t)(I(t)+C(t)) + \beta_2 V(t)(I(t)+C(t)) - (\mu + \gamma)I(t) \right) \\
& + \lambda_C \left(bk\phi C(t) + (1-u_3(t))\gamma I(t) - (\sigma + \mu + m + u_2(t))C(t) \right) \\
& + \lambda_R \left(\alpha V(t) + u_3(t)\gamma I(t) + (m + u_2(t))C(t) - \mu R(t) \right)
\end{aligned} \tag{33}$$

where $\lambda_S, \lambda_V, \lambda_I, \lambda_C$ and λ_R are the adjoint variable functions to be determined suitably by applying Pontryagin's Maximum Principle of the optimal control.

For an optimal control set u_1, u_2, u_3 that minimizes J over U, there are adjoint variables, $\lambda_S, \lambda_V, \lambda_I, \lambda_C$ and λ_R such that:

$$\begin{aligned}
\lambda_S' &= -\left[M_1 u_1(t) - (\beta_1(I(t)+C(t)) + (\mu + u_1(t)))\lambda_s + u_1(t)\lambda_v + \beta_1(I(t)+C(t))\lambda_I\right] \\
\lambda_V' &= -\left[\omega\lambda_S - \beta_2(I(t)+C(t))\lambda_V - (\omega+\mu+\alpha)\lambda_V + \beta_2(I(t)+C(t))\lambda_I + \alpha\lambda_R\right] \\
\lambda_I' &= -\left[1 + M_5 u_3(t) - \beta_1 S(t)\lambda_S - \beta_2 V(t)\lambda_V + \beta_1 S(t)\lambda_I + \beta_2 V(t)\lambda_I - (\mu+\gamma)\lambda_I + (1-u_3(t))\gamma\lambda_C + u_3(t)\gamma\lambda_R\right] \\
\lambda_C' &= -\left[1 + M_3 u_2(t) - bk\phi\lambda_S - \beta_1 S(t)\lambda_S - \beta_2 V(t)\lambda_V + \beta_1 S(t)\lambda_I + \beta_2 V(t)\lambda_I + bk\phi\lambda_C\right. \\
&\quad \left. - (m+\sigma+\mu+u_2(t))\lambda_C + u_2(t)\lambda_R + m\lambda_R\right], \\
\lambda_R' &= -\left[-\mu\lambda_R\right].
\end{aligned} \tag{34}$$

With transversality conditions, $\lambda_S(T) = 0, \lambda_V(T) = 0, \lambda_I(T) = 0, \lambda_C(T) = 0, \lambda_R(T) = 0.$ (35)

Furthermore, we obtain the control set (u_1^*, u_2^*, u_3^*) characterized by

$$u_1^*(t) = max\{0, min(u_{1max}, u_1)\},\ u_2^*(t) = max\{0, min(u_{2max}, u_2)\}, u_3^*(t) = max\{0, min(u_{3max}, u_3)\},$$

where $u_1 = \dfrac{(\lambda_S - \lambda_V - M_1)S(t)}{2M_2}, u_2 = \dfrac{(\lambda_C - \lambda_R - M_3)C(t)}{2M_4}, u_3 = \dfrac{(\lambda_C - \lambda_R - M_5)\gamma I(t)}{2M_6}.$

The form of adjoint equation and transversality condition are standard results from Pontryagin's Maximum Principle. We differentiate Hamiltonian function (33) with respect to S, V, I, C and R, respectively, and then the adjoint system can be written

$$\begin{aligned}
\lambda_S' &= -\frac{\partial H}{\partial S} = -\left[M_1 u_1(t) - (\beta_1(I(t)+C(t)) + (\mu + u_1(t)))\lambda_s + u_1(t)\lambda_v + \beta_1(I(t)+C(t))\lambda_I\right] \\
\lambda_V' &= -\frac{\partial H}{\partial V} = -\left[\omega\lambda_S - \beta_2(I(t)+C(t))\lambda_V - (\omega+\mu+\alpha)\lambda_V + \beta_2(I(t)+C(t))\lambda_I + \alpha\lambda_R\right] \\
\lambda_I' &= -\frac{\partial H}{\partial I} = -\left[1 + M_5 u_3(t) - \beta_1 S(t)\lambda_S - \beta_2 V(t)\lambda_V + \beta_1 S(t)\lambda_I + \beta_2 V(t)\lambda_I - (\mu+\gamma)\lambda_I + (1-u_3(t))\gamma\lambda_C + u_3(t)\gamma\lambda_R\right] \\
\lambda_C' &= -\frac{\partial H}{\partial C} = -\left[1 + M_3 u_2(t) - bk\phi\lambda_S - \beta_1 S(t)\lambda_S - \beta_2 V(t)\lambda_V + \beta_1 S(t)\lambda_I + \beta_2 V(t)\lambda_I\right. \\
&\quad \left. + bk\phi\lambda_C - (m+\sigma+\mu+u_2(t))\lambda_C + u_2(t)\lambda_R + m\lambda_R\right] \\
\lambda_R' &= -\frac{\partial H}{\partial R} = -\left[-\mu\lambda_R\right].
\end{aligned} \tag{36}$$

Similarly, by the approach of Pontryagin et al. (1986), we solved the equation, $\dfrac{\partial H}{\partial u_i} = 0$ at u_i^*, for $i = 1, 2, 3$ and obtain:

$$\begin{aligned}
\frac{\partial H}{\partial u_1} &= M_1 S(t) + 2M_2 u_1(t) - S(t)\lambda_S + S(t)\lambda_V = 0 \Rightarrow u_1 = \frac{(\lambda_S - \lambda_V - M_1)S(t)}{2M_2} \\
\frac{\partial H}{\partial u_2} &= M_3 C(t) + 2M_4 u_2(t) + C(t)\lambda_R - C(t)\lambda_C = 0 \Rightarrow u_2 = \frac{(\lambda_C - \lambda_R - M_3)C(t)}{2M_4} \\
\frac{\partial H}{\partial u_3} &= M_5 I(t) + 2M_6 u_3(t) - \gamma I(t)\lambda_C + \gamma I(t)\lambda_R = 0 \Rightarrow u_3 = \frac{(\lambda_C - \lambda_R - M_5)\gamma I(t)}{2M_6}.
\end{aligned} \tag{37}$$

By using standard control arguments involving the bounds on the controls, we conclude

$$u_1^*(t) = \max\left\{0, \min\left(\frac{(\lambda_S - \lambda_V - M_1)S(t)}{2M_2}, u_{1max}\right)\right\}. \tag{38}$$

$$u_2^*(t) = \max\left\{0, \min\left(\frac{(\lambda_C - \lambda_R - M_3)C(t)}{2M_4}, u_{2max}\right)\right\}. \tag{39}$$

$$u_3^*(t) = \max\left\{0, \min\left(\frac{(\lambda_C - \lambda_R - M_5)\gamma I(t)}{2M_6}, u_{3max}\right)\right\}. \quad (40)$$

This completes the proof.

Numerical simulation

In this section, we show some numerical solutions on the optimal control model (29). We apply the Euler method to compute the optimality control solution consisting of the state equations (29) and the adjoint system (34). The parameters within this model are chosen as appropriate and are shown in Table 1 and we consider the entire period of $T = 10$ weeks.

Table 1 Parameter values of the model used in numerical study

Parameter	Description	Value	Ref
b	The birth rate of human	0.0121	Zou et al. (2010)
β_1	Transmission rate of susceptible individuals	0.8-20.94	Edmunds, Medley, and Nokes (1996a)
β_2	Transmission rate of vaccinated individuals	1	Edmunds et al. (1996a)
ϕ	The proportion of births vertically infected	0.11	Edmunds et al. (1996a)
u_1	The percentage of the vaccination of susceptible	0.5	assume
u_2	The efficiency of treatment of chronic carrier HBV	0.5	assume
ω	The vaccine efficacy wanes rate	0.5	Edmunds, Medley, and Nokes (1996b)
α	The vaccinated move to immune individuals rate	0.97	Mendy et al. (2013)
μ	The death rate of human	0.00693	Zou et al. (2010)
γ	The rate of acute infected individuals leave their class	4	Edmunds et al. (1996a)
q	The proportion of the acute infected move to immune class	0.885	WHO (2002)
m	The recovery by gaining natural immunity rate	0.005-0.025	Eikenberry, Hews, Nagy, and Kuang (2009)
σ	The death rate caused by infection	0.47	Nowak and May (2000)
k	The proportion of births who are unvaccinated	0.5	assume

Control with vaccination only

Under this strategy, we use the control u_1 to optimize the objective function while u_2 and u_3 is set to zero. Figure 2 shows that the number of susceptible individuals remains unchanged whereas there is a slightly increase in the number of vaccinated individuals. In addition, the number of both acute infected and chronic carrier individuals decreases with a lower peak whereas a large increase in immune individuals is obtained. Figure 2 (f) shows the strategy of u_1 that we need to give u_1 at 0.7 (= 70%) for about 9 weeks and gradually decreases to zero at the 10^{th} week.

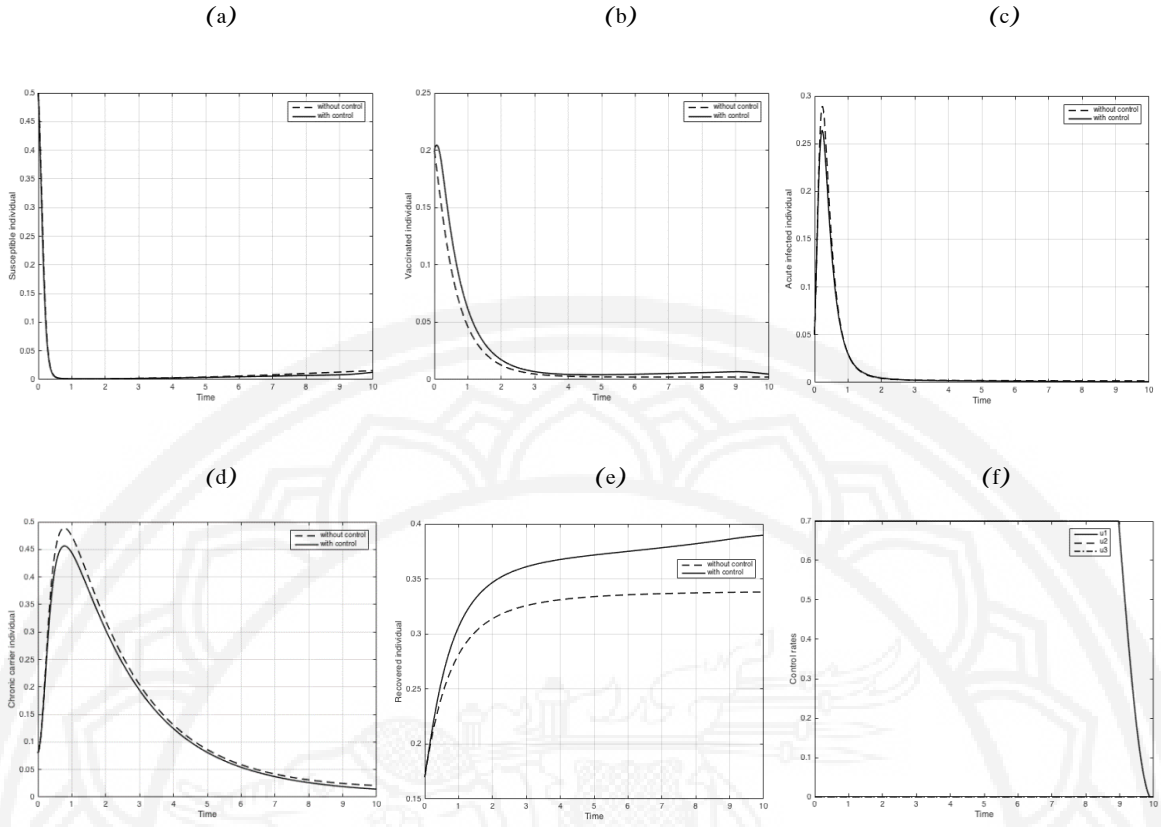

Figure 2 Simulation results of the HBV model (29) with one control (u_1 = 70%, u_2 = 0, $u_3 = 0$) and without control. (a) the number of susceptible individuals, (b) the number of vaccinated individuals, (c) the number of acute infected individuals, (d) the number of chronic HBV carrier individuals, (e) the number of immune individuals and (f) the strategy guideline of controls

Control with treatment of chronic carrier individuals only

Under this strategy, we use the control u_2 alone to optimize the objective function. With the control the number of susceptible individuals increased after the 3^{rd} week. The number of vaccinated and acute infected individuals remains unchanged. However, with the control u_2, it leads to a dramatic decrease in number of chronic carrier individuals and reaches zero level faster which is in the 6^{th} week, and it leads to a large increase in number of immune individuals by approximately 40%. Figure 3 (f) shows that we need to give u_2 at maximum level of 70% for about 9 weeks and gradually reduces to zero.

Control with treatment of acute infected individuals only

Under this strategy, we use the control u_3 alone to optimize the objective function. The results show that the treatment of acute infected individuals does not significantly affect the number of susceptible and vaccinated individuals. Interestingly, it gives a slightly decrease in number of acute infected and a dramatic decrease in number of chronic carrier individuals by about 30%, whereas it reaches zero level after 10^{th} week. Further, this strategy also leads to a large increase in number of immune individuals. Figure 4 (f) shows that we need to give u_3 at maximum level of 70% for almost all the time.

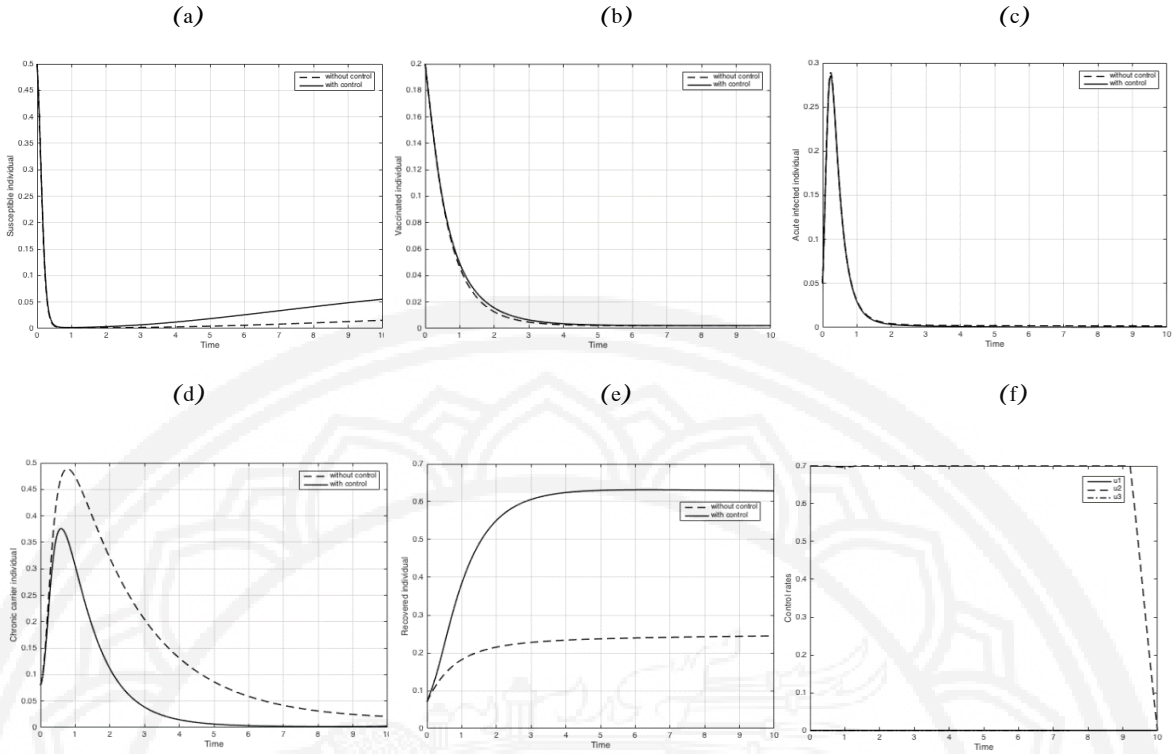

Figure 3 Simulation results of the HBV model (29) with one control (u_1 = 0, u_2 = 70%, $u_3 = 0$) and without control. (a) the number of susceptible individuals, (b) the number of vaccinated individuals, (c) the number of acute infected individuals, (d) the number of chronic HBV carrier individuals, (e) the number of immune individuals and (f) the strategy guideline of controls

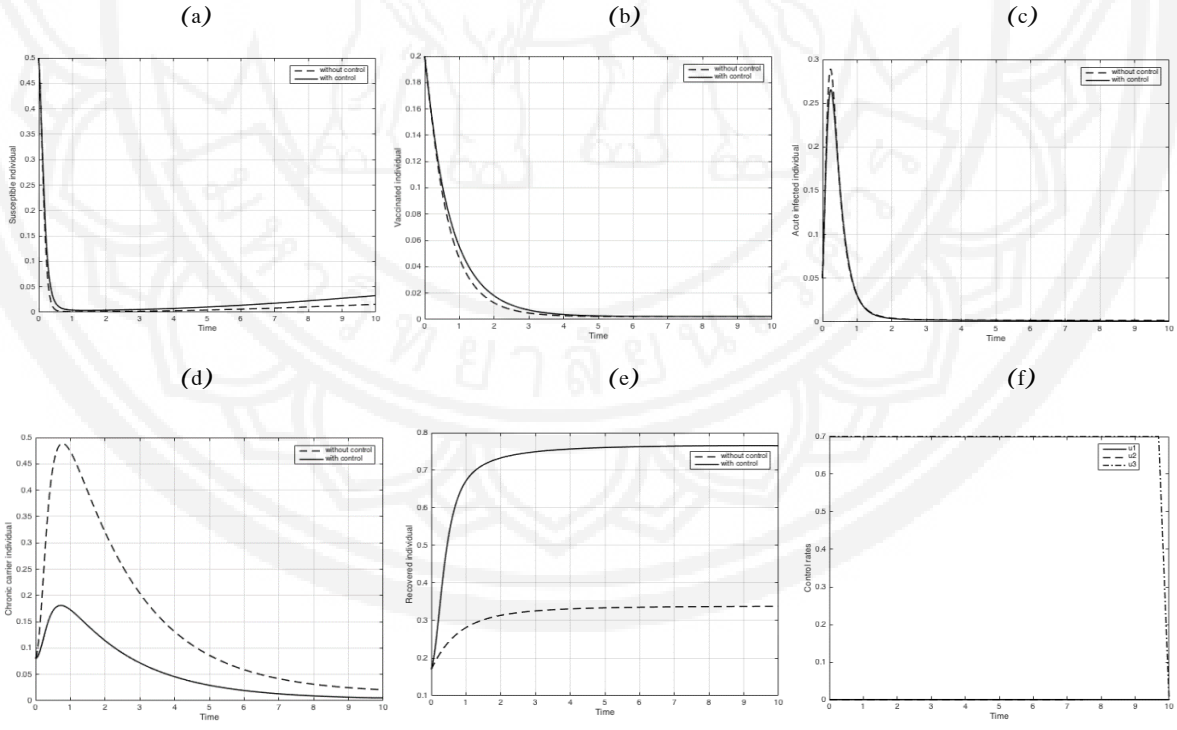

Figure 4 Simulation results of the HBV model (29) with one control (u_1 = 0, u_2 =0, u_3 =70%) and without control. (a) the number of susceptible individuals, (b) the number of vaccinated individuals, (c) the number of acute infected individuals, (d) the number of chronic HBV carrier individuals, (e) the number of immune individuals and (f) the strategy guideline of controls

Control with vaccination, treatment of chronic carried individuals and treatment of acute infected individuals

Under this strategy, we use all three controls to optimize the objective function. The results in Figure 5 demonstrate a slight increase in number of susceptible and vaccinated individuals, whereas they give a reduction in the peak of number of acute infected individuals. Further, this strategy leads to a dramatic decrease in number of chronic carrier individuals by approximately 35% and it reaches zero level faster than the previous three cases i.e. in the 4^{th} week. The number of immune individuals also largely increases by 55%. Finally, the guideline of these three controls suggests that we need to perform the control u_1 at the level of 70% for about 2.5 weeks and gradually reduces the level to zero by the 8^{th} week, whereas we need to perform the control u_2 and u_3 at the level of 70% for about 9 and 9.5 weeks, respectively.

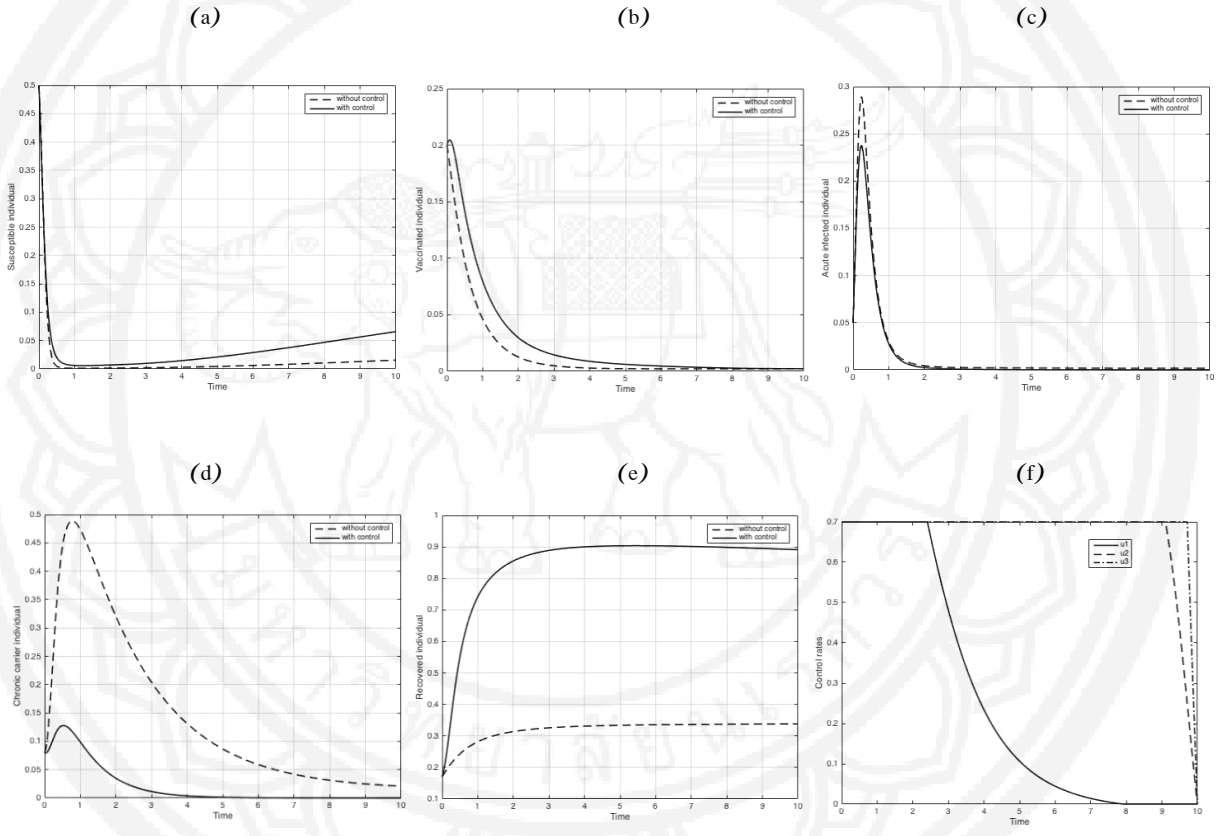

Figure 5 Simulation results of the HBV model (29) with all controls (u_1 = 70%, u_2 =70%, u_3 =70%) and without control. (a) the number of susceptible individuals, (b) the number of vaccinated individuals, (c) the number of acute infected individuals, (d) the number of chronic HBV carrier individuals, (e) the number of immune individuals and (f) the strategy guideline of controls

Discussion

With our numerical results above we could see that Figure 2 demonstrates that with vaccination control alone, a number of both acute HBV infected and chronic HBV carrier is reduced whereas a number of immuned individuals is increased. In Figure 3, with treatment of chronic HBV carrier individuals alone the results show

that a number of chronic HBV carrier is significantly reduced and a number of immuned individuals increases although there is no significant change in number of acute HBV infected. Interestingly, the results of scenario with treatment of acute HBV infected individuals alone in Figure 4 lead to a significant decrease in the number of chronic HBV carrier and a significant increase in the number of immuned individuals whereas only a small reduction is observed for the number of acute HBV infected. This could interpret that treatment of acute HBV infected individuals is essential and gives significant results in eradicating HBV transmission. Finally, a combination of all three controls in Figure 5 gives the best result comparing to the previous three cases i.e. there is a great reduction in acute HBV infected and a significant reduction in chronic HBV carrier whereas a large increase in immuned individuals. This confirms that all three controls should be encouraged and support in order to eventually eliminate the HBV transmission in human.

Conclusions

In this paper, a nonlinear mathematical model relating to vaccination class of population, vertical transmission of newborns and treatment of both acute HBV infected individuals and chronic HBV carriers is presented in order to investigate the dynamics of HBV transmission. The highlights of this model are that the model allows population in susceptible group to be able to take some vaccine and move to vaccinated class, the model divides the infected individuals into two types i.e. acute and chronic carriers, the vertical transmission is included in the model and some treatments for both acute and chronic carries are also included. With these highlights, our model therefore is more realistic than the model of Zhang and Zhou (2012) and Kimbir et al. (2014) that we have extended, therefore stronger results. Within the model two main equilibria are obtained and the magnitude of the basic reproduction number becomes the threshold of the qualitative behaviors of the model. When the basic reproduction number is less than one, the disease-free equilibrium is locally and globally stable, whereas it is unstable when the basic reproduction number is greater than one and the infection is uniformly persistent. By using the geometric approach of Li and Muldowney (1993) and Li and Muldowney (1996), we obatin that the endemic equilibrium is globally stable. Further, the model above is extended into optimal control model by adding three control variables which are prevention by vaccination, treatment of acute infected and treatment of chronic HBV carriers to minimize the transmission of HBV. Numerical simulations of the model show that among three controls, treatment of acute infected individuals gives the best impact in reducing the HBV infection. However, combination of three controls gives the best strategy for overall HBV infection reduction.

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