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Sensitivity Analysis of the Parameters of a Mathematical Model of Hepatitis B Virus Transmission

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Abstract In this paper, we developed a new mathematical model for the dynamics of hepatitis B virus (HBV) transmission in a population with vital dynamics, incorporating vertical transmission and sexual maturity. We obtained the basic reproduction number, R_0, proof the local and global stability of the disease-free equilibrium of the model. Sensitivity analysis of R_0 with respect to the model parameters were carried out. Our result shows that birth rate, death removal rate, HBV sexual transmission probability per contact rate, and the average total sexual contacts rate are highly sensitive parameters that affect the transmission dynamics of HBV in any population. Thus, vaccination, condom usage and reduced-average sexual partner(s) are good strategies that can lead to controlling HBV transmission.

Keywords Sensitivity Analysis, Hepatitis B Virus, Basic Reproduction Number, Stability

1. Introduction

Hepatitis (plural Hepatitides) is a general term that means injury to the liver characterized by the presence of inflammatory cells in the tissue of the organ (liver). Hepatitis B is a disease caused by hepatitis B virus (HBV). This disease reduces the liver's ability to perform life-preserving functions, including filtering harmful infectious agents from the blood, storing blood sugar and converting it to usable energy forms, and producing many proteins necessary for life.

Hepatitis B is fifty to one hundred times more infectious than HIV [1,2]. It has caused epidemics in part of Asia and Africa, and it is endemic in China [3] and Nigeria [2]. About a third of the world's population, more than two billion peoples have been infected with hepatitis B virus at some stage in their life time. Of these, about 360 million people remain chronically infected carriers of the disease, most of whom are unaware of their HBV status [4,5].

Transmission of hepatitis B virus results from exposure to infectious blood or body fluids containing blood. Possible forms of transmissions include (but are not limited to) unprotected sexual contact, blood transfusions, re-use of contaminated needles and syringes, and vertical transmission from mother to child during child birth [6].

Infection with the HBV has been a major public health problem. This has two phases: Acute and Chronic. The Acute phase causes liver inflammation, vomiting, and jaundice in which the individual is infectious. Chronic hepatitis B is an infection with hepatitis B virus that last longer than six months. Once the infection becomes chronic, it may never be cured completely, and may eventually cause liver cirrhosis and hepatocellular carcinoma (HCC) [5,7]. HBV causes approximately 600,000 deaths each year world-wide. Moreover, 10% of people infected with HIV (approximately four million people world-wide) are co-infected with HBV [8].

During the last two and a half decades, [9-15] have designed mathematical models to evaluate the effect of public health programs and provided long-term predictions regarding HBV prevalence and control in various region. These models are defined by a series of equations, input factors (variables and parameters) aimed at characterizing the process being investigated. The input factors are subject to change and errors which will likely affect the output of the model. Sensitivity Analysis which is define by [16] as the study of how the variation (uncertainty) in the output of a model (numerical or otherwise) can be apportioned (attributed) to different variations in the input of the model therefore becomes not only important but necessary to carry out in order to determine the relative importance of the different factors responsible for the transmission and prevalence of the disease. It may shed light into issues not anticipated at the beginning of a study. This in turn, may dramatically improve the effectiveness of the initial study and assist in the successful implementation of the final solution.

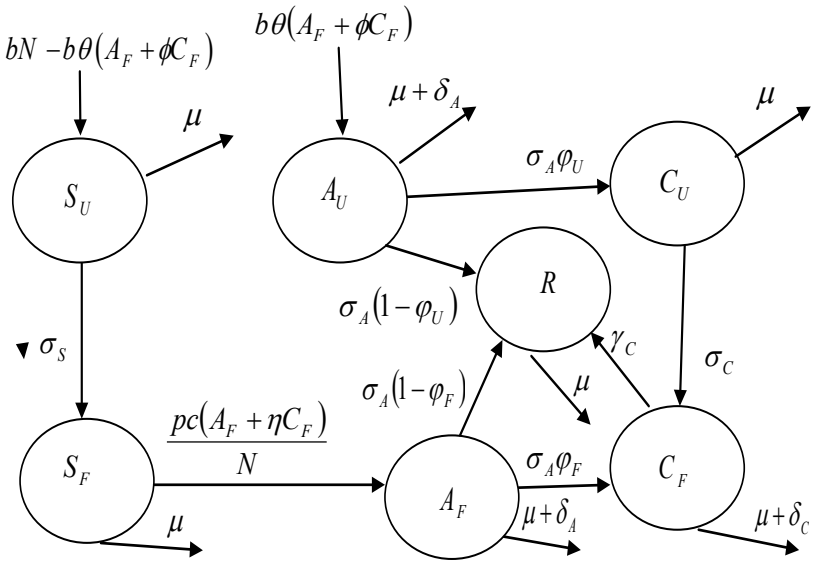

Figure 1. A schematic diagram of HBV transmission dynamics

In this paper, we developed a new HBV mathematical model incorporating vital dynamics (birth and death removal rates are not equal), vertical transmission, standard incidence function, disease induced death due to both acute and chronic infection and sexual maturity. We carried out stability analysis of the disease-free equilibrium as well as the sensitivity analysis of the basic reproduction number, R_0 with respect to the model parameters so as to know the strength and relevance of the input factors in determining the variation in the output.

2. Materials and Methods

2.1. Model Description and Formulation

We developed a model for the spread of HBV in the human population with the total population size at time, *t* given by *N(t)* with the following assumptions:

(i) There is homogeneous mixing of the population, where all people are equally likely to be infected by the infectious individuals in case of contact;

(ii) Individuals in S_U, A_U and C_U classes are not yet sexually active, while those in S_F, A_F and C_F are sexually active.

The total population is compartmentalized into seven (7) epidemiological classes shown in Figure l were the model variables and parameters are defined as follows:

$S_U(t)$ Susceptible individuals under fifteen (15) years of age at time t

$S_F(t)$ Susceptible individuals at or above fifteen (15) years of age at time t

$A_U(t)$ Acutely infected individuals under fifteen (15) years of age at time t

$A_F(t)$ Acutely infected individuals at or above fifteen (15) years of age at time t

$C_U(t)$ Chronically infected individuals under fifteen (15) years of age at time t

$C_F(t)$ Chronically infected individuals at or above fifteen (15) years of age at time t

$R(t)$ Removed individuals due to recovery from infection at time t

b Birth rate

μ Death removal rate

δ_A HBV-induced death removal rate by A_U and A_F

δ_C HBV-induced death removal rate by C_F

c Average total sexual contacts

p HBV-Sexual transmission probability per contact rate and therefore $\beta = pc$ is the effective sexual contact rate

η Modification parameter associated with reduced sexual transmission rate by chronic individuals

θ Proportion of HBV–positive birth

ϕ Modification parameter associated with reduced HBV–positive birth by C_F

σ_S Rate of moving from S_U to S_F

σ_A Rate of moving from acutely infected classes to chronically infected / removed classes

σ_C Rate of moving from C_U to C_F

φ_U Proportion of A_U which progresses to C_U, while $(1-\varphi_U)$ become removed and therefore $\sigma_A(1-\varphi_U)$ is the recovery rate from A_U to R

φ_F Proportion of A_F which progresses to C_F,

while $(1-\varphi_F)$ become removed and therefore $\sigma_A(1-\varphi_F)$ is the recovery rate from A_F to R

γ_C Rate of recovery from C_F to R

The S_U population are generated from daily recruitment of HBV uninfected individuals through birth given by $bN-b\theta(A_F+\phi C_F)$, where θ, $0<\theta<1$, is the fraction of the new birth that are born with HB virus into A_U class (vertical transmission), as in [17-18]. The parameter ϕ, $0<\phi<1$, is the modification parameter associated with reduced infectivity of C_F individuals as in [18].

The S_F population are generated from S_U class at the rate σ_S, where σ_S is the progression rate from S_U to S_F. They acquired infection and move to the A_F class via sexual transmission from individuals in the A_F and C_F compartments, given by $\frac{\beta(A_F+\eta C_F)}{N}$. The parameter β is the effective sexual contact rate (i.e. the product of the average total sexual contacts, *c* and the probability of HB virus transmission, *p*). η is the modification parameter associated with reduced sexual transmission rate by chronic individuals, as in [10,19].

Individuals in A_U, A_F and C_F classes acquired recovery from HBV infection with life immunity at the rate $\sigma_A(1-\varphi_U)$, $\sigma_A(1-\varphi_F)$ and γ_C respectively. Individuals in C_U class do not acquired recovery as recovery at chronic stage is mostly in late 50's of age. Individuals in both acute classes progresses to corresponding chronic classes at the rate σ_A. Furthermore, individuals in A_U and A_F classes suffer additional disease-induced death at a rate δ_A, while those in C_F class also suffer additional disease-induced death at a rate δ_C. And natural death occurs in all classes at a rate μ.

The corresponding mathematical equations of the schematic diagram can be described by a system of ordinary differential equations given in (1)-(7).

$$\frac{dS_U}{dt}=bN-b\theta(A_F+\phi C_F)-K_1S_U \quad (1)$$

$$\frac{dS_F}{dt}=\sigma_S S_U-\frac{pc(A_F+\eta C_F)}{N}S_F-K_2S_F \quad (2)$$

$$\frac{dA_U}{dt}=b\theta(A_F+\phi C_F)-K_3A_U \quad (3)$$

$$\frac{dA_F}{dt}=\frac{pc(A_F+\eta C_F)}{N}S_F-K_3A_F \quad (4)$$

$$\frac{dC_U}{dt}=\sigma_A\varphi_U A_U-K_4C_U \quad (5)$$

$$\frac{dC_F}{dt}=\sigma_A\varphi_F A_F+\sigma_C C_U-K_5C_F \quad (6)$$

$$\frac{dR}{dt}=\sigma_A(1-\varphi_U)A_U+\sigma_A(1-\varphi_F)A_F+\gamma_C C_F-\mu R \quad (7)$$

where:

$$K_1=(\sigma_S+\mu) \quad (8)$$

$$K_2=\mu \quad (9)$$

$$K_3=(\sigma_A+\mu+\delta_A) \quad (10)$$

$$K_4=(\sigma_C+\mu) \quad (11)$$

$$K_5=(\gamma_C+\mu+\delta_C) \quad (12)$$

and

$$N(t)=S_U(t)+S_F(t)+A_U(t)+A_F(t)+C_U(t)+C_F(t)+R(t) \quad (13)$$

so that

$$\frac{dN}{dt}=(b-\mu)N-\delta_A(A_U+A_F)-\delta_C C_F \quad (14)$$

in the biological-feasible region:

$$\Omega=\left\{\begin{array}{l}(S_U,S_F,A_U,A_F,C_U,C_F,R)\in\mathbb{R}_+^7:\\ S_U+S_F+A_U+A_F+C_U+C_F+R\le N\end{array}\right\} \quad (15)$$

2.2. Existence and Stability Analysis of Disease-free Equilibrium, E_0

The model has a disease-free equilibrium (DEF), obtained by setting the right-hand side of (1)–(7) to zero, given by

$$E_0:(S_U^*,S_F^*,A_U^*,A_F^*,C_U^*,C_F^*,R^*)=\left(\frac{bN^*}{K_1},\frac{\sigma_S bN^*}{K_1K_2},0,0,0,0,0\right) \quad (16)$$

Using the next generation operator technique described by [20] and subsequently analyzed by [21], we obtained the basic reproduction number, R_0 of the model (1)–(7) which is the spectral radius (ρ) of the next generation matrix, K. That is $R_0=\rho K$, where $K=FV^{-1}$. The matrices of F (for the new infection terms) and V (of the transition terms) are given, respectively, by

$$F = \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & \frac{bpc\sigma_S}{K_1K_2} & 0 & \frac{bpc\sigma_S}{K_1K_2} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

and

$$V = \begin{pmatrix} K_3 & -b_A & 0 & -b_C \\ 0 & K_3 & 0 & 0 \\ -\sigma_A\varphi_U & 0 & K_4 & 0 \\ 0 & -\sigma_A\varphi_F & -\sigma_C & K_5 \end{pmatrix}$$

Thus, the basic reproduction number is then given as:

$$R_0 = \frac{bpc\sigma_S}{K_1K_2K_3}\left(1+\frac{\eta\sigma_A\left(K_3K_4\varphi_F+\sigma_C\varphi_U b\theta\right)}{\left(K_3K_4K_5-\sigma_C\sigma_A\varphi_U b\theta\phi\right)}\right) \quad (17)$$

Theorem 1: The disease-free equilibrium, E_0 of the model equations (1)-(7) is locally asymptotically stable (LAS) in if $R_0 < 1$.

Linearization of the model equations around E_0, and applying qualitative matrix stability technique in the transformed upper triangular matrix using elementary-row transformation, established the result (see Appendix A for proof).

The epidemiological implication of the theorem is that HBV can be eliminated (control) from the population when $R_0 < 1$, if the initial size of the sub-populations of the model are in the basin of attraction of the DFE. Furthermore, using Castillo-Chavez et al. [22] global stability theorem, the following global stability result can be established (see Appendix B for proof).

Theorem 2: The disease- free equilibrium E_0 of the model equations (1)-(7) is globally asymptotically stable (GAS) in Ω if $R_0 < 1$.

Global stability of equilibrium removes the restrictions on the initial conditions of the model variables. In global asymptotic stability, solutions approach the equilibrium for all initial conditions. And similarly, the existence and local stability of the endemic equilibrium can be proved.

2.3. Sensitivity Analysis (SA) of the Basic Reproduction Number with Respect to the Model Parameters

One of the most important concerns about any infectious disease is its ability to invade a population. The basic reproduction number, R_0 is a measure of the potential for disease spread in a population, and is inarguably 'one of the foremost and most valuable ideas that mathematical thinking has brought to epidemic theory' [23]. It represents the average number of secondary cases generated by an infected individual if introduced into a susceptible population with no immunity to the disease in the absence of interventions to control the infection. If $R_0 < 1$, then on average, an infected individual produces less than one newly infected individual over the course of its infection period. In this case, the infection may die out in the long run. Conversely, if $R_0 > 1$, each infected individual produces, on average more than one new infection, the infection will be able to spread in a population. A large value of R_0 may indicate the possibility of a major epidemic. We thus, carried out sensitivity analysis of the basic reproduction number, R_0 with respect to the model parameters in order to determine the relative importance of the different factors responsible for the transmission and prevalence of the disease. This will assist in curtailing the transmission of the disease by using appropriate intervention strategies.

There are more than a dozen ways of conducting SA, all resulting in a slightly different sensitivity ranking [24]. Following [25-29], we used the normalized forward sensitivity index also called elasticity as it is the backbone of nearly all other SA techniques [24] and are computationally efficient [25]. The normalized forward sensitivity index of the basic reproduction number, R_0 with respect to a parameter value, P is given by:

$$S_P^{R_0} = \frac{\partial R_0}{\partial P} \times \frac{P}{R_0} \quad (18)$$

It is important to stress that with the exception of sensitivity indices of HBV-sexual transmission probability per contact, p and average total sexual contacts rate, c, i.e. $S_p^{R_0}$ and $S_c^{R_0}$ respectively, the expressions for the sensitivity indices of other parameters are complex with little obvious structure. We therefore, evaluate the sensitivity indices at the baseline parameter values given in Table 1, using Maple software.

3. Results and Discussion

It is important to stress that the sensitivity indices of all the parameters remain unchanged regardless of the baseline value of p and c. But changes with different baseline values of b and μ. We, thus considered three (3) different set values of μ. Table 2 shows that all the parameters have either positive or negative effects on the basic reproduction number. The death removal rate, μ have the highest sensitivity index followed by the birth rate, b. The HBV-sexual transmission probability per contact rate, p and the average total sexual contacts, c have high sensitivity index of +1 each in all cases. This means that R_0 is an increasing function of both p and c. Thus, decreasing (or increasing) p or c by 10% decreases (or increases)

Table 1. Baseline values for parameters of the model. Reasons for using these values are explained in Appendix C correct to three (3) decimal places value

S/N	Parameter	Value	Ref.	S/N	Parameter	Value	Ref.
1	b	0.007, 0.027, 0.048	C.1	9	σ_A	2.667	C.9
2	μ	0.011, 0.016, 0.021	C.2	10	σ_C	0.068	C.10
3	c	10, 20, 40	C.3	11	φ_U	0.885	C.11
4	p	0.006, 0.06, 0.12	C.4	12	φ_F	0.1	C.12
5	η	0.667	C.5	13	γ_C	0.015	C.13
6	θ	0.724	C.6	14	δ_A	0.007	C.14
7	ϕ	0.159	C.7	15	δ_C	0.001	C.15
8	σ_S	0.067	C.8	-	-	-	-

Table 2. Sensitivity indices of the basic reproduction number to model parameters. The parameters are ordered from the most sensitivity to the least. Parameter values used are as in Table 1

S/N	SA value for μ= 0.011		SA value forμ = 0.016		SA value for μ = 0.021	
1	μ	-1.558	μ	-1.683	μ	-1.775
2	b	1.131	b	1.107	b	1.090
3	p	+1	p	+1	p	+1
4	c	+1	c	+1	c	+1
5	η	0.884	η	0.863	η	0.842
6	φ_F	0.838	φ_F	0.820	φ_F	0.803
7	γ_C	-0.538	γ_C	-0.434	γ_C	-0.362
8	σ_A	-0.155	σ_S	0.193	σ_S	0.239
9	σ_S	0.141	σ_A	-0.171	σ_A	-0.186
10	θ	0.131	θ	0.107	θ	0.090
11	φ_U	0.131	φ_U	0.107	φ_U	0.090
12	ϕ	0.084	ϕ	0.064	ϕ	0.050
13	δ_C	-0.036	δ_C	-0.029	δ_C	-0.024
14	σ_C	0.018	σ_C	0.020	σ_C	0.021
15	δ_A	-0.003	δ_A	-0.003	δ_A	-0.003

R_0 by 10%. Similarly, the parameter with lowest SA in all the 3 set values of μ is the death rate due to acute infection, δ_A with sensitivity index of -0.003. This means that R_0 is a decreasing function of δ_A. Thus, increasing (or decreasing) δ_A by 10% decreases (or increases) R_0 by 0.03%. All the three human demographic parameters b, μ and c have high sensitive indices. Clearly, for c, the sign of the sensitivity index of R_0 agrees with an intuitive expectation, as the higher the average total sexual contacts, c the higher the transmission. Thus, with $c = 10y$, where 10 is the assumed average number of sexual contacts per year and y the average number of sexual partner(s); we show in Figure 2 the linear relationship between R_0 and the average number of sexual partner(s), y.

Similarly, for b we expected R_0 to be an increasing function of b. This is because increasing b increases the number of susceptible individuals that are likely going to be infected and infect many others more. This is evident on Table 2 were b has the second highest sensitivity index in all the 3 set values of μ. Furthermore, for μ, the higher the

death removal rate the lower the basic reproduction number. This is because as more people die there will be less to be infected. We illustrated on Figure 3 the relationship between the per capital birth rate, the natural death rate and the basic reproduction number, R_0.

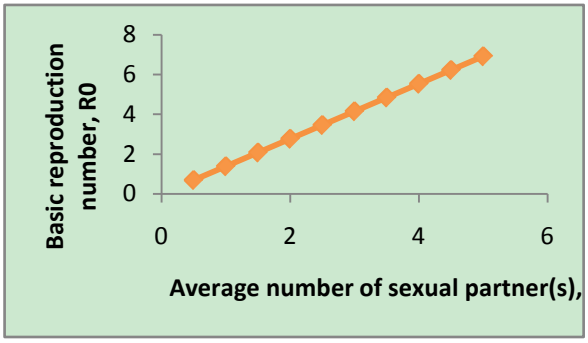

Figure 2. Effect of average number of sexual partner(s), y on basic reproduction number, R_0. Parameter values used are as in Table 1 with $b = 0.027, \mu = 0.021$ and $p = 0.06$

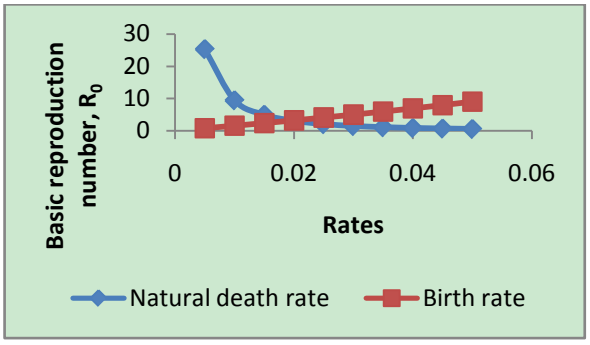

Figure 3. Effect of per capital birth rate, b, and natural death rate μ on basic reproduction number. Parameter values used are as in Table 1 with $c = 20, p = 0.06, b = 0.027$ (for μ) and $\mu = 0.016$ (for b)

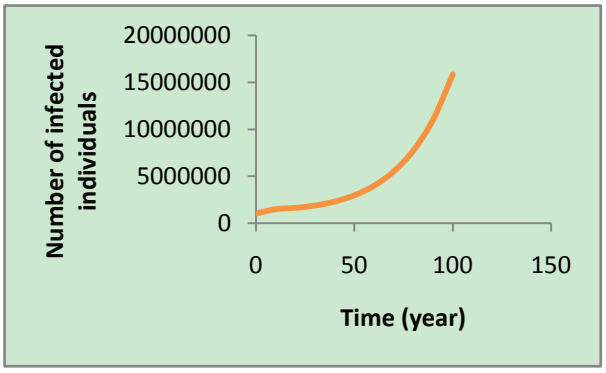

Figure 4. Effect of c, b and μ on human population. Parameter values used are as in Table 1 with
$c = 40, p = 0.06, b = 0.048$ and $\mu = 0.011$ with $R_0 = 64.088$

Figure 4 to Figure 6 shows the effects of different levels of the average total sexual contacts, birth and death removal rates on human population. The figures clearly illustrated that R_0 is an increasing function of the average total sexual contacts and the birth rates and a decreasing function of death removal rate. The initial population data used are: $S_U + S_F = 10,000,000$, $A_U + A_F + C_U + C_F = 1,000,000$ and $R = 1,000,000$, giving a total of $N = 12,000,000$.

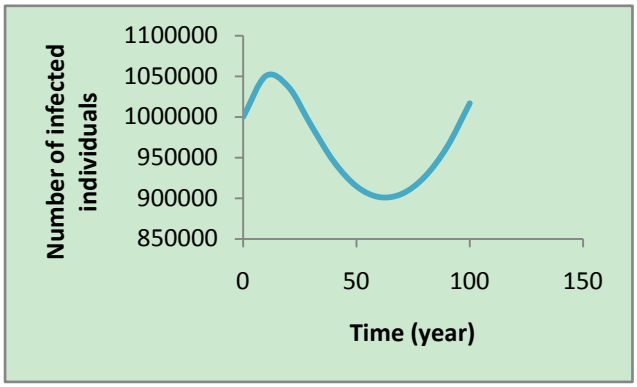

Figure 5. Effect of c, b and μ on human population Parameter values used are as in Table 1 with
$c = 20, p = 0.06, b = 0.027$ and $\mu = 0.016$ with $R_0 = 4.425$

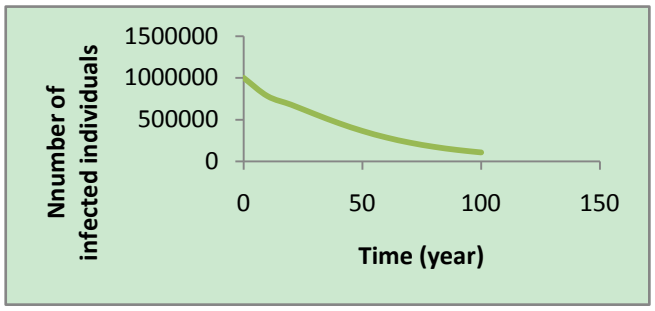

Figure 6. Effect of c, b and μ on human population. Parameter values used are as in Table 1 with
$c = 10, p = 0.06, b = 0.007$ and $\mu = 0.021$ with $R_0 = 0.335$

Other highly sensitive parameters are $\eta, \varphi_F, \sigma_A, \sigma_S$ and γ_C. These parameters sensitivity indices agree with our expectations. For η, it is the modification parameter associated with reduced sexual transmission rate by chronic individuals, and thus, it highly affects the transmission dynamics of the disease. The parameters φ_F and σ_A are the proportion and average rate of moving from acutely infected classes to chronic classes. There high sensitivity indices is due to the fact that acute stages have short duration (4.5 months on average) while chronic stages have long duration of years and in most cases lifelong and so moving from an acute stage to a chronic stage should be of high sensitivity. Similarly, for σ_S, the average rate of moving from S_U to S_F. It is clear that S_U's are not sexually active and hence contribute not to the transmission dynamics of the system. But with σ_S the S_U moves to S_F who are sexually active that can be infected and then infect others. Thus, σ_S is highly sensitive to the transmission dynamics of the disease. Furthermore,

γ_C contribute in reducing the transmission of HBV, as it is the rate of recovery of sexually active individuals that are chronically infected (and can infect others) from the disease to removed class. Thus, R_0 is a decreasing function of γ_C.

Interestingly, the sensitivity indices of θ and φ_U in all the 3 values for μ are low and equal. This is due to the fact that both parameters are for individuals that are infected but not yet infectious (not yet sexually active). Moreover, the proportion of A_U that progresses to C_U, φ_U are individuals that are born with hepatitis B virus, θ. Thus, low and equal.

Other parameters that are sensitive but with low indices are ϕ, σ_C, δ_C, and δ_A. All the parameters clearly agrees with expectation except for σ_C which ordinarily is expected to have a high sensitivity index since it is the average rate of moving from C_U to C_F. The reason for the counterintuitive result is due to the fact that majority of the chronically infected individuals under 15 years of age, C_U are sexually inactive and when they move to sexually active class, C_F, they are sexually-less infectious compare to A_F. Thus, σ_C does not contribute much to the transmission dynamics of the disease.

4. Conclusion

We developed a new mathematical model for hepatitis B virus (HBV) transmission dynamics in a population with vital dynamics, incorporating vertical transmission and sexual maturity. Sensitivity indices of the basic reproduction number with respect to the model parameters were computed. These sensitivity indices allowed us to determine the most influential parameters in controlling disease transmission and prevalence.

Our analysis shows that all the parameters are sensitive to the transmission and prevalence of HBV either positively or negatively. The most influential been the natural death rate, μ and birth rate, b. Next, are the HBV-sexual transmission probability contact rate, *p* and the total sexual contact rate, *c*, each with +1 sensitivity index. $\eta, b, \varphi_F, \sigma_A, \sigma_S$ and γ_C are also highly sensitive parameters. Others are $\theta, \phi, \varphi_U, \sigma_C, \delta_C$, and δ_A with low sensitivity indices.

For optimum control, intervention strategies should be target towards those parameters with high sensitivity index. Nevertheless, even the low sensitive parameters should be included in model formulation so as to determine the number of new HBV- positive birth, morbidity, as well as mortality due to both acute and chronic infection which undermines the social, economic and political systems of the human population concern.

Though, intervention strategies cannot directly target most of the highly sensitive parameters, they can be indirectly targeted through vaccination, condom usage and reduced-average sexual partner(s) by individuals in different classes.

Vaccination will reduce the number of susceptible individuals to be infected as those that are vaccinated are immune for at least 25 years [30]. Thus $\sigma_S, \sigma_A, \varphi_F, p, c$ and η are indirectly affected. With condom efficacy of 0.8 [19], appropriate and regular usage affects the effective sexual contact rates which undoubtedly reduces the transmission of the disease and hence p, c and η are indirectly affected. Furthermore, reducing the average number of sexual partner(s), *y* as illustrated in figure 2 reduces the basic reproduction number, R_0 and hence the disease transmission.

Finally, there is need to quantify the relationship between the parameters in our model and the possible intervention strategies such as vaccination (at birth, infant and adult) and condom usage in a human population. This would enable us determine the efficiency and cost-effectiveness of different intervention strategies on curtailing morbidity and mortality of hepatitis B virus in the population.

Appendix A. Proof for local stability of the disease-free equilibrium

In this appendix, we proof the local stability of the disease-free equilibrium for the model (1)-(7). We used the qualitative matrix stability technique of determining the local stability of a system. Now, we observed that the variable *R* does not appear in the first six (6) equations of the model, i.e. (1)-(6).

Using the relation:

$$R = N - S_U - S_F - A_U - A_F - C_U - C_F > 0 \quad \text{(A.1)}$$

allows us as explained in [31,32] to study (1)–(6).

Linearization of (1)-(6) at disease-free equilibrium gives the Jacobian matrix

$$J(E_0) = \begin{pmatrix} -K_1 & 0 & 0 & -b_A & 0 & -b_C \\ \sigma_S & -K_2 & 0 & -\frac{pcS_F^*}{N^*} & 0 & -\frac{pc\eta S_F^*}{N^*} \\ 0 & 0 & -K_3 & b_A & 0 & b_C \\ 0 & 0 & 0 & -K_{3n} & 0 & \frac{pc\eta S_F^*}{N^*} \\ 0 & 0 & \sigma_A\varphi_U & 0 & -K_4 & 0 \\ 0 & 0 & 0 & \sigma_A\varphi_F & \sigma_C & -K_5 \end{pmatrix} \quad \text{(A.2)}$$

where

$$K_{3n} = (\sigma_A + \mu + \delta_A) - \frac{pcS_F^*}{N^*} \quad \text{(A.3)}$$

Using elementary row-transformation, we have

$$J(E_0)=\begin{pmatrix} -K_1 & 0 & 0 & -b_A & 0 & -b_C \\ 0 & -K_2 & 0 & -M_1 & 0 & -M_2 \\ 0 & 0 & -K_3 & b_A & 0 & b_C \\ 0 & 0 & 0 & -K_{3n} & 0 & \frac{pc\eta S_F^*}{N^*} \\ 0 & 0 & 0 & 0 & -K_4 & M_3 \\ 0 & 0 & 0 & 0 & 0 & M_4 \end{pmatrix} \quad \text{(A.4)}$$

where

$$M_1=\left(\frac{pcS_F^*}{N^*}+\frac{\sigma_S b_A}{K_1}\right) \quad \text{(A.5)}$$

$$M_2=\left(\frac{pc\eta S_F^*}{N^*}+\frac{\sigma_S b_C}{K_1}\right) \quad \text{(A.6)}$$

$$M_3=\frac{\sigma_A\varphi_U}{K_3}\left(b_C+\frac{b_A pc\eta S_F^*}{K_{3n}N^*}\right) \quad \text{(A.7)}$$

$$M_4=-K_3+\frac{\sigma_A\varphi_F\alpha_C S_F^*}{K_{3n}N^*}+\frac{\sigma_A\sigma_C\varphi_U}{K_3K_4}\left(b_C+\frac{b_A\alpha_C S_F^*}{K_{3n}N^*}\right) \quad \text{(A.8)}$$

Thus, the eigenvalues of the row-transformed Jacobian matrix, (A.3) are given by

$$\lambda_1=-K_1<0,\ \lambda_2=-K_2<0,\ \lambda_3=-K_3<0,$$

$$\lambda_4=-K_{3n}<0,\ \lambda_5=-K_4<0, \text{ and}$$

$$\lambda_6=-K_5+\frac{\sigma_A\varphi_F\alpha_C S_F^*}{K_{3n}N^*}+\frac{\sigma_A\sigma_C\varphi_U}{K_3K_4}\left(b_C+\frac{b_A\alpha_C S_F^*}{K_{3n}N^*}\right)$$

Clearly $\lambda_1,\lambda_2,\lambda_3,\lambda_4,\lambda_5$ are all negative, For λ_6 to be negative, we should have,

$$-K_5+\frac{\sigma_A\varphi_F\alpha_C S_F^*}{K_{3n}N^*}+\frac{\sigma_A\sigma_C\varphi_U}{K_3K_4}\left(b_C+\frac{b_A\alpha_C S_F^*}{K_{3n}N^*}\right)<0$$

i.e.

$$\frac{\begin{pmatrix}-K_3K_{3n}K_4K_5N^*+\sigma_A\varphi_F pc\eta S_F^*K_3K_4\\ +\sigma_C\sigma_A\varphi_U b_C K_{3n}N^*+\sigma_C\sigma_A\varphi_U b_A pc\eta S_F^*\end{pmatrix}}{K_3K_{3n}K_4K_5N^*}<0$$

Simplifying, gives,

$$\frac{bpc\sigma_S}{K_1K_2K_3}\left(1+\frac{\eta\sigma_A\left(K_3K_4\varphi_F+\sigma_C\varphi_U b\theta\right)}{\left(K_3K_4K_5-\sigma_C\sigma_A\varphi_U b\theta\phi\right)}\right)<1$$

i.e.

$$R_0<1$$

Which implies that, $\lambda_6<0$ if $R_0<1$. Hence, the disease-free equilibrium, E_0 of (1)-(7) is locally asymptotically stable (LAS) if $R_0<1$.

Appendix B. Proof for global stability of the disease-free equilibrium

To establish the global stability of the disease-free equilibrium, the two conditions (H1) and (H2) as in [22] must be satisfied for $R_0<1$. We rewrite the model (1)-(7) in the form:

$$\frac{dX_1}{dt}=F\left(X_1,X_2\right) \quad \text{(B.1)}$$

$$\frac{dX_2}{dt}=G\left(X_1,X_2\right);\ G\left(X_1,0\right)=0 \quad \text{(B.2)}$$

where

$X_1=\left(S_U^*,S_F^*,R^*\right)$ and $X_2=\left(A_U^*,A_F^*,C_U^*,C_F^*\right)$, with the components of $X_1\in\mathbb{R}^3$ denoting the uninfected population and the components of $X_2\in\mathbb{R}^4$ denoting the infected population. Thus, the disease-free equilibrium is now denoted as:

$$E_0=\left(X_1^*,0\right),\ X_1^*=\left(\frac{bN^*}{K_1},\frac{\sigma_S bN^*}{K_1K_2},0\right)$$

Now, for the first condition, that is globally asymptotically stability of X_1^*, we have

$$\frac{dX_1}{dt}=F\left(X_1,0\right)=\begin{bmatrix}bN^*-K_1S_U^*\\ \sigma_S S_U^*-\mu S_F^*\\ -\mu R^*\end{bmatrix} \quad \text{(B.3)}$$

a linear differential equations. Solving, we have

$$S_U^*(t)=\frac{bN^*}{K_1}\left(1-e^{-K_1t}\right)+S_U^*(0)e^{-K_1t} \quad \text{(B.4)}$$

$$S_F^*(t)=\frac{\sigma_S S_U^*}{K_2}\left(1-e^{-K_2t}\right)+S_F^*(0)e^{-K_2t} \quad \text{(B.5)}$$

$$R^*(t)=R^*(0)e^{-\mu t} \quad \text{(B.6)}$$

Now, clearly from (16) we have

$$S_U^*(t)+S_F^*(t)+R^*(t)\to N^*(t) \text{ as } t\to\infty$$

regardless of the value of $S_U^*(0),S_F^*(0)$ and $R^*(0)$. Thus, $X_1^*=\left(\frac{bN^*}{K_1},\frac{\sigma_S bN^*}{K_1K_2},0\right)$ is globally asymptotically

stable.

Next, for the second condition, that is

$$\hat{G}(X_1, X_2) = AX_2 - G(X_1, X_2),$$

we have

$$A = \begin{bmatrix} -K_3 & b_A & 0 & b_C \\ 0 & -K_{3n} & 0 & \frac{\alpha_C S_F^*}{N^*} \\ \sigma_A \varphi_U & 0 & -K_4 & 0 \\ 0 & \sigma_A \varphi_F & \sigma_C & -K_5 \end{bmatrix} \quad \text{(B.7)}$$

This is clearly an M-matrix (the off-diagonal elements of A are non-negative).

$$G(X_1, X_2) = \begin{bmatrix} \left(b_A A_F^* + b_C C_F^*\right) - K_3 A_U^* \\ \left(\alpha_A A_F^* + \alpha_C C_F^*\right) S_F^* - K_3 A_F^* \\ \varphi_U \sigma_A A_U^* - K_4 C_U^* \\ \varphi_F \sigma_A A_F^* + \sigma_C C_U^* - K_5 C_F^* \end{bmatrix} \quad \text{(B.8)}$$

then,

$$\hat{G}(X_1, X_2) = AX_2 - G(X_1, X_2) = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}$$

i.e.

$$\hat{G}(X_1, X_2) = [0, 0, 0, 0]^T \quad \text{(B.9)}$$

It is thus obvious that $\hat{G}(X_1, X_2) = 0$. Hence, the proof is complete.

Appendix C. Estimation of model parameters values

Population parameters can be divided into two, namely: population-dependent and population-independent parameters. The population-dependent parameters values usually have to be estimated based on HBV epidemiology and the demographic profile of the population (country) concern. While the population-independent parameters value usually has to be estimated on HBV epidemiology and published data. Below we estimated the model parameters values given reasons in details correct to 3 decimal places value accuracy.

C.1. Birth rate, b

The estimated birth rate of countries varies from 6.85 to 47.60 births per year per 1000 people for the year 2012 [33]. As the birth rate in any country may be different, we used 3 levels of birth rates as our hypothetical values. These are low, moderate and high levels with 6.85, 27.225 and 47.60 births per year per 1000 people respectively. Thus, approximating correct to 3 decimal places value, we have:

low level birth rate $= \frac{6.85}{1000} yr^{-1} = 0.007 yr^{-1}$

moderate level birth rate $= \frac{27.225}{1000} yr^{-1} = 0.027 yr^{-1}$

high level birth rate $= \frac{47.60}{1000} yr^{-1} = 0.048 yr^{-1}$

C.2. Death removal rate, μ

The death removal rate (not crude death rate) is generally calculated as the multiplicative inverse of life expectancy at birth. The estimated life expectancy of countries varies from 48.69 for Chad to 89.68 for Monaco for the year 2012 [33]. We thus used 3 levels of death removal rates as our hypothetical values. These are low, moderate and high levels. Thus, approximating correct to 3 decimal places value, we have:

low level death removal rate

$$= \frac{1}{89.68} yr^{-1} = 0.011 yr^{-1}$$

Moderate level death removal rate

$$= \frac{0.011 + 0.021}{2} = 0.016 yr^{-1}$$

high level death removal rate

$$= \frac{1}{48.69} yr^{-1} = 0.021 yr^{-1}$$

C.3. Sexual transmission probability per contact, p

This is the probability of transmission of infection from infected individual to susceptible individual sexually which depends on both the pathology of the infectious organism (disease) and the current prevalence level in a population. A direct estimation of the HBV sexual transmission risk can be given by $p = 0.6x$, where 0.6 is the odds of HBV transmission per unprotected sexual act with an infected person and x is the prevalence rate in the population, which may differ; and thus, we used 3 different levels as our hypothetical values. These are low $(x = 1\%)$, moderate $(x = 10\%)$ and high $(x = 20\%)$ levels with sexual transmission risk of 0.006, 0.06, and 0.12 per year respectively.

C.4. Average total sexual contacts, c

This is the average total number of sexual contacts, effective or not, per year. As some individual may have more than one sexual partner it is necessary to take into consideration the mean number of sexual partners since sexual partnerships and disease spread are co-evolving dynamic process and the number of sexual partners is important for the determination of epidemic thresholds. The

rate of acquisition of new partners depends largely on social and environmental factors that determine the living conditions, resources and social opportunities [34]. Cultural and religious beliefs have an influence on the number of new partners one can acquire. In some cultural settings, men are allowed to have as many partners as they wish and this has a significant impact on the value of c. Many people indulge in risky behaviours due to poverty, need to get financial support, revenge for having been infected unjustifiably and lack of knowledge on disease dynamics [35]. Thus, a direct estimation of the average total sexual contacts can be given by $c = 10y$, where 10 is assumed average number of sexual contacts per year and y is the average number of sexual partners per year, which may differ; and thus, we used 3 different averages of sexual partner(s) as our hypothetical values. These are low $(y = 1)$, moderate $(y = 2)$ and high $(y = 4)$ levels with average total sexual contacts of 10, 20, and 40 per year respectively. It is important to stress that we are interested in population average total sexual contacts per year and not some individual's total sexual contacts. Thus, the effective contact rate represented by β is the product of the HBV-sexual transmission probability per contact and the average total sexual contacts per year, that is $\beta = p \times c$.

C.5. Modification parameter associated with reduce infection by chronic infected individual, η

The chronic infected class comprises of both carriers with HBeAg-positive and HBeAg-negative. The later are less infectious, which make chronic carriers less infectious to acute individuals by a rate η. This is in consistent with [10,36]. Assuming a 50% population of each carrier in chronic infection and 0.2 transmission probability (rate of infection) of HBeAg-negative individual, we have:

Rate of infection of chronic individuals'= rate of infection of HBeAg-positive + rate of infection of HBeAg-negative

$$= \left(\frac{50}{100} \times 0.6x\right) + \left(\frac{50}{100} \times 0.2x\right) = 0.04x$$

then, we have

$$0.6x \times \eta = 0.4x \Rightarrow \eta = 0.667$$

C.6. Rate of vertical transmission born to acutely infected mothers, θ

90% of babies born to HBsAg-positive and / or HBeAg-positive mothers, and 10% of babies born to HBsAg-positive and / or HBeAg-negative mothers have a chance of 90% of contracting HBV during childbirth [37]. With the above reference we accept [10] estimation of proportion of babies born infected to acute and chronic mothers as 0.724 and 0.115 respectively. That is $\theta = 0.724$.

C.7. Modification parameter associated with reduce rate of vertical transmission of chronic carrier mothers, ϕ

As in C.5 and from C.6, we have:

$$0.724 \times \phi = 0.115 \Rightarrow \phi = 0.159$$

C.8. Average progression rate from S_U to S_F, σ_S

The average duration of a born child to become sexually active is approximately 15years. Therefore, the average progression rate,

$$\sigma_S = \frac{1}{15} year^{-1} = 0.067 yr^{-1}$$

C.9. Average progression rate from acute to chronic stage/ recovered class, σ_A

Though, the maximum acute (both A_U and A_F) infection period is 6 months, the acutely infected individual clears the disease and become recovered or progress to chronic HBV carrier stage in 4.5 months on average [10,11]. That is:

$$\sigma_A = \frac{1}{4.5\ months} = \frac{1}{0.375 yr} = 2.667 yr^{-1}$$

Therefore, an individual progresses from acute infection to chronic carrier or become recovered at an average rate of 2.667 per year.

C.10. Progression rate from C_U to C_F, σ_C

The average time for a chronically infected child to become sexually active is 14 years 7.5 months. That is:

$$\sigma_C = \frac{1}{14.625 yr} = 0.068 yr^{-1}$$

C.11. Proportion of acute infant who progresses to chronic stage, φ_U or become recovered, $(1 - \varphi_U)$.

About 90% of children born infected are expected to become carriers [4,38]. That is, the maximum proportion of acute infected infants becoming carriers is 0.9, but the average rate can be less as some infants will progress to immune class due to one reason or another such as influence of nutrition (nutrient-sufficient). We therefore accept [10] value. That is, $\varphi_U = 0.885$ as the proportion of acute infected infants becoming carriers. And therefore, the proportion of acute infants who become recovered is $(1 - \varphi_U) = 0.115$.

C.12. Proportion of acute adults who progresses to chronic stage, φ_F or become recovered, $(1 - \varphi_F)$

About 10% of acutely infected adults are expected to become carriers [4,38]. i.e. $\varphi_F = 0.1$, this is also in consistence with [10]. And therefore, the proportion of acute individual who become recovered is $(1 - \varphi_F) = 0.9$

C.13. Average rate of recovery from C_F to R, γ_C

A few chronic carriers naturally clear HBV and become removed later at adult age. The age-related annual rate of the viral clearance has been reported to be as low as 1–2% (i.e. 0.01 – 0.02) on average [11,39]. We adopted [10]

approximation. That is, $\gamma_C = 0.015$.

C.14. Mortality rate due to acute HB infection, δ_A

A small portion of those with acute hepatitis B infection (0.1–0.6%) develop fulminant hepatitis B which kills about 70% of those affected [4, 37]. That is:

$$\delta_A = \frac{70}{100} \times \frac{0.35}{100} \times \frac{1}{4.5 months} = 0.007 yr^{-1}$$

C.15. Mortality rate due to chronic HB infection, δ_C

People with chronic HBV infection are called chronic carriers. About two-third of these people do not themselves get sick or die of the virus but can transmit it to others. The remaining one-third develops chronic hepatitis B, a disease of the liver that can be very serious. People with chronic hepatitis B have a chance of 15–25% of dying prematurely from hepatitis B related cirrhosis or liver cancer- often during the most productive adult years [4]. Assuming an average age of 51years as the usual age of patient at the time of diagnosis (with chronic hepatitis B), we have:

$$\delta_C = \frac{20}{100} \times \frac{1}{3} \times \frac{1}{51 year} = 0.001 yr^{-1}$$

This is in consistence with [40] estimation of about 470,000 deaths from cirrhosis or liver cancer out of 360 million HBV chronically infected individuals. That is

$$= \frac{470000}{360000000} = 0.001 yr^{-1}.$$

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