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A Mathematical Model of Hepatitis B Virus Transmission Dynamics considering HBV Mutants

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ABSTRACT

Hepatitis B is a global threat as approximately one third of the world's population has serological evidence of past or present infection with hepatitis B virus (HBV) and 350–400 million people are chronic HBV surface antigen (HBs Ag) carriers In this paper, a mathematical model for the transmission dynamics of hepatitis B virus infection considering HBV mutants is presented. First, the disease-free equilibrium state of the model was determined. The next generation method was used to compute the basic reproduction number, R_0, as a threshold parameter, in terms of the given model parameters. It was proved that the disease-free equilibrium state is locally asymptotically stable if the R_0 is below unity. Local stability of the endemic equilibrium state was established using the centre manifold theory. The result of the centre manifold theory on the endemic equilibrium state shows that the disease can persist as the value of R_0 increases above one. The results of numerical simulations show that the impact of carriers with HBV mutants can be significant. The findings of this study strongly suggest that effective intervention should be put in place to reduce the proportion of carriers with HBV mutants to the barest minimum.

Keywords: Mathematical model, disease-free equilibrium, endemic equilibrium, centre manifold

INTRODUCTION

Hepatitis means inflammation of the liver. Hepatitis B is a contagious liver disease that results from infection with the hepatitis B virus. When first infected, a person can develop an illness which can be mild, with few or no symptoms, or an illness that is serious, requiring hospitalization and sometimes leading to liver failure. Acute hepatitis B refers to the period when a person first becomes infected with the virus. This is the time a person is most likely to have symptoms. Some people develop antibodies (proteins found in the blood or body fluids that help

fight infection) and these people recover, which leads to protection from future infection. Other people, especially infants and young children, do not recover. Instead, the infection remains and becomes a "chronic" or lifelong infection. Chronic hepatitis B refers to infection when the hepatitis B virus continues to be active in the person's body for more than 6 months. Over time, chronic infection damages the liver and causes scarring, liver failure, and sometimes liver cancer. While there is no cure for hepatitis B infection, treatment can slow the damage to the liver. Infected children have up to a 90% chance of developing chronic infection (CDC, 2013).

Hepatitis B is one of the world's most serious health problems. Approximately one third of the world's population has serological evidence of past or present infection with hepatitis B virus (HBV) and 350–400 million people are chronic HBV surface antigen (HBsAg) carriers [EASL (2013),White and Fenner (1994), Platkov *et al;* (2001), Carriapa *et al; (*2004), Fernandez *et al (*2006), Onuzulike and Ogueri (2007)].

HBV infection can be transmitted from mother to child (vertical), contact with an infected person (horizontal transmission), sexual contact (homosexual and heterosexual transmission) with infected partners, exposure to blood or other infected fluids and contact with HBV contaminated instruments [WHO (2001), WHO (2002].

HBV control measures include vaccination, education, screening of blood and blood products; and treatment (CDC, 2005). However, hepatitis B viral mutants can emerge in patients as a result of selection pressure from either immune response or treatment options. The concern is that carriers with HBV mutants can still infect vaccinated individuals and mount resistance to antiviral drugs [Zanetti *et al;* (1988), Coleman (2006)].

Epidemiological models help to capture infection or disease transmission mechanisms in a population in a mathematical frame-work to predict the behavior of the disease spread through the population. Mathematical models have become important tools in analyzing the spread and control of infectious diseases. Understanding the transmission characteristics of infectious diseases in communities, regions and countries across the world in mathematical frame works can lead to better approaches to decreasing the transmission of these diseases (Anderson and May, 1991).

Recently, mathematical models have been used to study the transmission dynamics of HBV in various communities, regions and countries across the world. Anderson and May (1991) proposed a simple deterministic, compartmental mathematical model to investigate the effects of carriers on the transmission of HBV. Anderson *et al;* (1992) and Williams *et al;* (1996) presented models of sexual transmission of HBV, which include heterogeneous mixing with respect to age and sexual activity. Edmunds *et al;* (1993) explored the relation between the age at infection with HBV and the development of the carrier state. Medley *et al;* (2001) proposed 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 *et al;* (2008) applied the model of Medley *et al;* (2001) to predict chronic hepatitis B infection in New Zealand. The prevalence of HBV in developing countries is different from that in developed countries, since it appears that the rate of transmission in childhood is the major determinant of the level of HBV endemicity and little is known on the rates and patterns of sexual contact in developing countries (Edmunds *et al;* 1996c). Mclean and Blumberg (1994) and Edmunds *et al* (1996a) studied models of HBV transmission in developing countries and Williams *et al;* (1996) described a model of HBV in UK. O'Leary *et al;* (2008) proposed a mathematical model to investigate the effect of Hepatitis B vaccine and anti-viral

treatment among the Canadian Inuit population. An optimal control model of Hepatitis B transmission dynamics was proposed by Mehmood (2011). Zou *et al;* (2009) proposed a mathematical model to investigate the transmission dynamics and prevalence of HBV in mainland China. Zou *et al;* (2015) used a mathematical model to study the sexual transmission dynamics of hepatitis B virus in China. Zhang et al (2015) proposed a model to explore the transmission dynamics of hepatitis B virus in China.

Public health policy on the design of various HBV control programs has benefitted a lot from the recommendations of the previous mathematical modelers and much success has been recorded. However, available data in various regions on the prevalence of HBV infection show a slow pace of control (WHO, 2009). Much still needs to be done until HBV infection is eradicated from the global community.

The model by Zou *et al;* (2009) forms the motivation for this study. In their work, a mathematical model was proposed to study the transmission dynamics and prevalence of HBV infection in mainland China.

In this paper, their model is modified to study HBV transmission dynamics and prevalence, considering the role of HBV mutants.
The plan of this work is as follows. The model formulation is presented in section 2. Section 3 is devoted to deriving the basic reproduction number. Stability analysis of both the disease-free and endemic equilibrium states is carried out in section 4. Numerical simulation is performed in section 5. Results are discussed in section 6. Finally conclusion is passed in section 7.

FORMULATION OF THE MODEL

The Existing Model

We begin our model formulation by introducing the model by Zou *et al;* (2009). We, first, present the parameters and assumptions of the existing model.

Assumptions of the Existing model

The following are the assumptions of the existing model by Zou *et al;* (2009):

(i) The population is compartmentalized into the proportions of susceptible individuals $S(t)$, latent individuals $L(t)$, acutely infected individuals $I(t)$, chronic carriers $C(t)$, vaccinated individuals $V(t)$, and the recovered individuals $R(t)$ all at time t,

(ii) The population is homogeneous,

(iii) Influx into the population is by birth only,

(iv) Exit out of the population is by natural and HBV-related mortality only,

(v) The vaccinated individuals do not acquire permanent immunity,

(vi) The newborns to carrier mothers infected at birth proceed to carrier state immediately.

Variables and Parameters of the Existing Model

The population is partitioned into six compartments described as follows:

$S(t)$ = Proportion of the susceptible individuals at time t

$L(t)$ = Proportion of the latent individuals at time t

$I(t)$ = Proportion of the acutely infected individuals at time t

$C(t)$ = Proportion of the chronic carriers at time t

$R(t)$ = Proportion of the recovered individuals at time t

$V(t)$ = Proportion of the vaccinated individuals at time t

The following are the parameters of the existing model:

μ =birth rate
μ_0=natural mortality rate
μ_1 =HBV-related mortality rate
ω =proportion of births without vaccination
$(1-\omega)$ =proportion of births vaccinated
v =proportion of births vertically infected
Ψ =Rate of waning vaccine-induced immunity
σ =Rate of moving from latent state to acute state
β =Transmission coefficient
γ_1 = $r$ate of moving from acute to other compartments
q = Average probability that an individual fails to clear an acute infection and develops to carrier state
$q\gamma_1$ = Rate of moving from acute to carrier
$(1-q)\gamma_1$ = Rate of moving from acute to recovered class
γ_2 = $r$ate of moving from carrier to immune
γ_3 = Vaccination rate of the susceptible individuals
ε = Reduced transmission rate relative to acute infection by carriers
The following is a flow diagram for the existing model.

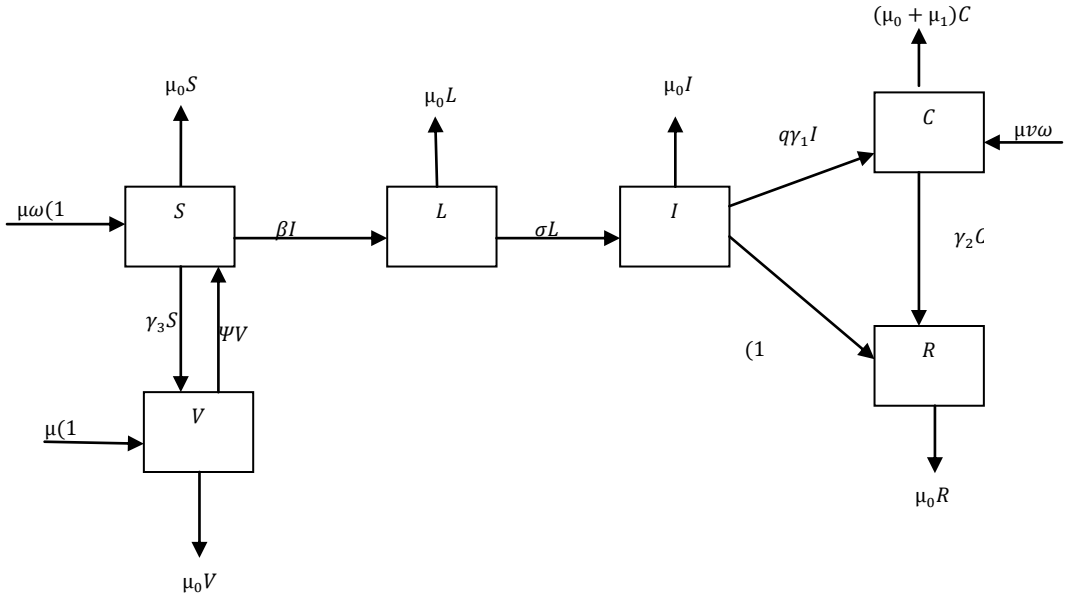

Figure 1: Flow diagram of HBV transmission dynamics for the existing model

The Equations of the Existing Model

Using the above assumptions, parameters and flow diagram, Zou *et al;* (2009) derived the following model equations.

$$\frac{dS}{dt} = \mu\omega(1 - vC) + \Psi V - \left(\mu_0 + \beta I + \varepsilon\beta C + \gamma_3\right)S \quad (1.1)$$

$$\frac{dL}{dt} = (\beta I + \varepsilon\beta C)S - (\sigma + \mu_0)L \quad (1.2)$$

$$\frac{dI}{dt} = \sigma L - \left(\mu_0 + \gamma_1\right)I \quad (1.3)$$

$$\frac{dC}{dt} = \mu v\omega C + q\gamma_1 I - \left(\mu_0 + \mu_1 + \gamma_2\right)C \quad (1.4)$$

$$\frac{dR}{dt} = (1 - q)\gamma_1 I + \gamma_2 C - \mu_0 R \quad (1.5)$$

$$\frac{dV}{dt} = \mu(1 - \omega) + \gamma_3 S - (\mu_0 + \Psi)V \quad (1.6)$$

The Modified Model

We shall use the following assumptions to derive the modified model used in this work.

Assumptions of the Modified Model

We make the following assumptions:

(i) The latent period after infection is ignored (Zou *et al,* 2015),

(ii) The carriers with HBV mutants can infect vaccinated individuals and their proportion is represented by p.

Equations of the Modified Model

Based on the above assumptions and parameters, we modify the model by Zou *et al;* (2009) as follows.

$$\frac{dS}{dt} = \mu\omega(1 - vC) + \Psi V - \left(\mu_0 + \beta I + \varepsilon\beta C + \gamma_3\right)S \quad (2.1)$$

$$\frac{dI}{dt} = (\beta I + \varepsilon\beta C)S + p\varepsilon\beta CV - \left(\mu_0 + \gamma_1\right)I \quad (2.2)$$

$$\frac{dC}{dt} = \mu v\omega C + q\gamma_1 I - \left(\mu_0 + \mu_1 + \gamma_2\right)C \quad (2.3)$$

$$\frac{dV}{dt} = \mu(1-\omega) + \gamma_3 S - (\mu_0 + \Psi + p\varepsilon\beta C)V \quad (2.4)$$

$$\frac{dR}{dt} = (1-q)\gamma_1 I + \gamma_2 C - \mu_0 R \quad (2.5)$$

$S(0) \geq 0, I(0) \geq 0, C(0) \geq 0, V(0) \geq, R(0) \geq 0.$

Because the models are in terms of proportions,

$$S(t) + I(t) + C(t) + R(t) + V(t) = 1 \quad (2.6)$$

at all time t.

The model is defined in the subset $D \times [0, \infty)$ of R_+^6, where

$D = \{(S, I, C, V, R) \in R_+^6 : 0 \leq S, I, C, V, R \leq 1, S + I + C + V + R \leq 1\}$

For ease of analysis, we use equations $(2.1 - 2.4)$, since there is no R term in them and R can always be found as:

$R(t) = 1 - [S(t) + I(t) + C(t) + V(t)]$.

THE BASIC REPRODUCTION NUMBER, R_0

We first, do variable transformation for ease of analysis as in the sequel.

Let $X = [x_1, x_2, x_3, x_4]^T = [S, I, C, V]^T$ so that equations (2.1)-(2.4) can be expressed in the form $\frac{dX}{dt} = F = (f_1\ f_2\ f_3\ f_4)$ such that

$$\frac{dx_1}{dt} = \mu\omega(1 - vx_4) + \Psi x_4 - (\mu_0 + \beta x_2 + \varepsilon\beta x_3 + \gamma_3)x_1 \quad (2.7)$$

$$\frac{dx_2}{dt} = (\beta x_2 + \varepsilon\beta x_3)x_1 - (\mu_0 + \gamma_1)x_2 + p\varepsilon\beta x_3 x_4 \quad (2.8)$$

$$\frac{dx_3}{dt} = \mu v\omega x_4 + q\gamma_1 x_3 - (\mu_0 + \mu_1 + \gamma_2)x_4 \quad (2.9)$$

$$\frac{dx_4}{dt} = \mu(1-\omega) + \gamma_3 x_1 - (\mu_0 + \Psi + p\varepsilon\beta x_3)x_4 \quad (2.10)$$

We now calculate the disease-free equilibrium state of the modified model. We begin this by setting the left hand sides of equations $(2.7) - (2.10)$ to zero and getting the disease-free equilibrium state as follows. The disease-free equilibrium state, $E_0 = (S_0, 0, 0, V_0)$, where $S_0 = \frac{\mu(\Psi + \mu_0\omega)}{\mu_0(\mu_0 + \gamma_3 + \Psi)}$ and $V_0 = \frac{\mu(\mu_0 + \gamma_3 - \mu_0\omega)}{\mu_0(\mu_0 + \gamma_3 + \Psi)}$. The recipe by Heffernan (2005) and Van Den Driessche and Watmough (2005) is followed to compute the basic reproduction number.

The vector $F(x)$ of the rates of new infections in compartments x_2 and x_3 is given by

$$F(x) = \begin{pmatrix} (\beta x_2 + \varepsilon\beta x_3)x_1 + p\varepsilon\beta x_3 x_4 \\ 0 \end{pmatrix}.$$

Also, the remaining transfer terms in compartments x_2 and x_3 are given by

$$V(x) = \begin{pmatrix} (\mu_0 + \gamma_1)x_2 \\ -(\mu v\omega x_3 + q\gamma_1 x_2) + (\mu_0+\mu_1+\gamma_2)x_3 \end{pmatrix}.$$

The matrix of partial derivatives of $F(x)$ at the disease-free equilibrium state $\bar{x} = E_0 = (S_0, 0,0, V_0)$ is given by

$$F_x(E_0) = \begin{pmatrix} \beta S_0 & \varepsilon\beta S_0 + p\varepsilon\beta C V_0 \\ 0 & 0 \end{pmatrix}, \text{ where } S_0 = \frac{\mu(\Psi+\mu_0\omega)}{\mu_0(\mu_0+\gamma_3+\Psi)}$$

and the matrix of partial derivatives of $V(x)$ at the disease-free equilibrium state $\bar{x} = E_0 = (S_0, 0,0, V_0)$ is:

$$V_x(E_0) = \begin{pmatrix} \mu_0 + \gamma_1 & 0 \\ -q\gamma_1 & \mu_0+\mu_1+\gamma_2 - \mu v\omega \end{pmatrix}.$$

It follows that the basic reproduction number R_0 is given by:

$$R_0 = \rho(F_x V^{-1}) = \frac{\beta S_0(\mu_0+\mu_1+\gamma_2-\mu v\omega)+\varepsilon\beta q\gamma_1(S_0+pV_0)}{(\mu_0+\gamma_1)(\mu_0+\mu_1+\gamma_2-\mu v\omega)} \qquad (2.11)$$

R_0 becomes biologically meaningful if $(\mu_0+\mu_1+\gamma_2) > \mu v\omega$.

STABILITY OF EQUILIBRIA

Existence and Local Stability Analysis of the Disease-free Equilibrium State (DFEs)

We will now examine the existence and local stability of DFEs. We compute the Jacobian matrix for the disease-free equilibrium state using equations (2.7) − (2.10) as follows.

The Jacobian matrix for the disease-free state J_{E_0} is given by

$$J(E_0) = \begin{pmatrix} -(\mu_0+\gamma_3) & -\beta S_0 & -(\mu v\omega + \varepsilon\beta S_0) & 0 \\ 0 & -(\mu_0+\gamma_1) & \varepsilon\beta S_0 + p\varepsilon\beta V_0 & 0 \\ 0 & q\gamma_1 & \mu v\omega - (\mu_0+\mu_1+\gamma_2) & 0 \\ \gamma_3 & 0 & -p\varepsilon\beta V_0 & -(\mu_0 + \Psi) \end{pmatrix}$$

Theorem 4.1: If $R_0 < 1$, then the disease-free equilibrium state E_0 is locally and asymptotically stable.

Proof: To prove theorem 4.1, it suffices to show that all the Eigen values of the characteristic equation for the Jacobian matrix $J(E_0)$ above have negative real parts.

The diagonal entries $-(\mu_0+\gamma_3) < 0$ and $(\mu_0 + \Psi) < 0$ are two of the eigenvalues of the characteristic equation for the Jacobian matrix $J(E_0)$. Thus, excluding these columns and the corresponding rows, we calculate the remaining eigenvalues. These eigenvalues are the roots of the characteristic equation of the reduced matrix of dimension two given by

$M = \begin{pmatrix} -(\mu_0+\gamma_1) & 0 \\ q\gamma_1 & \mu v\omega - (\mu_0+\mu_1+\gamma_2+\alpha) \end{pmatrix}$.

$Trace(M) = -(\mu_0+\gamma_1) + (\mu v\omega - \mu_0+\mu_1+\gamma_2) < 0.$

Recall that;

$$R_0 = \frac{\beta S_0(\mu_0+\mu_1+\gamma_2-\mu v\omega) + \varepsilon\beta q\gamma_1(S_0+pV_0)}{(\mu_0+\gamma_1)(\mu_0+\mu_1+\gamma_2-\mu v\omega)}$$

$$= \frac{\beta S_0(\mu_0+\mu_1+\gamma_2-\mu v\omega)}{(\mu_0+\gamma_1)(\mu_0+\mu_1+\gamma_2-\mu v\omega)} + \frac{\varepsilon\beta q\gamma_1(S_0+pV_0)}{(\mu_0+\gamma_1)(\mu_0+\mu_1+\gamma_2-\mu v\omega)}$$

Let $R_1 = \frac{\beta S_0(\mu_0+\mu_1+\gamma_2-\mu v\omega)}{(\mu_0+\gamma_1)(\mu_0+\mu_1+\gamma_2-\mu v\omega)}$ and $R_2 = \frac{\varepsilon\beta q\gamma_1(S_0+pV_0)}{(\mu_0+\gamma_1)(\mu_0+\mu_1+\gamma_2-\mu v\omega)}$ so that $R_0 = R_1 + R_2$.

$$Det(M) = (\mu_0+\gamma_1)(\mu v\omega - \mu_0+\mu_1+\gamma_2) - \varepsilon\beta q\gamma_1(S_0+pV_0)$$

$$= (\mu_0+\gamma_1)(\mu v\omega - \mu_0+\mu_1+\gamma_2)\left[1 - \frac{\varepsilon\beta q\gamma_1(S_0+pV_0)}{(\mu_0+\gamma_1)(\mu v\omega - \mu_0+\mu_1+\gamma_2)}\right]$$

$$= (\mu_0+\gamma_1)(\mu v\omega - \mu_0+\mu_1+\gamma_2)[1-R_2] < 0 \; for \; R_2 < 1.$$

Therefore, all the roots have negative real parts and the disease-free equilibrium state E_0 is locally asymptotically stable if $R_0 < 1$.

Existence and Stability of Endemic Equilibrium State

We shall discuss the stability of the endemic equilibrium state of our model equations $(2.1) - (2.4)$ using the transformed system $(2.7 - 2.10)$.

In the sequel, we shall employ the method of centre manifold theory to investigate the existence and stability of the endemic equilibrium state.

Analysis of Centre Manifold Near $x = E_0$ and $R_0 = 1$

In the previous section, we discussed the local stability of the disease-free equilibrium using the basic reproduction number and linearization method. The change of stability that occurs at $R_0 = 1$ is often followed by the emergence of a branch of steady state. This is referred to as bifurcation, and this may happen for values of R_0 slightly greater than (or less than) one. This is called a forward (backward) bifurcation. One way of determining the direction of bifurcation (forward or backward) in an epidemiological model is the use of the centre manifold method. This method reduces the system under consideration to a simpler system which has the same qualitative properties and which can be studied in a relatively easier way (Ameh, 2009).

In this section, we investigate the bifurcation behavior of a general epidemic model around the critical value $R_0 = 1$ in a neighbourhood of a disease-free equilibrium, E_0. Let $\varphi = R_0 - 1$ and rewrite our general epidemic model in the following way:

$$x' = f(x, \varphi) \qquad (2.12)$$

With the assumption that f is continuously differentiable at least twice. We have the following result.

Let $D_x f(E_0, 0)$ be the matrix of partial derivatives of f at the disease-free equilibrium. Also let u and v be the right and the left eigenvectors of $D_x f(E_0, 0)$ respectively.

Theorem 4.2: (Mukandavire *et al;* 2010). Consider the disease transmission model defined by (2.12) with the function $f(x, \varphi)$ φ is the parameter as described from the foregoing. Assume that the zero eigenvalue of $D_x f(E_0, 0)$ is simple. Let

$a = \sum_{k,i,j=1}^{n} v_k u_i v_j \frac{\partial^2 f_k}{\partial_{x_i} \partial x_j}(E_0,0)$, $b = \sum_{k,i=1}^{n} v_k u_i \frac{\partial^2 f_k}{\partial_{x_i} \partial_{\phi}}(E_0,0)$. Assume that $b \neq 0$. Then, there exists $\delta > 0$ such that

(i) If $a>0,\ \ b>0$, when $\varphi<0$ with $|\varphi|<1$, E_0 is locally asymptotically stable, and there exists a positive unstable equilibrium; when $0<\varphi<1$, E_0 is unstable and there exists a negative asymptotically stable equilibrium;

(ii) If $a<0,\ \ b<0$, when $\varphi<0$ with $|\varphi|<1$, E_0 is unstable; when $0<\varphi<1$, E_0 is asymptotically stable, and there exists a positive unstable equilibrium;

(iii) If $a>0,\ \ b<0$, when $\varphi<0$ with $|\varphi|<1$ E_0 is unstable, and there exists a locally asymptotically stable negative equilibrium; when $0<\varphi<1$, E_0 is stable and a positive unstable equilibrium appears

(iv) If $a<0,\ \ b>0$, when φ changes from negative to positive, E_0 changes its stability from stable to unstable. Corresponding negative equilibrium becomes positive and locally asymptotically stable.

Application of Centre Manifold Theory to Local Stability of Endemic Equilibrium

Using the centre manifold theory as described above, we now investigate the local asymptotic stability of the endemic equilibrium.
The Jacobian matrix of the system $(2.7)-(2.10)$at the disease-free equilibrium is given by

$$J(E_0)=\begin{pmatrix} -(\mu_0+\gamma_3) & -\beta S_0 & -(\mu v\omega+\varepsilon\beta S_0) & 0 \\ 0 & -(\mu_0+\gamma_1) & \varepsilon\beta S_0+p\varepsilon\beta V_0 & 0 \\ 0 & q\gamma_1 & \mu v\omega-(\mu_0+\mu_1+\gamma_2) & 0 \\ \gamma_3 & 0 & -p\varepsilon\beta V_0 & -(\mu_0+\Psi) \end{pmatrix}$$

It can be shown that the linearized system of transformed equations $(2.7)-(2.10)$ with $R_0=1$ has a simple zero eigenvalue when
$\beta=\beta^*=\frac{(\mu_0+\gamma_1)(\mu_0+\mu_1+\gamma_2-\mu v\omega)}{S_0(\mu_0+\mu_1+\gamma_2-\mu v\omega)+\varepsilon q\gamma_1(S_0+pV_0)}$.

Hence, the centre manifold theory (see, Driessche *et al*, 2005, Mukandavire *et al;* 2010), Ameh, 2009) can be used to analyse the

dynamics of the system. The Jacobian (J_{E_0}) of system (2.7) – (2.10) has a right eigenvector associated with zero eigenvalue given by $U = (u_1, u_2, u_3, u_4)^T$

Let $u_2 = 1$.

$$u_3 = \frac{\mu_0+\gamma_1}{\varepsilon\beta S_0+p\varepsilon\beta V_0} > 0,$$

$$u_1 = -\frac{\beta S_0(\varepsilon\beta S_0 + p\varepsilon\beta V_0) + (\mu_0+\gamma_1)(\mu v\omega + \varepsilon\beta S_0)}{\varepsilon\beta S_0 + p\varepsilon\beta V_0} < 0,$$

$$u_4 = -\frac{p\varepsilon\beta V_0(\mu_0+\gamma_1)}{(\mu_0 + \Psi)(\varepsilon\beta S_0 + p\varepsilon\beta V_0)}$$

The left eigenvector Jacobian (J_{E_0}) associated with the zero eigenvalue is given by

$V = [v_1\ v_2 v_3\ v_4\ ]^T$.

$v_1 = v_4 = 0$. Let $v_2 = 1 > 0,\ v_3 = \frac{(\varepsilon\beta S_0+p\varepsilon\beta V_0)}{(\mu_0+\mu_1+\gamma_2-\mu v\omega)} > 0.$

Now, $\frac{\partial^2 f_2}{\partial x_1 \partial x_2} = \beta, \frac{\partial^2 f_2}{\partial x_1 \partial x_3} = \varepsilon\beta, \frac{\partial^2 f_2}{\partial x_3 \partial x_4} = p\varepsilon\beta, \frac{\partial^2 f_2}{\partial x_2 \partial \beta} = S_0,\ and\ \frac{\partial^2 f_2}{\partial x_3 \partial \beta} = \varepsilon S_0 + p\varepsilon\beta V_0.$

Thus, $a = v_2u_1u_2\beta + v_2u_1u_3\varepsilon\beta + v_2u_3u_4\ p\varepsilon\beta < 0, b = v_2u_2S_0 + v_2u_3(\varepsilon S_0 + p\varepsilon V_0) > 0.$

Therefore, by item (iv) of theorem 4.2, the disease-free equilibrium becomes unstable and the endemic equilibrium becomes locally asymptotically stable as R_0 changes values from less than one to values slightly greater than one.

NUMERICAL SIMULATION

Numerical simulations are performed using the parameter values in Table 1.

Table1: Parameter values used in numerical simulations

Parameter/Variable	Value	Reference
ν	0.11	Zou *et al;* (2009)
ψ	0.1	Zou *et al;* (2009)
p	0-1	variable
β	0.95	Zou *et al;*(2009)
γ_1	4 per year	Zou *et al;* (2009)

q	0.885	Zou *et al;* (2009)
γ_2	0.025	Zou *et al;* (2009)
ε	0.16	Zou *et al;* (2009)
μ	0.042	fitted
μ_0	0.019	fitted
$S(0)$	0.7	Assumed
$I(0)$	0.05	Assumed
$C(0)$	$0.1 - 0.2$	Musa *et al;* (2015)
$R(0)$	0.1	Assumed

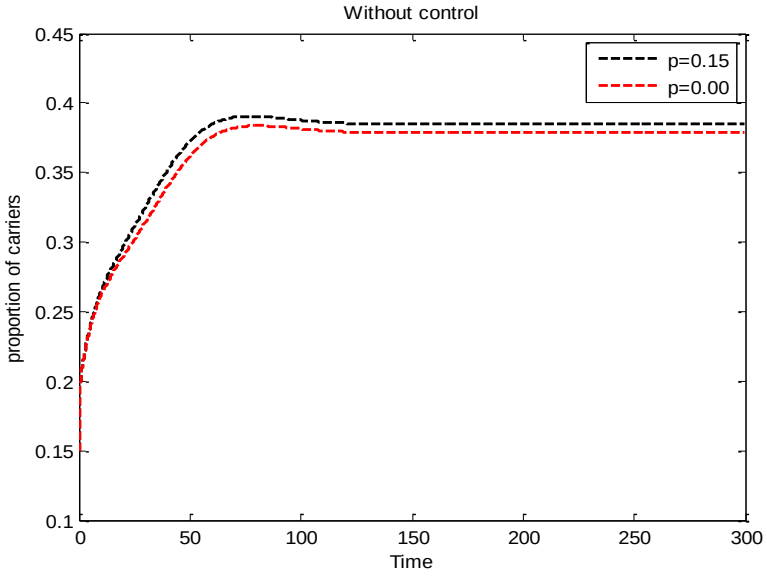

Figure 2: Graph showing the prevalence of carriers without control

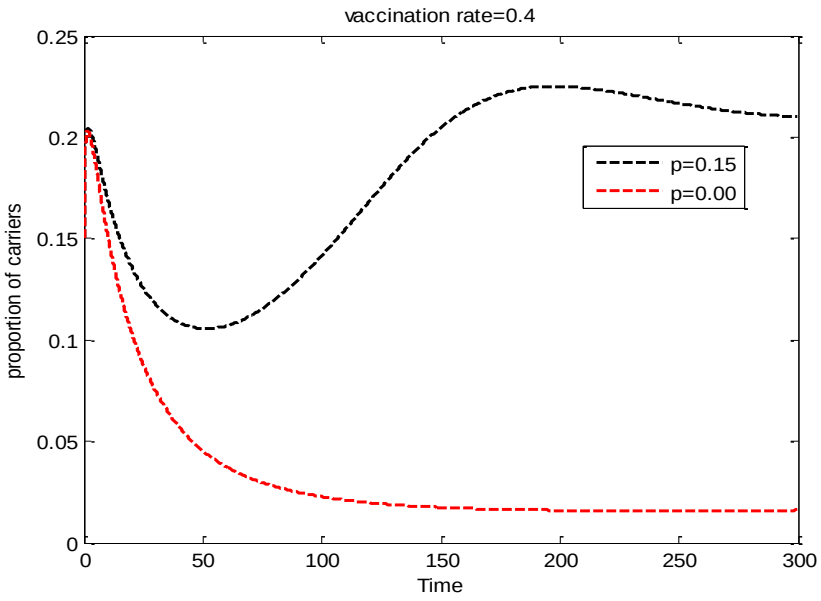

Figure 3: Graph showing the prevalence of carriers with 40% vaccination

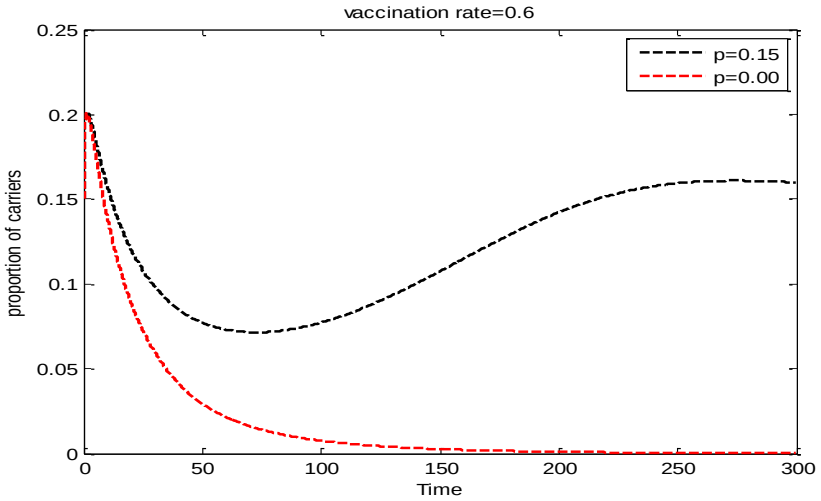

Figure 4: Graph showing the prevalence of carriers with 60% vaccination

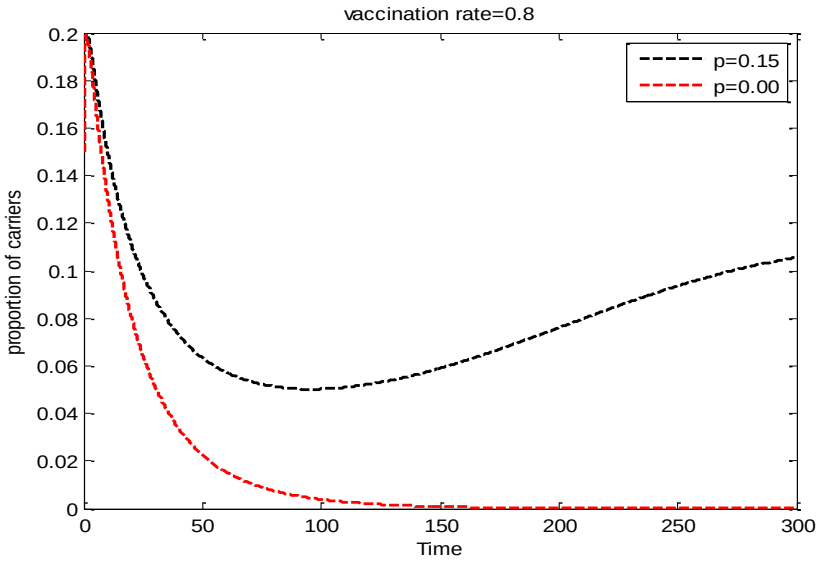

Figure 5: Graph showing the prevalence of carriers with 80% vaccination

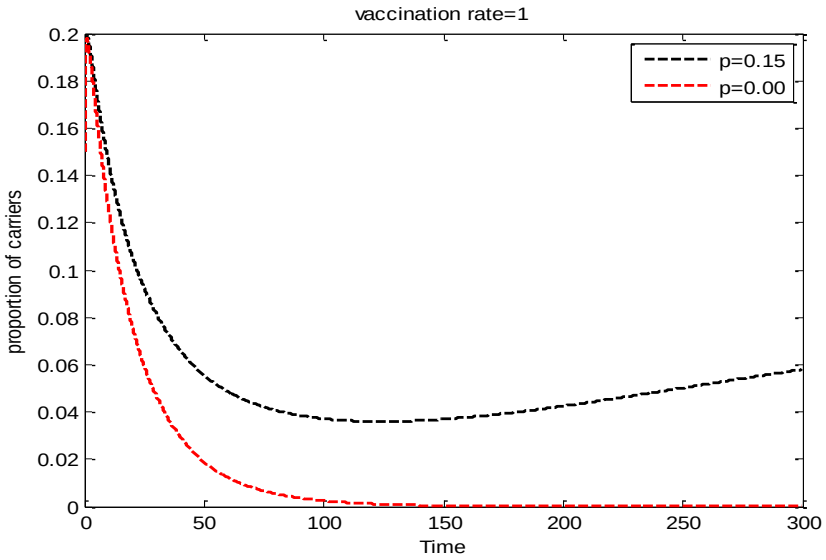

Figure 6: Graph showing the prevalence of carriers with 100% vaccination

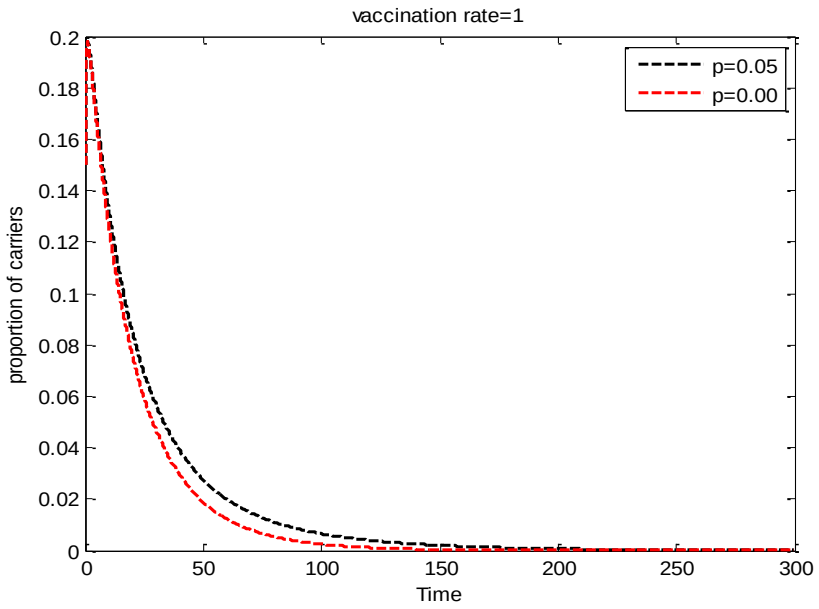

Figure 7: Graph showing the prevalence of carriers with 100% vaccination

DISCUSSION

In this study, we modified and analyzed a mathematical model for the transmission dynamics of HBV infection considering HBV mutants. The analytical results obtained are discussed as follows. Fundamental in our analytical results, is the basic reproduction number, R_0. R_0 serves as a threshold parameter that predicts whether an infection can spread, and is used as a guide to the public health or control agency on the amount of effort needed to control or eradicate a disease. The basic reproduction number, R_0 for the model was computed using the next generation method. The result of the stability analysis for the disease-free equilibrium state can be found in theorem 4.1. The result shows that if $R_0 < 1$, the DFEs are locally asymptotically stable. This means that the disease cannot spread and, therefore, the disease can be eliminated. The result of the centre manifold theory (theorem 4.2) shows that there exists a unique endemic equilibrium state that is locally and asymptotically stable for $R_0 > 1$. The results of numerical simulations of the modified model are discussed below. The results can be found in Figures 2 through 6. The parameter values are as shown in Table 1. The main aim is to

assess the impact of carriers with HBV mutants and the feasibility of their control for different values of vaccination parameter. Figures 2 through 7 show the prevalence of infection for two populations namely, one with carriers not having HBV mutants and the other with carriers having HBV mutants. We represent the proportion of carriers with HBV mutants with p. A zero value of p means no HBV mutants. Figure 2 shows the prevalence of infection for the two populations with $(p = 0.00, 0.15), \omega = 0, \gamma_3 = 0$. It shows a very high level of endemicity both in the presence of HBV mutants and in their absence. Figure 3 shows the prevalence of infection when $(p = 0.00, 0.15), \omega = 0, \gamma_3 = 0.4$. It shows a high level of endemicity in the presence of HBV mutants and low endemicity in their absence. Figures 4, 5 and 6 show the prevalence of infection when $\gamma_3 = 0.6, \gamma_3 = 0.8 \; and \; \gamma_3 = 1$ respectively, the values of p and ω as before. They show high endemicity in the presence of HBV mutants and control in their absence. Figure 7 shows the prevalence of infection when $(p = 0.00, 0.05), \omega = 0$ and $\gamma_3 = 1$. It shows control in the presence of HBV mutants and in their absence. This study confirms that even in the presence of 100% vaccination, the proportion of carriers with HBV mutants should be very low to guarantee control. Based on the findings in this study it is therefore recommended that effective treatment strategy for patients be put in place.

CONCLUSION

In this study, we modified and studied a mathematical model for the transmission dynamics of HBV infection considering HBV mutants in the host population. The model parameters and equations are given in Section (2).The disease-free equilibrium state of the model was determined. The basic reproduction number, R_0 for the model was computed using the next generation method. It was also proved that the disease-free equilibrium state was locally asymptotically stable if $R_0 < 1$. The existence and stability of the endemic equilibrium state was established through the centre manifold theory. Numerical simulations

were performed. The results show that the impact of carriers with HBV mutants on HBV transmission dynamics can be significant.

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