Mathematical Theory and Modeling
ISSN 2224-5804 (Paper) ISSN 2225-0522 (Online)
Vol.6, No.6, 2016
www.iiste.org

Hepatitis B Virus Disease: A Mathematical Model for Vertical Transmission with Treatment Strategy

Nyimvua Shaban[1*] and Doroth Manoza[2]

1. Department of Mathematics, University of Dar es Salaam, P.O. Box 35062, Dar es Salaam, Tanzania

2. National Institute of Transport, Dar es Salaam, Tanzania

Abstract
This paper presents a mathematical model that captures some essential information about the impacts of treatment on hepatitis B vertical transmission. The treatment induced reproduction number is compared with the basic reproduction number to assess the possible benefits to be obtained from this control measure. Numerical results and sensitivity analysis are carried out to support the analytical results and determine the parameters influencing the dynamics of the disease. It is indicated that in the presence of treatment, transmission of infection decreases, implying that the number of acute and chronic infected adult women decrease as well, resulting into fewer infected newborn babies.

Mathematics Subject Classification: 34D20

Key words: Hepatitis B virus, vertical transmission, treatment, reproduction number

1. Introduction

Hepatitis B is a liver disease that emanates from the infection with hepatitis B virus (HBV). The infection is spread when the body fluid of an infected individual enters the body of a person who is not yet infected (Sirilert *et al.*, 2014). Hepatitis B can either be acute or chronic, and an easily detectable sign of acute disease is the distinctive yellow jaundice that hepatitis B imparts to the skin of the infected individual. Some people with chronic hepatitis B do not experience acute symptoms, but may lose weight, feel tired, have abdominal pain and experience liver damage (Kamyad *et al*., 2014). Globally, about 360 million people are chronically infected with HBV (WHO 2012). Upon encountering the virus, adults have roughly 90% chance of undergoing an acute infection with clinical symptoms and subsequent clearance of the virus. However, children have usually mild or no clinical symptoms immediately after infection, but do not clear the virus, and hence they become chronic carriers (Shepard *et al*., 2006, Goldstein *et al* 2005). About 25% of chronic carriers will die from liver cancer induced by the virus (Nowak and May 2000). It is asserted that in highly endemic countries, mother to child (vertical) transmission accounts for most cases of chronic infections (see e.g. Borgia *et al*., 2012, Jonas 2009, Lavanchy 2004, Shepard *et a*l., 2006 for detail). This is the case, because transmission from an infected woman to her infant during delivery is efficient and is one of the most common routes of HBV infection worldwide.

Much work has been done in modelling the transmission dynamics of HBV in the community across various regions in the world. For example, the relationship between the age at infection with HBV and the development of carrier (Edmunds *et al*. 1993), dynamics and control of hepatitis B in China (Zou *et al*. 2010), challenges imposed by vertical transmission of HBV (Gentile and Borgia 2014), the impacts of vaccination and treatment on HBV transmission (Shepard *et al* 2006, Zhao et al 2000, Zou *et al* 2010), and transmission dynamics and optimal control of vaccination and treatment of hepatitis B virus (Kamyad *et al*., 2014). However, vaccination can greatly reduce the risk of infection but does not help people who are already infected. No previous study has focused on the effect of treatment and the disease drivers in chronically HBV infected adult women capable of giving birth to newborns. The present paper contributes to this work by proposing a mathematical model incorporating treatment of infected adult females for the sake of saving the newborns from contracting the infection during the delivery process. Another aim of the paper is to derive expressions for the reproduction numbers, without treatment as well as when treatment is implemented, and to analyse the efficiency of treatment in serving lives of infants born by infected women. The rest of the paper is organized as follows: In Section 2 we describe the model to incorporate treatment and discusses the existence of model solutions. Section 3 gives the analysis of the HBV model and describes the impacts of treatment as a control measure against HBV infection from mother to newborns. Section 4 provides numerical simulation results of the model. Finally, Section 5 discusses the results and provides some concluding remarks.

2. Model Formulation

We propose a mathematical model to understand the vertical transmission of HBV in the presence of treatment. The population under consideration is comprised of adult females capable of giving birth and juvenile persons. Each group in the host population is divided into the following epidemiological classes: the proportion of susceptible to infection $S_i(t)$, acute infections representing symptomatic cases $U_i(t)$, chronic carriers (asymptomatic) $I_i(t)$. Here $i = a, c$ denote respectively adult females and juveniles. Treatment is implemented only to infected adult females who are at acute stage and form a treated class denoted as $T_a(t)$. Susceptible adult females may acquire HBV infection at the rate λ after having sufficient contacts at the rate β with an infectious individual (possibly a sexual partner). The number of susceptible females is increased through recruitment of adult females at the rate Λ and maturing female from the juvenile group at the rate π. The number of susceptible juveniles is increased by birth at the rate b. Also, a proportion p of births from HBV acute females is assumed to be susceptible and the remaining $(1-p)$ of births are infected infants who are in acute status. Individuals who are in HBV acute status progress to chronic stage at the rates γ_a and γ_c for adult females and juveniles respectively. Adult females are treated at the rate ε and recover at the rate η and become susceptible. We assume that treatment is not perfect, and so some of the treated females may progress to chronic stage at the rate α. The proportion ρ of births from treated adult females is assumed to be susceptible and the remaining proportion $(1-\rho)$ is infected and join acute class. Adult females experience natural death at the rate μ and juveniles at the rate μ_c. Infected individuals will experience an additional disease induced death at the rate δ_a for adult females and δ_c for juveniles. The compartments and model variables are illustrated by the flow chart in Figure 2.1. The model is given by seven ordinary differential equations:

$$
\begin{aligned}
\frac{dS_c}{dt} &= bS_a + pbU_a + \rho bT_a - (\pi + \mu_c)S_c, \\
\frac{dU_c}{dt} &= (1-p)bU_a + (1-\rho)bT_a - (\mu_c + \gamma_c)U_c, \\
\frac{dI_c}{dt} &= \gamma_c U_c - (\delta_c + \mu_c)I_c, \\
\frac{dS_a}{dt} &= \Lambda + \pi S_c + \eta T_a - (\lambda + \mu)S_a, \\
\frac{dU_a}{dt} &= \lambda S_a - (\mu + \varepsilon + \gamma_a + b)U_a, \\
\frac{dI_a}{dt} &= \gamma_a U_a + \alpha T_a - (\delta_a + \mu)I_a, \\
\frac{dT_a}{dt} &= \varepsilon U_a - (\alpha + \mu + \eta + b)T_a,
\end{aligned}
\tag{2.1}
$$

where $\lambda = c\beta\left(\frac{U_a + \theta I_a + \tau T_a}{N_a}\right)$, with c being the average number of sexual partners per infected adult female, θ is a modifying parameter of the relative infectiousness of HBV chronic females and τ modifies the relative infectiousness of adult females undergoing treatment. We should note also that $N_a = S_a + U_a + I_a + T_a$ is the total of all adult females in the host population.

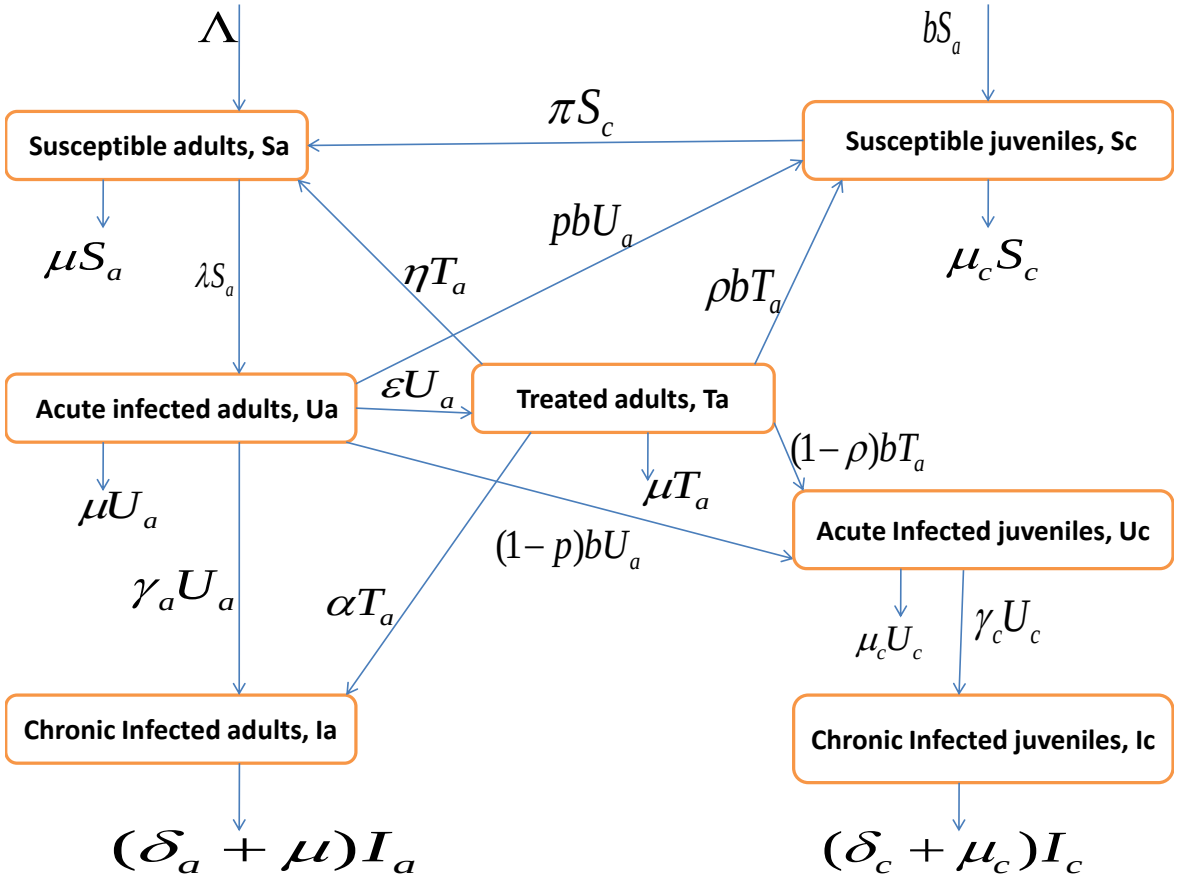

Figure 2.1: Model compartments and flow for HBV vertical transmission with treatment

2.1. Existence of Solutions

The model system (2.1) describes the dynamics of human population in the presence of HBV infection. All the model variables are non-negative. Hence, model (2.1) is biologically and mathematically well posed in the closed set

$$\Omega = \left\{ S_a, U_a, I_a, S_c, U_c, I_c \in \mathbb{R}^6 : 0 \le N_a \le \frac{\Lambda + \pi S_c}{\mu},\ 0 \le N_c \le \frac{1}{\mu_c}\left(bS_a + \pi S_c\right) \right\},$$

this is a positively invariant and attracting in the domain of Ω.

3. Analysis of the HBV Sub-models

3.1 The basic vertical transmission HBV model

This is obtained when $\rho = \alpha = \eta = \varepsilon = \tau = 0$. Thus, model (2.1) reduces to

$$\begin{aligned}
\frac{dS_c}{dt} &= bS_a + pbU_a - (\pi + \mu_c)S_c, \\
\frac{dU_c}{dt} &= (1-p)bU_a - (\mu_c + \gamma_c)U_c, \\
\frac{dI_c}{dt} &= \gamma_c U_c - (\delta_c + \mu_c)I_c, \\
\frac{dS_a}{dt} &= \Lambda + \pi S_c - (\lambda + \mu)S_a, \\
\frac{dU_a}{dt} &= \lambda S_a - (\mu + \gamma_a + b)U_a, \\
\frac{dI_a}{dt} &= \gamma_a U_a - (\delta_a + \mu)I_a,
\end{aligned} \qquad (3.1)$$

where the force of infection is $\lambda = c\beta\left(\frac{U_a + \theta I_a}{N_a}\right)$ and $N_a(t) = S_a + U_a + I_a$. The set

$\Omega_a = \left\{ S_a(t), U_a(t), I_a(t) \in \mathbb{R}^3_+ : N_a \le \frac{\Lambda + \pi S_c}{\mu} \right\}$ for adult females attracts all solutions in $\mathbb{R}^3_+$.

Similarly, the set $\Omega_c = \left\{ S_c(t), U_c(t), I_c(t) \in \mathbb{R}^3_+ : N_c \le \frac{1}{\mu}\left(bS_a + \pi S_c\right) \right\}$ for juveniles attracts all solutions in $\mathbb{R}^3_+$. The following Lemma summarizes the results:

Lemma 3.1: *Model (3.1) has solutions which are contained in the feasible region* $\Omega = \Omega_a \times \Omega_c$ *, implying that*

$$\Omega = \left\{ S_a, U_a, I_a, S_c, U_c, I_c \in \mathbb{R}^6_+ : 0 \le N_a \le \frac{\Lambda + \pi S_c}{\mu}, 0 \le N_c \le \frac{1}{\mu_c}(bS_a + \pi S_c) \right\}.$$

3.1.1 Disease Free Equilibrium and Stability

The disease free equilibrium points are steady state solutions where there is no disease (that is, HBV) in the community. It is the most important equilibrium state for disease control and its linear stability is governed by the basic reproduction number R_0 (see e.g. Hethcote 2000; Diekmann *et al*., 1990; Castillo-Chavez *et al*., 2002), mathematically defined as the spectral radius of the next generation matrix. It is a unitless threshold quantity for the disease control which defines the number of secondary infections produced by a single infected individual in a completely susceptible population. The disease free equilibrium for basic model of HBV with vertical transmission is given by

$$E_0 = \left(S_a^*, S_c^*, 0, 0, 0, 0\right) = \left(\frac{(\pi + \mu_c)\Lambda}{\mu(\pi + \mu_c) - b\pi}, \frac{b\Lambda}{\mu(\pi + \mu_c) - \pi b}, 0, 0, 0, 0 \right).$$

Applying the notations as in Van den Driessche and Watmough (2002) for the model system (3.1), the matrices F and V for the new the new infection terms and the remaining transfer terms are respectively given by

$$F=\begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & \beta c\dfrac{\mu(\pi+\mu_c)}{\mu(\pi+\mu_c)-\pi b} & \beta c\dfrac{\mu\theta(\pi+\mu_c)}{\mu(\pi+\mu_c)-\pi b} \\ 0 & 0 & 0 & 0 \end{bmatrix} \tag{3.2}$$

and

$$V=\begin{bmatrix} \mu_c+\gamma_c & 0 & 0 & 0 \\ -\gamma_c & \delta_c+\mu_c & 0 & 0 \\ 0 & 0 & \mu_a+\gamma_a+b & 0 \\ 0 & 0 & -\gamma_a & \delta_a+\mu \end{bmatrix}. \tag{3.3}$$

The basic reproduction number for HBV vertical transmission denoted by R_0 is

$$R_0=\rho\left(FV^{-1}\right)=\frac{\beta c\mu(\pi+\mu_c)(\mu+\delta_a+\theta\gamma_a)}{(\mu+\delta_a)(b+\gamma_a+\mu)\mu(\pi+\mu_c)-\pi b}.$$

Thus, using Theorem 2 of Van den Driessche and Watmough (2002) the following result is established.

Theorem 3.1: *The DFE of the model (3.1) is locally asymptotically stable if* $R_0<1$ *and unstable if* $R_0>1$.

The basic reproduction number measures the average number of new infections generated by a single infected individual in a completely susceptible population. Theorem 3.1 implies that HB disease can be eliminated from the community (when $R_0<1$) if the initial sizes of the subpopulations of the model are in the basin of attraction of the disease- free equilibrium.

3.2 HBV Model with Treatment

HBV infection during pregnancy poses particular problems. These include the effect of HBV infection in pregnancy, the effect of pregnancy on HBV infection, the mother to child transmission of HBV, and the management of drugs. The aim of this section is to examine in detail the current risk and the impact of treatment strategy to reduce or ideally eliminate this risk. The model system (2.1) incorporates treatment campaign and the analysis is done in the positively invariant region Ω.

3.2.1 Disease Free Equilibrium and Local Stability

The disease free equilibrium of the model (2.1) is given by

$$E_2=\left(S_a^{**},S_c^{**},0,0,0,0\right)=\left(\frac{(\pi+\mu_c)\Lambda}{\mu(\pi+\mu_c)-b\pi},\frac{b\Lambda}{\mu(\pi+\mu_c)-b\pi},0,0,0,0\right). \tag{3.4}$$

For the model system (2.1), the next generation matrix calculation (Van den Driessche and Watmough, 2002) shows that the reproduction number R_e in the presence of treatment is

$$\mathrm{R}_e=\frac{c\beta\left[\theta(\alpha\varepsilon+(b+\alpha+\eta+\mu)\gamma_a)+\tau(b+\alpha+\eta)+(b+\alpha+\eta+\mu)(\mu+\delta_a)\right]\mu(\pi+\mu_c)}{(b+\gamma_a+\varepsilon+\mu)(b+\alpha+\eta+\mu)(\mu+\delta_a)(\mu(\pi+\mu_c)-\pi b)} \tag{3.5}$$

It is noted that in the absence of treatment $R_e = R_0$, where R_0 is the basic reproduction number. From Theorem 2 in Van den Driessche and Watmough (2002), we have the following result:

Theorem 3.2: *The DFE of the model system (2.1) is locally asymptotically stable if* $R_e < 1$ *and unstable if* $R_e > 1$.

Biologically speaking, Theorem (3.2) implies that hepatitis B may be prevented from the community with treatment as a control strategy if the initial sizes of the sub-populations of the model are in the region of attraction of the disease free equilibrium.

3.2.2 Global Stability of Disease-Free Equilibrium

We have the following result on the global stability of the disease free equilibrium.

Theorem 3.3 *If* R_e *<1, the disease free equilibrium is globally asymptotically stable and unstable if* R_e *>1*

Proof: We can use the comparison theorem to prove the global stability.

The rate of change of the variables representing the infected components of the system (2.1) can be re-written as

$$\begin{bmatrix} U_c^{'}(t) \\ I_c^{'}(t) \\ U_a^{'}(t) \\ I_a^{'}(t) \\ T_a^{'} \end{bmatrix} \leq (F-V) \begin{bmatrix} U_c \\ I_c \\ U_a \\ I_a \\ T_a \end{bmatrix} - \begin{bmatrix} 0 \\ 0 \\ \dfrac{\beta c(U_a + \theta I_a + \tau T_a)S_a}{N_a} \\ 0 \\ 0 \end{bmatrix} \tag{3.6}$$

where matrix F and V in (3.7) are defined as in (3.2) and (3.3) respectively.

Hence, we have $\begin{bmatrix} U_c^{'}(t) \\ I_c^{'}(t) \\ U_a^{'}(t) \\ I_a^{'}(t) \\ T_a^{'}(t) \end{bmatrix} \leq (F-V) \begin{bmatrix} U_c \\ I_c \\ U_a \\ I_a \\ T_a \end{bmatrix}$. (3.7)

Therefore, all the eigenvalues of the matrix (3.7) have negative real parts, it follows that the above matrix is stable for $R_e < 1$, and as $t \to \infty$ we will have $(U_a, I_a, T_a, U_c, I_c) \to (0,0,0,0,0)$. By comparison theorem (Lakshmikantham *et al.*, (1989)) it follows that $(U_a, I_a, T_a, U_c, I_c) \to (0,0,0,0,0)$ as $t \to \infty$, evaluating the system (2.1) at $U_a = I_a = T_a = U_c = I_c = 0$ gives, $S_a = \dfrac{(\pi + \mu_c)\Lambda}{\mu(\pi + \mu_c) - b\pi}$ and $S_c = \dfrac{\Lambda b}{\mu(\pi + \mu_c) - \pi b}$ for $R_e < 1$ Hence, E_2 is globally and asymptotically stable.

3.2.3 Impact of Treatment strategy

The reproduction number is a measure of the ability of the disease to invade the population under conditions that facilitate maximal growth. Re-writing the reproduction number accrued during treatment R_e in terms of R_0 we get

$$R_e = R_0 M_1,$$

where $M_1 = \frac{(A+B)(\pi+\mu_c)(E-b\pi)}{DG\left[\mu(\pi+\mu_c)-b\pi\right]}$,

with $A = \theta(\alpha\varepsilon + \gamma_a(b+\alpha+\eta+\mu)) + \tau(b+\alpha+\eta)$,

$B = (b+c+\eta+\mu)(\mu+\delta_a)$,

$D = (b+\gamma_a+\varepsilon+\mu)(b+\alpha+\eta+\mu)(\mu+\delta_a)$,

$E = \mu(\mu+\delta_a)(b+\gamma_a+\mu)(\pi+\mu_c)$,

$G = (\pi+\mu_c)(\mu+\delta_a+\theta\gamma_a)$.

Now, using parameter values given in Table 4.1, it can easily be shown that $M_1 < 1$ implying that, M_1 is the factor by which treatment reduces the number of potential secondary HBV infections among pregnant women and hence $R_e < R_0$.

4. Numerical Results

We have explored the impact of treatment in reducing vertical transmission of HBV (i.e. from mother to the infants) during delivery process by simulations of model (2.1) using a set of parameter values given in Table 4.1. We have also performed sensitivity analysis to determine the relative importance of various parameters to the dynamic of the disease. The summary of the results for sensitivity analysis are shown in Table 4.2. The effectiveness of treatment is determined by comparing the dynamism of juvenile individuals before and after the implementation of the intervention. It is observed that value of the basic reproduction number (before treatment) is R_0 equals 3.7; whereas the treatment induced reproduction number (after treatment) R_e equals 0.94. This implies that treatment of the pregnant women infected with HBV can greatly serve lives of newborns by reducing the number of infections during delivery.

Figures 4.1 and 4.2 illustrate the change of the number of juvenile individuals in their respective classes before and after treatment respectively. Figure 4.1 (before treatment) shows that the number of juvenile individuals is decreasing in both classes of susceptible (Figure 4.1 (a)) and acute (Figure 4.1 (b)); whereas the number of juvenile with chronic infections increases (see Figure 4.1 (c)). The increase of chronic juvenile may be due to the fact that before treatment is put in place, majority of pregnant women with HBV infections are likely to give birth to already infected babies with hepatitis B chronic status because of their inability to clear viruses at their early stage of life.

Table 4.1: Parameters values for HBV vertical model with treatment

Parameters	Value $(yr)^{-1}$	Source
Λ	70	Gumel,(2003)
π	3.1	Assumed
b	0.8	Assumed
μ	0.4	Ciupe *et al*., (2007)
μ_c	0.0054	Assumed
γ_a	0.7	Assumed
γ_c	0.05	Assumed
ρ	0.6	Assumed
p	0.7	Assumed
δ_a	0.47	Nowak and May,(2000)
δ_c	0.04	Assumed
η	0.53	Assumed
ε	2.8	Assumed
c	1.5	Assumed
θ	0.88797	Assumed
τ	0.34	Assumed
β	0.5	Mayar (2013)
α	0.47	Assumed

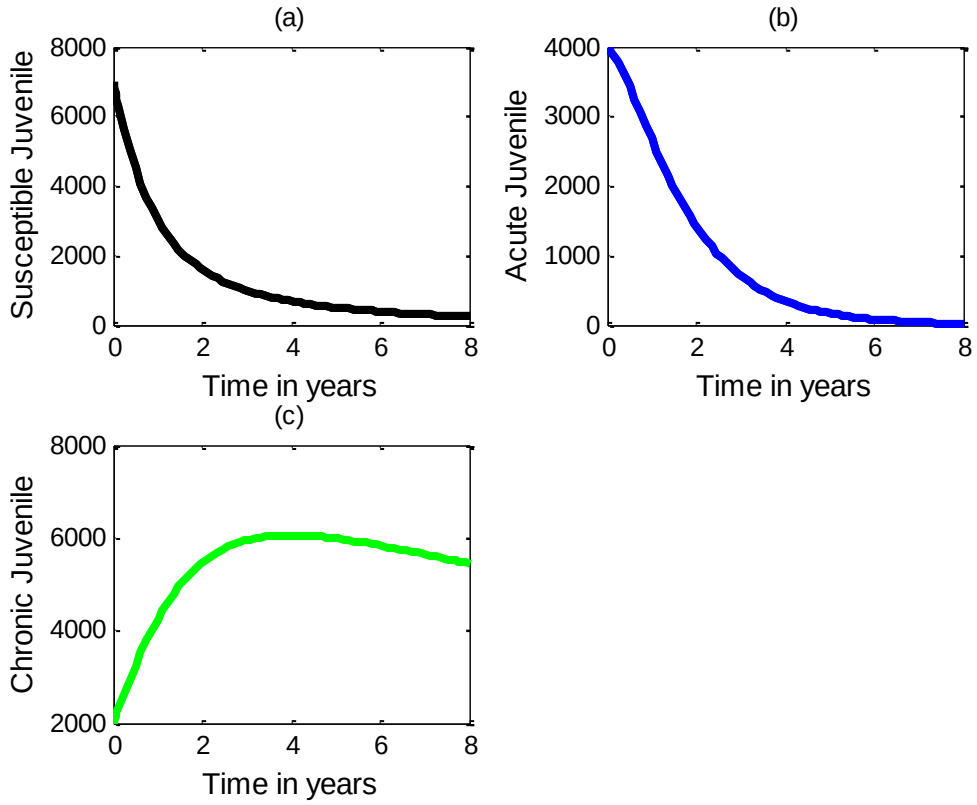

Figure 4.1: The dynamics of individuals in the juvenile population. In (a) and (b) the number of susceptible and acute juvenile respectively, decrease and in (c) the number of juvenile with chronic infections increase.

4.1 Implication of treatment on vertical HBV transmission

Figure 4.2 shows the dynamics of the state variables of the juvenile population under the presence of treatment intervention. The increase of susceptible juveniles in Figure 4.2(a) shows that by treating a good number of acute infected pregnant women may help in giving births to susceptible juveniles. Figures 4.2(b) and 4.2(c) show that

the number of both acute and chronic infected juveniles respectively, is decreasing a fact which may be due to few births from non treated female adults. Thus, we note that by treating majority of the pregnant women infected with HBV may greatly reduce or minimize the number of infected newborns occurring during delivery process. Also, Figure 4.3(a) shows that, the number of susceptible juvenile increases when the treatment rate is increased. But Figure 4.3(b) and Figure 4.3(c) show that acute and chronic infectious juveniles respectively, both decrease when treatment rate increases. Thus, the higher the treatment rates the fewer infected infants are likely to be born by acute pregnant women.

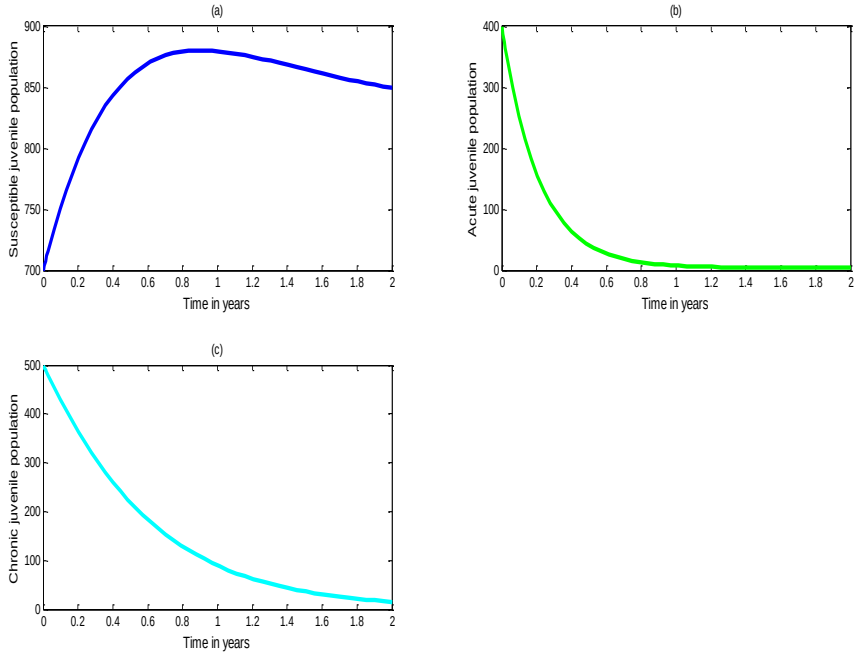

Figure 4.2: Simulation results showing the trends of the state variables of the HBV model with treatment for (a) susceptible juvenile population (b) acute juvenile population (c) chronic juvenile population

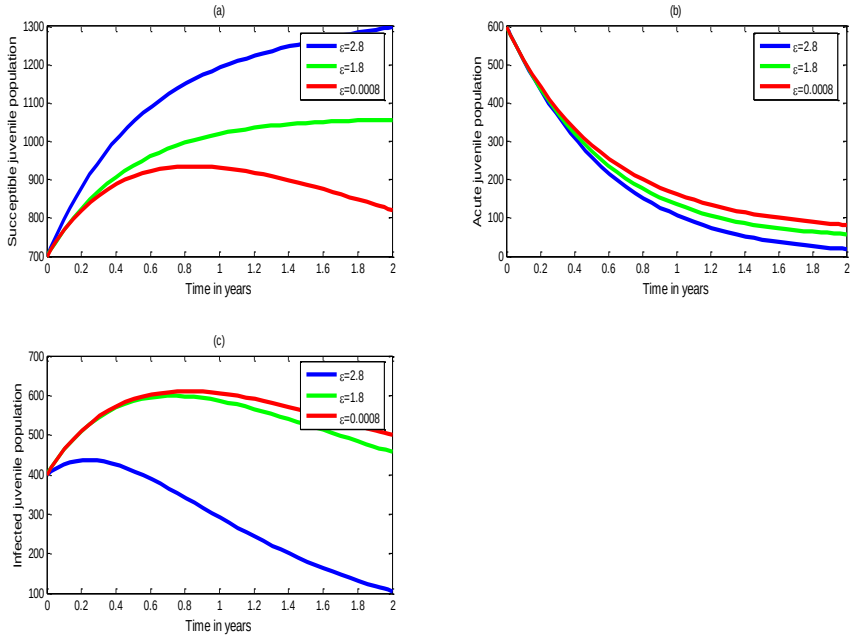

Figure 4.3: Simulation results showing the effect of varying treatment rates (ε) on (a) susceptible juvenile population (b) acute juvenile population (c) chronic juvenile population.

4.2 Sensitivity analysis

Sensitivity analysis is used to determine the relative importance of model parameters to HBV transmission and its prevalence. The analysis is performed by computing the sensitivity indices of the effective reproduction number R_e. According to Chitnis *et al*., (2008), sensitivity analysis is commonly used to determine the robustness of model predictions to parameter values. Sensitivity analysis determines parameters which have high impact on treatment induced (effective) reproduction number, and can be used to measure the relative change in the reproduction number to the relative change in the parameter. The negative sign of the sensitivity indices means that the increase in the corresponding parameter value leads to a decrease of the effective reproduction number and the positive indices show that increase in the corresponding parameter value leads to an increase of the effective reproduction number. In interpreting the sensitivity of the parameters, Table 4.2 shows that, parameters $\beta, b, \theta, c, \pi, \alpha, \tau$ and μ do have positive indices, implying that the reproduction number increases whenever the values of these parameters increase. They have to be targeted if any control measure of the disease is to be implemented otherwise a major outbreak may occur. Similarly, parameters $\gamma_a, \mu_c, \delta_a, \varepsilon$ and η do have negative indices, indicating that the reproduction number decreases even if the values of these parameters increase. The most, sensitive parameters are the effective contact rate β, and the average number of sexual partners *c*. Increasing or decreasing the value of β and *c* lead to the increase or decrease the reproduction number with the same proportional since the sensitivity index equal to one. Therefore, as β increases many individuals become infected, so HBV transmission increases in the community. Furthermore, when treatment rate increases it decreases R_e, showing that many infected individual recover from the disease after treatment.

Table 4. 2: Numerical values of sensitivity indices of R_e

Parameter symbol	Sensitivity index
β	+1
c	+1
b	+0.83445
γ_a	-0.4505
θ	+0.88797
τ	+0.00001
π	+0.85001
μ_c	-0.2027
δ_a	-0.0608
μ	-0.0090
ε	-0.365103
η	-0.210326
α	+0.399081

5 Conclusions

In the present paper we have studied the dynamics of vertical transmission of hepatitis B disease when treatment strategy is implemented to women who are in their child bearing age and are acute infected with hepatitis B. The aim was to incorporate treatment and determine its impact in reducing or minimizing the number of infant born with hepatitis infections. The reproduction numbers before and after treatment were derived and compared. It was shown through numerical simulations that an increase in the rates of providing treatment against HBV disease may generally result in the increase of the number of susceptible juveniles. Finally, because of the complication of HBV disease in terms of different transmission levels and different immunological status prevalent in different locations, some guidelines should be developed to give researchers and health professionals a more accurate foundation on the treatment of HBV infected mothers against vertical transmission of the disease.

The model developed in this paper is not fully realistic, but it is believed that it can capture some relevant properties also valid in more complex HBV infection models. For example, to make the model more realistic, the community can be considered to consist of individuals of different types, assuming that HBV transmission

depends on the type of individuals. For instance, it would be interesting to investigate the effect of public health education campaign and treatment in controlling vertical transmission of hepatitis B.

Acknowledgement

Authors gratefully acknowledge the support accrued from the Department of Mathematics of the University of Dar es Salaam.

References

Borgia, G., Calrleo, M.A., & Gaeta, G.B., Gentile, I., (2012). "Hepatitis B in pregnancy". *World J. Gastroenterol.* 18(34):4677-4683.

Castillo-Chavez, C., Feng, Z., and Huang, W., (2000). "On the computation of R0 and its role on global stability", *www.math.la.asu.edu/chavez/2002/JB276.pdf*

Chitnis, N., Hyman, J. M. and Cushing, J.M., (2008). "Determining important parameters in the spread of malaria through the sensitivity analysis of a mathematical model", *Butte in of Mathematical Biology*; DOI10.1007/s11538-008-9299-0.

Ciupe, S.M., Ribeiro, R.M and Nelson P.W., (2007). "Modelling of acute hepatitis b virus infected". *Theoretical Biology*, **247**: 23-35.

Diekmann, O., Heestebeek, J.A and Metz J.A.J., (1990). "The Definition and the computation of the Basic Reproduction Ratio, R_0 in Models of Infectious Disease in Heterogeneous Population". *J.Math. Biol*., Volume 70, pp1272-1296.

Edmunds, W.J., Medley, G.F., Nokes, D.J., Hall, A.J., and Whittle, H.C., (1993). "The influence of age on the development of the hepatitis B carrier state". *Proc. R. Soc. Lond. B* 253, 197-201.

Gentile I., and Borgia G. (2014). "Vertical transmission of hepatitis B virus: challenges and solutions". *International Journal of Women's Health*: 6, 605-611.

Goldstein S.T., Zhou F., Hadler S.C., Bell B.P., Mast E.E., and Margolis H.S (2005). "A mathematical model to estimate global hepatitis B disease burden and vaccination impact". *International Journal of Epidemiology*; 34:1329-1339.

Gumel, A.B., and Moghadas, S.M, (2003). "Qualitative study of a vaccination model with a non-linear incidence". *Applied Mathematics and Computational*, 143: 403-419.

Hethcote , H.W.,(2000). "The mathematics of infectious diseases", *SIAM Rev.* 42 (2000), 599-653.

Hyams, K.C., (1995). "Risk of chronicity following acute hepatitis B virus infection: a review". *Clin. Infect. Dis.* 20, 992-1000.

Jonas, M.M., (2009). "Hepatitis B and pregnancy: an underestimated issue". *Liver Int.*; 29 Suppl 1:133-139.

Kamyad, V.A., Akbari R., Heydari A..A. and Heydari A. (2014). "Mathematical modelling of transmission dynamics and optimal control of vaccination and treatment for hepatitis B virus". *Computational and Mathematical Methods in Medicine, Hindawi publishing Corporation,* volume 2014, Article ID 475451, 15 pages.

Lakshmikanthan V., Bainov D. and Simeonov P.S., (1989). "Theory of Impulsive differential equations", World Scientific Singapore.

Lavanchy D., (2004). "Hepatitis B virus epidemiology, disease burden, treatment and current and emerging prevention and control measures" *J. Viral. Hepat.* 11, 97-107.

Mayar, M., (2013). "Mathematical modelling of the role of public health education program on HBV transmission", *Unpublished MSc Dissertation*, University of Dar es Salaam

Nowak, M.A., and May, R.M., (2002). "Viral dynamics", Oxford university Press

Shepard, C.W, Simard, E.P., Finelli, L., Fiore, A.E., and Bell, B., P., (2006). "Hepatitis B virus infection: epidemiology and vaccination", *Epidemiol. Rev.* 28, 112-125.

Sirilert S., Traisrisilp K., Siritanapa P. and Tongsong T. (2014). "Pregnancy outcomes among chronic carriers of hepatitis B virus", *International Journal of Gynecology and Obstetrics* 126, 106-110.

Van den Driessche, P and Watmough, J., (2002). "Reproduction numbers and Sub-threshold endemic equilibria for compartmental models of disease transmission", *Mathematical Bio-sciences*, 180 29-48.

World Health Organization, (2012). "Prevention and Control of Viral Hepatitis Infection", WHO/HSE/PED/GHP 1

Zou L., Zhang W., Ruan S., (2010). "Modelling the transmission dynamics and control of hepatitis B virus in China", *Journal of Theoretical Biology* 262, 330-338