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RESEARCH ARTICLE

The impact of testing and treatment on the dynamics of Hepatitis B virus [version 1; peer review: 2 approved]

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Abstract

Despite the intervention of WHO on vaccination for reducing the spread of Hepatitis B Virus (HBV), there are records of the high prevalence of HBV in some regions. In this paper, a mathematical model was formulated to analyze the acquisition and transmission process of the virus with the view of identifying the possible way of reducing the menace and mitigating the risk of the virus. The models' positivity and boundedness were demonstrated using well-known theorems. Equating the differential equations to zero demonstrates the equilibria of the solutions i.e., the disease-free and endemic equilibrium. The next Generation Matrix method was used to compute the basic reproduction number for the models. Local and global stabilities of the models were shown via linearization and Lyapunov function methods respectively. The importance of testing and treatment on the dynamics of HBV were fully discussed in this paper. It was discovered that testing at the acute stage of the virus and chronic unaware state helps in better management of the virus.

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1. Introduction

Hepatitis is an inflammation/scarring of the liver that contributes to various health complications, including death. It occurs due to an immune system attack by the virus in the liver and damages this vital organ of the body in the process (Ciupe et al., 2014). The hepatitis B virus (HBV) can survive outside the body for at least seven days. If the virus enters the body of someone who is not protected by vaccination during this time, it can still cause infection. The average incubation time for HBV is 75 days, but it can range from 30 to 180 days. Within 30 to 60 days of infection, the virus may be detected, persist, and grow into chronic hepatitis B (CDC, 2019). Hepatitis B is most common in the Western Pacific region with prevalence rate 6.2% and Africa with prevalence rate of 6.1%, with the Americas region (0.7%) having the lowest prevalence (WHO, 2019).

In highly endemic areas, the most common form of transmission of hepatitis B is from mother to child at birth (vertical transmission) or through horizontal route (contact with infected blood), particularly from infected children to uninfected children during the first five years of life. Chronic infection develops in infants infected by their mothers or before the age of five. It is often transmitted through transdermal or mucosal contact of infected persons to infected blood and different body fluids, such as spittle, catamenial, vaginal and spermatic fluids and, to a lesser degree, perspiration, breast milk, tears, and urine. In particular, hepatitis B can be transmitted through sexual contact in unvaccinated men who have sex with men (MSM) and heterosexual people who have multiple sexual partners or have contact with sex workers. However, adult infection contributes to chronic hepatitis in less than 5% of cases. This transmission may similarly ensue when needles and syringes are reused, whether in healthcare settings or among drug users. Furthermore, an infection can occur during medical, surgical, and dental procedures, such as tattooing or using razors and other similar objects contaminated with infected blood (Mpeshe and Nyerere, 2019).

2. Mathematical formulation

Some chronic carriers are unaware of their status and as such transmit the virus unknowingly and also at higher risk of cirrhosis and makes treatment less effective (Niederau, 2014, Mcpherson et al., 2013, Cohen et al., 2011, Piorkowsky, 2009, Lin et al., 2009, Meffre et al., 2004).

In view of this, this model is developed to factor the aforementioned set of people. In the model, the population is divided into the following different groups: the susceptible, the acute, the chronic unaware carriers, the chronic aware carriers, the treated chronic aware and the recovered individuals.

The total population at time t, denoted by $N(t)$ is divided into the six subgroups corresponding to different epidemiological status: susceptible individuals $S(t)$, acute $A(t)$, unaware chronically infected $C_u(t)$, aware chronically infected $C_a(t)$, treated $T_c(t)$, and removed/recovered class $R(t)$. The model equation is subject to the initial conditions,

$$S(t) \geq 0, A(t) \geq 0, C_u(t) \geq 0, C_a(t) \geq 0, T_c(t) \geq 0, R(t) \geq 0 \tag{1}$$

Figure 1 represents schematically the epidemiology of HBV infected model. The different disease stages are reproduced by the different circle and the arrows indicate the way individual progress from one stage to the other. It is assumed that at
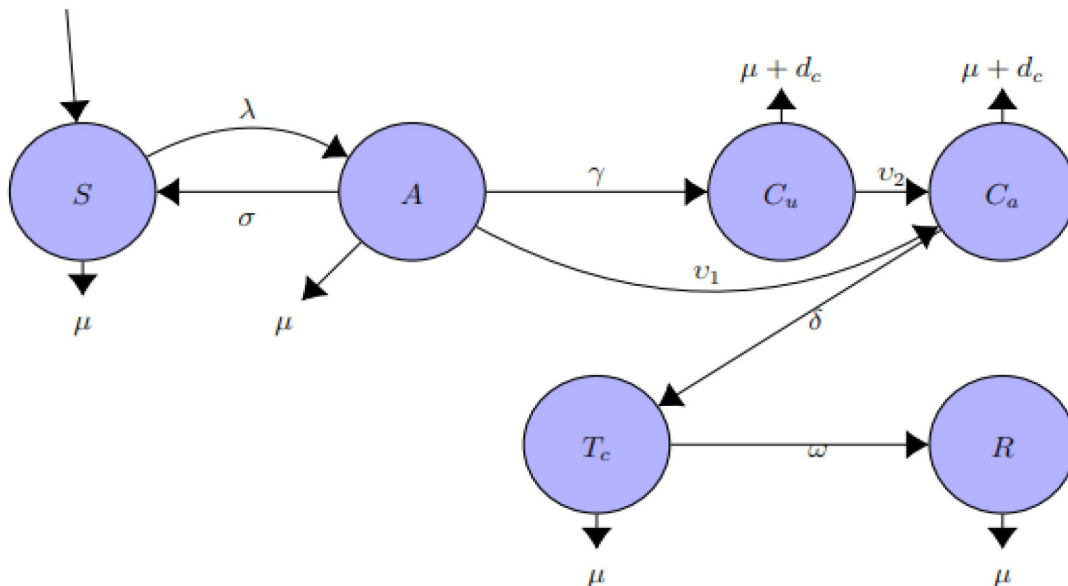
Figure 1. Compartmental flow diagram of HBV model.

time, t, susceptible individuals, S, enter the population at a constant rate, Π. For all classes, individuals die at a constant natural mortality rate, μ. HBV chronically infected individuals ($C_u(t)$, $C_a(t)$) have an additional death rate due to HBV, d_c (Zhang and Zhang (2018)). It is assumed that HBV infected individuals on treatment, $T_c(t)$ do not transmit HBV infection. Susceptible individuals, $S(t)$, may acquire HBV infection when in contact with individuals in A, C_u, and C_a, populace at a rate, λ (force of infection associated with HBV), where

$$\lambda = \frac{\beta(A + \alpha_1 C_u + \alpha_2 C_a)}{N} \tag{2}$$

Parameter β represents the probability that a contact will result in an HBV infection while $\alpha_1, \alpha_2 > 1$ respectively account for modification parameter of chronic HBV-infected individuals.

A proportion of the acute HBV-infected individuals, σ, spontaneously clear the virus, then return to being susceptible. The HBV acutely infected individuals develop to chronic without been aware if no testing at a rate, γ. The acutely infected and chronic unaware individual progress to chronic aware stage with a testing v_1, v_2 respectively and moved to treatment stage after testing at the rate δ. ω is the recovery rate of treated infected individual with full immunity.

These assumptions lead to the system of equations in (3)

$$\frac{dS}{dt} = \Pi - \lambda S + \sigma A - \mu S$$
$$\frac{dA}{dt} = \lambda S - (\sigma + \gamma + v_1)A$$
$$\frac{dC_u}{dt} = \gamma A - (v_2 + \mu + d_c)C_u$$
$$\frac{dC_a}{dt} = v_2 C_u + v_1 A - (\delta + \mu + d_c)C_a$$
$$\frac{dT_c}{dt} = \delta C_a - (\omega + \mu)T_c$$
$$\frac{dR}{dt} = \omega T_c - \mu R \tag{3}$$

where $\lambda = \frac{\beta(A + \alpha_1 C_u + \alpha_2 C_a)}{N}$

2.1 Positivity and boundedness of solutions

For the system of equations (3) to be epidemiologically meaningful, it is important to prove that all solution with non-negative initial conditions will remain non-negative.

Lemma 1: The initial values of the parameters are

$$\{S(0) \geq 0, A(0) \geq 0, C_u(0) \geq 0, C_a(0) \geq 0, T_c(0) \geq 0, R(0) \geq , 0 \text{ and } N(0) \geq 0\} \in \Phi$$

Then the solution of the model $\{S(t), A(t), C_u(t), C_a(t), T_c(t), R(t), N(t)\}$ is positive for all $t \geq 0$.

Proof

Considering the first equation in (3),

$$\frac{dS}{dt} = \Pi - \lambda S + \sigma A - \mu S$$

$$\frac{dS}{dt} \geq -(\lambda + \mu)$$
$$S \int \frac{1}{S} dS \geq \int -(\lambda + \mu)dt$$

$$S \geq S_0 e^{-(\lambda + \mu)t} \geq 0$$

Hence, $S \geq 0$

with respect to the second equation in (3);

$$\frac{dA}{dt} = \lambda S - (\sigma + \gamma + v_1)A$$

$$\frac{dA}{dt} \geq -(\sigma + \gamma + v_1)A$$

$$\int \frac{1}{A}dA \geq \int -(\sigma + \gamma + v_1)dt$$

$$A \geq A_0 e^{-(\sigma + \gamma + v_1)t} \geq 0$$

Hence, $A \geq 0$. Same goes for the other compartments

Clearly, the above state variables are positive on bounding plane $\mathbb{R}_+^6$.

For the boundedness the following calculation follows:

$$N(t) = S(t) + A(t) + C_u(t) + C_a(t) + T_c(t) + R(t)$$

$$N' = S' + A' + C_u' + C_a' + T_c' + R'$$

$$N' = \Pi - \lambda S + \sigma A - \mu S + \lambda S - (\sigma + \gamma + v_1)A + \gamma A - (v_2 + \mu + d_c)C_u + v_2 C_u + v_1 A$$
$$- (\delta + \mu + d_c)C_a + \delta C_a - (\omega + \mu)T_c + \omega T_c - \mu R \qquad (4)$$

Simplifying:

$$N' + \mu N = \Pi - d_c C_u \qquad (5)$$

$$N' + \mu N \leq \Pi \qquad (6)$$

Integrating gives:

$$N' \leq \frac{\Pi}{\mu} + k e^{-\mu t}$$

$$\max_{\lim_{n \to \infty}} N \leq \lim_{n \to \infty}\left(\frac{\Pi}{\mu} + k e^{-\mu t}\right) \leq \frac{\Pi}{\mu}$$

It follows that the solutions of the model system (3) are positive and bounded in the region

$$\mathcal{T} = \{(S + A + C_u + C_a + T_c + R)\} \in \mathbb{R}_+^6 : S + A + C_u + C_a + T_c + R \leq \frac{\Pi}{\mu}$$

It follows from Lemma 1 that it is sufficient to consider the dynamics of system (3) and the model can be considered to be epidemiologically well-posed.

2.2 Equilibrium points

The disease-free equilibrium of the equation (3) exists and is given by:

$$(E_0) = \left[\frac{\Pi}{\mu}, 0, 0, 0, 0, 0\right] \qquad (7)$$

The endemic steady states are calculated here which is done by setting system of equation in (3.3.3) to zero and setting $S = S^*, A = A^*, C_u = C_u^*, C_a = C_a^*, T_c = T_c^*, R = R^*$ so that

$$S^* = \left(\frac{\begin{array}{l}\Pi\left(\mu^3 + (\delta+\gamma+2d_c+v_1+v_2)\mu^2 + \left(d_c{}^2 + (v_1+v_2+\delta+\gamma)d_c + (v_2+\delta)\gamma + (v_2+\delta)v_1 + \delta v_2\right)\mu\right)\\ +\delta(v_1 d_c + v_2(v_1+\gamma))(v_1+\sigma+\gamma)\end{array}}{L} \right) \tag{8}$$

$$A^* = - \left(\frac{\begin{array}{l}(v_1-\beta+\gamma+\sigma)d_c{}^2 + ((2v_1-2\beta+2\gamma+2\sigma)\mu + (v_2+\delta-\beta\alpha_1)\gamma + (v_2+\delta-\beta\alpha_2)v_1 - (\beta-\sigma)(v_2+\delta))d_c\\ +(v_1-\beta+\gamma+\sigma)\mu^2 + ((v_2+\delta-\beta\alpha_1)\gamma + (v_2+\delta-\beta\alpha_2)v_1 - (\beta-\sigma)(v_2+\delta))\mu + ((-\delta\alpha_1-\alpha_2 v_2)\beta)\Pi\end{array}}{L} \right) \tag{9}$$

$$C_u{}^* = A^*\gamma \tag{10}$$

$$C_a{}^* = \frac{C_u{}^*((v_1+v_1\mu) + v_2(v_1+\gamma))}{\gamma} \tag{11}$$

$$T_c{}^* = - \left(C_a{}^* \left(\frac{\mu^2}{d_c{}^2} + \frac{\mu}{d_c} + \frac{v_2}{\mu^2} + \frac{1}{v_1+v_2} \right)\delta \right) \tag{12}$$

$$R^* = \omega T_c{}^* \tag{13}$$

where

$$
\begin{aligned}
L = & \left((v_2+\mu+d_c)(v_1+\gamma+\sigma)\mu^3 + ((2v_1+2\gamma+2\sigma)d_c) + (v_1+\gamma+\sigma)v_2 + (\beta+\delta)\gamma + (\beta+\delta)v_1 + \delta\sigma\right)\mu^2\\
& + \left((v_1+\gamma+\sigma)d_c{}^2 + ((v_1+\gamma+\sigma)v_2 - \gamma^2 + (2\beta+\delta-\sigma-2v_1)\gamma - v_1^2 + (2\beta+\delta-\sigma)v_1 + \delta\sigma)d_c\right.\\
& \left. + ((\beta+\delta)\gamma + (\beta+\delta)v_1 + \delta\sigma)v_2 + \beta(v_1+\gamma)(\gamma\alpha_1 + \alpha_2 v_1 + \delta))\mu - (v_1+\gamma)(v_1-\beta+\gamma+\sigma)d_c{}^2\right.\\
& + \left(-(v_1+\gamma)(v_1-\beta+\gamma+\sigma)v_2 + (\beta\alpha_1-\delta)\gamma^2 + ((-\delta+(\alpha_1+\alpha_2)\beta)v_1 + \delta(\beta-\sigma))\gamma + (\delta+\alpha_2 v_1)\beta v_1\right)d_c\\
& + \beta(\gamma\alpha_1 + \alpha_2 v_1 + \delta)v_2 + \delta\gamma\alpha_1)(v_1+\gamma)(\delta+\mu+d_c)(\mu+\omega)
\end{aligned}
$$

2.3 Basic reproduction number

The basic reproduction number (R_o) which is the number of secondary infections caused by an infectious individual is determined by the next generation matrix which is given by $\rho\left(FV^{-1}\right)$

where:

$$F = \begin{bmatrix} \beta & \beta\alpha_1 & \beta\alpha_2 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

$$V = \begin{bmatrix} \sigma+\gamma+v_1 & 0 & 0 \\ -\gamma & d_c+\mu+v_2 & 0 \\ -v_1 & -v_2 & d_c+\mu+\delta \end{bmatrix}$$

$$V^{-1} = \begin{bmatrix} \dfrac{1}{\sigma+\gamma+v_1} & 0 & 0 \\[3mm] \dfrac{\gamma}{(\sigma+\gamma+v_1)(d_c+\mu+v_2)} & \dfrac{1}{d_c+\mu+v_2} & 0 \\[3mm] \dfrac{\gamma v_2 + v_1\mu + v_1 d_c + v_1 v_2}{(\sigma+\gamma+v_1)(d_c+\mu+v_2)(d_c+\mu+\delta)} & \dfrac{v_2}{(d_c+\mu+v_2)(d_c+\mu+\delta)} & \dfrac{1}{(d_c+\mu+\delta)} \end{bmatrix}$$

$$R_o = \frac{\beta}{\sigma+\gamma+v_1} + \frac{\beta\alpha_1\gamma}{(\sigma+\gamma+v_1)(d_c+\mu+v_2)} + \frac{\beta\alpha_2(\gamma v_2+v_1\mu+v_1 d_c+v_1 v_2)}{(\sigma+\gamma+v_1)(d_c+\mu+v_2)(d_c+\mu+\delta)} \tag{14}$$

2.4 Local stability analysis of the disease-free equilibrium E_0

Theorem 1: E_0 is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.

Proof: The resulting matrix from the linearized model is $\frac{dX}{dt} = AX$

$$X = (x_1, x_2, x_3, x_4, x_5, x_6)^T, (x_1, x_2, x_3, x_4, x_5, x_6) \in R_+^6, \text{and}$$

The resulting Jacobian matrix at E_0 is

$$J(E_0) = \begin{bmatrix} -\mu-\lambda & -\beta+\sigma & -\beta\alpha_1 & -\beta\alpha_2 & 0 & 0 \\ 0 & \beta-\sigma-\gamma-v_1-\lambda & \beta\alpha_1 & \beta\alpha_2 & 0 & 0 \\ 0 & \gamma & -d_c-\mu-v_2-\lambda & 0 & 0 & 0 \\ 0 & v_1 & v_2 & -d_c-\mu-\delta-\lambda & 0 & 0 \\ 0 & 0 & 0 & \delta & -\omega-\mu-\lambda & 0 \\ 0 & 0 & 0 & 0 & \omega & -\mu-\lambda \end{bmatrix} \tag{15}$$

From (15), $\lambda_1 = -\mu, \lambda_2 = -\omega-\mu, \lambda_3 = -\mu$

and the resulting quadratic equation is:

$$(\beta-\sigma-\gamma-v_1-\lambda)(-d_c-\mu-v_2-\lambda)(-d_c-\mu-\delta-\lambda)-\beta\alpha_1(-d_c-\mu-\delta-\lambda)\gamma+\beta\alpha_2((-d_c-\mu-v_2-\lambda)v_1-\gamma v_2) \tag{16}$$

$$\begin{aligned} f(\lambda) = &\lambda^3 + (2\mu+v_1+v_2-\beta+\delta+\gamma+\sigma+2d_c)\lambda^2 + (\beta\alpha_2 v_1-\beta\delta-2\beta\mu-2\beta d_c-\beta v_2+\delta\gamma+\delta\mu+\delta\sigma+\delta d_c+\delta v_1 \\ &+\delta v_2+2\gamma\mu+2\gamma d_c+\gamma v_2+\mu^2+2\mu\sigma+2\mu d_c+2\mu v_1+\mu v_2+2\sigma d_c+\sigma v_2+d_c^2+2d_c v_1+d_c v_2+v_1 v_2-\gamma\beta\alpha_1)\lambda \\ &+\gamma\mu^2+\gamma d_c^2+\mu^2\sigma+\mu^2 v_1+\sigma d_c^2+d_c^2 v_1+\mu\sigma v_2+2\mu d_c v_1+\mu v_1 v_2+\sigma d_c v_2+d_c v_1 v_2-\beta\delta\mu-\beta\delta d_c-\beta\delta v_2 \\ &-2\beta\mu d_c-\beta\mu v_2-\beta d_c v_2-\beta\mu^2-\beta d_c^2+\delta\gamma\mu+\delta\gamma d_c+\delta\gamma v_2+\delta\mu\sigma+\delta\mu v_1+\delta\sigma d_c+\delta\sigma v_2+\delta d_c v_1+\delta v_1 v_2 \\ &+2\gamma\mu d_c+\gamma\mu v_2+\gamma d_c v_2+2\mu\sigma d_c-\beta\delta\gamma\alpha_1-\beta\gamma\mu\alpha_1-\beta\gamma\alpha_1 d_c+v_2\gamma\beta\alpha_2+v_1\beta\alpha_2 d_c+v_1\beta\alpha_2\mu+v_1\beta\alpha_2 v_2 \end{aligned} \tag{17}$$

Now, $\lambda_1, \lambda_2, \lambda_3 < 0$ since the values are assumed positive. If $R_0 < 1$, E_0 is stable and unstable when $R_0 < 1$.

2.5 Global stability of the disease-free equilibrium
The global behavior of the equilibrium system (3) is analyzed here in this section.

Theorem 2: For system (3), the disease-free equilibrium E_0 is asymptotically stable globally if $R_0 < 1$.

Proof: Considering the Lyapunov function defined as:

$$G(A, C_u, C_a) = \left(\frac{1}{B_0}\right)A + \left(\frac{\beta\alpha_1}{B_0 B_1} + \frac{\beta\alpha_2 v_2}{B_0 B_1 B_2}\right)C_u + \left(\frac{\beta\alpha_2}{B_0 B_2}\right)C_a \tag{18}$$

$$G'(A, C_u, C_a) = \left(\frac{1}{B_0}\right)A' + \left(\frac{\beta\alpha_1}{B_0 B_1} + \frac{\beta\alpha_2 v_2}{B_0 B_1 B_2}\right)C_u' + \left(\frac{\beta\alpha_2}{B_0 B_2}\right)C_a' \tag{19}$$

$$\begin{aligned} G'(A, C_u, C_a) = &\left(\frac{1}{B_0}\right)\left(\left(\frac{\beta(A+\alpha_1 C_u+\alpha_2 C_a)}{N}\right)S - (\sigma+\gamma+v_1)A\right) + \left(\frac{\beta\alpha_1}{B_0 B_1}+\frac{\beta\alpha_2 v_2}{B_0 B_1 B_2}\right)(\gamma A - (v_2+\mu+d_c)C_u) \\ &+\left(\frac{\beta\alpha_2}{B_0 B_2}\right)(v_2 C_u + v_1 A - (\delta+\mu+d_c)C_a) \end{aligned} \tag{20}$$

At DFE, S=N so that (20) becomes:

$$G'(A, C_u, C_a) = \left(\frac{1}{B_0}\right)(\beta(A + \alpha_1 C_u + \alpha_2 C_a) - (\sigma + \gamma + v_1)A) + \left(\frac{\beta\alpha_1}{B_0 B_1} + \frac{\beta\alpha_2 v_2}{B_0 B_1 B_2}\right)(\gamma A - (v_2 + \mu + d_c)C_u)$$

$$+ \left(\frac{\beta\alpha_2}{B_0 B_2}\right)(v_2 C_u + v_1 A - (\delta + \mu + d_c)C_a) \tag{21}$$

Expanding and simplifying (21) gives:

$$G' = \left[\frac{\beta}{B_0} + \frac{\beta\alpha_1\gamma}{B_0 B_1} + \frac{\beta\alpha_2 v_2\gamma}{B_0 B_1 B_2} + \frac{\beta\alpha_2 v_1}{B_0 B_2} - 1\right]A + \left[\frac{\beta\alpha_1}{B_0} - \frac{\beta\alpha_1 B_1}{B_0 B_1} - \frac{\beta\alpha_2 v_2 B_1}{B_0 B_1 B_2} + \frac{\beta\alpha_2 v_2}{B_0 B_2}\right]C_u + \left[\frac{\beta\alpha_2}{B_0} - \frac{\beta\alpha_2 B_2}{B_0 B_2}\right]C_a \tag{22}$$

$$G' = [R_0 - 1]A \le 0 \tag{23}$$

From Equation (23), it can be deduced that the DFE is globally stable since $R_0 < 1$.

2.6 Local stability of endemic equilibrium

Theorem 3: If $R_0 > 1$, then the endemic equilibrium is locally asymptotically stable.

Proof:

The endemic equilibria of system (3), denoted by $(S^*, A^*, C_u^*, C_a^*, T_c^*, R^*)$, can be rewritten as:

Let $S = x + S^*, A = y + A^*, C_u = z + C_u^*, C_a = h + C_a^*, T_c = p + T_c^*, R = j + R^*$

$$J = \begin{bmatrix} B_0 - \mu - \lambda & -B_1 + \sigma & -B_2 & -B_3 & B_4 & B_5 \\ -B_6 & B_7 - \sigma - \gamma - v_1 - \lambda & B_8 & B_9 & -B_{11} & -B_{12} \\ 0 & \gamma & -d_c - \mu - v_2 - \lambda & 0 & 0 & 0 \\ 0 & v_1 & v_2 & -d_c - \mu - \delta - \lambda & 0 & 0 \\ 0 & 0 & 0 & \delta & -\omega - \mu - \lambda & 0 \\ 0 & 0 & 0 & 0 & \omega & -\mu - \lambda \end{bmatrix} \tag{25}$$

From (25), $\lambda_1 = -\mu, \lambda_2 = -(\omega + \mu), \lambda_3 = -(d_c + \mu + v_2)$, then;

$$J = \begin{bmatrix} B_0 - \mu - \lambda & -B_1 + \sigma & -B_2 \\ -B_6 & B_7 - \sigma - \gamma - v_1 - \lambda & B_8 \\ 0 & \gamma & -d_c - \mu - v_2 - \lambda \end{bmatrix} \tag{26}$$

from (26);

$$\lambda^3 + (\gamma + 2\mu + \sigma - B_0 - B_4 + d_c + v_1 + v_2)\lambda^2 + (2\gamma\mu - B_0\gamma + \gamma d_c + \gamma v_2 + \mu^2 + 2\mu\sigma - \mu B_0 - 2\mu B_4 + \mu d_c + 2\mu v_1 + \mu v_2$$
$$- \sigma B_0 + \sigma B_3 + \sigma d_c + \sigma v_2 + B_0 B_4 - B_0 d_c - B_0 v_1 - B_0 v_2 - B_3 B_1 - B_4 d_c - B_4 v_2 + d_c v_1 + v_1 v_2)\lambda + B_5\gamma + \gamma\mu v_2 + \mu\sigma v_2$$
$$+ \mu v_1 v_2 + B_3 B_2\gamma + \gamma\mu^2 + \mu^2\sigma + \mu^2 v_1 + \mu d_c v_1 + \gamma\mu d_c + \mu\sigma d_c - \mu^2 B_4 - \gamma\mu B_0 - \gamma B_0 d_c - \gamma B_0 v_2 - \mu\sigma B_0 + \mu\sigma B_3 + \mu B_0 B_4$$
$$- \mu B_0 v_1 - \mu B_3 B_1 - \mu B_4 d_c - \mu B_4 v_2 - \sigma B_0 d_c - \sigma B_0 v_2 + \sigma B_3 d_c + \sigma B_3 v_2 + B_0 B_4 d_c + B_0 B_4 v_2 - B_0 d_c v_1 - B_0 v_1 v_2$$
$$- B_3 B_1 d_c - B_3 B_1 v_2$$

The result of the determinant of the Jacobian matrix is of the form:

$$a_0\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 \tag{27}$$

where

$$a_0 = 1$$

$$a_1 = \gamma + 2\mu + \sigma - B_0 - B_4 + d_c + v_1 + v_2$$

$$a_2 = 2\gamma\mu - B_0\gamma + \gamma d_c + \gamma v_2 + \mu^2 + 2\mu\sigma - \mu B_0 - 2\mu B_4 + \mu d_c + 2\mu v_1 + \mu v_2 - \sigma B_0 + \sigma B_3 + \sigma d_c + \sigma v_2 + B_0 B_4 - B_0 d_c$$
$$- B_0 v_1 - B_0 v_2 - B_3 B_1 - B_4 d_c - B_4 v_2 + d_c v_1 + v_1 v_2$$

$$a_3 = B_5\gamma + \gamma\mu v_2 + \mu\sigma v_2 + \mu v_1 v_2 + B_3 B_2 \gamma + \gamma\mu^2 + \mu^2\sigma + \mu^2 v_1 + \mu d_c v_1 + \gamma\mu d_c + \mu\sigma d_c - \mu^2 B_4 - \gamma\mu B_0 - \gamma B_0 d_c - \gamma B_0 v_2$$
$$- \mu\sigma B_0 + \mu\sigma B_3 + \mu B_0 B_4 - \mu B_0 v_1 - \mu B_3 B_1 - \mu B_4 d_c - \mu B_4 v_2 - \sigma B_0 d_c - \sigma B_0 v_2 + \sigma B_3 d_c + \sigma B_3 v_2 + B_0 B_4 d_c + B_0 B_4 v_2$$
$$- B_0 d_c v_1 - B_0 v_1 v_2 - B_3 B_1 d_c - B_3 B_1 v_2$$

By the Routh–Hurwitz criterion governing the polynomials of order 3, we have the following:

1. $a_2.a_3$ are positive

2. $a_1 a_2 > a_3$

From equation (27), 1 and 2 are satisfied.

Therefore, endemic equilibrium is locally asymptotically stable.

2.7 Global stability of the endemic equilibrium

Theorem 4: The equations of the model have a positive distinctive endemic equilibrium whenever $R_0 > 1$, which is said to be globally asymptotically stable.

Proof: Considering the Lyapunov function defined as:

$$L(S^*, A^*, C_u{}^*, C_a{}^*, T_c{}^*, R^*) = \left(S - S^* ln\left(\frac{S}{S^*}\right)\right) + \left(A - A^* ln\left(\frac{A}{A^*}\right)\right) + \left(C_u - C_u{}^* ln\left(\frac{C_u}{C_u{}^*}\right)\right)$$
$$+ \left(C_a - C_a{}^* ln\left(\frac{C_a}{C_a{}^*}\right)\right) + \left(T_c - T_c{}^* ln\left(\frac{T_c}{T_c{}^*}\right)\right) + \left(R - R^* ln\left(\frac{R}{R^*}\right)\right) \quad (28)$$

where L takes it derivative along the system directly as:

$$\frac{dL}{dt} = \left(1 - \frac{S^*}{S}\right)\frac{dS}{dt} + \left(1 - \frac{A^*}{A}\right)\frac{dA}{dt} + \left(1 - \frac{C_u{}^*}{C_u}\right)\frac{dC_u}{dt} + \left(1 - \frac{C_a{}^*}{C_a}\right)\frac{dC_a}{dt} + \left(1 - \frac{T_c{}^*}{T_c}\right)\frac{dT_c}{dt} + \left(1 - \frac{R^*}{R}\right)\frac{dR}{dt} \quad (29)$$

$$\frac{dL}{dt} = \left(1 - \frac{S^*}{S}\right)\left[\Pi - \left(\frac{\beta(A + \alpha_1 C_u + \alpha_2 C_a)}{N}\right)S + \sigma A - \mu S\right] + \left(1 - \frac{A^*}{A}\right)\left[\left(\frac{\beta(A + \alpha_1 C_u + \alpha_2 C_a)}{N}\right)S - (\sigma + \gamma + v_1)A\right]$$
$$+ \left(1 - \frac{C_u{}^*}{C_u}\right)[\gamma A - (v_2 + \mu + d_c)C_u] + \left(1 - \frac{C_a{}^*}{C_a}\right)[v_2 C_u + v_1 A - (\delta + \mu + d_c)C_a] + \left(1 - \frac{T_c{}^*}{T_c}\right)[\delta C_a - (\omega + \mu)T_c]$$
$$+ \left(1 - \frac{R^*}{R}\right)[\omega T_c - \mu R]$$

$$(30)$$

At equilibrium,

$$\Pi = \left(\frac{\beta(A* + \alpha_1 C_u* + \alpha_2 C_a*)}{N*}\right)S* - \sigma A* + \mu S*$$

$$(\sigma + \gamma + v_1) = \left(\frac{\beta(A* + \alpha_1 C_u* + \alpha_2 C_a*)}{AN*}\right)S*$$

$$(v_2 + \mu + d_c) = \frac{\gamma A*}{C_u*}$$

$$(\delta + \mu + d_c) = \frac{v_2 C_u*}{C_a*} + \frac{v_1 A*}{C_a*}$$

$$(\omega + \mu) = \frac{\delta C_a*}{T_c*}$$

$$\omega = \frac{\mu R*}{T_c*} \quad (31)$$

$$\begin{aligned}
\frac{dL}{dt} &= \left(1-\frac{S^*}{S}\right)\left[\left(\frac{\beta(A*+\alpha_1 C_u*+\alpha_2 C_a*)}{N*}\right)S* -\sigma A* +\mu S* -\left(\frac{\beta(A+\alpha_1 C_u+\alpha_2 C_a)}{N}\right)S+\sigma A-\mu S\right] \\
&\quad +\left(1-\frac{A^*}{A}\right)\left[\left(\frac{\beta(A+\alpha_1 C_u+\alpha_2 C_a)}{N}\right)S-\left(\frac{\beta(A*+\alpha_1 C_u*+\alpha_2 C_a*)}{AN*}\right)S*A\right]+\left(1-\frac{C_u^*}{C_u}\right)\left[\gamma A-\frac{\gamma A*}{C_u*}C_u\right] \\
&\quad +\left(1-\frac{C_a^*}{C_a}\right)\left[v_2 C_u+v_1 A-\frac{v_2 C_u*}{C_a*}+\frac{v_1 A*}{C_a*}C_a\right]+\left(1-\frac{T_c^*}{T_c}\right)\left[\delta C_a-\frac{\delta C_a*}{T_c*}T_c\right]+\left(1-\frac{R^*}{R}\right)\left[\frac{\mu R*}{T_c*}T_c-\mu R\right] \\
&= \left(1-\frac{S^*}{S}\right)\left[\frac{\beta A*S*}{N*}+\frac{\beta\alpha_1 C_u*S*}{N*}+\frac{\beta\alpha_2 C_a*S*}{N*}-\sigma A*+\mu S*-\frac{\beta AS}{N}-\frac{\beta\alpha_1 C_u S}{N}-\frac{\beta\alpha_2 C_a S}{N}+\sigma A-\mu S\right] \\
&\quad +\left(1-\frac{A^*}{A}\right)\left[\frac{\beta AS}{N}-\frac{\beta AS*}{N*}+\frac{\beta\alpha_1 C_u S}{N}-\frac{\beta\alpha_1 C_u*S*A}{A*N*}+\frac{\beta\alpha_2 C_a S}{N}-\frac{\beta\alpha_2 C_a*S*A}{A*N*}\right]+\left(1-\frac{C_u^*}{C_u}\right)\gamma A\left[1-\frac{A*C_u}{AC_u*}\right] \\
&\quad +\left(1-\frac{C_a^*}{C_a}\right)\left[v_2 C_u\left(1-\frac{C_u^*C_a}{C_u C_a*}\right)+v_1 A\left(1-\frac{A^*C_a}{AC_a*}\right)\right]+\delta C_a\left(1-\frac{T_c^*}{T_c}\right)\left[1-\frac{C_a*T_c}{C_a T_c*}\right] \\
&\quad -\mu R\left(1-\frac{R^*}{R}\right)\left[1-\frac{R*T_c}{RT_c*}\right]
\end{aligned}$$

(32)

$$\begin{aligned}
&= \left(1-\frac{S^*}{S}\right)\left[-\frac{\beta AS}{N}\left(1-\frac{A*S*N}{ASN*}\right)-\frac{\beta\alpha_1 C_u S}{N}\left(1-\frac{C_u*S*N}{C_u SN*}\right)+\frac{\beta\alpha_2 C_a S}{N}\left(1-\frac{C_a*S*N}{C_a SN*}\right)-\sigma A\left(1-\frac{A^*}{A}\right)-\mu S-\left(1-\frac{S^*}{S}\right)\right] \\
&\quad +\left(1-\frac{A^*}{A}\right)\left[\frac{\beta AS}{N}\left(1-\frac{A*S*N}{ASN*}\right)-\frac{\beta\alpha_1 C_u S}{N}\left(1-\frac{C_u*S*AN}{C_u SA*N*}\right)+\frac{\beta\alpha_2 C_a S}{N}\left(1-\frac{C_a*S*AN}{C_a SA*N*}\right)\right] \\
&\quad +\left(1-\frac{C_u^*}{C_u}\right)\gamma A\left[1-\frac{A*C_u}{AC_u*}\right]+\left(1-\frac{C_a^*}{C_a}\right)\left[v_2 C_u\left(1-\frac{C_u^*C_a}{C_u C_a*}\right)+v_1 A\left(1-\frac{A^*C_a}{AC_a*}\right)\right]+\delta C_a\left(1-\frac{T_c^*}{T_c}\right)\left[1-\frac{C_a*T_c}{C_a T_c*}\right] \\
&\quad -\mu R\left(1-\frac{R^*}{R}\right)\left[1-\frac{R*T_c}{RT_c*}\right]
\end{aligned}$$

(33)

$$\begin{aligned}
&= -\mu S\left(1-\frac{S^*}{S}\right)^2-\frac{\beta AS}{N}\left(1-\frac{S^*}{S}\right)\left(1-\frac{A*S*N}{ASN*}\right)-\frac{\beta\alpha_1 C_u S}{N}\left(1-\frac{S^*}{S}\right)\left(1-\frac{C_u*S*N}{C_u SN*}\right) \\
&\quad -\frac{\beta\alpha_2 C_a S}{N}\left(1-\frac{S^*}{S}\right)\left(1-\frac{C_a*S*N}{C_a SN*}\right)-\sigma A\left(1-\frac{S^*}{S}\right)\left(1-\frac{A^*}{A}\right)+\frac{\beta AS}{N}\left(1-\frac{A^*}{A}\right)\left(1-\frac{S*N}{SN*}\right) \\
&\quad +\frac{\beta\alpha_1 C_u S}{N}\left(1-\frac{A^*}{A}\right)\left(1-\frac{C_u*S*AN}{C_u SA*N*}\right)+\frac{\beta\alpha_2 C_a S}{N}\left(1-\frac{A^*}{A}\right)\left(1-\frac{C_a*S*AN}{C_a SA*N*}\right)+\sigma A\left(1-\frac{C_u^*}{C_u}\right)\left(1-\frac{A^*C_u}{AC_u*}\right) \\
&\quad +v_2 C_u\left(1-\frac{C_a^*}{C_a}\right)\left(1-\frac{C_u^*C_a}{C_u C_a*}\right)+v_1 A\left(1-\frac{C_a^*}{C_a}\right)\left(1-\frac{A^*C_a}{AC_a*}\right)+\delta C_a\left(1-\frac{T_c^*}{T_c}\right)\left(1-\frac{C_a*T_c}{C_a T_c*}\right) \\
&\quad -\mu R\left(1-\frac{R^*}{R}\right)\left(1-\frac{R*T_c}{RT_c*}\right)
\end{aligned}$$

$$= -\mu S\left(1-\frac{S^*}{S}\right)^2+P_1(S,A,C_a,C_u,T_c,R)+P_2(S,A,C_a,C_u,T_c,R) \tag{34}$$

where,

$$\begin{aligned}
P_1(S,A,C_a,C_u,T_c,R) &= -\frac{\beta AS}{N}\left(1-\frac{S^*}{S}\right)\left(1-\frac{A^*S^*N}{ASN*}\right)-\frac{\beta\alpha_1 C_u S}{N}\left(1-\frac{S^*}{S}\right)\left(1-\frac{C_u*S*N}{C_u SN*}\right) \\
&\quad -\frac{\beta\alpha_2 C_a S}{N}\left(1-\frac{S^*}{S}\right)\left(1-\frac{C_a*S*N}{C_a SN*}\right)-\sigma A\left(1-\frac{S^*}{S}\right)\left(1-\frac{A^*}{A}\right)-\mu R\left(1-\frac{R^*}{R}\right)\left(1-\frac{R*T_c}{RT_c*}\right)
\end{aligned}$$

$$\begin{aligned}
P_2(S,A,C_a,C_u,T_c,R) &= \frac{\beta AS}{N}\left(1-\frac{A^*}{A}\right)\left(1-\frac{S^*N}{SN*}\right)+\frac{\beta\alpha_1 C_u S}{N}\left(1-\frac{A^*}{A}\right)\left(1-\frac{C_u*S*AN}{C_u SA*N*}\right) \\
&\quad +\frac{\beta\alpha_2 C_a S}{N}\left(1-\frac{A^*}{A}\right)\left(1-\frac{C_a*S*AN}{C_a SA*N*}\right)+\sigma A\left(1-\frac{C_u^*}{C_u}\right)\left(1-\frac{A^*C_u}{AC_u*}\right) \\
&\quad +v_2 C_u\left(1-\frac{C_a^*}{C_a}\right)\left(1-\frac{C_u^*C_a}{C_u C_a*}\right)+v_1 A\left(1-\frac{C_a^*}{C_a}\right)\left(1-\frac{A^*C_a}{AC_a*}\right) \\
&\quad +\delta C_a\left(1-\frac{T_c^*}{T_c}\right)\left(1-\frac{C_a*T_c}{C_a T_c*}\right)
\end{aligned}$$

$P_1 \leq 0$ whenever

$$ASN* \geq A^*S^*N, C_uSN* \geq C_u{}^*S^*N, C_aSN* \geq C_a{}^*S^*N, RT_c* \geq R*T_c \tag{35}$$

and $P_2 \leq 0$ whenever

$$S^*N \geq SN*, C_u*S*AN \geq C_uSA*N*, C_a{}^*S^*AN \geq C_aSA*N*, A*C_u \geq AC_u*, C_u*C_a \geq C_uC_a{}^*, A*C_a \geq AC_a{}^*, C_a{}^*T_c \geq C_aT_c* \tag{36}$$

Thus, $\frac{dL}{dt} \leq 0$ if the condition in (35) and (36) holds.

therefore, by LaSalle asymptotic stability theorem (LaSalle, 1976), and Oke et al. (2020) the positive equilibrium state $\frac{dL}{dt}$ is globally asymptotically stable in the positive region R_+^6.

3. Numerical computation

The numerical study is carried out using maple software embedded code for the Runge-Kutta of fourth order. Here, the subsequent default values are assumed for the embedded parameters taken from theoretical studies in literatures $\gamma = 0.9, \beta = 0.008, \sigma = 0.59, d(c) = 0.00693, \mu = 0.00693, \omega = 0.1, v_1 = 0.002, v_2 = 0.002, \alpha_1 = 0.0016, \alpha_2 = 0.0016, \delta = 0.0085, \Pi = 0.07$. The values remain unchanged throughout* the computations except otherwise indicated.

The effects of varying the testing rate of the acute individuals (v_1), testing rate of chronic individuals (v_2) and treatment rate of chronic individuals (δ) on the population dynamics are shown in Figures 2 to 7. From Figures 2 and 3, an increase in the parameters values reduces susceptible and acute populations thereby reducing the spread HBV due to low interaction between the host immune system and the virus. Therefore, the appearance of HBV and the pathogenesis reduces, which in so doing, lessens the potential injury on the liver. Hence, the liver is shielded from hepatocellular carcinoma over time. The rate of chronic unaware and chronically aware individuals is examined in Figures 4 and 5. The parameter variations show a significant decrease in the chronic unaware population which implies that testing at that stage is a great tool for reducing the disease transmission. The transmission process dies down as the time progresses; this discourages liver inflammation as a result of lowering the infected individuals. Meanwhile, the chronic population in Figure 5, depicts a high significant influence of the acutely infected and chronically unaware infected individuals over
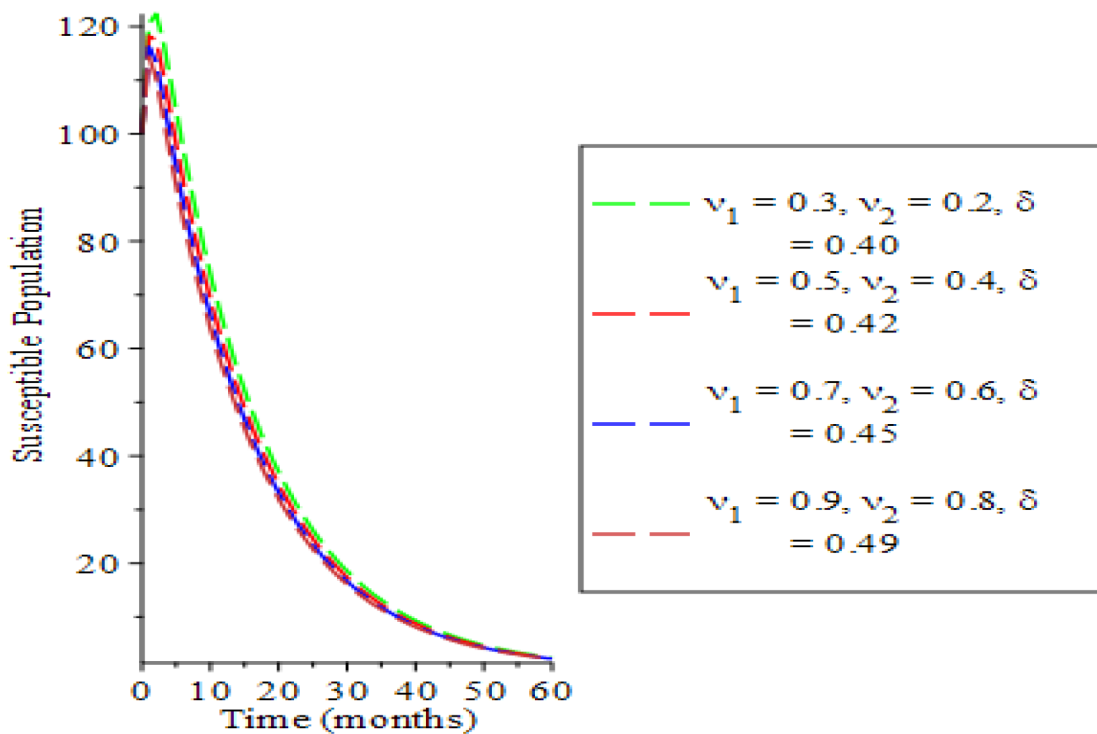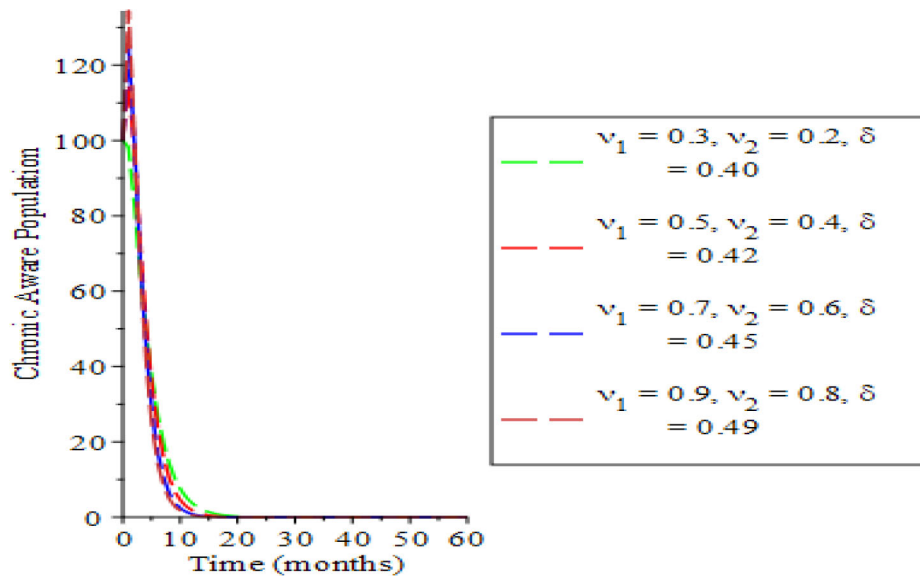

Figure 2. Behavioral dynamics of susceptible population when varying testing rate for acute and chronic individuals and treatment for chronic individuals.
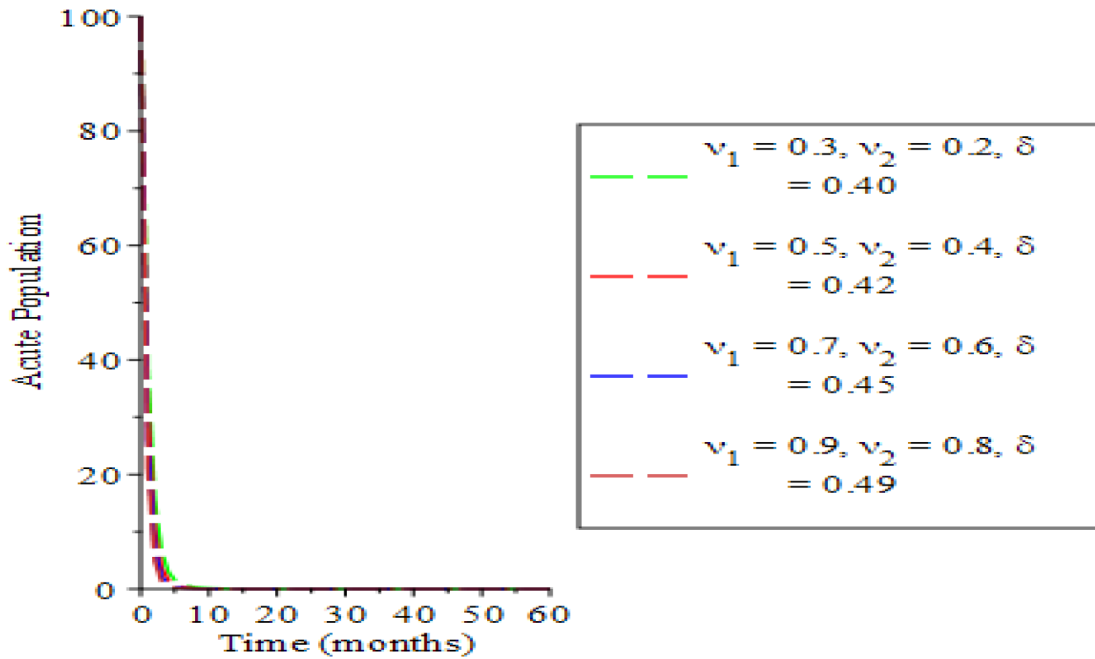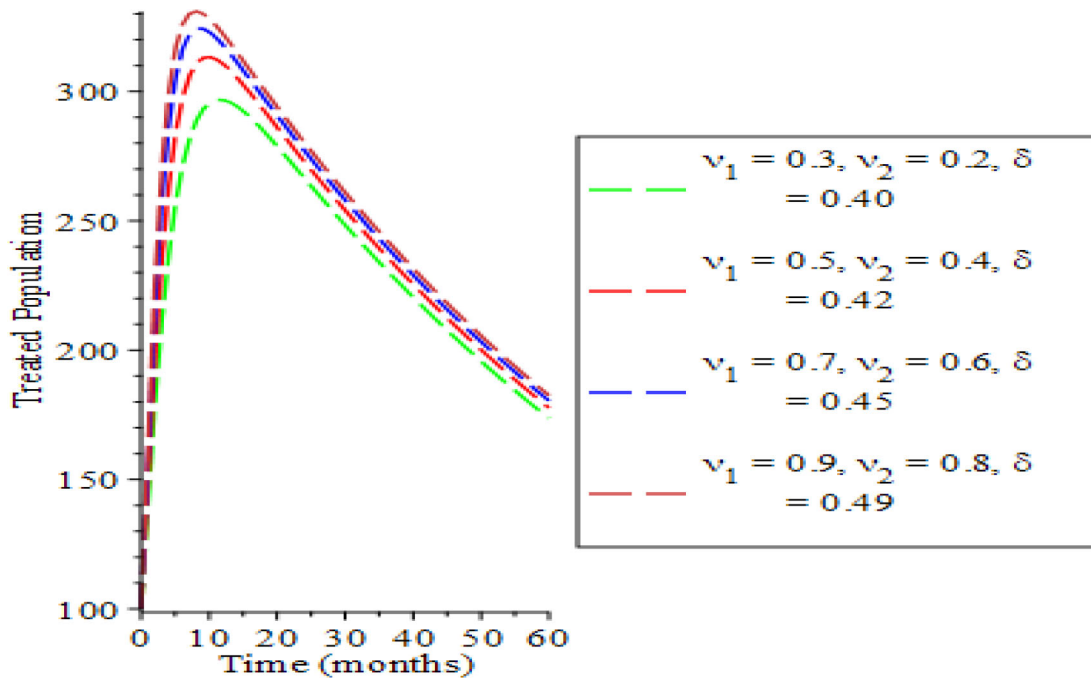
Figure 3. Behavioral dynamics of acute population when varying testing rate for acute and chronic individuals and treatment for chronic individuals.
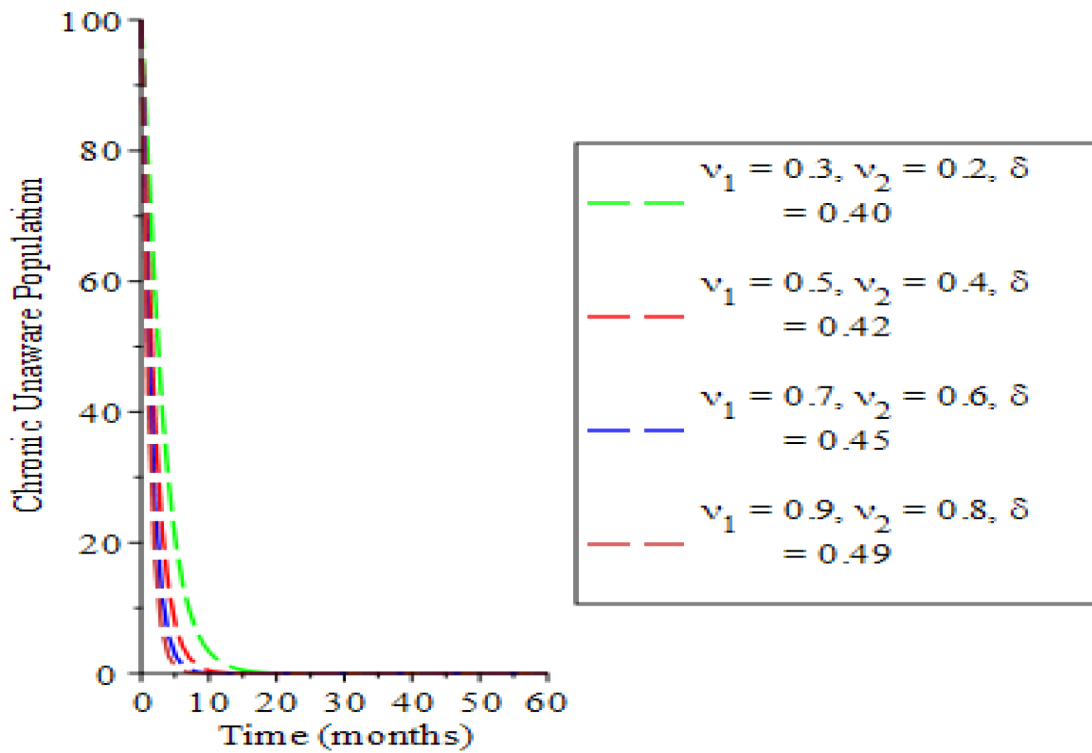
Figure 4. Behavioral dynamics of chronic unaware population when varying testing rate for acute and chronic individuals and treatment for chronic individuals.
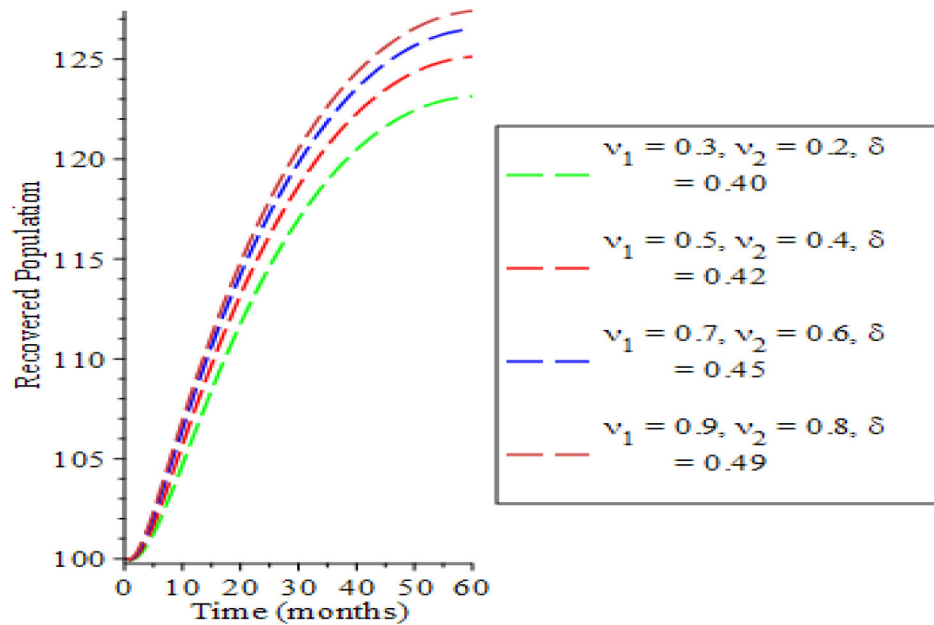
Figure 5. Behavioral dynamics of chronic aware population when varying testing rate for acute and chronic individuals and treatment for chronic individuals.

Figure 6. Behavioral dynamics of treated population when varying testing rate for acute and chronic individuals and treatment for chronic individuals.

time. A chronic infection phase is found at the time range $10 < t < 20$, as such, the individuals are exposed to liver carcinoma or cirrhosis. Hence, the chronic population diminishes as the parameters are increased.

In Figures 6 and 7, the impact of varying the testing rate of the acute individuals (v_1), testing rate of chronic individuals (v_2) and treatment rate of chronic individuals (δ) on the treated and the recovered population are presented. The treated population increases with parameters variation along the rising time (t) as a result of long time effect of parameter values. The recovery rate is enhanced as observed in Figure 7 due to significant simulation of surface antibodies of Hepatitis B.

Figure 7. Behavioral dynamics of recovered population when varying testing rate for acute and chronic individuals and treatment for chronic individuals.

This is in conformity with the works of Pang *et al.* (2010) and Ullah *et al.* (2019). This result implies that an intensification in testing at all infectious states and rise in treatment of chronic individual will bring about a reduction in the HBV transmission process which is a response to the WHO goal for 2030 that concentrating efforts on awareness program and campaign will sure bring about a decrease or eradication in the transmission process of the virus (WHO, 2020).

4. Conclusion
A deterministic model of hepatitis B testing was developed and investigated, which included testing in the chronic unaware state as well as testing in all infectious states. The model has disease-free and endemic equilibria. The basic reproduction number was calculated using the next generation matrix method. The equilibria's local and global stability were discussed and shown to be asymptotically stable. The testing and treatment rate effects were thoroughly discussed.

Data availability
No data are associated with this article.

Grant information
None declared.

Competing interests
None declared.

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Reviewer Report 17 December 2021

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✔ **Segun oke** iD

Department of Mathematical and Applied Mathematics, University of Pretoria, Pretoria, South Africa

The authors worked on the impact of testing and treatment on the dynamics of Hepatitis B virus. Although the manuscript is well presented and gives new insight into the Hepatitis B virus, especially for unvaccinated men who have sex with men (MSM) and heterosexual people who have multiple sexual partners or have contact with sex workers.

In their paper, a mathematical model was formulated to analyse the acquisition and transmission process of the virus with the view of identifying the possible way of reducing the menace and mitigating the risk of the virus. The models' positivity and boundedness were demonstrated using well-known theorems. Equating the differential equations to zero demonstrates the equilibria of the solutions i.e., the disease-free and endemic equilibrium. The next Generation Matrix method was used to compute the basic reproduction number for the models. Local and global stabilities of the models were shown via linearization and contrition of Lyapunov function methods respectively. The authors concluded by showing disease-free, endemic equilibria. The basic reproduction number was calculated using the next-generation matrix method. The equilibria's local and global stability were discussed and shown to be asymptotically stable. The testing and treatment rate effects were thoroughly discussed. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Some minor comments:
1. The authors need to review more literature to back up their claims.

2. The introduction is too short and is not well cited. For example:

"In highly endemic areas, the most common form of transmission of hepatitis B is from mother to child at birth (vertical transmission) or through horizontal route (contact with infected blood), particularly from infected children to uninfected children during the first five years of life. vaginal and spermatic fluids and, to a lesser degree, perspiration, breast milk, tears, and urine. In

particular, hepatitis B can be transmitted through sexual contact in unvaccinated men who have sex with men (MSM) and heterosexual people who have multiple sexual partners or have contact with sex workers" there is no citation here.

3. The authors need to add epidemiological interpretation and recommendations to the manuscript.

4. The conclusion needs to be rewritten.

Is the work clearly and accurately presented and does it cite the current literature?
No

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Not applicable

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Mathematical modelling, Mathematical Oncology, Optimal control, Epidemiology, etc

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 06 October 2021

✔ **Sulyman Olakunle Salawu**
Department of Mathematics, Landmark University, Omu-aran, Nigeria

Reviewer Reports on the impact of testing and treatment on the dynamics of Hepatitis B virus. The impacts of different parameters were examined. The manuscript is well written and presented logically. The abstract captures accurately the whole work and the introduction is sound. However, I have the following comments and queries for the authors:

1. The authors should explain what prompted the choice of method of solution used over other techniques.

2. The significance and motivation of the study are not clear. The authors should clarify these.

3. There is a need to reference equation (3) to establish its correctness and source.

4. Some grammatical mistakes should be checked through.

5. Why have the authors chosen to engage in this study?

6. A likely extension of the study should be stated or recommended.

The manuscript should be indexed subject to minor correction.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Not applicable

Are all the source data underlying the results available to ensure full reproducibility?
No source data required

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Mathematical Modeling and flow dynamic

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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