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MATHEMATICAL MODELLING OF THE DYNAMICS OF HEPATITIS B VIRUS INFECTION IN THE PRESENCE OF LIVER SIZE, EFFECTOR AND REFRACTOR CELLS

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Abstract

In this work, we proposed a mathematical model of the dynamics of Hepatitis B virus infection taken in to consideration the effect of liver size, effector and, refractor cells. The model was developed using a set of five ordinary differential equations including a delay factor. The disease free equilibrium state was obtained and analyzed for stability. We obtained the basic reproduction number, R_0 ***which can be used to control the infection dynamics of the virus and thus, established the conditions for local stability of the infection free-equilibrium using Routh-Hurwitz criterion. Also global stability of the infection free equilibrium was acquired using Castillo-Chavez method. Numerical experiments carried out on the system shows that the size of the liver have effect on the infection dynamics of Hepatitis B, expansion of immune effector cells reduces the number of infected hepatocytes liver cells through killing or changing them to a refractor cells. We therefore recommend that government to provide drugs that will activate the release of immune effector cells as soon as infection is detected and ways of preventing younger ones' to exposure to the disease should be put in place.***

Keywords: Hepatitis B, viral infection, effector cell, refractor cell, reproduction number, stability

1. Introduction

Hepatitis B is a potentially life-threatening liver infection caused by the hepatitis B virus (HBV). It is characterized by the presence of inflammatory cells in the tissue of the liver. This disease reduces the liver's ability to perform life-preserving functions, including filtering harmful infectious agents from the blood, storing blood sugar and converting it to usable energy forms, and producing many proteins necessary for life[1]. It is a major global health problem causing both acute and chronic infection and puts people at high risk of death from cirrhosis and liver cancer [2].The breakthrough understanding of hepatitis came in 1963 when Dr. Baruch Blumberg discovered an antigen that detected the presence of hepatitis B virus blood samples. He did not set out to discover hepatitis, but his work led to a major breakthrough and increase understanding of the disease. Together with his team identified an unusual antigen from a blood sample of an Australian Aborigine, which they called the "Australia antigen". After further research, this turned out to be the antigen that caused Hepatitis B, which was officially recognized in 1967[3].

There are five viruses that cause hepatitis, called hepatitis A, B, C, D and E. Hepatitis A and E viruses cause infectious hepatitis transmitted by eating food contaminated with faecal material from infected individuals. Viruses B, C and D are originally known as "serum hepatitis", and are transmitted by contact with blood or body fluidscontaining blood of an infected person [4,5].

Transmission of hepatitis B virus results from exposure to infectious blood or body fluids containing bloodin the same way as human immunodeficiency virus (HIV) although (HBV) is 50-100 times more infectious than HIV [4], unprotected sexual contact, blood transfusions, re-use of contaminated needles and syringes, and vertical transmission from mother to child during child birth[6]. Once infected with HBV virus, it can survive outside the body for at least 7 days. During this time, the virus can still cause infection if it enters the body of a person who is not protected by vaccine. The incubation period is 75

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days on average, but can vary from 30 to 180 days[2,7].During this period, symptoms of infection may last for several weeks and can include jaundice (yellowing of the skin), fatigue, nausea, vomiting and abdominal pain [1]. If the infection does not produce an infective immune response, chronic Hepatitis B(CHB) carrier state may develop, where the virus survives and continues to replicate in the body for many years. In this state, the antigen HBsAg remains detectable in the blood for six months after the initial infection [8]. Patient with CHB may develop cirrhosis (liver scarring) that can lead to liver failure, and they may also develop liver cancer. A small portion (1-6%) of chronic carriers will clear the virus naturally [9].

Hepatitis B is prevalence in WHO western Pacific Region and the WHO African Region, where 6.2 % and 6.1 % respectively of the adult population is infected. In the WHO Eastern Mediterranean Region, the WHO South-East Asia Region and WHO European Region, an estimated 3.3 %, 2.0 % and 1.6 % of the general population is infected respectively. 0.7 % of the population the WHO Region of the America is infected [2]. The pooled prevalence of Hepatitis B Virus in Nigeria from studies carried out between 2000 and 2013 is 13.6 % for children and was 11.5%for adults[9].

According to [10], chronic hepatitis B has been proven to be a difficult disease to overcome needing long therapies in many cases. However, it is not possible to predict how long the treatment will take (some treatments are 5 years long) [11]. There are currently seven approved drugs for the treatment of hepatitis B: two formulations of interferon (IFN), conventional and pegylated IFN (PEG-IFN); and five nucleos(t)ide analogues; lamivudine (LMV), telbivudine, adefovir, entecavir, and tenofovir [10]. All the nucleos(t)ide analogues are known to induce drug resistance so, in most cases, treatment is delayed or stopped which frequently results in a virus relapse [11]. Treatment using interferon is the most recommended but it has some downsides compared to tenofovir or entecavir: harder administration (injection vs pill), higher cost, and more side effects. These side effects are so inconvenient for the patient that IFN treatment usually stops after one year

Mathematical models have proven useful for the understanding of virus and drug dynamics under drug therapy in infections such as human immunodeficiency virus (HIV), hepatitis C (HCV), and HBV. Mathematical epidemiology is to understand how to control and eradicate diseases [12] .

Mathematical models were used in [13] to understand the factors that govern infectious disease progression in viral infections. They focused on hepatitis B virus (HBV) dynamics during the acute stages of the infection and analyzed the immune mechanisms responsible for viral clearance. In particular, they found that; a cell-mediated immune response plays an important role in controlling the virus after the peak in viral load.

Mathematical models were developed in [14, 15] to understand the effect of combining passive immunization with treatment of infectious hepatitis B in controlling its spread. They found that, the administration vaccines at birth protect children from early infection of hepatitis B, but the efficacy of the vaccines expires with time. Hence, they concluded that: effort must be made in bringing down the contact rate and also increasing the duration of efficacy of vaccines used in passive immunization.

Models that describes the dynamics of hepatitis B virus (HBV) infection were studied by [16, 17]. The model suggests that a rapid and vigorous CTL response is required for resolution of HBV infection. Also, a model in[18] studied the dynamics of the hepatitis B viral infection model with logistic hepatocyte growth and cytotoxic T-lymphocyte (CTL) response. Their results confirm that the cellular immunity may control viral replication and reduce the infection.

2. Mathematical Formulation

The basic virus infection model (BVIM) with application to Hepatitis B Virus infection was analysed in [19].

$$\begin{aligned} \frac{dx}{dt} &= \lambda - dx - \beta vx \\ \frac{dy}{dt} &= \beta vx - ay \\ \frac{dv}{dt} &= ky - \mu v \end{aligned} \qquad (1)$$

Model (1) can describe some aspect of the viral dynamics in HBV infection. But after the analyses they found the model to be defective biologically, for it showed that a large liver will be less resistant than smaller one. Therefore, they amended it to:

$$\begin{aligned} \frac{dx}{dt} &= \lambda - dx - \frac{\beta vx}{x+y} \\ \frac{dy}{dt} &= \frac{\beta vx}{x+y} - ay \\ \frac{dv}{dt} &= ky - \mu v \end{aligned} \qquad (2)$$

However, the model did not incorporate the effect of refractor cells and effector cells and liver size on the analysis on the virus infection. This paper proposes a mathematical model that takes into cognizance the effects of effector cells, refractor cells and liver size on the dynamics of HBV infection.

In the proposed model, we assume that effector cells can either cure infected cells or annihilate it, there is logistic recruitment of hepatocytes into susceptible cells, effector cells and refractor cells. We also assume that effector cells are at steady state before infection, size of the liver plays a vital role in the infection dynamics.

The population is divided into five compartments, namely: susceptible cells $X(t)$, infected cells $Y(t)$, free virus cells $V(t)$, immune effector cells $E(t)$, and refractor cells $R(t)$. The susceptible cells population increases as a result of generation of Hepatocytes cells described by a term $\varphi X\left(1-\frac{X+Y+R}{K}\right)$ where K is the carrying capacity and φ is hepatocytes maximum proliferation rate and due to refractor cells becoming susceptible at the rate ε. The class reduces as a result of death at the rate d and progression of cells from susceptible cells population to the infected cells population at the rate $\frac{\beta VX}{X+Y}$.

The infected cells class increases as a result of incoming of cells from the susceptible cells population at the rate $\frac{\beta VX}{X+Y}$ and due to the incoming of hepatocytes denoted by a term $\varphi Y\left(1-\frac{X+Y+R}{K}\right)$ with carrying capacity K and hepatocytes maximum proliferation rate φ. The population reduces due to the moving out of cells as a result of turning into refractor cells at the rate ρ as a result of successful cure of infected cells by immune effector cell, and reduces as a result of killing by immune effector cells at the rate a.

The immune effector cell population expand at a rate α at a delayed given time denoted by the term $\alpha Y(t-\tau)E(t-\tau)$. The effector cells are at steady state $\frac{\Lambda}{\mu_2}$ before infection.The class reduces due to the death of immune effector cells at the rate μ_2.

The free virus population grows as a result production of free virus by infected cells at the rate k and reduces due to the death of free virus at the rate μ.

The refractor cells , susceptible cells population increases as a result of generation of Hepatocytes cells described by a term $\varphi R\left(1-\frac{X+Y+R}{K}\right)$ where K is the carrying capacity and φ is hepatocytes maximum proliferation rate and due to recovery of infected cells class at the rate ρ. The class reduces due to the moving out of cells from refractor cells class to the susceptible cells class at the rate ε and due to death of refractor cells at the rate μ_1. The schematic diagram for the proposed model is presented in Figure 1.

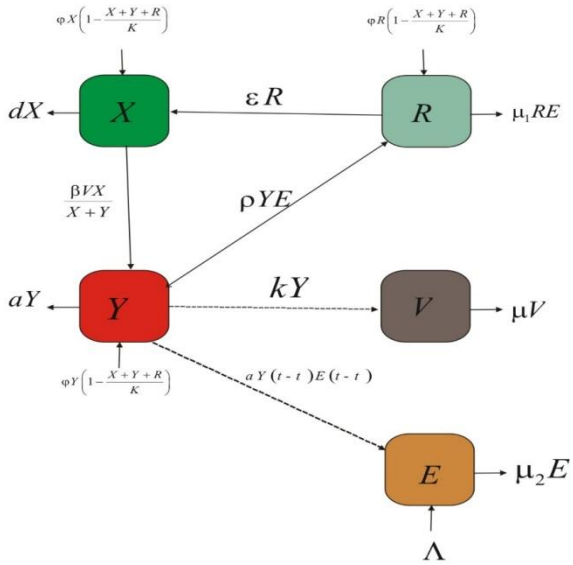


Figure 1: Schematic diagram of the model with liver size, effector and refractor cells

2.1 Model equations

$$\left.\begin{aligned}
\frac{dX}{dt} &= \varphi X\left(1-\frac{X+Y+R}{K}\right)+\varepsilon R-\frac{\beta VX}{X+Y}-dX\\
\frac{dY}{dt} &= \varphi Y\left(1-\frac{X+Y+R}{K}\right)+\frac{\beta VX}{X+Y}-aEY-\rho EY\\
\frac{dV}{dt} &= kY-\mu V\\
\frac{dE}{dt} &= \alpha Y(t-\tau)E(t-\tau)+\Lambda-\mu_2 E\\
\frac{dR}{dt} &= \varphi R\left(1-\frac{X+Y+R}{K}\right)+\rho EY-\varepsilon R-\mu_1 RE
\end{aligned}\right\} \qquad (3)$$

with the initial conditions

$$X(0)=X_0, Y(0)=Y_0, V(0)=V_0, E(0)=E_0, R(0)=R_0 \qquad (4)$$

Table1: Parameters and variables of model with liver size, effector and refractor cells

Variable/Parameter	Description
$X(t)$	Susceptible cells at time t.
$Y(t)$	Infected cells at time t.
$V(t)$	Free virusat time t.
$R(t)$	Refractor cells at time t.
$E(t)$	Immune effector cells at time t.
λ	Hepatocytes maximum proliferation rate.
d	Death rate of susceptible cells.
β	Maximum infection rate.
K	Liver size.
α	Expansion rate of immune effector cells.
ρ	Recovery rate of infected cells.
κ	Production rate of free new virusby infected cells.
μ	Virus clearance.
ε	Rate at which refractor cells becomes susceptible.
τ	Delay in days.
a	Death rate of infected cells.
μ_2	Death rate of immune effector cells.
Λ	Source term lymphocyte
μ_1	Death rate of refractor cells

3. Model Analysis

3.1 Equilibrium states

Theinfection – free equilibrium state $\left(E_f\right)$ of model (3) is

$$E_f=\left(X_f,Y_f,V_f,R_f,E_f\right)=\left(K\left(1-\frac{d}{\varphi}\right),0,0,0,0\right) \qquad (5)$$

and the endemic equilibrium state of the model is

$$X^* = \frac{\varepsilon \dfrac{\rho CM}{\varphi\left(1-\dfrac{T}{K}\right)-\varepsilon-\mu_1 M}}{d-\dfrac{\Lambda}{\mu_2 - C\left(\alpha C(t-\tau)(t-\tau)\right)}(a+\rho)+\beta\dfrac{k}{\mu}} \tag{6}$$

$$Y^* = \frac{A\left(E^*(a+\rho)-\varphi\left(1-\dfrac{T}{K}\right)-\beta\dfrac{k}{\mu}\right)}{\varphi\left(1-\dfrac{T}{K}\right)-(\rho+a)E^*} \tag{7}$$

$$V^* = \frac{kC}{\mu} \tag{8}$$

$$E^* = \frac{\Lambda}{\mu_2 - \left(\alpha C(t-\tau)(t-\tau)\right)} \tag{9}$$

$$R^* = \frac{\rho CM}{\varphi\left(1-\dfrac{T}{K}\right)-\varepsilon-\mu_1\dfrac{\Lambda}{\mu_2 - C\left(\alpha C(t-\tau)(t-\tau)\right)}} \tag{10}$$

Where

$T = X+Y+R,\ X^* = A,\ Y^* = C$ and $E^* = M$

3.2 Basic reproduction number

We apply the next generation matrix technique in[20] to obtain the basic reproduction number, R_0 by considering the infected compartments of the system (3).

Let F_i be the rate of appearance of new infection in the i compartment and V_i be the rate of transfer of individuals out of i, given the disease free equilibrium, then R_0 is the spectral radius (largest eigen values) of the next generation matrix denoted by $G = \rho\left(FV^{-1}\right)$. Let $X = (Y,V,R)^T$ which can be written in the form

$$\frac{dx}{dt} = F_i(x) - V_i(x)$$

where

$$F_i(x) = \begin{bmatrix} F_1 \\ F_2 \\ F_3 \end{bmatrix} = \begin{bmatrix} \dfrac{\beta VX}{X+Y} \\ 0 \\ 0 \end{bmatrix} \tag{11}$$

and

$$V_i(x) = \begin{bmatrix} V_1 \\ V_2 \\ V_3 \end{bmatrix} = \begin{bmatrix} \rho YE + aYE - \varphi Y\left(1-\dfrac{X+Y+R}{K}\right) \\ kY - \mu V \\ \varepsilon R + \mu_1 RE - \rho YE - \varphi R\left(1-\dfrac{X+Y+R}{K}\right) \end{bmatrix} \tag{12}$$

Evaluating the Jacobean matrix of $F(x)$ in (11) and (12) at disease free equilibrium E_f, we have

$$F = \begin{bmatrix} 0 & \beta & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \tag{13}$$

$$V = \begin{bmatrix} -d & 0 & 0 \\ k & -\mu & 0 \\ 0 & 0 & -(d-\varepsilon) \end{bmatrix} \tag{14}$$

Hence the reproduction number $G = \left|\rho\left(FV^{-1}\right) - \lambda I\right|$ is

$$R_0 = \frac{k\beta}{\mu d}$$

3.3 Stability analysis

3.3.1 Local stability of the infection free equilibrium

The infection free equilibrium point, E_f is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.

Proof:Let

$$\left.\begin{aligned} F_1 &= \varphi X\left(1-\frac{X+Y+R}{K}\right)+\varepsilon R-\frac{\beta VX}{X+Y}-dX \\ F_2 &= \varphi Y\left(1-\frac{X+Y+R}{K}\right)+\frac{\beta VX}{X+Y}-aEY-\rho EY \\ F_3 &= kY-\mu V \\ F_4 &= \alpha Y(t-\tau)E(t-\tau)+\Lambda-\mu_2 E \\ F_5 &= \varphi R\left(1-\frac{X+Y+R}{K}\right)+\rho EY-\varepsilon R-\mu_1 RE \end{aligned}\right\} \quad (15)$$

Thus, the Jacobean Matrix J(E) for the system of equations (15) is given by

$$J(E_f)=\begin{pmatrix} -(\varphi-d) & -(\varphi-d) & -\beta & 0 & 0 \\ 0 & -d & \beta & 0 & 0 \\ 0 & k & -\mu & 0 & 0 \\ 0 & 0 & 0 & -\mu & 0 \\ 0 & 0 & 0 & 0 & -(\varepsilon-d) \end{pmatrix} \quad (16)$$

Given

$$\left|J\left(E_f\right)-\lambda I\right|=0 \quad (17)$$

Substitute equation (16) into equation (17) we obtain

$$\begin{vmatrix} -(\varphi-d)-\lambda & -(\varphi-d) & -\beta & 0 & 0 \\ 0 & -d-\lambda & \beta & 0 & 0 \\ 0 & k & -\mu-\lambda & 0 & 0 \\ 0 & 0 & 0 & -\mu-\lambda & 0 \\ 0 & 0 & 0 & 0 & -(\varepsilon-d)-\lambda \end{vmatrix}=0 \quad (18)$$

Evaluating equation (18) we have

$$\left(-(\varepsilon-d)-\lambda\right)(-\mu-\lambda)(-(\varphi-d)-\lambda)\begin{vmatrix} -d-\lambda & \beta \\ k & -\mu-\lambda \end{vmatrix}=0 \quad (19)$$

The characteristic polynomial of equation (19) is given by

$$\left(-(\varepsilon-d)-\lambda\right)(-\mu-\lambda)(-(\varphi-d)-\lambda)\left[\lambda^2+(\mu+d)\lambda+\mu d-k\beta\right]=0 \quad (20)$$

From equation (20) we have

$$\lambda_1=-(\varphi-d),\ \lambda_2=-\left((\varphi-d)+\varepsilon\right),\ \lambda_3=-\mu$$

For the remaining quadratic factor, we use Routh-Hurwitzstability criterion in [21]which states that all roots of a polynomial have negative real part if and only if the coefficients A_i, are positive and the determinant of the matrices $H_i > 0$ for $i = 0, 1, 2$. Therefore, from equation (20) we have

$$\lambda^2+\lambda\left(\mu+d\right)+\mu d-k\beta=0 \quad (21)$$

Comparing with general quadratic equation

$$a_2\lambda^2+a_1\lambda+a_1=0$$

where

$$\left.\begin{aligned} a_2 &= 1 \\ a_1 &= \mu + d \\ a_0 &= \mu d - \beta k = \mu d\left(1 - R_0\right) \end{aligned}\right\} \quad (22)$$

From equation (22), $a_2 = 1,$ thus

$H_1 = 1 > 0$

$$H_2 = \begin{bmatrix} \mu + d & 0 \\ 1 & \mu d - \beta k \end{bmatrix}$$

(i) $H_1 = \mu + d > 0$

(ii) $H_2 = \left(\mu + d\right)\mu d\left(1 - R_0\right)$

This implies $H_2 > 0$ whenever $R_0 < 1$.

Therefore, all the eigen values of the polynomial (20) 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 $R_0 < 1$ we conclude that the disease-free equilibrium point is locally asymptotically stable.

3.3.2 Global stability of the infection free equilibrium

Two conditions are sufficient to guaranty the global stability of the infection free equilibrium point. Adopting the method in[22], we rewrite model (3) as:

$$\left.\begin{aligned} \frac{dS}{dt} &= F\left(S, I\right) \\ \frac{dI}{dt} &= G\left(S, I\right) \\ G\left(S, 0\right) &= 0 \end{aligned}\right\} \quad (23)$$

Where $S \in \mathbb{R}^1$ denote the number of uninfected cells and $I \in \mathbb{R}^3$ denote the number of infected cells, $E_f = (X_f, 0)$ denotes the infection free equilibrium of the model (3).

$H_1 : \frac{dS}{dt} = F(S, 0),$ S^* is globally asymptotically stable.

$H_2 : \frac{dI}{dt} = G(S, I) = AI - G(S, I) \geq 0$ for $(S, I) \in D_4$

Where $A = D_V G(S^*, 0)$ is M matrix (The off-diagonal elements are non-negative) and S is the region where the model makes biological sense. If the system (3) satisfies the above two conditions, then the system is said to be globally asymptotically stable.

Theorem 1:

The fixed point $E_f = (X_f, 0, 0, 0, 0)$ is globally asymptotically stable equilibrium of model (3) provided $R_0 < 1$ and the initial conditions in (4) are satisfied.

Proof:

Consider

$$S_1 = X, \quad S_2 = \begin{bmatrix} Y \\ V \\ R \end{bmatrix} \quad (24)$$

When $Y = V = R = 0,$ the uninfected subsystem (i.e. the equation for S) which has the solutionbecome

$$X\left(t\right) = K\left(1 - \frac{d}{\varphi}\right) + e^{-dt}\left(X(0) - K\left(1 - \frac{d}{\varphi}\right)\right) \quad (25)$$

Obviously, $X(t) \to X(0) - K\left(1 - \frac{d}{\varphi}\right)$ as $t \to \infty$ regardless of the initial value $X(0)$. Therefore, it shows that the first condition holds for our model.Next the right-hand side of the infectious systems (the equation for Y, V, R) can be written as

$$\frac{dS_2}{dt} = G(S_1, S_2) = \begin{bmatrix} -(aE + \rho E) + \varphi\left(1 - \frac{T}{K}\right) - \frac{\beta VX}{(X+Y)^2} \\ kY - \mu V \\ \varphi R\left(1 - \frac{T}{K}\right) + \rho EY - \varepsilon R - \mu_1 RE \end{bmatrix} \tag{26}$$

$$= \begin{bmatrix} -d & 0 & 0 \\ k & -\mu & 0 \\ 0 & 0 & -(d-\varepsilon) \end{bmatrix} \begin{bmatrix} Y \\ V \\ R \end{bmatrix} - \begin{bmatrix} -Y(aE + \rho E) + \varphi Y\left(1 - \frac{T}{K}\right) + \frac{\beta VX}{X+Y} \\ kY - \mu V \\ \varphi R\left(1 - \frac{T}{K}\right) + \rho EY - \varepsilon R - \mu_1 RE \end{bmatrix}$$

$$= \begin{bmatrix} \varphi\left(\frac{K}{T} - 1\right) + Y(aE + \rho E) - Yd - VX\frac{\beta}{X+Y} \\ 0 \\ R\left(2\varepsilon + \mu_1 E + \varphi\left(\frac{T}{K} - 1\right) - d\right) - Y\rho E \end{bmatrix} \tag{27}$$

$$= AS_2 - \hat{G}(S_1, S_2)$$

Where

$$A = \begin{bmatrix} -d & 0 & 0 \\ k & -\mu & 0 \\ 0 & 0 & -(d-\varepsilon) \end{bmatrix}$$

and $$\hat{G}(S_1, S_2) = \begin{bmatrix} -(aE + \rho E)Y + \varphi Y\left(1 - \frac{T}{K}\right) + \frac{\beta VX}{X+Y} \\ kY - \mu V \\ \varphi R\left(1 - \frac{T}{K}\right) + \rho EY - \varepsilon R - \mu_1 RE \end{bmatrix}$$

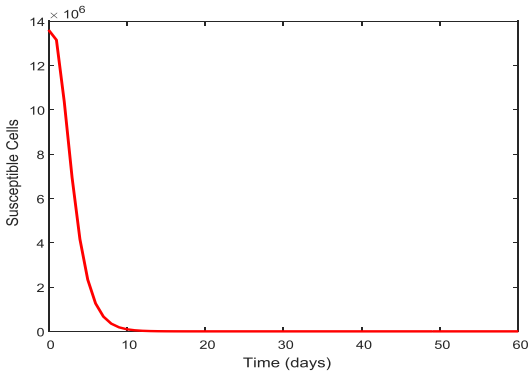
It is obvious that $X \le K\left(1 - \frac{d}{\varphi}\right)$, hence it is clear that $G(X, Y) \ge 0$ for all $(X, Y) \in \mathbb{R}^3_+$.We also notice that matrix A is an M-matrix since all of its off-diagonal elements are non-negative. Hence, this proves the global stability of the infection free equilibrium.

4. Numerical Results

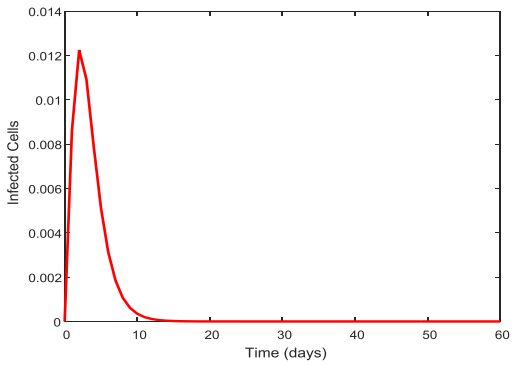
We performed some numerical experiments using ode45 function from MATLAB R2010a to study the behaviour of the system. The initial condition for each plot and parameter values were presented in Table 2. Figures 2 to 5 are the graphs generated from numerical simulations carried out on the model equations.

Table 2: Variables and parameters values used for computational results

Variable/Parameter	Values	Reference
φ	0.1	[23]
β	0.025	[19]
μ_1	0.5	[13]
μ_2	0.5	[13]
K	13600000,19000000,25000000	[13],[22],
d	0.011	[13]
α	0.00000073	[13]
k	200	[24]
μ	0.67	[13]
τ	(1-5), (5-20)	[18]
ε	0.071	[13]
a	0.011	[13] and [19]
Λ	10	[13]
ρ	0.1	[23]
$X(0)$	13600000	[13]
$Y(0)$	0	[13]
$V(0)$	0.33	[13]
$E(0)$	20	[13]
$R(0)$	0	[13]



(a)



(b)

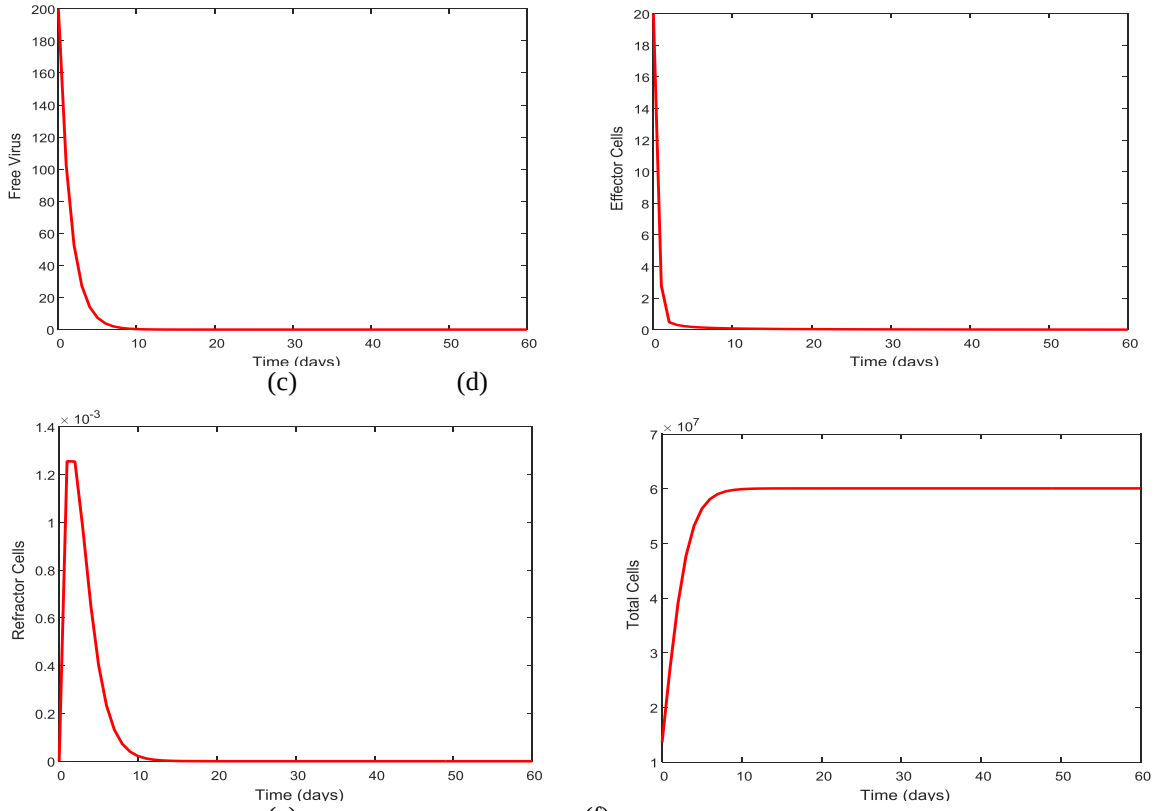
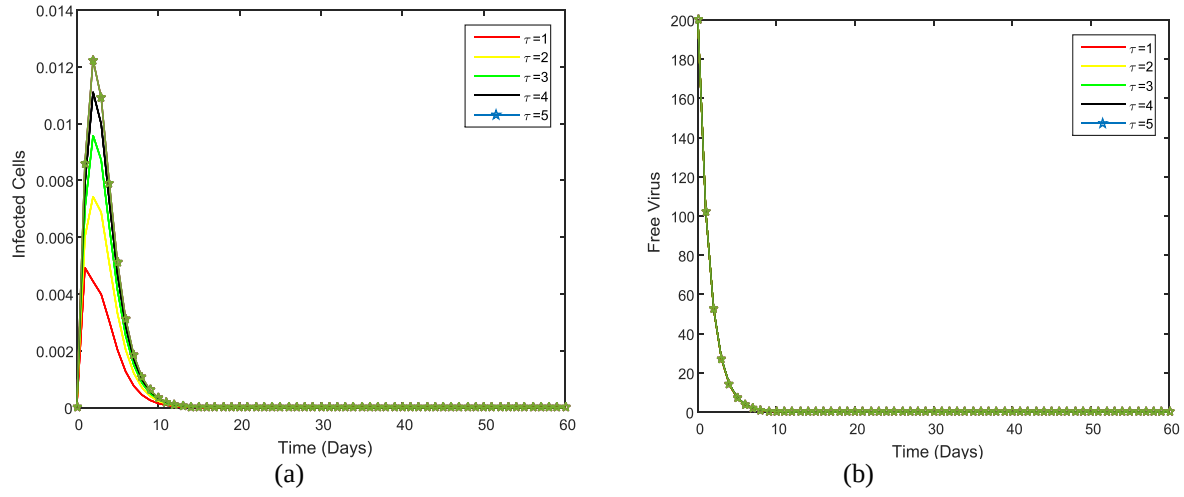
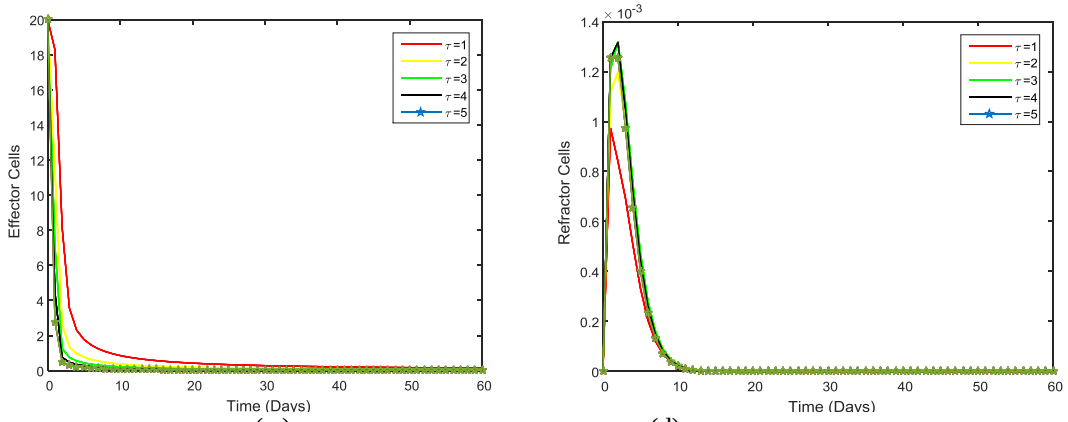


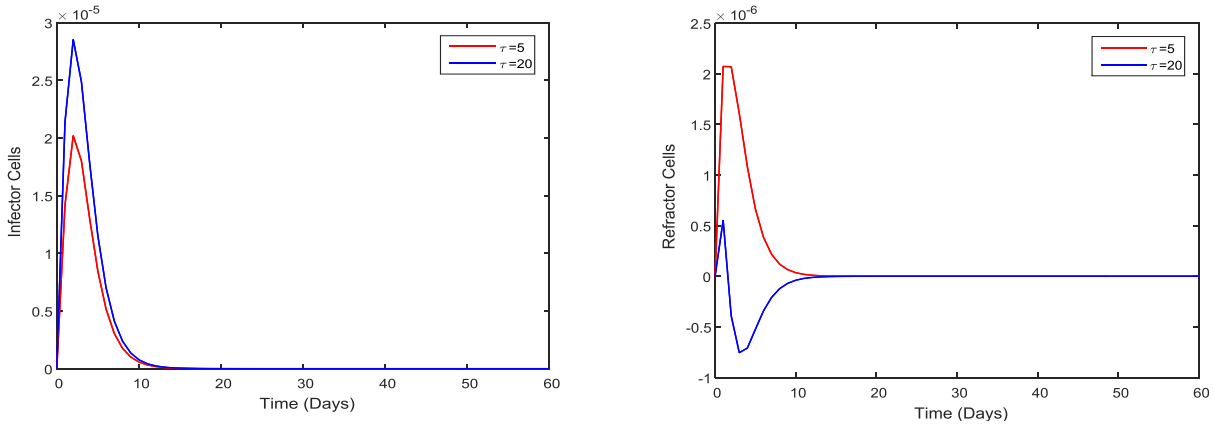
Figure 2.Evolutions of (a) susceptible cell, b) infected cells c) free virus d) effector cells e) refractor cell and (f) total liver cells, we used the parameter values $K = 1360000$ and $\tau = 1, 2, ...5$. All other parameter values are taken from Table 4.1to obtain the graphs





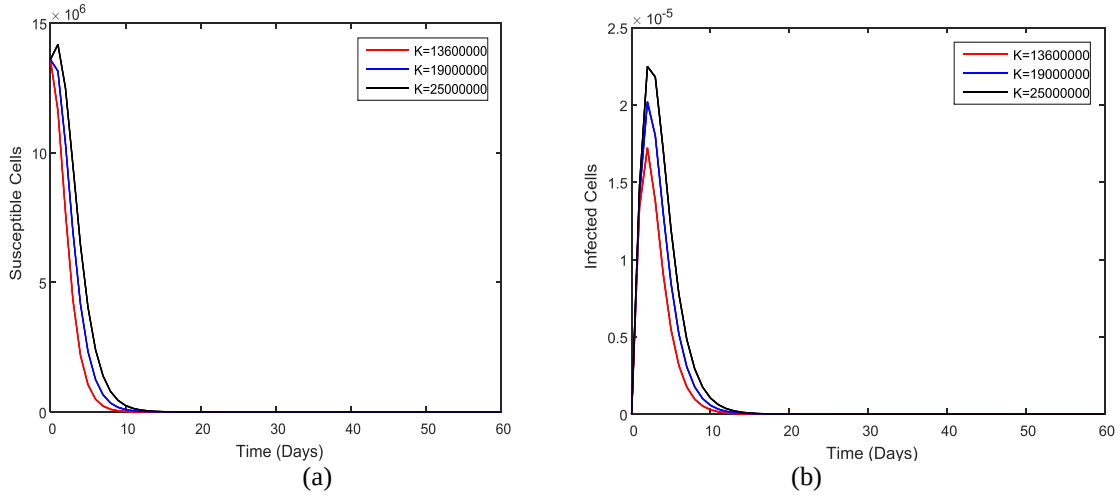
(c) (d)

Figure 3.Showing the effect of delay on the evolution of (a) infected cells (b) free virus (c) effector cells (d) refractor cells populations, we used $\tau = 1, 2, ..5$. All other parameters values are taken from Table 4.1.

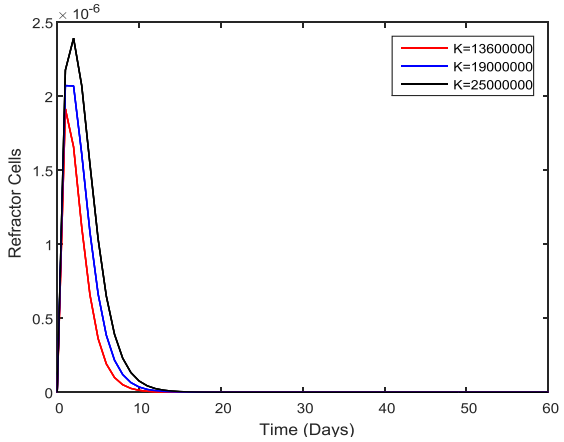


(a) (b)

Figure 4.Showing the effect of delay on the evolution of (a) infected cells and (b) refractor cells populations we used $\tau = 5, \tau = 20$. All other parameters values are taken from Table 4.1.



(a) (b)



(c)

Figure 5. showing the effect of liver size on (a) susceptible cells, (b) infected cells and (c) refractor cells for K=13600000, 19000000 and 25000000. All other parameter values are taken from Table 4.1.

5. Discussion of Results

We discuss our simulated results in three subsections namely: Individual liver cells, combined liver cells and the effects of time delay, and liver size on the population of susceptible infector and refractor cells, on the dynamics of the model.

Individual subpopulation for the liver cells

Observing Figure 2a, the number of susceptible liver cells' population dropped sharply. The infected liver cells population evolve up sharply and then begin to drop as shown in Figure 2b. Figure 2c illustrate the evolution of infected liver cells and the number of infected cells peaked at about 7 days after infection and drops sharply after a period of time. The population of immune effector cells falls as a result of declining of the population of infected hepatocytes that trigger its expansion, this is illustrated in Figure 2d. While the population of refractor cells rises and then begin to drop as a result of increase in its population due to the number of incoming recovered infected cells and death of the infected liver hepatocytes cells as shown in Figure 2e. The logistic growth of the liver hepatocytes is somewhat arbitrary but its qualitative form fits well with biological realistic liver growth, total population of liver cells continue to rise until it reaches a stable level as a result of homeostatic effect of liver organ as shown in Figure 2f.

Effects of time delay on the infected, free virus, effector and refractor cells on the dynamics of the model

Figures3a to 3d depict the effect of time delay on the evolution of infected cells, free virus, effector and refractor cells on the dynamics of the model. It is observed that if time is delayed for $\tau = 1, 2, \ldots 5$, may alter the dynamics of increase in the population of infected liver cells,which indicates the absence of effective expansion of immune effector cells that may hinder the growth of the infected cell as indicated in Figure 3a. Figure 3b has shown no effect of delay on the population of free virus cells, this implies that as the rate of expansion of immune effector cells is delayed between 1 to 5 days the virus production is undetectable. Immune effector cells population increases on the onset of the infection, but decline in the later days as shown in Figure 3c.Figure 3d shows that the population of refractor cells is affected by the delay as its population varies within the period of the delay.However if the delay is run between $\tau = 5$ and $\tau = 20$ there is increase in the population of refractor cells and decrease in the number of infected cells, this can be viewed as a result of triggering the effect of immune effector cells, that annihilate some of the infected cells or cure some, which translates into the rise in the refractor cells population as shown in Figures 4a and 4b.

Effects of varying liver size on the population of susceptible cells infected, and refractor cells on the dynamics of the model

Figure 5a depicts that the proliferation of susceptible cells depends the size of the liver organ, as the larger it is the more number of susceptible cells are accommodated. Figure 5b shows that the population of infected liver cells are governed by the size of the liver for the bigger the liver so also the number of infected cells that it can accommodate. The size of the liver also has effect on population of refractor cells as can be seen from Figure 5c that the larger the liver so also the larger the number of the refractor cells that will be present. Therefore, hepatocyte proliferation depends on the size of the liver.

6. Conclusion

In this paper, we have modified [19] using logistic hepatocytes growth considering the effect of liver size, immune effector and refractor cells in the dynamics of Hepatitis B virus infection. Analytical studies were carried. The disease free equilibrium and endemic equilibrium points were obtained and our results shows that the equilibrium point of the system is locally asymptotically stable if $R_0 < 1.$ The numerical simulation result of the model carried out indicates that the size of the liver and immune effector and refractor cells have significant effect on the infection dynamics of hepatitis b virus infection. Furthermore, the result of this work confirm that the cellular immunity may control viral replication and reduce hepatitis Bviral infection. It is recommended in view of the findings of this study, that government and pharmaceutical companies should fund research to produce a drug that can activate the action of immune effector cells earlier than the time it took now, as soon as a patient is infected with the hepatitis b virus, and encourage routine hepatitis check up in the early and later days,even if vaccination was administered.

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