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Mathematical Model and Optimal Control Strategy for the Dynamics of Hepatitis B Virus Disease Incorporating Treatment Failure and Advanced Stage Compartments

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ABSTRACT

In this paper, mathematical model for the dynamic of Hepatitis B virus infection was developed taking into cognizance the effect of rate of progression to the end stage (cirrhosis and HCC) by individuals who experience treatment failure in the treatment class and chronically infected class. In order to track the transmission of these diseases, the basic reproduction number which determines the rate of new secondary infection when an infected individual is introduced into a totally susceptible population was computed by next generation matrix method (NGM). The stability of the disease-free equilibrium point was also investigated using Routh-Hurwitz Criterion and the result proven to be Locally Asymptotically Stable (LAS) when the basic reproduction number $R_0^{HBV} < 1$. The global stability was also investigated by Castillo-Chavez method and the results show that the model is Globally Asymptotically (GAS) when $R_0^{HBV} < 1$. Sensitivity analysis was carried out on the parameters of the reproduction number, using forward normalized sensitivity index to ascertain those parameter of high impact on the reproduction number to aid the incorporation of the control variables appropriately. Numerical simulation was also carried using Forward-backward Runge-Kutta fourth order scheme to study the effect of these control strategies on the dynamics of the model and the results shows that the best strategy to implement to help eradicate HBV disease in the system is strategy E which is the combination of effective condom use, HBV vaccination, HBV Treatment and Behavioral change.

1. Introduction

Hepatitis B is a highly contagious and potentially life-threatening liver infection caused by the hepatitis B virus (HBV). It is a viral infection that attacks the liver and can cause both acute and chronic disease in the human body and sometimes leads to liver failure, cirrhosis, or cancer. Viral hepatitis B is a blood-borne infection; the virus is most commonly transmitted from mother to child during birth, but it can also be transmitted through sexual contact; sharing needles, syringes, or other drug injections; or exposure to sharp instruments (Wendy *et al.*, 2017). B virus disease occurs within the first six months of infection. In this stage, a few infected people are capable of clearing the infection; for others, the infection transfers to a chronic or lifelong disease and develop into a serious health problem. Hepatitis B disease obtained in adulthood causes chronic hepatitis in less than 5% of cases, but disease in infancy and early childhood causes chronic hepatitis in about 95% of cases (WHO, 2016). It is particularly difficult in the West Pacific and African regions, where 116 million and 81 million people, respectively, are chronically infected. Thus, Africa has the second-highest number of chronic HBV infections next to the West Pacific, and it is considered an area of high endemicity. Moreover, 5%-15% of individuals in developing and low-income countries are chronic carriers of the hepatitis B infection. (Kine *et al.*, (2021). Around the world, about 2 billion individuals are asymptomatic or symptomatic of the infection and about 360 million live with the highest degree of infection (Williams, 2006). About 25% of adults who become chronically infected during childhood later die from liver cancer or cirrhosis (scarring of the liver) caused by the chronic infection (European association for the Study of Liver, 2017).

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In 2015, close to one million deaths resulted from hepatitis B virus (HBV) infection, mainly due to the development of cirrhosis and hepatocellular carcinoma (HCC). HBV is 50 to 100 times more infectious than HIV and has constituted an important occupational hazard for health workers as 50 million new cases are diagnosed annually (WHO, 2016).

Different mathematical models have been developed in order to study effectively the mechanics of HBV with possible control measures. It has become an important tool in analyzing the spread and control of infectious diseases. Understanding the transmission characteristics of infectious diseases in a population (communities, regions and countries) in mathematical frame works can lead to better approaches to decreasing the transmission of these diseases (Khatun *et al.*, 2021). Jing & Suzia, 2018 studied the application and Optimal Control for an HBV Model with Vaccination and Treatment as control strategies. Numerical simulations were carried out and it was observed that increasing both the vaccination and treatment rates reduces the populations of both the acutely infected and chronic carriers which eventually leads to the containment of the disease. (Kimbir *et al.*, 2014) presented a mathematical model for the transmission dynamics of hepatitis B virus (HBV) infection incorporating vaccination and treatment as control parameters. The authors concluded that the combination of both vaccination and treatment with the use of a vaccine with a high efficacy is essential in the control of Hepatitis B virus disease. [Jannatun & Podder, 2014) developed a deterministic model to understand the underlying dynamics of HBV infection at population level. Anwarud *et al.*, 2021) proposed a mathematical model to study various stages of HBV besides its transmissibility and incidence rate. Therefore, the authors concluded that in order to eradicate the HBV from the general populace, control effort needed to be intensified. (Muhammad *et al.*, 20018) presented a transmission dynamics of HBV considering the media coverage. The numerical results show that the media coverage campaign, in the vaccination with educational campaign can decrease the infection from the community.

In this study, we formulated a mathematical model for the disease transmission of Hepatitis B virus with the new assumptions that individuals that experience treatment failure from the treated class can either move back to the chronically infected class or precede end stage class. And also individuals who do not have access to the treatment proceed directly to the end stage class from the chronically infected class. As per the literature, until now no one considered yet the transmission dynamics of Hepatitis B with end stage class, and thus according to the authors knowledge this work is a novel one. We extend the dynamics given in Jing & Suzia, 2018 by adding the end stage class due to treatment or lack of access to treatment. We use the standard incidence instead of bilinear in the model formulation. Further, to control and eradicate the severity of HBV disease in the population, we introduce four different time dependent control measures. These control measures are the effective condom use to prevent sexually active population from getting infected to the disease, impact of enhancement in the efficacy of vaccination of newborn babies to protect them from a severe infection, treatment of under treated individuals, and behavioral change (mitigation of some modifiable risk factors such as smoking, obesity) to stop the fast progression to the end stage class. We split the infectious HBV population into four different phases namely the acutely infected class, chronically class, treated class, as well as the end stage class (HCC).

This paper consists of seven sections. Section one deals with the background and some related literature review on Hepatitis B virus. A comprehensive description of the formulated HBV model and its associated parameters, some preliminary investigation and other necessary mathematical analysis of the HBV model are studied in the section two. The equilibrium states, the basic reproduction number and the stability analysis of the model were established in section three. In section four, sensitivity analysis of threshold quantity was investigated to ascertain parameters of the high impact on the reproduction number. Section five looked at the optimal control problem with existence and solution of the optimality system. Numerical simulations and the graphical interpretation along with a brief discussion is presented in Section six. The concluding remarks were presented in the final section.

2. The Hepatitis B Virus Model

2.1 Description of the model

Based on the natural history of HBV disease, we divided the entire population $N(t)$ into six compartments, susceptible individuals, acute infections, chronic carriers, treated patients, and immunized individuals, advanced stage which are denoted by $S(t)$, $I(t)$, $C(t)$, $T(t)$, $R(t)$, $H_c(t)$ respectively. Thus, the total population:
$$N(t) = S(t) + I(t) + C(t) + T(t) + H_c(t) + R(t).$$

The newborns, are assumed to be immunized successfully at rate bw or unsuccessfully at rate $b(1-w)$, with b being the birth rate and w being the successfully immunized proportion. When unsuccessfully immunized, the proportion $b(1-w)vC$ is assumed to enter into the chronic carriers, and the rest $b(1-w)(1-vC)$ stays in the susceptible state, with v denoting the probability of children developing to chronic state born to carrier mothers. We considered both horizontal and vertical transmission mode of HBV virus. The model assumed that proportion of individuals who had treatment failure $(1-\kappa)\varepsilon$ either move to advanced stage state or revert back to chronically infected class at a rate of ε and proportion $(1-\rho)\gamma_2$ assumed to proceed directly to the advanced stage state from the chronically infected class at a rate respectively. Also in the chronic class and advanced stage state, we incorporate disease-induced mortality at the rate δ_c and δ_H respectively.

The virus can also be horizontally transmitted by patients in the classes of I , C , T and H_c , their same transmission rates β respectively, with the assumption that individuals in the chronically infected class and those in the advanced stage state have reduced infectiousness as well as the individuals in the treated class at a rate \mathcal{I}_1 , \mathcal{I}_2 , \mathcal{I}_3 reflecting the fact that the acute patients are the most infectious in the four infected states where the force of infection is given by $\frac{\beta(I + \mathcal{I}_1 C + \mathcal{I}_2 T + \mathcal{I}_3 H_c)}{N}$. The acute infections are assumed to progress at rate γ_1 , splitting in $\eta\gamma_1$ to chronic class and $(1-\eta)\gamma_1$ to the immunized class due to different immune response in host (Jing and Suxia, 2018).

In chronic class, the carriers can clear virus and become immunized at rate γ_2 . The model takes consideration of treatment for both acute and chronic infection and assumes that there are rates of θ_1 and θ_2 in the acute and chronic class, respectively, receiving treatment and then moving to the treated class. Once being treated, some patients can be cured and then move to immunized class at rate σ . However, some people may experience treatment failure and move back to the chronic state at rate ε or proceed to the advanced stage at a rate $(1-\rho)\gamma_2$. In each class, natural death occur a rate μ . The transition from one compartment to other is explained in epidemiological diagram in Figure 1.

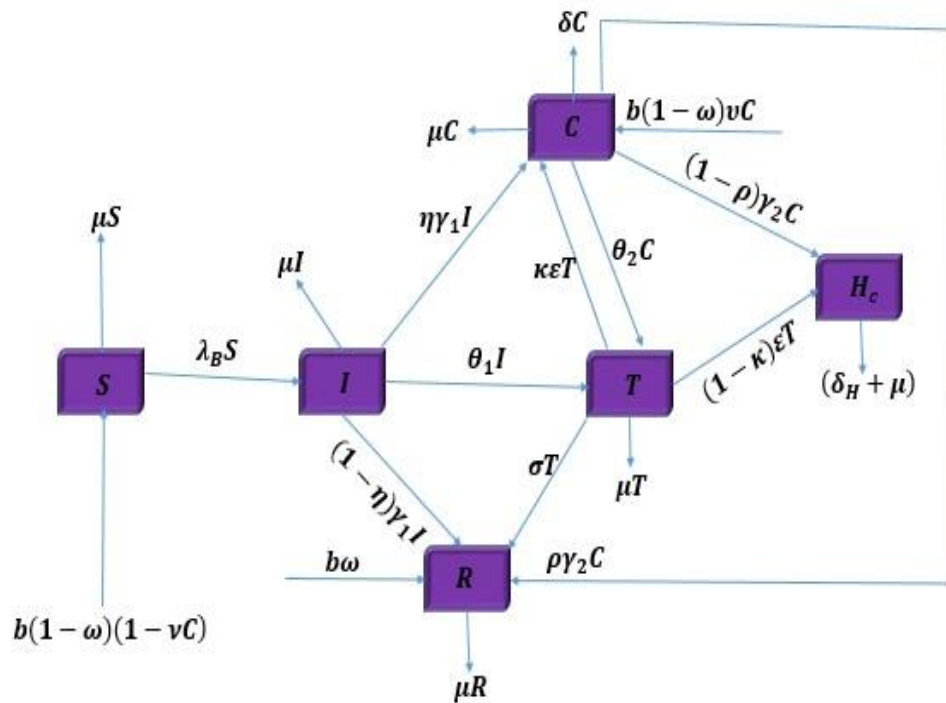


Figure. 1: Compartmental flow diagram

Considering the above assumptions and the compartmental flow diagram in Fig. 1 below, the model is governed by the following system.

2.2 HBV Model equations

$$\left. \begin{aligned}
 \frac{dS}{dt} &= b(1-w)(1-vC) - \lambda S - \mu S \\
 \frac{dI}{dt} &= \lambda S - (\mu + \gamma_1 + \theta_1)I \\
 \frac{dC}{dt} &= \eta\gamma_1 I + b(1-w)vC + \varepsilon T - (\theta_2 + \gamma_2 + \mu + \delta_c)C \\
 \frac{dT(t)}{dt} &= \theta_1 I + \theta_2 C - (\varepsilon + \sigma + \mu)T \\
 \frac{dH_c}{dt} &= (1-\rho)\gamma_2 C + (1-\kappa)\varepsilon T - (\delta_H + \mu)H_c \\
 \frac{dR}{dt} &= bw + (1-\eta)\gamma_1 I + \rho\gamma_2 C + \sigma T - \mu R
 \end{aligned} \right\} \quad (1)$$

with initial conditions

$$S(0) \geq 0, A(0) \geq 0, C(0) \geq 0, T(0) \geq 0, H(0) \geq 0, R(0) \geq 0$$

Table1: Parametric values for the simulation of HBV infection model.

Parameters	Description	Values	Units	Source
b	Birth rate	0.0960	$N_0 * Time^{-1}$	Jing & Suzia, 2018
ω	Proportion of births with successful vaccination		$Time^{-1}$	Zhao <i>et al.</i> , 2000
ν	Average probability of children born to carrier mother developing to chronic state	0.11	$Time^{-1}$	Jing & Suzia, 2018
β	Contact rate	0.8-20.49	$Time^{-1}$	Pang <i>et al.</i> , 2010
θ_1	Treatment rate for acutely infected class	0.0578	$Time^{-1}$	Jing & Suzia, 2018
θ_2	Treatment rate for chronically infected class.	0.0963	$Time^{-1}$	Jing & Suzia, 2018
σ	Recovery rate due to treatment	0.06-0.6	$Time^{-1}$	Zhao <i>et al.</i> , 2000
η	Progression rate from acute to carrier state	0.8850	$Time^{-1}$	Pang <i>et al.</i> , 2010
ε	Rate of treatment failure	0.3	$Time^{-1}$	Jing & Suzia, 2018
μ	Natural death rate.	0.0960	$Time^{-1}$	Jing & Suzia, 2018
δ_c	Disease-induced death rate for the chronic class.	0.01	$Time^{-1}$	Assumed
δ_H	Disease-induced death rate for the advanced stage patients.	0.003	$Time^{-1}$	Assumed
γ_2	Recovery rate of chronically infected due to immune response	0.025	$Time^{-1}$	Zhao <i>et al.</i> , 2000
ϱ_1	Modification parameter for reduced infectiousness in the chronically infected class	0.05	$Time^{-1}$	Assumed
ϱ_2	Modification parameter for reduced infectiousness in the treated infected class	0.05	$Time^{-1}$	Assumed
ϱ_3	Modification parameter for reduced infectiousness in the advanced stage infected class	0.04	$Time^{-1}$	Assumed
κ	Progression rate from treated class to HCC	0.5	$Time^{-1}$	Assumed
ρ	Progression rate to end stage, (HCC)from Chronically infected class	0.5	$Time^{-1}$	Assumed
γ_1	Rate of acutely infected population that recovered naturally due to immune response.	4	$Time^{-1}$	Zhao <i>et al.</i> , 2000

3. Results

3.1 Basic Properties of the Model

The invariant region and positivity of solution of dynamical system (1) is given, coupled with the fact that, the model describes human population. Hence, the study claims the following results.

3.2 Invariant region of the HBV model

Theorem 1: The closet $\Omega = \left(S, I, C, T, H_c, R \right) \in \mathfrak{R}_+^6; N \leq \frac{b}{\mu}$ is positively invariant and attracting with respect

to the model (1)

Proof:

In this section, the region in which the solutions of equations from (1) is bounded is obtained. To do this, the total population of Hepatitis B Virus N was considered, where

$$N = S(t) + I(t) + C(t) + T(t) + H(t) + R(t) \quad (2)$$

Then, differentiating both sides of equation (2) with respect to t leads to

$$\frac{dN}{dt} = \frac{dS(t)}{dt} + \frac{dI(t)}{dt} + \frac{dC(t)}{dt} + \frac{dT(t)}{dt} + \frac{dH_c(t)}{dt} + \frac{dR(t)}{dt}$$

In the absence of disease-induced death, (i.e $\delta_c = \delta_{H_c} = 0$), then equation (2) becomes

$$\frac{dN}{dt} = b - \mu N \quad (3)$$

Solving equation by integrating factor method gives

$$N(t) = \frac{b}{\mu} + \left(N(0) - \frac{b}{\mu} \right) e^{-\mu t} \quad (4)$$

Further, by applying Theorem in [3] on equation (4), it can be observed that $N(t) \rightarrow \left(\frac{b}{\mu} \right)$, as $t \rightarrow \infty$. That is, the

total population size $N(t)$ takes off from the value $N(0)$ at the initial time $t = 0$ and ends up with the bounded value

$\frac{b}{\mu}$ as the time t grows to infinity. Thus, it can be concluded that $N(t)$ is bounded within $0 \leq N(t) \leq \frac{b}{\mu}$. Thus, the

feasible solution set of the system equation (1) of the model enters and remains in the region:

$\Omega = \left(S, I, C, T, H, R \right) \in \mathfrak{R}_+^6; N \leq \frac{b}{\mu}$, Hence, the HBV model is well posed and biologically meaningful.

2.3 Positivity of the solutions for the HBV model

In this section, we show all the solutions of the model equation (1) remain positive for future time if their respective initial values are positive.

Theorem 2: Let the initial data be $\{(S, I, C, T, H_c, R) > 0\} \in \Omega$, then all the solution sets;

$S(t), I(t), C(t), T(t), H_c(t), R(t)$ of the model equations (1) is non-negative for all time, $t > 0$.

Proof:

Positivity is verified separately for each of the model equation (1).

From the first equation, we have

$$\frac{dS}{dt} + (\lambda + \mu)S = b(1-w)(1-vC) \quad (5)$$

Solving equation (5) by method of Integrating Factor method where

$$\text{IF} = e^{\int (\lambda + \mu) dt}$$

Multiplying I.F by both side of equation (5) and integrate gives

$$S(t) \geq S(0)e^{-\int_0^t \lambda(u) du - \mu t} \quad (6)$$

Applying same to method to $I(t)$, $C(t)$, $T(t)$, $H_c(t)$, $R(t)$, it can be shown that the solution is positive for all time t .

3. Existence of Equilibrium

3.1 Hepatitis B Virus Free Equilibrium

The disease free equilibrium of the HBV model is obtained by setting the system of model equation (1) to zero. At disease free equilibrium, there are no infections and recovery. Therefore, the HBV free equilibrium is given by:

$$P_0 = \left\{ \frac{b(1-w)}{\mu}, 0, 0, 0, 0 \right\} \quad (7)$$

3.2 Endemic equilibrium point of the HBV model

The modified HBV endemic equilibrium points are steady-state solution where Hepatitis B Viral infection persists in the population. At endemic equilibrium, $I \neq C \neq 0, T \neq 0, H_c \neq 0$. To establish the existence of endemic equilibria of our HBV model, we solve equations (1) at steady state simultaneously and the resulting endemic equilibrium point is:

$$P_1 = \left(\begin{array}{c} S^* \\ I^* \\ C^* \\ T^* \\ H_c^* \\ R^* \end{array} \right) = \left\{ \begin{array}{l} \frac{b(1-w)[(p_2 - b(1-w)vp_3 - \varepsilon\kappa\theta_2]}{(\lambda_B + \mu)[(p_2 - b(1-w)vp_3 - \varepsilon\kappa\theta_2)p_1 + \lambda_B vb(1-w)(\varepsilon\kappa\theta_1 + \eta\gamma_2 p_3)} \\ \frac{\lambda_B b(1-w)[(p_2 - b(1-w)vp_3 - \varepsilon\kappa\theta_2]}{(p_2 - b(1-w)vp_3 - \varepsilon\kappa\theta_2)[p_1 + vb(1-w)(\varepsilon\kappa\theta_1 + \eta\gamma_2 p_3)\lambda_B + \mu p_1]} \\ \frac{\lambda_B b(1-w)(\varepsilon\kappa\theta_1 + \eta\gamma_2 p_3)}{(p_2 - b(1-w)vp_3 - \varepsilon\kappa\theta_2)[p_1 + vb(1-w)(\varepsilon\kappa\theta_1 + \eta\gamma_2 p_3)\lambda_B + \mu p_1]} \\ \frac{\lambda_B b(1-w)(p_2 - b(1-w)vp_3 - \varepsilon\kappa\theta_2)}{(p_2 - b(1-w)vp_3 - \varepsilon\kappa\theta_2)[p_1 + vb(1-w)(\varepsilon\kappa\theta_1 + \eta\gamma_2 p_3)\lambda_B + \mu p_1]} \\ \frac{\lambda_B b(1-w)[(\eta(1-\kappa)\theta_2 + \kappa(1-\rho)\theta_1)\gamma_2 + (p_2 - b(1-w)v)(1-\kappa)\theta_1 \varepsilon + \eta(1-\rho)\gamma_2^2 p_3]}{[(b(1-w)vp_1\theta_2)\lambda_B - \theta_2\mu p_1]\kappa\varepsilon + ((b(1-w)v\eta\gamma_2 + (p_2 - b(1-w)v)p_1(\lambda_B + \mu) + \eta b(1-w)v\gamma_2\lambda_B)p_4} \\ \frac{bw + (1-\eta)\gamma_1 I^* + \rho\gamma_2 C^* + \sigma T_b}{\mu} \end{array} \right. \quad (8)$$

3.3 Basic Reproduction Number of HBV Model

The concept of the next generation operator method in (Driessche & Watmough, 2002) was employed on the system of differential equations in model equation (1) to compute the basic reproduction number of the HBV infection model. The formulation of this matrix involves classification of all compartments of the model in to two classes: infected and non-infected. That is, the basic reproduction number cannot be determined from the structure of the mathematical model alone but depends on the definition of infected and uninfected compartments. The model equations are rewritten starting with newly infective classes. Then, by the principle of next-generation matrix, we obtained

$$F_{DFE} = \begin{pmatrix} \frac{\beta(1-w)}{\mu} & \frac{\beta\mathcal{G}_1(1-w)}{\mu} & \frac{\beta\mathcal{G}_2(1-w)}{\mu} & \frac{\beta\mathcal{G}_3(1-w)}{\mu} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \quad (9)$$

and

$$V_{DFE} = \begin{pmatrix} p_1 & 0 & 0 & 0 \\ -\eta\gamma_1 & p_2 - b(1-w)v & \kappa\varepsilon & 0 \\ -\theta_1 & -\theta_2 & p_3 & 0 \\ 0 & -(1-\rho)\gamma_2 & -(1-\kappa)\varepsilon & p_4 \end{pmatrix} \quad (10)$$

$$p_1 = (\theta_1 + \gamma_1 + \mu), \quad p_2 = (\theta_2 + \gamma_2 + \mu + \delta_c), \quad p_3 = (\varepsilon + \sigma + \mu), \quad p_4 = (\delta_H + \mu)$$

Thus, the effective reproductive number of system (1) is calculated from the spectral radius $\rho(FV^{-1})$ as:

$$R_o^{HBV} = \frac{\beta(1-w)}{\mu_b} \left(\frac{1}{p_1} + \frac{\mathcal{G}_1(\kappa\varepsilon\theta_1 - p_3\eta\gamma_1)}{p_1(b(1-w)vp_3 - \theta_2\kappa\varepsilon - p_2p_3)} + \frac{\mathcal{G}_2(b(1-w)v\theta_1 - \theta_1p_2 - \theta_2\eta\gamma_1)}{p_1(b(1-w)vp_3 - \theta_2\kappa\varepsilon - p_2p_3)} + \frac{\mathcal{G}_3\beta b(1-w)[(1-\kappa)\varepsilon(b(1-w)v\theta_1 - p_2\theta_1 - \theta_2\eta\gamma_1) + (1-\rho)(\kappa\varepsilon\gamma_2\theta_1 - \gamma_2p_3\eta\gamma_1)]}{p_4p_1(b(1-w)vp_3 - \theta_2\kappa\varepsilon - p_2p_3)} \right) \quad (11)$$

$$R_o^{HBV} = R_1 + R_2 + R_3 + R_4$$

where

$$R_1 = \frac{\beta(1-w)}{\mu p_1}$$

$$R_2 = \frac{\beta b(1-w)[\mathcal{G}_1(\kappa\varepsilon\theta_1 - p_3\eta\gamma_1)]}{\mu p_1(b(1-w)vp_3 - \theta_2\kappa\varepsilon - p_2p_3)}$$

$$R_3 = \frac{\beta b(1-w)[\mathcal{G}_2(b(1-w)v\theta_1 - \theta_1p_2 - \theta_2\eta\gamma_1)]}{p_1\mu(b(1-w)vp_3 - \theta_2\kappa\varepsilon - p_2p_3)}$$

$$R_4 = \frac{\beta\mathcal{G}_3(1-w)[(1-\kappa)\varepsilon(b(1-w)v\theta_1 - p_2\theta_1 - \theta_2\eta\gamma_1) + (1-\rho)(\kappa\varepsilon\gamma_2\theta_1 - \gamma_2p_3\eta\gamma_1)]}{\mu p_4 p_1(b(1-w)vp_3 - \theta_2\kappa\varepsilon - p_2p_3)}$$

3.4 Local stability of the modified HBV free equilibrium point

To prove the local stability of the HFE, the Jacobian of the proposed model system (1) is used. After that, the Jacobian is used to derive the characteristic equation, from which the eigenvalue result is obtained

Theorem 3: The HBV free equilibrium P_0 point of the model (1) is locally asymptotically stable (LAS) if $R_0^{HBV} < 1$ and unstable if $R_0^{HBV} > 1$.

Proof:

To proof this theorem first we obtained the Jacobian matrix of the model equation (1) at the disease-free equilibrium is given by:

$$J(P_0) = \begin{pmatrix} -\mu & -q_1 & -q_2 & -q_3 & -q_4 \\ 0 & -q_5 & q_2 & q_3 & q_4 \\ 0 & \eta\gamma_1 & -q_6 & \varepsilon & 0 \\ 0 & \theta_1 & \theta_2 & -q_7 & 0 \\ 0 & 0 & q_9 & q_{10} & -q_8 \end{pmatrix} \quad (12)$$

where

$$\left. \begin{aligned} q_1 &= \beta, q_2 = \beta\vartheta_1, \\ q_3 &= \beta\vartheta_2, q_4 = \beta\vartheta_3, \\ q_5 &= p_1, \\ q_6 &= p_2 - b(1-w)v, q_7 = p_3, q_8 = p_4, \\ q_9 &= (1-\rho)\gamma_2, q_{10} = (1-\kappa)\varepsilon \end{aligned} \right\} \quad (13)$$

$$\begin{vmatrix} -a_1 & b_1 & b_2 & b_3 \\ \eta\gamma_1 & -a_2 & \varepsilon & 0 \\ \theta_1 & \theta_2 & -a_3 & 0 \\ 0 & c_1 & c_2 & -a_4 \end{vmatrix} = 0$$

where

$$\left. \begin{aligned} a_1 &= p_1 - \beta, a_2 = p_2 - b(1-w)v, a_3 = p_3, a_4 = p_4 \\ b_1 &= \beta\vartheta_1, b_2 = \beta\vartheta_2, b_3 = \beta\vartheta_3, \\ c_1 &= (1-\rho), c_2 = (1-\kappa) \end{aligned} \right\} \quad (14)$$

The characteristic equation is

$$\lambda^4 + A_1\lambda^3 + A_2\lambda^2 + A_3\lambda + A_4 = 0$$

where

$$\left. \begin{aligned} A_0 &= 1 \\ A_1 &= a_1 + a_2 + a_3 + a_4 \\ A_2 &= a_3(a_2 + a_1) + a_2a_1 - \theta_1b_2 - \theta_2\varepsilon + a_4(a_1 + a_2 + a_3) - b_1\eta\gamma_1 \\ A_3 &= a_3(a_2a_1 - b_1\eta\gamma_1) + \theta_2(a_2\varepsilon - b_2\eta\gamma_1) - (a_2 + a_1)(\theta_1b_2 + \theta_2\varepsilon) + \theta_1(a_1b_2 - b_1\varepsilon) \\ &\quad - a_4(\theta_1b_2 - a_1a_2 - a_3(a_2 + a_1) + \theta_2\varepsilon + b_1\eta\gamma_1) - \theta_1c_2b_3 - c_1b_3\eta\gamma_1 \\ A_4 &= c_1(a_2b_3\eta\gamma_1 - \theta_1b_3\varepsilon + a_1b_3\eta\gamma_1) - (\theta_1c_2b_3 + c_1b_3\eta\gamma_1)(a_1 + a_2 + a_3) + a_4(a_3(a_1a_2 - b_1\eta\gamma_1) \\ &\quad + \theta_2(a_2\varepsilon - b_2\eta\gamma_1) - (a_2 + a_1)(\theta_1b_2 + \theta_2\varepsilon) + \theta_1(a_1b_2 - b_1\varepsilon)) + c_2(\theta_1a_1b_3 + \theta_1a_1b_3 + \theta_1a_3b_3 - \theta_2b_3\eta\gamma_1) \end{aligned} \right\} \quad (15)$$

Applying Routh-Hurwitz criterion which states that all roots of the polynomial (14) have negative real part if and only if the coefficient A_i are positive and the determinant of the matrices $H_i > 0$ for $i = 0, 1, 2, 3, 4$. Therefore, all the eigenvalues of the polynomial (14) have negative real parts, implying that $\lambda_1 < 0$, $\lambda_2 < 0$, $\lambda_3 < 0$, $\lambda_4 < 0$, $\lambda_5 < 0$. since all the values of $\lambda_i < 0$, for $i = 1, 2, 3, 4, 5$. when $R_0^{HBV} < 1$, we conclude that the disease-free equilibrium point is locally asymptotically stable.

3.5 Global stability of the modified HBV free equilibrium point

The global stability of the disease free equilibrium for the model (1) was investigated using the technique implemented in Castillo-Chavez, Feng and Huang (2002): First, the dynamical system (1) must be written in the form:

$$\begin{aligned} \frac{dX}{dt} &= F(X, Z) \\ \frac{dZ}{dt} &= G(X, Z), G(X, 0) = 0 \end{aligned} \quad (16)$$

Here, the component $X = (S, R)$ and $Z = (I, C, T, H_c)$, where $X \in \mathfrak{R}^2$ denotes the uninfected population and $Z \in \mathfrak{R}^4$ denotes the infected population. The disease free equilibrium point of the model is denoted by $P_0 = (X^*, 0)$. The point to be globally asymptotically stable equilibrium for the model provided that $R^{HB} < 1$ and the following conditions must be met:

(H_1): For $\frac{dX}{dt} = F(X, 0)$, X^* is globally asymptotically stable

(H_2): $G(X, Z) = PZ - \hat{G}(X, Z)$, $\hat{G}(X, Z) \geq 0$, is globally asymptotically stable, for $(X, Z) \in \Omega$ where $P = D_z G(X^*, 0)$ is a Metzler matrix (the off-diagonal elements of are non-negative) and Ω is the region where the model make biologically sense. If the model equation met the above two criteria, then the following theorem holds:

Theorem 4: The HBV-free model (1) is globally asymptotically stable provided that $R_0^{HBV} < 1$.

Proof: From system (1), we can have $F(X, Z)$ and $G(X, Z)$, where

$$\frac{dX}{dt} = F(X, Z) = \begin{bmatrix} b(1-w)(1-vC) - \lambda S - \mu S \\ bw + (1-\eta)\gamma_1 I + \rho\gamma_2 C + \sigma T - \mu R \end{bmatrix} \quad (17)$$

and

$$\frac{dZ}{dt} = G(X, Z) = \begin{bmatrix} \lambda_B S - (\mu + \gamma_1 + \theta_1) I \\ \eta\gamma_1 I + b(1-w)vC + \kappa\varepsilon T - (\theta_2 + \gamma_2 + \mu + \delta_c) C \\ \theta_1 I + \theta_2 C - (\varepsilon + \sigma + \mu) T \\ (1-\rho)\gamma_2 C + (1-\kappa)\varepsilon T - (\delta_H + \mu) H_c \end{bmatrix} \quad (18)$$

At P_0 ,

$$\frac{dX}{dt}\bigg|_{Z=0} = \begin{pmatrix} (b(1-w) - \mu S) \\ 0 \end{pmatrix} \quad (19)$$

From (6), it is obvious that $X^* = \left(\frac{b(1-w)}{\mu}, 0, 0, 0, 0 \right)$ is Globally Asymptotically Stable. This can be verified from

the solution, namely: $S(t) = \frac{b(1-w)}{\mu} + \left(S(0) - \frac{b(1-w)}{\mu} \right) e^{-\mu t}$ and $R(t) = R(0)e^{-\mu t}$ As $t \rightarrow \infty$, the solutions

$S(t) \rightarrow \frac{b(1-w)}{\mu}$ and $R(t) \rightarrow 0$ implying the global convergence of (6) in Ω and this satisfies condition H_1 .

Next, applying the second condition of the theorem H_2

From H_2 , $G(X, Z) = PZ - \hat{G}(X, Z)$, $\hat{G}(X, Z) \geq 0$, for $(X, Z) \in \Omega$.

Therefore, $\hat{G}(X, Z) = PZ - G(X, Z)$, where P is an $n \times n$ matrix, Z is a column vector and $G(X, Z)$ is a column vector formed from the infectious compartments.

We already know that

$$G(X, Z) = \begin{pmatrix} G_1(X, Z) \\ G_2(X, Z) \\ G_3(X, Z) \\ G_4(X, Z) \end{pmatrix} = \begin{pmatrix} \lambda S - (\mu + \gamma_1 + \theta_1)I \\ \eta\gamma_1 I + b(1-w)vC + \kappa\varepsilon T - (\theta_2 + \gamma_2 + \mu + \delta_c)C \\ \theta_1 I + \theta_2 C - (\varepsilon + \sigma + \mu)T \\ (1-\rho)\gamma_2 C + (1-\kappa)\varepsilon T - (\delta_H + \mu)H_c \end{pmatrix} \quad (20)$$

Now let compute P from infected compartments in the model we have:

$$P = \begin{pmatrix} \beta - p_1 & \beta\vartheta_1 & \beta\vartheta_2 & \beta\vartheta_3 \\ \eta\gamma_1 & b(1-w)v - p_2 & \kappa\varepsilon & 0 \\ \theta_1 & \theta_2 & -p_3 & 0 \\ 0 & (1-\rho)\gamma_2 & (1-\kappa)\varepsilon & -p_4 \end{pmatrix} \quad (21)$$

Since is P Metzler matrix, i.e. all off diagonal elements are nonnegative

$$PZ = \begin{pmatrix} \beta - p_1 & \beta\vartheta_1 & \beta\vartheta_2 & \beta\vartheta_3 \\ \eta\gamma_1 & b(1-w)v - p_2 & \kappa\varepsilon & 0 \\ \theta_1 & \theta_2 & -p_3 & 0 \\ 0 & (1-\rho)\gamma_2 & (1-\kappa)\varepsilon & -p_4 \end{pmatrix} \begin{pmatrix} A \\ C \\ T \\ H_c \end{pmatrix} \quad (22)$$

Thus, using $\hat{G}(X, Z) = PZ - G(X, Z)$, we obtain

$$\hat{G}(X, Z) = \begin{pmatrix} (\beta + \beta\vartheta_1 + \beta\vartheta_2 + \beta\vartheta_3) \left(1 - \frac{S}{N} \right) \\ 0 \\ 0 \\ 0 \end{pmatrix} \quad (23)$$

Hence, from (13), $\hat{G}_1(X, Z), \hat{G}_2(X, Z), \hat{G}_3(X, Z), \hat{G}_4(X, Z) \geq 0$ If and only if $S \leq N$ Hence, P_0 may be

globally asymptotically stable whenever $R_0^{HBV} < 1$, and the fight against hepatitis B virus may be won if case are kept at bare minimal. This completes the proof.

4. Sensitivity Analysis

It is crucial to investigate how sensitive the HBV model (1) is to changes in each of its parameters in order to identify control strategies that will assist in the lowering of the infection trajectory. In other words, conducting sensitivity analysis will assist in identifying what should be done or ignored in order to stop the spread of the HBV transmission. When a parameter changes, we can use sensitivity indices to calculate the relative change in a state variable. We employ the normalized forward sensitivity index of a variable to a parameter method provided in [4] in order to perform sensitivity analysis. The ratio of relative change in the variable to relative change in the parameter is known as the sensitivity index. The sensitivity index may also be defined using partial derivatives when the variable is a differentiable function of the parameter. Therefore, as stated in [4], the normalized forward sensitivity index (SI) of

a threshold, R_0^{HBV} , that is differentiable with respect to a parameter, x , is defined as: $\Delta_x^{R_0^{HSV}} = \frac{\partial R_0^{HSV}}{\partial x} \times \frac{x}{R_0^{HSV}}$.

The sensitivity of each of the eight parameters $\beta, \varrho_1, \varrho_2, \varrho_3, \kappa, \theta_1, \theta_2, \eta$, are presented in Table 2 is calculated using the effective reproduction number given below

$$R_o^{HBV} = \beta_1 S_0 \left(\frac{1 + \frac{\varrho_1(\kappa\varepsilon\theta_1 - p_3\eta\gamma_1)}{p_1(b(1-w)vp_3 - \theta_2\kappa\varepsilon - p_2p_3)} + \frac{\varrho_2(b(1-w)v\theta_1 - \theta_1p_2 - \theta_2\eta\gamma_1)}{p_1(b(1-w)vp_3 - \theta_2\kappa\varepsilon - p_2p_3)} + \frac{\varrho_3(b(1-w)\varepsilon v(1-\kappa)\theta_1 - \varepsilon(1-\kappa)p_2\theta_1 - \varepsilon(1-\kappa)\theta_2\eta\gamma_1 + \kappa\varepsilon(1-\rho)\gamma_2\theta_1 - (1-\rho)\gamma_2p_3\eta\gamma}{p_4p_1(b(1-w)vp_3 - \theta_2\kappa\varepsilon - p_2p_3)} \right) \quad (24)$$

Positive SI values, as shown in Table 1 reveal that an increase in these parameters values increases R_0^{HBV} , which brings about the infection attacking the population. While the parameters that have negative SI, that is, an increase in these parameters values decrease R_0^{HBV} , and as a result, the infection gradually fades from the population.

Table 2: Sensitivity indices for R_0^{HBV}

Parameter	Baseline values	References	Sensitivity Index	Remarks
β	12.4929	NBS,2016	+1.0000	Positive
ϱ_1	0.6500	Assumed	+0.7510	Positive
ϱ_2	0.5000	Assumed	+0.1661	Positive
ϱ_3	0.4000	Assumed	+0.0220	Positive
θ_1	0.5780	Jing & Suxia, 2018	-0.0098	Negative
θ_2	0.0936	Zhao <i>et al.</i> , (2000)	-0.1143	Negative
γ_1	4.0000	Zhao <i>et al.</i> , (2000)	+0.9294	Positive
γ_2	0.0250	Zhao <i>et al.</i> , (2000)	+0.0064	Positive
σ	0.0600	Jing & Suxia, (2018)	-0.0172	Negative
ρ	0.5000	Assumed	0.0064	Positive
κ	0.5000	Assumed	0.0733	Positive
η	0.8850	Pang <i>et al.</i> , (2010)	+0.9294	Positive
ω	0.65	Jing & Suxia, (2018)	-0.1642	Negative
ν	0.1100	Zhao <i>et al.</i> , (2000)	0.0096	Positive

5. Formulation of optimality control problem

The control of infectious disease outbreaks is a huge challenge to the health authorities. It is not easy to adopt appropriate control interventions to eradicate or minimize infection in a community. The optimal control analysis provides a clue to set an appropriate optimal control which can be effectively implemented against the spread of disease. This section is devoted to developing an optimal control problem for the HBV model (1) by considering four control variables. The control measures are adopted under the consideration of the sensitivity results carried out in the previous section. Based on the sensitivity indices, the first effective intervention which will be helpful to minimize the HBV incidence is to reduce the probability of transmission per contact of the infected people with the susceptible population. This intervention will reduce the effective contacts rates ($\beta, \mathcal{G}_1, \mathcal{G}_2, \mathcal{G}_3$). The second effective control measure or variable is to enhance the vaccine efficacy (i.e., to increase w). The third control variable taken in consideration in this study is to ensure or maximize the treatment of HBV infected people (i.e., to increase θ_1, θ_2). Finally, the fourth control is educating people about some modifiable risk factors such as obesity, alcoholic intake etc). To formulate the mathematical control model in order to analyze the impact of all the aforementioned control measures on the disease dynamics, we added four time-dependent variables in the HBV model (1). These control variables are denoted by $u_1(t), u_2(t), u_3(t)$ and $u_4(t)$ were used for effective condom use, the enhancement of vaccination efficacy of the newborn babies, to enhance the treatment control and behavioral change respectively. Thus, the control system is described as follows:

$$\left. \begin{aligned} \frac{dS}{dt} &= b(1-u_2w)(1-vC) - \frac{(1-u_1)(\beta I + \beta \mathcal{G}_1 C + \beta \mathcal{G}_2 T + \beta \mathcal{G}_3 H_c)S}{N} - \mu S \\ \frac{dI}{dt} &= \frac{(1-u_1)(\beta I + \beta \mathcal{G}_1 C + \beta \mathcal{G}_2 T + \beta \mathcal{G}_3 H_c)S}{N} - (\mu + \gamma_1 + u_3\theta_1)I \\ \frac{dC}{dt} &= \eta\gamma_1 I + b(1-u_2w)vC + \kappa\varepsilon T - u_3\theta_2 C - (1-u_4)(1-\rho)\gamma_2 C - (\mu + \delta_c)C \\ \frac{dT(t)}{dt} &= u_3\theta_1 I + u_3\theta_2 C - \kappa\varepsilon T - (1-u_4)(1-\kappa)\varepsilon T - (\sigma + \mu)T_b \\ \frac{dH_c}{dt} &= (1-u_4)(1-\rho)\gamma_2 C + (1-u_4)(1-\kappa)\varepsilon T - (\delta_H + \mu)H_c \\ \frac{dR}{dt} &= u_2bw + (1-\eta)\gamma_1 I + \rho\gamma_2 C + \sigma T - \mu R \end{aligned} \right\} \quad (25)$$

with initial conditions: $S(0) = S_0, I(0) = I_0, C(0) = C_0, T(0) = T_0, H_c(0) = H_{c0}, R(0) = R_0$

the objective functional is:

$$J = \min_{u_i} \int_0^{T_f} \left[(C_1 I_A + C_2 I_C + C_3 I_T + C_4 I_{H_c}) + \frac{1}{2} X_1 u_1 + \frac{1}{2} X_2 u_2 + \frac{1}{2} X_3 u_3 + \frac{1}{2} X_4 u_4 \right] dt \quad (26)$$

Subject to (25) with the respective balancing cost factors constants shown by $C_i, X_j, i = 1, 2, 3, 4. j = 1, 2, 3, 4.$

where T_f account for the final time and the term $\frac{1}{2} X_i u_i^2$ measures the cost of intervention strategies.

The main focus is to evaluate the optimal controls u_1, u_2, u_3 and u_4 such that

$$J(u_1^*, u_2^*, u_3^*, u_4^*) = \min \{ J(u_1, u_2, u_3, u_4) \mid (u_1, u_2, u_3, u_4) \in U \} \quad (27)$$

where the control set is shown as follows:

$U = f(u_1, u_2, u_3, u_4)$ such that u_i are measurable with

$\{0 \leq u_1(t) \leq 1, 0 \leq u_4(t) \leq \psi, 0 \leq u_5(t) \leq e, 0 \leq u_6 \leq 1, 0 \leq t \leq T\} : \forall t \in [0, T]$ is the set of admissible control.

5.1 Existence of the control problem

The existence of the optimal control u^* can be established since the integrand in (26) and the right hand side of the optimality control problem (15) denoted by $f = (f_1, f_2, f_3, f_4, f_5)$ are continuously differentiable functions and concave in both (S, I, C, H_c) and $u = (u_1, u_2, u_3, u_4)$.

Now, we utilize the well-known Pontryagin's Maximum Principle [16] in order to investigate the necessary conditions of optimal control in the HBV model. This technique shifts (26) and (25) into a problem of minimizing point-wise the Hamiltonian function H with respect to the optimal controls $u_1(t)$, $u_2(t)$, $u_3(t)$ and $u_4(t)$. Thus, the Hamiltonian function is as follows:

$$\begin{aligned}
 H = & C_1 I_A + C_2 I_C + C_3 I_T + C_4 I_H + \frac{X_1 u_1^2}{2} + \frac{X_2 u_2^2}{2} + \frac{X_3 u_3^2}{2} - \frac{X_4 u_4^2}{2} \\
 & + \lambda_S (b(1-u_4 w)(1-vC) - \frac{(1-u_1)(\beta I + \beta \vartheta_1 C + \beta \vartheta_2 T + \beta \vartheta_3 H_c) S}{N} - \mu S) \\
 & + \lambda_I \left(\frac{(1-u_1)(\beta I + \beta \vartheta_1 C + \beta \vartheta_2 T + \beta \vartheta_3 H_c) S}{N} - (\mu + \gamma_1 + u_3 \theta_1) I \right) \\
 & + \lambda_C (\eta \gamma_1 I + b(1-u_2 w)vC + \kappa \varepsilon T - u_3 \theta_2 C - (1-u_4)(1-\rho)\gamma_2 C - (\mu + \delta_c) C) \\
 & + \lambda_T (u_3 \theta_1 I + u_3 \theta_2 C - \kappa \varepsilon T - (1-u_4)(1-\kappa)\varepsilon T - (\sigma + \mu) T) \\
 & + \lambda_{H_c} ((1-u_4)(1-\rho)\gamma_2 C + (1-u_4)(1-\kappa)\varepsilon T - (\delta_H + \mu) H_c) \\
 & + \lambda_R (u_2 b w + (1-\eta)\gamma_1 I + \rho \gamma_2 C + \sigma T - \mu R)
 \end{aligned} \tag{28}$$

where $\lambda_S, \lambda_I, \lambda_C, \lambda_T, \lambda_{H_c}, \lambda_R$ are the adjoint variable or co-state variable.

Theorem 5: There exist an optimal control set of u_1, u_2, u_3, u_4 and corresponding solution,

$\lambda_S, \lambda_I, \lambda_C, \lambda_T, \lambda_{H_c}, \lambda_R$ that minimize $J_B(u_1, u_2, u_3, u_4)$ over U_B . Furthermore, there exist adjoint functions

$\lambda_S, \lambda_I, \lambda_C, \lambda_T, \lambda_{H_c}, \lambda_R$ satisfying $\frac{d\lambda_i}{dt} = -\frac{dH_B}{d\lambda_i}$ for $i = S, I, C, T, H_c, R$

Thus,

$$\left. \begin{aligned}
 \frac{d\lambda_S}{dt} &= -\frac{\partial H_B}{\partial \lambda_S} = (1-u_1)(\lambda_S - \lambda_I) \frac{(\beta I + \beta \vartheta_1 C + \beta \vartheta_2 T + \beta \vartheta_3 H_c)S}{N} + \mu \lambda_S \\
 \frac{d\lambda_I}{dt} &= -\frac{\partial H_B}{\partial \lambda_I} = -C_1 + (\mu + \gamma_1 + u_5 \theta_1) \lambda_I - \eta \gamma_1 \lambda_C - (1-\eta) \gamma_1 \lambda_R + \frac{\beta S}{N} (\lambda_S - \lambda_I) \\
 \frac{d\lambda_C}{dt} &= -\frac{\partial H_B}{\partial \lambda_C} = -C_2 + u_5 \theta_2 (\lambda_C - \lambda_{T_b}) + \frac{\beta \vartheta_1 S}{N} (\lambda_S - \lambda_I) + (\mu + \delta_c) \lambda_C + b(1-u_4 w) v (\lambda_S - \lambda_C) + (1-u_6)(1-\rho) \gamma_2 (\lambda_C - \lambda_{H_c}) - \rho \gamma_2 \lambda_R \\
 \frac{d\lambda_{T_b}}{dt} &= -\frac{\partial H_B}{\partial \lambda_{T_b}} = -C_3 + \mu \lambda_{T_b} + \kappa \varepsilon (\lambda_{T_b} - \lambda_C) + (1-u_6)(1-\kappa) \varepsilon (\lambda_{T_b} - \lambda_{H_c}) + \sigma (\lambda_{T_b} - \lambda_R) + \frac{\beta \vartheta_2 S}{N} (\lambda_S - \lambda_I) \\
 \frac{d\lambda_{H_c}}{dt} &= -\frac{\partial H_B}{\partial \lambda_{H_c}} = -C_4 + (\delta_H + \mu) \lambda_{H_c} + \frac{\beta \vartheta_3 S}{N} (\lambda_S - \lambda_I) \\
 \frac{d\lambda_R}{dt} &= -\frac{\partial H_B}{\partial \lambda_R} = \mu \lambda_R
 \end{aligned} \right\} \quad (29)$$

with transversality conditions

$$\lambda_S(t_f) = \lambda_I(t_f) = \lambda_C(t_f) = \lambda_{T_b}(t_f) = \lambda_{H_c}(t_f) = \lambda_R(t_f) = 0$$

and the controls $u_1, u_2, u_3,$ and u_4 satisfy the optimality conditions:

$$\left. \begin{aligned}
 u_1^* &= \min \left\{ 1, \max \left(0, \frac{\lambda_b S (\lambda_I - \lambda_S)}{X_1} \right) \right\} \\
 u_2^* &= \min \left\{ 1, \max \left(0, \frac{b w v C (\lambda_C - \lambda_S) + b w (\lambda_S - \lambda_R)}{X_2} \right) \right\} \\
 u_3^* &= \min \left\{ 1, \max \left(0, \frac{\theta_2 C (\lambda_C - \lambda_{T_b}) + \theta_1 I (\lambda_I - \lambda_{T_b})}{X_3} \right) \right\} \\
 u_4^* &= \min \left\{ 1, \max \left(0, \frac{\gamma_2 C (1-\rho) (\lambda_{H_c} - \lambda_C) + \varepsilon T (\kappa - 1) (\lambda_{H_c} - \lambda_{T_b})}{X_4} \right) \right\}
 \end{aligned} \right\} \quad (30)$$

Proof:

The differentiable equations governing the adjoint variables are obtained by differentiating the Hamiltonian function evaluated at the optimal control. Thus the adjoint system is

$$\left. \frac{d\lambda_S}{dt} = -\frac{\partial H_B}{\partial S}, \frac{d\lambda_I}{dt} = -\frac{\partial H_B}{\partial I}, \frac{d\lambda_C}{dt} = -\frac{\partial H_B}{\partial C}, \frac{d\lambda_{T_b}}{dt} = -\frac{\partial H_B}{\partial T}, \frac{d\lambda_{H_c}}{dt} = -\frac{\partial H_B}{\partial H_c}, \frac{d\lambda_R}{dt} = -\frac{\partial H_B}{\partial R} \right\} \quad (31)$$

$$\begin{aligned}
\frac{d\lambda_S}{dt} &= -\frac{\partial H_B}{\partial \lambda_S} = (1-u_1)(\lambda_S - \lambda_I)\lambda_b + \mu\lambda_S \\
\frac{d\lambda_I}{dt} &= -\frac{\partial H_B}{\partial \lambda_I} = -C_1 + (\mu + \gamma_1 + u_3\theta_1)\lambda_I - \eta\gamma_1\lambda_C - (1-\eta)\gamma_1\lambda_R + \frac{\beta S}{N}(\lambda_S - \lambda_I) \\
\frac{d\lambda_C}{dt} &= -\frac{\partial H_B}{\partial \lambda_C} = -C_2 + [(u_3\theta_2 + \gamma_2 + \mu + \delta_c) - b(1-u_2)v]\lambda_C - u_3\theta_2\lambda_T - (1-u_4)(1-\rho)\gamma_2\lambda_{H_c} - \rho\gamma_2\lambda_R + \frac{\beta\theta_1 S}{N}(\lambda_S - \lambda_C) \\
\frac{d\lambda_T}{dt} &= -\frac{\partial H_B}{\partial \lambda_T} = -C_3 + (\varepsilon + \sigma + \mu)\lambda_T - \kappa\varepsilon\lambda_C - (1-u_4)(1-\kappa)\varepsilon\lambda_{H_c} - \sigma T\lambda_R + \frac{\beta\theta_2 S}{N}(\lambda_S - \lambda_T) \\
\frac{d\lambda_{H_c}}{dt} &= -\frac{\partial H_B}{\partial \lambda_{H_c}} = -C_4 + (\delta_H + \mu)\lambda_{H_c} + \frac{\beta\theta_3 S}{N}(\lambda_S - \lambda_{H_c}) \\
\frac{d\lambda_R}{dt} &= -\frac{\partial H_B}{\partial \lambda_R} = \mu\lambda_R
\end{aligned} \tag{32}$$

with transversality conditions

$$\lambda_S(t_f) = \lambda_I(t_f) = \lambda_C(t_f) = \lambda_T(t_f) = \lambda_{H_c}(t_f) = \lambda_R(t_f) = 0$$

Hence, solving $\frac{\partial H}{\partial u_1}$, $\frac{\partial H}{\partial u_2}$, $\frac{\partial H}{\partial u_3}$, and $\frac{\partial H}{\partial u_4}$ and equating the result to zero gives the characterization of the controls:

$$\begin{aligned}
0 &= \frac{du_1}{dt} = X_1 u_1 - \lambda_b S \lambda_S + \lambda_b S \lambda_I \\
u_1^* &= \frac{\lambda_b S (\lambda_I - \lambda_S)}{X_1} \\
0 &= \frac{du_2}{dt} = X_2 u_2 + bw(vC - 1)\lambda_S - bwvC\lambda_C + bw\lambda_R \\
u_2^* &= \frac{bwvC(\lambda_C - \lambda_S) + bw(\lambda_S - \lambda_R)}{X_2} \\
0 &= \frac{du_3}{dt} = X_3 u_3 - \theta_2 C \lambda_C - \theta_1 I \lambda_T - \theta_2 C \lambda_T \\
u_3^* &= \frac{\theta_2 C (\lambda_C + \lambda_T) + \theta_1 I (\lambda_I - \lambda_T)}{X_3} \\
0 &= \frac{du_4}{dt} = -X_4 u_4 + \gamma_2 C (1-\rho)\lambda_C - \gamma_2 C (1-\rho)\lambda_{H_c} + \varepsilon T_b (1-\kappa)\lambda_T - \varepsilon T_b (1-\kappa)\lambda_{H_c} \\
u_4^* &= \frac{\gamma_2 C (1-\rho)(\lambda_C - \lambda_{H_c}) + \varepsilon T_b (1-\kappa)(\lambda_T - \lambda_{H_c})}{X_4}
\end{aligned} \tag{32}$$

By standard control arguments involving the bound on the controls, it was concluded that

$$u_i = \begin{cases} 0 & \text{if } u_i \leq 0 \\ u_i & \text{if } 0 < u_i < 1 \\ 1 & \text{if } u_i \geq 1 \end{cases}, \quad \text{For } i \in 1, 2, 3, 4 \text{ and} \quad (33)$$

where

$$\left. \begin{aligned} u_1^* &= \frac{\lambda S(\lambda_I - \lambda_S)}{X_1} \\ u_2^* &= \frac{b w v C(\lambda_C - \lambda_S) + b w(\lambda_S - \lambda_R)}{X_2} \\ u_3^* &= \frac{\theta_2 C(\lambda_C - \lambda_T) + \theta_1 I(\lambda_I - \lambda_T)}{X_3} \\ u_4^* &= \frac{\gamma_2 C(1 - \rho)(\lambda_{H_c} - \lambda_C) + \varepsilon T(1 - \kappa)(\lambda_{H_c} - \lambda_T)}{X_4} \end{aligned} \right\} \quad (34)$$

6. Numerical simulations

The numerical simulations of the proposed HBV model with controls (25) and without controls (1) were analyzed in order to illustrate the usefulness of the controls considered. A numerical technique in (Abulfatai *et al.*, 2023a; Abulfatai *et al.*, 2023b; Abulfatai *et al.*, 2023c; Abulfatai *et al.*, 2021a, Abulfatai *et al.*, 2021b, Abulfatai *et al.*, 2021c) is used to find out the model's optimal solution. The values of the parameters used in the simulation procedure are given in Table 2. The time level in the graphical interpretation is taken in years. The weight as well as balancing constants are considered as $C_1 = 0.01$, $C_1 = 0.05$, $C_1 = 0.05$, $C_1 = 0.04$, $X_1 = 2.0$, $X_2 = 1.7$, $X_3 = 2.5$, $X_4 = 2.7$. In Figures 1-5, the dynamics of the different population classes in with the implication of no control measures are demonstrated by dashed blue curves whereas the red bold curves showed the population behavior with control variables. In the following, using different set of the said four control variables, we studied five different strategies for the eradication of HBV infection. The influence and effectiveness of each case on the disease eradication are depicted graphically. Disease aversion was also calculated for the infectious state variables and the result presented in Tables 1-5

Control strategies A: Effective condom use, HBV vaccination and HBV treatment

We start by the first the strategy by making the control $u_4 = 0$ (i. e., behavioral change) and use the HBV effective condom use, the HBV vaccination and treatment control measures, i.e ($u_1 \neq 0, u_2 \neq 0, u_3 \neq 0$) and provide the results graphically and the table of aversion follows. The sub-graphs (ah) of Fig. 3 demonstrate the graphical impact of the first strategy on HBV dynamics. It is clear that using this set of controls, the acute, chronic and individuals under treatment as well as individuals in the HCC state are decreased significantly as this is further numerically presented in Table 1. Figure. 3(e) shows the corresponding control profile of the current strategy. The graphical results of this case reveal that the combined application of u_1, u_2 and u_3 and is useful and can be used to minimize the HBV infection from the community.

Table 2 shows the results of the infected variables in the system without control, with controls and the infection aversion as a result of the use of effective condom, control on HBV vaccination and control on the HBV treatment are implemented. This strategy when implemented could put down about 8694 potentials infective from the population.

Control Strategy B: Effective condom use, HBV vaccination and behavioral change.

This strategy demonstrates the impact of the implementation of effective condom use, HBV vaccination coupled with behavioral change control which is denoted by u_1, u_2 and u_4 respectively, on the dynamics of HBV infection. For this purpose, the HBV treatment control is taken as zero (that is, $u_3 = 0$) in the control model (25), the desired numerical results graphically are given in Figure. 3. The effect of effective condom use, HBV vaccination coupled with behavioral change control on different population classes are shown graphically in Figure 4 with sub-plots (a-e). It can be observed that the overall effect of strategy B is seems to be less in comparison to strategy A. this can further be noticed in the number of infections presented in Table 4. Accordingly, about 8181 cases of infection were averted by the implementation of strategy B. The corresponding control profile have been given in Figure 4(e).

Control Strategy C: Effective condom use, HBV treatment and behavioral change.

In this case, we put the HBV vaccination control equals to zero i.e., $u_2 = 0$ and consider the effective condom use, isolation coupled with the vaccination control to illustrate the dynamics of the HBV infection. Figure. 5(a-e) shows the impact of this strategy graphically, whereas the sub-plot 5(e) demonstrates the corresponding control profile of this case. In comparison to previous strategies, one can easily judge that without HBV vaccination there is low performance notably as can be seen in table of infection aversion presented in Table 5. Implementation of this strategy averted about 6706 So, this third strategy is not much effective to control the disease. This indicated that vaccination as a means of controlling HBV is of paramount importance.

Control Strategy D: HBV vaccination and HBV Treatment and behavioral change.

This strategy implemented the dynamics of infection using HBV vaccination, HBV treatment and behavioral change while setting the effective condom use to zero. i.e $u_1 = 0$. Figure. 6(a-e) shows the impact of this strategy graphically, whereas the sub-plot 6(e) demonstrates the corresponding control profile of this case. In comparison to previous strategies, one can easily judge that without effective condom use there is low performance notably as can be seen in table of infection aversion presented in Table 6. Implementation of this strategy averted about 4473 So, this third strategy is not much effective to control the disease. This indicated that effective condom use as a means of controlling HBV is very vital.

Control Strategy E: Effective condom use, HBV vaccination and HBV treatment and behavioral change.

In the previous cases, we analyzed the effects of different sets of controls and provided the dynamics of population classes graphically. We observed that these strategies are useful for some classes instead of all individuals. Finally, in this case, we consider all the four controls at the same time, that is $u_1 \neq 0, u_2 \neq 0, u_3 \neq 0, u_4 \neq 0$. The graphical solution related to this strategy is shown in Fig. 7, while the corresponding control profile is depicted in 7(e). From the graphical interpretations of all the five set of controls discussed cases, one can easily interpret that this fourth strategy is the best option in order to the elimination of HBV infection in the community. This can further be seen at glance from the graphs as well as from the table of aversion presented in Table 7. It was discovered that the control strategy averted about 11912 cases of infection when implemented.

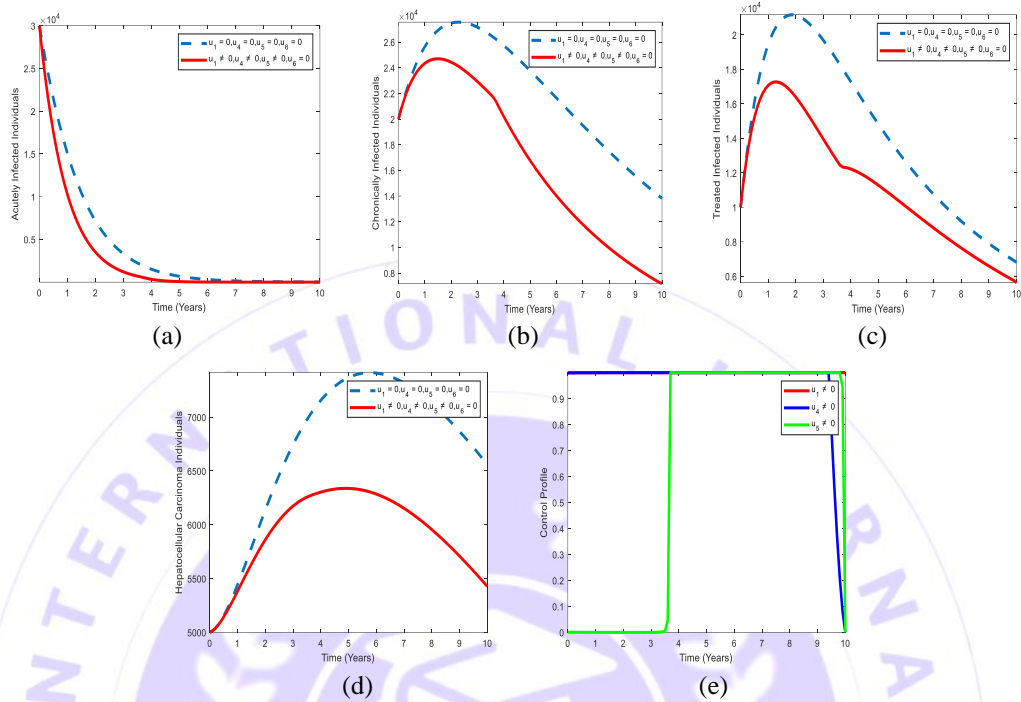
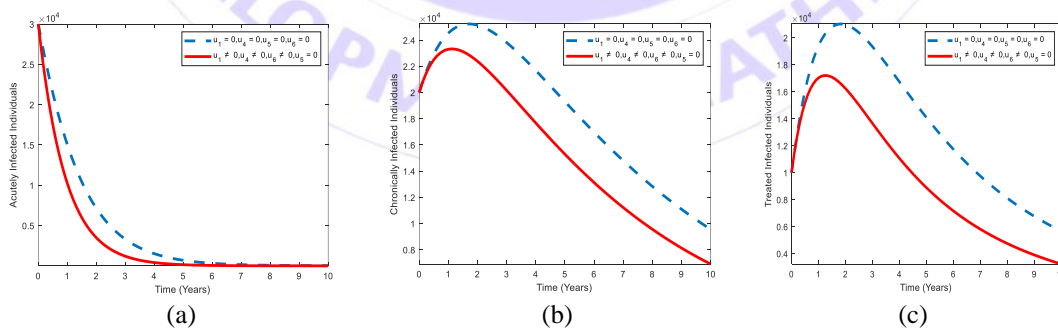


Figure 1. The effective condom use, HBV vaccination and HBV treatment.

Table 2: HBV aversion when the effective condom use, HBV vaccination and HBV treatment are implemented.

Variables	Without Control	With Control Strategy E	Infection Averted
I	16.3625	0.0171	16.3454
C	13812	7182.4	6629.6
T	6816.2	5631.4	1184.8
H_c	6559.7	5426.9	1132.8
TIA			8964



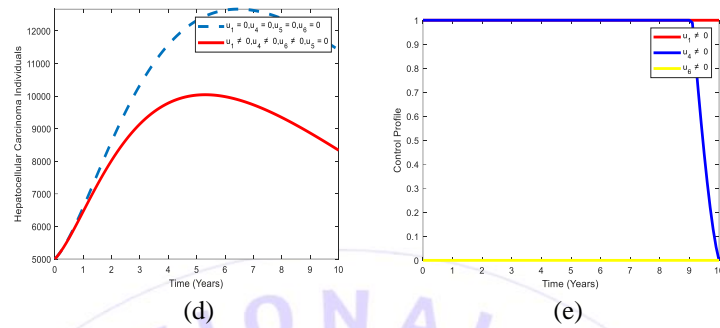


Figure 2. The Effective Condom use, HBV Vaccination and Behavioral change.

Table 3 HBV Aversion when the Effective condom use, HBV Treatment and Behavioral change is implemented.

Variables	Without Control	With Control Strategy B	Infection Averted
I	16.7386	0.6498	16.0888
C	9559.9	6906.9	2653
T	5662.1	3225.4	2436.7
H_c	11414	8338.4	3075.6
TIA			8181

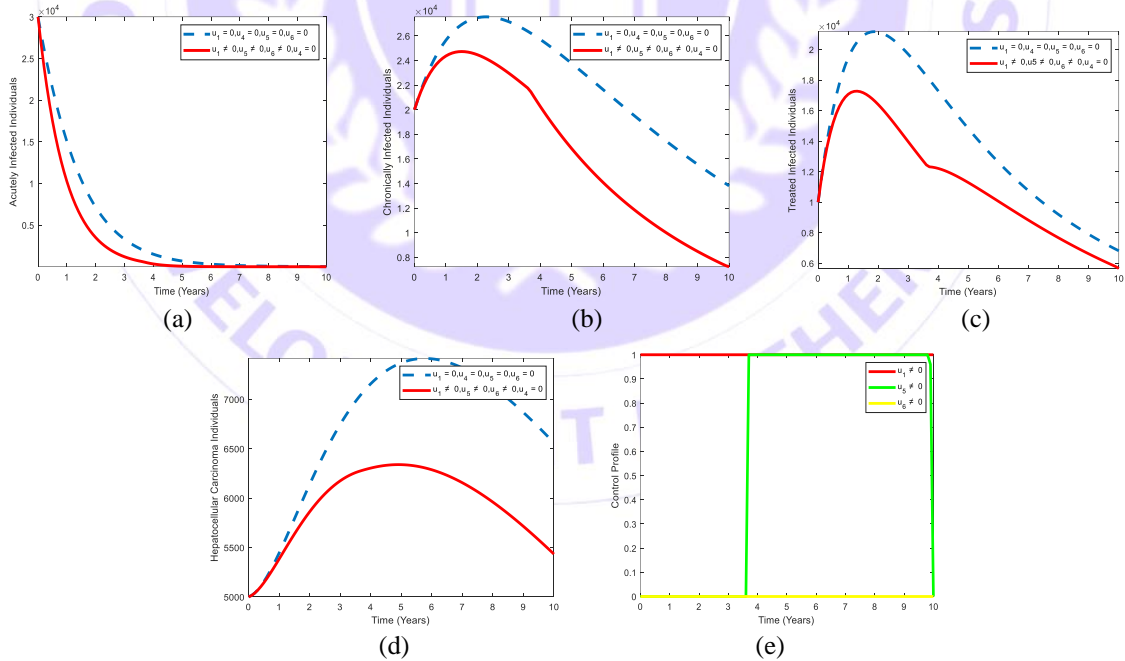


Figure 5. The effective condom use, HBV treatment and behavioral change

Table 4 HBV aversion when the effective condom use, HBV treatment and behavioral change are implemented.

Variables	Without Control	With Control Strategy C	Infection Averted
I	16.8547	0.0157	16.8390
C	8268.2	3960.9	2653
T	5296.7	3974.5	1322.2
H_c	12893	10152	2714
TIA			6706

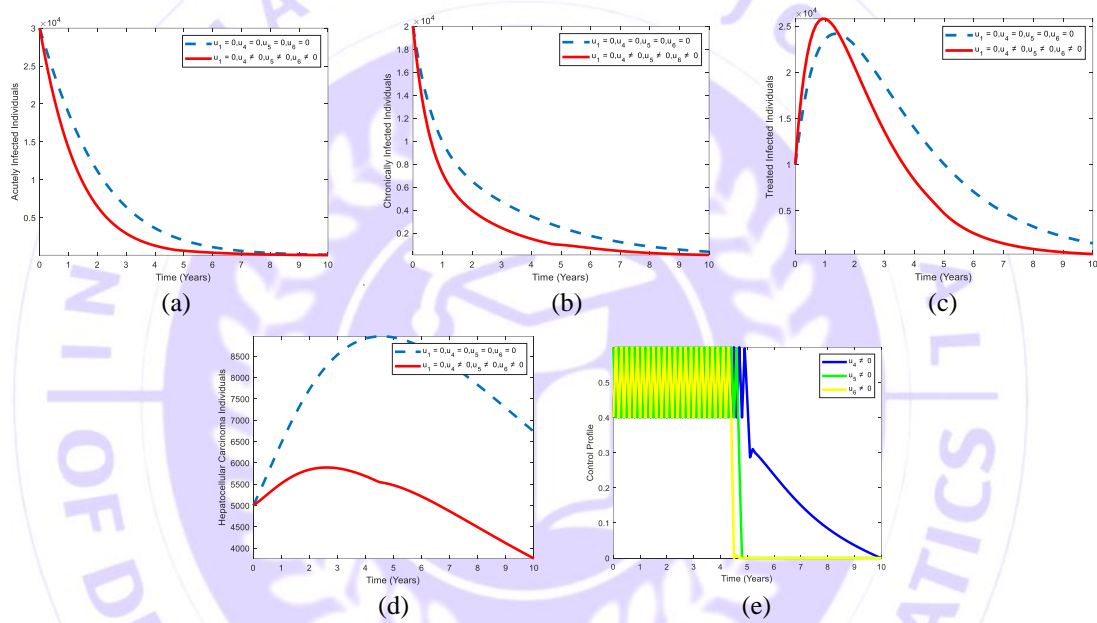


Figure 6. HBV vaccination, HBV treatment and behavioral change.

Table 5: HBV aversion when HBV vaccination, HBV treatment and behavioral change are implemented.

Variables	Without Control	With Control Strategy D	Infection Averted
I	105.7158	51.9479	53.7679
C	372.1629	92.8979	279.265
T	1457.5	289.0761	1168.4239
H_c	6729.2	3757.2	2972
TIA			4473

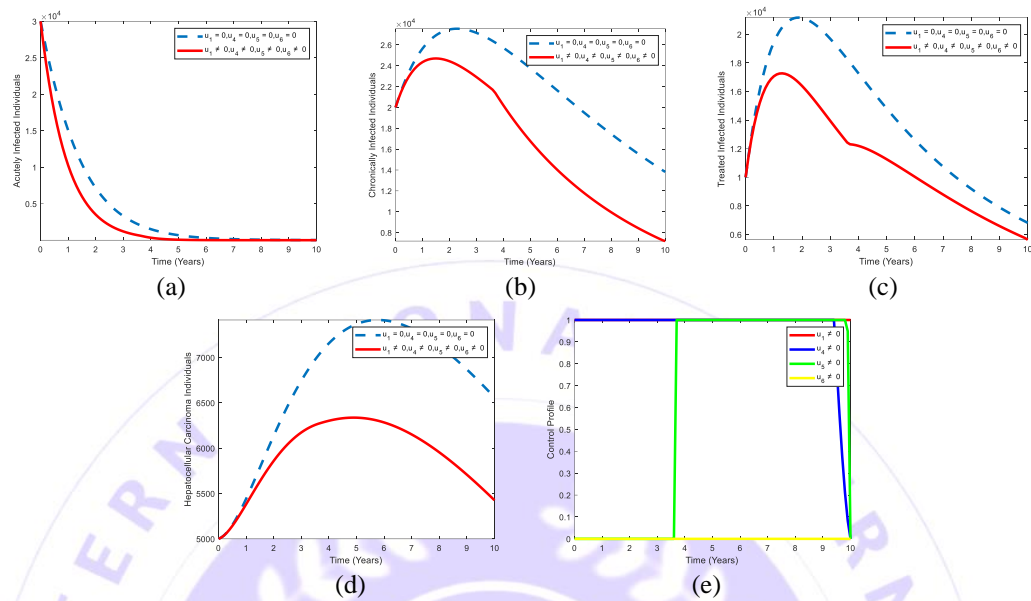


Figure 7. The effective condom use, HBV vaccination, HBV treatment and behavioral change

Table 6: HBV aversion when the effective condom use, HBV vaccination and HBV treatment and behavioral change are implemented.

Variables	Without Control	With Control Strategy E	Infection Averted
I	157.2996	1.4542	155
C	14469	7488	6981
T	8324.4	5606.2	2718.2
H_c	7504.8	5446.7	2058.1
TIA			11912

7. Conclusion

In this study, mathematical model for the dynamic of Hepatitis B virus infection was developed taking into cognizance the effect of rate of progression to the end stage (cirrhosis and HCC) by individuals who experience treatment failure in the treatment class and chronically infected class. In order to track the transmission of these diseases, the basic reproduction number which determined the rate of new secondary infection was computed and the disease-free equilibrium point was investigated and proven to be locally and globally asymptotically stable when the basic reproduction number is less than unity. Sensitivity analysis shows the impact of the parameters on the reproduction number, that, raising one of the parameters with positive indices will increase the risk of the disease outbreak and raising parameters with negative indices will reduce the disease outbreak. Numerical simulation shows the reduction of the disease spread when the control strategies were implemented. The best strategy to implement to help eradicate HBV disease in the system is strategy E which is the combination of effective condom use, HBV

vaccination, HBV Treatment and Behavioral change as shown in figure 7.

References

- Abdulfatai Atte Momoh, Yohanna Afiniki, Abubakar Audu and Dione Dethie (2023a). Curtailing the Spread of Typhoid Fever: An Optimal Control Approach. *Results in Control and Optimization*. <https://doi.org/10.1016/j.rico.2023.100326> .
- Abdulfatai Atte Momoh, Dione Dethie, Nafisa Sulaiman Isah, Washachi Jacob Dekera, James A. Adewale and Ali Inalegwu Michael (2023b). Mathematical Modeling and Optimal Control of a Vector-Borne Rice Yellow Mottle Virus Disease. *International Journal of Dynamics and Control*.. <https://doi.org/10.1007/s40435-023-01188-4>.
- Abdulfatai Atte Momoh, Abubakar Audu, Dione Dethie, and Ali Inalegwu Michael (2023c). On the Control of Intervention Strategies for Hepatitis B Model. *Abstract and Applied Analysis*. (Hindawi). Article ID 8255686. <https://doi.org/10.1155/2023/8255686>
- Abdulfatai Atte Momoh**, Abdullahi Alhassan, M. O. Ibrahim and S. A. Amoo (2021a). Curtailing the Spread of Drug-abuse and Violence Co-menace: An Optimal Control Approach. *Alexandria Engineering Journal*. <https://doi.org/10.1016/j.aej.2021.10.002>.
- Abdulfatai Atte Momoh**, Yusuf Bala, Dekera Jacob Washachi and Dione Dethie (2021b). Mathematical Analysis and optimal Control Interventions for Sex Structured Syphilis Model with Three Stages of Infection and Loss of Immunity. *Advances in Difference Equations*. 2021-285. <https://doi.org/10.1186/s13662-021-03432-7>.
- Abdulfatai Atte Momoh**, Harrisu Abdullahi, Nurudeen G. A. Abimbola and Ali I. Michael. (2021c). Modelling, Optimal Control of Intervention Strategies and Cost Effectiveness Analysis for a Buruli-Ulcer Model. *Alexandria Engineering Journal*. 60, 2245-2264.
- Aja R.O, Omale D and Mbah, G.C.E (2021) A Mathematical Model On the control and Simulation of Hepatitis B Virus (Hbv) Infection Transmission Dynamics in a Population. *Abacus (Mathematics Science Series)*: 48(2)
- Anwarud, D., Yongjin, L. I. and Ali, S.M. (2021) The Complex Dynamics of Hepatitis B Infected Individuals with Optimal Control. *J Syst Sci Complex*, 34: 1301–132.
- Birkhoff, G and Rota G. C. (1989) *Ordinary differential equation*, John Wiley and sons, New York, N Y, USA, USA 4th edition.
- Blower, M. and Dowlatabadi, H. (1994) “Sensitivity and Uncertainty Analysis of Complex Models of Disease Transmission: an HIV Model as an Example,” *International Statistical Institute, Great Britain*, vol. 62, pp. 229–243
- Brauer, F. (2004) Backward bifurcations in simple vaccination models. *J. Math. Anal. Appl.*, 298, 418–431.
- Carr, J. (1981) *Applications of Centre Manifold Theory*. New York: Springer.
- Centre for Disease Control and Prevention (2022) Genital Herpes-CDC Fact Detailed Sheet. <https://www.cdc.gov/ng/std/herpes/stdfactherpesdetailed.htm>. Retrieved January, 2022.
- Castillo-Chavez, C., Feng, Z., and Huang, W. (2002). On the Computation of and its Role on Global Stability, *Mathematical Approaches for Emerging and Reemerging Infectious Diseases*, 125,229-250.

<https://doi.org/10.1007/978-1-4757-3667-0-13>

Driessche, P. V. and Watmough, J. (2002) "Reproduction numbers and sub-threshold endemic equilibria for Compartmental models of disease transmission," *Mathematical Biosciences*, vol. 180, no. 1-2, pp. 29–48.

European Association for the Study of the Liver. (2017) EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. *Journal of Hepatology*, 67(2), 370–398. <https://doi.org/10.1016/j.jhep.2017.03.021>

Hussam A., Mohammad A. Safi, Mahmoud H. D., Bashir A., Saif U., Muhammad A. K., Syed Azhar Ali Shah (2020) optimal control analysis of hepatitis B virus with treatment and vaccination.

Jannatun, N. and Podder, C.N. (2014) A Mathematical Study on the Vaccination Impact on the Disease Dynamics of HBV. *IOSR Journal of Mathematics (IOSR-JM)* 10(6);26-44, e-ISSN: 2278-5728.

Jing Z, and Suxia Z. (2018) Application and optimal control for an HBV model with vaccination and treatment. *Discrete Dyn. Nat. Soc.* (2018), 2076983

Kimbir, A.R, Aboiyar, T. Abu, O. and Onah, E.S. (2014) Simulation of A Mathematical Model of Hepatitis B Virus Transmission Dynamics in The Presence of Vaccination and Treatment. *Mathematical Theory and Modeling*: 4(12).

Khatun, Z., Islam, S., and Ghosh, U. (2021) Mathematical modeling of hepatitis B virus infection incorporating immune responses. *Sensors International*.

Kinfe, H. E., Sendo, G., and Gebremedhin, K. B. "Prevalence of hepatitis B virus infection and factors associated with hepatitis B virus infection among pregnant women presented to antenatal care clinics at Adigrat General Hospital in Northern Ethiopia," *Health*, vol. 13.

Muhammad, A.K., Saeed, I., & Zaman, G., (2018) Media coverage campaign in Hepatitis B transmission model. *Applied mathematics and Computation*, Vol.331, 378-393.

Pang, J. Cui, J. A., and Zhou, X. (2010). Dynamical Behavior of a Hepatitis B Virus Transmission Model with Vaccination. *Journal of Theoretical Biology*, 265(4), 572–578. <https://doi.org/10.1016/j.jtbi.2010.05.038>

Pontryagin, L.S., Boltyanskii, V.G., Gamkrelidze, R.V., and Mishchenko, E.F. (1962) *The Mathematical Theory of Optimal Processes*, John Wiley & Sons, London, UK, 1962.

Shaban, N. and Manzo, D. (2016) Hepatitis B Virus Disease: A Mathematical Model for Vertical Transmission with Treatment Strategy. *Mathematical Theory and Modeling*, (6), 2224-5804.

Tilahun, G.T., Makinde, O.D. and Malonza, D. (2017) Modelling and Optimal Control of Typhoid Fever Disease with Cost-Effective Strategies. *Computational and Mathematical Methods in Medicine*, Volume 2017, Article ID 2324518, <https://doi.org/10.1155/2017/2324518>.

Williams R. (2006) Global Challenges In Liver Disease, *Journal of Hepatology*. 2006; 44(3):521–526.

Wendy C. S., Afihene, M., Ally, R. *et al.*, (2017) "Hepatitis b in sub-Saharan Africa: strategies to achieve the 2030 elimination targets," *The Lancet Gastroenterology & Hepatology*, vol. 2, no. 12, pp. 900–909, 2017.

World Health Organization, Hepatitis B. WHO/CDS/CSR/ LYO/2002.2, Hepatitis B, 2002.

World Health Organization (2016) Hepatitis B. WHO. Combating hepatitis B and C to reach elimination by 2030. 20p.2016a.https://apps.who.int/iris/bitstream/handle/10665/206453/WHO_HIV_2016.04_eng.pdf [Accessed 20th September 2022].

World Health Organization, (2022) <https://www.who.int/news-room/fact-sheets/detail/hepatitis-b> [Accessed 20th September 2022]

Zhao S. J., Xu Z.Y., and Lu Y (2000) A mathematical model of hepatitis B virus transmission and its application for vaccination strategy in China, " *International Journal of Epidemiology*, 29(4), pp. 744–752.

