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# OPTIMAL CONTROL OF HEPATITIS B VIRUS DISEASE IN A POPULATION WITH INFECTED IMMIGRANTS

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**Abstract.** This paper firstly presents a nonlinear extended deterministic model for assessing the impact of immigration on the spread of the Hepatitis B Virus (HBV) pandemic in a population with acute and chronic groups. This model studies the impact of optimal control on the treatment of immigrants and vaccination of HBV on the transmission dynamics of the disease in a homogeneous population with constant immigration. First, we derived the condition in which disease free equilibrium is locally and globally asymptotically stable. Second, we investigated by formulating the costs function problem as an optimal control problem, and we then use the Pontryagins Maximum Principle to solve the optimal control problems. The impact of each control mechanism individually and the combinations of these strategies in the control of HBV is also investigated. Numerical simulation of the model is implemented to investigate the sensitivity of certain key parameters on the treatment and vaccination of infected immigrants on the spread of the disease with acute and chronic group.

**Keywords:** Hepatitis B Virus; Optimal Control; Infected Immigrants.

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## 1. Introduction

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Hepatitis B is a serious and common infectious disease of the liver, affecting millions of people throughout the world [1],[7],[8]. Hepatitis B virus (HBV) causes an enormous amount of human suffering, particularly in Asia, sub-Saharan Africa, parts of the Arabian Peninsula, the South Pacific, tropical South America, and arctic North America [3]. More than 2,000 million people alive today have been infected with HBV at some time in their lives. Three quarters of the worlds population live in areas where there are high levels of infection.

Africa has the second largest number of chronic carriers after Asia and is considered a region of high endemicity. The exact burden of hepatitis B in Africa is difficult to assess due to inaccurate records and under-reporting, but between 70% and 95% of the adult population show evidence of past exposure to HBV infection and the estimated HBsAg seroprevalence ranges from 6-20% [10], [11].

The virus targets the liver, and about 17.5% (350 million) of those who harbor an active HBV infection suffer chronic hepatitis [16]. Up to 0.06% of HBV-infected persons are likely to die from complications associated with the disease within the year [9], [13]. But mortality is not the only way HBV impacts the human population. All who suffer HBV infection experience significant morbidity, ranging from weeks to months of nausea, fatigue, jaundice, and joint pain associated with acute disease to liver cirrhosis or hepatocellular carcinoma characteristic of late-stage chronic infection.

Every year there are over 4 million acute clinical cases of HBV, and about 25% of carriers, 1 million people a year, die from chronic active hepatitis, cirrhosis or primary liver cancer [10].

Hepatitis B (HBV) affects many people and ranks behind HIV as the tenth leading cause of death in the world. In Ghana, HBV is largely a disease of children and young adults aged 10-50 years. About 0.7 to 1.6 million Ghanaians are chronic hepatitis B carriers.

In most cases, a new infection (acute HBV) may go away on its own in the first six months of infection. Most people do not need any therapy at the early stage of the disease. Thus, if an adult gets infected with the HBV virus, there is about 90% chance that the persons immune system (the bodys defense system) will fight the disease off in the first six months (the acute phase) and no treatment might be necessary.

Despite the vast population of infected persons, efforts to prevent and control HBV have met with increasing levels of success and hold promise for large reductions in disease burden in the future. A great deal of credit for achievements to date stems from the introduction of hepatitis B vaccines. First licensed in the United States in 1981, hepatitis B vaccine is now one of the most widely used vaccines in the world and is part of the routine vaccination schedule for many of the worlds infants and children. It is the worlds first cancer prevention vaccine and the first vaccine to prevent a sexually transmitted disease. In countries where large-scale vaccination efforts were made in the first decade after introduction of the vaccine, the epidemiology of hepatitis B and HBV infection has been transformed, and there are early signs that the burden of HBV-related sequelae will be significantly reduced as vaccinated populations age.

Several models have been introduced for understand the HBV dynamics [21]. However, the complex characteristics of human HBV make theoretical researchers difficult to determine the specific kinetic parameters of HBV infection, immune responses, and development of liver disease [5].

## 2. Model formulation

In this thisis we are going to present a model to describe the macro method of infection for the hepatitis B virus with infected immigrant. The proposed model with the population under study is divided into compartments. The total population at time $t$, denoted by $N$ is subdivided into 4 mutually exclusive classes namely, Susceptible group $(S)$, Acute Infected group $(I)$, Chronic Infected group $(C)$, Vaccinated group $(V)$, such that

$$P = S + I + C + V.$$

The susceptible group are recruited at a rate $(1-\pi_i)P$ where $\pi_i (i = I, C, V)$ are the rates at which acute infected group $(I)$, chronic infected group $(C)$ and vaccinated group $(V)$ enters the population respectively and become infected with the disease at the rate $\lambda$, where

$$\lambda = (\beta I + \gamma C)$$

$\beta$ is the effective contact rate of individuals with acute hepatitis B disease in the $I$ class whiles $\gamma$ is the effective contact rate of individuals with chronic hepatitis B disease in the $C$ class and the recovery rates due to efficacy of treatment from the acute infected group is $m$. A proportion of the acute infected immigrants enters the population at a rate $\pi_1$ and decrease the poulation by developing disease symptoms at a rate $\delta$. A proportion of chronic infected immigrants enters the population at a rate $\pi_2$ and die due to induced chronic infection at a rate $\rho$. Finally a proportion of vaccinated immigrats enters the population at a rate $pi_3$ and progression to susceptible group from vaccinated group due waning immunity at a rate $\sigma$. Individuals in all classes die at a natural death rate $\mu$. Taking into account the above considerations, we then have the following schematic flow diagram (Figure 1):

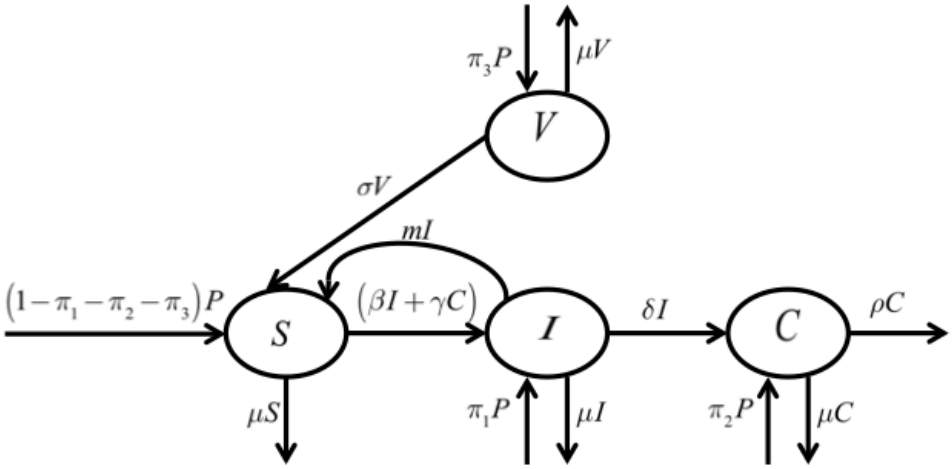



FIGURE 1. Compartmental model of hepatitis B virus disease in a population with infected immigrants

From the model formulation and the schematic flow diagram above we now present the model equations:

$$
\begin{aligned}
\frac{dS}{dt} &= (1-\pi_1-\pi_2-\pi_3)P-(\beta I+\gamma C)S-\mu S+mI+\sigma V,\\
\frac{dI}{dt} &= \pi_1 P+(\beta I+\gamma C)S-(\mu+\delta+m)I,\\
\frac{dC}{dt} &= \pi_2 P+\delta I-(\mu+\rho)C,\\
\frac{dV}{dt} &= \pi_3 P-(\mu+\sigma)V.
\end{aligned} \tag{1}
$$

## 2.1. Positivity of solutions

Since the model monitors human population we need to show that all the state variables remain non-negative at all times.

**Theorem 2.1.** *Let* $\Omega = \left\{(S,I,C,V) \in \mathbb{R}^4_+ : S(0) > 0, I(0) > 0, C(0) > 0\right\}$ *then the solutions of* $\{S(0),I(0),C(0),V(0)\}$ *of the system (1) are positive for all* $t \geq 0$.

**Proof.** Note that $\lim_{t\to\infty} sup(S+I+C+V) \leq \frac{P}{\mu}$. Thus the considered region for the system (1) is

$$\Omega = \left\{(S,I,C,V) : (S+I+C+V) \leq \frac{P}{\mu}, S > 0, I > 0, C > 0, V > 0\right\}.$$

The vector fields points to the interior of $\Omega$ on the part of the boundary when $(S+I+C+V) = \frac{P}{\mu}$ for $t > 0$ and $\Omega$ is positively invariant. The model system (1) has a disease free equilibrium given by $E_0 = \left(\frac{P}{\mu}, 0, 0, 0\right)$. Taking the first equation of (5.1), we have

$$\begin{aligned}
\frac{dS}{dt} &= (1-\pi_1-\pi_2-\pi_3)P - (\lambda+\mu)S + mI + \sigma V,\\
\frac{dS}{dt} &\geq -(\lambda+\mu)S,\\
\frac{dS}{S} &\geq -(\lambda+\mu)dt,\\
\int \frac{dS}{S} &\geq \int -(\lambda+\mu)dt,\\
S(t) &\geq S(0)e^{-(\lambda+\mu)dt} \geq 0.
\end{aligned}$$

From the second equation of (1), we have

$$\begin{aligned}
\frac{dI}{dt} &= \pi_1 P + \lambda S - (\mu+\delta+m)I,\\
\frac{dI}{dt} &\geq -(\mu+\delta+m)I,\\
\frac{dI}{I} &\geq -(\mu+\delta+m)dt,\\
\int \frac{dI}{I} &\geq \int -(\mu+\delta+m)dt,\\
I(t) &\geq I(0)e^{-(\mu+\delta+m)dt} \geq 0.
\end{aligned}$$

Similarly the third equation of (1), we have

$$\begin{aligned}
\frac{dC}{dt} &= \pi_2 P + \delta I - (\mu+\rho)C,\\
\frac{dC}{dt} &\geq -(\mu+\rho)C,\\
\frac{dC}{C} &\geq -(\mu+\rho)dt,\\
\int \frac{dC}{C} &\geq \int -(\mu+\rho)dt,\\
C(t) &\geq C(0)e^{-(\mu+\rho)dt} \geq 0.
\end{aligned}$$

Finally, the fourth equation of (1), we have

$$\begin{aligned}
\frac{dV}{dt} &= \pi_3 P - (\mu+\sigma)V,\\
\frac{dV}{dt} &\geq -(\mu+\sigma)V,\\
\frac{dV}{V} &\geq -(\mu+\sigma)dt,\\
\int \frac{dV}{V} &\geq \int -(\mu+\sigma)dt,\\
V(t) &\geq V(0)e^{-(\mu+\sigma)dt}.
\end{aligned}$$

Given that the parameters are all non-negative, it has been shown that starting with non-negative initial conditions implies that the solution will always be non-negative. Therefore we have shown that the state variables of the model system (1) are all positive for all $t \geq 0$.

### 2.2. Invariant Region

**Theorem 2.2.** *The system (1) has solutions which are contained in feasible region* $\Omega$

**Proof.** Let $(S,I,C,V) \in \mathbb{R}^4_+$ be any solution of the system with non negative initial conditions the adding the equations of the system (1), we have

$$\frac{dS}{dt} + \frac{dI}{dt} + \frac{dC}{dt} + \frac{dV}{dt} = P - \mu(S+I+C+V) - \rho C \leq \frac{P}{\mu}$$

is positively invariant. Hence, the system is both mathematically and epidemiologically well-posed. Therefore, for initial starting point $(S,I,C,V) \in \mathbb{R}^4_+$, the trajectory lies in $\Omega$. Thus, we can restrict our analysis to the region $\Omega$.

TABLE 1. Estimated parameter values used for the HBV infected immigrant model

| | Parameter | Values | Reference |
|---|---|---|---|
| 1 | $\pi_1$ | 0.0002 | Estimated |
| 2 | $\pi_2$ | 0.0001 | Estimated |
| 3 | $\pi_3$ | 0.0004 | Estimated |
| 4 | $\beta$ | 0-1 | Pang *et. al.*, 2010 |
| 5 | $\gamma$ | 0.5 | Pang *et. al.*, 2010 |
| 6 | $m$ | 0.1 | Estimated |
| 7 | $\mu$ | 0.0143 | Yuan *et. al.*, 2008 |
| 8 | $\delta$ | 0.3 | Yuan *et. al.*, 2008 |
| 9 | $\sigma$ | 0.5 | Estimated |
| 10 | $\rho$ | 0.1 | WHO, 2002 |
| 11 | $P$ | 0.0384 | Estimated |

Figure 2 below, shows the distribution of proportion of population with time in all classes with the rates of infective immigrants $\pi_i(i = 1,2,3)$ . It is found that initially proportion of susceptible group decreases with time, due to immigration of infected immigrants and then increases with time due to waning immunity $\sigma$, and the efficacy of treatment $m$ and then reaches its equilibrium position. Also the susceptible class decreases with time since individuals shifted to acute infected group at the rate $\beta$ .The acute infected group decreases with time since infected group shifted to chronic infected group. As the rate of vaccinated group increases, the infective group decreases with time leading to the increase of susceptible group and reaches its equilibrium position.

## 3. Local stability analysis

In the absence of infectious immigrants entering the population $\pi_i = 0, i = I,C,V$ (which can be interpreted as a quarantine program), the system of equations (1) has a disease-free eqilibrium, obtained by setting the right-hand sides of the equations in the model to zero, given

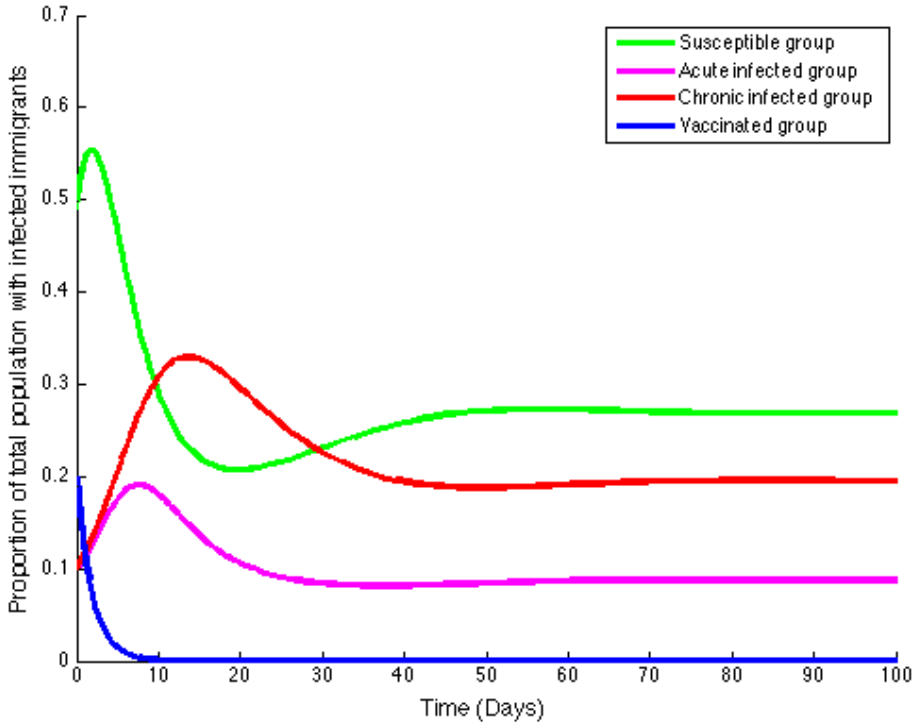



FIGURE 2. The plot shows HBV disease transmission in a population with infected immigrants

by

$$E_0 = \left(\frac{P}{\mu}, 0, 0, 0\right).$$

The linear stability of $E_0$ can be established using the next generation operator method in [19] on the system (1), the matrices $F$ and $V$, for the new infection terms and the remaining transfer terms, are, respectively, given by,

$$F = \begin{pmatrix} \frac{\beta P}{\mu} & \frac{\gamma P}{\mu} & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix},$$

and

$$V = \begin{pmatrix} \mu+\delta+m & 0 & 0 \\ -\delta & \mu+\rho & 0 \\ 0 & 0 & \mu+\sigma \end{pmatrix}.$$

It follows that the reproductive number of the model (1), denoted by $\mathscr{R}_0$ is given by

$$\mathscr{R}_0 = \frac{\beta P(\mu+\rho)+\gamma P\delta}{\mu(\mu+\delta+m)(\mu+\rho)}. \tag{2}$$

The threshold quantity $\mathscr{R}_0$ is the basic reproduction number of the model (1) for HBV infection in a population with infected immigrants. It measures the average number of new HBV infections generated by a single infected individual in a completely susceptible population.

**Lemma 3.1.***The disease-free equilibrium of the model (1) with infected immigrants is locally asymptotically stable if* $\mathscr{R}_0 < 1$ *and unstable* $\mathscr{R}_0 > 1$.

Epidemiologically, Lemma 3.1, above implies that HBV can be eliminated from the community when $\mathscr{R}_0 < 1$ if the initial size of the sub-population of the model are in the basin of attraction of the disease free equilibrium $\mathscr{R}_0$.

This is to say, if $\mathscr{R}_0 < 1$, then on average an infected individual produce less than one new infected individual over the cause of its infectious period, and the infection can not grow, from (2), for $\mathscr{R}_0$ to be less than 1, this will only be possible when $m$ (efficacy of treatment) is increased without bound in collaboration with other intervention strategies to all people including immigrants in a given locality which may result into the decreasing effect on $\beta, \pi_1, \gamma$ and $\pi_2$ provided that acute infectives $(I)$ will take all necessary precaution measures against transmission of HBV since they are aware of their infection.

Conversely, if $\mathscr{R}_0 > 1$, then each infected individual produces on average more than one new infection, and the disease can invade the population, this situation can be realized easily when we try to assess the contribution of $(I)$ and $(C)$ in terms of $\beta, \pi_1$ and $\gamma, \pi_2$ respectively from (2) above,

$$\mathscr{R}_{0_1} = \frac{\beta P}{\mu(\mu+\delta+m)}, \qquad \mathscr{R}_{0_2} = \frac{\gamma P\delta}{\mu(\mu+\delta+m)(\mu+\rho)}, \tag{3}$$

where

$$\mathscr{R}_0 = \mathscr{R}_{0_1} + \mathscr{R}_{0_2} \tag{4}$$

from the equation (3) it is clear that $\mathscr{R}_{0_1} > \mathscr{R}_{0_2}$ which implies that chronic infectives $(C)$ are the one contributing much on the transmission of the infection and keeping the disease endemic

$(say, \mathscr{R}_0 > 1)$ in the population through $\gamma$ and $\pi_2$ compared to acute infective $(I)$ under $\beta$ and $\pi_1$. In the absence of infection, the population size approaches the stead state $\frac{P}{\mu}$.

Then, $\mathscr{R}_0$ is the number of secondary infections made by a topical newly infective individual entering the population at the disease-free equilibrium during his or her average infective period. So $\mathscr{R}_0$ is the basic reproduction number when new members of immigration are all susceptible, or $\pi_1 + \pi_2 + \pi_3 = 0$.

**Theorem 3.2.** *Suppose $\pi_1 + \pi_2 + \pi_3 = 0$ or new members of immigration are all susceptible. Then*

*(1) The point $E_0 = \left(\frac{P}{\mu}, 0, 0, 0\right) \in \Omega$, the disease-free equilibrium of the system (1) and it exists for all nonnegative values of its parameters. $E_0$ is globally asymptotically stable when $\mathscr{R}_0 \leq 1$ and it is unstable when $\mathscr{R}_0 > 1$.*

*(2) When $\mathscr{R}_0 > 1$, the solutions of the system (1) starting sufficiently close to $E_0$ in $\Omega$ move away from $E_0$ except those starting on the invariant $S-$axis which approach $E_0$ along this axis.*

Further, using ([20], Theorem 2), the following result is established. The disease-free equilibrium is locally asymptotical stable if $\mathscr{R}_0 < 1$ and unstable if $\mathscr{R}_0 > 1$

### 3.1. Stability and existence of endemic equilibrium

In the presence of HBV, that is $I(t) \neq 0, C(t) \neq 0$, the model system (1) has an equilibrium point, called the endemic equilibrium point, denoted by $E_1$ given by:

$$E_1 = (S^*, I^*, C^*, V^*) \neq 0.$$

$E_1$ is the steady state endemic equilibrium point where the disease persist in the population. For the existence and uniqueness of $E_1$ its coordinate has to satisfy the following conditions.

$$0 < S^*, 0 < I^*, 0 < C^*, 0 < V^*.$$

The equilibria for (1) can be found by setting the right sides of the four differential equations of (1) equal to zero, giving the algebraic system,

$$\begin{aligned}
&(1-\pi_1-\pi_2-\pi_3)P+mI+\sigma V=(\beta I+\gamma C)S+\mu S,\\
&\pi_1 P+(\beta I+\gamma C)S=(\mu+\delta+m)I,\\
&\pi_2 P+\delta I=(\mu+\rho)C,\\
&\pi_3 P=(\mu+\sigma)V.
\end{aligned} \tag{5}$$

Adding all equations in (5), we obtain

$$C^*=\frac{1}{\rho}(P-\mu N^*).$$

Then $S^*$, $I^*$ and $V^*$ can be expressed in terms of $N^*$ as

$$S^*=\frac{(1-\pi_1-\pi_2-\pi_3)P+mI^*+\sigma V^*}{\mu+\beta I^*+\frac{\gamma}{\rho}(P-\mu N^*)},$$

$$I^*=\frac{\pi_1 P+\frac{\gamma S^*}{\rho}(P-\mu N^*)}{(\mu+\delta+m)-\beta S^*},$$

$$V^*=\frac{\pi_3 P}{\mu+\sigma},$$

where $N^*=S^*+I^*+C^*+V^*$. We note that $\omega=(S^*,I^*,C^*,V^*)$ are always positive and this has a unique endemic equilibrium when $\mathscr{R}_0>0$. Therefore, we state without proof the following Lemma.

**Lemma 3.3.** *The endemic equilibrium $\omega$ exists and is positive if and only if $\mathscr{R}_0>0$.*

We will analyze the local asymptotic stability of endemic equilibrium by using the Center Manifold theory [18] as described in (Theory 4.1) . In this case we make the following change of variables in order to apply the Center Manifold theory $S=x_1, I=x_2, C=x_3$ and $V=x_4$. We now use the vector notation $X=(x_i)^T$ $(i=1,2,3,4)$. Then the model equation (5.1) can be written in the form

$$\left(\frac{dx}{dt}\right)=F(X)=(f_1,f_2,f_3,f_4)^T,$$

such that

$$
\begin{aligned}
x_1^{'} &= f_1 = (1-\pi_1-\pi_2-\pi_3)P-(\beta x_2+\gamma x_3)x_1-\mu x_1+mx_2+\sigma x_3,\\
x_2^{'} &= f_2 = \pi_1 P+(\beta x_2+\gamma x_3)x_1-(\mu+\delta+m)x_2,\\
x_3^{'} &= f_3 = \pi_2 P+\delta x_2-(\mu+\rho)x_3,\\
x_4^{'} &= f_4 = \pi_3 P-(\mu+\sigma)x_4.
\end{aligned} \tag{6}
$$

The Jacobia matrix of the system (5.6) is given by,

$$
J|_{DFE} = \begin{pmatrix}
-\mu & -\frac{\beta P}{\mu}+m & -\frac{\gamma P}{\mu}+\sigma & 0\\
0 & \frac{\beta P}{\mu}-\mu-\delta-m & \frac{\gamma P}{\mu} & 0\\
0 & \delta & -\mu-\rho & 0\\
0 & 0 & 0 & -\mu-\sigma
\end{pmatrix},
$$

Let $\beta=\beta^*$ be a bifurcation parameter and if we consider the case $\mathscr{R}_0=1$ and solve for $\beta=\beta^*$ gives $\beta^*=\frac{\mu(\mu+\delta+m)(\mu+\rho)-\gamma P\delta}{\mu^2}$. The the system of the transformed equation with $\beta=\beta^*$ has a simple zero eigenvalues. Hence the Center Manifold theory [18] can be used to analyse the dynamics of $\left(\frac{dx}{dt}\right)=F(X)=(f_1,f_2,f_3,f_4)^T$ near $\beta=\beta^*$. It can be shown that the Jacobian of $\left(\frac{dx}{dt}\right)=F(X)=(f_1,f_2,f_3,f_4)^T$ at $\beta=\beta^*$ has an eigenvector associated with the zero eigenvalues given by $U=(U_1,U_2,U_3,U_4)^T$, where

$$
U_1=-\mu, U_2=-\mu-\sigma, U_{3,4}=\frac{-B\pm\sqrt{B^2-4AC}}{A}, \tag{7}
$$

where

$$
\begin{aligned}
A &= \mu,\\
B &= -2\mu^2-\rho\mu+\beta P-\mu\delta-\mu m,\\
C &= \mu^3-\mu^2\rho-\mu^2\delta-\mu^2 m-\mu\beta P.
\end{aligned}
$$

## 4. Global stability of disease-free equilibruim

We present the global stability of disease-free equilibrium $(DFE)$ of the system (1). We define and contruct Lyapunvor function for the global stability of $DFE$. Furthermore, we use the Lyapunvor function to find its global asymptotical stability for the endemic equilibrium.

**Theorem 4.1.** *For $\mathscr{R}_0 \leq 0$, the disease-free equilibrium of the system (1) is stable globally asymptotically, if $S = S^0$ and unstable for $\mathscr{R}_0 > 1$.*

**Proof.** Here, we define the Lyapunov function for the global stability of disease-free equilibrium, given by

$$L(t) = \left[d_1(S - S^0) + d_2 I + d_3 C + d_4 V\right]. \tag{8}$$

Differentiating the previous function with respect to $t$ and using the system (1),

$$L^{'}(t) = d_1 S^{'} + d_2 I^{'} + d_3 C^{'} + d_4 V^{'},$$

$$\begin{aligned} L^{'}(t) = d_1 &\left[(1-\pi_1-\pi_2-\pi_3)P - (\beta I(t) + \gamma C(t))S(t) - \mu S(t) + mI(t) + \sigma V(t)\right], \\ &+d_2\left[\pi_1 P + (\beta I(t) + \gamma C(t))S(t) - (\mu + \delta + m)I(t)\right], \\ &+d_3\left[\pi_2 P + \delta I(t) - (\mu + \rho)C(t)\right], \\ &+d_4\left[\pi_3 P - (\mu + \sigma)V(t)\right], \end{aligned} \tag{9}$$

where $d_i, i = 1, ..., 4$ are some positive constants to be chosen later. After the arrangement, we obtain

$$\begin{aligned} L^{'}(t) = &\left[d_2 - d_1\right](\beta I + \gamma C)S + \left[d_3\delta - d_2(\mu + \delta + m)\right]I + \left[d_1 - d_4(\mu + \sigma)\right]V \\ &-d_3(\mu + \rho)C - d_1\mu S + d_1 mI + \left[d_2 - d_1\right]\pi_1 P + \left[d_3 - d_1\right]\pi_2 P \\ &\left[d_4 - d_1\right]\pi_3 P + d_1 P. \end{aligned} \tag{10}$$

Choosing the constants, $d_1 = d_2 = \delta$, $d_3 = \mu + \delta + m$, and $d_4 = \frac{\delta\sigma}{\mu+\sigma}$. After the simplification, we get

$$L^{'}(t) = \left(S - S^0\right) - \delta mI - (\mu + \delta + m)(\mu + \rho)C, \tag{11}$$

where $S^0 = \frac{(\mu+m)\pi_2 P + \left(\frac{\mu\delta}{\mu+\sigma}\right)\pi_3 P + \delta P}{\delta\mu}$. $L^{'}(t) = 0$ if and only if $S = S^0$ and $I = C = V = 0$. Also, $L^{'}(t)$ is negative for $S > S^0$. So, by [12], the DFE is globally asymptotically stable in $\Omega$. Hence the prove.

The figures below shows the phase portrait of proportion of acute, chronic and vaccinated groups plotted against the proportion of susceptible population. This shows the dynamic behaviour of the endemic equilibrium of the model (1) using the estimated parameter values in table 1 for different starting values in four cases as shown below.

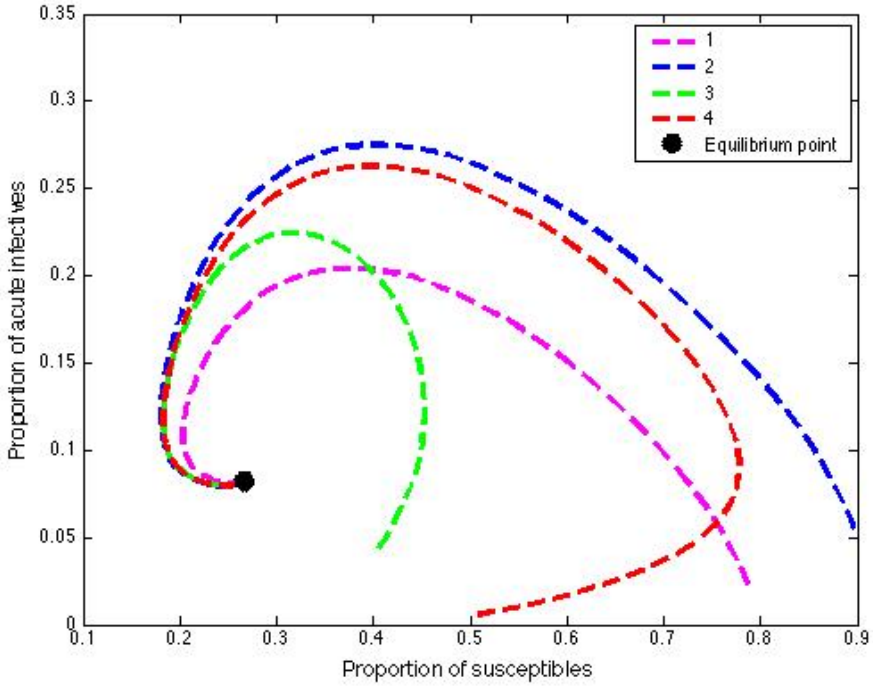



FIGURE 3. Phase portrait: Proportion of acute infected group agaist proportion of susceptible group

In the above Figures 3-5, it is seen that for any initial start, the solution curves tend to the endemic equilibrium point $E_1$. Hence, we infer that the system (1) is globally stable about the endemic equilibrium point $E_1$ for the set of parameters in table 1.

## 5. Sensitivity analysis of model parameters

In the determination of the best strategy for controlling an infection, it is important to identify what factors among all are the most crucial in its transmission. Determining how sensitive $\mathscr{R}_0$ is to parameters, as mostly used in mathematical modeling of biological systems, has been an insightful tool. A sensitivity analysis is conducted to determine the impact of several parameters in our model on various output measures. Therefore, we will calculate sensitivity indices of all the parameters used in this model. For the sensitivity analysis, we employ the normalised forward sensitivity index of a variable to be the ratio of the relative change in a variable to a change in a parameter [2].

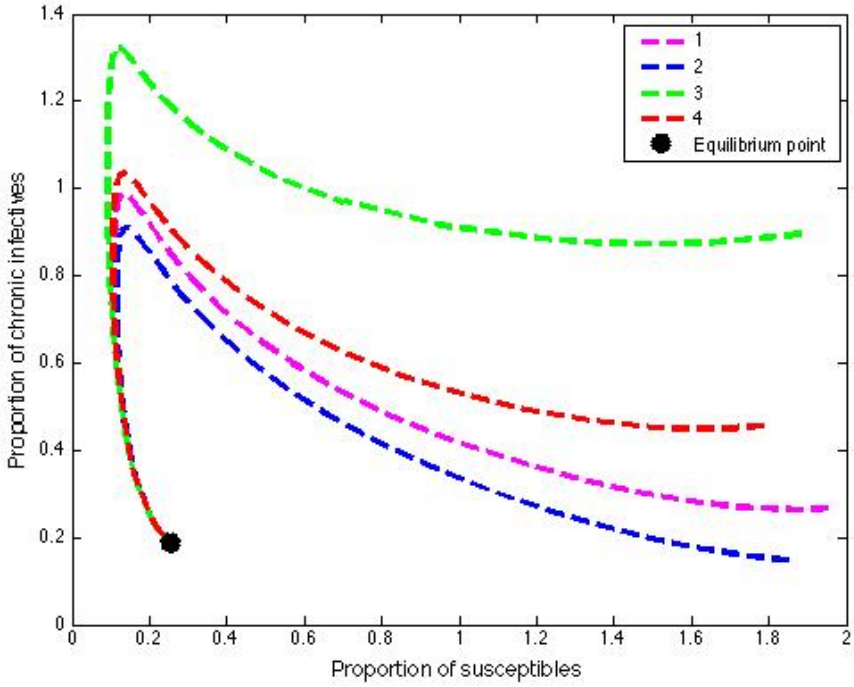



FIGURE 4. Phase portrait: Proportion of chronic infected group agaist proportion of susceptible group

**Definition 5.1.** The normalised forward sensitivity index of a variable, $u$, that depends differentiably on a parameter, $p$, is defined as:

$$\Upsilon_p^u = \frac{\partial u}{\partial p} \times \frac{p}{u}. \tag{12}$$

As we have an explicit formula for $\mathscr{R}_0$ in equation (12), we derive an analytical expression for the sensitivity of $\mathscr{R}_0$ as $\Upsilon_p^{\mathscr{R}_0} = \frac{\partial \mathscr{R}_0}{\partial p} \times \frac{p}{\mathscr{R}_0}$, to each of parameters involved in $\mathscr{R}_0$. For example the sensitivity index of $\mathscr{R}_0$ with respect to $\beta$,

$$\Upsilon_\beta^{\mathscr{R}_0} = \frac{\partial \mathscr{R}_0}{\partial \beta} \times \frac{\beta}{\mathscr{R}_0} = 0.7534.$$

## 6. Optimal control analysis

We have seen that under some suitable threshold limits of different parameters, the HBV model (1) is locally asymptotically stable around the endemic equilibrium $E_1$. But during the

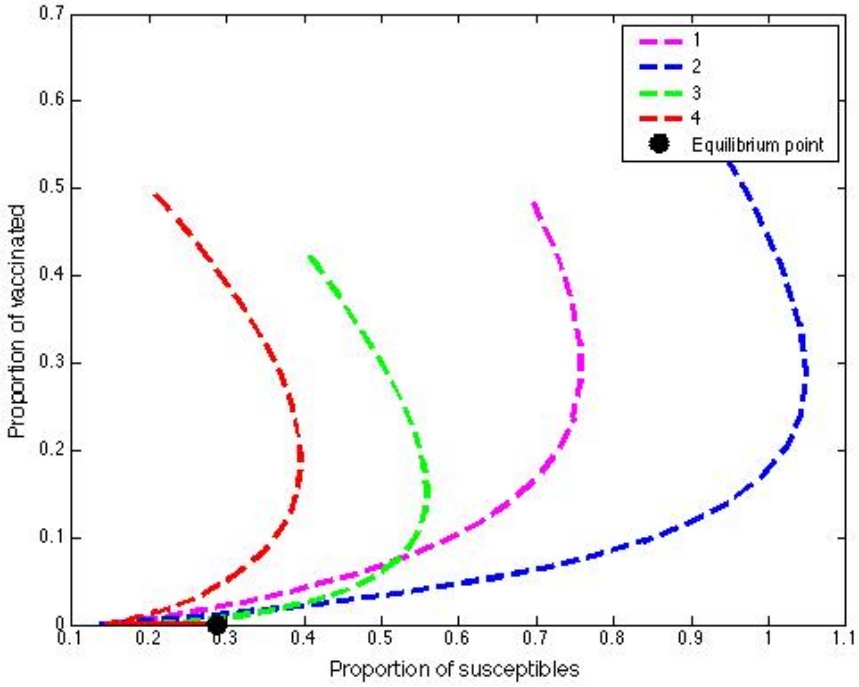



FIGURE 5. Phase portrait: Proportion of vaccinated infected group agaist proportion of susceptible group

TABLE 2. Sensitivity indices of model parameters to $\mathscr{R}_0$

| Para. | Description | Sensitivity index |
|---|---|---|
| $\pi_1$ | Proportion of acute infected immigrants into population | +(ve) |
| $\pi_2$ | Proportion of chronic infected immigrants into population | +(ve) |
| $\pi_3$ | Proportion of vaccinated immigrants into popu. | +(ve) |
| $P$ | Total recruitment into population by birth or immigrant | +(ve) |
| $\beta$ | Contact rate of individual with acute Hepatitis B | +(ve) |
| $\gamma$ | Contact rate of individual with chronic Hepatitis B | +(ve) |
| $m$ | Efficacy of treatment rate | -(ve) |
| $\mu$ | Natural death rate | +(ve) |
| $\rho$ | Death due to chronic hepatitis B infection | +(ve) |
| $\delta$ | Rate of progression from acute to chronic infection | +(ve) |
| $\sigma$ | Rate of progression due to waning immunity | +(ve) |

process of applying control measures such as vaccination or treatment, there is an obvious question of incurring some cost and allied benefit in the whole process. We apply optimal control method using Pontryagins Maximum Principle to determine the necessary conditions for the optimal control of the Hepatitis B disease. We incorporate time dependent controls into the model (1) to determine the optimal strategy for controlling the disease. We rewrite the model as

$$\begin{aligned}
\frac{dS}{dt} &= (1-\pi_1-\pi_2-\pi_3)P-(\beta I+\gamma C)S-\mu S+u_1 mI+\sigma V-u_2 S,\\
\frac{dI}{dt} &= \pi_1 P+(\beta I+\gamma C)S-(\mu+\delta+u_1 m)I,\\
\frac{dC}{dt} &= \pi_2 P+\delta I-(\mu+\rho)C,\\
\frac{dV}{dt} &= \pi_3 P-(\mu+\sigma)V+u_2 S.
\end{aligned} \tag{13}$$

Thus the objective is to quantify the units to express the net profit during the given time of treatment. In other words, this is to construct an economic model out of the given dynamic model of control. In this case the problem reduces to an optimal control problem. Our task is then to formulate an optimal policy when the control measures in the system are already defined in a mathematical form and finally to find out the restrictions on the economic parameters of the model.

The control functions, $u_1(t)$ and $u_2(t)$ are bounded, Lebesgue integrable functions. The control $u_1(t)$ represents the effort from screening and treatment of acute infected to reduce the movement of individuals that may be infectious into chronic group. The control $u_2(t)$ represents the effort from vaccination of susceptible group to reduce the movement of individuals that may be infectious into acute infected group. The objective functional is defined as:

$$J(u_1(t),u_2(t)) = \max_{u_1,u_2} \int_0^{t_f} \left[k_1 I + k_2 V - \left(A_1 u_1^2 + A_2 u_2^2\right)\right] dt, \tag{14}$$

where, $t_f$ is the final time and the co-efficient $k_1, k_2, A_1, A_2$ are balancing cost factors.

Our target is to maximize the objective functional defined in (14) by minimizing the acute infected group and maximizing the vaccinated group. In order words, we seek to find the optimal pair $u_1^*$ and $u_2^*$ such that

$$J(u_1^*,u_2^*) = \max_{\mathbb{U}} J(u_1,u_2),$$

where $\mathbb{U} = \{(u_1(t), u_2(t)) : a_1 \leq (u_1(t), u_2(t)) \leq b_i, i = 1,2 \quad t = [0, t_f]\}$ is the control set. Here $a_i$ and $b_i$ are constant in [0,1]. The necessary conditions that an optimal solution must satisfy come from the [17] Maximum Principle. This principle converts (13)-(14) into a problem of maximizing pointwise a Hamiltonian $H$, with respect to $u_1$ and $u_2$.

$$
\begin{aligned}
H = {} & k_1 I + k_2 V - (A_1 u_1^2 + A_2 u_2^2) \\
& + \lambda_S \{(1 - \pi_1 - \pi_2 - \pi_3)P - (\beta I + \gamma C)S - \mu S + u_1 m I + \sigma V - u_2 S\} \\
& + \lambda_I \{\pi_1 P + (\beta I + \gamma C)S - (\mu + \delta + u_1 m)I\} \\
& + \lambda_C \{\pi_2 P + \delta I - (\mu + \rho)C\} \\
& + \lambda_V \{\pi_3 P - (\mu + \sigma)V + u_2 S\}.
\end{aligned} \tag{15}
$$

**Theorem 6.1.** *There exist optimal control $u_1^*, u_2^*$ and solutions $S^*, I^*, C^*, V^*$ of the corresponding state system (13) that maximizes $J(u_1, u_2)$ over $\mathbb{U}$. Furthermore, there exist $\lambda_S, \lambda_I, \lambda_C, \lambda_V$ satisfying:*

$$
\begin{aligned}
\frac{d\lambda_S}{dt} &= -\frac{\partial H}{\partial S}, \\
\frac{d\lambda_I}{dt} &= -\frac{\partial H}{\partial I}, \\
\frac{d\lambda_C}{dt} &= -\frac{\partial H}{\partial C}, \\
\frac{d\lambda_V}{dt} &= -\frac{\partial H}{\partial V},
\end{aligned}
$$

*with transversality conditions $\lambda_i(t_f) = 0, i = S, I, C, V$. Moreover, the optimal control is given by:*

$$
u_1^*(t) = min\left\{b_1, max\left(a_1, \frac{mI(\lambda_S - \lambda_I)}{2A_1}\right)\right\} \tag{16}
$$

*and*

$$
u_2^*(t) = min\left\{b_2, max\left(a_2, \frac{S(\lambda_V - \lambda_S)}{2A_2}\right)\right\}. \tag{17}
$$

**Proof.** Corollary 4.1 of [6] gives the existence of an optimal control pair due to the convexity of the integrand of (14) with respect to the control $u_1$ and $u_2$, a priori boundedness of the state solutions and the Lipschitz property of the state system with respect to the state variables.

The differential equations governing the adjoint variables are obtained by differentiation of the Hamiltonian function, evaluated at the control pair.

The adjoint system can be written as:

$$
\begin{aligned}
-\frac{d\lambda_S}{dt} &= \frac{\partial H}{\partial S}, \lambda_S(t_f) = 0,\\
-\frac{d\lambda_I}{dt} &= \frac{\partial H}{\partial I}, \lambda_I(t_f) = 0,\\
-\frac{d\lambda_C}{dt} &= \frac{\partial H}{\partial C}, \lambda_C(t_f) = 0,\\
-\frac{d\lambda_V}{dt} &= \frac{\partial H}{\partial V}, \lambda_V(t_f) = 0,
\end{aligned}
$$

where

$$
\begin{aligned}
\frac{\partial H}{\partial S} &= -\left[-(\beta I + \gamma C) - \mu - u_2\right]\lambda_S + \left[\beta I - \gamma C\right]\lambda_I - u_2\lambda_V,\\
\frac{\partial H}{\partial I} &= k_1 - u_1 m\lambda_S + \left[\beta S - (\mu + \delta + u_1 m)\right]\lambda_I - \delta\lambda_C,\\
\frac{\partial H}{\partial C} &= -\gamma S\lambda_S + \gamma S\lambda_I - (\mu + \rho)\lambda_C,\\
\frac{\partial H}{\partial V} &= k_2 + \sigma\lambda_S - (\mu + \sigma)\lambda_V.
\end{aligned} \tag{18}
$$

Solving for $u_1^*$ and $u_2^*$ subject to the constraints, the chracterization (16)-(17) can be derived and we have

$$
\begin{aligned}
0 = \frac{\partial H}{\partial u} &= -2A_1u_1 + mI\lambda_S - mI\lambda_I,\\
0 = \frac{\partial H}{\partial u_2} &= -2A_2u_2 - S\lambda_S + S\lambda_V.
\end{aligned} \tag{19}
$$

Hence, we obtain [20].

$$
\begin{aligned}
u_1^*(t) &= \tfrac{mI(\lambda_S - \lambda_I)}{2A_1},\\
u_2^*(t) &= \tfrac{S(\lambda_V - \lambda_S)}{2A_2}.
\end{aligned}
$$

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

$$
u_1^* = \begin{cases}
a_1 & if \quad \frac{mI^*}{2A_1}(\lambda_S - \lambda_I) \le a_1,\\
\frac{mI^*}{2A_1}(\lambda_S - \lambda_I) & if \quad a_1 < \frac{mI^*}{2A_1}(\lambda_S - \lambda_I) \le b_1,\\
b_1, & if \quad \frac{mI^*}{2A_1}(\lambda_S - \lambda_I) \ge b_1.
\end{cases}
$$

$$
u_2^* = \begin{cases}
a_2 & if \quad \frac{S^*}{2A_2}(\lambda_V - \lambda_S) \le a_2,\\
\frac{S^*}{2A_2}(\lambda_V - \lambda_S) & if \quad a_2 < \frac{S^*}{2A_2}(\lambda_V - \lambda_S) \le b_2,\\
b_2, & if \quad \frac{S^*}{2A_2}(\lambda_V - \lambda_S) \ge b_2.
\end{cases}
$$

Due to the a priori boundedness of the state system, the adjoint system and the resulting Lipschitz structure of the ODEs, we obtain the uniqueness of the optimal control for small $t_f$. The uniqueness of the optimal control follows from the uniqueness of the optimality system that consists in (18) and transversality condition with characterization (16)-(17). Next, we discuss the numerical solutions of the optimality system and the corresponding results of varying the optimal controls $u_1$ and $u_2$ , the parameter choices, and the interpretations from various cases.

## 7. Numerical simulation

The solution of the optimal control prob- lem is obtained by solving the optimality system which consists of the state and adjoint systems (13) and (18), respectively. For computational illustration, the values of parameters in Table 2 were employed and the solution is obtained by using the following iterative scheme.

Step 1. Make a guess of the controls.

Step 2. Use the values of the controls together with the initial conditions to solve the state equations, using a forward numerical scheme.

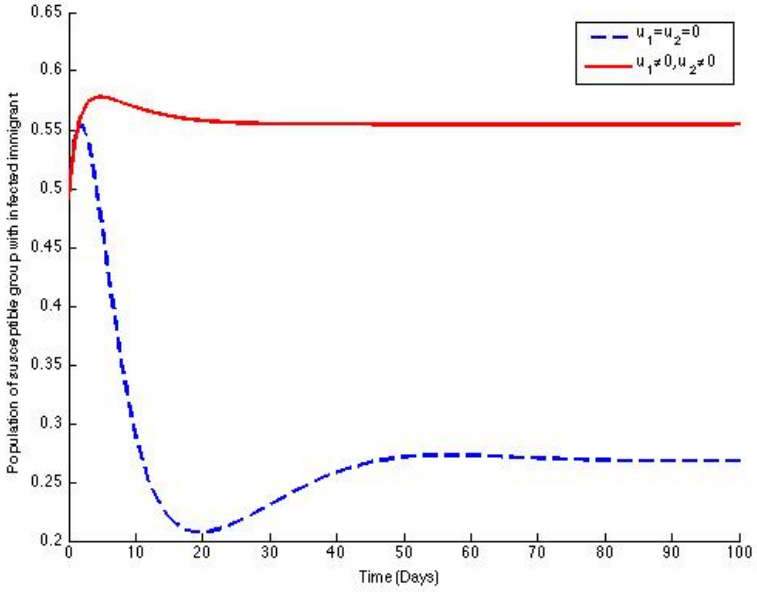
Step 3. Using the current solution of the state system together with the transversality conditions, solve the adjoint equations using a backward numerical scheme. We use a backward scheme for the costate system because the transversality conditions are final time conditions.

Step 4. Update the controls using the characterizations in (16)-(17).

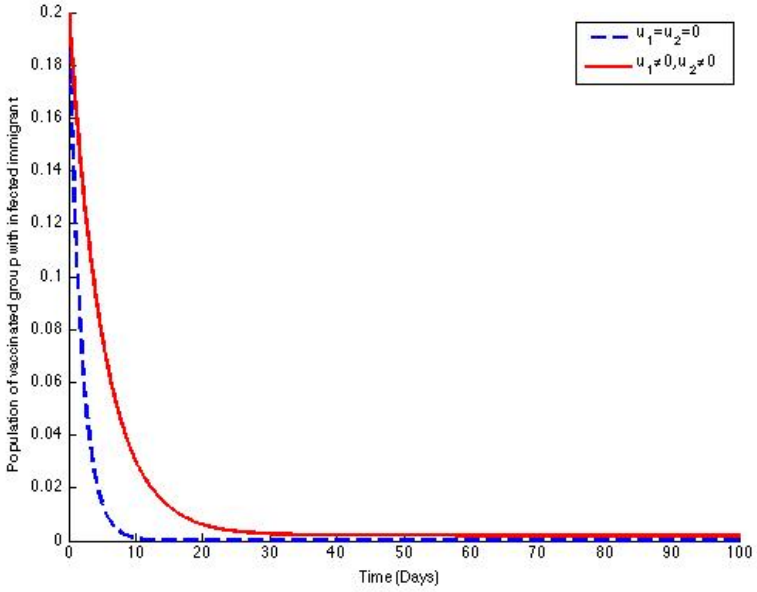
Step 5. Repeat Steps 2 to 4 until the values of the unknowns at the current iteration are very close to those of the previous iteration [14].

## 8. Cost effectiveness analysis

A cost-effectiveness analysis was performed using a decision-analysis model involving a Markov process to model HBV to evaluate the cost-effectiveness of three vaccination strategies in a cohort of newly-arriving immigrants who were all assumed to be unaware of their HBV infection status and asymptomatic, if chronically infected. These strategies were compared to

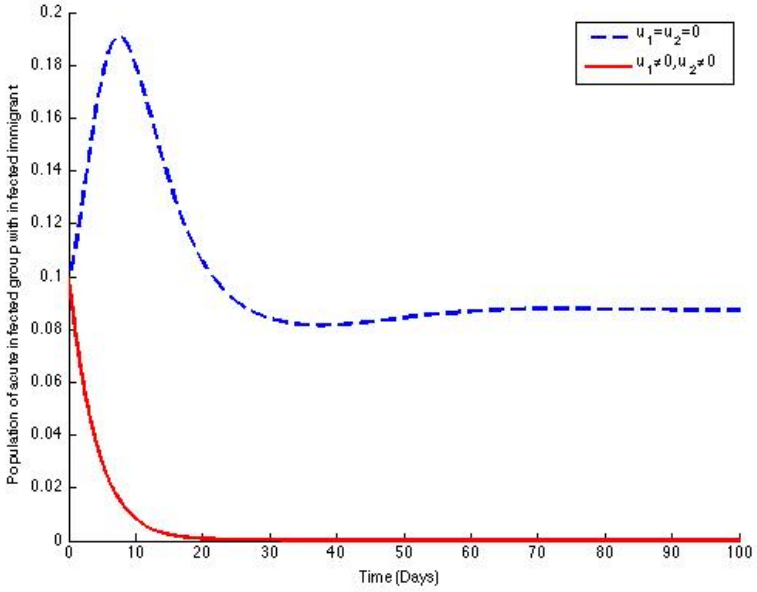



(*a*)

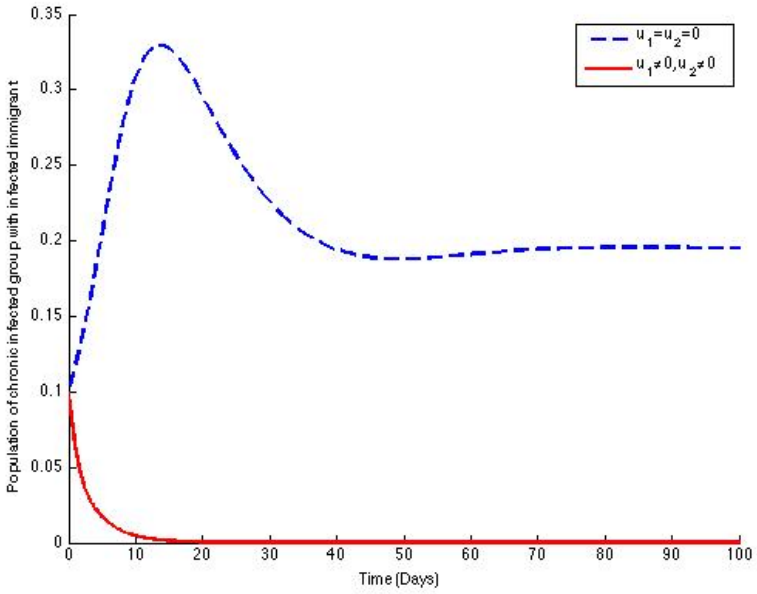



(*b*)

FIGURE 6. The susceptible group (S) indicates significant increase with optimal control compared to the case without control in (a) the vaccinated group (V) with optimal control compared to the case without control in (b).

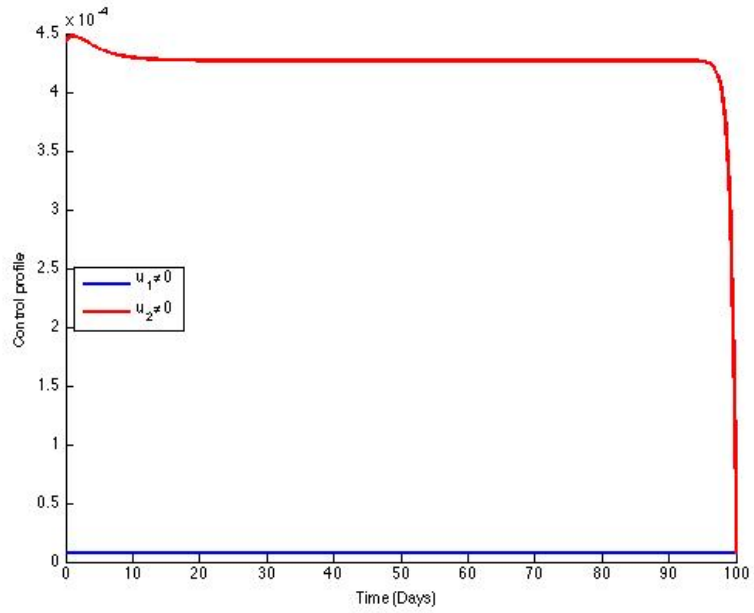



$(a)$

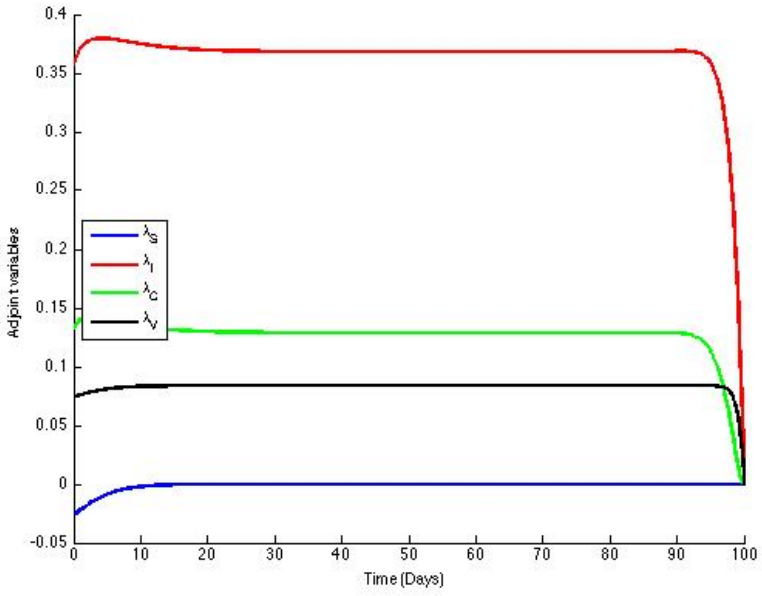



$(b)$

FIGURE 7. Acute infected (I) with optimal control compared to the case without control in (a) and the chronic (C) infected individuals indicates significant decrease in time in (b).




(*a*)




(*b*)

FIGURE 8. The effect of control strategy on HBV transmission in (a), and the control profile suggests control $u_2$ to be at the upper bound for 99 days before dropping gradually to the lower bound, while control $u_1$ to be maintained at the lower bound throughout the intervention period in (b)

the status quo of no targeted vaccination for new immigrants by computing their incremental cost-effectiveness ratios (ICER), defined as the additional health benefit of an intervention, measured in QALYs gained, with the next least costly undominated strategy [4]. The incremental cost effectiveness ratio (ICER) is calculated as the marginal cost of an intervention divided by the marginal effectiveness. It measures how much additional bang for the buck could be achieved by switching from one intervention to another. This can be written as

$$ICER = \frac{Costs_{new\ strategy} - Costs_{current\ practice}}{Effect_{new\ strategy} - Effect_{current\ practice}}.$$

TABLE 3. Direct Costs and Health Outcomes of Treatment and Vaccination in a Cohort of 10,000 Immigrants

| **Strategy** | **Average Cost per person** | **Hepatitis B related deaths** | **Deaths Prevented** | **Average Effectiveness (QALY)** | **Incremental Cost per QALY gained, compared to Status Quo** |
|---|---|---|---|---|---|
| **Status Quo** | \$148,799 | 3,029.126 | ... | 24.686 | ... |
| **Vaccination** | \$152,401 | 3,028.509 | 0.617 | 24.781 | \$38,157 |
| **Treatment** | \$152,527 | 2,697.034 | 332.092 | 24.785 | \$37,675 |
| **Both Treatment and Vaccination** | \$152,566 | 2,695.881 | 333.245 | 24.785 | \$38,051 |

## 9. Conclusions

We present the mathematical model of the transmission dynamics of HBV infection with infected immigrants. We calculated the basic reproduction number, investigated the existence and stability of equilibria. The disease-free equilibrium is locally as well as globally asymptotically stable for $\mathscr{R}_0 \leq 1$. We obtained the local and global asymptotical stability for the endemic equilibrium. For the reproduction number $\mathscr{R}_0 > 1$, the endemic equilibrium is, locally as well

as globally, asymptotically stable. Furthermore, we have solved the compartment model numerically, and performed optimal control analysis of the model. Applying optimal control, we derived and analyzed the conditions for optimal control of the disease with effective treatment regime and vaccination measures using the Pontryagins Maximum Principle [17]. Finally, numerical simulations of the resulting control problem are carried out to determine the effectiveness of various controls. The control profile suggests control $u_2$ to be at the upper bound for 99 days before dropping gradually to the lower bound, while control $u_1$ to be maintained at the lower bound throughout the intervention period. In all cases, the status quo remained the least costly and least effective strategy. Furthermore, the ranking of interventions, in terms of their cost-effectiveness ratios, remained unchanged. The treatment strategy was always the most cost-effective and the vaccination strategies were always dominated prohibitively expensive. Vaccination would not be cost-effective in this population because the cost associated with preventing a small number of new infections in adults was outweighed by the cost of immunizing a large population and the cost of existing untreated chronic HBV infections.

## Conflict of Interests

The authors declare that there is no conflict of interests.

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