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Modelling Hepatitis B Virus Transmission Dynamics In The Presence of Vaccination and Treatment

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ABSTRACT

Hepatitis B is a global threat as over a billion people have been infected and about 300 million people die annually across the world. In this paper, a mathematical model for the transmission dynamics of hepatitis B virus infection considering vaccination and treatment as control parameters in the host population is presented. First, the disease-free equilibrium state of the model was determined. The next generation method was used to determine the basic reproduction number, R_0, as a threshold parameter, in terms of the given model parameters. R_0 was analytically evaluated for its sensitivity to vaccination and treatment parameters. It was proved that the disease-free equilibrium state is locally asymptotically stable if the R_0 is below unity, otherwise, it is unstable. Local stability of the endemic equilibrium state was established using the centre manifold theory. The analytical results of the R_0 show that increasing the proportion of people who receive vaccines, either at birth or later in life, reduces it below unity. Similarly, increasing the proportion of carriers who receive treatment achieves the same purpose. The result of the local stability analysis of the disease-free equilibrium state shows that the disease can be eliminated if R_0 is below unity. 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 findings of this study strongly suggest a combination of effective vaccination and treatment as a control strategy is crucial to the success of HBV disease control.

1. Introduction

Hepatitis B is a disease that is characterized by inflammation of the liver and is caused by infection by the hepatitis B virus. Hepatitis may be caused by drugs or viral agents. These viral agents include the hepatitis A, B, C, D, E, F, G and H viruses (WHO, 2002).

Hepatitis B is one of the world's most serious health problems. More than a billion people around the world have serological indicators of past or present infection with hepatitis B virus (HBV). Over 300 million people are chronic carriers of the virus (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, 2002).

HBV control measures include vaccination, education, screening of blood and blood products; and treatment (CDC, 2005).

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. Zou *et al* (2009) proposed a mathematical model to investigate the transmission dynamics and prevalence of HBV in mainland China. The model is formulated from that of Medley *et al* (2001) based on the characteristics of HBV in China.

Public health policy on the design of various HBV control programs has benefitted a lot from the recommendations of the previous mathematical modellers and much success has been recorded. However, available data in various regions on the prevalence of HBV infection shows 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.

They assumed that the newborns to carrier mothers infected at birth do not stay in a latent period, so that they instantaneously become carriers. However, as pointed out by Anderson and May (1991) and White and Fenner (1994), an HBV carrier must have harboured the virus in the blood for at least six months. By this newborns to carrier mothers infected at birth are latently infected individuals. Mehmood (2011) supported the same view in his study and assumed that the proportion of the infected newborns to carrier mothers is latent. The role of treatment of HBV carriers as a measure of control was not considered in their model.

In our paper, we study the impact of vaccination and treatment on HBV transmission dynamics. We also assume that the newborns to carrier mothers infected at birth are latently infected individuals and, therefore, shall include them in the latent compartment.

The plan of this work is as follows. The model equations are formulated in section 2. Section 3 is devoted to deriving the basic reproduction number. Stability analysis of both the disease-free and endemic equilibria is carried out in section 4. Results are discussed in section 5. Finally conclusion is passed in section 6.

2. Formulation of the Model Equations

2.1. 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.

2.2. 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.

2.3. 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 = rate 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 = rate 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.

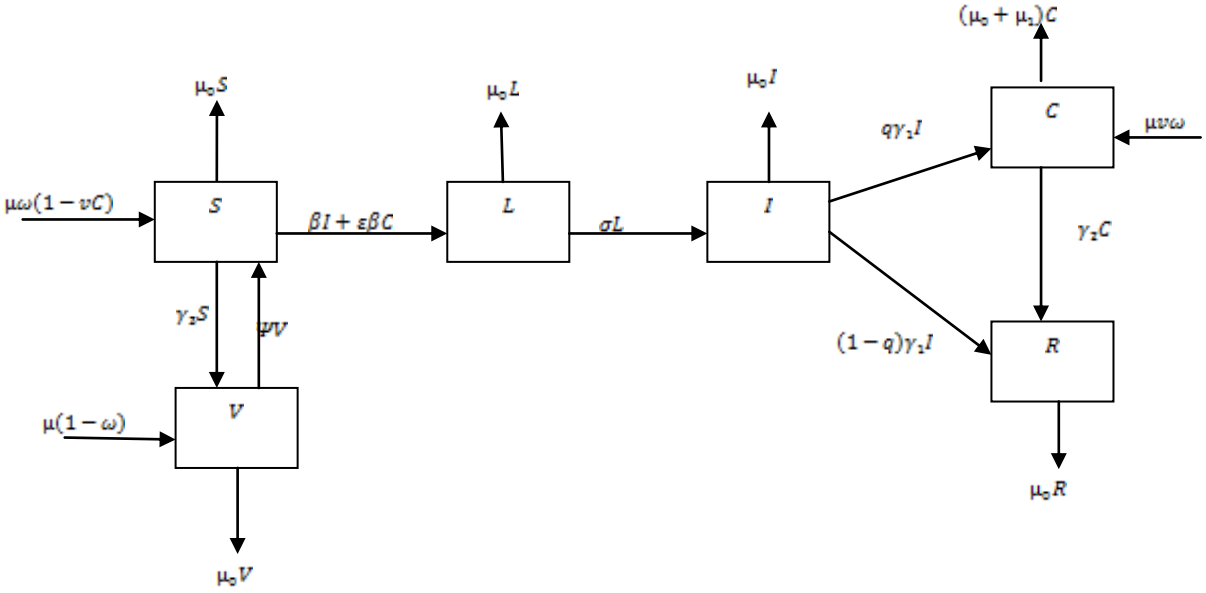

Figure 1: Flow diagram of HBV transmission dynamics for the existing model

2.4. The Equations of the Existing Model

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

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

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

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

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

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

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

2.5The Extended Model

We shall use the following assumptions and flow diagram to derive the extended model used in this work.

2.6. Assumptions of the Extended Model

In addition to the assumptions by Zou *et al* (2009) except (vi), we make the following assumptions:

(i) The chronic carriers are treated at the rate α. Acute infections are not subjected to antiviral treatment because of possibility of relapse and resistance (WHO, 2001),

(ii) The newborns to carrier mothers infected at birth, first, enter the latent class (Mehmood, 2011),

(iii) The treated individuals recover (O'Leary *et al*, 2008).

The flow diagram for the existing model is now amended to obtain the flow diagram for the extended model as follows:

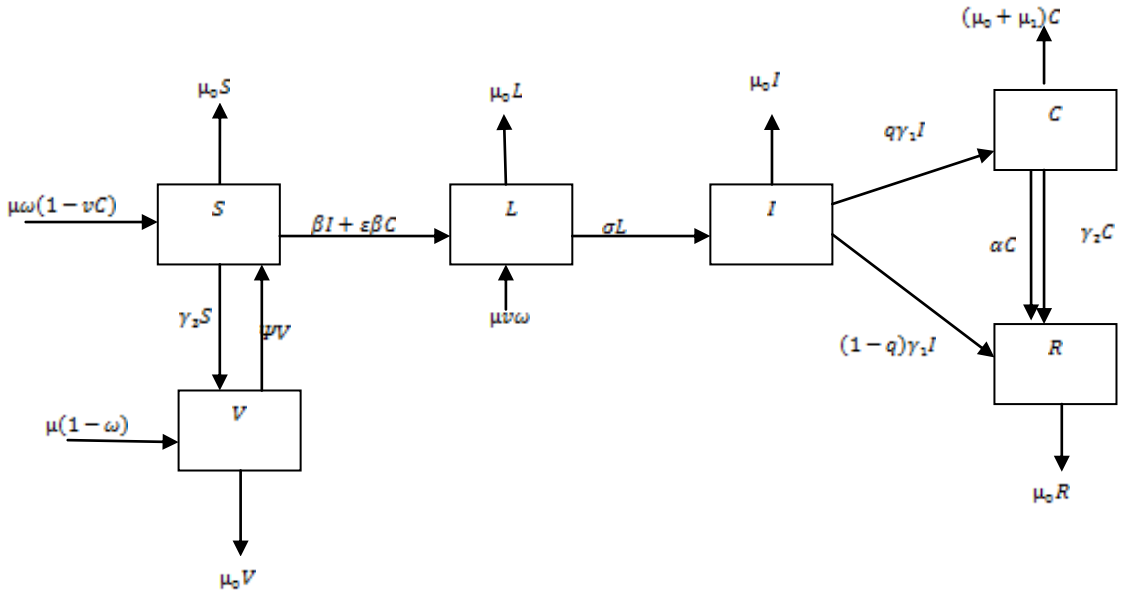

Figure 2: Flow diagram of HBV transmission dynamics for the extended model

2.7. Equations of the Extended Model

The infected newborns are now moved to the second equation instead of the fourth equation in the existing model. Also, chronic individuals are now treated at a rate α and this is incorporated in the last term in the fourth equation.

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

$$\frac{dS}{dt} = \mu\omega(1-vC) + \Psi V - (\mu_0 + \beta I + \varepsilon\beta C + \gamma_2)S \qquad (2.1)$$

$$\frac{dL}{dt} = \mu v\omega C + (\beta I + \varepsilon\beta C)S - (\sigma + \mu_0)L \qquad (2.2)$$

$$\frac{dI}{dt} = \sigma L - (\mu_0 + \gamma_1)I \qquad (2.3)$$

$$\frac{dC}{dt} = q\gamma_1 I - (\mu_0 + \mu_1 + \gamma_2 + \alpha)C \qquad (2.4)$$

$$\frac{dV}{dt} = \mu(1-\omega) + \gamma_3 S - (\mu_0 + \Psi)V \qquad (2.5)$$

$$\frac{dR}{dt} = (1-q)\gamma_1 I + (\gamma_2 + \alpha)C - \mu_0 R \qquad (2.6)$$

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

Because the models are in terms of proportions,

$$S(t) + L(t) + I(t) + C(t) + R(t) + V(t) = 1 \qquad (2.7)$$

for all time t.

The model is defined in the subset $D \times [0, \infty)$ of R_+^7, where

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

3. The Basic Reproduction Number, R_0

We now calculate the disease-free equilibrium state of the extended model. We begin this by setting the left hand sides of equations $(2.1) - (2.5)$ to zero and get the disease-free equilibrium state as follows. The disease-free equilibrium state, $E_0 = (S_0, 0, 0, 0, V_0)$, where $S_0 = \frac{\mu(\Psi + \mu_0\omega)}{\mu_0(\mu_0 + \gamma_3 + \Psi)}$ and $V_0 = \frac{\mu(\mu_0 + \gamma_3 - \mu_0\omega)}{\mu_0(\mu_0 + \gamma_3 + \Psi)}$.

Remark 1: For SEIR models, the rate of appearance of new infections is given by the new infection terms in the latent-compartment. See, for example, Van Driesche and Watmough (2002), Heffernan *et al* (2005) and Ameh (2009).

From the equations $(2.1) - (2.5)$ of the extended model, we have the following:

The vector $F(x)$ of the rates of new infections in compartments L, I and C is given by

$$F(x) = \begin{pmatrix} \mu v\omega C + (\beta I + \varepsilon\beta C)S \\ 0 \\ 0 \end{pmatrix}.$$

Also, the remaining transfer terms in compartments L, I and C are given by

$$V(x) = \begin{pmatrix} (\sigma + \mu_0)L \\ -\sigma L + (\mu_0 + \gamma_1)I \\ -q\gamma_1 I + (\mu_0 + \mu_1 + \gamma_2 + \alpha)C \end{pmatrix}.$$

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

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

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

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

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

$$R_0 = \rho(F_x V^{-1}) = \frac{\sigma\beta S_0}{(\sigma+\mu_0)(\mu_0+\gamma_1)} + \frac{q\gamma_1\sigma(\mu\nu\omega+\varepsilon\beta S_0)}{(\sigma+\mu_0)(\mu_0+\gamma_1)(\mu_0+\mu_1+\gamma_2+\alpha)} \quad (2.8)$$

R_0 leads to the following results.

Proposition 3.1 R_0 is a strictly decreasing function of $\gamma_3 \in (0, 1)$.

Proof:

The partial derivative of R_0 with respect to γ_3 is given by

$$\frac{\partial R_0}{\partial \gamma_3} = -\frac{[\sigma\beta\mu(\Psi+\mu_0\omega)(\mu_0+\mu_1+\gamma_2+\alpha)+q\gamma_1\sigma\varepsilon\beta\mu(\Psi+\mu_0\omega)]}{\mu_0(\mu_0+\gamma_3+\Psi)(\sigma+\mu_0)(\mu_0+\gamma_1)(\mu_0+\mu_1+\gamma_2+\alpha)^2} < 0.$$

Therefore, R_0 is a strictly decreasing function of $\gamma_3 \in (0, 1)$.

Proposition 3.2 R_0 is a strictly decreasing function of $\alpha \in (0, 1)$.

Proof:

Also, the partial derivative of R_0 with respect to α is given by

$$\frac{\partial R_0}{\partial \alpha} = -\frac{q\gamma_1\sigma[\mu\nu\omega\mu_0(\mu_0+\gamma_3+\Psi) + \varepsilon\beta\mu(\Psi+\mu_0\omega)]}{\mu_0(\mu_0+\gamma_3+\Psi)(\sigma+\mu_0)(\mu_0+\gamma_1)(\mu_0+\mu_1+\gamma_2+\alpha)^2} < 0.$$

Therefore, R_0 is a strictly decreasing function of $\alpha \in (0, 1)$.

Proposition 3.3 R_0 is strictly decreasing on $(1-\omega) \in (0, 1)$.

Proof:

The partial derivative of R_0 with respect to $(1-\omega)$ is

$$\frac{\partial R_0}{\partial (1-\omega)} = \frac{-[\sigma\beta\mu\mu_0(\mu_0+\mu_1+\gamma_2+\alpha) + q\gamma_1\sigma\mu\nu\mu_0(\mu_0+\gamma_3+\Psi) + q\gamma_1\sigma\varepsilon\beta\mu_0]}{\mu_0(\mu_0+\gamma_3+\Psi)(\sigma+\mu_0)(\mu_0+\gamma_1)(\mu_0+\mu_1+\gamma_2+\alpha)} < 0.$$

Therefore, R_0 is a strictly decreasing function of $(1-\omega)$.

The basic reproduction number is a decreasing function of both vaccination and treatment rates.

4. Stability of Equilibria

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

We will now examine the existence and local stability of DFEs. We shall first compute the Jacobian matrix for the disease-free equilibrium state using equations $(2.1) - (2.5)$ as done in Zou *et al* (2009).

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

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

For ease of analysis, we perform the following operations:

(1) Subtract column 5 from column 1,
(2) Add row 1 to row 5.

By these operations, we have the following equivalent matrix:

$$J_{E_{01}} = \begin{pmatrix} -(\mu_0+\gamma_3+\Psi) & 0 & -\beta S_0 & -(\mu v\omega + \varepsilon\beta S_0) & \Psi \\ 0 & -(\sigma+\mu_0) & \beta S_0 & \mu v\omega + \varepsilon\beta S_0 & 0 \\ 0 & \sigma & -(\mu_0+\gamma_1) & 0 & 0 \\ 0 & 0 & q\gamma_1 & -(\mu_0+\mu_1+\gamma_2+\alpha) & 0 \\ 0 & 0 & -\beta S_0 & -(\mu v\omega + \varepsilon\beta S_0) & -\mu_0 \end{pmatrix}$$

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

Proof: To prove theorem 4.1, it suffices to show that all the eigenvalues of the characteristic equation for the Jacobian matrix $J_{E_{01}}$ above have negative real parts.

The diagonal entries $-(\mu_0+\gamma_3+\Psi) < 0$ and $-\mu_0 < 0$ are the two of the eigenvalues of the characteristic equation of Jacobian matrix $J_{E_{01}}$. 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 three given by

$$M = \begin{pmatrix} -(\sigma+\mu_0) & \beta S_0 & \mu v\omega + \varepsilon\beta S_0 \\ \sigma & -(\mu_0+\gamma_1) & 0 \\ 0 & q\gamma_1 & -(\mu_0+\mu_1+\gamma_2+\alpha) \end{pmatrix}.$$

To simplify the notations, we let

$$B_0 = (\sigma+\mu_0),\ B_1 = (\mu_0+\gamma_1),\ B_2 = (\mu_0+\mu_1+\gamma_2+\alpha),\ B_3 = (\mu v\omega + \varepsilon\beta S_0)$$

so that

$$M = \begin{pmatrix} -B_0 & \beta S_0 & B_3 \\ \sigma & -B_1 & 0 \\ 0 & q\gamma_1 & -B_2 \end{pmatrix}.$$

Therefore, the corresponding characteristic equation to M is

$$\lambda^3 + (B_0 + B_1 + B_2)\lambda^2 + (B_0B_1 + B_0B_2 + B_1B_2 - \sigma\beta S_0)\lambda + B_0B_1B_2 - \beta S_0B_2 - \sigma q\gamma_1 B_3$$

$$= \lambda^3 + A\lambda^2 + B\lambda + C = 0 \qquad (2.9)$$

where,

$A = B_0 + B_1 + B_2$,

$B = B_0B_1 + B_0B_2 + B_1B_2 - \sigma\beta S_0$ and

$C = B_0B_1B_2 - \beta S_0B_2 - \sigma q\gamma_1 B_3$.

The Routh-Hurwitz conditions (Murray, 2002) are the sufficient and necessary conditions on the coefficients of the characteristic equation (2.9).

By Routh-Hurwiz criteria, all the roots of the characteristic equation (2.9)

have negative real parts if A, B, $C > 0$ and $AB - C > 0$.

$A = B_0 + B_1 + B_2 > 0$,

$$AB - C = (B_0 + B_1 + B_2)(B_0B_1 + B_0B_2 + B_1B_2 - \sigma\beta S_0) - (B_0B_1B_2 - \sigma\beta S_0B_2 - \sigma q\gamma_1 B_3)$$

$$= B_0^2B_1 + B_0^2B_2 + B_0B_1B_2 - B_0\sigma\beta S_0 + B_0B_1^2 + B_0B_1B_2 + B_1^2B_2 - B_1\sigma\beta S_0 +$$

$$+B_0B_2^2 + B_1B_2^2 + B_3\sigma q\gamma_1.$$

To show that $AB - C > 0$, we apply R_0 as a threshold. Observe that the basic reproduction number as shown in (2.9) is:

$$R_0 = \frac{\sigma\beta S_0}{(\sigma + \mu_0)(\mu_0+\gamma_1)} + \frac{q\gamma_1\sigma(\mu\nu\omega + \varepsilon\beta S_0)}{(\sigma + \mu_0)(\mu_0+\gamma_1)(\mu_0+\mu_1+\gamma_2 + \alpha)}.$$

Substituting $B_0 = (\sigma + \mu_0)$, $B_1 = (\mu_0+\gamma_1)$, $B_2 = (\mu_0+\mu_1+\gamma_2 + \alpha)$, $B_3 = \mu\nu\omega + \varepsilon\beta S_0$ in R_0 gives

$$R_0 = \frac{\sigma\beta S_0}{B_0B_1} + \frac{q\gamma_1\sigma B_3}{B_0B_1B_2}$$

Let $R_1 = \frac{\sigma\beta S_0}{B_0B_1}$ and $R_2 = \frac{q\gamma_1\sigma B_3}{B_0B_1B_2}$ so that $R_0 = R_1 + R_2$.

$R_0 < 1$ implies that $R_1 < 1, R_2 < 1$. R_1 and R_2 are terms of R_0. Rearranging the terms in $AB - C$ gives

$$AB - C = B_0^2B_1 + B_0^2B_2 - B_0\sigma\beta S_0 + B_0B_1B_2 + B_0B_1^2 - B_1\sigma\beta S_0 + B_0B_1B_2 + B_1^2B_2$$

$$+B_0B_2^2 + B_1B_2^2 + B_3\sigma q\gamma_1$$

$$= B_0^2B_2 + B_0^2B_1 - B_0\sigma\beta S_0 + B_0B_1B_2 + B_1(B_0B_1 - \sigma\beta S_0) + B_0B_1B_2 + B_1^2B_2$$

$$+B_0B_2^2 + B_1B_2^2 + B_3\sigma q\gamma_1$$

$$= B_0^2B_2 + B_0(B_0B_1)\left(1 - \frac{\sigma\beta S_0}{B_0B_1}\right) + B_0B_1B_2 + B_1(B_0B_1)\left(1 - \frac{\sigma\beta S_0}{B_0B_1}\right) + B_0B_1B_2$$

$$+B_1{}^2 B_2 + B_0 B_2{}^2 + B_1 B_2{}^2 + B_3\sigma q\gamma_1$$

$$= B_0{}^2 B_2 + B_0(B_0B_1)(1 - R_1) + B_0B_1 B_2 + B_1(B_0B_1)(1 - R_1) + B_0B_1 B_2 + B_1{}^2 B_2$$

$$+B_0 B_2{}^2 + B_1 B_2{}^2 + B_3\sigma q\gamma_1 > 0 \text{ if } R_1 < 1.$$

To show that $B > 0$, we also apply R_1 as a threshold as follows.

$$B = B_0B_1 + B_0 B_2 + B_1 B_2 - \sigma\beta S_0$$

$$= B_0 B_2 + B_1 B_2 + B_0B_1 - \sigma\beta S_0$$

$$= B_0 B_2 + B_1 B_2 + B_0B_1\left(1 - \frac{\sigma\beta S_0}{B_0B_1}\right)$$

$$= B_0 B_2 + B_1 B_2 + B_0B_1(1 - R_1) > 0 \text{ if } R_1 < 0.$$

To show that $C > 0$, we also apply R_0 as a threshold as follows. We also recall that

$$R_0 = \frac{\sigma\beta S_0}{B_0B_1} + \frac{q\gamma_1\sigma B_3}{B_0B_1B_2}$$

$$= \frac{\sigma\beta S_0B_2 + q\gamma_1\sigma B_3}{B_0B_1B_2}$$

Therefore,

$$C = B_0B_1B_2 - \sigma\beta S_0B_2 - \sigma q\gamma_1B_3$$

$$= B_0B_1B_2\left(1 - \frac{\sigma\beta S_0B_2 + q\gamma_1\sigma B_3}{B_0B_1B_2}\right)$$

$$= B_0B_1B_2(1 - R_0) > 0 \text{ if } R_0 < 1.$$

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

This means that infection can be eliminated from the population if $R_0 < 1$.

However, if $R_0 > 1$, then

$$C = B_0B_1B_2(1 - R_0) < 0.$$

This means that not all of the eigenvalues of the characteristic equation (2.9) have negative real parts and, therefore, E_0 is unstable.

4.2 Existence and Stability of Endemic Equilibrium State

We shall discuss the stability of the endemic equilibrium state of our model equations $(2.1) - (2.5)$.

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

4.3 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 states. 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:

$$x' = f(x, \varphi) \qquad (2.10)$$

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 $D_x f(E_0, 0)$.

Theorem 4.2 (Mukandavire *et al* 2010). Consider the disease transmission model defined by (2.10) 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

$a = \sum_{k,i,j=1}^{n} v_k u_i v_j \frac{\partial^2 f_k}{\partial_{x_i}}(E_0,0)$, $b = \sum_{k,i=1}^{n} v_k u_i \frac{\partial^2 f_k}{\partial_{x_i} \partial_{\phi}}(E_0,0)$. 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.

4.4 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. We make the following change of variables to system $(2.1) - (2.5)$ in order to apply the centre manifold theory: $S = x_1, L = x_2, I = x_3, C = x_4, V = x_5$. We use the notation $X = [x_1\ x_2\ x_3\ x_4\ x_5]^T$. Then the model system $(2.1) - (2.5)$ can be expressed in the form $\frac{dX}{dt} = F = (f_1\ f_2\ f_3\ f_4\ f_5)$ such that

$$\frac{dx_1}{dt} = \mu\omega(1 - vx_4) + \Psi x_5 - (\mu_0 + \beta x_3 + \varepsilon\beta x_4 + \gamma_3)x_1 \qquad (2.11)$$

$$\frac{dx_2}{dt} = \mu v\omega x_4 + (\beta x_3 + \varepsilon\beta x_4)x_1 - (\sigma + \mu_0)x_2 \qquad (2.12)$$

$$\frac{dx_3}{dt} = \sigma x_2 - (\mu_0 + \gamma_1)x_3 \qquad (2.13)$$

$$\frac{dx_4}{dt} = q\gamma_1 x_3 - (\mu_0 + \mu_1 + \gamma_2 + \alpha)x_4 \qquad (2.14)$$

$$\frac{dx_5}{dt} = \mu(1 - \omega) + \gamma_3 x_1 - (\mu_0 + \Psi)x_5 \qquad (2.15)$$

The Jacobian matrix of the system $(2.11) - (2.15)$ at the disease-free equilibrium is given by

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

It can be found that the linearized system of transformed equations $(2.11) - (2.15)$ with $R_0 = 1$ has a simple zero eigenvalue. Hence, the centre manifold theory (see, Driessche *et al*, 2005, Mukandavire *et al*, 2010), Ameh, 2009) can be used to analyse the dynamics of system $(2.11) - (2.15)$. The Jacobian (J_{E0}) of system $(2.11) - (2.15)$ has a right eigenvector associated with zero eigenvalue given by $U = [u_1 \quad u_2 \quad u_3 \quad u_4 \quad u_5]$.

Let $u_2 = 1$.

$$u_3 = \frac{\sigma}{\mu_0+\gamma_1} > 0, u_4 = \frac{q\gamma_1 u_3}{(\mu_0+\mu_1+\gamma_2+\alpha)} > 0, u_5 = -\frac{\beta S_0 u_3 + (\mu v\omega + \varepsilon\beta S_0)u_4}{\mu_0} < 0,$$

$$u_1 = -\frac{\beta S_0 u_3 + (\mu v\omega + \varepsilon\beta S_0)u_4 - \Psi u_5}{\mu_0 + \gamma_3} < 0.$$

The left eigenvector Jacobian (J_{E0}) associated with the zero eigenvalue is given by

$$V = [v_1 \; v_2 v_3 \; v_4 \; v_5]^T.$$

$v_1 = 0$. Let $v_2 = 1 > 0, v_3 = \frac{(\sigma+\mu_0)}{\sigma} > 0, v_4 = \frac{\mu v\omega + \varepsilon\beta S_0}{(\mu_0+\mu_1+\gamma_2+\alpha)} > 0, v_5 = 0.$

$$\frac{\partial^2 f_2}{\partial x_1^2} = 0, \frac{\partial^2 f_2}{\partial x_1 \partial x_2} = 0, \frac{\partial^2 f_2}{\partial x_1 \partial x_3} = \beta, \frac{\partial^2 f_2}{\partial x_1 \partial x_4} = \varepsilon\beta,$$

$$a = \sum_{k,i,j=1}^{n} v_k u_i u_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(x_0, 0) = v_2[u_1 u_3 \beta + u_1 u_4 \varepsilon\beta] < 0.$$

$$\frac{\partial^2 f_2}{\partial x_1 \partial \varphi} = \frac{\partial^2 f_2}{\partial x_1 \partial \varphi} \cdot \frac{\partial \varphi}{\partial \beta} = 0, \frac{\partial^2 f_2}{\partial x_3 \partial \varphi} = \frac{\partial^2 f_2}{\partial x_3 \partial \varphi} \cdot \frac{\partial \varphi}{\partial \beta} = S_0, \frac{\partial^2 f_2}{\partial x_1 \partial \varphi} \cdot \frac{\partial \varphi}{\partial \beta} = \frac{\partial^2 f_2}{\partial x_1 \partial \beta} = \varepsilon S_0,$$
$$b = v_2[u_3 S_0 + u_4 \varepsilon S_0] > 0.$$

Therefore, by (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.

5. Discussion

In this study, we extended and analyzed a mathematical model for the transmission dynamics of HBV infection considering vaccination and treatment as control measures. 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. R_0 was analytically evaluated for its sensitivity to the vaccination rate of susceptible individuals γ_3, the treatment rate α, the proportion of newborns vaccinated $(1-\omega)$. The results can be found in propositions 3.1, 3.2, and 3.3. The results show that increasing the proportion of people who receive vaccines, either at birth or later as susceptible individuals, can reduce the basic reproduction number below unity. Similarly, increasing the proportion of carriers who receive treatment achieve the same purpose. Thus, R_0 decreases with both vaccination and treatment rates, pointing out to the fact that the two are useful in controlling the infection. This also suggests that taking vaccination and treatment in combination as a control strategy gives a better result than either of them.

The result of the stability analysis for the disease-free equilibrium state can be found in theorem 4.1. The result show that if $R_0 < 1$, the DFEs is locally asymptotically stable. This means that the disease cannot spread and, therefore, the disease can be eliminated. Otherwise, the DFEs is unstable if $R_0 > 1$. Thus, there is a possibility of the disease invading the population and becoming endemic. The result of the centre manifold theory (theorem 5.1) shows that there exists a unique endemic equilibrium state that is locally and asymptotically stable.

6. Conclusion and Recommendations

6.1 Conclusion

In this study, we extended and studied a mathematical model for the transmission dynamics of HBV infection considering vaccination and treatment as control measures in the host population. The model parameters are given in Section (2). The model was derived with the aid of a flow diagram in Figure 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. R_0 was analytically evaluated for its sensitivity to the vaccination rate of the susceptible individuals, the proportion of the newborns vaccinated and the treatment rate. It was also proved that the disease-free equilibrium state was locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.
The existence and stability of the endemic equilibrium state was established through the centre manifold theory.
Our analytical results show that R_0 is a decreasing function of the susceptible vaccination rate, the newborn vaccination rate and the treatment rate. Effective vaccination or treatment is a good control strategy for HBV infection. However, a combination of effective vaccination and treatment is a better control strategy for the disease.

6.2Recommendations

Based on the findings in the research study, we make the following recommendations.

(1) The Governments should include effective vaccination and treatment in combination as a control strategy on HBV control programs.

(2) Vaccination of every individual susceptible to HBV and treatment of every individual chronically infected with HBV may be impossible because of resources. However, this study gives threshold values for vaccination and treatment to be used for optimal results.

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