Modelling the Effects of Carriers on the Transmission Dynamics of Hepatitis B Virus

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ABSTRACT
In the last couple of decades, mathematical models have been used to study the transmission dynamics of Hepatitis B Virus (HBV) in various communities, regions and countries. Therefore, this study aims at evaluating the effect of screening, vaccination and treatment on the transmission dynamics of hepatitis B virus. A mathematical model is designed to study the effects of carriers on the transmission dynamics of Hepatitis B. The basic reproduction number is derived using the next generation method. The local stability of the disease-free equilibrium state is established via the basic reproduction number. Also, the local stability of the endemic equilibrium state is proved using the centre manifold theory. It is revealed that using item iv of theorem 1, the unique endemic equilibrium for model system (8 – 12) exists and is locally asymptotically stable whenever $R_0 > 1$

Keywords: Hepatitis B, mathematical model, basic reproduction number, disease-free equilibrium state, endemic equilibrium state, stability centre manifold theory.

INTRODUCTION
Hepatitis B is a disease of the liver characterized by inflammation and is caused by infection with hepatitis B virus (HBV) (White and Fenner, 1994). According to Abraham (2004), Hepatitis B is one of the serious world’s health problems. World Health Organization’s statistics show that about 2 billion people around the world have been infected with hepatitis B virus and about 350 million live with chronic HBV infection (Kalajzievska and Li, 2011). A published article by Odusanya et al (2011) also affirms that about 600,000 die each year from HB-related liver disease or hepatocellular carcinoma. Chronic carriers of HBV form the main reservoir for transmission of HBV in any population that is endemic with the virus infection. As pointed out in the article by Kalajzievska and Li (2011), about 30% of people infected with HBV do not show symptoms.

These people are asymptomatic carriers. The two major interventions for the control of HBV transmission are vaccination and treatment. However, as pointed out by Armbuster and Brandeau (2010), a key public health challenge in managing chronic viral diseases, HB alike, is identifying the infected, asymptomatic individuals so that they can receive treatment. Individuals identified before symptoms develop typically derive greater benefit from treatment than individuals who receive treatment only in an advanced stage of the disease. Early management and treatment of chronic HBV infection can provide significant health benefits for treated individuals and reduce prevalence at the population level. Since a sizeable proportion of the HBV carriers is asymptomatic, treatment can be effective if
the individuals can be screened for their HBV status from the nearby health centre. While the susceptible individuals are vaccinated, the carriers are placed on treatment. The purpose of this study is to evaluate the effect of screening, vaccination and treatment on the transmission dynamics of hepatitis B. In the last couple of decades, mathematical models have been used to study the transmission dynamics of HBV in various communities, regions and countries. Anderson and May (1992) and Williams, Nokes, Medley and Anderson (1996) presented models of sexual transmission of HBV, which include heterogeneous mixing with respect to age and sexual activity. Edmunds et al (1993) studied the relation between the age at infection with HBV and the progression to the carrier state. Medley, Lindop, Edmunds and Nokes (2001) formulated a model to show that the prevalence of infection is largely determined by a feedback mechanism that relates the rate of transmission, average age at infection and age-related probability of developing carriage following infection. Thornley, Bullen and Robert (2008) applied the model of Medley, Lindop, Edmunds and Nokes (2001) to predict chronic hepatitis B infection in New Zealand. Mclean and Blumberg (1994) and Edmunds et al (1996a) studied models of HBV transmission in developing countries and Williams, Nokes, Medley and Anderson (1996) described a model of HBV in UK. Zou and Zhang (2009) proposed a mathematical model to study the transmission dynamics and prevalence of HBV in mainland China.

Several mathematical models such as that of Anderson and May (1991), Kalajzievska (2006), Kalajzievska and Li (2011) study the effects of HBV carriers on transmission of HBV. While Anderson and May (1991) used simple mathematical models without control parameters, Kalajzievska (2006), Kalajzievska and Li (2011) applied more general models. In this work, a mathematical model to study the effects of carriers on the transmission of hepatitis B is proposed. The difference in our own model lies in the model structure, specificity and control interventions applied. For instance, their models do not capture the latent and acute stages of development of HBV infection. In our model we have incorporated screening, vaccination and treatment parameters in combination as a strategy.

**Formulation of the Model Equations**

In this study, we first formulate the model equations, compute the basic reproduction number and prove the existence and stability of the disease-free equilibrium (DFE) and the endemic equilibrium (EE) states. The following diagram will be found useful in formulating the model equations.

![Flow diagram for the transmission of HBV](image)

**Fig.1:** A flow diagram for the transmission of HBV
From the above assumptions and the flow diagram the following equations are formulated

\[
\frac{dS}{dt} = \mu(1-v)C - (1-\omega) pS - (\mu_o + \beta_1 + \beta C + \beta_2 C_2)S \\
\frac{dL}{dt} = \mu v \alpha \gamma \beta_2 C + \beta_1 (C + \beta_2 C_1)S - (\mu_o + \sigma)L \\
\frac{dC}{dt} = (\gamma_2 + \gamma_1) - (\mu_o + \mu_i + \pi + \alpha + \alpha_i)C \\
\frac{dC_i}{dt} = (\alpha + \alpha_i)C - (\mu_i + \mu_2 + \pi_1)C_i \\
\frac{dR}{dt} = (1+\omega)pS + (\gamma_2 + \gamma_1 + \pi C + \pi_1 C - \mu_o R \\
\frac{dN}{dt} = \mu - \mu_o N - \mu_i C - \mu_2 C_1 - \mu - \mu_o N
\]

Table 1: Model parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$S(t)$</td>
<td>Proportion of susceptible at time $t$</td>
</tr>
<tr>
<td>$L(t)$</td>
<td>Proportion of infected latent individuals at time $t$</td>
</tr>
<tr>
<td>$I(t)$</td>
<td>Proportion of infected acute individuals at time $t$</td>
</tr>
<tr>
<td>$C(t)$</td>
<td>Proportion of chronic carriers at time $t$</td>
</tr>
<tr>
<td>$C_i(t)$</td>
<td>Proportion of carriers receiving treatment at time $t$</td>
</tr>
<tr>
<td>$R(t)$</td>
<td>Proportion of individuals recovered at time $t$</td>
</tr>
<tr>
<td>$\mu$</td>
<td>The Birth Rate</td>
</tr>
<tr>
<td>$\nu$</td>
<td>Proportion of unimmunized children</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>Natural Death Rate</td>
</tr>
<tr>
<td>$\beta$</td>
<td>Transmission coefficient for the acute individuals</td>
</tr>
<tr>
<td>$\pi_1$</td>
<td>Transmission coefficient for the chronic carriers</td>
</tr>
<tr>
<td>$\alpha_i$</td>
<td>Infectiousness of a chronic carrier relative to an infected acute individual</td>
</tr>
<tr>
<td>$\gamma_1$</td>
<td>Transmission coefficient for the carriers receiving treatment</td>
</tr>
<tr>
<td>$\gamma_1$</td>
<td>Infectiousness of a carrier receiving treatment relative to an infected acute individual</td>
</tr>
<tr>
<td>$\rho$</td>
<td>Proportion of the non-newborn susceptible relative to the newborns</td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>Rate at which latent individuals move to the acute stage</td>
</tr>
<tr>
<td>$\beta_2$</td>
<td>Rate at which infected acute individuals move to the carrier state</td>
</tr>
<tr>
<td>$\gamma_2$</td>
<td>Rate at which infected acute individuals move to the recovered compartment</td>
</tr>
</tbody>
</table>
\( \mu_1 \) = HBV – Induced death rate for the chronic carriers

\( \mu_2 \) = HBV - Induced death rate for the carriers receiving treatment

\( \pi \) = Rate at which chronic carriers naturally recover

\( \pi \) = Rate at which carriers receiving treatment recover

\( \alpha \) = Rate at which asymptomatic carriers naturally become symptomatic

\( \alpha \) = Rate at which asymptomatic carriers are detected through screening

**The Feasible Region and the Disease-free Equilibrium State**

From equation 7,

\[
\frac{dN}{dt} = \mu - \mu_0 \bar{N}
\]

Therefore, \( \bar{N}(t) = \frac{\mu}{\mu_0} + ke^{-\mu_0 t} \)

This implies that \( \bar{N}(t) \to \frac{\mu}{\mu_0} \) as \( t \to \infty \)

Therefore, \( \lim \sup_{t \to \infty} N(t) \leq \frac{\mu}{\mu_0} \). The equation for \( R \) can be omitted in our analysis since terms in \( R \) do not appear in other equations. Therefore, our model can be studied in the feasible region given as follows:

\[
D = \left\{ (S, L, I, C, C_t) \in \mathbb{R}^5 : S + L + I + C + C_t \leq \frac{\mu}{\mu_0} \right\}
\]

We shall first determine the disease-free equilibrium. Let \( E_0 \) be the disease-free equilibrium state of the model equations 1 - .7. At \( E_0, L = I = C = C_t = 0 \) so that from equation 1

This implies that \( S = S_0 = \frac{\mu_0}{(1-\omega)p + \mu_0} \)

Therefore, \( E_0 = (S_0, L_0, I_0, C_0, C_t_0) = \left( \frac{\mu_0}{(1-\omega)p + \mu_0}, 0, 0, 0, 0 \right) \)

**The Next Generation Method and the Basic Reproduction Number**

In this section, we shall apply the next generation method to compute the basic reproduction number for our model. The next generation method, introduced by Diekmann, Heesterbeek and Metz (1990) is a general method of deriving \( R_0 \) in any situation in which the population is divided into discrete, disjoint classes with multiple classes of infectious individuals. For instance, this method can be seen in Van den Driessche and Watmough (2002), Heffernan (2005), Ameh (2009) among others. We compute the basic reproduction number for our model using the recipe by Van den Driessche and Watmough (2002) as follows.

Let \( F_i(x) \) be the rate of appearance of new infections in compartment \( i = 1, \ldots, m \).

Let \( F(x) = (F_1(x), F_2(x), \ldots, F_m(x)). \)

Let \( V_i(x) = V_i^- (x) - V_i^+ (x) \) be the difference between outflow and inflow terms in compartment \( i \) aside \( F_i(x) \) where \( V_i^+ (x) \) is the rate of transfer into compartment \( i \) by all other means and \( V_i^- (x) \) is the rate of transfer of individuals out of the \( i \)th compartment.
Let $V(x) = (V_1(x), V_2(x), \ldots, V_m(x))$

The difference $F_i(x) - V_i(x)$ gives the rate of change of $x_i$ in compartment $i$.

From our model

$$F(x) = \begin{pmatrix}
\mu \nu \omega + (\beta I + \beta_1 C + \beta_2 C, S) \\
0 \\
0 \\
0
\end{pmatrix}$$

$$F(x)_i = \begin{pmatrix}
0 & \beta S_0 & \mu \nu \omega + \beta_1 S_0 & \beta_2 S_0 \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0
\end{pmatrix}$$

$$V(x) = \begin{pmatrix}
(\mu_0 + \sigma)L \\
-\sigma L + (\mu_0 + \gamma_1 + \gamma_2)I \\
-\gamma_1 I + (\mu_0 + \mu_1 + \sigma + \alpha + \alpha_1)C \\
-(\alpha + \alpha_1)C + (\mu_0 + \mu_2 + \pi_1)C, C_i
\end{pmatrix}$$

$$V(x)_i = \begin{pmatrix}
\mu_0 + \sigma & 0 & 0 & 0 \\
-\sigma & \mu_0 + \gamma_1 + \gamma_2 & 0 & 0 \\
0 & -\lambda_i & \mu_0 + \mu_1 + \sigma + \alpha + \alpha_1 & 0 \\
0 & 0 & -(\alpha + \alpha_1) & (\mu_0 + \mu_2 + \pi_1)
\end{pmatrix}$$

$$\lambda = \frac{\beta S_0 (\mu_0 + \mu_1 + \sigma + \alpha + \alpha_1)(\mu_0 + \mu_2 + \pi_1) + \gamma \sigma (\mu_0 + \sigma + \alpha + \alpha_1)(\mu_0 + \mu_2 + \pi_1) + \gamma \sigma (\alpha + \alpha_1) \beta S_0}{(\mu_0 + \sigma)(\mu_0 + \gamma_1 + \gamma_2)(\mu_0 + \mu_1 + \sigma + \alpha + \alpha_1)(\mu_0 + \mu_2 + \pi_1)}$$

It follows that the basic reproduction number is given by

$$R_0 = \frac{\beta S_0 (\mu_0 + \mu_1 + \sigma + \alpha + \alpha_1)(\mu_0 + \mu_2 + \pi_1) + \gamma \sigma (\mu_0 + \sigma + \alpha + \alpha_1)(\mu_0 + \mu_2 + \pi_1) + \gamma \sigma (\alpha + \alpha_1) \beta S_0}{(\mu_0 + \sigma)(\mu_0 + \gamma_1 + \gamma_2)(\mu_0 + \mu_1 + \sigma + \alpha + \alpha_1)(\mu_0 + \mu_2 + \pi_1)}$$

**Local Stability of the Disease-Free Equilibrium (DFE) state**

Using Theorem 2 in Van den Driessche and Watmough (2002), the following result is established.

**Lemma 1:** The disease-free equilibrium of the HBV model system 1 - 5 is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.

**Local Stability of the Endemic Equilibrium (EE) state**

We shall employ the centre manifold theory described in Van den Driessche and Watmough (2002) to investigate the local asymptotic stability of the endemic equilibrium. We make the following transformation of variables in order to apply the centre manifold theory

$S = x_1$, $L = x_2$, $I = x_3$, $C = x_4$, $C_i = x_5$ and $R = x_6$. 

We now use the vector $X = (x_1, x_2, x_3, x_4, x_5, x_6)^T$.

Then the model system (equation 1 - 6) can be expressed in the form

$$\frac{dx}{dt} = f = (f_1, f_2, f_3, f_4, f_5, f_6)^T$$

such that the model system 1 - 6 become

$$\frac{dx_1}{dt} = \mu\alpha(1-\nu x_4) - (\nu + \gamma_1 + \gamma_2) x_2$$

$$\frac{dx_2}{dt} = \mu\nu x_4 + (\beta + \gamma_3 + \beta_2 x_3) x_2 - (\mu + \sigma) x_2$$

$$\frac{dx_3}{dt} = \alpha x_2 - (\mu_0 + \gamma_4) x_3$$

$$\frac{dx_4}{dt} = \gamma_5 x_3 - (\mu_0 + \mu + \pi + \alpha + \alpha_1) x_3$$

$$\frac{dx_5}{dt} = (\alpha + \alpha_1) x_4 - (\mu + \mu_2 + \pi_1) x_5$$

$$\frac{dx_6}{dt} = (1-\omega) \rho x_1 + (\beta + \gamma_{12} + \pi x_4 + \pi x_5 - \mu_0 x_6$$

We shall use model equations 8 - 12 to establish the local stability of the endemic equilibrium.

The Jacobian matrix of the system of equations 8 - 12 at the DFE is given by

$$J(E_0) = \begin{pmatrix}
-\mu_0 + (1-\omega) \rho & 0 & -\beta S_o & -\mu_0 - \beta S_o & \beta S_o \\
0 & -\mu_0 + \sigma & -\beta S_0 & \mu_0 + \beta S_0 & 0 \\
0 & 0 & -\mu_0 + \gamma_1 + \gamma_2 & 0 & 0 \\
0 & 0 & \gamma_3 & -(\mu_0 + \mu + \pi + \alpha + \alpha_1) & 0 \\
0 & 0 & 0 & (\alpha + \alpha_1) & -(\mu_0 + \mu_2 + \pi_1)
\end{pmatrix}$$

Choosing $\beta$ as a bifurcation parameter and considering the situation where $R_0 = 1$ and solving for $\beta$, we have

The system of equations 8 - 12 with $\beta = \beta^*$ has a simple zero Eigen value. Thus, we can use the centre manifold theory to determine the behaviour of the system 8 - 12 near $\beta = \beta^*$. The left eigenvector $v = (v_1, v_2, v_3, v_4, v_5)^T$ of $J(E_0)$ is given by

$v_1 = 0, v_2 = v_1 > 0, v_3 = (\mu_0 + \sigma) v_2$,

$v_4 = 1 / \gamma_3 (\mu_0 + \gamma_1 + \gamma_2 - \beta S_o / (\mu_0 + \sigma)) (\mu_0 + \sigma) v_3$, 

$v_5 = 0$.
The right Eigenvector $u = (u_1, u_2, u_3, u_4, u_5)^T$ of $J(E_0)$ is given by

$$u_i = \frac{(\mu_i + \sigma)\mu_i}{(\mu_i + (1+\omega)v)^i} u_i = \frac{\sigma\mu_i}{\mu_i + \gamma_i + \gamma_2},$$

$$u_i = \frac{\sigma\gamma_i\mu_i}{(\mu_i + \gamma_i + \gamma_2)(\mu_i + \mu_i + \pi + \alpha + \alpha_1)} u_i = \frac{\sigma\gamma_i(\alpha - \alpha_1)\mu_i}{(\mu_i + \gamma_i + \gamma_2)(\mu_i + \gamma_i + \gamma_2)(\mu_i + \pi + \alpha + \alpha_1)}.$$  

We shall apply the following theorem used in Mukandavire, Das, Chiyyaka and Nyabadza (2010) to establish local stability of the endemic equilibrium.

**Theorem 1:** Consider the disease transmission model defined by equation 8 – 12 with the function $f(x, \phi)$, $\phi$ is the bifurcation parameter. Assume that the zero Eigen value is simple. Let $u$ and $v$ are the left and right eigenvectors respectively. Assume that $\delta > 0$ such that

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

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

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

(iv) If $a < 0$, when $\phi$ changes from negative to positive, changes its stability from stable to unstable. Corresponding negative equilibrium becomes positive and locally asymptotically stable. From theorem 1 above, the computations of $a$ and $b$ are done as follows:

$$a = v_2u_1\mu_1 + v_2u_1u_2\beta_1 + v_2u_1u_3\beta_2 < 0, b$$

$$= v_2u_1S_0 + v_2u_1eS_0 + v_2u_5eS_0 > 0$$

Thus, using item iv of theorem 1, the unique endemic equilibrium for model system (8 – 12) exists and is locally asymptotically stable whenever $R_0 > 1$.

**CONCLUSION**

In this work, a mathematical model is proposed to study the effects of carriers on the transmission dynamics of hepatitis B. The dynamics is described by a system of first order
ordinary differential equations of autonomous type. The basic reproduction number as a threshold is derived and the existence and local stability of both the disease-free and endemic equilibria are established.

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