IOSR Journal of Mathematics (IOSR-JM)
e-ISSN: 2278-5728, p-ISSN: 2319-765X. Volume 15, Issue 4 Ser. II (Jul – Aug 2019), PP 35-46
www.iosrjournals.org

Hepatitis B Virus with Non-Cytolytic Cure Process on Healthy Liver and Blood Cells: A Mathematical Model Analysis

[a]Tesfaye Tefera Mamo , [b]Temesgen Tibebu Mekonnen,
Department of Mathematics, Debre Berhan University, Debre Berhan Ethiopia
[b]Department of Mathematics, Debre Berhan University, Debre Berhan Post Code 445

Abstract: *In this work we considered nonlinear ordinary differential equations to study the dynamics of hepatitis B virus (HBV) epidemics within the host. We proved that the invariant and bounded ness of the solution of the dynamical system. We used a nonlinear stability analysis method for proving the local and global stability of the existing equilibrium points. We found that the diseases free equilibrium point and endemic equilibrium point exist for some conditions.We proved that the disease free equilibrium point is locally asymptotically stable and also globally asymptotically stable. We found that the basic reproduction number for the system is* $R_0 = \frac{p\theta}{(\delta+\omega)(\mu+\pi+\theta)} + \frac{q\pi}{(\lambda+\eta)(\mu+\pi+\theta)}$ *which depends on nine parameters. Using standard parameter estimation we found that the numerical value of the basic reproduction number is* $R_0 = 2.944234214$. *From this numerical value we conclude that the disease spreads in the host. Out of these nine parameters we identified four effective parameters which contribute significant role in the spread of the disease; and these are the death rate of free virus*μ*, rate of infection of healthy blood cell* π*, the rate of cure of infected blood cell* λ*and the death rate of infected blood cell*η*. Out of these four effective parameters we identified thatthe most influential parameter is the death rate of free virus* μ*. We also conduct numerical simulations which support the finding in the sensitivity analysis.*

Key words:*-Hepatitis B virus (HBV), local stability, global stability, reproduction number, sensitivity,* $CD8^+$ *T cells, numerical simulation.*

Date of Submission: 17-07-2019 Date of acceptance: 05-08-2019

I. Introduction

Hepatitis refers to inflammation of the liver. Such inflammation can be caused by alcohol, certain medications and chemicals or by viral infection. Possible forms of transmission include sexual contact, blood transfusions and transfusion with other human blood products and possibly from mother to child during childbirth. HBV is such viral pathogens which infect liver cells (hepatocytes) and blood cells [4, 10].HBV is known to be the most common causes of hepatocellular carcinoma in the world [15].More than 780, 000 people die every year due to the acute or chronic consequences of hepatitis B virus [14]. Hepatitis B is a potentially life-threatening liver infectioncaused by the hepatitis B virus. It is a major global health problem. It can cause chronic liver disease and chronic infection and puts people at high risk of death from cirrhosis of the liver and hepatocellular carcinoma (liver cancer) [13]. Infections of hepatitis B occur only if the virus is able to enter the blood streamand reach the liver. Once in the liver, the virus reproduces and releases large numbers of newviruses into the blood stream [1].

HBV – specific $CD8^+ T$ cells are believed to play a critical role in the control of HBV replication but are also implicated in the pathogenesis of the disease by destruction of infected liver cells [16, 11, 1, and 4]. This Ag-specific killing of infected hepatocytes was initially believed to be the main mechanism by which $CD8^+ T$ cells control HBV infection. However, this concept was challenged by a series of studies in HBV transgenic mice [3, 12] and HBV-infected chimpanzees which revealed the mechanism of non-cytolytic inhibition of HBV replication. HBV specific $CD8^+ T$ cells could inhibit HBV replication without lysis of infected hepatocytes. Upon activation these immune cells were shown to produce cytokines such asinterferon

(IFN – γ)and lamivudine (TNF – α), which suppressed HBV gene expression and replication without destroying the infected hepatocytes and blood cells. This key antiviral mechanism of non-cytolytic HBV control mediated by $CD8^+ T$ cells has not been fully examined using human effector and target cells [6, 8].

Mathematical Models in Epidemiology plays an important role to predict how the disease spread and gives strategies how to control it. The earliest account of mathematical modeling of spread of disease was carried out in 1766 by Daniel Bernoulli. Trained as a physician, Bernoulli created a mathematical model to defend the practice of inoculating against smallpox [5]. The modeling of infectious diseases is a tool which has

been used to study the mechanisms by which diseases spread, to predict the future course of an outbreak and to evaluate strategies to control an epidemic [2].

In the study of Global analysis of a general HBV infection model, Xinjian Zhuo[18, 17] considered a model which included the loss of free virus particles when free virus infected an uninfected cell and the loss of infected cells due to a non-cytolytic cure process. They showed that an endemic equilibrium point of their model was globally asymptotically stable. In their research on sensitivity and stability analysis of Hepatitis B Virus Model with Non-Cytolytic cure process and Logistic Hepatocyte Growth Koonprasert S, Moore EJ, Banyatlersthaworn .S. [7], includes a logistic growth term for uninfectedcells, a mass action term for infection of uninfected cells, a free virus term, a loss of free viruses on infection of a cell, and a non-cytolytic cure process.

In this paper, we consider a Mathematical model which includes a logistic growth term for both healthy liver and blood cells, a mass action term for infection of uninfected cells, a free virus term, a loss of free viruses on infection of a cell, and a non-cytolytic cure process with specific $CD8^+ T$ cells that could inhibit HBV replication. We study the equilibrium points of the model, prove their global asymptotic stability, and study their sensitivity to changes in parameter values.

II. The Mathematical Model

Our initial model [7] is represented by three ordinary differential equations which considered three compartments. The extended model considers five compartments and is represented by five ordinary differential equations by adding the following basic assumptions. Let $L_h(t)$ is the number of healthy liver cell (hepatocyte), $L_i(t)$ is the number of infected liver cell, $v(t)$is the concentration of free viruses in the liver and blood, $B_h(t)$ is the number of healthy blood cell and $B_i(t)$ is the number of infected blood cell at a time *t*.HBV attacks both healthy liver cell and blood cells. Once the liver cell and blood cell are infected they never infected again. Healthy liver cell and blood cell are replicate/proliferate because of stem cell by logistic growth $\sigma\left(1-\frac{L_h+L_i}{k_1}\right)$ and $\psi\left(1-\frac{B_h+B_i}{k_2}\right)$ respectively.The infected hepatocytes and blood cell does not proliferate.Healthy liver cell and blood cell are infected by the mass action low $\frac{\theta L_h v}{L_h+v}$ and $\frac{\pi B_h v}{B_h+v}$ respectively.Infected liver cell and blood cell are producing free additional viruses. Infected cells are cured by non-cytolytic cure processes. Infected cells and viruses are naturally died. To decrease or eliminate HBV production and viral infection in the liver,$\frac{\theta L_H v}{L_H+v}+\frac{\pi B_h v}{B_h+v}$, must be reduced.

Based on these assumptions we construct the following flow chart for the dynamical system of (1) – (5).

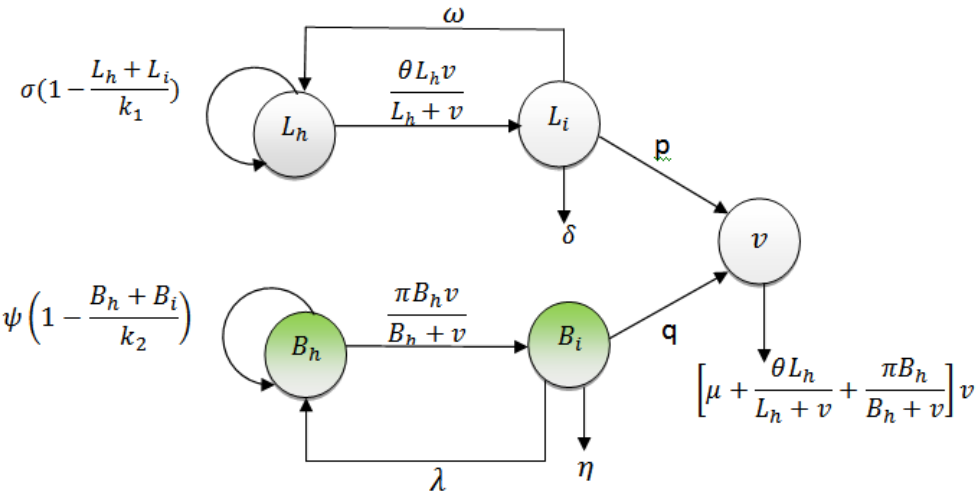

FIGURE1: The flow chart of the HBV model

The parameters and their expression in the model are defined in Table-1

Parameters	Expression
σ	intrinsic growth rate healthy liver cell
ψ	intrinsic growth rate healthy blood cell
k_1	carrying capacity of the liver for liver cell
k_2	carrying capacity of the blood for blood cell
θ	rate of infection of liver cell by free virus
π	rate of infection of blood cell by free virus
ω	rate of cure of infected liver cells by non-cytolytic cure process
λ	rate of cure of infected blood cells by non-cytolytic cure process
p	rate of release of free viruses by an infected liver cell

q	rate of release of free viruses by an infected blood cell
δ	death rate of infected liver cells
η	death rate of infected blood cells
μ	death rate of free virus

TABLE 1: Parameters representation and their expression

a. Dynamics of the model

Based on the above basic assumptions and flow chart we do have the following systems of ordinary differential equations which represents the dynamics of the considered HBV disease.

$$\frac{dL_h}{dt} = \sigma\left[1 - \frac{L_h+L_i}{k_1}\right]L_h + \omega L_i - \frac{\theta L_h v}{L_h+v} \quad (1)$$

$$\frac{dL_i}{dt} = \frac{\theta L_h v}{L_h+v} - (\delta+\omega)L_i \quad (2)$$

$$\frac{dv}{dt} = pL_i + qB_i - \left[\mu + \frac{\theta L_h}{L_h+v} + \frac{\pi B_h}{B_h+v}\right]v \quad (3)$$

$$\frac{dB_h}{dt} = \psi\left[1 - \frac{B_h+B_i}{k_2}\right]B_h + \lambda B_i - \frac{\pi B_h v}{B_h+v} \quad (4)$$

$$\frac{dB_i}{dt} = \frac{\pi B_h v}{B_h+v} - (\lambda+\eta)B_i \quad (5)$$

b. Positivity and boundedness

The feasible region of the model is the region in which all populations are nonnegative and bounded. We now prove that this region is invariant, i.e., if the initial populations are in the feasible region then they remain in the feasible region for all time. For the model equations (1) to (5) to be epidemiologically meaningful and well posed, we need to prove that all the state variables are non-negative.

Theorem-1 – for positivity of solutions:

Suppose$L_h(0) \geq 0, L_i(0) \geq 0, v(0) \geq 0, B_h(0) \geq 0$ *and* $B_i(0) \geq 0$, then the solution region $\{L_h(t), L_i(t), v(t), B_h(t), B_i(t)\}$of the system of equations (1) to (5) is always non negative for$t > 0$.

Proof

By considering the five ordinary differential equations and after taking some steps on finding their solution we do have

i. $\frac{dL_h}{dt} = \sigma\left[1 - \frac{L_h+L_i}{k_1}\right]L_h + \omega L_i - \frac{\theta L_h v}{L_h+v}$

Whose solution is $L_h = \frac{b \pm \sqrt{b^2 - 4a\left(d - e^{2d\left[t+c+\left(\frac{b}{2d}-v\right)\left[\frac{2}{\sqrt{4ad-b^2}}\tan^{-1}\frac{2L_h+b}{\sqrt{4ad-b^2}}\right]\right]}\right)}0}{2a} > 0$

By assuming$d > e^{2d\left[t+c+\left(\frac{b}{2d}-v\right)\left[\frac{2}{\sqrt{4ad-b^2}}\tan^{-1}\frac{2L_h+b}{\sqrt{4ad-b^2}}\right]\right]}$and $b^2 > 4a(d - e^{2a\left[t+c+\left(\frac{b}{2a}-v\right)\left[\frac{2}{\sqrt{4ad-b^2}}\tan^{-1}\frac{2L_h+b}{\sqrt{4ad-b^2}}\right]\right]}$

ii. $\frac{dL_i}{dt} = \frac{\theta L_h v}{L_h+v} - (\delta+\omega)L_i$ whose solution is $L_i(t) = \frac{\theta L_h v}{(\delta+\omega)(L_h+v)} + ce^{-(\delta+\omega)t} > 0$ since $\frac{\theta L_h v}{(\delta+\omega)(L_h+v)} > 0$ and $ce^{-(\delta+\omega)t} > 0$.

iii. $\frac{dv}{dt} = pL_i + qB_i - \left[\mu + \frac{\theta L_h}{L_h+v} + \frac{\pi B_h}{B_h+v}\right]v$ whose solution is

$v = \frac{\left[\frac{3ab}{2} + \left(f + e^{(-3\mu t + c_1)}\right) - \frac{a^3}{4}\right]}{\left(x^{\frac{1}{3}}\right)^2 + \left(y^{\frac{1}{3}}\right)^2 - \left(b - \frac{a^2}{4}\right)} - \frac{a}{2} > 0$. By letting

$$x = \left(\frac{\frac{3ab}{2} + \left(f + e^{-3\mu t + c_1}\right) - \frac{a^3}{4}}{2} + \sqrt{\frac{\left(\frac{a^3}{4} - \frac{3ab}{2} - \left(f + e^{-3\mu t + c_1}\right)\right)^2}{4} + \frac{\left(b - \frac{a^2}{4}\right)^3}{27}}\right)^{\frac{1}{3}} \text{ and}$$

$$y = \left(\frac{\frac{3ab}{2} + \left(f + e^{-3\mu t + c_1}\right) - \frac{a^3}{4}}{2} - \sqrt{\frac{\left(\frac{a^3}{4} - \frac{3ab}{2} - \left(f + e^{-3\mu t + c_1}\right)\right)^2}{4} + \frac{\left(b - \frac{a^2}{4}\right)^3}{27}}\right)^{\frac{1}{3}}, \text{ and by assuming } \frac{x^{\frac{1}{3}} + y^{\frac{1}{3}} - \left(b - \frac{a^2}{4}\right)}{\frac{3b}{2} + \frac{f + e^{(-3\mu t + c_1)}}{a} - \frac{a^2}{4}} < 2.$$

iv. $\frac{dB_h}{dt} = \psi\left[1 - \frac{B_h+B_i}{k_2}\right]B_h + \lambda B_i - \frac{\pi B_h v}{B_h+v}$ whose solution is

$B_h = \frac{b \pm \sqrt{b^2 - 4a\left(d - e^{2a[t+c+(\frac{b}{2a}-v)[\frac{2}{\sqrt{4ad-b^2}}\tan^{-1}(\frac{2aB_h+b}{\sqrt{4ad-b^2}})]]}\right)}}{2a} > 0$.By assuming

$b^2 > 4a(d - e^{2a[t+c+(\frac{b}{2a}-v)[\frac{2}{\sqrt{4ad-b^2}}\tan^{-1}(\frac{2aB_h+b}{\sqrt{4ad-b^2}})]]}$

v. $\frac{dB_i}{dt} = \frac{\pi B_h v}{B_h+v} - (\lambda+\eta)B_i$ whose solution is $B_i(t) = \frac{\pi B_h v}{(\lambda+\eta)(B_h+v)} + ce^{-(\lambda+\eta)t} > 0$ since $\frac{\pi B_h v}{(\lambda+\eta)(B_h+v)} > 0$ and $ce^{-(\lambda+\eta)t} > 0$.

Theorem – 2 – for boundedness of solutions

The feasible region Ω of the dynamical system (1) – (5) defined by

$\Omega = \left\{\begin{matrix}\left(L_h(t), L_i(t), B_h(t), B_i(t), v(t)\right) \in \Re_+^5 \cup (0,0,0,0,0) | 0 \le L_h(t) \le k_1, \le L_i(t) \le k_3, \\ 0 \le B_h(t) \le k_2, , 0 \le B_i(t) \le k_4, 0 \le v(t) \le \frac{pk_3+qk_4}{\mu}\end{matrix}\right\}$, it is bounded

Proof

We need to show thatif$\left(L_h(0), L_i(0), B_h(0), B_i(0), v(0)\right) \epsilon\ \Omega$, then the solution of $\left(L_h(t), L_i(t), B_h(t), B_i(t), v(t)\right) \in\ \Omega$ for all time$t$.

i. Consider the first ordinary differential equation

$\frac{dL_h}{dt} = \sigma\left[1 - \frac{L_h+L_i}{k_1}\right]L_h + \omega L_i - \frac{\theta L_h v}{L_h+v}$, and after some simplifications we have

$L_h(t) \le \frac{k_1}{1+\frac{(k_1-L_h(0))e^{-\sigma t}}{L_h(0)}}$

Thus,

$\lim_{t\to\infty}\sup L_h(t) \le \lim_{t\to\infty}\sup \frac{k_1}{1+\frac{(k_1-L_h(0))e^{-\sigma t}}{L_h(0)}} \le k_1$

Hence $L_h(t)$ is bounded.

ii. the second ordinary differential equation

$\frac{dL_i}{dt} = \frac{\theta L_h v}{L_h+v} - (\delta+\omega)L_i$, and after some simplifications we do have

$L_i(t) \le \frac{\theta k\text{Consider }_1 v}{\delta+\omega} + ce^{-(\delta+\omega)t}$.

Thus,

$\lim_{t\to\infty}\sup L_i(t) \le \lim_{t\to\infty}\sup\left(\frac{\theta k_1 v(t)}{\delta+\omega} + \left[L_i(0) - \frac{\theta k_1 v(0)}{\delta+\omega}\right]e^{-(\delta+\omega)t}\right) \le k_3$.

Hence $L_i(t)$ is bounded

iii. Consider the third ordinary differential equation,

$\frac{dv}{dt} = pL_i + qB_i - \left[\mu + \frac{\theta L_h}{L_h+v} + \frac{\pi B_h}{B_h+v}\right]v$

And after some simplifications we do have

$v(t) \le \frac{pk_3+qk_4}{\mu} - \frac{[pk_3+qk_4-\mu v(0)]}{\mu}e^{-\frac{t}{\mu}}$.

Thus,

$\lim_{t\to\infty}\sup v(t) \le \lim_{t\to\infty}\sup \frac{pk_3+qk_4}{\mu} - \frac{[pk_3+qk_4-\mu v(0)]}{\mu}e^{-\frac{t}{\mu}} \le \frac{pk_3+qk_4}{\mu}$. Hence $v(t)$ is bounded.

iv. Consider the fourth ordinary differential equation

$\frac{dB_h}{dt} = \psi\left[1 - \frac{B_h+B_i}{k_2}\right]B + \lambda B_i - \frac{\pi B_h v}{B_h+v}$

And after some simplifications we do have

$B_h(t) \le \frac{k_2}{1+[\frac{(k_2-B_h(0))}{B_h(0)}]e^{-\psi t}}$.

Thus,

$\lim_{t\to\infty}\sup B_h(t) \le \lim_{t\to\infty}\sup \frac{k_2}{1+[\frac{(k_2-B_h(0))}{B_h(0)}]e^{-\psi t}} \le k_2$. Hence $B_h(t)$ is bounded.

v. Consider the fifth ordinary differential equation

$\frac{dB_i}{dt} = \frac{\pi B_h v}{B_h+v} - (\lambda+\eta)B_i$

And after some simplifications, we have

$B_i(t) \le \frac{\pi k_2 v}{\lambda+\eta} + \left[B_i(0) - \frac{\pi k_2 v(0)}{\lambda+\eta}\right] e^{-(\lambda+\eta)t} \le \frac{\pi k_2 v}{\lambda+\eta} = k_4.$

Thus,

$\lim_{t\to\infty} \sup B_i(t) \le \lim_{t\to\infty} \sup(\frac{\pi k_2 v}{\lambda+\eta} + [B_i(0) - \frac{\pi k_2 v(0)}{\lambda+\eta}]e^{-(\lambda+\eta)t}) \le k_4$. Hence $B_i(t)$ is bounded.

III. Equilibrium points of the dynamical system

3.1. Disease Free Equilibrium point /DFE/

The disease equilibrium point is obtained by assuming that there is no hepatitis B virus, infected liver and blood cells. So the value of $L_i = B_i = v = 0$ And by making the right hand side of the dynamical system (1) - (5) equal to zero we get the disease free equilibrium point is $(L_h, L_i, v, B_h, B_i) = (k_1, 0, 0, k_2, 0)$.

3.2. Determination of basic reproduction Number R_0

The main concepts in modeling outbreaks of infectious diseases are the basic reproductive number, universally denoted by $\boldsymbol{R_0}$**.** The reproduction number is defined as the average number of secondary cases produced by a typical infected individual during his or her entire life as infectious or infectious period when introduced or allowed to live in a population of susceptible which can be calculated using the next-generation method of van den Driessche and Watmough [23]. In the dynamical system (1)-(5) the rate of appearance of new infections $\mathcal{F}$ and the transfer rate of individuals $\mathcal{V}$ at the disease free steady state $(L_h, L_i, v, B_h, B_i) = (k_1, 0, 0, k_2, 0)$ is $F = \begin{bmatrix} 0 & 0 & \theta & 0 & 0 \\ 0 & 0 & \pi & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}$, $V(X_0) = \begin{vmatrix} a & 0 & 0 & 0 & 0 \\ 0 & b & 0 & 0 & 0 \\ -p & -q & c & 0 & 0 \\ d & 0 & 0 & \sigma & 0 \\ 0 & e & 0 & 0 & \psi \end{vmatrix}$ and

$V^{-1} = \begin{bmatrix} 1/a & 0 & 0 & 0 & 0 \\ 0 & 1/b & 0 & 0 & 0 \\ p/ac & q/bc & 1/c & 0 & 0 \\ -d/\sigma a & 0 & 0 & 1/\sigma & 0 \\ 0 & -e/\psi b & 0 & 0 & 1/\psi \end{bmatrix}$. The spectral radius or Eigen value of $FV^{-}$is the required basic reproduction number obtained by $R_0 = \frac{p\theta}{(\delta+\omega)(\mu+\pi+\theta)} + \frac{q\pi}{(\lambda+\eta)(\mu+\pi+\theta)}$.

3.3. Local stability of the disease-free equilibrium point

Theorem – 3:

The disease free equilibrium point $(L_h, L_i, v, B_h, B_i) = (k_1, 0, 0, k_2, 0)$ of the dynamical system (1) - (5) is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$

Proof

The Jacobean matrix of the dynamical system (1) – (5) at the DFE point $(L_h, L_i, v, B_h, B_i) = (k_1, 0, 0, k_2, 0)$ is:

$J(k_1, 0, 0, k_2, 0) = J(D) = \begin{bmatrix} -\sigma & \omega-\sigma & -\theta & 0 & 0 \\ 0 & -(\delta+\omega) & \theta & 0 & 0 \\ 0 & p & -(\mu+\theta+\pi) & 0 & q \\ 0 & 0 & -\pi & -\psi & \lambda-\psi \\ 0 & 0 & \pi & 0 & -(\lambda+\eta) \end{bmatrix}$

The corresponding characteristic equation for the eigenvalue Z is

$\begin{vmatrix} -(\sigma+z) & d & -\theta & 0 & 0 \\ 0 & -(a+z) & \theta & 0 & 0 \\ 0 & p & -(c+z) & 0 & q \\ 0 & 0 & -\pi & -(\psi+z) & \lambda-\psi \\ 0 & 0 & \pi & 0 & -(b+z) \end{vmatrix} = 0$

That is $(\sigma+z)(\psi+z)\left[-(a+z)(b+z)(c+z) - [-p\theta(b+z) - q\pi(a+z)]\right] = 0$

$z_1 = -\sigma \ or \ z_2 = -\psi or \ [(a+z)(b+z)(c+z) - [p\theta(b+z) + q\pi(a+z)] = 0$

For the cubic equation

$[z^3 + (a+b+c)z^2 + (ab+ac+bc)z + abc - p\theta b - p\theta z - q\pi a - q\pi z] = 0$

We used RouthHurwitz stability criterion and we get the solution of are all negative. Therefore the disease free equilibrium point is locally asymptotically stable.

3.4. Global stability of disease-free equilibrium point

Theorem – 4:

If $R_0 < 1$, then the disease free equilibrium point $D(L_h, L_i, v, B_h, B_i) = (k_1, 0, 0, k_2, 0)$ of the dynamical system (1) - (5) is globally asymptotically stable.

Proof

Let the Liapunov function

$V:(R^+)^5 \longrightarrow R^+$ it is defined by

$V(L_h, L_i, v, B_h, B_i) = L_h - L_h^0 - L_h^0 \ln\left(\frac{L_h}{L_h^0}\right) + \frac{p}{\delta+\omega} L_i + v + B_h - B_h^0 - B_h^0 \ln\left(\frac{B_h}{B_h^0}\right) + \frac{q}{\lambda+\eta} B_i$ at the disease equilibrium point $(L_h^0, L_i^0, v^0, B_h^0, B_i^0) = (k_1, 0, 0, k_2, 0)$. V is continuous function for all $(L_h, L_i, v, B_h, B_i) \in (R^+)^5 \cup (0,0,0,0,0)$ and has 1^{st} order partial derivatives. V, it has minimum at $(L_h, L_i, v, B_h, B_i) = (k_1, 0,0, k_2, 0)$, which is $V(k_1, 0,0, k_2, 0) = 0$. Now $\frac{dV}{dt} = \frac{\partial V}{\partial L_h}\frac{dL_h}{dt} + \frac{p}{\delta+\omega}\frac{\partial V}{\partial L_i}\frac{dL_i}{dt} + \frac{\partial V}{\partial B_h}\frac{dB_h}{dt} + \frac{q}{\lambda+\eta}\frac{\partial V}{\partial B_i}\frac{dB_i}{dt} + \frac{\partial V}{\partial v}\frac{dv}{dt}$ which implies that $\dot{V} = \left(1 - \frac{L_h^0}{L_h}\right)\frac{dL_h}{dt} + \frac{p}{\delta+\omega}\frac{dL_i}{dt} + \frac{dv}{dt} + \left(1 - \frac{B_h^0}{B_h}\right)\frac{dB_h}{dt} + \frac{q}{\lambda+\eta}\frac{dB_i}{dt}$. That is $\frac{dV}{dt} = -\left[\frac{\sigma}{k_1}(k_1 - L_h)^2 + \frac{\psi}{k_2}(k_2 - B_h)^2\right] - \left[\left[\left(2 - \frac{p}{\delta+\omega}\right)L_h - k_1\right]\frac{\theta}{L_h+v} + \mu + \left[\left(2 - \frac{q}{\lambda+\eta}\right)B_h - k_2\right]\frac{\pi}{B_h+v}\right]v < 0.$

For $\left(1 - \frac{p}{\delta+\omega}\right)k_1 > 0 \; and \; \left(1 - \frac{q}{\lambda+\eta}\right)k_2 > 0$. Thus, for $v = 0 \; and \; t \to \infty$, we have $L_i \to 0, B_i \to 0, L_h \to k_1 \; and \; B_h \to k_2$; for $R_0 < 1, \dot{V} < 0$ and hence the disease free equilibrium point $D(L_h, L_i, v, B_h, B_i) = (k_1, 0,0, k_2, 0)$ of model (3.1) is globally asymptotically stable.

3.5. Endemic equilibrium point

To determine the endemic equilibrium point we make the right hand side of the dynamical system (1) - (5) equal to zero, that is

$$\frac{dL_h}{dt} = \sigma\left[1 - \frac{L_h + L_i}{k_1}\right]L_h + \omega L_i - \frac{\theta L_h v}{L_h + v} = 0$$

$$\frac{dL_i}{dt} = \frac{\theta L_h v}{L_h + v} - (\delta + \omega)L_i = 0$$

$$\frac{dv}{dt} = pL_i + qB_i - \left[\mu + \frac{\theta L_h}{L_h + v} + \frac{\pi B_h}{B_h + v}\right]v = 0$$

$$\frac{dB_h}{dt} = \psi\left[1 - \frac{B_h + B_i}{k_2}\right]B_h + \lambda B_i - \frac{\pi B_h v}{B_h + v} = 0$$

$$\frac{dB_i}{dt} = \frac{\pi B_h v}{B_h + v} - (\lambda + \eta)B_i = 0$$

Thus after some calculation we get the endemic equilibrium point is

$(L_h^*, L_i^*, v^*, B_h^*, B_i^*) =$

$\left(\frac{(c-dv^*)+\sqrt{(c-dv^*)^2+ev^*}}{f}, \frac{\theta\left[(c-dv^*)+\sqrt{(c-dv^*)^2+ev^*}\right]v^*}{a\left[(f-d)v^*+\sqrt{(c-dv^*)^2+ev^*}+c\right]}, v^*, \frac{(g-mv^*)+\sqrt{(g-mv^*)^2+rv^*}}{s}, \frac{\pi[(g-mv^*)+\sqrt{(g-mv^*)^2+rv^*}]v^*}{b[(s-m)v^*+\sqrt{(g-mv^*)^2+rv^*}+g]}\right)$

Provided that $R_0 > 1, 1 - \frac{p}{(\delta+\omega)} > 0 \; and \; 1 - \frac{q}{(\lambda+\eta)} > 0.$

3.6. Local stability of endemic equilibrium point

Theorem – 5:

The endemic equilibrium point

$\left(\frac{(c-dv^*)+\sqrt{(c-dv^*)^2+ev^*}}{f}, \frac{\theta\left[(c-dv^*)+\sqrt{(c-dv^*)^2+ev^*}\right]v^*}{a\left[(f-d)v^*+\sqrt{(c-dv^*)^2+ev^*}+c\right]}, v^*, \frac{(g-mv^*)+\sqrt{(g-mv^*)^2+rv^*}}{s}, \frac{\pi[(g-mv^*)+\sqrt{(g-mv^*)^2+rv^*}]v^*}{b[(s-m)v^*+\sqrt{(g-mv^*)^2+rv^*}+g]}\right)$ of the dynamical system (1) - (5)is locally asymptotically stable if $R_0 > 1$.

Proof

TheJacobean matrix of the dynamical system (1) - (5) at the endemic equilibrium point is

$$J = \begin{bmatrix} -(m+a) & -g & -b & 0 & 0 \\ a & -e & b & 0 & 0 \\ -a & p & -(\mu+b+d) & -c & q \\ 0 & 0 & -d & -(n+c) & -l \\ 0 & 0 & d & c & -f \end{bmatrix}$$ Where,

a=$\frac{\theta {v^*}^2}{\left(L_h^* + v^*\right)^2}, b = \frac{\theta {L_h^*}^2}{\left(L_h^* + v^*\right)^2}, c = \frac{\pi {v^*}^2}{\left(B_h^* + v^*\right)^2}, d = \frac{\pi {B_h^*}^2}{\left(B_h^* + v^*\right)^2}, e = \delta + \omega;$

$f = \lambda + \eta, g = \frac{\sigma}{k_1}L_h^* - \omega, l = \frac{\psi}{k_2}B_h^* - \lambda, m = \frac{\sigma}{k_1}[-k_1 + 2L_h^* + L_i^*];$

$n = \frac{\psi}{k_2}[-k_2 + 2B_h^* + B_i^*]$ and $h = \frac{\sigma}{k_1}L_h - \omega < \sigma - \omega > 0$, because $L_h < k_1$ and intrinsic growth rate is larger than the curing rate. Also $l = \frac{\psi}{k_2}B_h - \lambda < \psi - \lambda > 0.$

The corresponding characteristic equation for the eigenvalue t is

$$\begin{vmatrix} -(x+t) & -g & -b & 0 & 0 \\ a & -(e+t) & b & 0 & 0 \\ -a & p & -(y+t) & -c & q \\ 0 & 0 & -d & -(z+t) & -l \\ 0 & 0 & d & c & -(f+t) \end{vmatrix} = 0$$

Or

$$\left.\begin{matrix} [ag+(x+t)(e+t)][-(y+t)(z+t)(f+t)+cdl-cdq-(-dq(x+t)-cd(f+t)]- \\ -cq(y+t)]+[b(x+t)-ab][p(z+t)(f+t)+ \\ [-b(e+g+t)][-a(z+t)(f+t)-acl] \end{matrix}\right\} = 0$$

Or

$$\left.\begin{matrix} [t^2+(x+e)t+(ag+xe)]* \\ [-t^3-(f+y+z)t^2-(fy+fz+yz+dq-cd-cq)t-fyz+cdl-cdq+dqx-cdf-cqy]+ \\ p[b(x-a)+bt][t^2+(f+z)t+cq+fz]+a[bt+b(e+g)][t^2+(f+z)t+fz+cl] \end{matrix}\right\} = 0$$

Or

$$\left.\begin{matrix} -t^5-(c_3+c_1)t^4-(c_4+c_2-bp-ab)t^3-(c_5+c_1c_4+c_2c_3-bpc_7-pc_{26}-abc_7-ac_9)t^2- \\ (c_5+c_1c_4+c_2c_3-bpc_7-pc_{26}-abc_7-ac_9)t^2-(c_1c_5+c_2c_4-bpc_8-pc_6c_7-abc_{10})t- \\ (c_2c_5-pc_6c_8-ac_9c_{10}) \end{matrix}\right\} = 0$$

Where

$c_1 = x+e$
$c_2 = ag+xe$
$c_3 = f+y+z$
$c_4 = (fy+fz+yz+dq-cd-cq)$
$c_5 = fyz-cdl+cdq-dqx+cdf+cqy$
$c_6 = b(x-a)$
$c_7 = f+z$
$c_8 = cq+fz$
$c_9 = b(e+g)$
$c_{10} = fz+cl$

Let

$d_1 = c_3+c_1$
$d_2 = c_4+c_2-bp-ab$
$d_3 = c_5+c_1c_4+c_2c_3-bpc_7-pc_6-abc_7-ac_9$
$d_4 = c_1c_5+c_2c_4-bpc_8-pc_6c_7-abc_{10}$
$d_5 = c_2c_5-pc_6c_8-ac_9c_{10}$

We do have a fifth degree polynomial equation $t^5+d_1t^4+d_2t^3+d_3t^2+d_4t+d_5=0$

By applying RouthHurwitz stability criterion we get there is change of sign in the first column of Routh-Hurwitz array and the endemic equilibrium point is unstable.

3.7. Global stability of endemic equilibrium point

Theorem – 6:

If$R_0 > 1$, the endemic equilibrium pointof the dynamical system (1) – (5) is globally asymptotically stable.

Proof

Let the Liapunov function defined at the endemic equilibrium point is

$V(L_h^*, L_i^*, v^*, B_h^*, B_i^*) = L_h - L_h^* - L_h^* \ln\left(\frac{L_h}{L_h^*}\right) + \frac{p}{\delta+\omega}[L_i - L_i^* - L_i^* \ln\left(\frac{L_i}{L_i^*}\right)] + v - v^* - v^* \ln\left(\frac{v}{v^*}\right) + B_h - B_h^* - B_h^* \ln\left(\frac{B_h}{B_h^*}\right) + \frac{q}{\lambda+\eta}[B_i - B_i^* - B_i^* \ln\left(\frac{B_i}{B_i^*}\right)]$. V is continuous function for all $(L_h^*, L_i^*, v^*, B_h^*, B_i^*) \in \Re_+^5$and has first order partial derivatives.V has minimum at $(L_h^*, L_i^*, v^*, B_h^*, B_i^*)$which is $(L_h^*, L_i^*, v^*, B_h^*, B_i^*) = 0$. And now we do have

$$\frac{dV}{dt} = \frac{\partial V}{\partial L_h}\frac{dL_h}{dt} + \frac{p}{\delta+\omega}\frac{\partial V}{\partial L_i}\frac{dL_i}{dt} + \frac{\partial V}{\partial v}\frac{dv}{dt} + \frac{\partial V}{\partial B_h}\frac{dB_h}{dt} + \frac{q}{\lambda+\eta}\frac{\partial V}{\partial B_i}\frac{dB_i}{dt}$$

$$\frac{dV}{dt} = \left\{\begin{matrix} -\frac{\sigma}{k_1}(k_1-L_h)(L_h^*-L_h) - \frac{p\theta L_h^* v^*}{(\delta+\omega)(L_h^*+v^*)} - \left(\frac{\theta L_h^* v}{L_h+v} - \frac{\theta L_h^* v}{L_h+v}\right) + \frac{p\theta L_h^* v^*}{(\delta+\omega)(L_h^*+v^*)} + pL_i^* \\ -\left[\mu + \frac{\theta L_h}{L_h+v} + \frac{\pi B_h}{B_h+v}\right]v - pL_i^* - qB_i^* + \left(\mu + \frac{\theta L_h}{L_h+v} + \frac{\pi B_h}{B_h+v}\right)v^* - \frac{\psi}{k_2}(k_2-B_h)(B_h^*-B_h) \\ -\frac{q\pi B_h^* v^*}{(\lambda+\eta)(B_h^*+v^*)} - \left(\frac{\pi B_h^* v}{B_h+v} - \frac{\pi B_h^* v}{B_h+v}\right) + \frac{q\pi B_h^* v^*}{(\lambda+\eta)(B_h^*+v^*)} + qB_i^* \end{matrix}\right\}$$

$$\frac{dV}{dt} = -[\frac{\sigma}{k_1}(k_1 - L_h)(L_h^* - L_h) + \frac{\psi}{k_2}(k_2 - B_h)(B_h^* - B_h)] - \left(\mu + \frac{\theta L_h}{L_h + v} + \frac{\pi B_h}{B_h + v}\right)(v^* - v)$$

$\Longrightarrow \frac{dV}{dt} < 0$. For $L_h^* - L_h > 0, B_h^* - B_h < 0 \; and \; v^* - v > 0$

Therefore the endemic equilibrium point

$E^*(L_h^*, L_i^*, v^*, B_h^*, B_i^*) =$

$\left(\frac{(c-dv)+\sqrt{(c-dv)^2+ev}}{f}, \frac{\theta\left[(c-dv)+\sqrt{(c-dv)^2+ev}\right]v}{a\left[(f-d)v+\sqrt{(c-dv)^2+ev}+c\right]}, v^*, \frac{(g-mv)+\sqrt{(g-mv)^2+rv}}{s}, \frac{\pi[(g-mv)+\sqrt{(g-mv)^2+rv}]v}{b[(s-m)v+\sqrt{(g-mv)^2+rv}+g]}\right)$

is globally asymptotically stable for $R_0 > 1, 1 - \frac{p}{(\delta+\omega)} > 0 \; and 1 - \frac{q}{(\lambda+\eta)} > 0$.

IV. Parameter estimation for numerical simulation and sensitivity analysis.

To perform numerical simulation and sensitivity analysis we collect the following parameter values obtained from different sources.

Parameter	Value	Meaning	Unit	Source
σ	0.1	Intrinsic growth rate of healthy liver cell	$\frac{cell}{ml * day}$	Ref. [9]
ψ	0.0001	Intrinsic growth rate of healthy blood cell	$\frac{cell}{ml * day}$	Ref. [9]
k_1	1000	Carrying capacity of the liver for liver cell	$\frac{cell}{ml * day}$	Ref. [7]
k_2	1000	Carrying capacity of the blood for liver cell	$\frac{cell}{ml * day}$	Ref. [7]
θ	0.0014	Rate of infection of liver cell by free virus	$\frac{cell}{ml - day}$	Ref. [7]
π	0.0014	Rate of infection of blood cell by free virus	$\frac{cell}{ml - day}$	Ref. [7]
ω	0.1	Rate of cure of infected liver cells	$\frac{cell}{day}$	Ref. [7]
λ	0.1	Rate of cure of infected blood cells	$\frac{cell}{day}$	Ref. [7]
p	300	Rate of release of free viruses by an infected liver cell(average)	$\frac{virons}{cell - day}$	Ref. [9]
q	800	Rate of release of free viruses by an infected blood cell(average)	$\frac{virons}{cell - day}$	Ref. [9]
δ	0.003	Death rate of infected liver cells	day^{-1}	Ref. [9]
η	0.03	Death rate of infected blood cells	day^{-1}	Ref. [9]
μ	3.693	Death rate of free virus	day^{-1}	Ref. [7]

TABLE 2:Parameter estimation

4.1. Estimation of basic reproduction number R_0

$R_0 = \frac{p\theta}{(\delta+\omega)(\mu+\pi+\theta)} + \frac{q\pi}{(\lambda+\eta)(\mu+\pi+\theta)}$.

$\Longrightarrow R_0 = \frac{300\times0.0014}{(0.003+0.12)(3.693+0.0014+0.0014)} + \frac{800\times0.0014}{(0.12+0.03)(3.693+0.0014+0.0014)} = \frac{0.42}{0.4545834} + \frac{1.12}{0.55437}$ b

$\Longrightarrow R_0 = 0.923922870 + 2.020311344 = 2.944234214$

From this value of basic reproduction number we find that the disease spreads in the liver as $R_0 = 2.944234214 > 1$

4.2. Numerical simulation

The numerical analysis is obtained from the graphs of basic reproduction number with respect to the parameters obtained and given in Table-2.

4.2.1. Rate of infection of healthy blood cell by free virusπ

Graphical representation of the basic reproduction number R_0 versus rate of infection of healthy blood cell by free virusπ and keeping other parameters constant

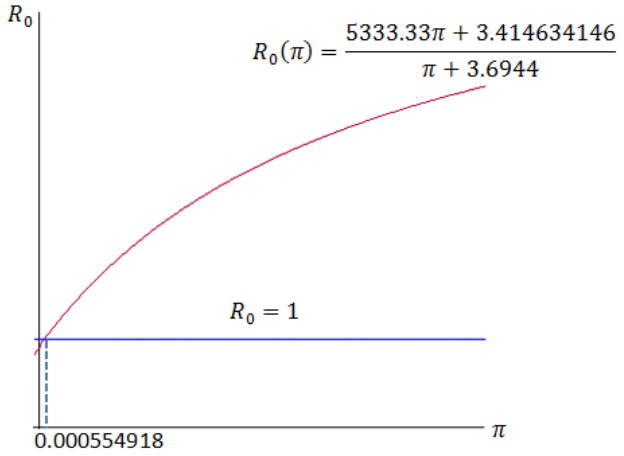

FIGURE 2: Graphs of reproduction number verses the rate of infection of healthy blood cell

From the graph of figure 2, we observe that there is intersection point$(0.000554918, 1)$ between basic reproduction number R_0 and the rate of infection of healthy blood cell πin the first quadrant. Here we observe that, when $R_0 < 1$, then $\pi < 0.000554918$; this means the spread of HBV disease decreases when π is less than0.000554918. If $R_0 > 1$, then $\pi > 0.000554918$; this means the disease of HBV spreads in the liver and blood when π is greater than 0.000554918.

4.2.2. Rate of cure of infected blood cell by non-cytolytic cure processes λ

Graphical representation of the basic reproduction number R_0 versus rate of cure of infected blood cell by non-cytolytic cure processes $\lambda$and keeping other parameters constant is as follows

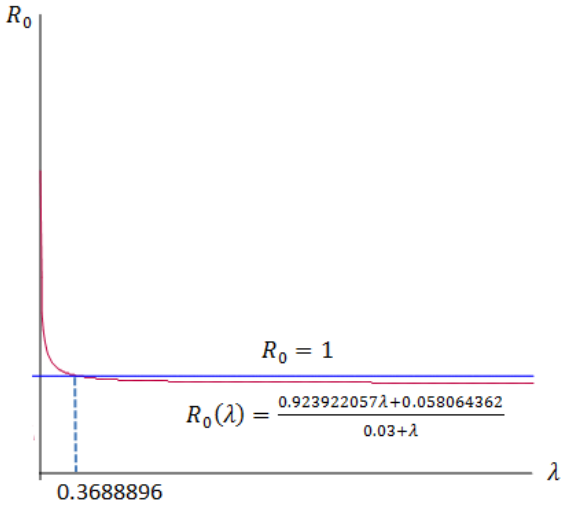

FIGURE 3: Graphs of reproduction number verses rate of cure of infected blood cell

From the graph of figure 3, we observe that there is intersection point$(0.3688896, 1)$ between basic reproduction number R_0 and the rate of cure of infected blood cell λ in the first quadrant. Here we observe that, when $R_0 < 1$, then $\lambda > 0.3688896$; this means the spread of HBV disease decreases when λ is greater than0.3688896. If $R_0 > 1$, then $\lambda < 0.3688896$; this means the disease of HBV spreads in the liver and blood when λ is less than 0.3688896

4.2.3. Drate of infected blood cell η

Graphical representation of the basic reproduction number R_0 versus death rate of infected blood cell $\eta$and keeping other parameters constant is represented as follows.

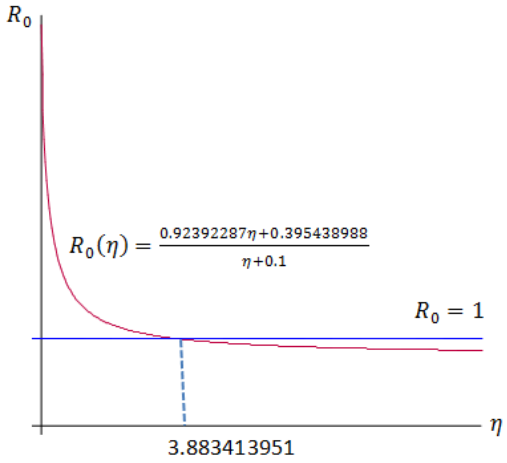

FIGURE 4: Graphs of reproduction number verses the death rate of infected blood cell

From the graph of figure 4, we observe that there is intersection point$(3.883413951, 1)$ between basic reproduction number R_0 and the death rate of infected blood cellη in the first quadrant. Here we observe that, when $R_0 < 1$, then $\eta > 3.883413951$; this means the spread of HBV disease decreases when η is greater than0.100138475. If $R_0 > 1$, then $\eta < 3.883413951$; this means the disease of HBV spreads in the liver and blood when η is less than 3.883413951.

4.2.4. Death rate of free virus μ

Graphical representation of the basic reproduction number R_0 versus Death rate of free virus $\mu$and keeping other parameters constant is as follows

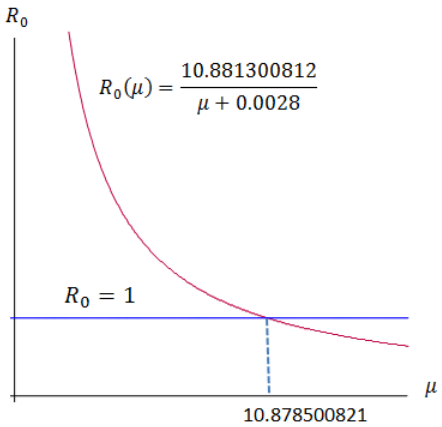

FIGURE 5: Graphs of reproduction number verses the death rate of free virus

From the graph of figure 5, we observe that there is intersection point$(10.878500821, 1)$ between basic reproduction number R_0 and the death rate of free virus μ in the first quadrant. Here we see that, when $R_0 < 1$, then $\mu > 10.878500821$; this means the spread of HBV disease decreases when μ is greater than 8.617695295. If $R_0 > 1$, then $\mu < 10.878500821$; this means the disease of HBV spreads in the liver and blood when μ is less than 10.878500821.

4.3. Sensitivity analysis

The basic reproduction number R_0 is a function of nine parameters $\theta, \pi, p, q, \delta, \omega, \mu, \lambda, and\ \eta$. Inorder to cure the disease it is necessary to control the parameter values to make $R_0 < 1$. We are therefore interested in finding the rate of change of R_0as the parameter values are changed. The rate of change of $R_0$for a change in value of parameter ϕcan be estimated from a normalized sensitivity index, $SI\ (\phi)$defined by $\mathrm{SI}(\phi) = \frac{\phi}{R_0}\frac{\partial R_0}{\partial \phi}$[8]. The normalized sensitivity indices of the reproduction number with respect to$\theta, \pi, p, q, \delta, \omega, \mu,\ \lambda, and\ \eta$are obtained by

$$SI(p) = \frac{p}{R_0}\frac{\partial R_0}{\partial p} = \frac{p\theta(\lambda+\eta)}{p\theta(\lambda+\eta)+q\pi(\delta+\omega)} = \frac{1}{1+\frac{q\pi(\delta+\omega)}{p\theta(\lambda+\eta)}}$$

$$SI(q) = \frac{q}{R_0}\frac{\partial R_0}{\partial q} = \frac{q\pi(\delta+\omega)}{q\pi(\delta+\omega)+p\theta(\lambda+\eta)} = \frac{1}{1+\frac{p\theta(\lambda+\eta)}{q\pi(\delta+\omega)}}$$

$$SI(\theta) = \frac{\theta}{R_0}\frac{\partial R_0}{\partial \theta} = \frac{[p(\lambda+\eta)(\mu+\pi)-q\pi(\delta+\omega)]}{[p\theta(\lambda+\eta)+q\pi(\delta+\omega)](\mu+\pi+\theta)} \times \theta$$

$$SI(\pi) = \frac{\pi}{R_0}\frac{\partial R_0}{\partial \theta} = \frac{[q(\delta+\omega)(\mu+\theta)-p\theta(\lambda+\eta)]}{[p\theta(\lambda+\eta)+q\pi(\delta+\omega)](\mu+\pi+\theta)} \times \pi$$

$$SI(\lambda) = \frac{\lambda}{R_0}\frac{\partial R_0}{\partial \theta} = -\frac{q\pi(\delta+\omega)}{[p\theta(\lambda+\eta)+q\pi(\delta+\omega)](\lambda+\eta)} \times \lambda$$

$$SI(\delta) = \frac{\delta}{R_0}\frac{\partial R_0}{\partial \delta} = -\frac{p\theta(\lambda+\eta)}{[p\theta(\lambda+\eta)+q\pi(\delta+\omega)](\delta+\omega)} \times \delta$$

$$SI(\eta) = \frac{\eta}{R_0}\frac{\partial R_0}{\partial \eta} = -\frac{q\pi(\delta+\omega)}{[p\theta(\lambda+\eta)+q\pi(\delta+\omega)](\lambda+\eta)} \times \eta$$

$$SI(\omega) = \frac{\omega}{R_0}\frac{\partial R_0}{\partial \omega} == -\frac{p\theta(\lambda+\eta)}{[p\theta(\lambda+\eta)+q\pi(\delta+\omega)](\delta+\omega)} \times \omega$$

$$SI(\mu) = \frac{\mu}{R_0}\frac{\partial R_0}{\partial \mu} == -\frac{\mu}{(\mu+\pi+\theta)}$$

Using the data in table-2, the resulting sensitivity indices of $R_0$to the nine different parameters in the model are shown in the following table in the order from most sensitive to least. The highest magnitude of the normalized sensitivity indices of the reproduction number with respect to parameters is the most sensitive one.

Order	Parameter	Sensitivity index
1	μ	-0.999242383
2	π	+0.715775246
3	q	+0.686192159
4	λ	-0.548956631
5	p	+0.313807531
6	θ	+0.313769358
7	ω	-0.306153689
8	η	-0.137238493
9	δ	-0.051025614

TABLE 3: The sensitivity index of the parameters

V. Results and Discussions

We considered non-linear system of ordinary differential equation to study the dynamics of HBV disease inside the host. In this study we adopted and extended the appropriate mathematical model on the dynamics of HBV and we found that an important aspect of mathematical epidemiology which is known to be basic reproduction number R_0 which determines how HBV spreads in the live and blood; and control it.

To decide if the spread of HBV in the liver and blood is high or low, we used the standard measurement which is known as the basic reproduction numberR_0. In our modified model we have derived the basic reproduction number$R_0 = \frac{p\theta}{(\delta+\omega)(\mu+\pi+\theta)} + \frac{q\pi}{(\lambda+\eta)(\mu+\pi+\theta)}$ which depends on nine parameters. We also found that the numerical value of the basic reproduction number based on the standard data taken from different journals is $R_0 = 2.944234214 > 1$. This in principle implies that the disease spreads in the liver and blood of the host. We observe from the above figures that we have four control parameters namely, the rate of infection of blood cell π, the rate of cure of infected blood cell λ, the death rate of infected blood cell η and the death rate of free virus μwhich influence the basic reproduction number. We discuss about these control parameters in detail as follows.

The graph in figure 2 tell us that how basic reproduction number$R_0$is affected by the rate of infection of blood cell π. From the graphical representation we get that$\pi = 0.000554918$ is our control parameter. If $\pi > 0.000554918$then the basic reproduction number is greater than one and HBV disease spreads in the liver and blood. If $\pi < 0.000554918$ then the basic reproduction number is less than one and the disease decrease its spread in the liver and blood.

The graph in figure 3, tell us that how basic reproduction number$R_0$is affected by the rate of cure of infected blood cell λ. From the graphical representation we get that$\lambda = 0.3688896$ is our control parameter. If $\lambda < 0.3688896$then the basic reproduction number is greater than one and HBV disease spreads in the liver and blood. If $\lambda > 0.3688896$then the basic reproduction number is less than one and the disease decrease its spread in the liver and blood.

The graph in figure 4 shows that how basic reproduction number$R_0$is affected by the death rate of infected blood cell η. From the graphical representation we get $\eta = 3.883413951$ is our control parameter. If $\eta < 3.883413951$then the basic reproduction number is greater than one and the disease spreads in the liver

and blood of the host. If $\eta > 3.883413951$then the basic reproduction number is less than one and the disease decrease its spread in the liver and blood.

The graph in figure 5 shows that how basic reproduction number$R_0$is affected by the death rate of free virus μ. From the graphical representation we get $\mu = 10.878500821$is our control parameter. If $\mu < 10.878500821$then the basic reproduction number is greater than one and the HBV disease spreads in the liver and blood of the host. If $\mu > 10.878500821$then the basic reproduction number is less than one and the disease decreases its spread in the liver and blood.

Out of the nine parameters that we consider in the reproduction number; p, q, θ, δ *and* $\omega$are not considered in the numerical analysis. The reason is that the graph of these respective parameters versus the reproduction number does not intersect in the first quadrant.

VI. Conclusions

From the dynamical system of the model, we obtain the reproduction number $R_0 = \frac{p\theta}{(\delta+\omega)(\mu+\pi+\theta)} + \frac{q\pi}{(\lambda+\eta)(\mu+\pi+\theta)}$. Based on standard data collected from different journals, the numerical value of reproduction number is $R_0 = 2.944234214$ which is greater than one. This in principle implies that the disease spreads in the liver and blood. We have observed that the disease free equilibrium point is locally asymptotically stable and globally asymptotically stable. Also the endemic equilibrium point is locally asymptotically stable and globally asymptotically stable. From the sensitivity index of the model we consider the most sensitive parameter is μ which is death rate of free virus. The list sensitive parameter is δ, which is death rate of infected liver cell. Therefore attention must be given to the death rate of free virus to control the HBV disease.

VII. Recommendations

In this study we observe that the basic reproduction number $R_0 = 2.944234214$is greater than one and this implies that the disease spreads in the liver and blood of the host. Therefore, we want to draw the following recommendations to make the basic reproduction number less than one. The rate infection of healthy blood cell π should be less than 0.000554918. The rate of cure of infected blood cell λ should be greater than 0.3688896. The death rate of infected blood cell η should be greater than 3.883413951. The death rate of free virus μ should be greater than 10.878500821.

Reference

[1]. CanadianCentre forOccupationalHealth and Safety, "HepatitisB," http://www.ccohs.ca/oshanswers/diseases/hepatitis b.html.
[2]. Daley, D. J. &Gani, J. (2005). Epidemic Modeling: An Introduction. NY: Cambridge University Press.
[3]. G. F. Medley, N. A. Lindop, W. J. Edmunds, and D. J.Nokes, "Hepatitis-B virus endemicity: heterogeneity, catastrophic dynamics and control," *Nature Medicine*, vol. 7, no. 5, pp. 619–624, 2001.
[4]. "Healthcare stumbling in RI's Hepatitis fight",*The Jakarta Post*,January 2011.
[5]. Hethcote, H. W. (2000). "The mathematics of infectious diseases." Society for Industrial and Applied Mathematics, 42, 599 – 653.
[6]. J. Mann and M. Roberts, "Modeling the epidemiology of hepatitis B in New Zealand," *Journal ofTheoretical Biology*, vol.269, no. 1, pp. 266–272, 2011.
[7]. Koonprasert S, Moore EJ, Banyatlersthaworn S. Sensitivity and Stability Analysis of Hepatitis B Virus Model with Non-Cytolytic Cure Process and Logistic Hepatocyte Growth. Global Journal of Pure and Applied Mathematics. 2016;12(3):2297-312.
[8]. Md. Samsuzzoha, Manmohan Singh, David Lucy, "Uncertainty and sensitivityanalysis of the basic reproduction number of a vaccinated epidemic model of influenza",Applied Mathematical Modelling 37, 2013, pp. 903–915.
[9]. Qesmi, R., Elsaadany, S., Heffernan, J.M.,Wu, J., *A Hepatitis B and C VirusModelWithAgeSince Infection That Exhibits Backward Bifurcation* SIAM J. Appl.Math. 71 (4), 1509-1530,2011. DOI: 10.1137/10079690X.
[10]. Qesmi, R., Wu, J., Wu, J. and Heffernan, J.M., 2010. Influence of backward bifurcation in a model of hepatitis B and C viruses. Mathematical Biosciences, 224(2), pp.118-125.
[11]. Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. Lancet 2015;386:1546–1555.
[12]. WHO, *Hepatitis B Fact Sheet No. 204*, The World Health Organisation, Geneva, Switzerland, 2013, http://www.who.int/mediacentre/factsheets/fs204/en/.
[13]. WHO, *Hepatitis B Fact Sheet No. 204*, The World Health Organization, Geneva, Switzerland, 2013, http://www.who.int/mediacenter/factsheets/fs204/en/.
[14]. World Health Organization (2014) Media Centre. Available: http://www.who.int/mediacentre/factsheets/fs204/en/. Accessed 2014 July 1.
[15]. World Health Organization,*Global Alert and Response (GAR) - Hepatitis: Frequently AskedQuestions*, WHO website, 2010-2013. http://www.who.int/csr/disease/hepatitis/world hepatitis day/question answer/en/. Accessed 02/08/13.
[16]. World Health Organization. Global hepatitis report 2017. World Health Organization, 2017.
[17]. Zhuo X. Analysis of a HBV infection model with non-cytolytic cure process. InSystems Biology (ISB), 2012 IEEE 6th International Conference on 2012 Aug 18 (pp. 148-151). IEEE.
[18]. Zhuo X. Global analysis of a general HBV infection model. InSystems Biology (ISB), 2011 IEEE International Conference on 2011 Sep 2 (pp. 313-318). IEEE.