

Simulation of A Mathematical Model Of Hepatitis B Virus Transmission Dynamics In The Presence Of Vaccination And Treatment

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ABSTRACT

In this paper, a mathematical model for the transmission dynamics of hepatitis B virus (HBV) infection incorporating vaccination and treatment as control parameters is presented. The basic reproduction number, R_0 , as a threshold parameter, was constructed, in terms of the given model parameters, by the next generation method. R_0 was numerically assessed for its sensitivity to vaccination and treatment parameters. A unique disease-free equilibrium state was determined, indicating possibility of control of HBV disease. The model was solved numerically using Runge-Kutta method of order four to evaluate the effects of vaccination and treatment parameters on the prevalence of the disease. The numerical results of the sensitivity analysis show that increasing either vaccination or treatment rate has the potential of reducing R_0 below unity. The results of the numerical simulations of the model show that effective vaccination, treatment or a combination of both of them as a control strategy can eradicate HBV disease, with the combination being far better than either of them. Finally, these findings strongly suggest that high coverage of vaccination and treatment are 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 in order 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 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. Anderson and May (1991) used a simple deterministic, compartmental mathematical model to study 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) investigated 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 this paper, the impact of vaccination and treatment on HBV transmission dynamics is investigated. We also assume that the proportion of 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 paper is as follows. The model equations are formulated in section 2. Section 3 is devoted to sensitivity analysis of the basic reproduction number. Numerical simulations of the model are treated in section 5. Section 5 gives the discussion of the results. Conclusive remarks are 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.

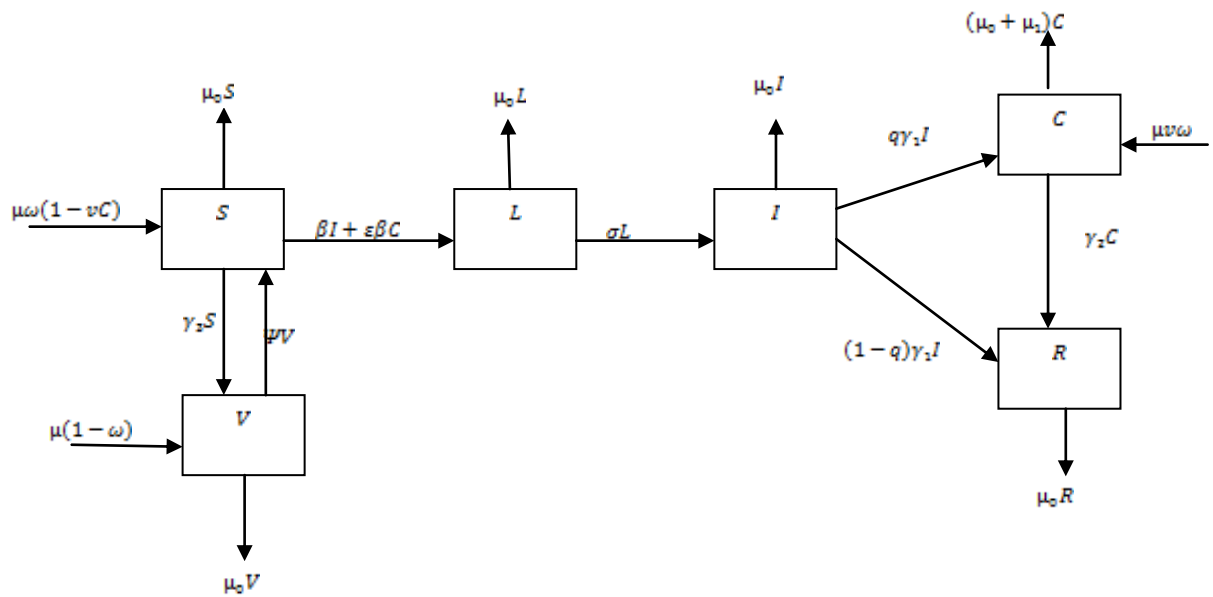


Figure 1: Flow diagram of HBV transmission dynamics for the existing model

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.

$$\frac{dS}{dt} = \mu\omega(1 - vC) + \Psi V - (\mu_0 + \beta I + \varepsilon\beta C + \gamma_2)S \quad (1.1)$$

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

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

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

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

$$\frac{dV}{dt} = \mu(1 - \omega) + \gamma_2 S - (\mu_0 + \Psi)V \quad (1.6)$$

2.5 The 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), 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:

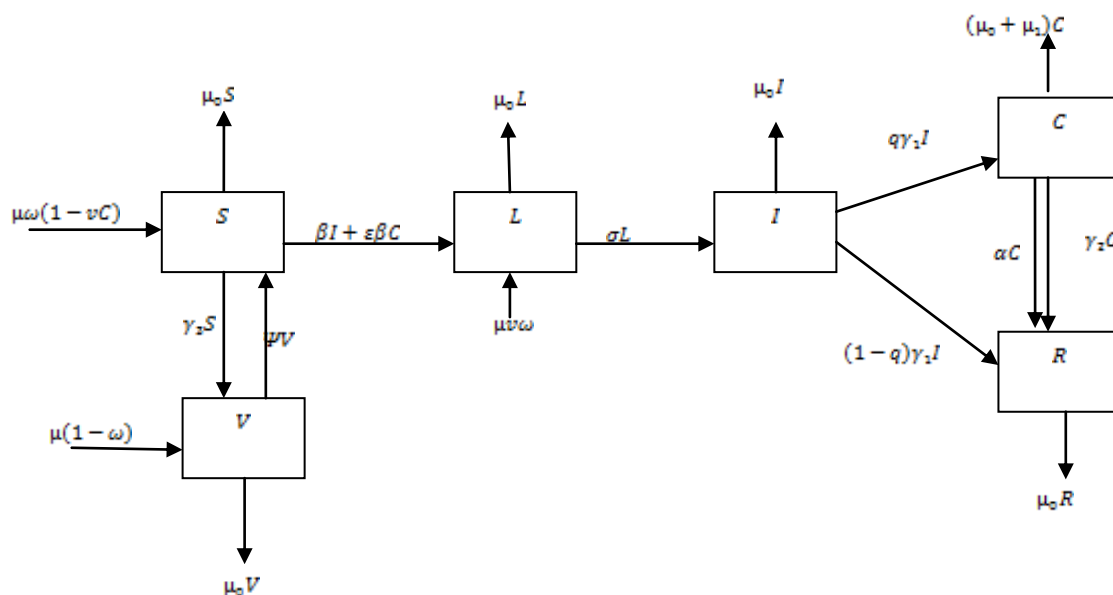


Figure 2: Flow diagram of HBV transmission dynamics for the extended model

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.

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

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

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

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

$$\frac{dV}{dt} = \mu(1 - \omega) + \gamma_2 S - (\mu_0 + \Psi)V \quad (2.5)$$

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

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

Because the models are in terms of proportions,

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

for all time t .

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

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

Table1: Parameter values used in numerical simulations

Parameter/Variable	Value	Reference
ν	0.11	Zou <i>et al</i> (2009)
ψ	0.1	Zou <i>et al</i> (2009)
σ	6 per year	Zou <i>et al</i> (2009)
β	0.95	Zou <i>et al</i> (2009)
γ_1	4 per year	Zou <i>et al</i> (2009)
q	0.885	Zou <i>et al</i> (2009)
γ_2	0.025	Zou <i>et al</i> (2009)
ε	0.16	Zou <i>et al</i> (2009)
μ	0.0367	USAID (2009)
μ_0	0.0166	USAID (2009)
$S(0)$	0.7	Assumed
$L(0)$	0.05	Assumed
$I(0)$	0.05	Assumed
$C(0)$	0.08	Olumuyiwa <i>et al</i> (2011)
$R(0)$	0.12	Assumed

3.1. Sensitivity Analysis of the Basic Reproduction Number, R_0

We now calculate the disease-free equilibrium state of the extended model. As done in Zou *et al* (2009), we begin this by setting the left hand sides of equations (2.2) – (2.6) 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 $V_0 = \frac{\mu(\mu_0 + \gamma_3 - \mu_0\omega)}{\mu_0(\mu_0 + \gamma_3 + \psi)}$.

Next generation method gives the basic reproduction number as follows.

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

R_0 leads to the following results.

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

This is proved numerically as follows.

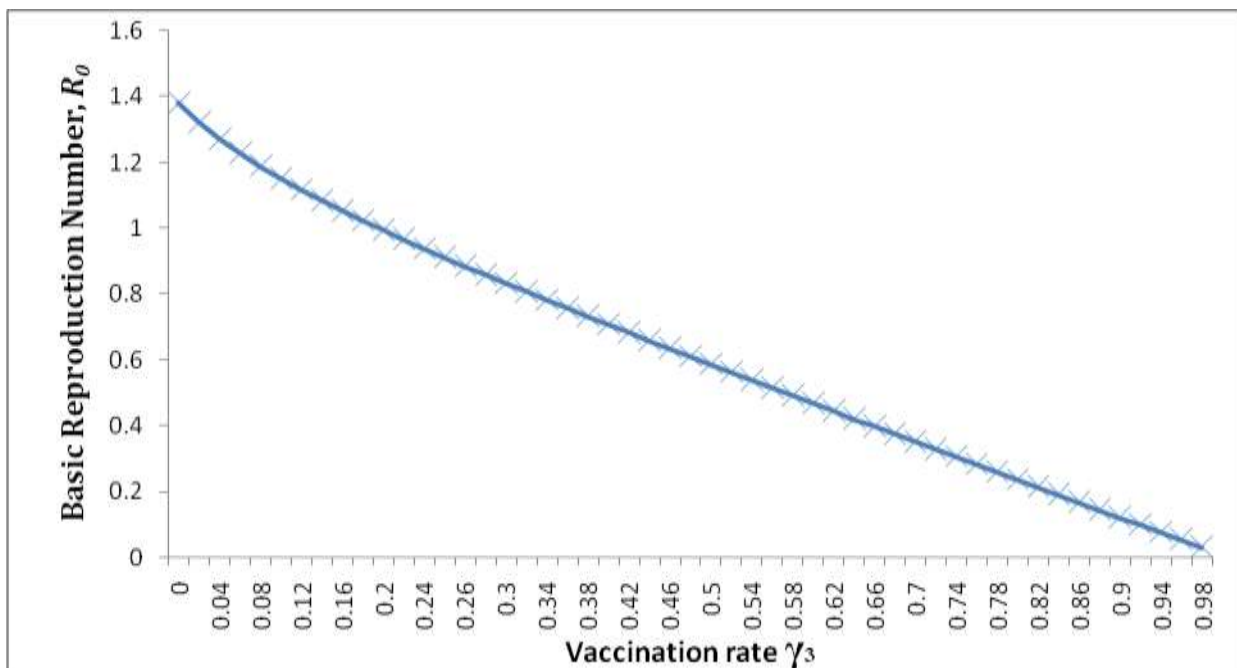


Figure 3: Impact of vaccination of susceptible individuals on the basic reproduction number. Other parameter values are as in Table 1.
 Proposition 3.2 R_0 is a strictly decreasing function of $\gamma_3 \in (0, 1)$.

The numerical proof is shown below.

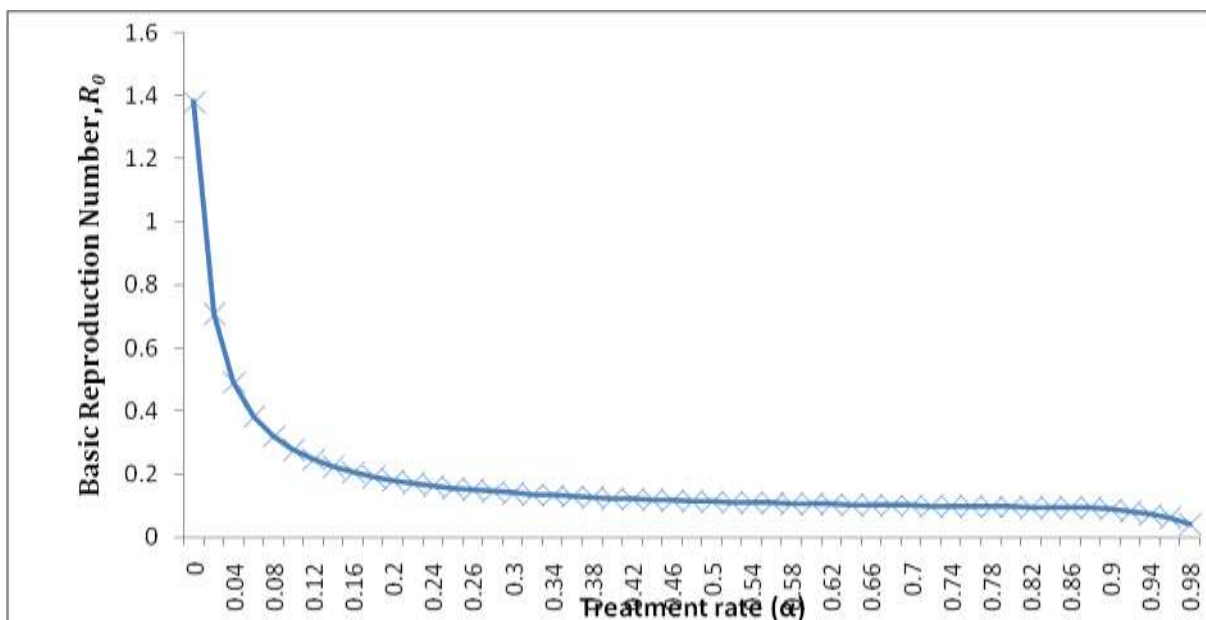
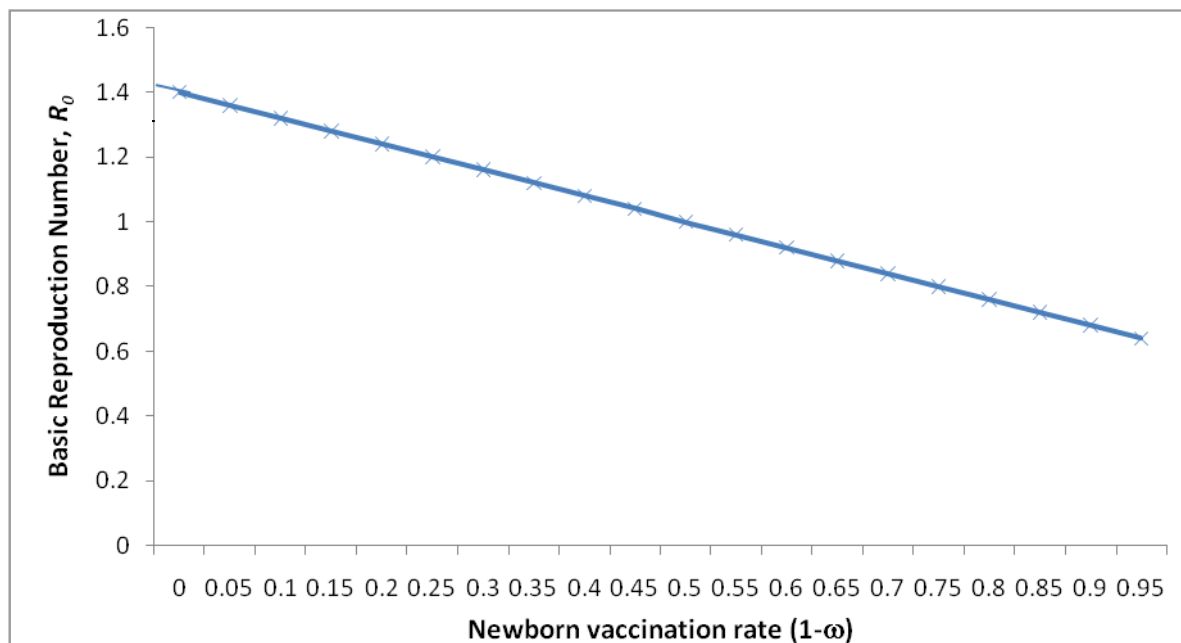


Figure 4: Impact of treatment on the basic reproduction number. Other parameter values are as in Table 1.

See the proof in the sequel.



4 Figure 5: Impact of newborn vaccination on the basic reproduction number. Other
 (parameter values are as in Table 1.

5 demonstrate numerically the feasibility of control of HBV transmission using vaccination and treatment parameters. To achieve this, the order four Runge-Kutta algorithm was coded in MATLAB to integrate our extended model. The values of our model parameters are based on published epidemiological data shown in Table 1 above. The target population for our numerical simulations is Nigeria population, and the vital statistics were obtained from USAID (2009), Abraham (2004), WHO (2001), Salawu *et al* (2010) and Olumuyiwa *et al* (2011).

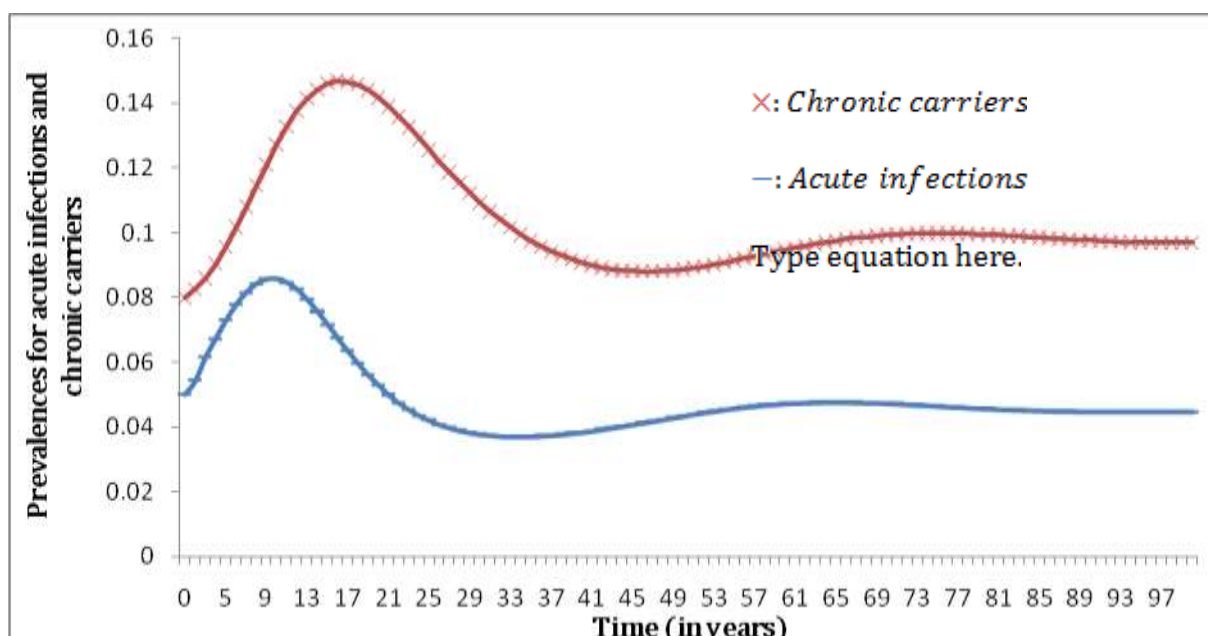


Figure 6: Graph showing the prevalences for acutely infected individuals and chronic carriers without any control measure. Here, $\alpha = 0, (1 - \omega) = 0, \gamma_3 = 0$. All other parameter values are as in Table 1.

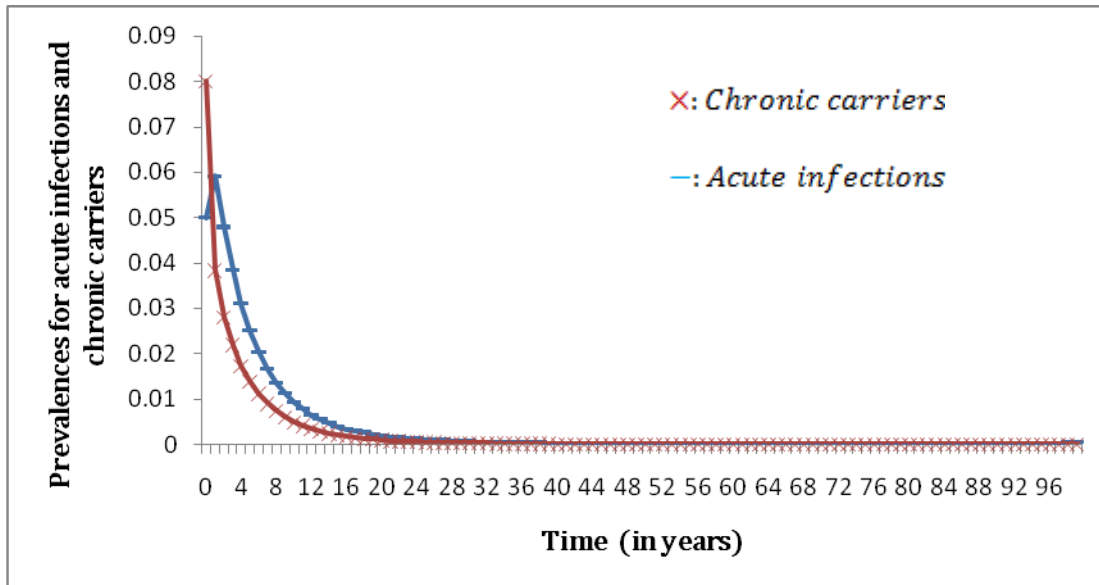


Figure 7: Graph showing the prevalences for acutely infected individuals and chronic carriers with high treatment rate ($\alpha = 0.6$) and no vaccination ($(1 - \omega) = 0, \gamma_3 = 0$). All other parameter values are as in Table 1.

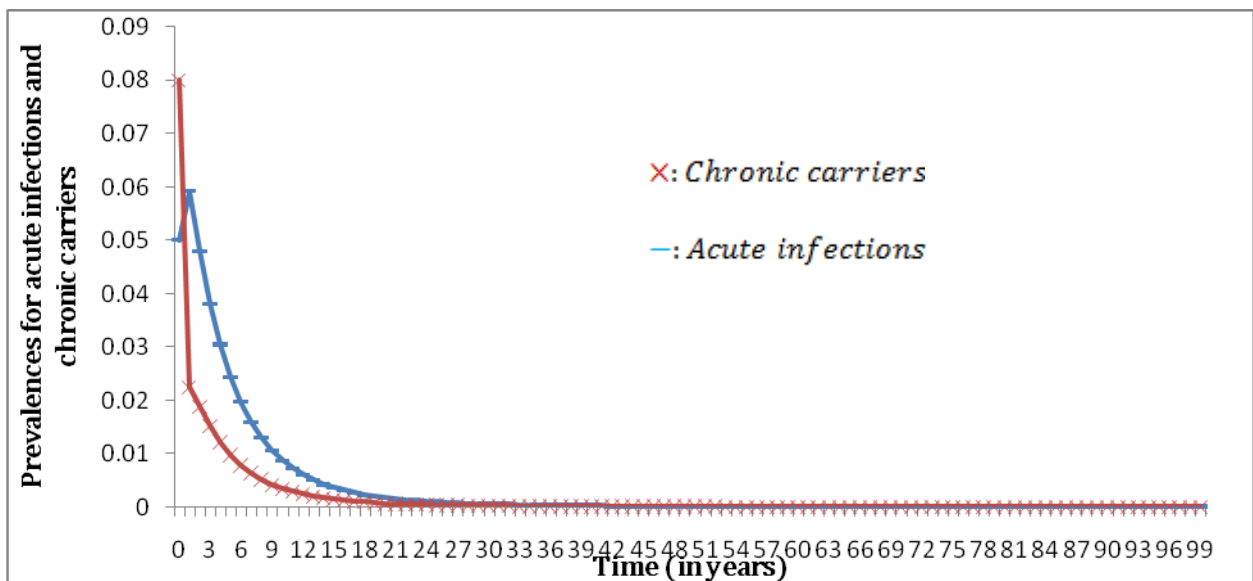


Figure 8: Graph showing the prevalences for acutely infected individuals and chronic carriers with a very high treatment rate ($\alpha = 0.8$) and no vaccination ($(1 - \omega) = 0, \gamma_3 = 0$). All other parameter values are as in Table 1.

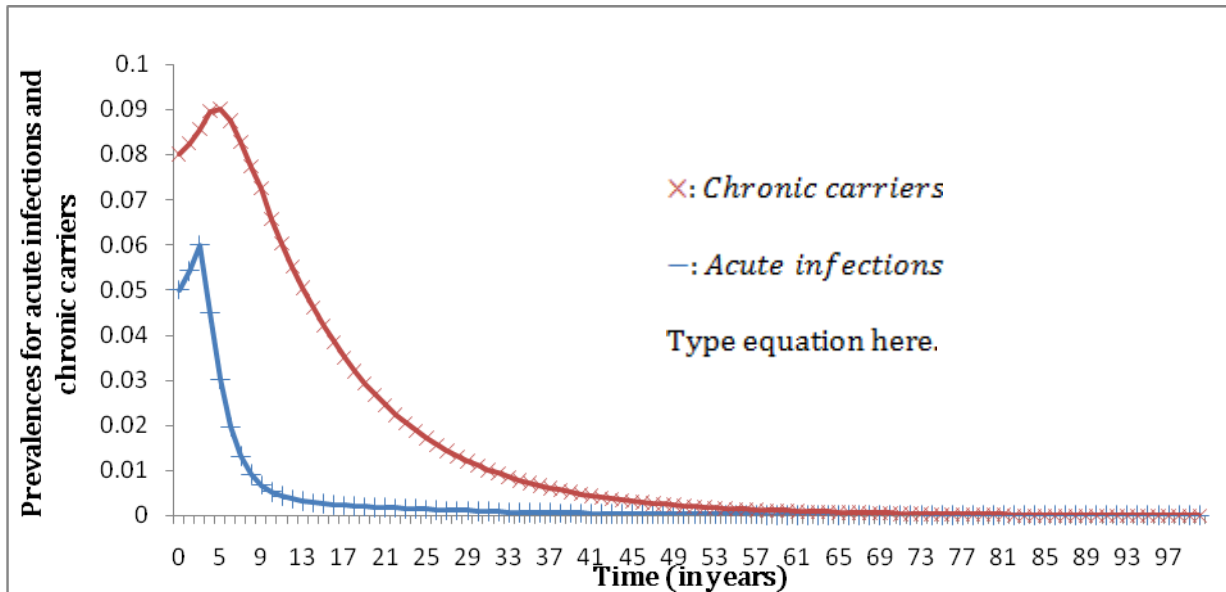


Figure 9: Graph showing the prevalences for acutely infected individuals and chronic carriers with high vaccination rate ($(1 - \omega) = 0.6, \gamma_3 = 0.6$) and no treatment ($\alpha = 0$). All other parameter values are as in Table 1

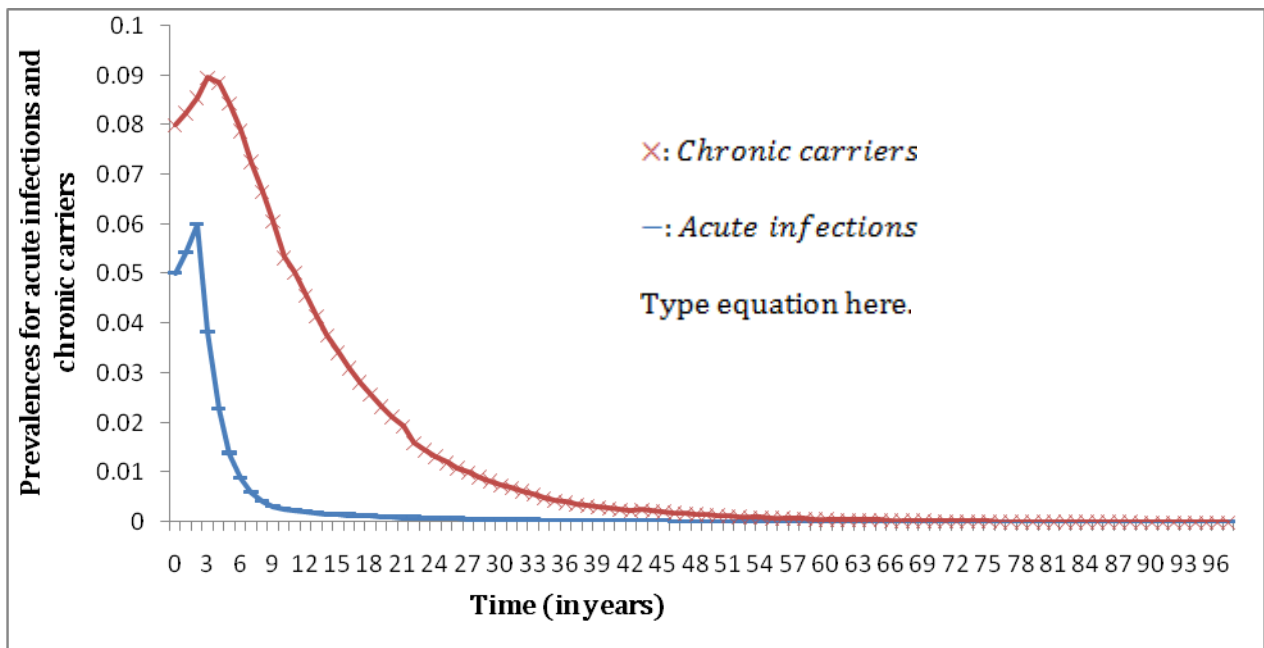


Figure 10: Graph showing the prevalences for acutely infected individuals and chronic carriers with a very high vaccination rate ($(1 - \omega) = 0.8, \gamma_3 = 0.8$) and no treatment ($\alpha = 0$). All other parameter values are as in Table 1.

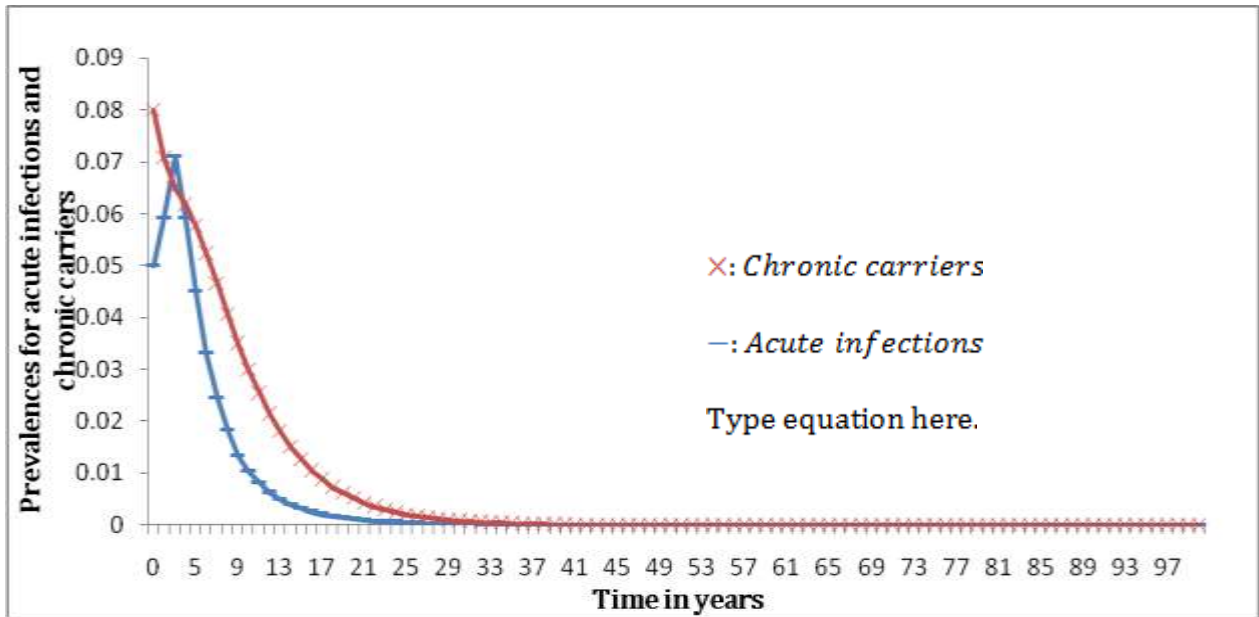


Figure 11: Graph showing the prevalences for acutely infected individuals and chronic carriers with high vaccination rate ($(1 - \omega) = 0.6$, $\gamma_3 = 0.6$) and low treatment ($\alpha = 0.3$). All other parameter values are as in Table 1.

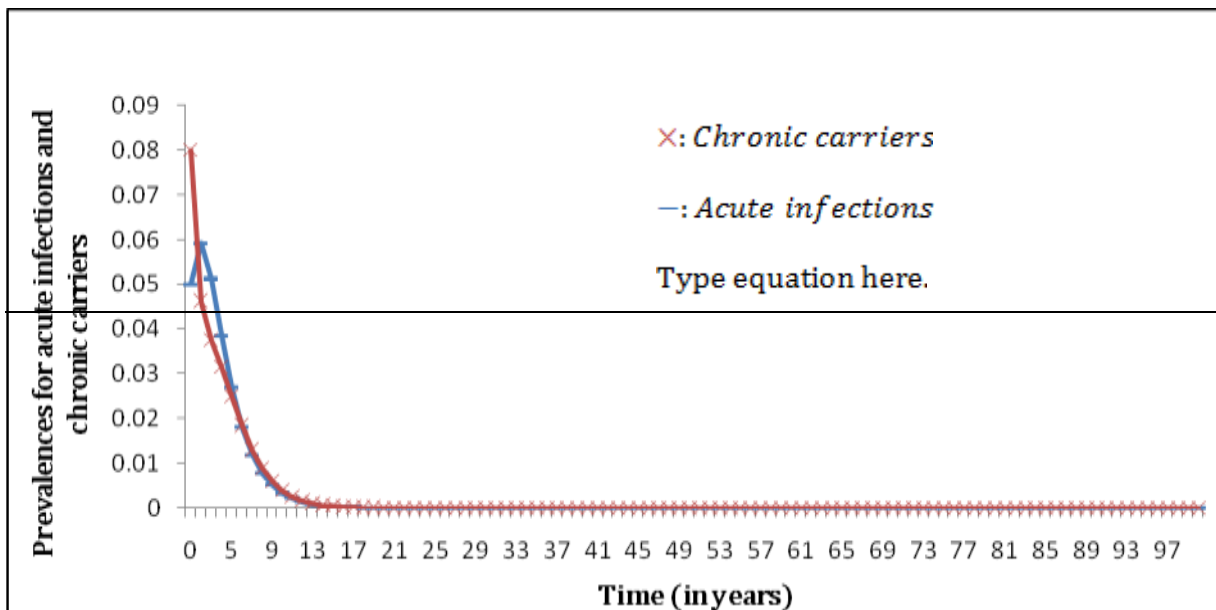


Figure 12: Graph showing the prevalences for acutely infected individuals and chronic carriers with high vaccination rate ($(1 - \omega) = 0.6$, $\gamma_3 = 0.6$) and high treatment ($\alpha = 0.6$). All other parameter values are as in Table 1.

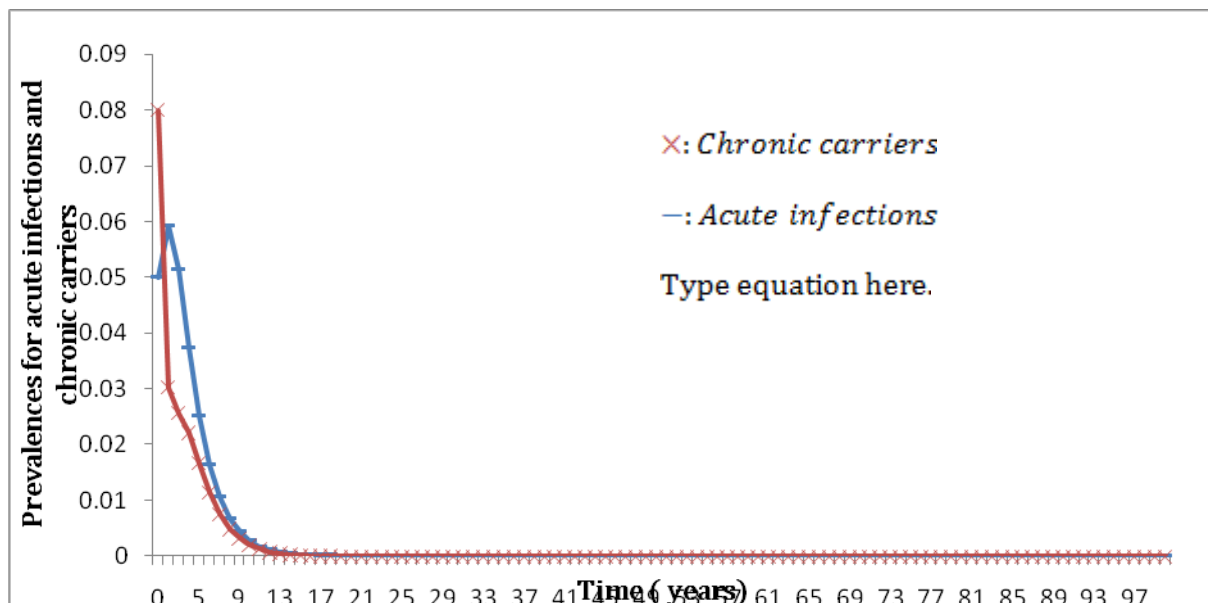


Figure 13: Graph showing the prevalences for acutely infected individuals and chronic carriers with a very high vaccination rate ($(1 - \omega) = 0.8, \gamma_3 = 0.8$) and a very high treatment rate ($\alpha = 0.8$). All other parameter values are as in Table 1.

5.1 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 model is presented in section 2. The numerical results are presented in the subsequent sections.

The results of our numerical experiments with the model are discussed as follows. The parameter values are as shown in Table 1.

The vaccination parameters γ_3 and $(1 - \omega)$, and the treatment parameter α have important effects on the basic reproduction number, R_0 . Therefore, R_0 was numerically explored for its sensitivity to the vaccination rate of the susceptible individuals γ_3 , the proportion of the newborns vaccinated $(1 - \omega)$ and the treatment rate α .

Figures 3, 4 and 5 show that R_0 is a decreasing function of $\gamma_3, (1 - \omega)$ and α . Figure 3 shows that minimum vaccination rate of 0.16 of susceptible individuals can reduce R_0 below unity while Figures 4 and 5 show that minimum treatment rate of 0.04 and minimum newborn vaccination rate of 0.6 each can achieve the same purpose. This shows that the treatment parameter is relatively the most sensitive and important parameter in controlling HBV infection (Medley, 2001; O'Leary, 2008).

The results of the numerical simulations of the extended model are discussed below. The parameter values are as shown in Table 1. The main aim is to assess the feasibility of control and eradication of HBV infection for different values of vaccination and treatment parameters. Figure 6 shows the prevalence of HBV infections in absence of any intervention ($\alpha = 0, (1 - \omega) = 0, \gamma_3 = 0$). It shows that prevalence of HBV infection increases to a peak, decreases and remains almost stable through the horizon at an alarming rate. The peak indicates the highest point of the epidemic and the almost stable horizon indicates endemicity of the HBV infection. This study confirms that without any intervention, the disease cannot be eradicated.

Figures 7 shows decreasing prevalence of HBV carriers when treatment rate is high ($\alpha = 0.6$) and no vaccination ($(1 - \omega) = 0, \gamma_3 = 0$). It shows a sharp rise of the prevalence of the acutely infected

individuals for a short while because of the pool of latently infected individuals progressing to the acute compartment. The Figure shows that with high treatment rate, the disease can be eradicated in the long run.

Similarly, Figure 8 shows more decreasing prevalence of HBV carriers when treatment rate is very high ($\alpha = 0.8$) and no vaccination ($(1 - \omega) = 0, \gamma_3 = 0$). In the same vein, a sharp rise of the prevalence of the acutely infected individuals occurs for a short while because of the pool of latently infected individuals progressing to the acute compartment. With a very high treatment rate, the disease can be eradicated in the long run. Thus, this study confirms that effective treatment can be a useful intervention for the control and eradication of HBV.

Figure 9 shows that there is a sharp rise in the prevalences of both carriers and acutely infected individuals for a short while, followed by an exponential decay after a long time to zero when vaccination rate is high ($(1 - \omega) = 0.6, \gamma_3 = 0.6$) and no treatment ($\alpha = 0$). Also, this Figure shows that with high vaccination rate, the disease be eradicated. Also, Figure 10 shows that there is a sharp rise in the prevalences of both carriers and acutely infected individuals for a short while, followed by an exponential decay after a long time to zero when vaccination rate is very high ($(1 - \omega) = 0.8, \gamma_3 = 0.8$) and no treatment ($\alpha = 0$). Also, this Figure shows that with a very high vaccination rate, the disease be eradicated faster. Hence, this study ascertains that effective vaccination can be a useful intervention for the control and eradication of HBV.

However, it can be inferred from Figures 7, 8, 9 and 10 that treatment as a control strategy reduces the prevalence and eradicates the disease faster than vaccination, making treatment a relatively more useful intervention (Medley, 2001; O'Leary, 2008).

Figure 11 shows decreasing prevalence of HBV infection with high vaccination rate ($(1 - \omega) = 0.6, \gamma_3 = 0.6$) and low treatment rate ($\alpha = 0.3$) combined, although there is a sharp rise in the prevalence of latently infected individuals because of the pool of latently infected individuals before intervention commences. This study shows that with a combination of high vaccination rate and low treatment rate, the disease can be eradicated within a shorter period than only vaccination.

Figures 12 shows rapid decreasing prevalence of HBV infection with high vaccination rate ($(1 - \omega) = 0.6, \gamma_3 = 0.6$) and high treatment rate ($\alpha = 0.6$) combined. This Figure shows that with a combination of high vaccination rate and high treatment rate, the disease can be eradicated in the shortest possible time. Similarly, Figure 13 shows the most rapid decreasing prevalence of HBV infection with a very high vaccination rate ($(1 - \omega) = 0.8, \gamma_3 = 0.8$) and a very high treatment rate ($\alpha = 0.8$) combined. In the same vein, this Figure shows that with a combination of a very high vaccination rate and a very high treatment rate, the disease be eradicated in the shortest possible time. Thus, this study confirms that a combination of vaccination and treatment as a control strategy is the most effective for the control and eradication of HBV infection.

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 numerically evaluated for its sensitivity to the vaccination rate of the susceptible individuals, the proportion of the newborns vaccinated and the treatment rate. The model was solved numerically by Runge-Kutta method of order four in MATLAB.

Our numerical results reveal that R_0 is a decreasing function of the vaccination rate, the newborn vaccination rate and treatment rate. Thus, increasing the vaccination and treatment rates reduces R_0 .

Numerical simulations of the model show that effective vaccination or treatment is a good control strategy for HBV infection. However, a combination of vaccination and treatment is a better control strategy for the disease.

6.2 Recommendations

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

- (1) The Governments and stakeholders should consider using a combination of effective vaccination and treatment as a control strategy on HBV control programmes.
- (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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