Mathematical analysis of Hepatitis B virus infection with logistic growth for proliferation of Hepatocytes cells

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Abstract

A logistic growth model was developed which investigates the proliferation of hepatocytes cells for hepatitis B virus infection. The results from the model analysis show that the disease-free equilibrium (DFE) is globally asymptotically stable (GAS) when the basic reproduction number (R_0) is equal to or below a unity value, and unstable when it is above the unity value. It also reveals that when R_0 is above the unity value with some conditions an endemic equilibrium of the model is GAS, indicating a real proliferation of the hepatocytes cells within the boundary of the liver. Numerical simulations are also carried out using maple software to illustrate the effects of fulminant, acute and chronic infections on the number of HBV, healthy and infected (unhealthy) hepatocytes.

Keywords and phrases: Hepatitis B Virus (HBV), hepatocytes cells, basic reproduction number, disease-free equilibrium (DFE), globally asymptotically stable (GAS)

1 Introduction

Hepatitis (plural: hepatitides) is derived from the Greek *hepar* meaning liver and the suffix – itis, meaning inflammation. Hepatitis therefore, is a medical condition defined by the inflammation of the liver and it is characterized by the presence of the inflammatory cells in the tissue of the organ. Among the most causes of hepatitis is the Hepatitis B Virus (HBV). Hepatitis B therefore, is an infectious disease caused by the hepatitis B virus (HBV) and the disease affects the liver which results to serious liver diseases like chronic hepatic insufficiency, hepatocellular carcinoma and cirrhosis. The disease interferes with the functions of the liver by replicating in the hepatocytes thereby reducing or hampering liver's ability to perform life preserving functions such as filtration of harmful infectious agents from the blood, storage of blood sugar and conversion to usable energy forms, and production of many proteins needed for life are either reduced or hampered. Hepatitis B can cause both acute and chronic infections.

Hepatitis is acute when it lasts less than six months and chronic when it lasts more than that. Initial symptoms of the acute infection are not specific and flu-like common to most acute viral diseases and there may be malaise, muscle and joint pains, fever, vomiting or nausea, headache and diarrhea. Specific symptoms which can be present in acute Hepatitis from any cause include choluria (dark urine), jaundice and discomfort in the abdomen. Chronic hepatitis causes symptoms which are non-specific such as malaise, tiredness and weakness. These are commonly identified through blood tests. Advanced liver damage is indicated by presence of jaundice through blood tests which on physical examination may be enlargement of liver. Great damage to and scarring of liver known as cirrhosis lead to loss of weight, easy bruising and bleeding, swelling of legs (peripheral edema) and accumulation of fluids in the abdomen (ascites). Eventual outcome of cirrhosis may lead to various complications to enlarged veins in the walls of oesophagus that can cause life threatening bleeding, confusion and coma, and kidney dysfunction.

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Hepatitis B is a global health problem and it is many times more infectious than many world known health diseases. To be specific, it is fifty to one hundred times more infectious than HIV [22]. It has caused epidemics in parts of Africa and Asia, and in China it is endemic [21]. In 2004, an estimated 350 million individuals were infected worldwide. Regional and national prevalence ranges from over 10 % in Asia to under 0.5 % in the United States and Northern Europe. About a third of world population have been infected with hepatitis B virus at some stages of their lifetime. Out of this significant portion of the world's population, about 360 million people remain chronically infected carriers of the disease, most of who are in darkness concerning their HBV status [6] and [14].

Infection with HBV has been a major public health challenge which led to the observation of July 28 as world's hepatitis day with aim to raise global awareness of hepatitis B and hepatitis C and encourage prevention, diagnosis and treatment. This campaign has been led by the World Hepatitis Alliance since 2007 which yielded a result in May 2010, when the World Health Organization (WHO) gave it a global endorsement and since then 28th of July of every year is set aside as a World Hepatitis Day. In March 2015 WHO issued its first guidelines for the treatment of chronic hepatitis B. This condition according to WHO, is affecting some 240 million people worldwide. These guidelines are the prevention, care and treatment of persons living with chronic hepatitis B. This infection has two stages: acute and chronic, but much attention is focussed on chronic stage as acute hepatitis B does not usually require treatment and must adult clear infection spontaneously [12] and [13]. Chronic stage on the other hand, may never be cured completely and may eventually cause liver cirrhosis and hepatocellular carcinoma-HCC [12] and [14].

Statistics released by WHO in July 2014 showed that over 750,000 people die every year of hepatitis B globally. Moreover, approximately 4 million people worldwide who represent 10% of people infected with HIV are co-infected with HBV [4]. Due to the fact that HBV is significant as a global public threat, the virus and its associated diseases have attracted considerable attention from mathematical and theoretical biologists. The work of [18], [19], [3] and [16] can testified to this assertion. Mathematical models when applied to biology medicine can describe and simulate possible not yet known scenarios. Mathematical models and computer simulations have numerous advantages and a major advantage of both of them is the capability to make predictions of biological systems and their behaviour that would be difficult to conduct experimentally.

Mathematical models therefore, provide opportunity to avoid costly and time consuming complicated laboratory experiments through virtual experiments. Furthermore, models are reproducible and not subject to biological variations. Another advantage of mathematical models is that models can project how infectious diseases progress to show the likely results of an epidemic and thus aid health interventions. William Hammer and Ronald Rose were early pioneers in disease modelling, who in the early twentieth century explained epidemic behaviour through application of the law of mass. Lowell Reed and Wade Hampton Frost later developed Reed-Frost epidemic model to describe the relationship between susceptible, infected and immune individuals in population. Immunopathogenesis of HBV when well understood can lead to an efficient way to prevent and treat the disease. Fundamental insight into the fine details of the interaction between HBV and immune system have been provided through molecular techniques, however, many biologically important questions are not primarily concerned with population dynamics of the immune response.

Mathematical models are often needed to answer these questions. Unlike many other viruses like HIV where cell culture systems allow in vitro infection and passagining of virus are not available for HBV, which is hepatotropic and noncytophatic. Studies conducted on pathogenesis in animal models recently demonstrated that the enhanced recruitment of virus-specific CTLs into the cells of liver is critical for the pathogenesis of HBV infection and hepatocellular carcinoma [24]; [16]. Despite the fact that mankind is blessed with various research works and availability of safe and effective drugs and vaccinations, HBV continue to be major threat to mankind all over world as its morbidity and mortality is on the increase. In the giant of Africa, Nigeria for instance, the prevalent rate of 12% which was reported in 2006 has risen to 13.6% in 2013 [17]. In fact latest statistics released by the Federal Ministry of Health indicated that one out of every ten Nigerians has Hepatitis [20].

Most existing mathematical models of Hepatitis B dynamics assume constant proliferation of hepatocytes and ignore biological limits imposed on liver cell growth. In this work, we introduce a novel model that incorporates logistic growth to capture the natural regeneration capacity and saturation of hepatocytes. Unlike previous studies that consider linear or constant target cell recruitment, our formulation reflects realistic homeostatic constraints of liver tissue.

We derive new analytical results on the existence and stability of infection-free and endemic equilibria under logistic hepatocyte dynamics. An explicit viral reproduction number is obtained, showing the critical conditions for viral persistence or clearance. Numerical simulations further confirm that logistic constraints significantly affect viral load trajectories and treatment responsiveness. Therefore, this study provides a more biologically accurate and predictive framework for understanding Hepatitis B infection and evaluating therapeutic strategies

2 Methodology/Model formulation

A mathematical model of HBV infection was developed improving on the existing models. The model incorporated standard incidence function and a logistic term for proliferation of hepatocytes. The model contains 5 variables namely: uninfected (healthy or target) hepatocytes (U), Exposed hepatocytes (E), Virus producing (infected) hepatocytes (I), total host (T) and free virus(V) . The following assumptions are taken into account in the construction of the model:

i. There is homogeneous mixing of the cells and the virus, where all cells are equally likely to be infected by the virus.

ii. The liver is considered to be a bounded space instead of being an unbounded space.

The uninfected hepatocytes (U) proliferate according to a signal that takes on a logistic form, with homeostatic liver size T^m, at a maximum per capita proliferation rate ρ. This is due to the fact that the hepatocytes cannot increase unboundedly. Uninfected hepatocytes become exposed by free virus at a rate β. All cells die naturally at a rate μ. Exposed cells proceed to infectious class at a rate σ. Infected hepatocytes (I) may be cured and revert to uninfected stage at a rate γ. This stage is described as non-cytolytic loss of infected hepatocytes through loss of all covalently closed circular DNA (cccDNA) from the nucleus [9]. N is the average number of virus produced by infected cells. Furthermore, the Exposed cells and the virus producing hepatocytes (I) additionally die due to infection at a rate μ_1 and μ_2 respectively. And the free virus decreases at the rates μ_3 due to natural death. Description of the variables and parameters are described in Table 1.

And a schematic diagram of the model is depicted in (**??**).

Based on the above assumptions and formulation, we arrived at the following nonlinear-coupled system of differential equations

$$\begin{cases} \frac{dU}{dt} = \rho U(1 - \frac{T}{T^m}) - \frac{\beta VU}{T} + \gamma I - \mu U \\ \frac{dE}{dt} = \frac{\beta VU}{T} - (\sigma + \mu + \mu_1)E \\ \frac{dI}{dt} = \sigma E - (\gamma + \mu + \mu_2)I \\ \frac{dV}{dt} = N\mu_2 I - \frac{\beta VU}{T} - \mu_3 V \end{cases} \tag{1}$$

Where

$$T = U + E + I \tag{2}$$

So that

$$\frac{dT}{dt} = \rho U(1 - \frac{T}{T^m}) - \mu T - (\mu_1 E + \mu_2 I) \tag{3}$$

Table 1: **Description of the variables and parameters of the model.**

Variable/ Parameter	Description
U(t)	Uninfected (healthy or target) hepatocytes at time t
E(t)	Exposed hepatocytes at time t
I(t)	Virus producing (infected) hepatocytes at time t
V(t)	Free virus at time t
T(t)	Total host at time t
ρ	Rate of proliferation of hepatocytes
β	Effective contact rate between V and U
μ	Natural death rate of hepatocytes
μ_1	Virus-induced death rate of exposed hepatocytes
μ_2	Virus-induced death rate of Virus producing hepatocytes
μ_3	Natural death rate of free virus
σ	Progression rate from E to I
γ	Rate of reversion from I to U due to clearance of virus by the immune response
N	Average number of virus produced by infected cells.
T^m	Maximum number of hepatocytes

2.1 Positivity and boundedness of solutions

Since the model is dealing with populations, all the variables and parameters of the model are positive. Thus, the closed set

$$\Omega = \Omega_1 \times \Omega_2 \subset R_+^3 \times R_+^1 \tag{4}$$

with

$$\Omega_1 = \left\{ \left(U, E, I \in R_+^3 : T \leq \frac{\rho U T^m}{(\rho U + \mu T^m)} \right) \right\} \tag{5}$$

and

$$\Omega_2 = \{V : V \geq 0\} \tag{6}$$

for hepatocytes and free virus population respectively, is positively-invariant set under the flow described by (1), so that no solution path leaves through any boundary of Ω . Hence, it is sufficient to consider the dynamics of the model in Ω_1 and Ω_2. Thus, the model is mathematically and epidemiologically well posed.

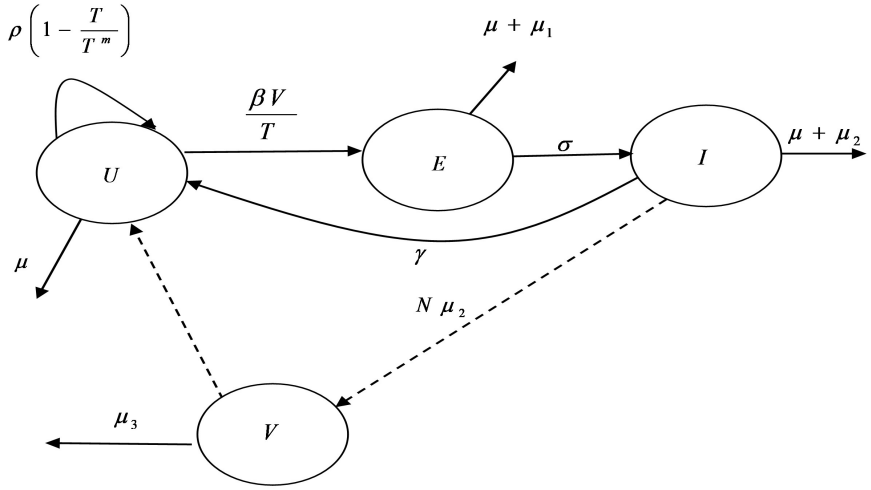

Figure 1: Schematic diagram of the HBV infection model

3 Reproduction Number and Stability of Virus-free Equilibrium (e^0)

The model (1) has a virus-free equilibrium states, given by

$$e^0 = (U^0, E^0, I^0, V^0) = \left(\frac{(\rho-\mu)T^m}{\rho}, 0, 0, 0\right) \tag{7}$$

3.1 Basic reproduction number, R_0 and Local stability of disease-free equilibrium state

Using the notations in van den Driessche and Watmough [10], the next generation operator method is applied on the system (1) to establish the local stability of the HBV-free equilibrium. Thus, the matrices F and V, for the new infection terms and the remaining transfer terms respectively, are given by;

$$\mathcal{F} = \begin{pmatrix} 0 & 0 & \frac{\beta u^0}{T^0} \\ 0 & 0 & 0 \\ 0 & N\mu_2 & 0 \end{pmatrix} \tag{8}$$

and

$$\mathcal{V} = \begin{pmatrix} -(\sigma+\mu+\mu_1) & 0 & 0 \\ \sigma & -(\gamma+\mu+\mu_2) & 0 \\ 0 & 0 & -(\beta+\mu_3) \end{pmatrix} \tag{9}$$

And from van den Driessche and Watmough [10], it follows that the basic reproduction number is

$$R_0 = \rho(\mathcal{F}\mathcal{V}^{-\infty}) = \frac{\beta N\sigma\mu_2 U^0}{(\sigma+\mu+\mu_1)(\gamma+\mu+\mu_2)(\beta+\mu_3)T^0} \tag{10}$$

i.e

$$R_0 = \frac{\beta N\sigma\mu_2}{(\sigma+\mu+\mu_1)(\gamma+\mu+\mu_2)(\beta+\mu_3)} \tag{11}$$

Thus, by Theorem 2 of [18], we established the following Theorem.

Theorem 1: The Virus-free equilibrium, E^0 of (1) is locally asymptomatically stable (LAS) if $R_0 < 1$ The epidemiological implication of the theorem is that the virus can be eliminated (control) from the population when $R_0 < 1$. i.e. if the initial size of the variable of the model are in the basin of attraction of the virus-free equilibrium.

4 Global stability of disease-free equilibrium (e^0)

In global asymptotic stability, solutions approach the equilibrium for all initial conditions. It removes the restrictions on the initial conditions of the model variables.

Theorem 2: The HBV-free equilibrium of the model (1) is globally asymptotically stable (GAS) if $R_0 > 1$

Proof: To establish the global stability of the virus-free equilibrium, we considered the Lyaponuv function:

$$F = N(\mu + \mu_2)\sigma L + N\mu_2(\sigma + \mu + \mu_1)I + (\sigma + \mu + \mu_1)(\gamma + \mu + \mu_2)V \tag{12}$$

Differentiating, we have

$$F' = N\mu_2\sigma L' + N\mu_2(\sigma + \mu + \mu_1)I' + (\sigma + \mu + \mu_1)(\gamma + \mu + \mu_2)V' \tag{13}$$

i.e

$$F' = N\mu_2\sigma(\frac{\beta VU}{T} - (\sigma + \mu_2)L) + N\mu_2(\sigma + \mu + \mu_1)(\sigma L - (\gamma + \mu + \mu_2)I) +$$

$$(\sigma + \mu + \mu_1)(\gamma + \mu + \mu_2)(N\mu_2 I - \frac{\beta VU}{T} - \mu_3 V) \tag{14}$$

simplifying

$$F' = (\sigma + \mu + \mu_1)(\gamma + \mu + \mu_2)(\frac{\beta U}{T} - \mu_3)V\left(\frac{N\mu_2\sigma\beta U}{(\sigma + \mu + \mu_1)(\gamma + \mu + \mu_1(\frac{\beta U}{T} + \mu_3)T)} - 1\right) \tag{15}$$

since $U \leq U^0; T \leq T^0$, then we have

$$F' \leq (\sigma + \mu + \mu_1)(\gamma + \mu + \mu_2)(\frac{\beta U^0}{T^0} - \mu_3)V\left(\frac{N\mu_2\sigma\beta U^0}{(\sigma + \mu + \mu_1)(\gamma + \mu + \mu_1(\frac{\beta U^0}{T^0} + \mu_3)T^0)} - 1\right) \tag{16}$$

and since $U^0 = T^0$, we have

$$F' \leq (\sigma + \mu + \mu_1)(\gamma + \mu + \mu_2)(\beta + \mu_3)V\left(\frac{N\mu_2\sigma\beta U^0}{(\sigma + \mu + \mu_1)(\gamma + \mu + \mu_1(\beta + \mu_3)T^0)} - 1\right) \tag{17}$$

i.e

$$F' \leq (\sigma + \mu + \mu_1)(\gamma + \mu + \mu_2)(\beta + \mu_3)V(R_0 - 1) \tag{18}$$

Since all model variables and parameters are nonnegative, it follows that $F' \leq 0$ if $R_0 \leq 1$, with $F' = 0$ holds when $R_0 = 1$ and $V = 0$. Thus, $V = 0$ is the largest invariant subset in the set $F' = 0$ Therefore, F is a lyapunov function on the Ω . Hence, by the LaSalle's invariance principle [ ], e^0 is overall globally asymptotically stable in $\Omega = \Omega_1 \times \Omega_2 \subset R^3_+ \times R^1_+$ and hence, the proof is complete.

5 Existence and Stability of Boundary Equilibrium (e^{**})

Theorem 3: The model(1) has a unique positive equilibrium, whenever $R_0 > 1$. **Proof:** At equilibrium state the rate of change of each variable is equal to zero i.e

$$\frac{dU}{dt} = \frac{dE}{dt} = \frac{dI}{dt} = \frac{dV}{dt} = \frac{dT}{dt} = 0 \tag{19}$$

Now, at endemic and any arbitrary equilibrium state, let

$$e^{**} = (U, E, I, V) = (U^{**}, E^{**}, I^{**}, V^{**}) \tag{20}$$

$$e^* = (U, E, I, V) = (U^*E^*, I^*, V^*) \tag{21}$$

respectively. Thus, from(1),(3),(19) and (21), we have;

$$\begin{cases} \rho U^*(1 - \frac{T^*}{T^m}) - \frac{\beta V^* U^*}{T^*} + \gamma I^* - \mu U^* = 0 \\ \frac{\beta V^* U^*}{T^*} - (\sigma + \mu + \mu_1)E^* = 0 \\ \sigma E^* - (\gamma + \mu + \mu_2)I^* = 0 \\ N\mu_2 I^* - \frac{\beta V^* U^*}{T^*} - \mu_3 V^* = 0 \\ \rho U^*(1 - \frac{T^*}{T^m}) - \mu T^* - (\mu_1 E^* + \mu_2 I^*) = 0 \end{cases} \tag{22}$$

Solving the equations in (22) simultaneously, we have;

$$\begin{cases} U^* = \frac{\Lambda^*(\sigma+\mu+\mu_1)(\gamma+\mu+\mu_2)}{(\mu_1(\sigma+\mu+\mu_1)(\gamma+\mu+\mu_2+(((\sigma+\mu+\mu_1)(\gamma+\mu+\mu_2)-\gamma\sigma)\lambda^*)} \\ E^* = \frac{\Lambda^*(\gamma+\mu+\mu_2)\lambda^*}{(\mu_1(\sigma+\mu+\mu_1)(\gamma+\mu+\mu_2+(((\sigma+\mu+\mu_1)(\gamma+\mu+\mu_2)-\gamma\sigma)\lambda^*)} \\ I^* = \frac{\sigma\Lambda^*\lambda^*}{(\mu_1(\sigma+\mu+\mu_1)(\gamma+\mu+\mu_2+(((\sigma+\mu+\mu_1)(\gamma+\mu+\mu_2)-\gamma\sigma)\lambda^*)} \\ V^* = \frac{\Lambda^*\{N\mu_3\sigma-(\sigma+\mu+\mu_1)(\gamma+\mu+\mu_2)\lambda^*}{\mu_4(\mu_1(\sigma+\mu+\mu_1)(\gamma+\mu+\mu_2+(((\sigma+\mu+\mu_1)(\gamma+\mu+\mu_2)-\gamma\sigma)\lambda^*)} \\ T^* = \frac{\Lambda^*\{(\sigma+\mu+\mu_1)(\gamma+\mu+\mu_2)+((\gamma+\mu+\mu_2)+\sigma)\lambda^*}{(\mu_1(\sigma+\mu+\mu_1)(\gamma+\mu+\mu_2+(((\sigma+\mu+\mu_1)(\gamma+\mu+\mu_2)-\gamma\sigma)\lambda^*)} \end{cases} \tag{23}$$

where;

$$\Lambda^* = \rho U^*(1 - \frac{T^*}{T^m}) \tag{24}$$

and;

$$\lambda^* = \frac{\beta V^*}{T^*} \tag{25}$$

Then, substituting (23) and (24) in to (25) and simplifying, gives;

$$\lambda^* = \frac{\beta\{N\mu_2\sigma - (\sigma + \mu + \mu_1)(\gamma + \mu + \mu_2)\lambda^*}{\mu_3\{(\sigma + \mu + \mu_1)(\gamma + \mu + \mu_2) + ((\gamma + \mu + \sigma)\lambda^*)} \tag{26}$$

i.e

$$\lambda^*\left\{\mu_3((\gamma + \mu + \mu_2) + \sigma)\lambda^* + \{\mu_3(\sigma + \mu + \mu_1)(\gamma + \mu + \mu_2) - \beta(N\mu_2\sigma - (\sigma + \mu + \mu_1)(\gamma + \mu + \mu_2))\}\right\} = 0 \tag{27}$$

This implies that;

$$\lambda^* = 0 \tag{28}$$

or

$$\lambda^* = \frac{\beta(N\mu_2\sigma - (\sigma + \mu + \mu_1)(\gamma + \mu + \mu_2)) - \mu_3(\sigma + \mu + \mu_1)(\gamma + \mu + \mu_2)}{\mu_3((\gamma + \mu + \mu_2) + \sigma)} \tag{29}$$

Thus,(28) implies existence of virus-free equilibrium (already discussed). Now, consider (29) at endemic equilibrium, e^{**} we have;

$$\lambda^{**} = \frac{\beta(N\mu_2\sigma - (\sigma + \mu + \mu_1)(\gamma + \mu + \mu_2)) - \mu_3(\sigma + \mu + \mu_1)(\gamma + \mu + \mu_2)}{\mu_3((\gamma + \mu + \mu_2) + \sigma)} \tag{30}$$

Simplifying, gives;

$$\lambda^{**} = \frac{(\sigma + \mu + \mu_1)(\gamma + \mu + \mu_2)(\beta + \mu_3)}{\mu_3((\gamma + \mu + \mu_2) + \sigma)}(R_0 - 1) \tag{31}$$

Thus, since λ^{**} cannot be negative, R_0 will not be less than 1. If $R_0 = 1$, then $\lambda^{**} = 0$, implying virus-free equilibrium analysed in the previous section. And if $R_0 > 1$, then $\lambda^{**} > 1$, resulting in an endemic equilibrium where each subpopulation is greater than zero. Thus from (23) and (31), the theorem is proved.

6 Bifurcation analysis

Theorem 4: The model (1) exhibit a forward bifurcation at $R_0 = 1$ whenever a bifurcation coefficient, denoted by a (given by [12]) is positive. Using the centre manifold theory as described in [2] for local stability analysis, we make the following change of variables. Let;

$$(x_1, x_2, x_3, x_4) = (U, E, I, V) \tag{32}$$

Further, by using the vector notation

$$X = (x_1, x_2, x_3, x_4)^T \tag{33}$$

the model can be written in the form

$$\frac{dX}{dt} = F = (f_1, f_2, f_3, f_4)^T \tag{34}$$

such that

$$\begin{cases} \frac{dx_1}{dt} = f_1 = \rho x_1(1 - \frac{x_1+x_2+x_3}{T_{max}}) - \frac{\beta x_1 x_4}{x_1+x_2+x_3} + \gamma x_3 - \mu x_1 \\ \frac{dx_2}{dt} = f_2 = \frac{\beta x_1 x_4}{x_1+x_2+x_3} - (\sigma + \mu + \mu_1)x_2 \\ \frac{dx_3}{dt} = f_3 = \sigma x_2 - (\gamma + \mu + \mu_2)x_3 \\ \frac{dx_4}{dt} = f_4 = N\mu_2 x_3 - \frac{\beta x_1 x_4}{x_1+x_2+x_3} - \mu_3 x_4 \end{cases} \tag{35}$$

Now, the Jacobian of the model equations (35) at the virus-free equilibrium is given by

$$\begin{pmatrix} -(2\rho x_1^0 + \mu T^m - \rho T^m) & -\rho x_1^0 & -(\rho x_1^0 - \gamma T^m) & \beta T^m x_1^0 \\ 0 & -(\sigma + \mu + \mu_1) & 0 & \beta \\ 0 & \sigma & -(\gamma + \mu + \mu_2) & 0 \\ 0 & 0 & N\mu_2 & -(\beta + \mu_3) \end{pmatrix} \tag{36}$$

Now, consider the case when $R_0 = 1$in (31). Suppose, further, that $N = N^*$ is chosen as a bifurcation parameter, since R_0 is often inconvenient to use directly as bifurcation parameter. Solving for N gives $R_0 = 1$ when

$$N = N^* = \frac{(\sigma + \mu + \mu_1)(\gamma + \mu + \mu_2)(\beta + \mu_3)}{\beta\mu_2\sigma} \tag{37}$$

Eigenvectors of $J(e^0)|_{N=N^*}$
Let V and W be the corresponding left and right eigenvectors associated with the zero eigenvalues of the Jacobian of(37) at $N = N^*$ (denoted by J_{N^*}) chosen such that $VJ(e^0) = 0$ and $J(e^0)W = 0$ with $VW = 1$, where; $V = [v_1, v_2, v_3, v_4]$, and $W = [w_1, w_2, w_3, w_4]$. Thus,

$$VJ(e^0) = (v_1, v_2, v_3, v_4)\begin{pmatrix} -(2\rho\lambda_1 + \mu T - \rho T) & -\rho\lambda_1 & -(\beta\lambda_1 - T) & -\beta T\lambda_1 \\ 0 & -(\sigma + \mu + \mu_1) & 0 & \beta \\ 0 & \sigma & -(\gamma + \mu + k_1) & 0 \\ 0 & 0 & N_1\beta & -(\beta T^* + \mu_3) \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} \tag{38}$$

thus, we have;

$$\begin{cases} v_1 = 0, \\ v_2 = \dfrac{\sigma N_1 \mu_2 v_4}{(\sigma + \mu + \mu_1)(\gamma + \mu + \mu_2)}, \\ v_3 = \dfrac{N_1 \mu_2 v_4}{(\gamma + \mu + \mu_2)}, \\ v_4 > 0 \quad \text{(can take any value).} \end{cases} \tag{39}$$

Similarly, for;

$$J(E^0)W = \begin{pmatrix} -(2\rho\lambda_1 + \mu T - \rho T) & -\rho\lambda_1 & -(\beta\lambda_1 - T) & -\beta T\lambda_1 \\ 0 & -(\sigma+\mu+\mu_1) & 0 & \beta \\ 0 & \sigma & -(\gamma+\mu+k_1) & 0 \\ 0 & 0 & N_1\beta & -(\beta T^* + \mu_3) \end{pmatrix} \begin{pmatrix} w_1 \\ w_2 \\ w_3 \\ w_4 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} \quad (40)$$

we have;

$$\begin{cases} w_1 = \dfrac{-\beta\big[\rho\lambda_1^0(\gamma+\mu+\mu_2) + (\rho\lambda_1^0 - \gamma T^m)\sigma + T^m\lambda_1^0(\sigma+\mu_E+k_{E1})(\gamma+\mu_E+k_{E2})\big]v_4}{(\sigma+\mu+\mu_1)(\gamma+\mu+\mu_2)\big[(2\rho\lambda_1^* + \mu T^m - \rho T^m)\big]}, \\ w_2 = \dfrac{\beta v_4}{(\sigma+\mu+\mu_1)}, \\ w_3 = \dfrac{\sigma\beta v_4}{(\sigma+\mu+\mu_1)(\gamma+\mu+\mu_2)}, \\ w_4 > 0 \quad \text{(can take any value).} \end{cases} \quad (41)$$

Computation of a and b For a, which gives;

$$a = \sum_{k,i,j=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0) \quad (42)$$

For the model, gives n=4 and for k=1,$v_1 = 0 \implies a_1 = 0$,we therefore compute the associated non-zero partial derivatives of F at VFE for the VFE for f_2, f_3 and f_4. Thus, the associated non-zero partial derivatives of F at the virus-free equilibrium for the sign of are given by:

$$\begin{cases} \dfrac{\partial^2 f_2}{\partial x_1 \partial x_4}(0,0) = \dfrac{\beta}{T}, \quad \dfrac{\partial^2 f_2}{\partial x_4 \partial x_1}(0,0) = \dfrac{\beta}{T}, \\ \dfrac{\partial^2 f_4}{\partial x_1 \partial x_4}(0,0) = -\dfrac{\beta}{T}, \quad \dfrac{\partial^2 f_4}{\partial x_4 \partial x_1}(0,0) = -\dfrac{\beta}{T}. \end{cases} \quad (43)$$

which follows from (41) that;

$$a = 2v_1 w_4 \frac{\beta}{T}(v_2 - v_4) < 0 \quad \text{since } v_2 > v_4 \text{ and } w_1 < 0 \quad (44)$$

Similarly, for b, given that;

$$b = \sum_{k,i=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0,0) \quad (45)$$

for $k = 1, v_1 = 0 \implies b_1 = 0$, the associated non-zero partial derivatives of F at the virus-free equilibrium for f_2, f_3 and f_4 , where $\phi = N = N^*$ is the computed. And thus, the associated non-zero partial derivatives of F at the virus-free equilibrium for the sign of b is given by:

$$b = \frac{\partial^2 f_4}{\partial x_3 \partial N^*}(0,0) = \mu_3 > 0 \quad (46)$$

Thus, a<b and b>0. So by Theorem 2 of [2] the following result is established. **Theorem 5:**The positive endemic equilibrium state of the model equations (1) is locally asymptotically stable (LAS) when $R_0 > 1$ but close to 1. The epidemiological implication of Theorem 5 is that HBV will continue to persist within the host population when $R > 1$ and the initial size of the sub-populations of the model are in the basin of attraction of the endemic state.

7 Effects of Fulminant, Acute and Chronic Infections on the Number of HBV, Healthy and Infected Hepatocytes

Model variables and parameter values usually have to be estimated based on the virus in study. The values of parameter and variables utilized in this research are tabulated in Tables 2 and 3, with references been made to their sources.

Table 2: **Variables values of HBV in-vivo dynamics**

Symbols	Range Values	Source Used values
U(0)	1.1×10^{11} cells	Eikenberry et al. (2009)
L(0)	0 cells	Assumed
I(0)	0 cells	Assumed
T(0)	1.1×10^{11} cells	Eikenberry et al. (2009)
V(0)	1.0×10^{3} virons	Assumed

Table 3: **Parameters values of HBV in-vivo dynamics.**

Symbols	Range Values	Sources	Used values
ρ	0 – 1	Hews *et al.* (2009)	0.3
μ	0.002 – 0.053	Eikenberry *et al.* (2009), Long *et al.* (2008), Dong *et al.* (2010), Zheng *et al.* (2009)	0.0039
μ_1	0.001 – 0.002	Eikenberry *et al.* (2009), Long *et al.* (2008), Dong *et al.* (2010), Zheng *et al.* (2009)	0.0015
μ_2	0.001 - 0.003	Eikenberry *et al.* (2009), Long *et al.* (2008), Dong *et al.* (2010), Zheng *et al.* (2009), Hattaf and Yousfi (2011)	0.002
μ_3	0.58 – 0.693	Eikenberry *et al.* (2009), Long *et al.* (2008), Dong *et al.* (2010), Zheng *et al.* (2009), Hattaf and Yousfi (2011), Hews *et al.* (2009)	0.67
T^m	2×10^{11}	Eikenberry *et al.* (2009), Hews *et al.* (2009)	2×10^{11}
N	>0	Eikenberry *et al.* (2009), Long *et al.* (2008), Hattaf and Yousfi (2011), Hews *et al.* (2009)	varies
β	0 – 1	Eikenberry *et al.* (2009), Long *et al.* (2008), Hattaf and Yousfi (2011), Hews *et al.* (2009)	varies
γ	0 – 1	Long *et al.* (2008)	varies

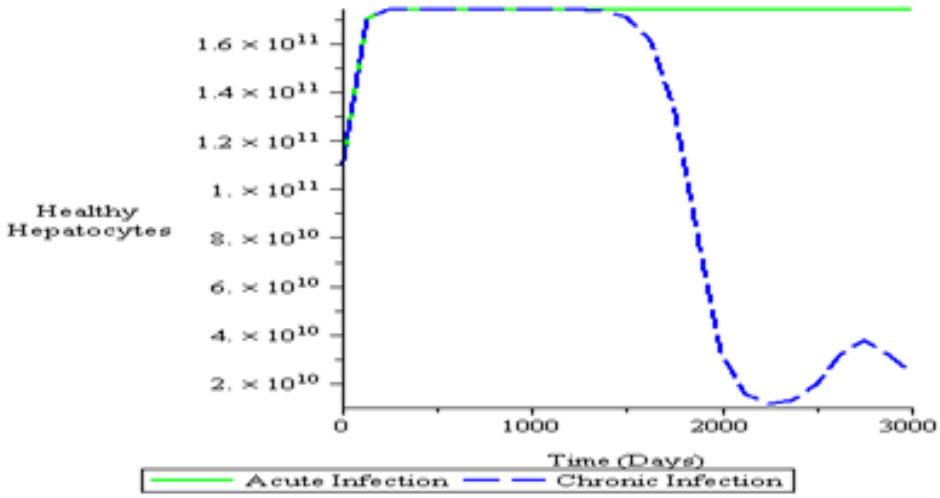

Figure 2: **Comparison between the effects of acute and chronic infections on the number of healthy hepatocytes.**

Figure 2 reveals the difference between acute and chronic infections in terms of healthy hepatocytes. In acute infection state the number of healthy hepatocytes rises and maintain a steady maximum level throughout the given period, while during chronic infection state, the number of healthy cells also behaved the same way from beginning of the infection but maintaining the steady maximum level only up to around 1700 days and then started to decrease gradually almost to 0 after 2000 days and then rises and falls in an oscillatory manner. This account for the reason why a person that is infected with a chronic hepatitis B (CHB) virus can live with the virus for quite some time before other complications which may lead to death.

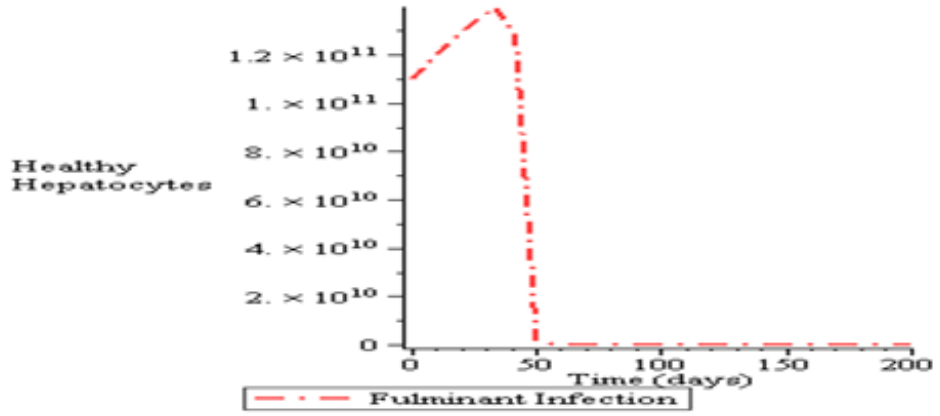

Figure 3: **The effects of fulminant infection on the number of healthy hepatocytes.**

Figure 3 reveals the effect of fulminant type of infection on the healthy cells. The hepatocytes started increasing at the onset of infection up to the peak and then suddenly dropped to zero level within period of 50 days. The reason will be stated under the explanatory notes of Figure 4. The consequence of this account for sudden death of the infected person as almost all the healthy hepatocytes are infected with the virus.

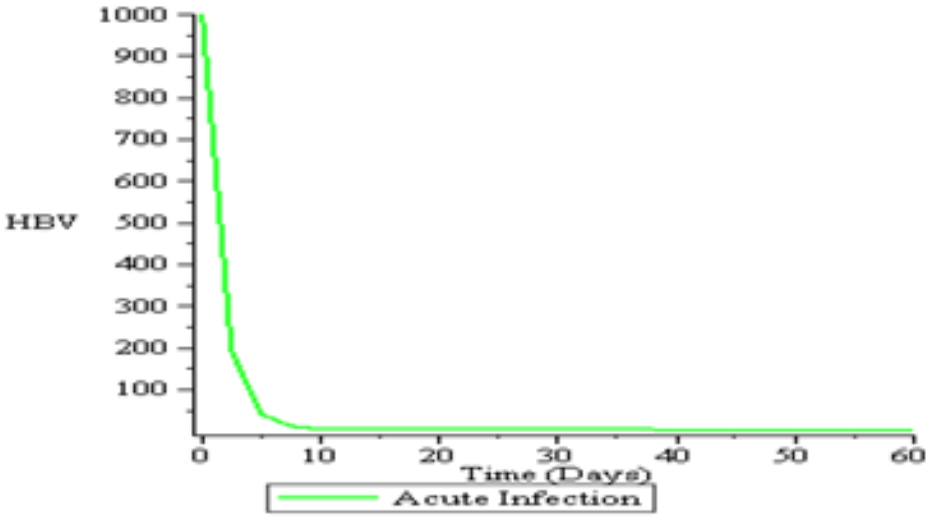

Figure 4: **The effects of acute infection on the number of hepatitis B virus.**

Clearly, we observed from figure 4 that viruses are at their maximum level at the beginning of the infection and gradually declining to zero level (absence of virus) after few days, this accounts for how HBV can cause an acute infection resulting in a short time inflammation of the liver before the virus is removed by a strong immune system.

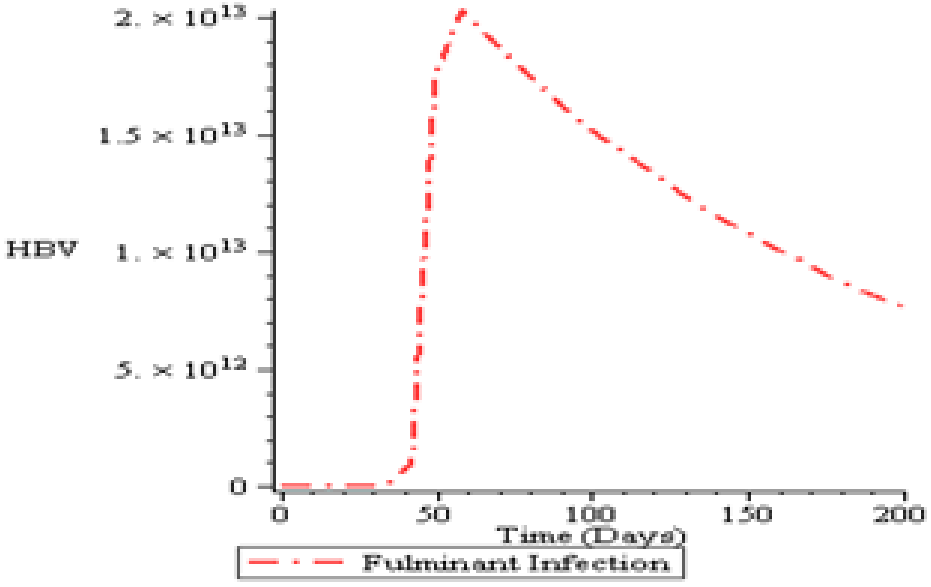

Figure 5: **The effects of fulminant infection on the number of hepatitis B virus.**

Figure 5 shows the effect of fulminant infection on the number of hepatitis B virus. In this case viruses gradually rise and suddenly rose to the maximum peak as result of vigorous replication due to their strong infectious capability infecting almost every hepatocyte in the liver within 50 days. The infected cells are in turn destructed by a strong immune system response through cytotoxic T lymphocytes (CTLs) resulting in necrosis of liver which lead to liver dysfunction. Hence this figure explains why fulminant type of Hepatitis B infection kills suddenly as its mortality is between 60 to 90 % [14]. This explains more, figure 3.

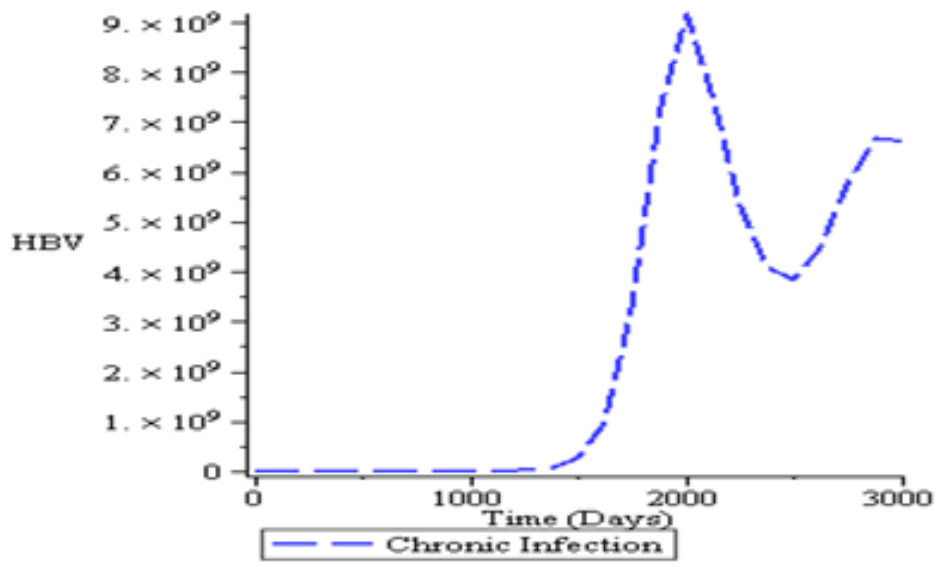

Figure 6: **The effects of chronic infection on the number of hepatitis B virus.**

Figure 6 explains behaviour of the virus during the course of chronic infection. This stage of infection occurs if the immunity system is too weak to clear the virus or in other words, not able to fight off the virus within 6 months. There is gradual rising of number of the virus reaching its peak at around 2000 days and gradually declining and rising in a continuous manner. This oscillatory behaviour of number of the virus' accounts for the reason why a person infected with CHB virus can live with the virus for some time.

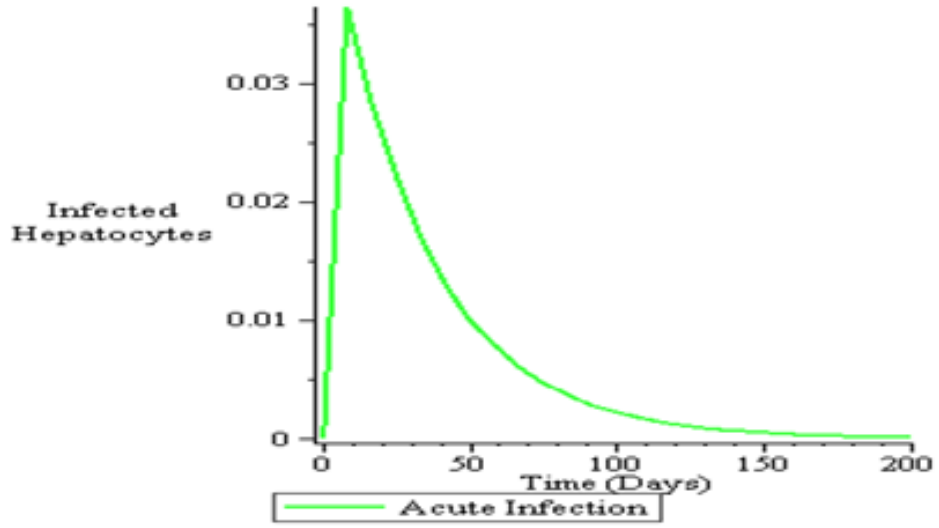

Figure 7: **The effects of acute infection on the number of infected hepatocytes**

Figure 7 reveals how infected hepatocytes gradually build up after infection reaching maximum level at around 50 days, and gradually falls to 0 within 6 months. This accounts for cytolitic clearance of infected cells which cures the infected hepatocytes and they become healthy cells.

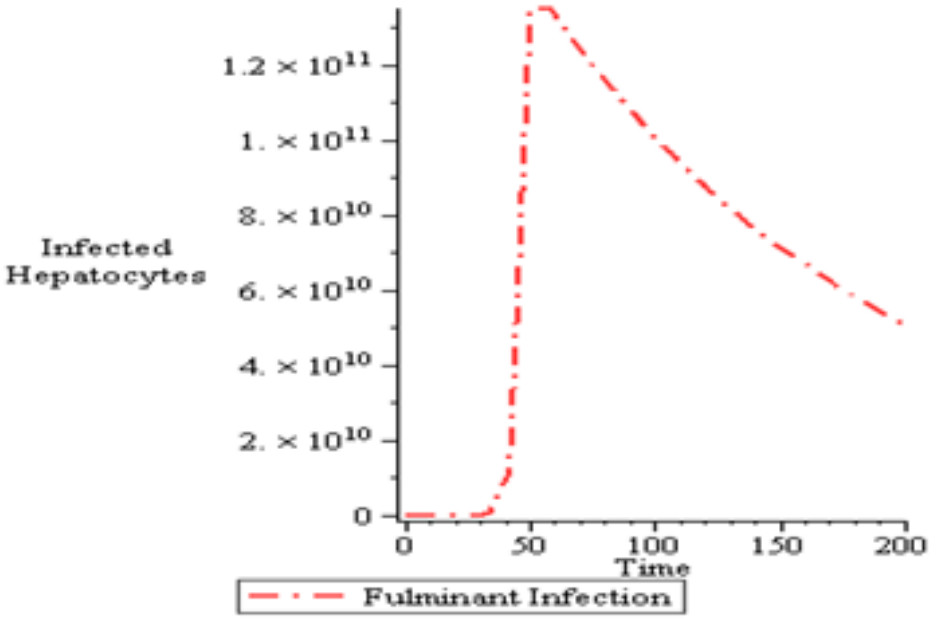

Figure 8: **The effects of fulminant infection on the number of infected hepatocytes**

Figure 8 illustrates the condition of infected hepatocytes during fulminant infection, showing gradual increment of infected hepatocytes as result of high level of proliferative activities of virus which prompt severe and vigorous immunity response through CTLs which has a devastating consequence. Here the infected person is most likely to die within 50 days as almost all the liver cells are infected and the attempt to clear them through CTLs is fatal.

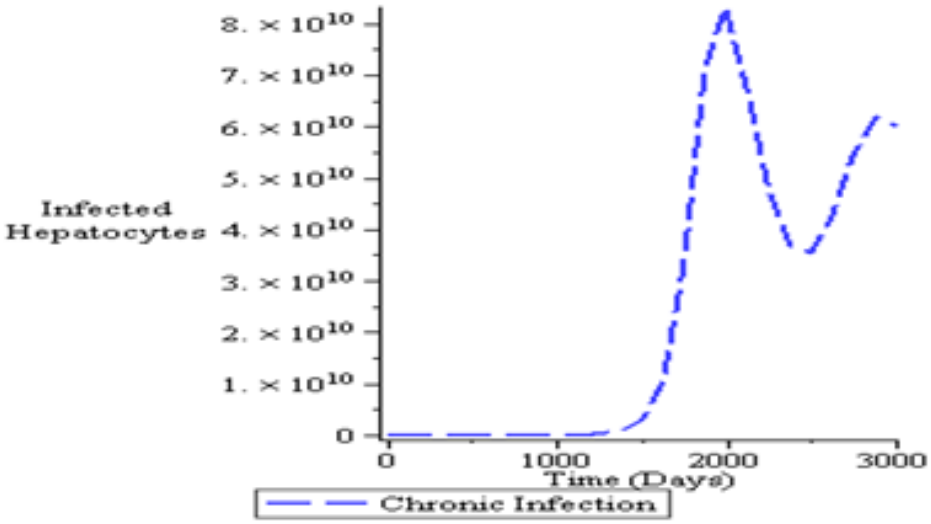

Figure 9: **The effects of chronic infection on the number of infected hepatocytes.**

Figure 9 has the same explanation as that of figure 6 but here we are more concerned with infected cells which rise in number reaching the peak at around 2000 days and begin to fall and then rise subsequently in an oscillatory manner. This accounts for what we said before in figure 6.

8 Conclusion

In this study a mathematical model for hepatitis B virus within host was developed taking into consideration the logistic growth for the proliferation of hepatocytes cells. We obtained the basic reproduction rate (R_0). The effective reproduction number in this work represents the average number of secondary cases generated by an infected cell if introduce into a susceptible population of hepatocytes cells. We also analysed both virus free equilibrium and endemic equilibrium states for stability. The following findings were made;

i. Existence and global stability of virus free equilibrium if $R_0 \leq 1$.

ii. Existence and global stability of endemic equilibrium if $R_0 > 1$

iii. Existence of a high level of proliferation of the hepatocytes cells during a fulminant infection within the infected person which will remain within the body for some time.

iv. A consequences for sudden death of the infected person when almost all the healthy hepatocytes cells are infected with the virus.

v The virus can cause an acute infection, which can result in a short time inflammation of the liver before the virus is removed by a strong immune system.

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