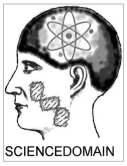
British Journal of Mathematics & Computer Science
15(1): 1-21, 2016, Article no.BJMCS.23120
ISSN: 2231-0851

SCIENCEDOMAIN *international*
www.sciencedomain.org



Mathematical Study of In-host Dynamics of Hepatitis B Virus in Absence of Immunity System

Jannatun Nayeem[1*] and Chandra N. Podder[2]

[1]Department of Arts and Sciences, Ahsanullah University of Science and Technology, Bangladesh.
[2]Department of Mathematics, University of Dhaka, Bangladesh.

Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJMCS/2016/23120
Editor(s):
(1) Feliz Manuel Minhos, Professor, Department of Mathematics, School of Sciences and Technology, University of Évora, Portugal.
Reviewers:
(1) Anonymous, University of Ngaoundere, Cameroon.
(2) J. Prakash, University of Botswana, Botswana.
(3) Olusegun Adeyemi Olaiju, Federal Polytechnic Ilaro, Nigeria.
Complete Peer review History: http://sciencedomain.org/review-history/13525

Original Research Article

Received: 15th November 2015
Accepted: 9th January 2016
Published: 3rd March 2016

Abstract

We develop a mathematical model to understand the dynamics of HBV-in host infection of individuals in vivo. The model incorporates the uninfected host cells, short lived infected cells, chronically infected cells, free virus particles, humoral immune response of HBV specific antibodies and cell mediated immune response of CTLs is analysed to gain its characteristic within human cell mechanism. At first we have analyzed the stability analysis of host cells and infected cells without the effect of immunity system and also discuss the graphical analysis with immunity system. Present study represents a mathematical model, which exhibit two equilibrium points namely, the virus free equilibrium (VFE) and virus present equilibrium (VPE). It is found that using Lyapunov function the virus free equilibrium (VFE) is globally asymptotically stable (GAS) when $R_0 < 1$. And also the virus present equilibrium point (VPE) is locally asymptotically stable when $R_0 > 1$.

Keywords: Hepatitis B virus in host (HBV-in host); basic reproduction number; equilibrium points; local and global stability; Laypunov function.

**Corresponding author: E-mail: jannataust@gmail.com;*

1 Introduction

Hepatitis B virus is a potentially life-threading liver infection caused by the hepatise B virus. It is a major global health problem. It can cause chronic infection (long-standing) and puts people at high risk of death from cirrhosis and liver cancer [1].

The infection has been preventable by vaccination since 1982 [2,3]. Vaccination is recommended by the World Health Organization in the first day of life if possible. Two or three more doses are required at a later time for full effect. This vaccine works about 95% of the time. About 180 countries gave the vaccine as part of national programs as of 2006 [4].

About one third of the world population has been infected at one point in their lives, including 240 million to 350 million who have chronic infection [3,5]. Over 750,000 people die of Hepatitis B each year [3]. The disease is now only common in sub-Saharan Africa and East Asia; where between 5-10% of the adult population is chronically infected. High rates of chronic infection are also found in the Amazon and the southern parts of eastern and central Europe, in the Middle East and the Indian subcontinent, an estimate 2-5% of the general population is chronically infected [3]. Less than 1% of the population in Western Europe and North America is chronically infected [1].

Transmission of hepatitis B virus results from exposure to infection blood or body fluids containing blood. Possible forms of transmission include sexual contact [6] blood transfusion and transfusion with other human blood product [7] are use of contaminated needles and syringes [8] and vertical transmission from mother to child (MTCT) during childbirth. Without intervention, a mother is also positive for HBsAg has a 20% risk of passing the infection to her offspring at the time of birth. The risk is as high as 90% if the mother is also positive for HBeAg [9].

The hepatitis B virus 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 the vaccine. The incubation period of the hepatitis B virus is 75 days on average, but can vary from 30 to 180 days. The virus may be detected within 30-60 days after infection and can persist and develop into Chronic Hepatitis B [1].

The likelihood that infection with the virus becomes chronic depends upon the age at which a person becomes infected. 30-50% of children infected before the age of 6 years develop chronic infection. 20-30% of adults who are chronically infected will develop cirrhosis and liver cancer [1].

Treatment strategies include drug therapy (for HBV) and liver transplantation in cases of end-stage liver disease. However, these treatments are expensive and can produce significant side effects [10]. It is known that many patients with liver transplants have experienced HBV re infection, illustrating that treatments may not result in a permanent cure [11]. There is still limited access to diagnosis and treatment of hepatitis B in many resource-constrained setting, and many people are diagnosed only when they already have advanced liver diseases. Liver cancer progresses rapidly and treatment option are limited. In low-income settings, most people with liver cancer die within months of diagnosis [3]. Thus, in order to analyze the with-host dynamics of HBV, mathematical modeling is introduced.

Here we simplified a mathematical model of immune responds to HBV infection. This focuses on the control of the infection by the interferon, the innate and adaptive immunity. Much interest has been devoted to mathematical modelling of in vivo dynamics of viral infections. These in-host models are formulated to explore possible mechanisms and dynamical behaviours of the viral infection process. There is little evidence that humeral immunity plays a major role in the clearance of established infection. Cell-mediated immune responses, particularly those involving cytotoxic T-lymphocytes (CTLs) seems to be very important [12,13]. During HBV infection, the host immune response causes both hepatocellular damage and viral clearance. Although the innate immune response does not play a significant role in these processes, the adaptive immune response, in particular virus-specific cytotoxic T lymphocytes (CTLs), contributes to most of the liver injury associated with HBV infection. CTLs eliminate HBV infection by killing infected cells

and producing antiviral cytokines, which are then used to purge HBV from viable hepatocytes [14]. Although liver damage is initiated and mediated by the CTLs, antigen-nonspecific inflammatory cells can worsen CTL-induced immunopathology, and platelets activated at the site of infection may facilitate the accumulation of CTLs in the liver [15].

Here we construct a simplified, biologically justified, mathematical model of the dynamics of HBV infection and want to focus on three important components of the immune response; the interferon and cellular components of innate immunity and the adaptive immunity. Innate host responses during the early phases of viral infections are mainly characterized by the production of type-I interferon (IFN) and the activation of natural killer (NK) cells [14]. Innate immunity generally plays a role immediately after infection to limit the spread of the pathogen and initiate efficient development of an adaptive immune response.

Our goal of this study is how the early virological and immunological events might influence the development of activation of adaptive immunity necessary to control HBV infection. All of these have the same goal of limiting the concentration of the virus and the damage of the system.

The interaction between the HBV virus and both the innate and adaptive immune response determines the final outcome of the infection. Current treatments are effective in suppressing HBV viral replication but in most cases fail to clear the virus [10]. Increased knowledge of the virological and immunological events secondary to HBV infection allows us to define the mechanisms involved in viral clearance and persistence.

Here, we explore the natural history of hepatitis B in host, and if possible the mathematical formulation of its dynamics *in vivo* and the construction of epidemiological aspects within a mathematical model. The paper is organized by, model formulation, analysis of the model, evaluation of the basic reproduction number and determines the existence and stability of the virus free and virus present endemic equilibrium of the model.

2 Formulation of Model

We design a mathematical model to understand the transmission dynamics and prevalence of HBV-in host. The model is constructed based on the characteristics of HBV-in host transmission. In our model, the total homogenously mixing population at time t, is denoted by N (t). The total host population is sub-individual into six epidemiological groups: $H(t)$ represent the uninfected target host cells at time t and short lived infected cells $I(t)$, chronically infected cells $C(t)$, and free virus particles $V(t)$. The A (t) represent the density of HBV specific antibodies produce by the humoral immune response at time t and Z (t) represents the density of CTLs produced by the cell mediated immune response at time t, so that

$$N(t) = H(t) + I(t) + C(t) + V(t) + \mathrm{A}\,(\mathrm{t}) + \mathrm{Z}\,(\mathrm{t})$$

The susceptible host cell is decreased by infection, which can be acquired following effective contact with free virus particles, at a rate $\boldsymbol{\lambda}$ given by

$$\lambda = \frac{\beta V}{1 + \alpha V} \tag{1}$$

The uninfected target cell consist of constant recruitment rate of uninfected healthy cells and the rate of infection is given by saturation functional response which describes the interaction of the virus with uninfected cells (at a rate $\beta(1-\sigma)$, and $\alpha > 0$ where σ is the vaccination efficacy, $0 \leq \sigma \leq 1$) and infected hepatocytes can be cured and move back into the target population at that rate ρ and host cells is decreased by the natural death rate, μ. Thus the rate of uninfected target cell is given by

$$\frac{dH}{dt} = \pi - \mu H - \frac{(1-\sigma)\beta HV}{1 + \alpha V} + \rho I$$

The short-lived infected cells consist of the interaction of the virus with uninfected cells (at a rate $\beta(1-\sigma)(1-\varphi)$, and $\alpha > 0$ where φ is the fraction of infection depends on the short lived and chronically

infected cells, $0 < \varphi < 1$) and decreases by the death rate δ of the short-lived infected cells and infected hepatocytes can be cured and move back into the target population at the rate ρ and the density of CTLs produced by the cell mediated immune response of infected cells at the rate P and progression rate η of short-lived infected cells. Thus the governing equation is

$$\frac{dI}{dt} = \frac{(1-\varphi)(1-\sigma)\beta HV}{1+\alpha V} - \delta I - \rho I - PIZ - \eta I$$

The chronically infected cells consist of the interaction of the virus with uninfected cells (at a rate $\beta(1-\sigma)\varphi$, and $\alpha > 0$) and decreases by the death rate a of the chronically infected cells and the density of CTLs produced by the cell-mediated immune response of chronically infected cells. It is further increased by the progression rate η of short-lived infected cells. Thus the governing equation is

$$\frac{dC}{dt} = \frac{\varphi(1-\sigma)\beta HV}{1+\alpha V} - aC - PCZ + \eta I$$

The free virus particles consist of the average number of virus produced during the lifetime of short-lived infected cells. It is also increased by the average number of virus produced during the lifetime of chronically infected cells and decreases clearance the free virus (at rate γ), by humeral immune response against HBV infection of free virus particles (at a rate q) and by the density of CTLs produced by the cell-mediated immune response of free virus particles. Thus the governing equation is

$$\frac{dV}{dt} = N_I \delta I + N_c aC - \gamma V - qVA - PVZ$$

The humeral immune response consists of the production rate of antibodies (at the rate α_A depends on the number of short-lived and chronically infected cells and decreases by the lost of the antibodies (at a rate μ_A). Hence

$$\frac{dA}{dt} = \alpha_A(I+C)A - \mu_A A$$

The cell mediate immune response consist of the export of precursor CTL cells from the thymus at the rate b and CTL cells also expand in response to viral antigen derived from infected cells such as short-lived and chronic infection (at a rate c_1 and is decreased by the lost of CTL (at a rate μ_z). Therefore, the governing equation is

$$\frac{dZ}{dt} = b + c_1(I+C)Z - \mu_z Z$$

Based on the characteristics of HBV transmission within in-host the non-linear differential equations (associated variables and parameters are describes in Table 1) are given by

$$\begin{aligned}
\frac{dH}{dt} &= \pi - \mu H - \frac{(1-\sigma)\beta HV}{1+\alpha V} + \rho I \\
\frac{dI}{dt} &= \frac{(1-\varphi)(1-\sigma)\beta HV}{1+\alpha V} - \delta I - \rho I - PIZ - \eta I \\
\frac{dC}{dt} &= \frac{\varphi(1-\sigma)\beta HV}{1+\alpha V} - aC - PCZ + \eta I \\
\frac{dV}{dt} &= N_I \delta I + N_c aC - \gamma V - qVA - PVZ \\
\frac{dA}{dt} &= \alpha_A(I+C)A - \mu_A A \\
\frac{dZ}{dt} &= b + c_1(I+C)Z - \mu_z Z
\end{aligned} \tag{2}$$

2.1 Analysis of the model

Consider the model (2), with absence of immune response (i.e. model (2) with $P = q = \alpha_A = b = c_1 = 0$). Then the model (2) in the reduced form is:

$$\frac{dH}{dt} = \pi - \mu H - \frac{(1-\sigma)\beta HV}{1+\alpha V}$$

$$\frac{dI}{dt} = \frac{(1-\varphi)(1-\sigma)\beta HV}{1+\alpha V} - \delta I - \rho I - \eta I \tag{3}$$

$$\frac{dC}{dt} = \frac{\varphi(1-\sigma)\beta HV}{1+\alpha V} - aC + \eta I$$

$$\frac{dV}{dt} = N_I \delta I + N_c aC - \gamma V$$

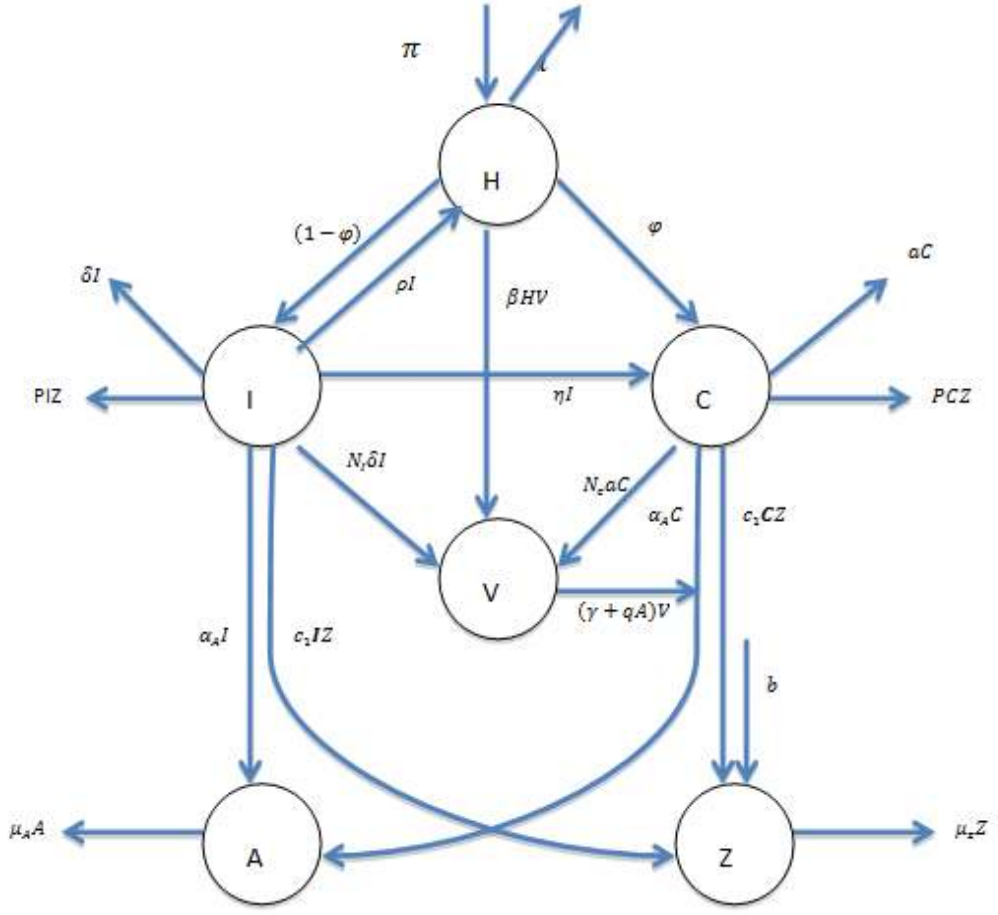


Fig. 1. Model diagram of HBV in-host cell structure

Table 1. Data summary and description of parameters of the model

Parameters	Description	Values
π	Constant rate of production of healthy host cells	100 [16]
μ	Natural death rate of healthy cells	varies
σ	The vaccination efficacy	$0 \leq \sigma \leq 1$
β	The interaction rate	0.01 [17]
μ_z	The lost rate of antibody	0.066 [17]
α_A	Production rate of antibodies	0.43 [18]
ρ	Cured rate of infected hepatocytes	4 [18]
μ_A	The lost rate of CTL cells	0.43 [19]
φ	The fraction of infection depends on the short lived and chronically infected cells	$0 \leq \varphi \leq 1$
δ	The death rate of the short-lived infected cells	0.5 [20]
η	Progression rate of short lived to chronically infected cell	0.012 [21]
P	Cell-mediated immune response	0.5 [varies]
A	The death rate of the chronically infected cells	Varies
γ	The free virus clearance rate	0.67 [22]
Q	The antibody neutralization rate	Varies
b	The export of precursor CTL cells from the thymus	0.12 [23]
α	The saturation infection rate	varies
N_I	The average number of virions produced during the lifetime of short lived infected cell	varies
N_c	The average number of virions produced during the lifetime of chronically infected cell	varies
c_1	HBV specific CTL stimulation rate	varies

2.2 Existence and the local stability of virus free equilibrium points (VFE)

The reduced model (2) has a VFE, obtained by setting the R.H.S of the equations in (2) to zero, which is given by

$$\varepsilon_0 = (H^*, I^*, C^*, V^*) = \left(\frac{\pi}{\mu}, 0,0,0\right).$$

The local stability of ε_0 can be established using the next generation operator method. The matrices F and Q for the new infection terms and the remaining transfer terms from the model at the VFE are respectively given by,

$$F = \begin{bmatrix} 0 & 0 & \frac{\beta\pi(1-\varphi)(1-\sigma)}{\mu(1+\alpha V)^2} \\ 0 & 0 & \frac{\beta\pi\varphi(1-\sigma)}{\mu(1+\alpha V)^2} \\ 0 & 0 & 0 \end{bmatrix} = \begin{bmatrix} 0 & 0 & \frac{\beta\pi(1-\varphi)(1-\sigma)}{\mu} \\ 0 & 0 & \frac{\beta\pi\varphi(1-\sigma)}{\mu} \\ 0 & 0 & 0 \end{bmatrix}$$

and $$Q = \begin{bmatrix} \delta+\rho+\eta & 0 & 0 \\ -\eta & a & 0 \\ -N_I\delta & -N_c a & \gamma \end{bmatrix}$$

The associated reproduction number, denoted by $R_0 = \rho(FQ^{-1})$, where ρ denotes the spectral radius (dominant eigenvalue in magnitude) of the next generation matrix FQ^{-1}. It follows that

$$R_0 = \rho(FQ^{-1}) = \frac{\beta\pi\{(1-\sigma)\{\varphi N_c\delta + \varphi N_c\rho + \eta N_c + N_I\delta(1-\varphi)\}\}}{\mu(\delta+\rho+\eta)\gamma}$$

Lemma 1: The disease free equilibrium, ε_0 of the model (2), is locally asymptotically stable (LAS) if $R_0 < 1$, and unstable if $R_0 > 1$.

The threshold quantity , R_0 is the reproduction number for the model. The epidemiological implication of Lemma 1 is that HBV in-host spread can be effectively controlled in the community (when $R_0 < 1$) if the initial sizes of the population of the model are in the basin of attraction of the disease free equilibrium ε_0.

2.3 Global stability of VFE of the model

Lemma 2: The model (2) does not undergo backward bifurcation at $R_0 = 1$ in the absence of immunity (i.e., when $P = q = \alpha_A = b = c_1 = 0$).

The result given in lemma 2(discounting the possibility of backward bifurcation when $P = q = \alpha_A = b = c_1 = 0$) suggest that the DEF, ε_0, of the model (2), may be globally asymptotically stable (GAS) when $R_0 < 1$ and $P = q = \alpha_A = b = c_1 = 0$ this is explored below.

Theorem 1: The DEF, ε_0, of the model (2), with $P = q = \alpha_A = b = c_1 = 0$ is GAS in *D* if $R_0 < 1$.

Proof: Consider the Lyapunov function

$$F = f_1 I + f_2 C + f_3 V$$

Where,

$$f_1 = \frac{\eta N_c + N_I\delta}{\delta+\rho+\eta},$$

$$f_2 = N_c,$$

$$f_3 = 1$$

With Lyapunov derivative given by (when dot represent differential with respect to t)

$$\dot{F} = f_1\dot{I}(t) + f_2\dot{C}(t) + f_3\dot{V}(t)$$

$$= \frac{\eta N_c + N_I\delta}{\delta+\rho+\eta}\left[\frac{(1-\varphi)(1-\sigma)\beta HV}{1+\alpha V} - \delta I - \rho I - \rho IZ - \eta I\right] + N_c\left[\frac{\varphi(1-\sigma)\beta HV}{1+\alpha V} - aC - \rho CZ + \eta I\right] + 1[N_I\delta I + N_c aC - \gamma V - qVZ - PVZ]$$

$$= \frac{\beta\pi V(\eta N_c + N_I\delta)(1-\sigma)}{\mu(\delta+\rho+\eta)(1+\alpha V)} - \frac{\beta\pi V\varphi(1-\sigma)(\eta N_c + N_I\delta)}{\mu(\delta+\rho+\eta)(1+\alpha V)} - \frac{(\eta N_c + N_I\delta)}{\delta+\rho+\eta}\mathrm{I}(\delta+\rho+\eta) + \eta IN_c + N_I\delta I - \gamma V + \frac{\varphi N_c(1-\sigma)\beta\pi V}{\mu(1+\alpha V)}$$

$$= \frac{\beta\pi V(\eta N_c+N_I\delta)(1-\sigma)}{\mu(\delta+\rho+\eta)(1+\alpha V)} - \frac{\beta\pi V\varphi(1-\sigma)(\eta N_c+N_I\delta)}{\mu(\delta+\rho+\eta)(1+\alpha V)} + \frac{\varphi N_c(1-\sigma)\beta\pi V}{\mu(1+\alpha V)}$$

$$-\eta IN_c - N_I I\delta + \eta IN_c + N_I\delta I - \gamma V + \frac{\varphi N_c(1-\sigma)\beta\pi V}{\mu(1+\alpha V)}$$

$$= \frac{\beta\pi V(\eta N_c + N_I\delta)(1-\sigma) - \beta\pi V\varphi(1-\sigma)(\eta N_c + N_I\delta) - \gamma V\mu(\delta+\rho+\eta)(1+\alpha V) + \varphi N_c\beta\pi V(1-\sigma)(\delta+\rho+\eta)}{\mu(\delta+\rho+\eta)(1+\alpha V)}$$

$$= \frac{\varphi N_c(1-\sigma)\beta\pi V\delta + \varphi N_c(1-\sigma)\beta\pi V\rho + \eta N_c\beta\pi V(1-\sigma) + \beta\pi V(1-\sigma)N_I\delta - \beta\pi V\varphi(1-\sigma)N_I\delta}{\mu(\delta+\rho+\eta)(1+\alpha V)} - \gamma V$$

$$= \frac{\gamma V}{(1+\alpha V)}[R_0 - 1] - \frac{\gamma V}{(1+\alpha V)}\alpha V < \frac{\gamma V}{(1+\alpha V)}[R_0 - 1] \leq 0$$

Thus, $\dot{F} \leq 0$ if $R_0 \leq 1$ with $\dot{F} = 0$ if and only if v=0 (since $\lambda = \frac{\beta V}{1+\alpha V} = 0$). It follows, from the LaSalle's Invariance Principle [24] that $V \to 0\ as\ t \to \infty$.

2.4 Existence of virus present equilibrium point (VPE):

In this section, the possible existence and stability of virus present (positive) equilibria of the model (2) (that means, equilibria where at least one of the infected components of the model is non-zero) will be consider in the absence of immunity, that is when ($P = q = \alpha_A = b = c_1 = 0$).

Let $\varepsilon_1 = (H^{**}, I^{**}, C^{**}, V^{**})$ represent any arbitrary virus present equilibrium of the model (2) with $= q = \alpha_A = b = c_1 = 0$. Solving the equation of the system (2), we have the following virus present equilibrium point (VPE)

$$\frac{dH}{dt} = \pi - \mu H - (1-\sigma)\lambda H + \rho I \tag{4}$$

$$\frac{dI}{dt} = (1-\varphi)(1-\sigma)\lambda H - \delta I - \rho I - \eta I \tag{5}$$

$$\frac{dC}{dt} = \varphi(1-\sigma)\lambda H - aC + \eta I \tag{6}$$

$$\frac{dV}{dt} = N_I\delta I + N_c aC - \gamma V \tag{7}$$

From (4) we get the first equilibrium point,

$$\pi - \mu H^{**} - (1-\sigma)\lambda^{**}H^{**} + \rho I^{**} = 0$$

$$\Rightarrow \pi + \rho I^{**} = [\mu + (1-\sigma)\lambda^{**}]H^{**}$$

$$\Rightarrow H^{**} = \frac{\pi + \rho I^{**}}{\mu + (1-\sigma)\lambda^{**}} \tag{8}$$

From (5) we get, $(1-\varphi)(1-\sigma)\lambda^{**}H^{**} - (\delta+\rho+\eta)I^{**} = 0$

$$\Rightarrow I^{**} = \frac{(1-\varphi)(1-\sigma)\lambda^{**}H^{**}}{(\delta+\rho+\eta)} \tag{9}$$

From (6), $\varphi(1-\sigma)\lambda^{**}H^{**} - aC^{**} + \eta I^{**} = 0$

$$\Rightarrow \varphi(1-\sigma)\lambda^{**}H^{**} - aC^{**} + \frac{\eta(1-\varphi)(1-\sigma)\lambda^{**}H^{**}}{(\delta+\rho+\eta)} = 0$$

$$\Rightarrow C^{**} = \frac{[\varphi(1-\sigma)(\delta+\rho+\eta) + \eta(1-\varphi)(1-\sigma)]\lambda^{**}H^{**}}{a(\delta+\rho+\eta)} \tag{10}$$

And from the equation (7) we have,

$$N_I\delta I^{**} + N_c a C^{**} - \gamma V^{**} = 0$$

$$\Rightarrow N_I\delta\frac{(1-\varphi)(1-\sigma)\lambda^{**}H^{**}}{(\delta+\rho+\eta)} + N_c a\frac{[\varphi(1-\sigma)(\delta+\rho+\eta)+\eta(1-\varphi)(1-\sigma)]\lambda^{**}H^{**}}{a(\delta+\rho+\eta)} - \gamma V^{**} = 0$$

$$\Rightarrow \frac{\{N_I a\delta(1-\varphi)(1-\sigma) + N_c a[\varphi(1-\sigma)(\delta+\rho+\eta)+\eta(1-\varphi)(1-\sigma)]\}\lambda^{**}H^{**}}{a(\delta+\rho+\eta)}$$
$$-\gamma a(\delta+\rho+\eta)V^{**} = 0$$

$$\Rightarrow V^{**} = \frac{\{N_I a\delta(1-\varphi)(1-\sigma) + N_c a[\varphi(1-\sigma)(\delta+\rho+\eta)+\eta(1-\varphi)(1-\sigma)]\}\lambda^{**}H^{**}}{\gamma a(\delta+\rho+\eta)} \quad (11)$$

So, we have positive virus present equilibrium points only where $R_0 > 1$. The expression for λ, at the endemic steady state, denoted by λ^{**}, is given by

$$\lambda^{**} = \frac{\beta V^{**}}{1+\alpha V^{**}} \quad (12)$$

$$\Rightarrow \lambda^{**}(1+\alpha V^{**}) = \beta V^{**}$$
$$\Rightarrow -\frac{1}{\gamma(\delta+\rho+\eta)}\big(\lambda(-\gamma\delta-\gamma\eta-\gamma\rho-\alpha\lambda\delta H^{**}N_I+\alpha\lambda\delta H^{**}N_I\sigma+\alpha\lambda\delta H^{**}N_I\varphi-\alpha\lambda\delta H^{**}N_I\varphi\sigma$$
$$-\alpha\lambda H^{**}N_C\varphi\delta-\alpha\lambda H^{**}N_C\varphi\rho+\alpha\lambda H^{**}N_C\varphi\delta\sigma+\alpha\lambda H^{**}N_C\varphi\sigma\rho-\alpha\lambda H^{**}N_C\eta$$
$$+\alpha\lambda H^{**}N_C\sigma\eta)\big)$$
$$=\frac{\beta\{N_I a\delta(1-\varphi)(1-\sigma)+N_c a[\varphi(1-\sigma)(\delta+\rho+\eta)+\eta(1-\varphi)(1-\sigma)]\}\lambda H^{**}}{\gamma a(\delta+\rho+\eta)}$$

$$\Rightarrow\frac{\lambda[\gamma(\delta+\rho+\eta)+\alpha\lambda\delta H^{**}N_I-\alpha\lambda\delta H^{**}N_I\sigma-\alpha\lambda\delta H^{**}N_I\varphi+\alpha\lambda\delta H^{**}N_I\varphi\sigma+\alpha\lambda H^{**}N_C\varphi\delta+\alpha\lambda H^{**}N_C\varphi\rho-\alpha\lambda H^{**}N_C\varphi\delta\sigma-\alpha\lambda H^{**}N_C\varphi\sigma\rho+\alpha\lambda H^{**}N_C\eta-\alpha\lambda H^{**}N_C\sigma\eta]}{\gamma(\delta+\rho+\eta)}$$
$$=\frac{\beta\{N_I a\delta(1-\varphi)(1-\sigma)+N_c a[\varphi(1-\sigma)(\delta+\rho+\eta)+\eta(1-\varphi)(1-\sigma)]\}\lambda H^{**}}{\gamma a(\delta+\rho+\eta)}$$

$$\Rightarrow \lambda a[\gamma(\delta+\rho+\eta)+\alpha\lambda\delta H^{**}N_I-\alpha\lambda\delta H^{**}N_I\sigma-\alpha\lambda\delta H^{**}N_I\varphi+\alpha\lambda\delta H^{**}N_I\varphi\sigma+\alpha\lambda H^{**}N_C\varphi\delta$$
$$+\alpha\lambda H^{**}N_C\varphi\rho-\alpha\lambda H^{**}N_C\varphi\delta\sigma-\alpha\lambda H^{**}N_C\varphi\sigma\rho+\alpha\lambda H^{**}N_C\eta-\alpha\lambda H^{**}N_C\sigma\eta]$$
$$=\beta\{N_I a\delta(1-\varphi)(1-\sigma)+N_c a[\varphi(1-\sigma)(\delta+\rho+\eta)+\eta(1-\varphi)(1-\sigma)]\}\lambda H^{**}$$

$$\Rightarrow \lambda a[\gamma(\delta+\rho+\eta)+\alpha\lambda\delta H^{**}N_I(1-\sigma)-\alpha\lambda\delta H^{**}N_I\varphi(1-\sigma)+\alpha\lambda H^{**}N_C\varphi\delta(1-\sigma)+\alpha\lambda H^{**}N_C\varphi\rho(1$$
$$-\sigma)+\alpha\lambda H^{**}N_C\eta(1-\sigma)]$$
$$=\beta a\{N_I\delta(1-\varphi)(1-\sigma)+N_c[\varphi(1-\sigma)(\delta+\rho+\eta)+\eta(1-\varphi)(1-\sigma)]\}\lambda H^{**}$$

$$\Rightarrow \lambda a[\gamma(\delta+\rho+\eta)+(1-\sigma)(\alpha\lambda\delta H^{**}N_I-\alpha\lambda\delta H^{**}N_I\varphi+\alpha\lambda H^{**}N_C\varphi\delta+\alpha\lambda H^{**}N_C\varphi\rho+\alpha\lambda H^{**}N_C\eta)]$$
$$=\beta a\{N_I\delta(1-\varphi)(1-\sigma)+N_c[\varphi(1-\sigma)(\delta+\rho+\eta)+\eta(1-\varphi)(1-\sigma)]\}\lambda H^{**}$$

$$\Rightarrow \lambda a[\gamma(\delta+\rho+\eta)+(1-\sigma)\{\alpha\lambda\delta H^{**}N_I(1-\varphi)+\alpha\lambda H^{**}N_C\varphi\delta+\alpha\lambda H^{**}N_C\varphi\rho+\alpha\lambda H^{**}N_C\eta)]$$
$$=\beta a\{N_I\delta(1-\varphi)(1-\sigma)+N_c[\varphi(1-\sigma)(\delta+\rho+\eta)+\eta(1-\varphi)(1-\sigma)]\}\lambda H^{**}$$

$$\Rightarrow \lambda[\gamma(\delta+\rho+\eta)+[(1-\sigma)\{\delta N_I(1-\varphi)+N_C\varphi\delta+N_C\varphi\rho+N_C\eta\}]\alpha\lambda H^{**}$$
$$=\beta\{N_I\delta(1-\varphi)(1-\sigma)+N_c\varphi\delta(1-\sigma)+N_c\varphi\rho(1-\sigma)+N_c\varphi\eta(1-\sigma)+N_c\eta(1-\sigma)$$
$$-N_c\varphi\eta(1-\sigma)\}\lambda H^{**}$$

$$\Rightarrow \lambda[\gamma(\delta+\rho+\eta)+[(1-\sigma)\{\delta N_I(1-\varphi)+N_C\varphi\delta+N_C\varphi\rho+N_C\eta\}]\alpha\lambda H^{**}$$
$$=\beta\{(1-\sigma)\{N_I\delta(1-\varphi)+N_c\varphi\delta+N_c\varphi\rho+N_c\eta\}\}\lambda H^{**}$$

$$\Rightarrow \lambda\gamma(\delta+\rho+\eta)\left[1+\frac{(1-\sigma)\{\delta N_I(1-\varphi)+N_C\varphi\delta+N_C\varphi\rho+N_C\eta}{\gamma(\delta+\rho+\eta)}\alpha\lambda H^{**}\right]$$
$$=\beta\{(1-\sigma)\{N_I\delta(1-\varphi)+N_c\varphi\delta+N_c\varphi\rho+N_c\eta\}\}\lambda H^{**}$$

$$\Rightarrow \lambda\left[1+\frac{(1-\sigma)\{\delta N_I(1-\varphi)+N_C\varphi\delta+N_C\varphi\rho+N_C\eta}{\gamma(\delta+\rho+\eta)}\alpha\lambda H^{**}\right]$$
$$=\frac{\beta\{(1-\sigma)\{N_I\delta(1-\varphi)+N_c\varphi\delta+N_c\varphi\rho+N_c\eta\}\}}{\gamma(\delta+\rho+\eta)}\lambda H^{**}$$

$$\Rightarrow \lambda\left[1+\frac{\alpha R_0}{\beta}\lambda\right]=R_0\lambda$$

$$\Rightarrow \frac{\alpha R_0}{\beta}\lambda^2+\lambda-R_0\lambda=0$$

$$\Rightarrow \frac{\alpha R_0}{\beta}\lambda^2+\lambda(1-R_0)=0$$

$$\Rightarrow \frac{\alpha R_0}{\beta}\lambda+(1-R_0)=0$$

$$\Rightarrow \frac{\alpha R_0}{\beta}\lambda=R_0-1$$

$$\Rightarrow \lambda=\frac{R_0-1}{\frac{\alpha R_0}{\beta}}$$

$$\Rightarrow \lambda=\frac{\beta(R_0-1)}{\alpha R_0}$$

$$=\frac{\beta}{\alpha}\left(1-\frac{1}{R_0}\right) \quad \text{If } R_0>1 \; then \; \lambda>0.$$

Lemma 3: The model (2) with $P=q=\alpha_A=b=c_1=0$ has a unique virus present equilibrium point , given by ε_1 whenever $R_0>1$.

2.5 Local stability of VPE point: (HBV- in host without immunity system)

The local stability of the virus present unique equilibrium point (VPE) ε_1, will now be explored for the reduced model (2). Using the substitution $H^{**}=N^{**}-I-C-V$, gives the following reduced model:

$$\frac{dI}{dt}=\frac{(1-\varphi)(1-\sigma)\beta V}{1+\alpha V}[N^{**}-I-C-V]-(\delta+\rho+\eta)I$$
$$\Rightarrow \frac{dI}{dt}=[-(1-\varphi)(1-\sigma)a_1-k_1]I+[-(1-\varphi)(1-\sigma)a_1]C+(1-\varphi)(1-\sigma)[a_2-a_1]V$$

$$\Rightarrow \frac{dI}{dt}=(-ma_1-k_1)I+(-ma_1)C+m(a_2-a_1)V$$

$$\frac{dC}{dt}=\frac{\varphi(1-\sigma)}{1+\alpha V}[N^{**}-I-C-V]-aC+\eta I \tag{13}$$

$$\Rightarrow \frac{dC}{dt} = [-\varphi(1-\sigma)a_1 + \eta]I + [-\varphi(1-\sigma)a_1 - a]C + \varphi(1-\sigma)[a_2 - a_1]V$$

$$\Rightarrow \frac{dC}{dt} = (-na_1 + \eta)I + (-na_1 - a)C + n[a_2 - a_1]V$$

$$\frac{dV}{dt} = N_I\delta I + N_c aC - \gamma V$$

Theorem 2: The unique virus present equilibrium point, ε_1 of the model (2), is locally asymptotically stable (LAS) if $R_0 > 1$.

Proof: The proof is based on using the technique in [25], which employs a Krasnoselskii sub- linearity trick. The essentially entails that the linearization of the system (13), has solution of the form

$$\bar{z}(t) = \bar{z_0}e^{\theta t} \tag{14}$$

Substituting a solution of the form (14) into the linearized system of (13), gives the following linear system

$$\theta z_1 = (-ma_1 - k_1)z_1 + (-ma_1)z_2 + (a_2 - a_1)z_3 \tag{15}$$

$$\theta z_2 = (-na_1 + \eta)z_1 + (-na_1 - a)z_2 + [a_2 - a_1]z_3 \tag{16}$$

$$\theta z_3 = N_I\delta z_1 + N_c a z_2 - \gamma z_3 \tag{17}$$

Where, $\lambda^{**} = \frac{\beta V^{**}}{1+\alpha V^{**}} = a_1$, $\frac{\beta H^{**}}{1+\alpha V^{**}} = a_2$, $(1-\varphi)(1-\sigma) = m$, $\varphi(1-\sigma) = n$, $k_1 = \delta + \rho + \eta$.

Firstly, all the negative terms in the equation (17) are moved to their respective left hand sides. Solving the equation of (17) and substituting the result into the remaining equations we have,

From (17) we have, $\theta z_3 = N_I\delta z_1 + N_c a z_2 - \gamma z_3$

$$\Rightarrow (\theta + \gamma)z_3 = N_I\delta z_1 + N_c a z_2$$

$$\Rightarrow z_3 = \frac{N_I\delta z_1 + N_c a z_2}{(\theta+\gamma)} \tag{18}$$

Firstly, all the negative terms in the equation (16) are moved to their respective left hand sides and solving the equation of (16).

From (16) we get, $\theta z_2 = (-na_1 + \eta)z_1 - (na_1 + a)z_2 + [a_2 - a_1]\left[\frac{N_I\delta z_1 + N_c a z_2}{(\theta+\gamma)}\right]$

$$\Rightarrow \theta z_2 + na_1 z_2 + az_2 + na_1 z_1 + \frac{a_1 N_I\delta}{(\theta+\gamma)}z_1 + \frac{a_1 N_c a}{(\theta+\gamma)}z_2 \quad = \eta z_1 + \frac{a_2 N_I\delta}{(\theta+\gamma)}z_1 + \frac{a_2 N_c a}{(\theta+\gamma)}z_2$$

$$\Rightarrow \left[\theta + (na_1 + a) + \frac{a_1 N_c a}{(\theta+\gamma)}\right]z_2 + \left[na_1 + \frac{a_1 N_I\delta}{(\theta+\gamma)}\right]z_1 = \left[\eta + \frac{a_2 N_I\delta}{(\theta+\gamma)}\right]z_1 + \frac{a_2 N_c a}{(\theta+\gamma)}z_2 \tag{19}$$

Firstly, all the negative terms in the equation (15) are moved to their respective left hand sides and solve that equation.

From (15), $\theta z_1 + ma_1 z_1 + k_1 z_1 + ma_1 z_2 = (a_2 - a_1)\left[\frac{N_I\delta z_1 + N_c a z_2}{(\theta+\gamma)}\right]$

$$\Rightarrow [\theta + (ma_1 + k_1)]z_1 + ma_1 z_2 + \frac{a_1 N_I \delta}{(\theta+\gamma)} z_1 + \frac{a_1 N_c a}{(\theta+\gamma)} z_2 = \frac{a_2 N_I \delta}{(\theta+\gamma)} z_1 + \frac{a_2 N_c a}{(\theta+\gamma)} z_2$$

$$\Rightarrow \left[\theta + (ma_1 + k_1) + \frac{a_1 N_I \delta}{(\theta+\gamma)}\right] z_1 + \left[ma_1 + \frac{a_1 N_c a}{(\theta+\gamma)}\right] z_2 = \frac{a_2 N_I \delta}{(\theta+\gamma)} z_1 + \frac{a_2 N_c a}{(\theta+\gamma)} z_2 \quad (20)$$

From (18) we have, $\left[1 + \frac{\theta}{\gamma}\right] z_3 = \frac{N_I \delta}{\gamma} z_1 + \frac{N_c a}{\gamma} z_2$.

Adding the equations (19) and (20) we observe that,

$$\left[\theta + k_1 + (m+n)a_1 + \frac{2a_1 N_I \delta}{(\theta+\gamma)}\right] z_1 + \left[\theta + a + (m+n)a_1 + \frac{2a_1 N_c a}{(\theta+\gamma)}\right] z_2 = \left[\eta + \frac{2a_2 N_I \delta}{(\theta+\gamma)}\right] z_1 + \frac{2a_2 N_c a}{(\theta+\gamma)} z_2$$

$$\Rightarrow \left[1 + \frac{\theta}{k_1} + \frac{(m+n)a_1}{k_1} + \frac{2a_1 N_I \delta}{k_1(\theta+\gamma)}\right] z_1 + \left[1 + \frac{\theta}{a} + \frac{(m+n)a_1}{a} + \frac{2a_1 N_C a}{a(\theta+\gamma)}\right] z_2$$
$$= \left[\frac{\eta}{k_1} + \frac{2a_2 N_I \delta}{k_1(\theta+\gamma)}\right] z_1 + \frac{2a_2 N_c}{(\theta+\gamma)} z_2$$

$$\therefore [1 + F_1(\theta)]z_1 + [1 + F_2(\theta)]z_2 = \left[\frac{\eta}{k_1} + \frac{2a_2 N_I \delta}{k_1(\theta+\gamma)}\right] z_1 + \frac{2a_2 N_c}{(\theta+\gamma)} z_2$$
$$[1 + F_3(\theta)]z_3 = \frac{N_I \delta}{\gamma} z_1 + \frac{N_c a}{\gamma} z_2. \quad (21)$$

Where, $F_1(\theta) = \frac{\theta}{k_1} + \frac{(m+n)a_1}{k_1} + \frac{2a_1 N_I \delta}{k_1(\theta+\gamma)}$

$$F_2(\theta) = \frac{\theta}{a} + \frac{(m+n)a_1}{a} + \frac{2a_1 N_C}{(\theta+\gamma)}$$

$$F_3(\theta) = \frac{\theta}{\gamma}$$

With, $M = \begin{bmatrix} \frac{a_2 N_I \delta}{k_1 \gamma} & \frac{a_2 N_c a}{k_1 \gamma} & 0 \\ \frac{\eta}{a} + \frac{a_2 N_I \delta}{a\gamma} & \frac{a_2 N_c}{\gamma} & 0 \\ \frac{N_I \delta}{\gamma} & \frac{N_c a}{\gamma} & 0 \end{bmatrix}$

Note that, the notation $M(\bar{Z}_i)$ (with i=1, 2, 3) denotes the *i-th* co-ordinate of the vector $M(\bar{Z})$. It should further be noted that the M matrix has non-negative entries and equilibrium $\varepsilon_1 = (H^{**}, I^{**}, C^{**}, V^{**})$ satisfies $\varepsilon_1 = M\varepsilon_1$. Furthermore, since the co-ordinate of ε_1 are all positive, it follows then that if $\bar{Z}$ is a solution of (21), then it is possible to find a minimal positive real numbers s, depending on $\bar{Z}$, such that

$$\|\bar{Z}\| \leq s\varepsilon_1 \quad (22)$$

Where $\|\bar{Z}\| = (\overline{Z_1}, \overline{Z_2}, \overline{Z_3})$ with the lexicographic order and $\|.\|$ is a norm in $\mathbb{C}$. Now we want to show that $Re(\theta) < 0$. Deny it, we distinguish two cases: $\theta = 0$ and $\theta \neq 0$. In the first case, the determinate of the homogeneous linear system (13) in the variable Z_i $(i = 1,2,3)$ corresponds to that Jacobean matrix.

Then, for $\theta = 0$, the only solution of the system (21) is the trivial one which implies that $\theta \neq 0$. Assume now that $\theta \neq 0$, and $Re(\theta) \geq 0$. Let $F(\theta) = \min\{|1 + F(\theta)|, i = 1,2,3\}$. It is easy to prove that in this

case $|1 + F(\theta)| >$ for all i, and therefore $F(\theta) > 1$. Taking norms on both sides of (21), and using the fact that M is non- negative, we obtain the following inequatiy:

$$F(\theta)\|\bar{Z}\| = M\|\bar{Z}\| \tag{23}$$

Using (22) and (23), we get

$$F(\theta)\|\bar{Z}\| \leq sM\varepsilon_1 = s\varepsilon_1$$

which implies, $\|\bar{Z}\| \leq \frac{s}{F(\theta)}\varepsilon_1 < s\varepsilon_1$

But this contradicts the minimality of s. Therefore, $Re\,(\theta) < 0$. In this way we proved the following theorem.

Theorem 3: If $R_0 > 1$, then the positive endemic virus present equilibrium state ε_1 of the system (2) is locally asymptotically stable on the set *D.*

2.6 Global stability analysis of VPE

Theorem 4: **T**he unique VPE of the reduced model (13). Consider the following non-linear Lyapunov function:

$$\begin{aligned}\dot{L} &= \left(1-\frac{H^{**}}{H}\right)\dot{H} + \frac{\rho}{k_1}\left(1-\frac{I^{**}}{I}\right)\dot{I} \\ &= \left(1-\frac{H^{**}}{H}\right)\left[\mu H^{**} + \frac{(1-\sigma)\beta H^{**}V^{**}}{1+\alpha V^{**}} - \rho I^{**} - \mu H - \frac{(1-\sigma)\beta HV}{1+\alpha V} + \rho I\right] \\ &\quad + \frac{\rho}{k_1}\left(1-\frac{I^{**}}{I}\right)\left[\frac{(1-\varphi)(1-\sigma)\beta HV}{1+\alpha V} - k_1 I\right]\end{aligned}$$

$$= \mu H^{**} + \frac{(1-\sigma)\beta H^{**}V^{**}}{1+\alpha V^{**}} - \rho I^{**} - \mu H - \frac{(1-\sigma)\beta HV}{1+\alpha V} + \rho I - \frac{\mu(H^{**})^2}{H} - \frac{(1-\sigma)\beta(H^{**})^2V^{**}}{H(1+\alpha V^{**})} + \frac{\rho H^{**}I^{**}}{H} + \mu H^{**} + \frac{(1-\sigma)\beta H^{**}V}{1+\alpha V} - \frac{\rho H^{**}I}{H} + \frac{\rho}{k_1}\left[\frac{(1-\varphi)(1-\sigma)\beta HV}{1+\alpha V} - k_1 I - \frac{(1-\varphi)(1-\sigma)\beta HVI^{**}}{I(1+\alpha V)} + k_1 I^{**}\right]$$

$$= 2\mu H^{**} - \mu H - \frac{\mu(H^{**})^2}{H} + \frac{(1-\sigma)\beta H^{**}V^{**}}{1+\alpha V^{**}} - \frac{(1-\sigma)\beta HV}{1+\alpha V} - \frac{(1-\sigma)\beta(H^{**})^2V^{**}}{H(1+\alpha V^{**})} + \frac{\rho H^{**}I^{**}}{H} + \frac{(1-\sigma)\beta H^{**}V}{1+\alpha V} - \frac{\rho H^{**}I}{H} + \frac{\rho(1-\varphi)(1-\sigma)\beta HV}{k_1(1+\alpha V)} - \frac{\rho(1-\varphi)(1-\sigma)\beta HVI^{**}}{I(1+\alpha V)}$$

$$= 2\mu H^{**} - \mu H - \frac{\mu(H^{**})^2}{H} + \frac{(1-\sigma)\beta H^{**}V^{**}}{1+\alpha V^{**}} - \pi + \mu H^{**} - \rho I^{**} - \frac{(1-\sigma)\beta(H^{**})^2V^{**}}{H(1+\alpha V^{**})} + \frac{\rho H^{**}I^{**}}{H} + \frac{(1-\sigma)\beta H^{**}V}{1+\alpha V} - \frac{\rho H^{**}I}{H} + \frac{\rho}{k_1}[k_1 I^{**}] - \frac{\rho I^{**}}{I} k_1 I^{**}$$

$$= 2\mu H^{**} - \mu H - \frac{\mu(H^{**})^2}{H} + \frac{(1-\sigma)\beta H^{**}V^{**}}{1+\alpha V^{**}} - \left[\mu H^{**} + \frac{(1-\sigma)\beta H^{**}V^{**}}{(1+\alpha V^{**})} - \rho I^{**}\right] + \mu H^{**} - \rho I^{**} - \frac{(1-\sigma)\beta(H^{**})^2V^{**}}{H(1+\alpha V^{**})} + \frac{\rho H^{**}I^{**}}{H} + \frac{(1-\sigma)\beta H^{**}V}{1+\alpha V} - \frac{\rho H^{**}I}{H} + \rho I^{**} - \frac{\rho k_1 (I^{**})^2}{I}$$

$$= 2\mu H^{**} - \mu H - \frac{\mu(H^{**})^2}{H} - \frac{(1-\sigma)\beta H^{**}V^{**}}{1+\alpha V^{**}} \cdot \frac{H^{**}}{H} + \rho I^{**} \cdot \frac{H^{**}}{H} + \frac{(1-\sigma)\beta H^{**}V}{1+\alpha V} - \rho I \cdot \frac{H^{**}}{H} + \rho I^{**} - \frac{\rho k_1 I^{**2}}{I}$$

$$= 2\mu H^{**} - \mu H - \frac{\mu(H^{**})^2}{H} - \frac{(1-\sigma)\beta H^{**}V^{**}}{1+\alpha V^{**}} \cdot \frac{H^{**}}{H} + \rho I^{**} \cdot \frac{H^{**}}{H} + \frac{(1-\sigma)\beta HV}{1+\alpha V} \cdot \frac{H^{**}}{H} - \rho I \cdot \frac{H^{**}}{H} + \rho I^{**} - \rho k_1 I^{**} \cdot \frac{I^{**}}{I}$$

$$= 2\mu H^{**} - \mu H - \frac{\mu(H^{**})^2}{H} - \frac{(1-\sigma)\beta H^{**}V^{**}}{1+\alpha V^{**}} \cdot \frac{H^{**}}{H} + \rho I^{**} \cdot \frac{H^{**}}{H} + [\pi - \mu H^{**} + \rho I^{**}] \cdot \frac{H^{**}}{H} - \rho I \cdot \frac{H^{**}}{H} + \rho I^{**} - \rho k_1 I^{**} \cdot \frac{I^{**}}{I}$$

$$= 2\mu H^{**} - \mu H - \frac{\mu(H^{**})^2}{H} - \frac{(1-\sigma)\beta H^{**}V^{**}}{1+\alpha V^{**}} \cdot \frac{H^{**}}{H} + \rho I^{**} \cdot \frac{H^{**}}{H} + \left[\mu H^{**} + \frac{(1-\sigma)\beta H^{**}V^{**}}{(1+\alpha V^{**})} - \rho I^{**} - \mu H^{**} + \rho I^{**}\right] \cdot \frac{H^{**}}{H} - \rho I \cdot \frac{H^{**}}{H} + \rho I^{**} - \rho k_1 I^{**} \cdot \frac{I^{**}}{I}$$

$$= 2\mu H^{**} - \mu H - \frac{\mu(H^{**})^2}{H} + \rho I^{**} \cdot \frac{H^{**}}{H} \cdot -\rho I \cdot \frac{H^{**}}{H} + \rho I^{**} - \rho k_1 I^{**} \cdot \frac{I^{**}}{I}$$

$$= 2\mu H^{**} - \mu H - \frac{\mu(H^{**})^2}{H} + \rho I \cdot \frac{H^{**}}{H} \cdot \frac{I^{**}}{I} - \rho I \cdot \frac{H^{**}}{H} + \rho I^{**} - \rho k_1 I^{**} \cdot \frac{I^{**}}{I}$$

$$= 2\mu H^{**} - \mu H - \frac{\mu(H^{**})^2}{H} + \left[-\pi + \mu H^{**} + \frac{(1-\sigma)\beta H^{**}V^{**}}{1+\alpha V^{**}}\right] \cdot \frac{I^{**}}{I} \cdot \frac{H^{**}}{H} - \rho I \cdot \frac{H^{**}}{H} + \rho I^{**} - \rho k_1 I^{**} \cdot \frac{I^{**}}{I}$$

$$= 2\mu H^{**} - \mu H - \frac{\mu(H^{**})^2}{H} + \left[-\mu H^{**} - \frac{(1-\sigma)\beta H^{**}V^{**}}{1+\alpha V^{**}} + \rho I^{**} + -\mu H^{**} + \frac{(1-\sigma)\beta H^{**}V^{**}}{1+\alpha V^{**}}\right] \cdot \frac{I^{**}}{I} \cdot \frac{H^{**}}{H} - \rho I \cdot \frac{H^{**}}{H} + \rho I^{**} - \rho k_1 I^{**} \cdot \frac{I^{**}}{I}$$

$$= 2\mu H^{**} - \mu H - \frac{\mu(H^{**})^2}{H} + \rho I^{**} \cdot \frac{I^{**}}{I} \cdot \frac{H^{**}}{H} - \rho I \cdot \frac{H^{**}}{H} + \rho I^{**} - \rho k_1 I^{**} \cdot \frac{I^{**}}{I}$$

$$= 2\mu H^{**} - \mu H - \frac{\mu(H^{**})^2}{H} + \rho I^{**} \cdot \frac{I^{**}}{I} \cdot \frac{H^{**}}{H} - \left[-\pi + \mu H^{**} + \frac{(1-\sigma)\beta H^{**}V^{**}}{1+\alpha V^{**}}\right] \cdot \frac{H^{**}}{H} + \rho I^{**} - \rho k_1 I^{**} \cdot \frac{I^{**}}{I}$$

$$= 2\mu H^{**} - \mu H - \frac{\mu(H^{**})^2}{H} + \rho I^{**} \cdot \frac{I^{**}}{I} \cdot \frac{H^{**}}{H} - \rho I^{**} \cdot \frac{H^{**}}{H} + \rho I^{**} - \rho k_1 I^{**} \cdot \frac{I^{**}}{I}$$

$$= 2\mu H^{**} - \mu H - \frac{\mu(H^{**})^2}{H} + \rho I^{**} \cdot \frac{I^{**}}{I} \cdot \frac{H^{**}}{H} - \rho I^{**} \cdot \frac{H^{**}}{H} + \rho I \cdot \frac{I^{**}}{I} - \rho k_1 I^{**} \cdot \frac{I^{**}}{I}$$

$$= 2\mu H^{**} - \mu H - \frac{\mu(H^{**})^2}{H} + \rho I^{**} \cdot \frac{I^{**}}{I} \cdot \frac{H^{**}}{H} - \rho I^{**} \cdot \frac{H^{**}}{H} + \left[-\pi + \mu H^{**} + \frac{(1-\sigma)\beta H^{**}V^{**}}{1+\alpha V^{**}}\right] \cdot \frac{I^{**}}{I} - \rho k_1 I^{**} \cdot \frac{I^{**}}{I}$$

$$= 2\mu H^{**} - \mu H - \frac{\mu(H^{**})^2}{H} + \rho I^{**} \cdot \frac{I^{**}}{I} \cdot \frac{H^{**}}{H} - \rho I^{**} \cdot \frac{H^{**}}{H} + \rho I^{**} \cdot \frac{I^{**}}{I} - \rho k_1 I^{**} \cdot \frac{I^{**}}{I}$$

$$= 2\mu H^{**} - \mu H - \frac{\mu(H^{**})^2}{H} + \rho I^{**} \cdot \frac{H^{**}}{H}\left(1 - \frac{I^{**}}{I}\right) - \rho I^{**} \cdot \frac{I^{**}}{I}(k_1 - 1)$$

$$= \mu H^{**}\left(2 - \frac{H}{H^{**}} - \frac{H^{**}}{H}\right) - \rho I^{**} \cdot \frac{H^{**}}{H}\left(1 - \frac{I^{**}}{I}\right) - \rho I^{**} \cdot \frac{I^{**}}{I}(k_1 - 1)$$

Since the arithmetic mean exceeds the geometric mean, it follows then that

$$2 - \frac{H}{H^{**}} - \frac{H^{**}}{H} \leq 0$$

Also, if we consider $\frac{I^{**}}{I} < 1$ then the sign of the quantity $\rho I^{**} \cdot \frac{H^{**}}{H}\left(1 - \frac{I^{**}}{I}\right)$ is positive.

Considering the parameter values from Table 2, the value of k_1 is greater than 1. So the last term of the above expression is also positive.

Hence $\dot{L} < 0$ for $R_0 > 1$. Hence, L is a Lyapunov function of the system (13) on $\frac{D}{D_0}$. Thus, by the Lyapunov function L and the LaSalle's Invariance principle [24], every solution to the equation of the reduced model (13) approaches (VPE) as $t \to \infty$ for $R_0 > 1$.

3 Numerical Simulation and Discussion

In this section, we have drawn some graphical presentation using data from Table 1. Here we have collected some data from [26] and we assumed some data for our convenience.

In Fig. 2, consider the different rate of immune response parameters (P, q, α_A, b, c_1) for the reduced model (2). We see that the total number of short lived infected cells are slowly decreases with immune response when R_0 is less than 1 (i.e.R_0=0.0831<1).

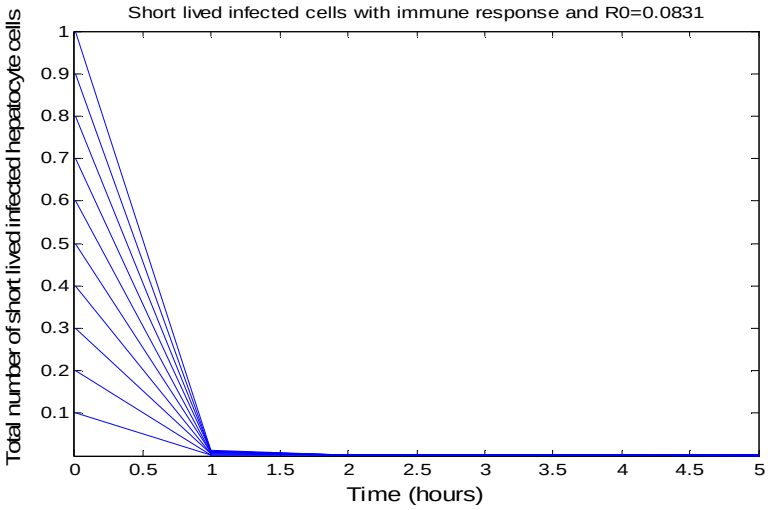


Fig. 2. Short lived infected cells with immune response when R_0=0.0831<1

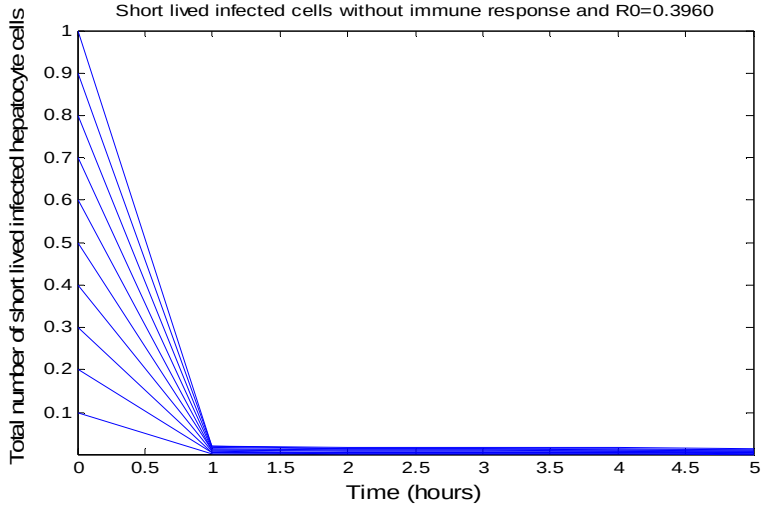


Fig. 3. Short lived infected cells without immune response when R_0=0.3960<1

In Fig. 3, consider the absence of immune response parameters ($P = q = \alpha_A = b = c_1 = 0$) for the reduced model (2). We see that the total number of short lived infected cells are also slowly decreases without immune response when R_0 is less than 1 (i.e.R_0=0.3960<1). But the reduced rate is comparatively slow than the role of immune response.

In Fig. 4, consider the different rate of immune response parameters (P, q, α_A, b, c_1) for the reduced model (2). We see that the total number of short lived infected cells are slowly decreases within the initial time and after that it is increases and due to the immune response short lived infected cells are reduces when R_0 is greater than 1 (i.e.R_0=4.5856>1).

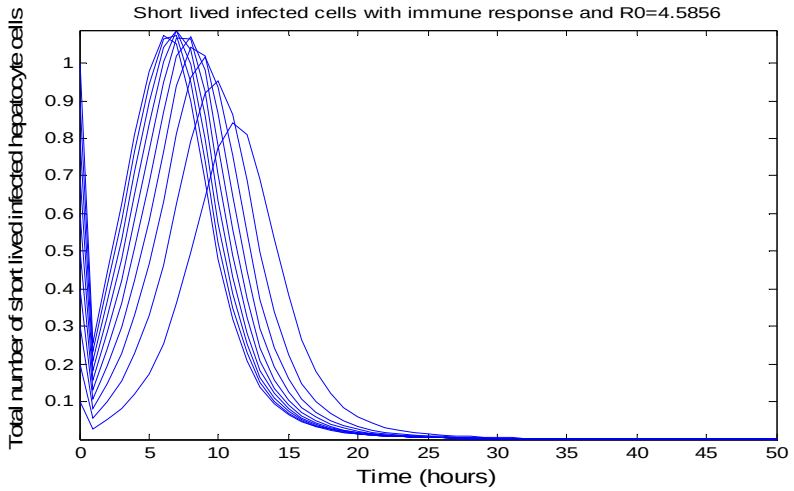


Fig. 4. Short lived infected cells with immune response when R_0=4.5856 >1

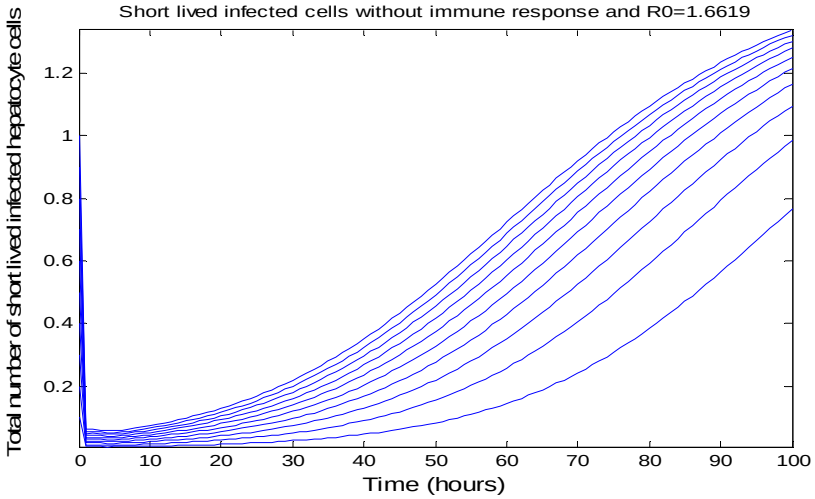


Fig. 5. Short lived infected cells without immune response when R_0=1.6619>1

In Fig. 5, consider the absence of immune response parameters ($P = q = \alpha_A = b = c_1 = 0$) for the reduced model (2). We see that the total number of short lived infected cells are slowly decreases within the initial

time and after that it is gradually increases due to absence of immune response when R_0 is greater than 1 (i.e.R_0=1.6619>1).

In Fig. 6, consider the different rate of immune response parameters (P, q, α_A, b, c_1) for the reduced model (2). We see that the total number of chronically infected cells are slowly decreases with immune response when R_0 is less than 1 (i.e.R_0=0.7919<1).

In Fig. 7, consider the absence of immune response parameters $(P = q = \alpha_A = b = c_1 = 0)$ for the reduced model (2). We see that the total number of chronically infected cells are also slowly decreases without immune response when R_0 is less than 1 (i.e.R_0=0.7919<1). But the reduced rate is comparatively slow than the role of immune response.

In Fig. 8, consider the different rate of immune response parameters (P, q, α_A, b, c_1) for the reduced model (2). We see that the total number of chronically infected cells are slowly decreases within the initial time and after that it is increases and also decreases due to the immune responses. In the long term the infected cells tends to a stable situation when R_0 is greater than 1 (i.e.R_0=7.8940>1).

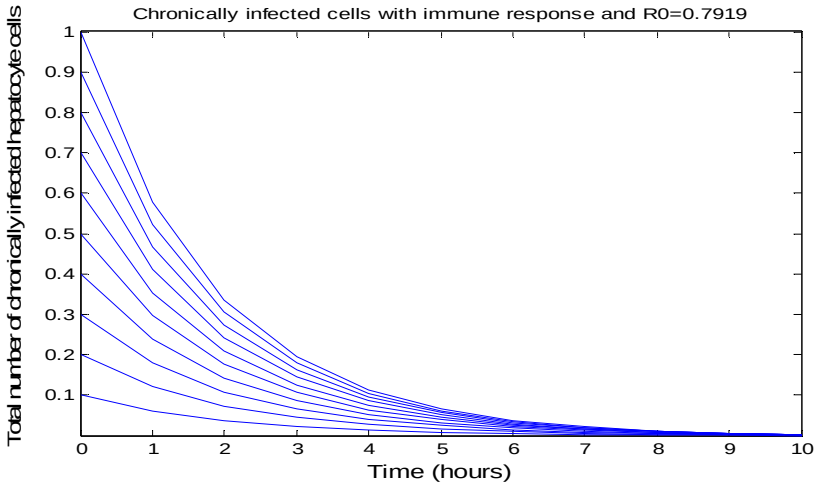


Fig. 6. Chronically infected cells with immune response when R_0=0.7919<1

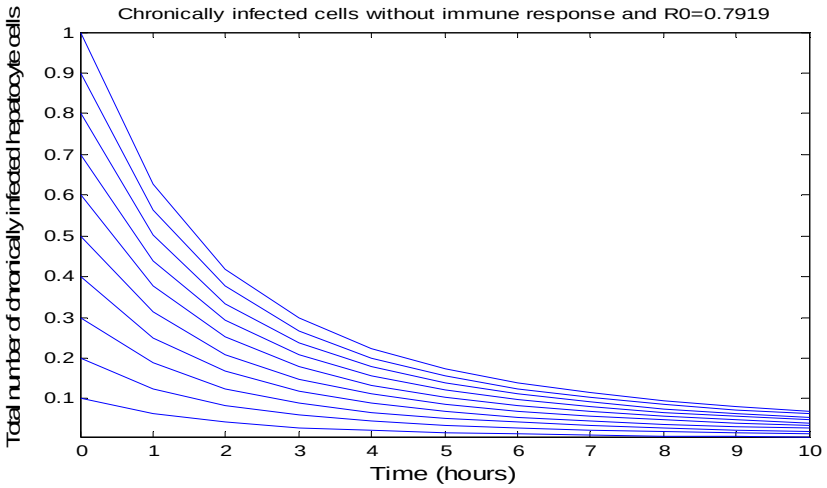


Fig. 7. Chronically infected cells without immune response when R_0=0.7919<1

In Fig. 9, consider the absence of immune response parameters ($P = q = \alpha_A = b = c_1 = 0$) for the reduced model (2). We see that the chronically infected cells are gradually increases due to the absence of immune response and in the long term the infected cells tends to a stable situation when R_0 is greater than 1 (i.e.R_0=7.8940>1).

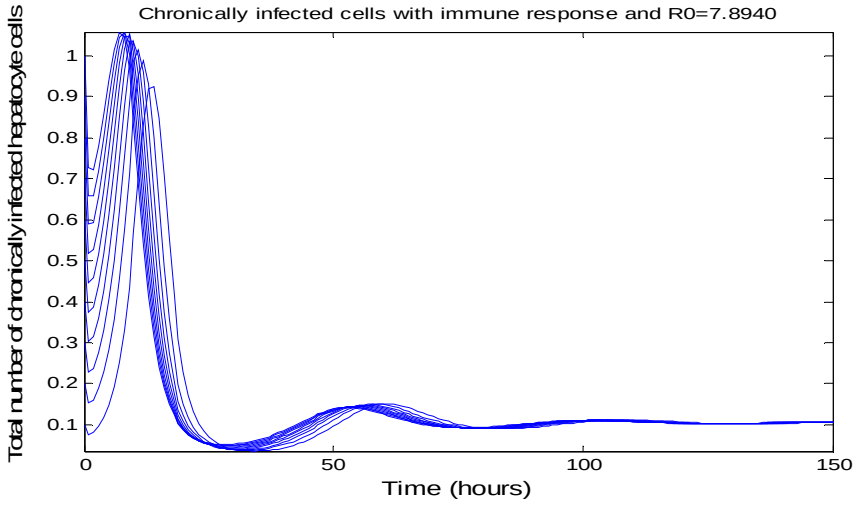


Fig. 8. Chronically infected cells with immune response when R_0=7.8940>1

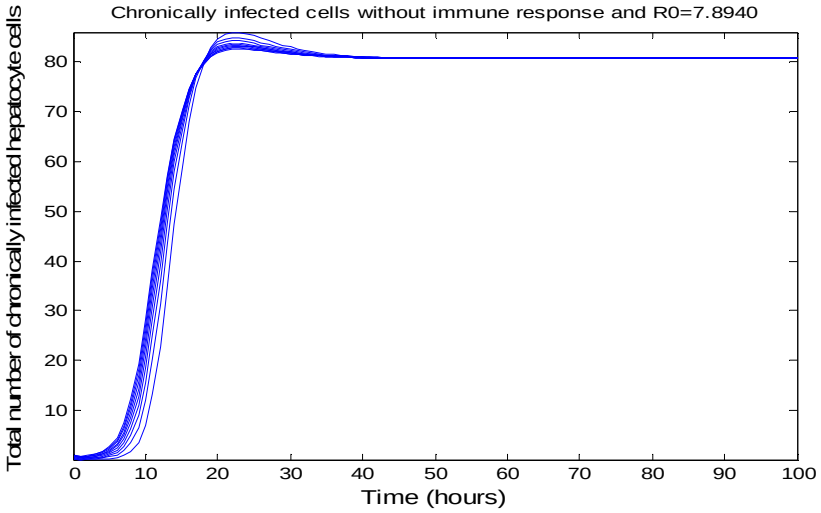


Fig. 9. Chronically infected cells without immune response when R_0=7.8940>1

4 Summary of Contributions

We rigorously analyzed (mathematically and numerically) the dynamics of HBV in vivo in our model. The model equations are solved numerically and the results are presented graphically based on our simulations. The immune response can be sufficient to clear the HBV infection from hepatocyte cells of an individual. But in the absence of immunity, the viral load is brought down to very low levels although not completely

cleared . Most important, we also showed that the virus-free equilibrium is stable while the virus present equilibrium is also stable depending on the various values of the model parameters. Some mathematical and epidemiological findings of our study are given below:

1. The model has a virus free equilibrium (VFE), which is asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$. We also found that, the model has a unique virus present equilibrium point and discuss the local stability at VPE using Sub-linearity trick when $R_0 > 1$ and global stability of that point using non linear Lyaponuv functions when $R_0 > 1$.
2. The decreases rate of infected cells with immune response is comparatively better than that of without immune responses.

5 Conclusion

In this paper, we have proposed a deterministic model for the dynamics of HBV inside the body of an infected human host. The model describes the interaction of the virus with the uninfected and infected cells taking into without immune response. The infection rate is given by saturation functional response which is depends on total viral load. We have shown that the dynamics of the model is fully determined by threshold parameter R_0. The model have shown a globally asymptotically stable virus free equilibrium (VFE) whenever a certain epidemiological threshold, known the basic reproduction number, is less than unity. It has a unique virus present equilibrium (VPE) whenever the threshold quantity exceeds unity. By constructing Lyapunov function and using Lasalle's invariance principle, we have investigated the global stability of equilibrium of the model. We have proven that if $R_0 \leq 1$ the VFE is GAS and under certain condition VPE is also globally asymptotically stable if $R_0 > 1$. Finally, numerical simulations have been performed the disease stability on the basis of immune response.

Acknowledgement

The first author would like to thanks Ms. Ayesha Akter, MS student of Mathematics at Ahsanullah University of Science and Technology.

Competing Interests

Authors have declared that no competing interests exist.

References

[1] Hepatitis B fact sheet N°204. WHO. Int; 2015.

[2] Pungpapong S, Kim WR, Poterucha JJ. Natural history of hepatitis B virus infection: An update for clinicians. Mayo Clinic Proceedings. 2007;82(8):967–975.

[3] Hepatitis B fact sheet N°204. WHO.int; 2014.

[4] Williams R. Global challenges in liver disease. Hepatology (Baltimore, Md.). 2006;44(3):521–526.

[5] Schilsky ML. Hepatitis B "360". Transplantation Proceedings. 2013;45(3):982–985.

[6] Fairley CK, Read TR. Vaccination against sexually transmitted infections. Current Opinion in Infectious Diseases. 2012;25(1):66–72.

[7] Bundaberg F, Schimmer BB, Spahn DR. Transfusion-transmissible infections and transfusion-related immune modulation. Best Practice & Research. Clinical Anaesthesiology. 2008;22(3):503–17.

[8] Hughes RA. Drug injectors and the cleaning of needles and syringes. European Addiction Research. 2000;6(1):20–30.

[9] Hepatitis B – the facts: IDEAS –Victorian Government Health Information, Australia. State of Victoria; 2009-07-28.

[10] Daniel C. Over view of hepatitis treatments and About.com-Health: Hepatitis; 2009. Available:http://hepatitis.about.com/od/treatment/a/treatment.htm
(Accessed 01/08/13)

[11] Krajden M, Kuo M, Zagorski B, Alvaez M, Yu A, Krahn M. Health care costs associated with hepatitis C: A longitudinal cohort study, Canadian Journal of Gaston- theology. 2010;24(12):717-726. PMCID: PMC3004444

[12] Robinson WS. Hepatitis B virus and hepatitis D virus. In: Mandell GL, Bennett JE, Dolin R, eds. Principles and practice of infectious diseases, 4th ed. New York, Churchill Livingstone. 1995;1406-143.

[13] Robinson WS. Hepatitis B viruses. General features (human). In: Webster RG and Granoff A, eds. Encyclopaedia of Virology, London, Academic Press Ltd. 1994;554-569.

[14] Iannacone M, Sitia G, Ruggeri ZM, Guidotti LG. HBV pathogenesis in animal models: Recent advances on the role of platelets. Journal of Hepatology. 2007;46(4):719–726

[15] Iannacone M, Sitia G, Isogawa M, Marchese P, Castro MG, Lowenstein PR, et al. Platelets mediate cytotoxic T lymphocyte-induced liver damage. Nat. Med. 2009;11(11):1167–9.

[16] Zdanor VM, Bakrinskaja AG. Myxovimises reproduction. Medicina. Mascow, Russia; 1969.

[17] Bocharov GA, Romanyukha AA. Mathematical model of antiviral immune response.III. Influenza A virus infection. J. Theor. Biol. 1994;167:323-360.

[18] Keenan KP, Combs JW, McDowell EM. Regeneration of hamster tracheal epithelium after mechanical injury. I. Focal lesions: quantitative morphologic study of cell proliferation. Virchows Arch. B Cell Pathol. Incl. Mol. Pathol. 1982;41:193-214.

[19] Marchuk GI, Petrov RV, Romanyukha AA, Bocharov GA. Mathematical model of antiviral immune response. I. Data analysis, generalized picture construction and parameters evaluation for hepatitis B. J. Theor. Biol. 1991;151:1-40.

[20] Rehermann B, Lau D, Hoofnagle JH, Chisari FV. Cytotoxic T lymphocyte responsiveness after resolution of chronic hepatitis B virus infection. J. Clin. Invest. 1996;97:1655-1665.

[21] Jannatun Nayeem CN, Podder. A mathematical study on the vaccination impact on the disease dynamics of HBV. IOSR Journal of Mathematics (IOSR-JM). 2014;10(5).

[22] Ciupe SM, et al. Modeling the mechanisms of acute hepatitis B virus Infection. Journal of Theoretical Biology. 2007;247(1):23-35.

[23] Gennady Bocharov, Burkhard Ludewig, Antonio Bertoletti, Paul Klenerman, Tobias Junt, Philippe Krebs, Tatyana Luzyanina, Cristophe Fraser, Roy M. Anderson. Underwhelming the immune response: Effect of slow virus growth on CD8-T-lymphocyte responses. Journal of Virology. 2004;78(5):2247–2254.

[24] LaSalle JP. The stability of dynamical systems. Regional Conference Series in Applied Mathematics. SIAM, Philadelphia; 1976.

[25] Hethcote HW, Thieme HR. Stability of the endemic equilibrium in epidemic models with sub populations. Math. Bioscience. 1985;75:205-227.

[26] Wiah EN, Dontwi IK, Adetunde IA. Using mathematical model to depict yhe immune response to hepatitis b virus infection. Journal of Mathematics Research. 2011;3(2).

Peer-review history:
The peer review history for this paper can be accessed here (Please copy paste the total link in your browser address bar)
http://sciencedomain.org/review-history/13525