Mathematical Analysis of Hepatitis B Virus Dynamics

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Submitted By
Jannatun Nayeem
Registration No. : 01

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Under the Supervision of

Professor Dr. Chandra Nath Podder
Department of Mathematics
University of Dhaka

Professor Dr. Abba Gumel
School of Mathematical and Statistical Sciences
Arizona State University, U.S.A.
(Co Supervisor)

Professor Dr. Md. Shahidul Islam
Department of Mathematics
University of Dhaka
(Co Supervisor)

Department of Mathematics

Faculty of Science

University of Dhaka

Abstract

Hepatitis B is a life-threatening liver infection due to the hepatitis B virus. Hepatitis B virus (HBV) infection is one of the predominant public health challenges globally. We develop a deterministic model to understand the underlying dynamics of HBV infection at the population level. The model, which incorporates the vaccination and treatment of individuals, the re-infections of infected classes, is rigorously analyzed to gain insight into its dynamical features. The mathematical analysis reveals that the model exhibits a backward bifurcation due to exogenous re-infection. It is shown that, in the absence of re-infection, the model has a disease-free equilibrium (DFE) which is globally asymptotically stable using Lyapunov function and LaSalle Invariance Principle whenever the associated reproduction threshold is less than unity. Further, the model has a positive unique endemic equilibrium (EEP) which is globally asymptotically stable (GAS) when the associated threshold quantity is greater than one. Next, we incorporate optimal control strategies as vaccination and creating awareness in the model. A system of differential equations with control variables is considered and Pontryagin's Maximum Principle is applied to characterise the optimal controls. In the optimal control system, the main focus is to minimize the cost of two controls as well as to decrease the disease burden. The numerical simulations indicate that the optimal control strategy is effective not only to minimize the infection but also the most successful way to control the infection. Furthermore, we have extended the model considering dose-structured vaccination for assessing the impact of vaccines among the population. Here we have analysed the stability of equilibria and threshold analysis for imperfect vaccine impact on population-level. The local sensitivity analysis is done and observed that some parameters play a prominent role to determine the magnitude of the threshold. Latin Hypercube sampling-PRCC analysis illustrates that disease transmission rate, the fraction of the acutely infected individuals

who developed the chronic infection, development rate of symptomatic chronic carriers and disease complications are the most influential parameters in the disease dynamics. Additionally, we have formulated and rigorously analysed a new basic model for HBV *in vivo* to attain insight into its qualitative aspects. The numerical analyses reveals that the model has a globally-asymptotic stable (GAS) virus-free equilibrium (VFE) and a positive virus persistent equilibrium (VPE) when the basic reproduction number is less than and greater than one, respectively. Finally, the basic HBV model is extended incorporating the effect of immune systems namely cell-mediated and humoral immune responses. Numerical simulations show that the humoral immune system is more effective (to control HBV burden *in vivo*) than the cell-mediated immune system because of the increasing antibody level within the host due to vaccine impact.

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Dedication

To my parents and my lovely family.

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Chapter 1

Introduction

1.1 Hepatitis B Virus

A virus that created disease is a small infectious particle that could simply replicate inside into the cells of an organ. Hepatitis B virus, abbreviated HBV, is partially a DNA virus, a species of Orthohepadnavirus. It is a member of the hepadnavirus family [1]. Hepatitis B is an infectious disease because of the HB virus that affects the liver, that is called viral hepatitis [2]. The disease has two stages, such as, acute phase and chronic carrier phase. Many people do not have any symptoms at the beginning of the infection. At the acute infection phase, a few people may also increase illness with vomiting, yellowish skin, weakness, dark yellow urine and both lower and upper abdominal ache. It can take 30 to 180 days for symptoms to start [3].

Persistent liver infection that means chronic infection of the liver can keep people at high risk of death from liver cirrhosis or liver cancer [4]. The virus enters the body and reaches the liver through the bloodstream. When the virus is in the liver, it releases a large number of new viruses into the bloodstream. The hepatitis B virus can survive for a minimum of 7 days outside of the human body. But by this time, the virus can cause infection if it enters the body of someone who is not immunized by the vaccine. The incubation period is approximately 75 days but it can vary from 30 to 180 days for hepatitis B virus [3]. The virus can be detected between 30 to 60 days after infection and can persist and progress to chronic infection [3]. The infection with the virus becomes

chronic if the virus persists within-host at least more than 6 months. Within the age of 6 years, $30\% - 50\%$ infected children become chronic carriers of the infection [3]. $20\% - 30\%$ of adults who are chronic carriers will progress to liver cirrhosis or liver cancer [3].

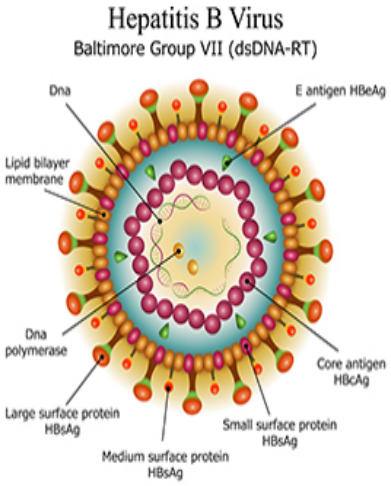

FIGURE 1.1: Structure of Hepatitis B Virus (Source:[32]).

1.2 Transmission of HBV

The hepatitis B virus is usually transmitted by the contaminated blood or infected body fluids of an infected individual and perinatally from mother to baby for the duration of childbirth and from person to person. HBV also can be transmitted through unprotected sex, used needles and syringes by an infected individual and during transfusion of blood [5]. Hepatitis B infection can also be caused by sharing inanimate objects with infected blood, such as washcloths, towels, razors or toothbrushes. Other risk factors for transmitting HBV to others are if someone working in healthcare, dialysis, living together with an infected individual, travel in those countries with high infection rates. The hepatitis B virus cannot outspread by holding hands, kissing, hugging, coughing, sneezing, or breastfeeding and the faecal-oral route [6, 7]. HBV can be transmitted along with the mucous membrane of infectious blood and body fluids of an infected person containing contaminated blood.

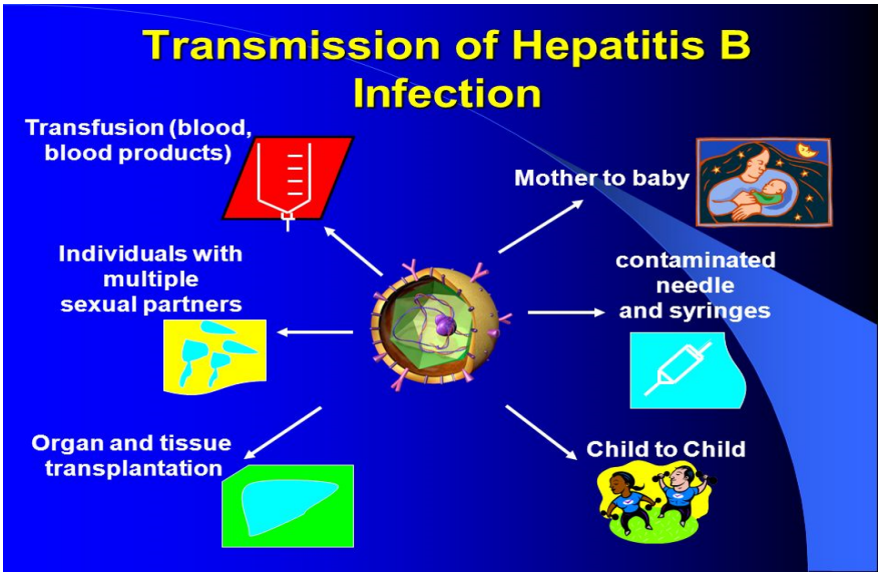

FIGURE 1.2: Transmission of Hepatitis B Viral infection (Source:[32]).

1.3 Public health and Socio-economic Impact

Hepatitis B is one of the common infectious diseases and public health concerns in the world. Hepatitis B is the main reason for chronic liver disease and is a substantial public health problem. The World Health Organization (WHO) reported that more than 250 million people have a chronic liver infection and more than 800,000 people die worldwide each year due to hepatitis B, and its prevalence is the highest in sub-Sahara Africa and East Asia [13]. The disease is common in sub-Saharan Africa and East Asia, wherein $5\% - 10\%$ of the adult has the persistent (chronic) infection. Such chronic infections are also observed in the Amazon and central Europe. About $2\% - 5\%$ of the general population is chronically infected in the Middle East and some Indian subcontinent [11].
Viral hepatitis is the most typical liver infection in Bangladesh. Since Bangladesh is a country of the Asia Pacific region, it is considered a high-risk country for both hepatitis A and B [17]. In Bangladesh, this infection becomes a public health issue and there are about 10 million population are chronically infected with the hepatitis B virus [18]. A proportion of them is hepatitis B carriers and another proportion is affected by the long-standing consequences of this infection. Those who have long term infections can also progress to chronic hepatitis eventually leading to liver cirrhosis and hepatocellular carcinoma. Early detection of HBsAg can save many lives from the dangerous complications of cirrhosis and hepatocellular carcinoma by proper treatment. The HBV vaccination program has proved

to be constructive to enhance long term immunity against hepatitis B infection and is suggested for decreasing HBV-related disease burden [14]. Understanding the significance of HBV vaccination, WHO approved the inclusion of HBV vaccination at the birth time in the country wide immunization programs [15]. There are some social and economic factors that affect hepatitis B prevalence, such as, age, gender, migration, education, employment, training and awareness [16]. It is important to identify which factors are affecting HBV prevalence of the disease. The most crucial policy for controlling the factors is increasing obligatory immunization programmes for all. Vaccination for all is acceptable based on economic evaluation. Increasing the level of education, increasing awareness of society people and gathering knowledge about the disease also helps us to decrease the spread of HBV [16].

1.4 Control Strategies against HBV

To prevent HBV infection a safe and effective vaccine is must for all age groups. The vaccine is introduced for the prevention of the disease in 1982 [8]. The hepatitis B vaccine consists of an antigen that stimulates the body to make preventative antibodies [10]. For the full effect of vaccination, two or three doses are required for a person. Including scheduled infant vaccination, 150 countries or more than have vaccine immunization programs [19].

For controlling the disease progression and to stop viral replication, efficient therapy is very important. It is predicted that without taking treatment, who are chronically infected, among them approximately $15\% - 25\%$ could progress liver cirrhosis and Hepatocellular carcinoma at the last stage of infection [20]. With long-term virological response in a patient, it is evident that antiviral therapy can develop liver histology by giving indirect support and possibly can control liver damage [21, 22].

About 95% acutely hepatitis B infected individuals need no treatment because of their own immune system and can clear the virus within by six months [9]. From the opposite aspect, treatment of chronic carriers may be essential to reduce the risk of liver cirrhosis and liver cancer. Chronic carriers are usually used antiviral medication, namely tenofovir or interferon [3]. Liver replacement is sometimes required for liver cirrhosis. Some antiviral

drugs, namely, lamivudine, adefovir, tenofovir, telbivudine and entecavir, and interferon-alpha immune system can also control the disease complications. But these regular drugs can not properly clear the infection. They are able to only prevent viral replication and suppress liver cirrhosis and cancer. But, some infected people are much more likely to respond than others and this is probably due to the genotype of the virus. The primary motives for analyzing infectious diseases is to develop control techniques and to get rid from the infection. The optimal control strategy is such a technique of mathematics that is broadly used to control the outspread of infectious diseases. It is an important mathematical tool that can help us to make resolutions related to complicated biological situations [24].

1.5 Literature Review

Mathematical models are developed and used for finding the mechanism insight into the transmission dynamics of hepatitis B at a population level. Many of the models in the literature are formed using a deterministic system of continuous-time differential equations. A number of mathematical models, notably by G. F. Medley *et. al.* [25–28] developed a simple SIR model of hepatitis B to describe the transmission of HBV dynamics. Without considering vaccinated individuals separately, I. K. Dontwi *et. al.* [29] considered a SIR model of Kermack and Mckendrickand for hepatitis B with vaccine parameter. Jianhua Pang *et. al.* [30] used a model to investigate the effect of vaccination and other controlling system for the HBV infection. In [26, 27], a compartmental mathematical model (SECIR) is constructed at the population level considering age classes. They focused to eliminate HBV in New Zealand using control strategies. They also estimated that the vaccination campaign has substantially reduced the value of basic reproduction number below one. K. Wang *et. al.* [31] considered a diffusion model and analysed the properties of hepatitis B virus infection.

1.6 Thesis Outline

This thesis is comprised of seven self-contained chapters and they are organized as follows: Chapter 1 presents an introduction about HBV transmission including control strategies against HBV infection, literature reviews and the outline of the thesis. In Chapter 2, we have presented some elementary mathematical preliminaries (related to the thesis) which will be required to analyze the models in different chapters of the thesis. In Chapter 3, a basic HBV transmission model at a population level is formulated and analyzed mathematically and numerically. HBV dynamics *in vivo* is rigorously analyzed qualitatively and numerically in Chapter 4. In chapter 5, we have considered the model of HBV using optimal control technique and presented the analysis of the behavior of the disease dynamics. Chapter 6 is contained the HBV vaccination model. Finally, the main mathematical and epidemiological implications of the models in this thesis are presented in Chapter 7.

Chapter 2

Preliminaries

Necessary definitions, theorems and epidemiological preliminaries from [24, 33, 34], which are related to the thesis, are presented here in this chapter.

2.1 Equilibria of System

Let

$$\dot{x} = g\left(x, t; \alpha\right),\ x \in P \subset \mathbb{R}^n,\ t \in \mathbb{R}^1, \text{ and } \alpha \in Q \subset \mathbb{R}^p. \tag{2.1}$$

where, P, Q are respectively the open sets in $\mathbb{R}^n$, $\mathbb{R}^p$ and α is a parameter. The above equation is an *ordinary differential equation* (ODE) and g is a **vector field**. A **non-autonomous** system is explicitly depends on time whereas an **autonomous** system does not depend explicitly on time.

Let the system be

$$\dot{x} = g\left(x\right),\ x \in \mathbb{R}^n. \tag{2.2}$$

Definition 2.1. [33]. The number $\overline{x}$ is known as **equilibrium point** of above ODE (2.2), which has an equilibrium solution $x = \overline{x} \in \mathbb{R}^n$ if $g(\overline{x}) = 0$.

Theorem 2.1. (Existence and Uniqueness Theorem [33]). If $g(t, w)$ and $\frac{dg}{dw}$ are continuous functions of t and w in the region $R(a_1, a_2)$ of $\mathbb{R}^n \times \mathbb{R}^n$, where,

$$R(a_1, a_2) = \{(t, w) : |t - t_0| \leq a_1,\ |w - w_0| \leq a_2\},$$

there exists a unique solution $w(t)$ to the following IVP:

$$\dot{w} = g(t, w), \quad w(t_0) = w_0.$$

on

$$|t - t_0| \leq h \leq a_1, \; h = \min\left(a_1, \frac{a_2}{M}\right), \; M = \max_{(t,w)\in R} g(t, w).$$

Definition 2.2. [33]. The Jacobian matrix of g at $\overline{x}$ is given by

$$Df(\overline{x}) = \begin{pmatrix} \frac{\partial g_1}{x_1}(\overline{x}) & \cdots & \frac{\partial g_1}{x_n}(\overline{x}) \\ \vdots & \vdots & \vdots \\ \frac{\partial g_n}{x_1}(\overline{x}) & \cdots & \frac{\partial g_n}{x_n}(\overline{x}) \end{pmatrix}.$$

2.2 Stability analysis

Definition 2.3. [34]. The equilibrium $\overline{x}(t)$ is **stable** if for any $\mathcal{E} > 0$, $\exists$ a $\delta = \delta(\mathcal{E}) > 0 \ni$ for any arbitrary solution $u(t)$ of (2.2), the inequality

$$|\overline{x}(t_0) - u(t_0)| < \delta \Rightarrow |\overline{x}(t) - u(t)| < \mathcal{E}, \quad \forall \; t > t_0, \; t_0 \in \mathbb{R} \text{ holds.}$$

Definition 2.4. [34]. If the solution $\overline{x}(t)$ of (2.2) is stable then it is called **asymptotically stable** and $\exists$ a constant quantity $\delta_0 > 0 \ni$ for arbitrary solution $u(t)$ of (2.2) satisfy the condition $|\overline{x}(t_0) - u(t_0)| < \delta_0$, then

$$\lim_{t\to\infty} |\overline{x}(t) - u(t)| = 0.$$

Definition 2.5. [34]. The equilibrium $\overline{x}(t)$ of (2.2) is **unstable** when it is not stable.

Theorem 2.2. [34]. If all the eigenvalues of the Jacobian matrix have negative real parts then the equilibrium solution of (2.2) is LAS (*locally asymptotically stable*) and the solution is *unstable* if at least one of the eigenvalues has a positive real part.

Theorem 2.3. (Castillo-Chavez and Song [60]). Let the ordinary differential equations with a parameter ξ
$\frac{dx}{dt} = h(x, \xi), h : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R}^n \text{and} h \in \mathbb{C}^2(\mathbb{R}^n \times \mathbb{R})$,
where, 0 is the equilibrium point of the system $(h(0, \xi) \equiv 0 \; \forall \; \xi)$

1. $B = D_x h(0,0) = \left(\frac{\partial h_i}{\partial x_j}(0,0)\right)$ is a linearization matrix of the ordinary differential equations system around 0 with ξ estimated at the equilibrium point 0;
2. 0 is a eigenvalue of B and all other eigenvalues have *-ve* real parts;
3. Matrix B has corresponding right and left eigenvectors (w and v) to the simple eigenvalue, 0.

Let h_r be the r^{th} component of h and

$$\begin{aligned} a_1 &= \sum_{r,i,j=1}^{n} v_r w_i w_j \frac{\partial^2 h_r}{\partial x_i \partial x_j}(0,0), \\ b_1 &= \sum_{r,i=1}^{n} v_r w_i \frac{\partial^2 h_r}{\partial x_i \partial \xi}(0,0). \end{aligned} \tag{2.3}$$

By the signs of a_1 and b_1 we can illustrate the local dynamics of the required system around the point 0. On the other hand, if $a_1 > 0$ and $b_1 > 0$, there exists a backward bifurcation that occurs at $\xi = 0$.

(i) $a_1 > 0, b_1 > 0$. When $\xi < 0$ with $\mid \xi \mid \leq 1$ then the equilibrium point is LAS and $\exists$ a positive unstable equilibrium point, when $0 < \xi \leq 1$, the equilibrium point is unstable and $\exists$ a negative LAS equilibrium;

(ii) $a_1 < 0, b_1 < 0$. When $\xi < 0$ with $\mid \xi \mid \leq 1$ then the equilibrium point is unstable, when $0 < \xi \leq 1$, the equilibrium point is LAS and $\exists$ a positive unstable equilibrium;

(iii) $a_1 > 0, b_1 < 0$. When $\xi < 0$ with $\mid \xi \mid \leq 1$ then the equilibrium point is unstable and $\exists$ a LAS negative equilibrium , when $0 < \xi \leq 1$, the equilibrium point is stable and a positive unstable equilibrium occurs;

(iv) $a_1 < 0, b_1 > 0$. When ξ changes from negative to positive, the equilibrium point changes its stability and a *-ve* unstable equilibrium point becomes *+ve* and is locally asymptotically stable (LAS).

2.3 Methods for LAS of Equilibria

There are two standard methods for the local stability analysis around the equilibria. The methods are discussed below:

2.3.1 Linearization

To establish the stability of $\bar{x}(t)$ we have to understand the behavior of solutions near $\bar{x}(t)$. Consider

$$x = \bar{x}(t) + \epsilon, \tag{2.4}$$

Substitute (2.4) in (2.2) and g is two times differentiable function. The expression of Taylor series around the equilibrium gives

$$\dot{x} = \dot{x}(t) + \dot{\epsilon} = Dg(\bar{x}(t))\epsilon + O(|\epsilon|^2) \tag{2.5}$$

where, $|.|$ denotes norm. Therefore,

$$\dot{\epsilon} = Dg(\bar{x}(t))\epsilon + O(|\epsilon|^2) \tag{2.6}$$

The above expression (2.6) represents the evaluation of orbits in the neighbourhood of $\bar{x}(t)$. The solution's behavior close to $\bar{x}(t)$ is obtained by the associated linear system

$$\dot{\epsilon} = Dg(\bar{x}(t))\epsilon, \tag{2.7}$$

Here if $\bar{x}(t)$ is an equilibrium then $Dg(\bar{x}(t)) = Dg(\bar{x})$ is a Jacobian matrix with constant entries and the solution ((2.7)) through the point $\epsilon_0(t) \in \mathbb{R}^n$ at $t = 0$ gives

$$\epsilon(t) = \exp(Dg(\bar{x}(t)))\epsilon_0, \tag{2.8}$$

Theorem 2.4. [34]. If all the eigenvalues of $Dg(\overline{x})$ have *-ve* real parts then the equilibrium $x = \overline{x}$ of (2.2) is LAS(**locally asymptotically stable**) and if at least one eigenvalue has positive real part then $x = \overline{x}$ is **unstable**.

Example 2.1. *Let we have the following ODE system*

$$\dot{x} = g_1(x, u) = u^3 - 2x, \dot{u} = g_2(x, u) = x^2 - 4u.$$

Suppose $\bar{x} = (0, 0)$ *is the equilibrium point. The Jacobian matrix* J *can be expressed as*

$$J(x, y) = Dg(x) = \begin{pmatrix} \frac{\partial g_1}{\partial x} & \frac{\partial g_1}{\partial u} \\ \frac{\partial g_2}{\partial x} & \frac{\partial g_2}{\partial u} \end{pmatrix} = \begin{pmatrix} -2 & 3u^2 \\ 2x & -4 \end{pmatrix};$$

Evaluating J *at* $\bar{x}$ *gives*

$$J(0, 0) = \begin{pmatrix} -2 & 0 \\ 0 & -4 \end{pmatrix}$$

Here, the eigenvalues of $J(0, 0)$ *are* $\lambda_1 = -2$, $\lambda_2 = -4$. *Since the eigenvalues have negative real parts so the equilibrium* $\bar{x} = (0, 0)$ *is asymptotically stable.*

2.3.2 The Next Generation Operator Method

The above linearization method is applied to analyze the local stability of an equilibrium point. But to establish the local asymptotic stability of (DFE), another linearization technique, which is known as next-generation method, is also used. The method was first proposed by Diekmann and Heffernan et al.[35, 36] and applied for different epidemic models by van den Driessche and Watmough [37].

Assume the epidemic disease model, with positive initial conditions and can be represented as:

$$\dot{x_j} = g(x_j) = F_j(x) - V_j(x), j = 1, \ldots, n, \tag{2.9}$$

where, $V_j = V_j^- - V_j^+$ and the function g satisfy the following properties.

$$X_s = \{x \geq 0 | x_j = 0, j = 1, \ldots, m\}$$

is represented non-infected state variables as well as the disease-free states of the model, where, the number of individuals of the model is denoted by $x = (x_1, \ldots, x_n)^t, x_i \geq 0$.

(1) if $x \geq 0$, then $F_j, V_j^+, V_j^- \geq 0$ for $j = 1, \ldots, m$,

(2) if $x_j = 0$ then $V_j^- = 0$. Particularly, if $x \in X_s$ then $V_j^- = 0$ when $j = 1, \ldots, m$,

(3) if $F_j = 0$ for $j > m$,

(4) if $x \in X_s$ then $F_j(x) = 0$ and $V_j^+(x) = 0$ when $j = 1, \ldots, m$,

(5) If $F(x)$ is set to zero, then all eigenvalues of $Dg(x_0)$ have negative real part.

Here, $F_j(x)$ represents the new infection terms in different compartments j; whereas $V_j^+(x)$ denotes the rate of transfer of individuals into compartment j by all other means, and $V_j^-(x)$ denotes the rate of transfer of individuals out from compartment j. It is assumed that these functions are at least two times continuously differentiable [37].

Definition 2.6. An $n \times n$ matrix such as, V is said to be an M-matrix if and only if every off-diagonal elements of V is negative and the diagonal elements are all positive.

Lemma 2.1. *(van den Driessche and Watmough [37]). If $\bar{x}$ is a DFE of (2.9) and the function g satisfy (1)-(5), then the derivatives $DF(\bar{x})$ and $DF(\bar{x})$ are given as*

$$DF(\bar{x}) = \begin{pmatrix} F & 0 \\ 0 & 0 \end{pmatrix}, DF(\bar{x}) = \begin{pmatrix} V & 0 \\ J_3 & J_4 \end{pmatrix},$$

where F and V are the $m \times m$ matrices such as,

$$F = \left[\frac{\partial F_j(\bar{x})}{\partial x_k} \right], V = \left[\frac{\partial V_j(\bar{x})}{\partial x_k} \right] \quad \text{with } 1 \leq j, k \leq m$$

Further, F is a positive matrix and V is a non-singular M-matrix, $J_3 and J_4$ are matrices associated with the transition terms of the epidemic model and all eigenvalues of J_4 have positive real parts.

Theorem 2.5. (van den Driessche and Watmough [37]). Let (2.9) is the disease transmission model with $g(x)$ satisfying properties (1)-(5). The DFE $(\bar{x})$ is locally asymptotically stable if $\mathcal{R}_0 = \rho(FV^{-1}) < 1$ (where ρ is dominant eigenvalue of matrix), but unstable if $\mathcal{R}_0 > 1$.

2.4 Global Asymptotic Stability (GAS)of Equilibrium Point

If x^* is an equilibrium that attracts all the solutions of a feasible region containing that equilibrium then it is LAS. Otherwise, the equilibrium is globally asymptotically stable (GAS). There are different techniques for analysing the global asymptotic stability of equilibrium. One of the important techniques is constructed by the Lyapunov function and LaSalle's Invariance Principle and this is discussed below.

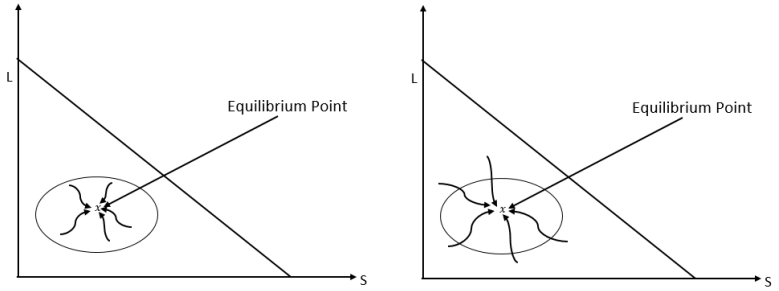

FIGURE 2.1: (2.1A) illustrating LAS and (2.1B) GAS of equilibria (Source: [33]).

2.4.1 The Lyapunov functions and LaSalle's Invariance Principle

The Lyapunov Functions

Lyapunov functions are such functions that decrease along trajectories [38].

Theorem 2.6. [34]. Let us consider

$$\dot{x} = g(x), \ x \in \mathbb{R}^n. \tag{2.10}$$

Suppose that $\overline{x}$ is an equilibrium of the above system (2.10) and let $S : T \to \mathbb{R}$ is a C^1 function defined on some neighborhood T of equilibrium $(\overline{x})$ such that

1) S is positive

2) $\dot{S}(x) \leq 0$ in $T \backslash \{\overline{x}\}$ then the equilibrium $(\overline{x})$ is **stable**.

3) $\dot{S}(x) < 0$ in $T \backslash \{\overline{x}\}$ then the equilibrium $(\overline{x})$ is **asymptotically-stable**.

If S satisfies the above conditions is called a Lyapunov function[34, 35]. If $T = \mathbb{R}^n$, then the equilibrium $(\overline{x})$ is GAS whenever (1) and (3) hold.

Example 2.2. *[33].: Let*

$$\dot{x} = 3y - 2x^3,$$
$$\dot{y} = -3x - 2y^3.$$

Suppose the system has a solution at $(x, y) = (0, 0)$. *Let* $S(x, y) = x^2 + y^2$. *It is clear that* $S(0, 0) = 0$ *and* $S(x, y) > 0$ *in any deleted neighborhood of* $(0, 0)$. *Further,*

$$\begin{aligned}\dot{S}(x) &= 2x\dot{x} + 2y\dot{y} \\ &= 2x(3y - 2x^3) + 2y(-3x - 2y^3) \\ &= -4(x^4 + y^4) < 0.\end{aligned}$$

Hence, $\dot{S} < 0$ *if* $(x, y) \neq (0, 0)$. *Therefore, by the above Theorem 2.6, the equilibrium solution* $(0, 0)$ *is asymptotically-stable.*

Invariance Principle

Since the epidemiology models are constructed on human populations, it is necessary to consider that associated population sizes are always positive.

Definition 2.7. [34]. Suppose $S \subset \mathbb{R}^n$ is a non empty set. Then, S is called invariant under vector field $\dot{x} = g(x)$ if for arbitrary $x_0 \in S$, we get $x(t, 0, x_0) \in S \ \forall \ t \in \mathbb{R}$.
If we restrict for positive times (i.e., $t \geq 0$), then S is a **positively-invariant set**. That means, all solutions in a positively-invariant set remain there for all time. If we go backward in time then the set is known as **negatively-invariant** .

Theorem 2.7. (LaSalle's Invariance Principle [39, 40]). Let $V : \mathbb{R}^n \to \mathbb{R}$ is a continuously differentiable, positive definite, and unbounded function such that

$$\frac{\partial V}{\partial x}(x - \overline{x})f(x) \leq W(x) \leq 0, \ \forall \ x \in \mathbb{R}^n.$$

Then, the equilibrium, $\overline{x}$ is GAS. The solution $x(t)$ converges to the largest invariant set S contained in $B = \{x \in \mathbb{R}^n : W(x) = 0\}$.

2.5 Epidemiological Preliminaries

2.5.1 The Incidence Functions

Disease incidence is defined as the number of new infections in that community is generated per unit of time. In the disease models, the incidence is generally characterized by an incidence function. Different types of incidence functions [41] have been used in epidemic models.

Let $X(t)$, $Y(t)$ and $N(t)$ respectively denote the number of susceptible, infected and the total number of population at time t. Suppose the effective contact rate per person is $\beta(N)$. Then $\beta(N)Y/N$ is the average number of contacts with infected individuals that makes a susceptible individual infected at time t. Thus, the newly infected individuals move from the susceptible individuals (X) at the rate λX, where $\lambda = \beta(N)Y/N$ is called the force of infection. If we consider $\beta(N) = \beta$, then λX is known as a *standard incidence function*.

2.5.2 The Basic Reproduction Threshold

The basic reproductive threshold is used to calculate the potential of the disease to repeat and is represented by $\mathcal{R}_0$. That is expressed because of the expected quantity of secondary cases reproduced by the infection of one infected person in his or her total infectious period. While $\mathcal{R}_0 < 1$, every infected person can produce on average less than one new infected individual throughout his or her total infectious duration. In this case, the disease will no longer persist among the population and may be eliminated. But when $\mathcal{R}_0 > 1$, every infected individual during the total infectious period can be able to produce more than one new infection among the population. In this situation, the disease can persist for a long time among the population.

The dynamical behaviour of the disease models are generally determined by a threshold, $\mathcal{R}_0$ [41]. Generally, when $\mathcal{R}_0 < 1$, then the infected individuals will not create large outbreaks and the disease can eradicate (when the associated *DFE* is *LAS*. Again, if $\mathcal{R}_0 > 1$ then the disease will persist (where *EEP* is stable and exists). At *forward*

bifurcation, $\mathcal{R}_0 = 1$ the *DFE* and an *EEP* exchange their stability. Figure 2.2 illustrate forward bifurcation phenomenon.

For disease transmission models forward bifurcation exhibits, $\mathcal{R}_0 < 1$ is the necessary and

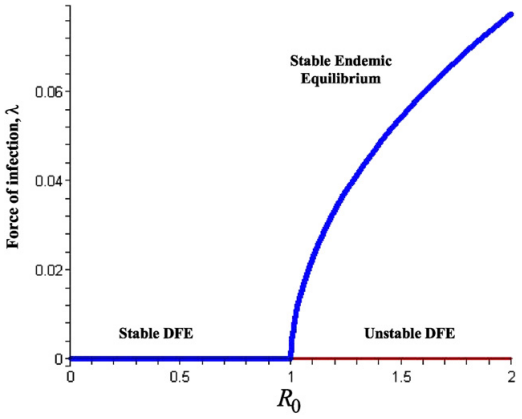

FIGURE 2.2: Forward bifurcation diagram (Source: [42]).

sufficient condition for disease elimination. We can say that the number of infectives depends on $\mathcal{R}_0$.

Some studies have established that $\mathcal{R}_0 < 1$ is only necessary but not sufficient for disease elimination. Again when a stable *EEP* exists with a stable *DFE* for $\mathcal{R}_0 < 1$ then the *backward bifurcation* occurs.

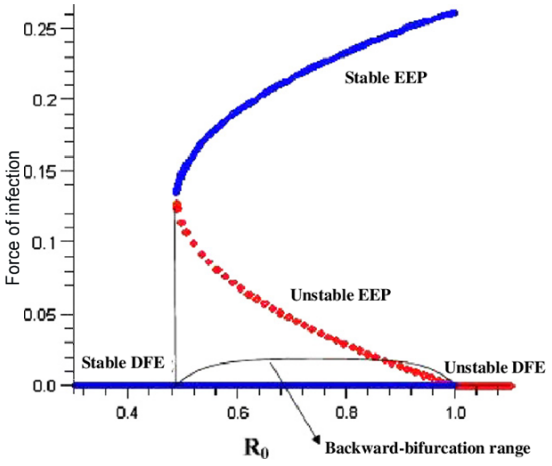

FIGURE 2.3: Backward bifurcation diagram.(Source: [42]).

2.6 Basic Definitions and Theorems related to optimal control

The following definitions and necessary related theorems and results are presented from [24]:

Definition 2.8. [24] A function $m(t)$ is called concave on $[a_1, a_2]$ when

$$\theta m(t_1) + (1-\theta)m(t_2) \leq m(\theta t_1 + (1-\theta)t_2)$$

$\forall\ 0 \leq \theta \leq 1$ and arbitrarily $a_1 \leq t_1, t_2 \leq a_2$.

Definition 2.9. [24] A function $m(t)$ is called convex on $[a_1, a_2]$ when

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$\forall\ 0 \leq \theta \leq 1$ and arbitrarily $a_1 \leq t_1, t_2 \leq a_2$.

2.6.1 Method of Optimality

For an optimal control problem of ODE, generally we use $u(t)$ for the control parameter and the state variable is denoted by $x(t)$. The state variable which is depends on control parameter satisfies the following system of differential equation :

$$x^{'}(t) = f(t, x(t), u(t)).$$

here, $x^{'}$ denotes derivative of the function w.r.t. to time t. Both the control parameter $(u(t))$ and state variable $(x(t))$ contribute to the optimality problem, as the control function changes then the behave of the solution of the differential equation is also changed. The basic optimal control problem consists of the control parameter $(u(t))$ and the corresponding state variable $(x(t))$ that either maximize or minimize the given objective functional. The basic

optimal control problem can be defined as follows:

$$\begin{aligned} \max_{u} \int_0^{t_1} g(t, x(t), u(t))dt \\ \text{subject to theconstraint } x^{'}(t) = f(t, x(t), u(t)) \\ where, x(t_0) = x_0 \text{ and } x(t_1)\ is free. \end{aligned} \tag{2.11}$$

Theorem 2.8. **Pontryagin's Maximum Principle**: *If* $u^*(t)$ *and* $x^*(t)$ *are optimal pair, then there is a piecewise differentiable adjoint variable* $\lambda(t)$ *as* $H(t, x^*, u(t), \lambda(t)) \leq H(t, x^*, u^*(t), \lambda(t))$
for each control u *at time* t*, where the Hamiltonian* H *is given by*

$$H = g(t, x(t), u(t)) + \lambda(t) f(t, x(t), u(t)),$$

and

$$\lambda^{'}(t) = -\frac{\partial H(t, x^*(t), u^*(t), \lambda(t))}{\partial x},$$
$$\lambda(T) = 0.$$

Here, g represents the integrand of the objective function and f represents the right hand side of the dynamical system. The optimal control variable u^* must maximize the Hamiltonian.

2.6.2 Existence Theorem

Several proofs are required for determining control parameters in an optimality problem. At first, we have to prove by using theorem the existence of a control parameter of a given system and the associated objective functional. To prove existence, we use theory from Fleming and Rishel [44].

Theorem 2.9. Let

$$\bar{x}(t) = \begin{bmatrix} x_1(t) \\ \vdots \\ x_n(t) \end{bmatrix}.$$

be a system of n state variables and $u(t)$ is a control variable satisfying the differential equation system $x_i^{'}(t) = f_i(t, x_i(t), u(t))$ *where* $i = 1, \ldots n$, with corresponding objective functional

$$MaximizeG(u) = \int_{t_1}^{t_2} (g(t, \bar{x}(t), u(t))dt$$

There exists an optimal control minimizing $G(u)$ if the conditions are hold:
(i) The system is non-empty.
(ii) The set of controls must be closed and convex.
(iii) The system of state variables must be continuous and bounded above by a linear combination of the control and the state.
(iv) The integrand of the objective functional is convex and is bounded below by $-B_1 + B_1(u)^{\chi}$ with $B_1 > 0$ and $\chi > 1$.

To prove that the system of control parameters with associated state is non-empty, here we used a result in Boyce and DiPrima ([45]., Theorem 7.1.1): and by the following theorem.

Theorem 2.10. Suppose that $G_1, \ldots, G_n$ and their partial derivatives $\frac{\partial G_1}{\partial x_1}, \ldots \frac{\partial G_n}{\partial x_1}, \ldots, \frac{\partial G_n}{\partial x_1}, \ldots, \frac{\partial G_n}{\partial x_n}$ are continuous in a feasible region Φ of t. $x_1 x_2, \ldots, x_n$ is denoted by $\gamma < t < \eta$, $\gamma_1 < x_1 < \eta_1, \ldots, , \gamma_n < x_1 < \eta_n$, and consider $(t_0, \ldots, x_1^0, x_2^0, \ldots, x_n^0)$ be in Φ. Thus there is an interval $[t, t_0] < \delta$ and $\exists$ a unique solution $x_1 = \psi_1(t), \ldots, x_n = \psi_n(t)$ of the differential equations system

$$\begin{aligned} x_1^{'} &= G_1(t, x_1, \ldots, x_n), \\ x_2^{'} &= G_2(t, x_1, \ldots, x_n), \\ &\vdots, \\ x_n^{'} &= G_n(t, x_1, \ldots, x_n), \end{aligned} \tag{2.12}$$

also satisfies the initial conditions

$$x_1(t_0) = x_1^0,\ x_2(t_0) = x_2^0, \ldots, x_n(t_0) = x_n^0. \tag{2.13}$$

All the numerical calculations including detecting the eigenvalues, inverse and Jacobian matrices, are done by using Maple, Mathematica and MATLAB software. These packages are also used for numerical simulations in this thesis.

Chapter 3

The Dynamics of Mathematical Modeling on HBV

3.1 Introduction

Hepatitis B virus (HBV) is a part of the Hepadnaviridae family of viruses. HBV is caused by toxins that are responsible for human liver inflammation [48]. There are different routes for transmitting the hepatitis B virus. This disease especially spreads through physical contact, during transfusion of blood, percutaneous and mucous membrane exposures to infectious blood and some body fluids that contain contaminated blood and from the affected mother to their child to born at the time of pregnancy [46, 47]. Globally, Hepatitis B Infection is one of the most deadly infectious diseases and it is affecting the whole world greatly [13]. It is commonly categorized as acute (when the virus persists for less than 6 months) and chronic (when the virus persists for more than 6 months). Acute hepatitis may cure without causing any major damage to the liver whereas chronic hepatitis can cause cirrhosis [9]. Those who have had the infection for a long time can develop chronic infection and that gradually leads to hepatocellular carcinoma. Chronic infection puts people at high risk of liver cancer at the late stage of liver disease [3]. So, early detection of HBsAg among the healthy population can save many lives from the dangerous complications of cirrhosis and hepatocellular carcinoma by proper treatment. The infection has also been preventable by vaccination since 1982 [8, 11]. For getting the full effect of the

vaccine, two or three doses are required in the life of every person.

In this chapter, we develop a deterministic model to understand the dynamics of HBV infection at population level. The model, which incorporates the vaccination and treatment of individuals, the re-infection of latent, carrier and recovery individuals, is rigorously analysed to gain insight into its dynamical features [12]. We have studied the stability analysis of disease free equilibrium (DFE) and endemic equilibrium (EE). Numerical analysis of the model are carried out and presented in this chapter along with conclusion.

3.2 Formulation of the Model

To assess the transmission disease dynamics and prevalence of HBV we have designed a deterministic model based on the model of [25]. In [25], the author considered five epidemiological classes (Susceptible, Latent, Acute infection, Carrier and Protective immunity) and in our model we have added the recovered and vaccinated classes. Some studies (such as [74] and [50]) considered heterogeneous mixing with age and sexual activity in their HBV transmission model. In [27], the author considered the model [25] to predict chronic hepatitis B infection in New Zealand. In our model, we consider that the latent, carrier and recovered individuals may become re-infected at any time by the contact of HBV infected individuals. Some studies [52–55] have shown that nowadays the hepatitis B acute infection found in newborns from infected mothers.

The total homogeneously-mixing population at time t, is denoted by $N(t)$, is sub-divided into six epidemiological groups; such as the susceptible individuals ($X(t)$), individuals who are protective immunized by vaccination $Y(t)$, infected but not yet infectious (latent) individuals ($L(t)$), acute infected individuals ($I(t)$), chronic HBV carriers ($C(t)$) and recovered individuals ($R(t)$) and so that

$$N(t) = X(t) + Y(t) + L(t) + I(t) + C(t) + R(t).$$

The susceptible population is decreased by the force of infection λ, where,

$$\lambda = \frac{\beta(I + \eta C)}{N}. \tag{3.1}$$

In (3.1), β is the contact rate and η is modification parameter, where, $0 < \eta < 1$ and the infectiousness of chronic carriers is less than acute infections.
The susceptible individuals increased by the unprotective immunized newborn carriers to carrier mothers (at a rate $\mu\omega(1-\nu C)$), unsuccessful vaccination (at a rate $(1-\sigma)$) and decreased by vaccination (at a rate σ) and natural death of individuals, at the rate, μ_1. Thus the rate of change of the susceptible population is given by

$$\frac{dX}{dt} = \mu\omega(1-\nu C) - \lambda X - \sigma X + (1-\sigma)Y - \mu_1 X. \tag{3.2}$$

The protective immunized individual is increased by the recruitment of successfully immunized newborns at rate μ(1-ω)and vaccinated susceptible individuals (at a rate σ) and decreased by unsuccessful vaccination or vaccine waning (at a rate (1-σ)) and natural death (at a rate μ_1). So the rate of change of protective immunized population is given by

$$\frac{dY}{dt} = \mu(1-\omega) + \sigma X - (1-\sigma)Y - \mu_1 Y. \tag{3.3}$$

Here, ν represents the portion of unvaccinated children who are born to carrier mothers. They get infection perinatally during the birth time and enter to the latent class. ξ is the fraction of newly infected individuals with no clinical disease symptoms. These individuals are slow progressors and moved to latent class (L). The other fraction, 1-ξ, of the newly infected individuals with immediate disease symptoms, known as fast progressors and forwarded to the acute class (I). Exposed or latent individuals are decreased by the progression (at a rate ε_1) to acute HBV class by a fraction (at a rate ω_1) who develop symptoms. These individuals are also reduced by the transmission probability, β_1, with transfer rate ε_2 to carrier class, by the reinfection at a rate $\omega_2\psi_e\lambda$, (where, ω_2 is the fraction of re-infected latent individuals who are detected) and by natural death (at a rate μ_1). Thus

$$\frac{dL}{dt} = \mu\omega\nu C + \xi\lambda X - \omega_1\varepsilon_1 L - \beta_1\varepsilon_2 L - \omega_2\psi_e\lambda L - \mu_1 L. \tag{3.4}$$

The population of acute HBV is increased by the symptomatic infection (at the rate $(1-\xi)\lambda$) and symptomatic latent individuals (at the rate $\omega_1\varepsilon_1$). This class is also increased by the re-infection of latent individuals (at the rate $\omega_2\psi_e\lambda$) and chronic carriers (at the rate $\omega_3\psi_c\lambda$, where, ω_3 is the portion of re-infected detected carriers). The acute HBV individuals are

decreased by the transmission probability, β_2, with the transfer rate ε_3 from acute to carrier class and by getting treatment (at the rate t_1) the individuals are transmitted with the probability, β_3, from acute to recover class and by disease-related death rate, μ_2. Thus the governing equation is

$$\frac{dI}{dt} = (1-\xi)\lambda X + \omega_1\varepsilon_1 L + \omega_2\psi_e\lambda L + \omega_3\psi_c\lambda C - \beta_2\varepsilon_3 I - \beta_3 t_1 I - \mu_2 I. \tag{3.5}$$

The population of chronic carriers are increased by the transfer rate, $\beta_1\varepsilon_2$, from latent class and the transfer rate, $\beta_2\varepsilon_3$, from acute class and re-infection of recovered individuals (at the rate $\omega_4\psi_r\lambda$, here, ω_4 is the portion of re-infected detected recovered individuals). These individuals are decreased by re-infection of carriers (at the rate $\omega_3\psi_c\lambda$) and by getting treatment (at the rate t_1), with the transmission probability, β_4, from carriers to recovered individuals. It is further reduced by natural death (at a rate μ_1) and disease related death (at the rate μ_2). Hence

$$\frac{dC}{dt} = \beta_1\varepsilon_2 L + \beta_2\varepsilon_3 I - \omega_3\psi_c\lambda C - \beta_4 t_1 C - \mu_1 C - \mu_2 C + \omega_4\psi_r\lambda R. \tag{3.6}$$

Recovery means recovery from illness but can get infected at any time. These individuals are increased by getting treatment (at the rate t_1) with transmission probabilities, β_3, and β_4, from acute and carriers, respectively. But recovery rate is negligible and after some times these individuals can get re-infection and go back to the carrier class (at the rate $\omega_4\psi_r\lambda$) and decreased by the natural death rate, μ_1. Hence

$$\frac{dR}{dt} = \beta_3 t_1 I + \beta_4 t_1 C - \omega_4\psi_r\lambda R - \mu_1 R. \tag{3.7}$$

Considering all the above mentioned aspects and based on the characteristics of HBV transmission dynamics the diagram and system of non-linear differential equations of the model are given below. The description of variables and parameters are also presented in

Table 3.1 and Table 3.2 respectively.

$$\begin{aligned}
\frac{dX}{dt} &= \mu\omega(1-\nu C) - \lambda X - \sigma X + (1-\sigma)Y - \mu_1 X,\\
\frac{dY}{dt} &= \mu(1-\omega) + \sigma X - (1-\sigma)Y - \mu_1 Y,\\
\frac{dL}{dt} &= \mu\omega\nu C + \xi\lambda X - \omega_1\varepsilon_1 L - \beta_1\varepsilon_2 L - \omega_2\psi_e\lambda L - \mu_1 L,\\
\frac{dI}{dt} &= (1-\xi)\lambda X + \omega_1\varepsilon_1 L + \omega_2\psi_e\lambda L + \omega_3\psi_c\lambda C - \beta_2\varepsilon_3 I - \beta_3 t_1 I - \mu_2 I,\\
\frac{dC}{dt} &= \beta_1\varepsilon_2 L + \beta_2\varepsilon_3 I - \omega_3\psi_c\lambda C - \beta_4 t_1 C - \mu_1 C - \mu_2 C + \omega_4\psi_r\lambda R,\\
\frac{dR}{dt} &= \beta_3 t_1 I + \beta_4 t_1 C - \omega_4\psi_r\lambda R - \mu_1 R.
\end{aligned} \tag{3.8}$$

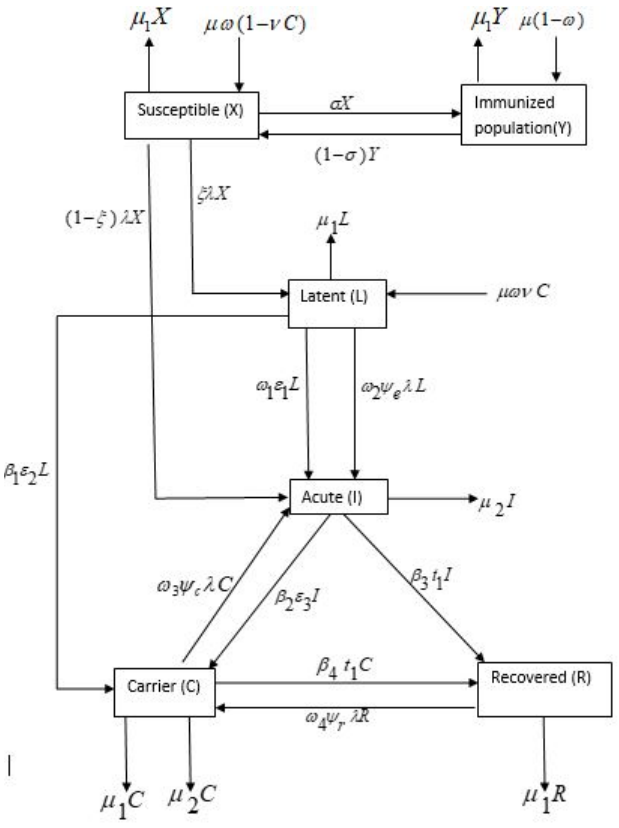

FIGURE 3.1: Model diagram of HBV vaccination model.

The main properties of the model (3.8) are summarized below:

(i) disease can be transmited by the individuals in the latent (L), acute (I) and carrier (C) classes;

(ii) latent individuals show their disease symptoms (at the rate ω_1) and move to the acute class;

(iii) re-infection of latent, carrier and recovered individuals (at the rates $\psi_e\lambda$, $\psi_c\lambda$, $\psi_r\lambda$ respectively);

(iv) disease progression rates of the latent class and acute classes are $\xi\lambda$ and $(1-\xi)\lambda$, respectively;

(v) re-infection individuals who develop symptoms (due to re-infection of disease) into the acute and carrier classes ;

(vi) allows for the treatment (at a rate t_1), temporarily release from the disease into acute and carrier classes and moves to recovered class and can get re-infection at any time.

The model (3.8) extends some of the previous studies in [27, 28, 30, 50, 51] by including treatment to the infected individuals. Furthermore it extends the study [28, 30] using standard incidence function and considering re-infection. Additionally, the model incorporates the slow and fast progression rates of HBV disease in the latent (L) and acutely infected (C) classes. Here we consider the unprotective immunized newborn carrier from chronic carrier to latent class [30].

3.3 Model Analysis

Lemma 3.1. *The closed set* $\mathcal{K} = \left\{(X, Y, L, I, C, R) \in \mathbb{R}^6_+ : N \leq \frac{\mu}{\mu_1}\right\}$ *is positively-invariant with respect to the extended model* (3.8).

Proof. By adding all the equations of the model (3.8), we get the rate of change of the total population is

$$\frac{dN}{dt} = \mu - \mu_1 N - \mu_1 I - \mu_2 C \tag{3.9}$$

If $N > \frac{\mu}{\mu_1}$ then $\frac{dN}{dt} < 0$. Further, since $\frac{dN}{dt} \leq \mu - \mu_1 N$, it is clear that $N(t) \leq \frac{\mu}{\mu_1}$ if $N(0) \leq \frac{\mu}{\mu_1}$. Therefore, for all $t > 0$ all the solutions of the model with initial conditions in $\mathcal{K}$ remains in $\mathcal{K}$. Hence, the w-limit sets of the system (3.8) are contained in $\mathcal{K}$. Thus, $\mathcal{K}$ is

Variables	Description
μ	birth rate
ω	proportion of birth rate without protective immunity
$(1-\omega)$	proportion of birth rate with protective immunity
σ	vaccination rate
$(1-\sigma)$	unsuccessful vaccination rate
μ_1	natural mortality rate
μ_2	mortality rare due to HBV
λ	rate of force of infection
β	effective contact rate for HBV infection
η	rate of infectiousness of carrier relative to acute infections
ε_1	transfer rate from latent to acute
ε_2	transfer rate from latent to carrier
ε_3	transfer rate from acute to carrier
β_1	transmission probability from latent to carrier
β_2	transmission probability from acute to carrier
β_3	transmission probability from acute to recovered acquiring treatment
β_4	transmission probability from carrier to recovered acquiring treatment
t_1	rate of treatment
$(1-\xi)$	fast progression rate to display immediate disease symptoms
$\psi_e\lambda$	reinfection rate, latent individuals have reduced infection rate in comparison to wholly susceptible individuals
ω_1	fraction of latent individuals who develop symptoms are infected
ω_2	a fraction of latent individuals who are re-infected
ω_3	a fraction of carrier individuals who are re-infected
ω_4	a fraction of recovered individuals who are re-infected

TABLE 3.1: Variable's description of the model (3.8)

positively-invariant and attracting. So, the model is epidemiologically and mathematically well-proposed within the region $\mathcal{K}$ [62]. □

Disease Free Equilibrium (DFE):

DFE (ε_0) is given by

$$\varepsilon_0 = (X^*, Y^*, L^*, I^*, C^*, R^*) = \left(\frac{\mu(1-\sigma)+\mu\mu_1\omega}{\mu_1+\mu_1^2}, \frac{\mu\sigma+\mu\mu_1(1-\omega)}{\mu_1+\mu_1^2}, 0, 0, 0, 0\right). \tag{3.10}$$

The stability analysis of the DFE, ε_0, is done by the method of next generation [49]. The matrices F and V are as follows:

Parameters	Values	Reference
μ	0.0247	[61]
ω	[0,1]	[28]
$(1-\omega)$	0.995	[61]
σ	0.98	[61]
$(1-\sigma)$	0.3	[variable]
μ_1	0.008	[61]
μ_2	0.31	[61]
β	0.95-20.49	[28]
η	[0,1]	[variable]
ϵ_1	$\frac{6}{365}$	[28]
ϵ_2	$\frac{8}{365}$	[variable]
ϵ_3	$\frac{4}{365}$	[28]
β_1	0.1	[variable]
β_2	0.1	[variable]
β_3	0.99	[variable]
β_4	0.98	[variable]
t_1	0.025	[28]
ξ	0.67	[variable]
ψ_e, ψ_c, ψ_r	10	[variable]
ω_1	0.045	[variable]
ω_2	0.4	[variable]
ω_3	0.6	[variable]
ω_4	0.6	[variable]
ν	0.11	[28]

TABLE 3.2: Values of the parameters of the model (3.8)

$$F = \begin{bmatrix} 0 & \frac{\xi\beta X^*}{N} & \frac{\xi\beta\eta X^*}{N} \\ 0 & \frac{(1-\xi)\beta X^*}{N} & \frac{(1-\xi)\beta\eta X^*}{N} \\ 0 & 0 & 0 \end{bmatrix},$$

$$V = \begin{bmatrix} k_1 & 0 & -\mu\omega\nu \\ -\omega_1\varepsilon_1 & k_2 & 0 \\ -\beta_1\varepsilon_2 & -\beta_2\varepsilon_3 & k_3 \end{bmatrix},$$

where, $k_1 = \omega_1\varepsilon_1 + \beta_1\varepsilon_2 + \mu_1$, $k_2 = \beta_2\varepsilon_3 + \beta_3 t_1 + \mu_2$ and $k_3 = \beta_4 t_1 + \mu_1 + \mu_2$
and $X^* = \frac{\mu(1-\sigma)+\mu\mu_1\omega}{\mu_1+\mu_1^2}$. The reproduction number, $\mathcal{R}_0$, is defined by $\mathcal{R}_0 = \rho(FV^{-1})$, where

$$\mathcal{R}_0 = \frac{\beta X^*(1-\xi)k_1k_3 + \beta X^*\eta\beta_2(1-\xi)k_1 + \beta X^*\xi\eta k_4 + \beta X^*\xi\omega_1 k_3 + N\mu\omega\nu k_4}{Nk_1k_2k_3 + \beta_1(1-\xi)\beta X^*\mu\omega\nu} \tag{3.11}$$

with,

$$k_1 = \omega_1\varepsilon_1 + \beta_1\varepsilon_2 + \mu_1, k_2 = \beta_2\varepsilon_3 + \beta_3 t_1 + \mu_2, k_3 = \beta_4 t_1 + \mu_1 + \mu_2, k_4 = \beta_1 k_2 + \omega_1\beta_2.$$

Hence, the following result is established from Theorem 2 of [49] .

Lemma 3.2. *If $\mathcal{R}_0 < 1$, then the DFE, ε_0 is locally asymptotically stable (LAS) otherwise unstable (i.e. if $\mathcal{R}_0 > 1$).*

The epidemiological implication of the above statement (Lemma 3.2) is, the spread of HBV infection burden may be managed within the community (while the threshold quantity, $\mathcal{R}_0 < 1$) if the initial sizes of the populations are in the basin of attraction of the DFE ($varepsilon_0$) of the model.
Here we consider the HBV model with re-infection in some stages. Usually, the model with re-infections is often shown the backward bifurcation (where a stable DFE and a stable EEP co-exists) when $\mathcal{R}_0 < 1$. It is also an indication to determine whether or not the model (3.8) exhibits this dynamical feature [12]. The result is explored here.

Theorem 3.1. The model undergoes a backward bifurcation at $\mathcal{R}_0 = 1$ if the inequality (3.15) holds.

Proof. By using the centre manifold theory [56] we can proof the theorem. For convenience let $X = x_1$, $Y = x_2$, $L = x_3$, $I = x_4$, $C = x_5$ and $R = x_6$, so that $N = x_1+x_2+x_3+x_4+x_5+x_6$. Further, by introducing the vector notation $\mathbf{x} = (x_1, x_2, x_3, x_4, x_5, x_6)^T$, the model (3.8) can

be written in the form $\frac{d\mathbf{x}}{dt} = F(\mathbf{x})$, where $F = (f_1, f_2, f_3, f_4, f_5, f_6)^T$, as follows:

$$\begin{aligned}
\frac{dx_1}{dt} &= f_1 = \mu\omega(1-\nu x_5) - \frac{\beta(x_4+\eta x_5)x_1}{x_1+x_2+x_3+x_4+x_5+x_6} - \sigma x_1 + (1-\sigma)x_2 - \mu_1 x_1,\\
\frac{dx_2}{dt} &= f_2 = \mu(1-\omega) + \sigma x_1 - (1-\sigma)x_2 - \mu_1 x_2,\\
\frac{dx_3}{dt} &= f_3 = \mu\omega\nu x_5 + \frac{\xi\beta(x_4+\eta x_5)x_1}{x_1+x_2+x_3+x_4+x_5+x_6} - \omega_1\varepsilon_1 x_3 - \beta_2\varepsilon_2 x_3\\
&\quad - \frac{\omega_2\psi_e\beta(x_4+\eta x_5)x_3}{x_1+x_2+x_3+x_4+x_5+x_6} - \mu_1 x_3\\
\frac{dx_4}{dt} &= f_4 = \frac{(1-\xi)\beta(x_4+\eta x_5)x_1}{x_1+x_2+x_3+x_4+x_5+x_6} + \omega_1\varepsilon_1 x_3 - \beta_2\varepsilon_3 x_4 - \beta_3 t_1 x_4\\
&\quad + \frac{\omega_2\psi_e\beta(x_4+\eta x_5)x_3}{x_1+x_2+x_3+x_4+x_5+x_6} + \frac{\omega_3\psi_c\beta(x_4+\eta x_5)x_5}{x_1+x_2+x_3+x_4+x_5+x_6} - \mu_2 x_4,\\
\frac{dx_5}{dt} &= f_5 = \beta_1\varepsilon_2 x_3 + \beta_2\varepsilon_3 x_4 - \frac{\omega_3\psi_c\beta(x_4+\eta x_5)x_5}{x_1+x_2+x_3+x_4+x_5+x_6} - \beta_4 t_1 x_5 + \frac{\omega_4\psi_r\beta(x_4+\eta x_5)x_6}{x_1+x_2+x_3+x_4+x_5+x_6}\\
&\quad - (\mu_1+\mu_2)x_5,\\
\frac{dx_6}{dt} &= f_6 = \beta_3 t_1 x_4 + \beta_4 t_1 x_5 - \frac{\omega_4\psi_r\beta(x_4+\eta x_5)x_6}{x_1+x_2+x_3+x_4+x_5+x_6} - \mu_1 x_6.
\end{aligned} \tag{3.12}$$

where, $\lambda = \frac{\beta(x_4+\eta x_5)}{N}$. The Jacobian matrix of the system (3.12) evaluated at the DFE (ε_0) is

$$J(\mathcal{E}_0) = \begin{bmatrix}
-(\sigma+\mu_1) & 1-\sigma & 0 & -A & -(\mu\omega\nu+B) & 0\\
\sigma & -(1-\sigma+\mu_1) & 0 & 0 & 0 & 0\\
0 & 0 & -k_1 & \xi A & \mu\omega\nu+\beta B & 0\\
0 & 0 & \omega_1\varepsilon_1 & (1-\xi)A-k_2 & (1-\xi)B & 0\\
0 & 0 & \beta_1\varepsilon_2 & \beta_2\varepsilon_3 & -k_3 & 0\\
0 & 0 & 0 & \beta_3 t_1 & \beta_4 t_1 & -\mu_1
\end{bmatrix},$$

where $A = \frac{\beta x_1^*}{x_1^*+x_2^*}$; $B = \frac{\beta\eta x_1^*}{x_1^*+x_2^*}$; $k_1 = \omega_1\varepsilon_1 + \beta_1\varepsilon_2 + \mu_1$; $k_2 = \beta_2\varepsilon_3 + \beta_3 t_1 + \mu_2$
and $k_3 = \beta_4 t_1 + \mu_1 + \mu_2$.

Now when $\mathcal{R}_0 = 1$, consider a bifurcation parameter (β). Hence solving (3.11) for $\mathcal{R}_0 = 1$, so we have

$$\beta = \beta^* = \frac{N^* k_1 k_2 k_3 + \beta_1 x_4^* \mu\omega\nu(1-\xi)}{x_4^* k_1 k_3(1-\xi) + x_4^*\eta k_1\beta_2(1-\xi) + x_4^*\xi\eta k_4 + x_4^*\xi\omega_1 k_3 + N^*\mu\omega\nu k_4}$$

where k_1 , k_2 , k_3 , k_4 , x_4^* *and* N^* are mentioned earlier in Section 3.3. The linearized system of (3.12) with $\beta = \beta^*$, has a zero eigenvalue. Therefore, the Centre Manifold theory [56] can be used to analyze the dynamics of (3.12) near $\beta = \beta^*$.

Eigenvectors of $J(\mathcal{E}_0)|_{\beta=\beta^*}$

We have to find the eigenvalues for analysing the dynamics of (3.12) at DFE. The jacobian matrix has a right eigenvector of the form: V=$(v_1,\ v_2,\ v_3,\ v_4,\ v_5,\ v_6)^T$, where,

$$\begin{aligned} v_1 &= 0, \\ v_2 &= 0, \\ v_3 &= \frac{\omega_1\varepsilon_1 v_4 + \beta_1\varepsilon_2 v_5}{k_1}, \\ v_4 &= free, \\ v_5 &= free, \\ v_6 &= = 0 \end{aligned}$$

and a left eigenvector of the form: W=$(w_1,\ w_2,\ w_3,\ w_4,\ w_5,\ w_6)^T$,
where,

$$\begin{aligned} w_1 &= \frac{((1-\sigma)+\mu_1)w_2}{\sigma}, \\ w_2 &= free, \\ w_3 &= \frac{\xi A w_4 + (\mu\omega\nu + \xi B)w_5}{k_1}, \\ w_4 &= free, \\ w_5 &= free, \\ w_6 &= \frac{\beta_3 t_1 w_4 + \beta_4 t_1 w_5}{\mu_1} \end{aligned}$$

Computations of a **and** b

Using Theorem in [60], a and b are defined by

$$\begin{aligned} a &= \sum_{k,i,j=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0), \\ b &= \sum_{k,i=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0,0). \end{aligned} \tag{3.13}$$

For the partial derivatives for a is given by:

$$a = \sum_{k,i,j=1}^{6} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j},$$

$$\begin{aligned} &= \frac{-2\beta^*(w_5\eta + w_4)}{(x_1^* + x_2^*)^2}[(1-\xi)(v_4 w_5 x_1^* + v_4 w_2 x_1^* + v_4 w_4 x_1^* + v_4 w_3 x_1^* \\ &+ v_4 w_6 x_1^* + v_4 w_1 x_2^*) + (x_1^* + x_2^*)(v_4 w_5 \omega_3 \psi_c - v_5 w_5 \omega_3 \psi_c + v_4 w_3 \omega_2 \psi_e \\ &+ v_5 w_6 \omega_4 \psi_r - v_3 w_3 \omega_2 \psi_e) - v_3 w_5 \xi x_1^* - v_3 w_2 \xi x_1^* - v_3 w_4 \xi x_1^* - v_3 w_1 \xi x_2^* \\ &+ v_3 w_6 \xi x_1^* + v_3 w_3 \xi x_1^*], \end{aligned} \tag{3.14}$$

from which it can be shown that $a > 0$ if

$$B_1 > B_2 \tag{3.15}$$

where, $B_1 = v_3 \xi x_1^*(w_3 + w_6) + (x_1^* + x_2^*)(v_4 w_5 \omega_3 \psi_c + v_4 w_3 \omega_2 \psi_e + v_5 w_6 \omega_4 \psi_r)$,

$$\begin{aligned} B_2 = v_4 x_1^*[(1-\xi)(w_1 + w_2 + w_3 + w_4 + w_5 + w_6)] + v_3 \xi x_1^*(w_2 + w_4 + w_5) + v_3 w_1 \xi x_2^* \\ + (x_1^* + x_2^*)(v_5 w_5 \omega_3 \psi_c + v_3 w_3 \omega_2 \psi_e). \end{aligned}$$

For the sign of b it can be shown that

$$\begin{aligned} b &= \sum_{k,i=1}^{6} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \beta^*} \\ &= \frac{x_1^*[v_3\xi + (1-\xi)v_4](w_5\eta + w_4)}{x_1^* + x_2^*} > 0 \ . \end{aligned}$$

Therefore, at $\mathcal{R}_0 = 1$ we expect that the transformed system of the model (3.8) undergoes backward bifurcation. This analysis is summarised below. □

Theorem 3.2. The model (3.8) exhibits backward bifurcation at $\mathcal{R}_0 = 1$ whenever $B_1 > B_2$.

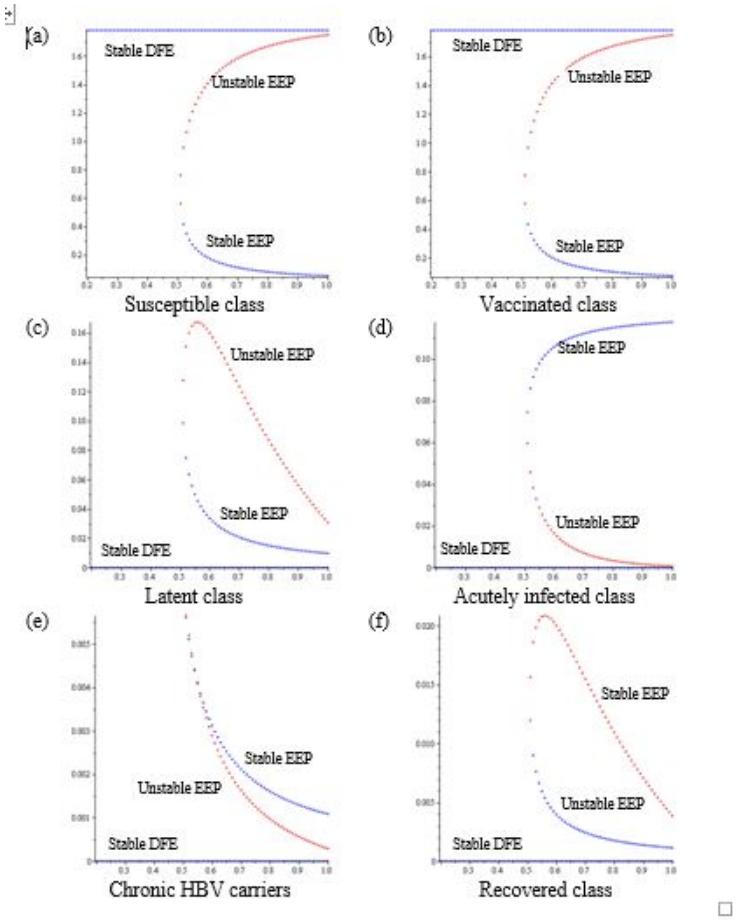

FIGURE 3.2: Backward Bicurcation diagram of HBV vaccination model.

In the absence of re-infection terms (i.e. when $\psi_e = \psi_c = \psi_r = 0$), the backward bifurcation co-efficient, a in the expression (3.14) reduces to

$$a = \frac{-2\beta(w_5\eta + w_4)}{(x_1^* + x_2^*)^2}[(v_4 x_1^*(1-\xi) + v_3\xi x_1^*)(w_2 + w_3 + w_4 + w_5 + w_6)$$
$$+ w_1(v_4 x_2^*(1-\xi) + v_3\xi x_2^*)] < 0,$$

All the parameters and the eigenvectors w and v are positive or zero and $0 < \xi < 1$ so, in the absence of re-infection the model will not have backward bifurcation at $\mathcal{R}_0 = 1$.

Lemma 3.3. *In the absence of re-infection (when $\psi_e = \psi_c = \psi_r = 0$), the model (3.8) does not undergo backward bifurcation at $\mathcal{R}_0 = 1$.*

3.4 Global Stability analysis of DFE

From the above Lemma we can say that the DFE, $\mathcal{E}_0$, of the model (3.8), is globally-asymptotically stable (GAS) if $\mathcal{R}_0 < 1$ and $\psi_e = \psi_c = \psi_r = 0$. This is explored below.

Theorem 3.3. The DFE, $\mathcal{E}_0$, of the model (3.8) with $\psi_e = \psi_c = \psi_r = 0$, is GAS in $\mathcal{K}$ if $\mathcal{R}_0 < 1$.

Proof. Let us consider the following Lyapunov function

$$\mathcal{F} = f_1 L + f_2 I + f_3 C$$

where,

$$\begin{aligned} f_1 &= \omega_3 k_3 + \eta\omega_1\beta_2 + \eta\beta_1 k_2, \\ f_2 &= K_1 k_3 - \beta_1\mu\omega\nu + \eta k_1\beta_2, \\ f_3 &= \mu\omega\nu\omega_1 + \eta k_1 k_2 \end{aligned}$$

Now

$$\begin{aligned} \dot{\mathcal{F}} &= f_1\dot{L} + f_2\dot{I} + f_3\dot{C}, \\ &= f_1[\mu\omega\nu C + \xi\lambda X - \omega_1\varepsilon_1 L - \beta_1\varepsilon_2 L - \mu_1 L] + f_2[(1-\xi)\lambda X + \omega_1\varepsilon_1 L - \beta_2\varepsilon_3 I - \beta_3 t_1 I - \mu_2 I] \\ &+ f_3[\beta_1\varepsilon_2 L + \beta_2\varepsilon_3 I - \beta_4 t_1 C - \mu_1 C - \mu_2 C], \\ &= \frac{I}{N}[Nk_1k_2k_3 + \beta X^*\mu\omega\nu(1-\xi)] \\ &\left(\frac{\beta X^*(1-\xi)k_1k_3 + \beta X^*\eta\beta_2(1-\xi)k_1 + \beta X^*\xi\eta k_4 + \beta X^*\xi\omega_1 k_3 + N\mu\omega\nu k_4}{Nk_1k_2k_3 + \beta_1(1-\xi)\beta X^*\mu\omega\nu} - 1\right) \\ &+ \frac{1}{N}\eta C[Nk_1k_2k_3 + \beta X^*\mu\omega\nu(1-\xi)] \\ &\left(\frac{\beta X^*(1-\xi)k_1k_3 + \beta X^*\eta\beta_2(1-\xi)k_1 + \beta X^*\xi\eta k_4 + \beta X^*\xi\omega_1 k_3 + N\mu\omega\nu k_4}{Nk_1k_2k_3 + \beta_1(1-\xi)\beta X^*\mu\omega\nu} - 1\right), \\ &= [k_1k_2k_3 + \frac{\beta X^*}{N}\beta_1(1-\xi)\mu\omega\nu][R_0 - 1](I + \eta C), \end{aligned}$$

Thus, $\dot{\mathcal{F}} < 0$ if $\mathcal{R}_0 < 1$ with $\dot{\mathcal{F}} = 0$ if and only if $I = C = 0$, where, $\lambda = \frac{\beta[I+\eta C]}{N} = 0$. So from the LaSalle's Invariance Principle[40], it is clear that $I \to 0$, $C \to 0$ as $t \to \infty$. □

3.5 Existence of Endemic Equilibrium Point (EEP) for a special case

For the existence and stability of positive endemic equilibrium point (EEP) of the model (3.8), where, any infectious component may be non-zero and we consider the case of no re-infection (i.e., $\psi_e = \psi_c = \psi_r = 0$).

Let $\mathcal{E}_1 = (X^{**}, Y^{**}, L^{**}, I^{**}, C^{**}, R^{**})$ represents any arbitrary endemic equilibrium of the model (3.8) with $\psi_e = \psi_c = \psi_r = 0$, where,

$$\begin{aligned}
X^{**} &= \frac{x_0}{R_0} \\
Y^{**} &= \frac{1}{(1-\sigma+\mu_1)2}[\mu(1-\omega) + \frac{x_0\sigma}{R_0}] \\
L^{**} &= \frac{\mu(1-\sigma+\omega\mu_1)[R_0-1]}{R_0(1-\sigma+\mu_1)}\left[\frac{\beta_2\mu\omega\nu(1-\xi) + k_2k_3\xi + \mu\omega\nu k_4(1-\xi)}{k_1k_2k_3 + \mu\omega\nu k_1\beta_2(1-\xi)}\right] \\
I^{**} &= \frac{\mu(1-\sigma+\omega\mu_1)[R_0-1]}{R_0(1-\sigma+\mu_1)}\left[\frac{k_1k_3(1-\xi) + \xi\omega_1k_3 + \mu\omega\nu k_4(1-\xi)}{k_1k_2k_3 + \mu\omega\nu k_1\beta_2(1-\xi) + \mu\omega\nu\beta_1(1-\xi)}\right] \\
C^{**} &= \frac{\mu(1-\sigma+\omega\mu_1)[R_0-1]}{R_0(1-\sigma+\mu_1)}\left[\frac{k_1\beta_2(1-\xi) + \xi k_4 + \mu\omega\nu k_4(1-\xi)}{k_1k_2k_3 + \mu\omega\nu k_1\beta_2(1-\xi)}\right] \\
R^{**} &= \frac{\beta_3}{\mu_1}I^{**} + \frac{\beta_4}{\mu_1}C^{**}.
\end{aligned} \tag{3.16}$$

So, we have positive endemic equilibrium points only where $R_0 > 1$. At the endemic steady state, λ^{**} is given by

$$\lambda^{**} = \frac{\beta(I^{**} + \eta C^{**})}{N^*}. \tag{3.17}$$

Lemma 3.4. *The model (3.8) with $\psi_e = \psi_c = \psi_r = 0$ has a unique endemic equilibrium, $\mathcal{E}_1$, whenever $\mathcal{R}_0 > 1$.*

3.6 Local Stability analysis of EEP for a special case

The local stability of the unique EEP, $\mathcal{E}_1$, will now be explored for the special case where the disease-related mortality rate $\mu_2 = 0$ is negligible, no fast progression disease symptoms (i.e.,

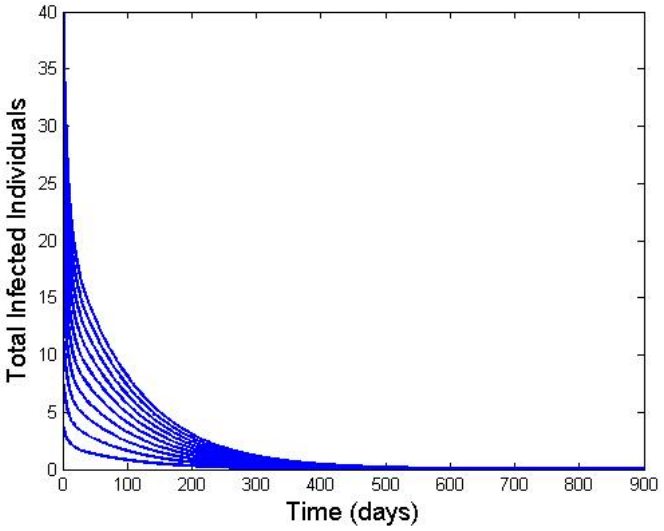

FIGURE 3.3: Illustrates the total number of infected individuals for $\mathcal{R}_0 = 0.8680 < 1$, where, $\beta = 0.95$ and other parameter values are given in Table 3.2.

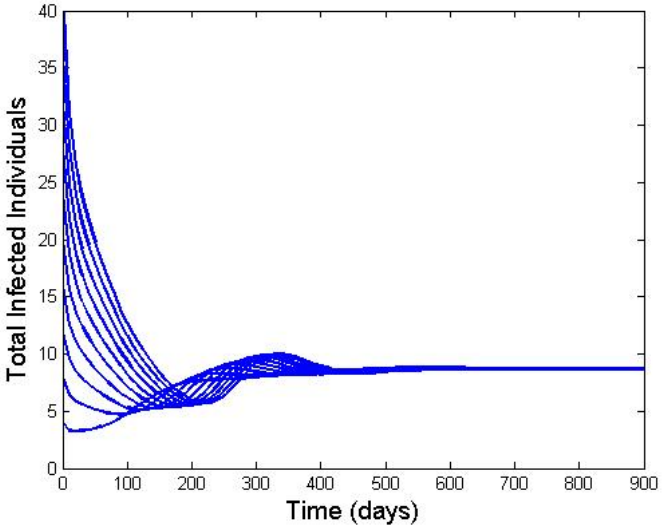

FIGURE 3.4: Illustrates the total number of infected individuals for $\mathcal{R}_0 = 2.3339 > 1$, where, $\beta = 1.59$ and other parameter values are given in Table 3.2.

$\xi = 1$) and re-infection does not occur (so that, $\psi_e = \psi_c = \psi_r = 0$). Using the substitution

$X = N^* - Y - L - I - C - R$ and $\xi = 1$ in the model (3.8), the reduced model is:

$$\begin{aligned}
\frac{dY}{dt} &= \mu(1-\omega) + \sigma[N^* - Y - L - I - C - R] - (1-\sigma)Y - \mu_1 Y,\\
\frac{dL}{dt} &= \mu\omega\nu C + \frac{\beta(I+\eta C)}{N}[N^* - Y - L - I - C - R] - \omega_1\varepsilon_1 L - \beta_2\varepsilon_2 L - \mu_1 L,\\
\frac{dI}{dt} &= \omega_1\varepsilon_1 L - \beta_2\varepsilon_2 I - \beta_3 t_1 I,\\
\frac{dC}{dt} &= \beta_1\varepsilon_2 L + \beta_2\varepsilon_3 I - \beta_4 t_1 C - \mu_1 C,\\
\frac{dR}{dt} &= \beta_3 t_1 I + \beta_4 t_1 C - \mu_1 R,
\end{aligned} \tag{3.18}$$

We have easily shown that the system has a positive unique EEP, $\mathcal{E}_2 = \mathcal{E}_1|_{\mu_2=\psi_e=\psi_c=\psi_r=0,\xi=1}$, whenever $\mathcal{R}_{01} > 1$. We claim the following:

Theorem 3.4. If $\mathcal{R}_{01} > 1$ then the reduced model has a LAS positive unique endemic equilibrium point, $\mathcal{E}_2$.

Proof. To proof of the above theorem here we consider the technique in [62] (see also [12, 58, 63]), which is known as Krasnoselskii sub-linearity trick. This approach showing that the linearization of the system (3.18), around the equilibrium $\mathcal{E}_2$, has solutions of the form

$$\bar{\mathbf{Z}}(t) = \bar{\mathbf{Z}}_0 e^{\theta t}, \tag{3.19}$$

Around the equilibrium, $\mathcal{E}_2$, substitute (3.19) in the system of linearization of (3.18) we have

$$\begin{aligned}
\theta Z_1 &= (-b-\sigma)Z_1 - \sigma(Z_2 + Z_3 + Z_4 + Z_5),\\
\theta Z_2 &= -a_1 Z_1 + (-a_1 - k_1)Z_2 + (a_2 - a_1)Z_3 + (\mu\omega\nu + \eta a_2 - a_1)Z_4 - a_1 Z_5,\\
\theta Z_3 &= \omega_1 Z_2 - k_2 Z_3,\\
\theta Z_4 &= \beta_1 Z_2 + \beta_2 Z_3 - k_3 Z_4,\\
\theta Z_5 &= \beta_3 Z_3 + \beta_4 Z_4 - \mu_1 Z_5.
\end{aligned} \tag{3.20}$$

where, $b = 1 - \sigma + \mu_1$, $\omega_1\varepsilon_1 = \omega_1$, $\beta_1\varepsilon_2 = \beta_1$, $\beta_2\varepsilon_3 = \beta_2$, $\beta_3 t_1 = \beta_3$, $\beta_4 t_1 = \beta_4$, $k_1 = \omega_1 + \beta_1 + \mu_1$, $k_2 = \beta_2 + \beta_3$, $k_3 = \beta_4 + \mu_1$, $a_1 = \frac{\beta(I+\eta C)}{N}$, $a_2 = \frac{\beta X}{N}$

At first, consider all the negative terms in the last three equations of the system (3.20) and shift them to the left hand sides of the equations. Solving these equations of (3.20) and

substituting the result into the remaining equations and simplifying,

$$\begin{aligned} Z_1[1+F_1(\theta)] + Z_2[1+F_2(\theta)] &= \frac{a_2}{k_1}Z_3 + \frac{\mu\omega\nu+\eta a_2}{k_1}Z_4, \\ Z_3[1+F_3(\theta)] &= \frac{\omega_1}{k_2}Z_2, \\ Z_4[1+F_4(\theta)] &= \frac{\beta_1}{k_3}Z_2 + \frac{\beta_2}{k_3}Z_3, \\ Z_5[1+F_5(\theta)] &= \frac{\beta_3}{\mu_1}Z_3 + \frac{\beta_4}{\mu_1}Z_4, \end{aligned} \tag{3.21}$$

where,

$$\begin{aligned} F_1(\theta) &= \frac{\theta+\sigma}{b} + \frac{a_1}{k_1}, \\ F_2(\theta) &= \frac{\theta}{b} + \frac{\theta+a_1}{k_1} + [\frac{\sigma}{b} + \frac{a_1}{k_1}][\frac{\omega_1}{\theta+k_2} + \frac{\beta_1(\theta+k_2)+\omega_1\beta_2}{(\theta+k_3)(\theta+k_2)}] + \frac{\beta_1\omega_1(\theta+k_3)+\beta_1\beta_4(\theta+k_2)+\omega_1\beta_2\beta_4}{(\theta+k_3)(\theta+k_2)(\theta+\mu_1)}, \\ F_3(\theta) &= \frac{\theta}{k_2}, \\ F_4(\theta) &= \frac{\theta}{k_3}, \\ F_5(\theta) &= \frac{\theta}{\mu_1}, \end{aligned} \tag{3.22}$$

with,

$$M = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{a_2}{k_1} & \frac{\mu\omega\nu+\eta a_2}{k_1} & 0 \\ 0 & \frac{\omega_1}{k_2} & 0 & 0 & 0 \\ 0 & \frac{\beta_1}{k_3} & \frac{\beta_2}{k_3} & 0 & 0 \\ 0 & 0 & \frac{\beta_3}{\mu_1} & \frac{\beta_4}{\mu_1} & 0 \end{pmatrix},$$

Here, the notation $M(\bar{Z})_i$ for $i = 1, 2, 3, 4, 5$ represents the ith coordinate of the vector $M(\bar{Z})$. The matrix M has positive or zero elements and $\mathcal{E}_2$ satisfies $\mathcal{E}_2 = M\mathcal{E}_2$. Furthermore, if the

system (3.21) has a solution $\bar{Z}$, then there exists a minimal positive real number s such that

$$|| \bar{\mathbf{Z}} ||\leq s\mathcal{E}_2, \tag{3.23}$$

where, $|| \bar{\mathbf{Z}} ||= (|| Z_1 ||, || Z_2 ||, || Z_3 ||, || Z_4 ||, || Z_5 ||)$ with the lexicographic order, and $|| \cdot ||$ is a norm in $\mathbb{C}$.

We need to prove $Re(\theta) < 1$. Suppose that $Re(\theta) \geq 0$. Now we have two cases: $\theta = 0$ and $\theta \neq 0$. At first assume the case (i.e., $\theta = 0$). Then, (3.20) is a homogeneous linear system of Z_i $(i = 1, 2, 3, 4, 5)$. The determinant of the system (3.20) evaluated at $\mathcal{E}_2$,

$$\triangle= -A_1 + \mu_1(b + \sigma)(k_1k_2k_3 - \mu\omega\nu k_4)\left[R_{01}\frac{X^*}{N^*} - 1\right], \tag{3.24}$$

where, $A_1 = b\mu_1a_1k_4 + ba_1\omega_1\beta_3k_3 + ba_1\mu_1k_2k_3 + ba_1\mu_1\omega_1k_3 + ba_1\beta_4k_4$ and $k_1k_2k_3 - \mu\omega\nu k_4 > 0$ (we proved in section 3.3).

It can be shown that $\frac{X^*}{N^*} = \frac{1}{R_{01}}$ and then $\triangle< 0$. Consequently, the system (3.20) can only have the trivial solution $\bar{Z} = \bar{0}$ (which corresponds to the DFE, $\mathcal{E}_0$). Now considering the case $\theta \neq 0$. In this case, $Re(F_i(\theta)) \geq 0$ $(i = 1, 2, 3, 4, 5)$ since, by assumption, $Re(\theta) \geq 0$. It is easy to see that this implies $\mid 1 + F_i(\theta) \mid> 1$ for all i. Define $F(\theta) = min \mid 1 + F_i(\theta) \mid> 1$; (for $i = 1, 2, 3, 4, 5$). Then, $F(\theta) > 1$. Hence, $\frac{s}{F(\theta)} < s$. The minimality of s implies that $|| \bar{Z} ||> \frac{s}{F(\theta)}\mathcal{E}_2$. On the other hand, taking norms of both sides of the third equation of (3.21), and using the fact that the matrix M is non-negative, gives

$$F(\theta) || Z_3 ||\leq M(|| Z ||)_3 \leq s(M || \varepsilon_2 ||)_3 \leq sI^{**}. \tag{3.25}$$

Then we have $|| Z_3 ||\leq \frac{s}{F(\theta)}I^{**}$, which contradicts our assumption that $Re(F_i(\theta)) \geq 0$, therefore only $Re(\theta) < 0$. Hence the endemic equilibrium, $\mathcal{E}_2$, is locally asymptotically stable (i.e. LAS) for $\mathcal{R}_{01} > 1$. □

3.7 Global Stability analysis of EEP for a special case

The global asymptotic stability of EEP, $\mathcal{E}_2$, of the reduced model (3.18) is considered for a special case when after taking vaccine some people get complete immunity. At this situation, putting $\sigma = 1$ into the reduced model (3.18), and using the substitution $\beta_0 = \frac{\beta}{N^*}$, it can be shown that the reproduction threshold of the reduced model (3.18) with $\xi = 1$ and $\sigma = 1$, denoted by $\mathcal{R}_{02}$, is given by

$$\mathcal{R}_{02} = \frac{\eta\beta_0 X^* k_4 + \mu\omega\nu k_4 + \beta_0 X^* \omega_1 k_3}{k_1 k_2 k_3}, \tag{3.26}$$

where X^*, k_1, k_2, k_3 are defined in Section 3.3. Furthermore, using the same technique given in Section 3.4, it can be shown that the reduced system (3.18), where, $\sigma = 1$, has a unique EEP, of the form

$$\mathcal{E}_3 = \mathcal{E}_2|_{(1-\sigma)=0} = (X^{**}, Y^{**}, L^{**}, I^{**}, C^{**}, R^{**}),$$

where, $X^{**} > 0, Y^{**} > 0, L^{**} > 0, I^{**} > 0, C^{**} > 0, R^{**} > 0$ whenever $\mathcal{R}_{02} > 1$.

Theorem 3.5. The unique EEP, $\mathcal{E}_3$, of the reduced model (3.18) when $\sigma = 1$, is globally asymptotic stable (GAS) in $\mathcal{K} \setminus \mathcal{K}_0$ if $\mathcal{R}_{02} > 1$.

Proof. Let $\sigma = 1$ and $\mathcal{R}_{02} > 1$. Let the non-linear Lyapunov function is:

$$\begin{aligned}\mathcal{L} = &\left(X - X^{**} - X^{**} ln\frac{X}{X^{**}}\right) + \left(L - L^{**} - L^{**} ln\frac{L}{L^{**}}\right) \\ &+ \frac{\beta_0 X^{**}[(\mu_1 + \beta_4) + \eta\beta_2]}{(\mu_1 + \beta_4)(\beta_2 + \beta_3)}\left(I - I^{**} - I^{**} ln\frac{I}{I^{**}}\right) \\ &+ \frac{\beta_0 \eta X^{**}}{\mu_1 + \beta_4}\left(C - C^{**} - C^{**} ln\frac{C}{C^{**}}\right),\end{aligned} \tag{3.27}$$

Now Lyapunov derivative is:

$$\dot{\mathcal{L}} = \left(1 - \frac{X^{**}}{X}\right)\dot{X} + \left(1 - \frac{L^{**}}{L}\right)\dot{L} + \frac{\beta_0 X^{**}[(\mu_1+\beta_4)+\eta\beta_2]}{(\mu_1+\beta_4)(\beta_2+\beta_3)}\left(1 - \frac{I^{**}}{I}\right)\dot{I} + \frac{\beta_0\eta X^{**}}{\mu_1+\beta_4}\left(1 - \frac{C^{**}}{C}\right)\dot{C},$$

$$\begin{aligned}
&= \left(1 - \frac{X^{**}}{X}\right)[\mu\omega\nu C^{**} + \beta_0 I^{**}X^{**} + \beta_0\eta C^{**}X^{**} + \sigma X^{**} + \mu_1 X^{**} - \mu\omega\nu C - \beta_0 IX \\
&- \beta_0\eta CX - \sigma X + \mu_1 X] + \left(1 - \frac{L^{**}}{L}\right)[\mu\omega\nu C + \beta_0 IX + \beta_0\eta CX - \omega_1 L - \beta_1 L - \mu_1 L] \\
&+ \frac{\beta_0 X^{**}[(\mu_1+\beta_4)+\eta\beta_2]}{(\mu_1+\beta_4)(\beta_2+\beta_3)}\left(1 - \frac{I^{**}}{I}\right)[\omega_1 L - \beta_2 I - \beta_3 I] + \frac{\beta_0\eta X^{**}}{\mu_1+\beta_4}\left(1 - \frac{C^{**}}{C}\right)[\beta_1 L + \beta_2 I - \beta_4 C - \mu_1 C],
\end{aligned}$$

$$\begin{aligned}
&= \mu\omega\nu C^{**} + \beta_0 I^{**}X^{**} + \beta_0\eta C^{**}X^{**} + \sigma X^{**} + \mu_1 X^{**} - \sigma X - \mu_1 X - \mu\omega\nu C^{**}\frac{X^{**}}{X} - \beta_0 I^{**}X^{**}\frac{X^{**}}{X} \\
&- \beta_0\eta C^{**}X^{**}\frac{X^{**}}{X} - \sigma X^{**}\frac{X^{**}}{X} - \mu_1 X^{**}\frac{X^{**}}{X} + \mu\omega\nu C\frac{X^{**}}{X} + \beta_0 IX^{**} + \beta_0\eta CX^{**} + \sigma X^{**} + \mu_1 X^{**} \\
&- (\omega_1+\beta_1+\mu_1)L - \mu\omega\nu C\frac{L^{**}}{L} - \beta_0 IX\frac{L^{**}}{L} - \beta_0\eta CX\frac{L^{**}}{L} + (\omega_1+\beta_1+\mu_1)L^{**} \\
&+ \frac{\beta_0\omega_1}{\beta_2+\beta_3}[LX^{**} - LX^{**}\frac{I^{**}}{I}] - \beta_0 IX^{**} + \beta_0 I^{**}X^{**} + \frac{\eta\omega_1\beta_0\beta_2}{(\mu_1+\beta_4)(\beta_2+\beta_3)}[LX^{**} - LX^{**}\frac{I^{**}}{I}] \\
&+ \frac{\eta\beta_0\beta_2}{\mu_1+\beta_4}[I^{**}X^{**} - X^{**}I] + \frac{\beta_0\beta_1\eta}{\mu_1+\beta_4}[LX^{**} - LX^{**}\frac{C^{**}}{C}] + \frac{\beta_0\beta_2\eta}{\mu_1+\beta_4}[IX^{**} - IX^{**}\frac{C^{**}}{C}] \\
&- \beta_0\eta CX^{**} + \beta_0\eta C^{**}X^{**},
\end{aligned}$$

$$\begin{aligned}
&= \mu\omega\nu C^{**} + \beta_0 I^{**}X^{**} + \beta_0\eta C^{**}X^{**} + \sigma X^{**} + \mu_1 X^{**} - \sigma X - \mu_1 X - \mu\omega\nu C^{**}\frac{X^{**}}{X} - \beta_0 I^{**}X^{**}\frac{X^{**}}{X} \\
&- \beta_0\eta C^{**}X^{**}\frac{X^{**}}{X} - \sigma X^{**}\frac{X^{**}}{X} - \mu_1 X^{**}\frac{X^{**}}{X} - \beta_0 I^{**}X^{**}\frac{X^{**}}{X}\frac{C}{C^{**}} - \beta_0\eta CX^{**}\frac{X^{**}}{X} + \mu\omega\nu C^{**}\frac{C}{C^{**}}\frac{X^{**}}{X} \\
&+ \beta_0 I^{**}X^{**}\frac{C}{C^{**}}\frac{X^{**}}{X} + \beta_0\eta C^{**}X^{**}\frac{C}{C^{**}}\frac{X^{**}}{X} + \sigma X^{**} + \mu_1 X^{**} - \mu\omega\nu C^{**}\frac{L}{L^{**}} - \beta_0 I^{**}X^{**}\frac{L}{L^{**}} \\
&- \beta_0\eta C^{**}X^{**}\frac{L}{L^{**}} - \mu\omega\nu C\frac{L^{**}}{L} - \beta_0 IX\frac{L^{**}}{L} - \beta_0\eta CX\frac{L^{**}}{L} + \mu\omega\nu C^{**} + \beta_0 I^{**}X^{**} + \beta_0\eta C^{**}X^{**} \\
&+ \frac{\beta_0 I^{**}}{L^{**}}[LX^{**} - LX^{**}\frac{I^{**}}{I}] + \beta_0 I^{**}X^{**} + \frac{\beta_0\eta C^{**}}{L^{**}}[LX^{**} - LX^{**}\frac{I^{**}}{I}] + \frac{\beta_0\eta C^{**}}{I^{**}}[I^{**}X^{**} - X^{**}I] \\
&+ \frac{\beta_0\eta C^{**}}{L^{**}}[LX^{**} - LX^{**}\frac{C^{**}}{C}] + \frac{\beta_0\eta C^{**}}{I^{**}}[IX^{**} - IX^{**}\frac{C^{**}}{C}] + \beta_0\eta C^{**}X^{**},
\end{aligned}$$

$$= \sigma X^{**}[2 - \frac{X}{X^{**}} - \frac{X^{**}}{X}] + \mu_1 X^{**}[2 - \frac{X}{X^{**}} - \frac{X^{**}}{X}] + \beta_0 I^{**} X^{**}[3 - \frac{X^{**}}{X} - \frac{L}{L^{**}}\frac{I^{**}}{I} - \frac{X}{X^{**}}\frac{L^{**}}{L}\frac{I}{I^{**}}]$$
$$+ \beta_0 \eta C^{**} X^{**}[4 - \frac{X^{**}}{X} - \frac{L}{L^{**}}\frac{C^{**}}{C} - \frac{I}{I^{**}}\frac{C^{**}}{C} - \frac{X}{X^{**}}\frac{L^{**}}{L}\frac{C}{C^{**}} + \frac{L}{L^{**}} - \frac{L}{L^{**}}\frac{I^{**}}{I}]$$
$$+ \mu\omega\nu C^{**}[2 - \frac{X^{**}}{X} + \frac{C}{C^{**}}\frac{X^{**}}{X} - \frac{L}{L^{**}} - \frac{L^{**}}{L}],$$

$$= \sigma X^{**}[2 - \frac{X}{X^{**}} - \frac{X^{**}}{X}] + \mu_1 X^{**}[2 - \frac{X}{X^{**}} - \frac{X^{**}}{X}] + \mu\omega\nu C^{**}[2 - \frac{L}{L^{**}} - \frac{L^{**}}{L}]$$
$$+ \beta_0 I^{**} X^{**}[3 - \frac{X^{**}}{X} - \frac{L}{L^{**}}\frac{I^{**}}{I} - \frac{X}{X^{**}}\frac{L^{**}}{L}\frac{I}{I^{**}}] + \beta_0 \eta C^{**} X^{**}[4 - \frac{X^{**}}{X} - \frac{L}{L^{**}}\frac{I^{**}}{I} - \frac{I}{I^{**}}\frac{C^{**}}{C} - \frac{X}{X^{**}}\frac{L^{**}}{L}\frac{C}{C^{**}}],$$

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

$$\begin{aligned}
2 \quad & -\frac{X}{X^{**}} - \frac{X^{**}}{X} \leq 0, \\
2 \quad & -\frac{L}{L^{**}} - \frac{L^{**}}{L} \leq 0, \\
3 \quad & -\frac{X^{**}}{X} - \frac{L}{L^{**}}\frac{I^{**}}{I} - \frac{X}{X^{**}}\frac{L^{**}}{L}\frac{I}{I^{**}} \leq 0, \\
4 \quad & -\frac{X^{**}}{X} - \frac{L}{L^{**}}\frac{I^{**}}{I} - \frac{I}{I^{**}}\frac{C^{**}}{C} - \frac{X}{X^{**}}\frac{L^{**}}{L}\frac{C}{C^{**}} \leq 0,
\end{aligned}$$

Again, from the above expression we have,

$$\begin{aligned}
&\beta_0 \eta C^{**} X^{**}\left[\frac{L}{L^{**}} - \frac{L}{L^{**}}\frac{C^{**}}{C}\right] + \mu\omega\nu C^{**}\left[-\frac{X^{**}}{X} + \frac{C}{C^{**}}\frac{X^{**}}{X}\right] \\
&= \beta_0 \eta C^{**} X^{**}\frac{L}{L^{**}}\left(1 - \frac{C^{**}}{C}\right) - \mu\omega\nu C^{**}\frac{X^{**}}{X}\left(1 - \frac{C}{C^{**}}\right)
\end{aligned}$$

Here, if we consider $\frac{C}{C^{**}} \leq 1$, then the sign of $\mu\omega\nu C^{**}\frac{X^{**}}{X}\left(1 - \frac{C}{C^{**}}\right)$ is positive and the sign of $\beta_0 \eta C^{**} X^{**}\frac{L}{L^{**}}\left(1 - \frac{C^{**}}{C}\right)$ is negative. So that $\dot{\mathcal{L}} < 0$ for $\mathcal{R}_{02} > 1$. Thus, using $\mathcal{L}$ (Lyapunov function) and the LaSalle's Invariance Technique [40], every solutions of the reduced model (3.18) tends to $\mathcal{E}_3$ as $t \to \infty$ when $\mathcal{R}_{02} > 1$. □

3.8 Numerical Illustrations and Discussions

In this section, we have presented some graphical representations using parameter values from Table 3.2. In Figure 3.5, prevalence slowly decreases with vaccination, when $\mathcal{R}_0 = 0.8595$

and also decreases without vaccination, when $\mathcal{R}_0 = 0.8611$. In Figure 3.6, prevalence is very high when $\mathcal{R}_0 = 1.1204$ in the absence of vaccination and prevalence is gradually increasing when $\mathcal{R}_0 = 1.1101$ in the presence of vaccination. In Figure 3.7, total infection decreases when $\mathcal{R}_0 = 0.8611$ in the absence of vaccination and also decreases and reduces to zero when $\mathcal{R}_0 = 0.8595$ in the presence of vaccination. In Figure 3.8, total infection is increased without vaccination when $\mathcal{R}_0 = 1.1204$ and with vaccination, at the beginning disease increasing and smoothly increases when $\mathcal{R}_0 = 1.1101$. So that, it is clear that the vaccine has a positive impact for the reduction of infection in comparison to the case when the vaccination is not used.

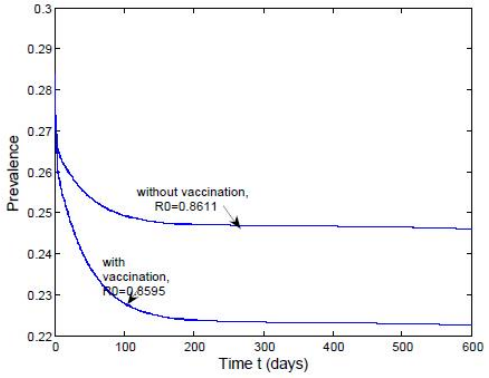

FIGURE 3.5: The figure illustrates the prevelence in the presence and absence of vaccination for $\mathcal{R}_0 < 1$.

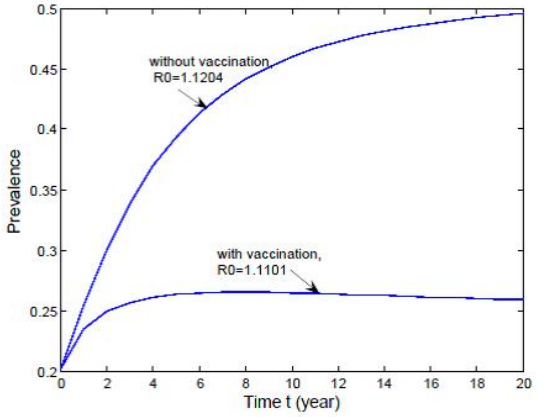

FIGURE 3.6: Simulation of the model (3.8) shows the prevalence considering the presence and absence of a vaccine for $\mathcal{R}_0 > 1$.

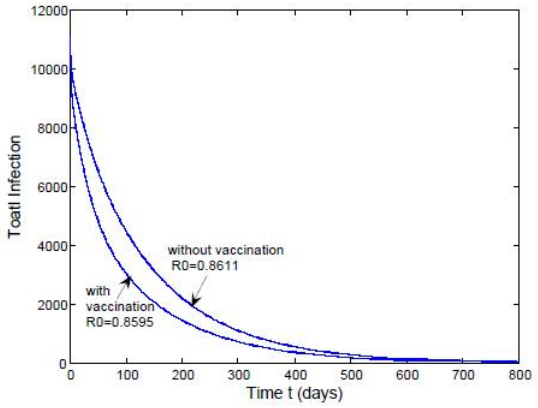

FIGURE 3.7: The total number of infected individuals considering the presence and absence of a vaccine for $\mathcal{R}_0 < 1$.

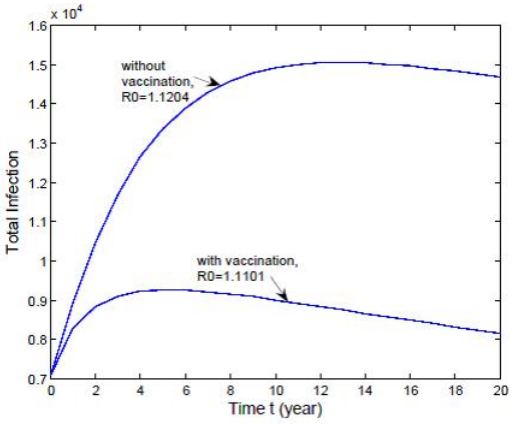

FIGURE 3.8: Total number of infected individuals considering the presence and absence of a vaccine for $\mathcal{R}_0 > 1$.

3.9 Summary of Analysis

In this chapter, a new deterministic HBV model among population is formulated. Qualitative as well as quantitative analysis have done rigorously. We can summarize some of the results of the study as follows:

(i) The model has a locally-asymptotically stable disease free equilibrium (Lemma 3.2) when the associated basic reproduction number $\mathcal{R}_0 < 1$. By Lyapunov function and LaSalle Invariance Principle, the *DFE* is GAS whenever $\mathcal{R}_0 < 1$.

(ii) The model has a locally stable unique endemic equilibrium point whenever $\mathcal{R}_0 > 1$. And *EEP* is GAS where the vaccine is fully effective (Theorem 3.5).

(iii) The model exhibits backward bifurcation when $\mathcal{R}_0 < 1$.

(iv) When there is no re-infection, the model does not undergo backward bifurcation.

Chapter 4

HBV Dynamics *in vivo*

4.1 Introduction

Here, we have presented a mathematical model of immune responses to HBV infection. This study focuses on how to control the infection by using immune responses, such as innate and adaptive immunity. There may be little evidence that humoral immunity performs a major role in viral clearance from infected hosts. But cell-mediated immune responses, especially cytotoxic T-lymphocytes (CTLs) are very vital for viral clearance [64, 65]. At the time of HBV infection, hepatocellular damage and viral clearance both occure by the host immune responses. But in this process, the innate immune response does not play a significant role. The adaptive immune response such as, cytotoxic T lymphocytes (CTLs), contributes the liver injuries related to HBV infection. In an unvaccinated person, the hepatitis B virus causes the chronic diseases. Nowadays *alum adsorbed hepatitis B vaccine* is used for prophylactic immunization and that effectively increases humoral immune response. It is evident that cell-mediated immune response is also a major component to control the disease burden *in vivo* [66]. HBV infection is still the leading killer among diseases. Our mathematical model describes the production of antibodies depends on the life span of short-lived and chronically infected cells. We expect that sufficient levels of antibodies, either pre-present in vaccinated people, can control the infection as well as the viral clearance. But, while the antibody levels are not sufficient, cell-mediated immune responses are needed to control the virus. Also antibodies work in late stages to reduce viral clearance [67]. Immune

responses such as cell-mediated and humoral both are very important for HBV infection clearance. Even though it is evident that the immune responsibilities for clearing viruses are not fully understood.

The goal of this chapter is to understand better the dynamics of HBV in the infected host and what is the role of the immune system on HBV disease dynamics *in vivo*. Some mathematical models [68, 69] have been constructed and used to study the transmission disease dynamics of HBV *in vivo* in the population level . Here, we explore the dynamics of hepatitis B *in vivo* through mathematical formulation. This chapter is organised by giving model formulation, basic properties, local stability analysis of virus-free equilibrium point (VFE) and virus present equilibrium point (VPE). Numerical simulations are presented at the end of the chapter.

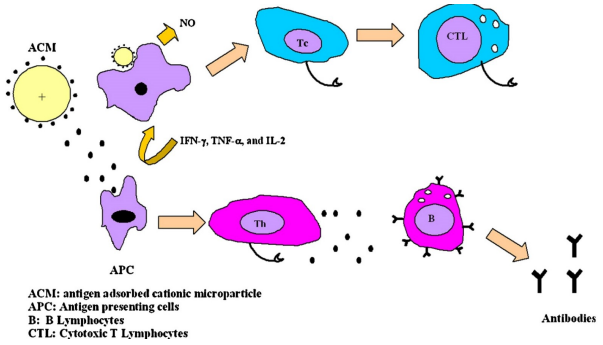

FIGURE 4.1: Graphical representation of HBV in host (Source:[66]).

4.2 Formulation of Model

The formulation of the model is based on the characteristics of transmission dynamics of HBV *in vivo*. In this model, the total host population at time t, is represented by $N(t)$. The host population, $N(t)$ is sub-individual into six epidemiological groups: the uninfected target host cells $H(t)$, the short-lived infected cells $I(t)$, the chronically infected cells $C(t)$, the concentration of free virus particles $V(t)$, the density of HBV specific antibodies $A(t)$, which is humoral immune response and the density of CTLs cells $Z(t)$, produced by the cell-mediated immune response, so

$$N(t) = H(t) + I(t) + C(t) + V(t) + A(t) + Z(t).$$

The uninfected host cell is reduced by infection, which can be acquired by effective contact with free virus particles, at a rate λ, where,

$$\lambda = \frac{\beta V}{1 + \alpha V} \tag{4.1}$$

where, β is the rate of infection and $\alpha > 0$ is saturation incidence rate.
The uninfected target cell (H) is increased by a constant recruitment rate (Π) of uninfected healthy cells. It is decreased by the rate $\lambda(1-\sigma)$ and σ $(0 \leq \sigma \leq 1)$ is the vaccination efficacy. Short-lived infected hepatocytes (I) can be cured at a rate ρ and move to the target host cell (H). This class is also reduced by the natural death of cells at a rate μ. So

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

The short-lived infected cells (I) is generated by the infection rate of uninfected healthy host cells at $\beta(1-\sigma)(1-\xi)$, where, $0 < \xi < 1$ is the fraction of infection depends on the short-lived and chronically infected cells. This class is decreased by the death rate (δ), cured rate (ρ), the cell-mediated immune response for short-lived infected cells at a rate p and by the progression rate (η). So the governing equation is

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

The chronically infected cells (C) is produced by the infection of healthy cells at a rate $\beta(1-\sigma)\xi$ and the progression rate of short-lived infected cells at η. They are further decreased by the death rate (a) and the cellular immune response for chronically infected cells at the rate p. Therefore

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

The free virus particles (V) is generated by the number of virus production during the life span of short-lived and chronically infected cells. Note that, the chronically infected cells produce much smaller amounts of viruses and die at a slower rate than the short-lived infected cells [71]. Further, it is reduced by the virus clearance (at the rate γ), by the antibody neutralization rate q and the response of cell-mediated immune system for virus

particles at the rate p. Hence

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

The humoral immune response produced by the production rate of antibodies (α_A), where, α_A is proportional to the number of short-lived and chronically infected cells. It is also decreased by the loss of the antibodies (at a rate μ_A). Thus

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

The cell-mediated immune response consists of constant recruitment of CTL cells from the thymus (at a rate b) and also expanded by the viral antigen which is derived from the infected cells (at a rate $c_1(I + C)$), where, c_1 is CTL response stimulation rate. This is decreased by the loss of CTL (at a rate μ_Z). Therefore, the governing equation is

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

Considering the characteristics of HBV transmission within the host, the non-linear differential equations of the system (description of variables and parameters are given in Table 4.1) are given below:

$$\begin{aligned}
\frac{dH}{dt} &= \Pi - \mu H - \frac{(1-\sigma)\beta HV}{1+\alpha V} + \rho I,\\
\frac{dI}{dt} &= \frac{(1-\xi)(1-\sigma)\beta HV}{1+\alpha V} - \delta I - \rho I - pIZ - \eta I,\\
\frac{dC}{dt} &= \frac{\xi(1-\sigma)\beta HV}{1+\alpha V} - aC - pCZ + \eta I,\\
\frac{dV}{dt} &= N_I\delta I + N_C aC - \gamma V - qVA - pVZ,\\
\frac{dA}{dt} &= \alpha_A(I + C) - \mu_A A,\\
\frac{dZ}{dt} &= b + c_1(I + C) - \mu_Z Z.
\end{aligned} \tag{4.2}$$

The main features of the model (4.2) are:

(i) Cell-mediated immune response against the infection of HBV: for infected cells and for virus particle (at a rate p);

(ii) Humoral immune response against the infection of HBV (at a rate q),where q is the antibody nutralization rate;

(iii) Two viral ifected classes: one short-lived infected class (I) and the other chronically infected class(C);

(iv) HBV transmitted from cell to cell (at a rate β);

(v) Short-lived infected cells becomes chronically infected cells (at a rate η);

(vi) Production rate of antibody (at a rate α_A) which is proportional to the short-lived and chronically infected cells;

(vii) HBV specific CTL stimulation (at a rate c_1);

(viii) HBV infected hepatocytes can be cured (at a rate ρ) and move to the target healthy cells [47];

The model (4.2), in the absence of immune response ($p = q = \alpha_A = b = c_1 = 0$), reduces to the following:

$$\begin{aligned}
\frac{dH}{dt} &= \Pi - \mu H - \frac{(1-\sigma)\beta HV}{1+\alpha V} + \rho I,\\
\frac{dI}{dt} &= \frac{(1-\xi)(1-\sigma)\beta HV}{1+\alpha V} - \delta I - \rho I - \eta I,\\
\frac{dC}{dt} &= \frac{\xi(1-\sigma)\beta HV}{1+\alpha V} - aC + \eta I,\\
\frac{dV}{dt} &= N_I \delta I + N_C aC - \gamma V.
\end{aligned} \tag{4.3}$$

4.3 Model without Immune Response

4.3.1 Positivity of solutions of the Reduced Model (4.3)

For the epidemiologically well proposed, we have to prove that the solutions of the reduced model (4.3), with nonnegative initial condition, will remain nonnegative for $t > 0$.

Parameters	Description	Baseline values
π	Constant rate of production of healthy host cells	$10mm^{-3}d^{-1}$ [69]
μ	Natural death rate of healthy cells	$0.01d^{-1}$ [69]
σ	The vaccination efficacy	[0,1] [assumed]
β	The infection rate	$0.001mm^3d^{-1}$ [69]
μ_Z	The lost rate of CTL cells	$0.1d^{-1}$ [69]
α_A	Production rate of antibodies	0.9 [assumed]
ρ	Cured rate of infected hepatocytes	0 [67]
μ_A	The lost rate of antibodies	$0.43d^{-1}$ [assumed]
ξ	The fraction of infection depends on the short lived and chronically infected cells	[0,1] [assumed]
δ	short-lived infected cell's death rate	$0.0494d^{-1}$ [67]
η	Progression rate of short lived to chronically infected cell	[0,1] [assumed]
p	Cell-mediated immune response	$0.005mm^3d^{-1}$ [69]
a	chronically infected cell's death rate	$0.1d^{-1}$ [69]
γ	The free virus clearance rate	$0.67d^{-1}$ [67]
q	The antibody neutralization rate	$0.01mm^3d^{-1}$ [69]
b	Constant recruitment rate of CTL cells from the thymus	0.12 [assumed]
N_I	The average number of virus particles produced during the life span of short lived infected cell	10 [69]
N_C	The average number of virus particles produced during the life span of chronically infected cell	5 [69]
c_1	HBV specific CTL stimulation rate	0.5 [assumed]
H_0	Target host cells at initial time	13.6×10^6 per ml [67]
I_0	Short-lived infected cells at initial time	0 [67]
C_0	Chronically infected cells at initial time	0 [assumed]
V_0	Free virus particle at initial time	0.33 per ml [67]

TABLE 4.1: Parameter description of the model (4.2)

Theorem 4.1. Let us consider the initial condition is $H(0) \geq 0$, $I(0) \geq 0$, $C(0) \geq 0$ and $V(0) \geq 0$. Then, the solutions (H, I, C, V) of the reduced model (4.3) are positive or zero for all time $t > 0$.

Proof. Assume that, $T = \sup\{t > 0 : H(t) > 0, I(t) > 0, C(t) > 0, V(t) > 0\}$. Then for $T > 0$, the first equation of (4.3) can be written as follows:

$$\frac{dH}{dt} + [\lambda(t) + \mu]H = \Pi + \rho I(t), \quad where \quad \lambda(t) = \frac{(1-\sigma)\beta V(t)}{1 + \alpha V(t)}.$$

Thus,

$$\frac{d}{dt}\left\{H(t)\exp\left[\int_0^T \lambda(u)du + \mu T\right]\right\} = (\Pi + \rho I(t)\exp\left[\int_0^T \lambda(u)du + \mu T\right],$$

so that,

$$H(T)\exp\left[\int_0^T \lambda(u)du + \mu T\right] - H(0) = \int_0^T (\Pi + \rho\int_0^x I(u)du\exp\left[\int_0^x \lambda(u)du + \mu x\right].$$

Hence,

$$\begin{aligned} H(T) &= H(0)\exp\left\{-\left[\int_0^T \lambda(u)du + \mu T\right]\right\} \\ &\quad + \exp\left\{-\left[\int_0^T \lambda(u)du + \mu T\right]\right\} \times \int_0^T (\Pi + \rho\int_0^x I(u)du\exp\left[\int_0^x \lambda(u)du + \mu x\right] \\ &\quad > 0. \end{aligned}$$

Similarly, it can also be proved that $I(t) > 0$, $C(t) > 0$ and $V(t) > 0$ for all time $t > 0$. Therefore, all the solutions of the reduced model (4.3) remains non-negative for all initial conditions. □

4.4 Existence and Stability analysis of Equilibria

4.4.1 Local stability analysis of virus-free equilibrium (VFE)

The reduced model (4.3) has a VFE of the form,

$$\mathcal{E}_0 = (H^*, I^*, C^*, V^*) = \left(\frac{\Pi}{\mu}, 0, 0, 0\right). \tag{4.4}$$

For analysing the stability of $\mathcal{E}_0$, here we consider the next generation operator method [37]. Considering the new infection terms and transfer terms from the model equations, we have the following F and Q matrices, respectively,

$$F = \begin{bmatrix} 0 & 0 & \frac{\beta\Pi(1-\xi)(1-\sigma)}{\mu} \\ 0 & 0 & \frac{\beta\Pi\xi(1-\sigma)}{\mu} \\ 0 & 0 & 0 \end{bmatrix},$$

and,

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

Thus,

$$\mathcal{R}_0 = \rho(FQ^{-1}) = \frac{\beta\Pi(1-\sigma)(\xi_C\delta + \xi N_C\rho + \eta N_C + N_I\delta(1-\xi))}{\mu(\delta+\rho+\eta)\gamma}, \tag{4.5}$$

Hence, the following result is established [37].

Lemma 4.1. *If $\mathcal{R}_0 < 1$ then the VFE, $\mathcal{E}_0$, of the reduced model (4.3) of the form given in (4.4) is locally-asymptotically stable (LAS), and otherwise unstable (i.e. if $\mathcal{R}_0 > 1$).*

The above threshold quantity, $\mathcal{R}_0$, is the basic reproduction number of the model. The epidemiological meaning of Lemma 4.1 is that HBV infection *in vivo* can be controlled when $\mathcal{R}_0 < 1$. To establish that, whenever $\mathcal{R}_0 < 1$, the viral clearance is independent of the sub-populations of the model. For which it is very important to show that the VFE is globally-asymptotically stable (GAS).

4.4.2 Global stability analysis of VFE

Theorem 4.2. The VFE, $\mathcal{E}_0$, of the reduced model (4.3), is globally asymptotically stable (GAS) for $\mathcal{R}_0 < 1$.

Proof. Consider the following Lyapunov function

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

where,

$$\begin{aligned} f_1 &= \frac{\eta N_C + \delta N_I}{\delta + \rho + \eta}, \\ f_2 &= N_C, \\ f_3 &= 1, \end{aligned}$$

now Lyapunov derivative is

$$\begin{aligned} \dot{\mathcal{F}} &= f_1 \dot{I}(t) + f_2 \dot{V_C}(t) + f_3 \dot{L_V}(t), \\ &= f_1 [\frac{(1-\xi)(1-\sigma)\beta H(t)V(t)}{1+\alpha V(t)} - \delta I(t) - \rho I(t) - \eta I(t)] \\ &+ N_C [\frac{\xi(1-\sigma)\beta H(t)V(t)}{1+\alpha V(t)} - aC(t) + \eta I(t)] \\ &+ 1[N_I \delta I(t) + N_C a C(t) - \gamma V(t)], \\ &= \frac{(\eta N_C + N_I\delta)(1-\xi)(1-\sigma)\beta \Pi V}{\mu(\delta+\rho+\eta)(1+\alpha V)} - \frac{\delta I(\eta N_C + N_I \delta)}{\delta+\rho+\eta} \\ &- \frac{\rho I(\eta N_C + N_I\delta)}{\delta+\rho+\eta} - \frac{\eta I(\eta N_C + N_I\delta)}{\delta+\rho+\eta} + \frac{\xi N_C(1-\sigma)\beta\pi V}{\mu(1+\alpha V)} + \eta I N_C + B_I \delta I - \gamma V, \\ &= \frac{1}{\mu(\delta+\rho+\eta)(1+\alpha V)} \times [\beta \Pi V(1-\sigma)(\eta N_C + N_I\delta) - \beta \Pi V \xi (1-\sigma)(\eta N_C + N_I \delta) \\ &- \gamma V \mu(\delta+\rho+\eta)(1+\alpha V) + \xi N_C (1-\sigma)\beta \Pi V(\delta+\rho+\eta)], \end{aligned}$$

which can be simplified to

$$\begin{aligned}\dot{\mathcal{F}} &= \frac{\gamma V}{1+\alpha V}\left[\frac{\xi N_C(1-\sigma)\beta\Pi\delta + \xi N_C(1-\sigma)\beta\Pi\rho + \beta\Pi(1-\sigma)\eta N_C + \beta\Pi(1-\sigma)N_I\delta - \beta\Pi\xi(1-\sigma)N_I\delta}{\mu(\delta+\rho+\eta)\gamma}\right.\\ &- \left.(1+\alpha V)\right]\\ &= \frac{\gamma V}{1+\alpha V}\left[\mathcal{R}_0 - 1\right] - \frac{\gamma V}{1+\alpha V}\alpha V\\ &\leq \frac{\gamma V}{1+\alpha V}(\mathcal{R}_0 - 1).\end{aligned}$$

Here, all the parameters and variables of the model are positive for all time $t > 0$ (Theorem 4.1), so it follows that $\dot{\mathcal{F}} < 0$ for $\mathcal{R}_0 < 1$ and only if $V(t) = 0$ then $\dot{\mathcal{F}} = 0$. Thus, we have $V \to 0$ as $t \to \infty$ (by using Lasalle Invariance Principle [40]). □

The epidemiological significance of Theorem 4.2 is that the threshold, $\mathcal{R}_0$ is less than unity (i.e. $\mathcal{R}_0 < 1$) is necessary and sufficient condition for HBV clearance from an infected host. Figure 4.2 reveals the solution trajectories of the reduced model (4.3) for $\mathcal{R}_0 < 1$, which shows convergence of the total infected hepatocytes cells to VFE, $\mathcal{E}_0$(Theorem 4.2).

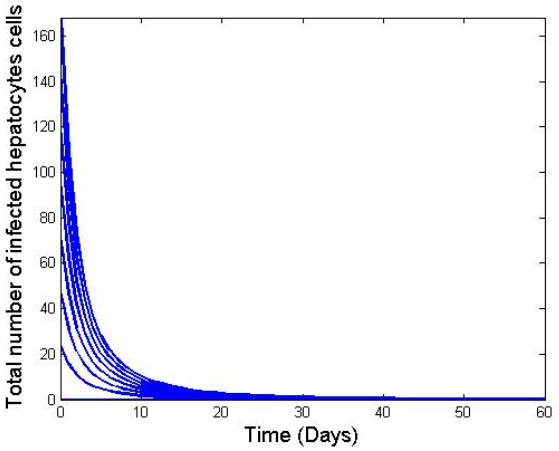

FIGURE 4.2: Figure illustrates the total density of the infected hepatocytes cells, where, $\mathcal{R}_0 = 0.8521 < 1$, $\beta = 0.01$ and other parameters are taken from Table 4.1.

4.5 Existence of virus present equilibrium point (VPE)

In this section, we want to show the existence and stability analysis of positive virus present equilibria of the model (4.3) in the absence of immunity ($p = q = \alpha_A = b = c_1 = 0$). Let $\mathcal{E}_1 = (H^{**}, I^{**}, C^{**}, V^{**})$ be any arbitrary endemic equilibrium point. Consider

$$\lambda^{**} = \frac{\beta V^{**}}{1 + \alpha V^{**}}. \tag{4.6}$$

which is the *forces of infection* of the reduced model (4.3) at steady-state. To find the conditions for the existence of the VPE, we have to solve the model equations (4.3) in terms of force of infection, which gives

$$\begin{aligned}
H^{**} &= \frac{\Pi + \rho I^{**}}{\mu + (1-\sigma)\lambda^{**}}, \\
I^{**} &= \frac{(1-\xi)(1-\sigma)\lambda^{**} H^{**}}{(\delta + \rho + \eta)}, \\
C^{**} &= \frac{[\xi(1-\sigma)(\delta+\rho+\eta) + \eta(1-\xi)(1-\sigma)]\,\lambda^{**} H^{**}}{a(\delta+\rho+\eta))}, \\
V^{**} &= \frac{N_I \delta(1-\xi)(1-\sigma) + N_C\,[\{\xi(1-\sigma)(\delta+\rho+\eta) + \eta(1-\xi)(1-\sigma)\}]\,\lambda^{**} H^{**}}{\gamma(\delta+\rho+\eta)}.
\end{aligned} \tag{4.7}$$

Substituting (4.7) into the expression for λ^{**} in (4.6), gives

$$\lambda^{**}(1 + \alpha V^{**}) = \beta V^{**}. \tag{4.8}$$

Substituting the non-zero VPE in the above expression and simplify:

$$
\begin{aligned}
&\lambda^{**}\left[\gamma(\delta+\rho+\eta)+\left((1-\sigma)\left\{\xi N_C\delta+\xi N_C\rho+N_C\eta+N_I\delta(1-\xi)\right\}\right)\alpha\lambda^{**}H^{**}\right]\\
&=\beta\left\{(1-\sigma)(1-\xi)N_I\delta+\xi N_C\delta(1-\sigma)+\xi N_C\rho(1-\sigma)+N_C\eta(1-\sigma)\right\}\lambda^{**}H^{**}\\
&\Rightarrow\lambda^{**}\left[\gamma(\delta+\rho+\eta)+\left[(1-\sigma)\left\{\xi N_C\delta+\xi N_C\rho+N_C\eta+N_I\delta(1-\xi)\right\}\right]\alpha\lambda^{**}H^{**}\right]\\
&=\beta\left\{(1-\sigma)\left\{\xi N_C\delta+\xi N_C\rho+N_C\eta+N_I\delta(1-\xi)\right\}\right\}\lambda^{**}H^{**}\\
&\Rightarrow\left[1+\frac{(1-\sigma)\left\{\xi N_C\delta+\xi N_C\rho+N_C\eta+N_I\delta(1-\xi)\right\}}{\gamma(\delta+\rho+\eta)}\alpha\lambda^{**}H^{**}\right]\\
&=\frac{\beta\left\{(1-\sigma)\left\{\xi N_C\delta+\xi N_C\rho+N_C\eta+N_I\delta(1-\xi)\right\}\right\}}{\gamma(\delta+\rho+\eta)}\lambda^{**}H^{**}\\
&\Rightarrow\frac{\alpha\mathcal{R}_0}{\beta}\lambda^{**^2}+\lambda^{**}-\mathcal{R}_0\lambda^{**}=0\\
&\Rightarrow\lambda^{**}=\frac{\beta}{\alpha}\left(1-\frac{1}{\mathcal{R}_0}\right)>0.
\end{aligned}
$$

Lemma 4.2. *The model (4.3) with ($p=q=\alpha_A=b=c_1=0$) has a positive unique endemic equilibrium, $\mathcal{E}_1$ when $\mathcal{R}_0>1$.*

4.6 Local Stability analysis of VPE

Using the substitution $H^{**}=N^{**}-I-C-V$ in the model (4.3) with $p=q=\alpha_A=b=c_1=0$ we get the reduced model:

$$
\begin{aligned}
\frac{dI}{dt}&=\frac{(1-\xi)(1-\sigma)\beta V}{1+\alpha V}[N^{**}-I-C-V]-(\delta+\rho+\eta)I,\\
\frac{dC}{dt}&=\frac{\xi(1-\sigma)\beta V}{1+\alpha V}[N^{**}-I-C-V]-aC+\eta I,\\
\frac{dV}{dt}&=N_I\delta I+N_C aC-\gamma V,
\end{aligned}
\tag{4.9}
$$

To show the system has a positive unique VEP, $\mathcal{E}_1$, whenever $\mathcal{R}_0>1$, we claim the following:

Theorem 4.3. If $\mathcal{R}_0>1$ then the reduced model has a LAS positive unique endemic equilibrium, $\mathcal{E}_1$.

Proof. Here we use Krasnoselskii sub-linearity trick [58, 63]. We linearilize the system (4.9) around the eqilibrium $\mathcal{E}_1$ and obatin the given of solution

$$\bar{\mathbf{Z}}(t) = \bar{\mathbf{Z}}_0 e^{\theta t}, \tag{4.10}$$

Substitute the above solution form in the system (4.9) around the equilibrium $\mathcal{E}_1$ and we get the following linear system

$$\begin{aligned}
\theta Z_1 &= (-ma_1 - k_1)Z_1 + (-ma_1)Z_2 + m(a_2 - a_1)Z_3, \\
\theta Z_2 &= (-na_1 + \eta)Z_1 + (-na_1 - a)Z_2 + n(a_2 - a_1)Z_3, \\
\theta Z_3 &= N_I\delta Z_1 + N_C a Z_2 - \gamma Z_3.
\end{aligned} \tag{4.11}$$

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

Solving the equations of (4.11) and after simplification

$$\begin{aligned}
[1 + G_1(\theta)]Z_1 + [1 + G_2(\theta)]Z_2 &= \left[\frac{\eta}{a} + \frac{na_2N_I\delta}{a(\theta+\gamma)} + \frac{ma_2N_I\delta}{k_1(\theta+\gamma)}\right]Z_1 \\
&+ \left[\frac{na_2N_C}{(\theta+\gamma)} + \frac{ma_2N_Ca}{k_1(\theta+\gamma)}\right]Z_2, \\
[1 + G_3(\theta)]Z_3 &= \frac{N_I\delta}{\gamma}Z_1 + \frac{N_Ca}{\gamma}Z_2.
\end{aligned} \tag{4.12}$$

where,

$$\begin{aligned}
G_1(\theta) &= \frac{\theta}{k_1} + \frac{ma_1}{k_1} + \frac{ma_1N_I\delta}{k_1(\theta+\gamma)} + \frac{na_1}{a} + \frac{na_1N_I\delta}{a(\theta+\gamma)}, \\
G_2(\theta) &= \frac{\theta}{a} + \frac{na_1}{a} + \frac{na_1N_C}{\theta+\gamma} + \frac{ma_1}{k_1} + \frac{ma_1N_Ca}{k_1(\theta+\gamma)}, \\
G_3(\theta) &= \frac{\theta}{\gamma}.
\end{aligned} \tag{4.13}$$

with,

$$M = \begin{pmatrix} \frac{ma_2N_I\delta}{\gamma k_1} & \frac{ma_2N_Ca}{\gamma k_1} & 0 \\ \frac{\eta}{a} + \frac{na_2N_I\delta}{\gamma a} & \frac{na_2N_C}{\gamma} & 0 \\ \frac{N_I\delta}{\gamma} & \frac{N_Ca}{\gamma} & 0 \end{pmatrix},$$

The above form $M(\bar{Z})_i$ (with $i = 1, 2, 3$) represents the ith coordinate of the vector $M(\bar{Z})$. Here, M has positive or zero entries, and the endemic equilibrium $\mathcal{E}_1 = (H^{**}, I^{**}, C^{**}, V^{**})$ satisfies the expression $\mathcal{E}_1 = M\mathcal{E}_1$. Since $\mathcal{E}_1$ is positive, so system (4.12) has a solution $\bar{Z}$, if only there exists a minimal positive real number s such that

$$|| \bar{\mathbf{Z}} ||\leq s\mathcal{E}_1, \tag{4.14}$$

where, $|| \bar{\mathbf{Z}} ||= (|| Z_1 ||, || Z_2 ||, || Z_3 ||)$ with the lexicographic order, and consider the norm in $\mathbb{C}$.

Now, we want to establish that $Re(\theta) < 0$. Let us assume $Re(\theta) \geq 0$. Then we have the cases $\theta = 0$ and $\theta \neq 0$. For $\theta = 0$ the system (4.11) is a linear with Z_i, where $i = 1, 2, 3$. Determinant of (4.11) evaluated at $\mathcal{E}_1$, is given by

$$\triangle= A + \gamma(\delta + \rho + \eta)(\mathcal{R}_0M)\frac{\mu}{\Pi} > 0. \tag{4.15}$$

where, $A = (1-\xi)(1-\sigma)M\delta a + (1-\sigma)\xi\delta\gamma M + (1-\sigma)\xi\rho\gamma M > 0$ and
$M = \frac{a\gamma(\delta+\rho+\eta)}{(1-\sigma)\{\gamma a(1-\xi)+N_I\delta a(1-\xi)+(\xi\delta+\xi\rho+\eta)(\gamma+N_Ca)\}} > 0.$

From the above expression (4.15), it is clear that $\triangle> 0$. So, the system (4.11) has only the trivial solution $\bar{Z} = \bar{0}$ which is also the *VFE*. Next, we consider $\theta \neq 0$. Since $Re(\theta) \geq 0$, in this case, $Re(G_i(\theta)) \geq 0$ for $i = 1, 2, 3$. Thus $\mid 1 + G_i(\theta) \mid> 1$ for all i. If $G(\theta) = min \mid 1 + G_i(\theta) \mid> 1$ for $i = 1, 2, 3$. then $G(\theta) > 1$. Hence, $\frac{s}{G(\theta)} < s$. For the real positive number s implies $|| \bar{Z} ||> \frac{s}{G(\theta)}\mathcal{E}_1$. On the other hand, taking norms in the third

equation of (4.11) and using the non-negative M matrix gives

$$G(\theta) \mid\mid Z_3 \mid\mid \leq M(\mid\mid Z \mid\mid)_3 \leq s(M \mid\mid \mathcal{E}_1 \mid\mid)_3 \leq sV^{**}. \tag{4.16}$$

Then, it follows from the above inequality that $\mid\mid Z_3 \mid\mid \leq \frac{s}{G(\theta)}V^{**}$, which contradicts our assumption that $Re(G_i(\theta)) \geq 0$. Therefore, $Re(\theta) < 0$, so that if $\mathcal{R}_0 > 1$, then $\mathcal{E}_1$, is LAS. □

From the epidemiological aspects of Theorem 4.3, we can say that the disease will persist in the infected body if $\mathcal{R}_0 > 1$. Hence $\mathcal{R}_0 > 1$ is the necessary condition for the HBV persistence within the infected hepatocytes cells for our reduced model (4.3). Figure (4.3) portrays the solution trajectories of the reduced model (4.3) for $\mathcal{R}_0 > 1$, which shows convergence of the healthy cells, infected hepatocytes cells and virus cells density to the *VPE*, $\mathcal{E}_1$.

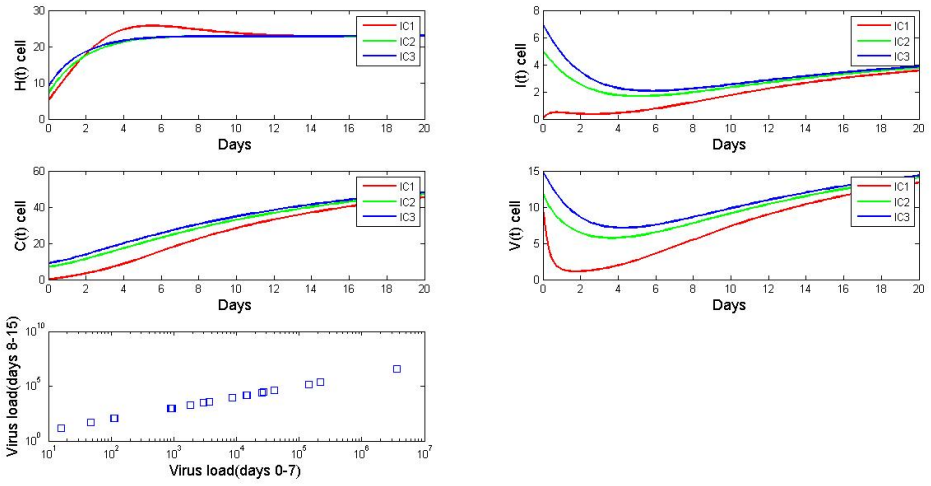

FIGURE 4.3: Plot illustrates the density of healthy and infected hepatocytes cells and virus particles using different initial conditions, where $\mathcal{R}_0 = 1.89 > 1$ and $\beta = 0.05$. The corellation of the virus concentration of (0-7) days and (8-15) days after acute infection. The parameters values are given in Table 4.1.

4.7 Global stability analysis of VPE

Theorem 4.4. If $\mathcal{R}_0 > 1$ then the unique VPE, $\mathcal{E}_1$, of the reduced model (4.3) is globally asymptotically stable (GAS).

Proof. Let us consider the following non-linear Lyapunov function:

$$\mathcal{L} = \left(H - H^{**} - H^{**}ln\frac{H}{H^{**}}\right) + a_1\left(I - I^{**} - I^{**}ln\frac{I}{I^{**}}\right) + a_2\left(C - C^{**} - C^{**}ln\frac{C}{C^{**}}\right) + a_3\left(V - V^{**} - V^{**}ln\frac{V}{V^{**}}\right), \tag{4.17}$$

where, $a_1 = \frac{\rho}{k_1}$, $a_2 = 0$ *and* $a_3 = 0$. with Lyapunov derivative given by,

$$\begin{aligned}
\dot{\mathcal{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] \\
&+ \frac{\rho}{k_1}\left(1 - \frac{I^{**}}{I}\right)\left[\frac{(1-\xi)(1-\sigma)\beta HV}{1+\alpha V} - k_1 I\right] \\
&= \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-\xi)(1-\sigma)\beta HV}{1+\alpha V} - k_1 I - \frac{(1-\xi)(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-\xi)(1-\sigma)\beta HV}{k_1(1+\alpha V)} - \frac{\rho(1-\xi)(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^{**}} - \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} + \left[\Pi - \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},
\end{aligned}$$

$$
\begin{aligned}
&= 2\mu H^{**} - \mu H - \frac{\mu(H^{**})^2}{H} + \left[-\Pi + \mu H^{**} + + \frac{(1-\sigma)\beta H^{**}V^{**}}{1+\alpha V^{**}}\right] \cdot \frac{I^{**}}{I} \cdot \frac{H^{**}}{H} \\
&- \rho I \cdot \frac{H^{**}}{H} + \rho I^{**} - \rho k_1 I^{**} \cdot \frac{I^{**}}{I}, \\
&= 2\mu H^{**} - \mu H - \frac{\mu(H^{**})^2}{H} + \rho I^{**} \cdot \frac{I^{**}}{I} \cdot \frac{H^{**}}{H} - \left[-\Pi + \mu H^{**} + \frac{(1-\sigma)\beta H^{**}V^{**}}{1+\alpha V^{**}}\right] \cdot \frac{H^{**}}{H} \\
&+ \rho I^{**} - \rho k_1 I^{**} \cdot \frac{I^{**}}{I}, \\
&= 2\mu H^{**} - \mu H - \frac{\mu(H^{**})^2}{H} + \rho I^{**} \cdot \frac{I^{**}}{I} \cdot \frac{H^{**}}{H} - \rho I^{**} \cdot \frac{H^{**}}{H} + \rho I \cdot \frac{I^{**}}{I} - \rho k_1 I^{**} \cdot \frac{I^{**}}{I}, \\
&= 2\mu H^{**} - \mu H - \frac{\mu(H^{**})^2}{H} + \rho I^{**} \cdot \frac{I^{**}}{I} \cdot \frac{H^{**}}{H} - \rho I^{**} \cdot \frac{H^{**}}{H} + \left[-\Pi + \mu H^{**}\right. \\
&\left. + \frac{(1-\sigma)\beta H^{**}V^{**}}{1+\alpha V^{**}}\right] \cdot \frac{I^{**}}{I} - \rho k_1 I^{**} \cdot \frac{I^{**}}{I}, \\
&= 2\mu H^{**} - \mu H - \frac{\mu(H^{**})^2}{H} + \rho I^{**} \cdot \frac{I^{**}}{I} \cdot \frac{H^{**}}{H} - \rho I^{**} \cdot \frac{H^{**}}{H} + \rho I^{**} \cdot \frac{I^{**}}{I} - \rho k_1 I^{**} \cdot \frac{I^{**}}{I}, \\
&= 2\mu H^{**} - \mu H - \frac{\mu(H^{**})^2}{H} - \rho I^{**} \cdot \frac{H^{**}}{H}\left(1 - \frac{I^{**}}{I}\right) - \rho I^{**} \cdot \frac{I^{**}}{I}\left(k_1 - 1\right), \\
&< \mu H^{**}\left(2 - \frac{H}{H^{**}} - \frac{H^{**}}{H}\right).
\end{aligned}
$$

The following expression occurs when the arithmetic mean exceeds the geometric mean.

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

Here, $\dot{\mathcal{L}} < 0$ for $\mathcal{R}_0 > 1$. Hence, by using LaSalle's Invariance Principle [40], we can say that every solution of the reduced model (4.9) approaches to $\mathcal{E}_1$ as $t \to \infty$ for $\mathcal{R}_0 > 1$. □

From the epidemiological view point, Theorem 4.4 implies (when $\mathcal{R}_0 > 1$) that HBV infection will persist within the infected host.
In summary, we have the following:

(i) If $\mathcal{R}_0 < 1$ then the reduced model (4.3) has a VFE, $\mathcal{E}_0$, which is GAS;

(ii) The reduced model (4.3) has a unique VPE, $\mathcal{E}_1$.

(iii) If $\mathcal{R}_0 > 1$ then the reduced model (4.3) has a positive unique VPE, $\mathcal{E}_1$ and the infection will persist within the infected host.

4.8 Analysis of the Model with Immune Response

4.8.1 Basic Properties of the Model (4.2)

4.8.1.1 Positivity of solutions

To prove the following theorem here we use the same approach described in Subsection 4.3.1.

Theorem 4.5. Let us consider the initial condition be $H(0) \geq 0$, $I(0) \geq 0$, $C(0) \geq 0$, $V(0) \geq 0$, $A(0) \geq 0$ and $Z(0) \geq 0$. Then, the solutions (H, I, C, V, A, Z) of the model (4.2) are positive for all time $t > 0$.

4.8.2 Existence and Stability analysis of Equilibria

4.8.2.1 Local Stability analysis of VFE (with immune response)

The model (4.2) has a VFE of the form

$$\mathcal{E}_{01} = (H^*, I^*, C^*, V^*, A^*, Z^*) = \left(\frac{\Pi}{\mu}, 0, 0, 0, 0, 0\right). \tag{4.18}$$

Using the next generation method the matrices F_1 and Q_1 from the model (4.2) are respectively given by:

$$F_1 = \begin{bmatrix} 0 & 0 & \frac{\beta\Pi(1-\xi)(1-\sigma)}{\mu} & 0 & 0 \\ 0 & 0 & \frac{\beta\Pi\xi(1-\sigma)}{\mu} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix},$$

and,

$$Q_1 = \begin{bmatrix} \delta+\rho+\eta & 0 & 0 & 0 & 0 \\ -\eta & a & 0 & 0 & 0 \\ -N_I\delta & -N_C a & \gamma & 0 & 0 \\ 0 & 0 & 0 & \mu_A & 0 \\ 0 & 0 & 0 & 0 & \mu_Z \end{bmatrix},$$

so that,

$$\mathcal{R}_{01} = \rho(F_1 Q_1^{-1}) = \mathcal{R}_0. \tag{4.19}$$

Hence, it follows, from Theorem 2 of [37], that:

Lemma 4.3. *If $\mathcal{R}_{01} < 1$ then the model (4.2) has a LAS VFE, $\mathcal{E}_{01}$ and otherwise unstable.*

4.8.2.2 Global stability of VFE (with immune response)

Theorem 4.6. The VFE, $\mathcal{E}_{01}$, of the model (4.2), is GAS if $\mathcal{R}_{01} < 1$.

Proof. Consider the following Lyapunov function

$$\mathcal{F} = f_1 I(t) + f_2 C(t) + f_3 V(t) + f_4 A(t) + f_5 Z(t),$$

where,

$$\begin{aligned} f_1 &= \frac{N_I\delta + N_C\eta}{\delta+\rho+\eta}, \\ f_2 &= N_C, \\ f_3 &= 1, \\ f_4 &= 0, \\ f_5 &= 0, \end{aligned}$$

Now Lyapunov derivative with respect to t is

$$\begin{aligned} \dot{\mathcal{F}} &= f_1\dot{I}(t) + f_2\dot{C}(t) + f_3\dot{V}(t) + f_4\dot{A}(t) + f_5\dot{Z}(t), \\ &= \frac{N_I\delta + N_C\eta}{\delta+\rho+\eta}\left[\frac{(1-\xi)(1-\sigma)\beta HV}{1+\alpha V} - (\delta+\rho+\eta)I - pIZ\right] + N_C\left[\frac{\xi(1-\sigma)\beta HV}{1+\alpha V} - aC - pCZ + \eta I\right] \\ &+ 1\left[N_I\delta I + N_C aC - \gamma V - qAV - pVZ\right] \end{aligned}$$

Which can be simplified according to the approach in Subsection 4.4.2 to prove the following result.

$$\begin{aligned} \dot{\mathcal{F}} &= \frac{\gamma V}{1+\alpha V}\left[\mathcal{R}_{01} - 1\right] - \frac{\gamma V}{1+\alpha V}\cdot\alpha V \\ &< \frac{\gamma V}{1+\alpha V}\left[\mathcal{R}_{01} - 1\right] \end{aligned}$$

Since all the parameters and variables of the model are positive for all time $t > 0$ (Theorem 4.1), therefore $\dot{\mathcal{F}} < 0$ for $\mathcal{R}_{01} < 1$ and $\dot{\mathcal{F}} = 0$ if and only if $V(t) = 0$. Thus, by using the Lasalle Invariance Principle [40], it is clear that $V \to 0$ as $t \to \infty$. Thus, for arbitrary $\epsilon > 0$ there exists a $t_e > 0$ such that if $t > t_e$, then $I(t) < \epsilon$, $C(t) < \epsilon$, $V(t) < \epsilon$,$A(t) < \epsilon$ and $Z(t) < \epsilon$. Consequently, for $t > t_e$ we get the following expression from the first equation of

the model (4.2)

$$H(t) \geq \frac{\Pi}{\lambda\epsilon + \mu}. \tag{4.20}$$

where $\lambda = \frac{\beta HV}{1+\alpha V}$ so that, by a comparison theorem [72], since $\epsilon > 0$ is very small so let $\epsilon \to 0$ in (4.20) gives

$$\liminf_{t\to\infty} H(t) = \frac{\Pi}{\mu},$$

so that,

$$\lim_{t\to\infty} H(t) = \frac{\Pi}{\mu}.$$

Hence,

$$\lim_{t\to\infty}(H(t), I(t), C(t), V(t), A(t), Z(t)) = \left(\frac{\Pi}{\mu}, 0, 0, 0, 0, 0\right) = \mathcal{E}_{01}.$$

Therefore, every solution of the model (4.2) approaches to the VFE, $\mathcal{E}_{01}$, as $t \to \infty$, for $\mathcal{R}_{01} < 1$. □

The result of Theorem 4.6 implies that if $\mathcal{R}_{01} < 1$ then HBV infection will be removed from the infected host.

4.8.2.3 Existence of VPE for a special case

For the existence of VPE we consider a special case where the response of cell-mediated immunity is very low due to alum adsorb HBsAg vaccine (i.e. $p = 0$) and the response of humoral immunity (q) is comparatively better than the response of cell-mediated immunity [66]. Let,

$$\mathcal{E}_2 = (H^{***}, I^{***}, C^{***}, V^{***}, A^{***}, Z^{***}),$$

be any arbitrary positive equilibrium point of (4.2). Assume that

$$\lambda_1^{***} = \frac{\beta V^{***}}{1 + \alpha V^{***}}, \quad \lambda_2^{***} = qA^{***}, \tag{4.21}$$

where λ_1^{***} be the force of infection. Solving the model equations (4.2) we have the following VPE with immune response. The VPE are

$$\begin{aligned}
H^{***} &= \frac{\Pi(\delta+\rho+\eta)}{\mu(\delta+\rho+\eta)+\lambda_1^{***}(1-\sigma)(\delta+\xi\rho+\eta)},\\
I^{***} &= \frac{\Pi\lambda_1^{***}(1-\sigma)(1-\xi)}{\mu(\delta+\rho+\eta)+\lambda_1^{***}(1-\sigma)(\delta+\xi\rho+\eta)},\\
C^{***} &= \frac{\Pi\lambda_1^{***}(1-\sigma)(\xi\delta+\xi\rho+\eta)}{a\left\{\mu(\delta+\rho+\eta)+\lambda_1^{***}(1-\sigma)(\delta+\xi\rho+\eta)\right\}},\\
V^{***} &= \frac{\Pi\lambda_1^{***}\left\{(1-\sigma)(N_C\xi\rho+N_C\xi\delta+N_C\eta+N_I\delta(1-\xi))\right\}}{(\gamma+\lambda_2^{***})\left\{\mu(\delta+\rho+\eta)+\lambda_1^{***}(1-\sigma)(\delta+\xi\rho+\eta)\right\}},\\
A^{***} &= \frac{\alpha_A\Pi\lambda_1^{***}\left\{(1-\sigma)((\eta+\xi\rho+\xi\delta)+a(1-\xi))\right\}}{a\left\{\mu(\delta+\rho+\eta)+\lambda_1^{***}(1-\sigma)(\delta+\xi\rho+\eta)\right\}\mu_A},\\
Z^{***} &= \frac{\lambda_1^{***}b\mu(1-\sigma)(\delta+\rho+\eta)[ba(\delta+\xi\rho+\eta)+c_1\Pi\left\{(\eta+\xi\delta+\xi\rho)+a(1-\xi)\right\}]}{\left\{\mu(\delta+\rho+\eta)+\lambda_1^{***}(1-\sigma)(\delta+\xi\rho+\eta)\right\}\mu_Z}.
\end{aligned} \tag{4.22}$$

Substituting (4.22) into the expression for λ_1^{***} in (4.21), gives,

$$
\begin{aligned}
\lambda_1^{***} &= \frac{\beta V^{***}}{1+\alpha V^{***}} \\
&\Rightarrow \lambda_1^{***}(1-\sigma)(\gamma\delta a\mu_A + \gamma\rho\xi a\mu_A + \alpha\Pi N_C\xi\rho a\mu_A + \alpha\Pi N_C\eta a\mu_A + \alpha\Pi N_C\xi\delta a\mu_A - \alpha\Pi N_I\delta\xi a\mu_A \\
&+ \alpha\Pi N_I\delta a\mu_A + q\alpha_A\Pi\rho\xi + q\alpha_A\Pi\eta + \delta q\alpha_A\Pi\xi - q\alpha_A\Pi a\xi + q\alpha_A\Pi a + \gamma\eta a\mu_A) + \gamma\mu a\mu_A(\delta+\rho+\eta) \\
&= \beta\Pi a\mu_A\{(1-\sigma)(N_C\xi\rho + N_C\xi\delta + N_C\eta + N_I\delta(1-\xi))\} \\
&\Rightarrow \lambda_1^{***}(1-\sigma)[\gamma a\mu_A(\delta+\eta+\xi\rho) + q\alpha_A\Pi a(1-\xi) + \alpha\Pi N_I\delta a\mu_A(1-\xi) \\
&+ \alpha\Pi N_C a\mu_A(\eta+\xi\delta+\xi\rho) + q\alpha_A\Pi(\eta+\xi\delta+\xi\rho)] \\
&= \beta\Pi a\mu_A\{(1-\sigma)(N_C\xi\rho + N_C\xi\delta + N_C\eta + N_I\delta(1-\xi))\} - \gamma\mu a\mu_A(\delta+\rho+eta) \\
&\Rightarrow \lambda_1^{***}(1-\sigma)[\gamma a\mu_A(\delta+\eta+\xi\rho) + (1-\xi)(q\alpha_A\Pi a + \alpha\Pi N_I\delta a\mu_A) \\
&+ (\eta+\xi\delta+\xi\rho)(\alpha\Pi N_C a\mu_A + q\alpha_A\Pi)] = a\mu_A[\beta\Pi(1-\sigma)(N_C\xi\rho + N_C\xi\delta + N_C\eta + N_I\delta(1-\xi)) \\
&- \gamma\mu(\delta+\rho+\eta)] \qquad (4.23) \\
&\Rightarrow \lambda_1^{***}\Bigg[(1-\sigma)(\gamma a\mu_A(\delta+\eta+\xi\rho) + (1-\xi)(q\alpha_A\Pi a + \alpha\Pi N_I\delta a\mu_A) + (\eta+\xi\delta+\xi\rho)(\alpha\Pi N_C a\mu_A \\
&+ q\alpha_A\Pi))\Bigg] - a\mu_A\left[\gamma(\delta+\rho+\eta)\mu\frac{\beta\Pi(1-\sigma)(N_C\xi\rho + N_C\xi\delta + N_C\eta + N_I\delta(1-\xi))}{\gamma(\delta+\rho+\eta)\eta} - 1\right] = 0 \\
&\Rightarrow \lambda_1^{***}\Bigg[(1-\sigma)(\gamma a\mu_A(\delta+\eta+\xi\rho) + (1-\xi)(q\alpha_A\Pi a + \alpha\Pi N_C\delta a\mu_A) + (\eta+\xi\delta+\xi\rho)(\alpha\Pi N_C a\mu_A \\
&+ q\alpha_A\Pi))\Bigg] - a\mu_A\Big[\gamma(\delta+\rho+\eta)\mu(\mathcal{R}_{01}-1)\Big] = 0 \\
&\Rightarrow a_1\lambda_1^{***} - a_0 = 0 \\
&\Rightarrow \lambda_1^{***} = \frac{a_0}{a_1} > 0.
\end{aligned}
$$

since $a_0 = a\mu_A[\gamma(\delta+\rho+\eta)\mu(\mathcal{R}_{01})] > 0$ where $\mathcal{R}_{01} > 1$ and
$a_1 = (1-\sigma)[\gamma a\mu_A(\delta+\eta+\xi\rho) + (1-\xi)(q\alpha_A\Pi a + \alpha\Pi N_I\delta a\mu_A) + (\eta+\xi\delta+\xi\rho)(\alpha\Pi N_C a\mu_A + q\alpha_A\Pi)] > 0$.

The model (4.2) with immunity system has a positive unique virus present equilibrium (VPE), when $\mathcal{R}_{01} > 1$.

Theorem 4.7. If $\mathcal{R}_{01} > 1$ then the model (4.2) has a positive unique VPE, $\mathcal{E}_2$.

4.9 Local Stability of virus present equilibrium point (VPE) with immune response

Now the local stability analysis of the positive unique VEP, $\mathcal{E}_2$ is established for a case $p = 0$ in the model (4.2). Using the substitution $H^{***} = N^{***} - I - C - V - A - Z$ in the model (4.2) we get the following reduced model:

$$\begin{aligned}
\frac{dI}{dt} &= \frac{(1-\xi)(1-\sigma)\beta V}{1+\alpha V}[N^{***} - I - C - V - A - Z] - (\delta + \rho + \eta)I,\\
\frac{dC}{dt} &= \frac{\xi(1-\sigma)\beta V}{1+\alpha V}[N^{**} - I - C - V - A - Z] - aC + \eta I,\\
\frac{dV}{dt} &= N_I\delta I + N_C aC - \gamma V - qVA,\\
\frac{dA}{dt} &= \alpha_A(I + C) - \mu_A A,\\
\frac{dZ}{dt} &= b + c_1(I + C) - \mu_Z Z,
\end{aligned} \tag{4.24}$$

It can be easily shown that the system has a positive unique VEP, $\mathcal{E}_2$ whenever $\mathcal{R}_{01} > 1$.

Theorem 4.8. The unique virus present equilibrium point, $\mathcal{E}_2$, of the reduced model is locally asymptotically stable when $\mathcal{R}_{01} > 1$.

Proof. The proof is similar to theorem 4.3. This approach shows that the linearization of the system (4.24), around $\mathcal{E}_2$ has the following form of solutions

$$\bar{\mathbf{Z}}(t) = \bar{\mathbf{Z}}_0 e^{\theta t}, \tag{4.25}$$

Substitute the above solution into the linearized system of (4.24), around $\mathcal{E}_2$, we get the reduced following linear system

$$\begin{aligned}
\theta Z_1 &= (-ma_1 - k_1)Z_1 + (-ma_1)Z_2 + m(a_2 - a_1)Z_3 - ma_1 Z_4 - ma_1 Z_5,\\
\theta Z_2 &= (-na_1 + \eta)Z_1 + (-na_1 - a)Z_2 + n(a_2 - a_1)Z_3 - na_1 Z_4 - na_1 Z_5,\\
\theta Z_3 &= N_I\delta Z_1 + N_C aZ_2 - (\gamma + qA)Z_3 - qVZ_4,\\
\theta Z_4 &= \alpha_A Z_1 + \alpha_A Z_2 - \mu_A Z_4,\\
\theta Z_5 &= c_1 Z_1 + c_1 Z_2 - \mu_Z Z_5.
\end{aligned} \tag{4.26}$$

where, m, n, k_1, a_1 and a_2 are mentioned earlier in section 4.6. Solving and simplifying the equations of (4.26):

$$\begin{aligned}
&[1+F_1(\theta)]Z_1 + [1+F_2(\theta)]Z_2 + [1+F_3(\theta)]Z_3 = \frac{\eta + N_I\delta}{k_1}Z_1 + \frac{N_C a}{a}Z_2 + \frac{a_2(m+n)}{\gamma}Z_3,\\
&[1+F_4(\theta)]Z_4 = \frac{\alpha_A}{\mu_A}Z_1 + \frac{\alpha_A}{\mu_A}Z_2,\\
&[1+F_5(\theta)]Z_5 = \frac{c_1}{\mu_Z}Z_1 + \frac{c_1}{\mu_Z}Z_2.
\end{aligned} \tag{4.27}$$

where,

$$\begin{aligned}
F_1(\theta) &= \frac{\theta}{k_1} + \frac{a_1(m+n)}{k_1} + \frac{qV^{***}\alpha_A}{k_1(\theta+\mu_A)} + \frac{\alpha_A a_1(m+n)}{k_1(\theta+\mu_A)} + \frac{c_1 a_1(m+n)}{k_1(\theta+\mu_Z)},\\
F_2(\theta) &= \frac{\theta}{a} + \frac{a_1(m+n)}{a} + \frac{qV^{***}\alpha_A}{a(\theta+\mu_A)} + \frac{\alpha_A a_1(m+n)}{a(\theta+\mu_Z)} + \frac{c_1 a_1(m+n)}{a(\theta+\mu_Z)},\\
F_3(\theta) &= \frac{\theta}{\gamma} + \frac{qA^{***}}{\gamma} + \frac{a_1(m+n)}{\gamma},\\
F_4(\theta) &= \frac{\theta}{\mu_A},\\
F_5(\theta) &= \frac{\theta}{\mu_Z}.
\end{aligned} \tag{4.28}$$

with,

$$R = \begin{pmatrix}
\frac{\eta}{k_1} & 0 & \frac{a_2}{a_1} & 0 & 0\\
\frac{\eta+N_I\delta}{k_1} & N_C & \frac{a_2(m+n)}{\gamma} & 0 & 0\\
\frac{N_I\delta}{\gamma} & \frac{N_C a}{\gamma} & 0 & 0 & 0\\
\frac{\alpha_A}{\mu_A} & \frac{\alpha_a}{\mu_A} & 0 & 0 & 0\\
\frac{c_1}{\mu_Z} & \frac{c_1}{\mu_Z} & 0 & 0 & 0
\end{pmatrix},$$

The above matrix $R(\bar{Z})_i$ for $i = 1, 2, 3, 4, 5$ represents the ith coordinate of the vector $R(\bar{Z})$. It is clear that all entries of the matrix R are positive and $\mathcal{E}_2$ satisfies $\mathcal{E}_2 = M\mathcal{E}_2$. Hence, for

the solution, $\bar{Z}$ of (4.27) there exists a minimal positive real number l

$$|| \bar{\mathbf{Z}} ||\leq l\mathcal{E}_2, \tag{4.29}$$

where, $|| \bar{\mathbf{Z}} ||= (|| Z_1 ||, || Z_2 ||, || Z_3 ||, || Z_4 ||, || Z_5 ||)$ with the lexicographic order. Our aim is to prove $Re(\theta) < 0$. Let us consider $Re(\theta) \geq 0$. There are two cases: $\theta = 0$, $\theta \neq 0$.
If $\theta = 0$ then the linear system (4.27) is homogeneous. The determinant of the system (4.27) evaluated at $\mathcal{E}_2$ is

$$\triangle= a\mu_Z(1-\xi)f_1 + \mu_Z f_2 \{\eta_\xi(\delta+\rho)\} - R < 0. \tag{4.30}$$

where, $f_1 = \mu_A N_I \delta - \alpha_A q V^{***} < 0$, $f_2 = a\mu_A N_C - \alpha_A q V^{***} < 0$ and
$R = \alpha_A \mu_A (1-\sigma) q V^{***} [a(1-\xi) + \eta + \xi\delta + \xi\rho] > 0$.

Since $\triangle< 0$. So the system (4.27) has only the trivial solution $\bar{Z} = \bar{0}$, which is the *VFE*. Next if we consider the case $\theta \neq 0$ then $Re(F_i(\theta)) \geq 0$ $(for i = 1, 2, 3, 4, 5)$. If $F(\theta) = min \mid 1 + F_i(\theta) \mid > 1$; (for $i = 1, 2, 3, 4, 5$), then $F(\theta) > 1$. Hence, $\frac{l}{F(\theta)} < l$. For the minimal positive number, l implies that $|| \bar{Z} ||> \frac{l}{F(\theta)}\mathcal{E}_2$. Taking norms in the fourth equation of (4.28) and also using the positive matrix R,

$$F(\theta) || Z_4 ||\leq R(|| Z ||)_4 \leq l(R || \mathcal{E}_2 ||)_4 \leq lA^{***}. \tag{4.31}$$

Then, from the above inequality $|| Z_4 ||\leq \frac{l}{F(\theta)}A^{***}$, that contradicts our assumption $Re(F_i(\theta)) \geq 0$. Therefore, $Re(\theta) < 0$ and the virus present equilibrium (VPE), $\mathcal{E}_2$, is LAS when $\mathcal{R}_{01}$ is bigger than unity. □

4.10 Model Validitation

There are many statistical techniques for model validation. One of the most popular method is Non Linear Least Square Method. This method demonstrate the least error between the simulated data and the real data.

4.10.1 Non Linear Least Square Method

The least-squares technique is a statistical technique to discover the suitable fit for fixed data records by minimizing the sum of the residuals of points from the plotted curve. Least squares regression is used to expect the conduct of dependent variables.
Here we expect that the time coordinates of the real data are exact, but their corresponding virions data of a patient in the y-coordinate may be deformed. We adjust the solution curve through the real data such that the sum of the squares of the vertical distances from the real data points to the points on the solution curve is the lowest possible. This distance is generally known as the least square error.

4.10.2 Parameter Estimation

Certain parameters are taken directly from the Table 4.1 and remaining parameters $\theta = (\gamma, \beta, \delta, \rho, \eta)$ are estimated from the set of data of a patient's sample obtained from [70] at the acute stage of HBV infection. Using initial guess $\theta_0 = (0.67, 0.001, 0.0494, 0, 0 - 1)$ for the parameters from Table 4.1 and with initial conditions $(H_0, I_0, C_0, V_0, A_0, Z_0) = (13.6 \times 10^6, 0, 0, 0.33, 0, 0)$, we obtained most credible estimated parameters using above method in the following table:

Parameters	Description	Value
γ	The free virus clearance rate	$0.61d^{-1}$ [Estimated]
β	The rate of infectionn	$0.005mm^3d^{-1}$ [Estimated]
δ	short-lived infected cell's death rate	$0.0124d^{-1}$ [Estimated]
ρ	Cured rate of infected hepatocytes	0.4 [Estimated]
η	Progression rate of short lived to chronically infected cell	0.012 [Estimated]

TABLE 4.2: Parameter best estimates of model (4.2)

From Figure 4.4, we can see that the virus and the fitting curve behave exactly as expected for $\mathcal{R}_0 = 1.9962$. Upon initialization of infection, the virus particles increase significantly until it reaches the peak of viral load. It is also clear from the figure that the high viral peak was observed during the patient's acute infection phase. Moreover, the best estimates predict that virus clearance occurs following infection in the patient after 40 days. It is

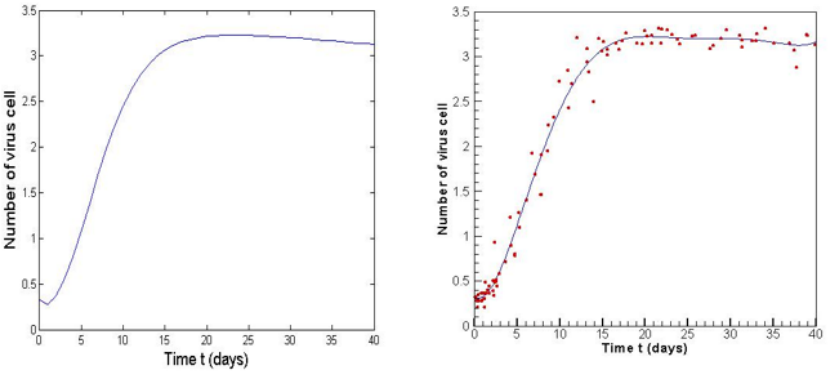

FIGURE 4.4: Figure illustrating (4.4A) solution curve of virus cells with $\mathcal{R}_0 = 1.9962 > 1$ and (4.4B) fitting curve of $V(t)$ as given by the model (solid line) to a patient's data (dot)(Source: [70]).

also predicted from the figure that the virus clearance rate decreases due to developing high antibody levels in the patient for vaccination.

4.11 Numerical Results and Discussions

In this section, using different parameter values given in Table 4.1, we have numerically analysed the model (4.2) with immune system to know the impact of immune system on HBV dynamics *in vivo*. It is mentioned that real data of the parameters are not available so the chosen parameter values for simulation may not be biologically realistic.

4.11.1 Humoral immune system strategy

The model (4.2) is considered only in the presence of humoral immune system only (when the cell-mediated immune system is absent $p = 0$). For numerical simulation we consider different levels of effectiveness of humoral immune system and contact rates.
The following arbitrarily levels of effectiveness are observed:

(i) humoral immune response at low level (i.e. $q = 0.09$);

(ii) humoral immune response at moderate level (i.e. $q = 0.06$);

(iii) humoral immune response at high level (i.e. $q = 0.03$);

When the effective contact rate is decreased from $\beta = 0.5$ to 0.005, the number of short-lived infected cells increases at a slower rate. In all the cases, the number of infected cells increases initially and become constant after some time.
However, when the effective contact rate is $\beta = 0.5$, the number of infected cells increases to a maximum value and becomes constant. On the other hand for $\beta = 0.005$, the number of infected cells slight decreases. In all three cases, the number of infected cells decreases at a slow rate when the humoral immune response shows a high effectiveness rate. (See Figure 4.5)
So from Figure 4.5, it is obvious that a smaller contact rate and a higher response of humoral immune system helps to decrease the infection rate of healthy cells. However, the high effective level of the humoral immune system strategy has a significant role to reduction of HBV burden *in vivo*.

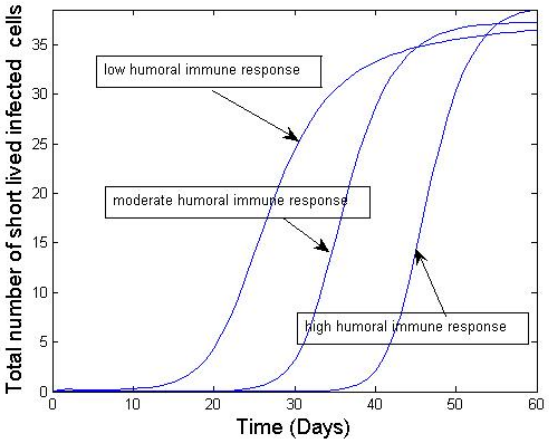

FIGURE 4.5: Plot illustrates the total density of the short lived infected cells with $p = 0$, different humoral immune response ($q = 0.03, 0.06, 0.09$) and $\beta = 0.5, 0.05, 0.005$. Other parameters value are taken from Table 4.1.

4.11.2 Cell-mediated immune system strategy

In this scenario, different level of cell-mediated immune system is considered (i.e. $p = 0.005 = 0.007 = 0.009$). Also, for numerical simulation here we consider different levels of effectiveness of immune response and contact rate.
The following arbitrary effectiveness levels of cell-mediated immune system are considered:

(i) cell-mediated immune response at low level (i.e. $p = 0.005$);

(ii) cell-mediated immune response at moderate level (i.e. $p = 0.007$);

(iii) cell-mediated immune response at high level (i.e. $p = 0.009$);

When the effective contact rate is decreased from $\beta = 0.5$ to 0.005, the number of short-lived infected cells initially increases and after some days gradually decreases to a constant value. However, if the effective contact rate is $\beta = 0.5$ then the number of infected cells increases to a maximum value and becomes constant after some time. On the other hand for $\beta = 0.005$, the number of infected cells behave as in the previous case , but at a slower rate. In all three cases the number of short-lived infected cells increases initially but after some days decreases at a slow rate when the cellular immune system shows a high rate of effectiveness. (See Figure 4.6)

So from Figure 4.6, it is observed that a smaller contact rate and a higher presence rate of cell- mediated immune system helps to decrease the infection rate of cells. Therefore, the high effective level of the cell-mediated immune system strategy also plays a significant role to reduce the HBV burden *in vivo*.

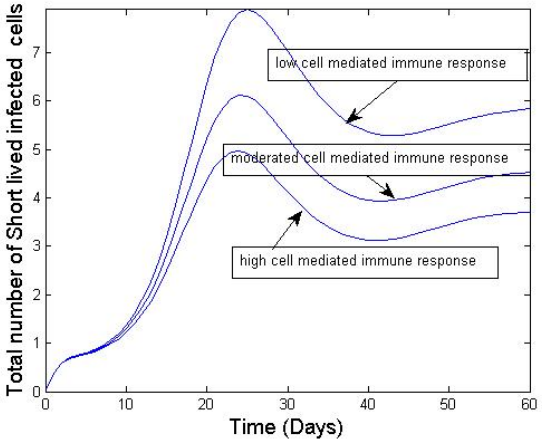

FIGURE 4.6: Plot illustrates the total density of the short lived infected cells with $q = 0$, different cell-mediated immune response (i.e. $p = 0.005, 0.007, 0.009$) and $\beta = 0.5, 0.05, 0.005$. Other parameters value are taken from Table 4.1.

Figure 4.7 show that the absence of cell-mediated immune response and effective level of humoral immune response with a high level of contact rate brings the number of short-lived infected cells to a constant rate quickly. Again, when only the cell-mediated response

is effective with a high level of contact rate then the number of short-lived infected cells increases unboundedly. Moreover, a similar scenario is seen in Figure 4.8 that without immune response the number of infected cells increases gradually than with immune response. Moreover, the rate of contact and both the immune response will lessen HBV infection *in vivo* if they are comparatively low and high respectively.

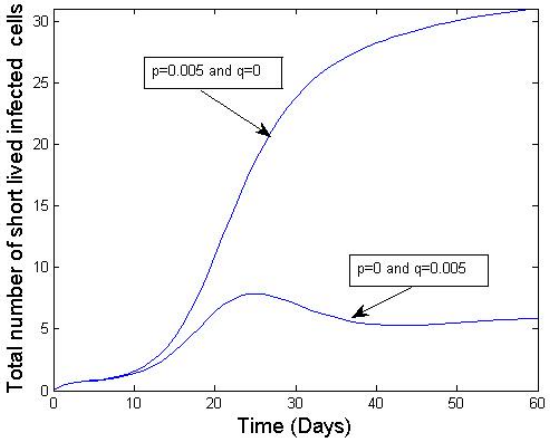

FIGURE 4.7: Plot illustrates the total density of the short lived infected cells with $\beta = 0.5$ and $\mathcal{R}_0 > 1$. Model simulation considering only humoral immune response ($p = 0$ and $q = 0.005$) and only cell-mediated immune response ($p = 0.005$ and $q = 0$). Other parameters value are taken from Table 4.1.

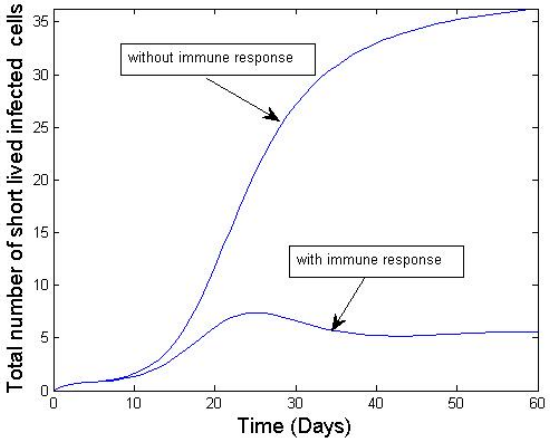

FIGURE 4.8: Plot illustrates the total density of the short lived infected epithelial cells without and with immune response(i.e.$p = q = 0$ and $p = q = 0.005$) with high contact rate $\beta = 0.5$ and $\mathcal{R}_0 > 1$. Other parameters value are taken from Table 4.1.

4.12 Summary of Contributions

A new basic (without immune response) deterministic model for the transmission disease dynamics of HBV *in vivo* is constructed and numerically analysed. The basic model is extended for cell-mediated and humoral immunity systems against HBV *in vivo*. The major findings are itemized below:

Mathematical Aspect:

(i) If $\mathcal{R}_0 < 1$ then the reduced model (4.3) has a globally asymptotically stable VFE ;

(ii) The reduced model (4.3) has at least one locally asymptotically stable VPE, $\mathcal{E}_1$, whenever $\mathcal{R}_0 > 1$. In this situation the infection persist *in vivo*);

(iii) The extended model incorporating immune system (4.2) has a GAS VFE when $\mathcal{R}_{01} < 1$;

(iv) The extended model with immune system (4.2) has also at least one VPE, $\mathcal{E}_2$, for $\mathcal{R}_{01} > 1$, which is also locally asypmtotically stable (and the infection will persist *in vivo* under this situation;

(v) An HBV vaccine is fully effective for reducing disease burden *in vivo* when it increases the rate of humoral immune response such as antibody level against HBV infection.

Epidemiological Importance:

(i) The humoral immune response with high effective level has a positive impact with low contact rate in reducing HBV burden *in vivo*;

(ii) Due to vaccine impact, the humoral immune strategy is more effective than the cell-mediated immune strategy for controlling HBV burden;

(iii) The high effective level of both immune system strategies provides the greatest reduction of HBV burden *in vivo*;

(iv) The low contact rate can also reduce the life threat of HBV *in vivo*.

Chapter 5

Optimal Control of Vaccination and Awareness in Hepatitis B Virus (HBV) Infection

5.1 Introduction

Hepatitis B infection is a life long liver disease. The disease has two stages namely the acute phase and the chronic phase. Persistent liver inflammation can put a human's life at excessive risk of death from liver cirrhosis or liver cancer.[4]. The virus enters the body through the contaminated blood or body fluid of an infected person and reaches the liver through the bloodstream, where it replicates itself, releasing a large number of new viruses into the bloodstream. Most infectious diseases can be controlled reasonably within the community if some precautions such as vaccination, treatment, awareness and educational campaign etc. are taken in a timely manner. However, many of these infectious diseases become endemic in our society due to the lack of such effective measures and timely taken steps. So, it is important to identify the causes of epidemic and effective mechanisms to control the transmission of the infection.

Mathematical modelling technique plays an important role for analyzing the spread and control of infectious diseases. Mathematical models have been used for planning, comparing, optimizing various detection for implementation, prevention, therapy, in order

to minimize costs for control measures and control programs [73]. Mathematical modelling has contributed to the analysis of epidemiological surveys, suggested crucial data that should be collected, identified trends, made general forecasts, and estimated the uncertainty in forecasts [41]. The theory and application of Pontryagin's Maximum Principle [43] may apply to measure the optimal controls in dynamics of hepatitis B virus infection mathematically. Treatment is not needed for acute hepatitis B infection and most of the acutely infected adults can recover thanks to their own immune response [23]. Less than 1% patients who are immuno compromised need antiviral treatment at the chronic stage of infection. However, this treatment is essential to reduce the risk of liver cirrhosis and cancer.

Mathematical models can help us to optimize the use of limited resources or simply to target control measures more efficiently. Anderson *et al.* [74] constructed a simple mathematical model to describe the effects of carriers on the transmission of HBV. Medley *et al.* [25] developed a Hepatitis B virus mathematical model to establish a strategy for eliminating HBV in New Zealand [27, 75]. Wang *et al.* [31] presented and analyzed a diffusion model of hepatitis B virus infection. Xu and Ma [76] proposed a HBV model with spatial diffusion and saturation response of the infection rate was investigated. Zou *et al.* [28] also used a mathematical model to understand the transmission dynamics and prevalence of HBV in China. In [30], Pang *et al.* constructed a model to find out the vaccine impact of HBV infection.

In our study, we have applied the technique of optimal control to determine the vaccination impacts and awareness among the population for the eradication of the disease.

5.2 Optimal Control Method

The state variable $x(t)$ which depends on the control variable $u(t)$ and satisfies a differential equation such as:

$$x^{'}(t) = g(t, x(t), u(t)).$$

Here, $x^{'}$ denotes the derivative with respect to time t. We consider $u(t)$ as a piecewise continuous function and the given objective functional is maximised or minimized by the

state variable, $x(t)$. We assume the following:

$$\begin{aligned} Maximize\, J(u) &= \int_0^T f(t, x(t), u(t))dt \\ \text{subject to } \; x^{'}(t) &= g(t, x(t), u(t)) \\ x(0) &= x_0 \text{ and } \; x(T) \text{ free.} \end{aligned} \tag{5.1}$$

The main objective of the optimal control problem is to solve a set of necessary conditions that $x(t)$ and $u(t)$ must satisfy. Pontryagin's Maximum Principle provides necessary conditions for the optimal control using the Hamiltonian [24].

5.3 Formulation of Model

The total population, $N(t)$ is divided into sub compartments of homogeneously mixing individuals who are unvaccinated susceptible $(S(t))$, vaccinated $V(t))$, acutely infected individuals $(A(t))$, asymptomatic chronic carriers $(C_n(t))$, symptomatic chronic carriers $(C_s(t))$, individuals with disease complications $(D_c(t))$and recovered individuals $(R(t))$, so that

$$N(t) = S(t) + V(t) + A(t) + C_n(t) + C_s(t) + D_c(t) + R(t)$$

The population of unvaccinated susceptible individuals is increased at a rate $\Pi(1-p)$ into the community, where, Π is the birth rate and p is the proportion of newborns vaccinated. It is also increased due to waning of the vaccine (at a rate ω) in the vaccinated individuals. This class is decreased by the administration of vaccine dose (at a rate ψ), natural death (which is assumed to occur in all compartments at a rate μ) and by the acquisition of infection at a rate λ, where, β means the probability of infection acquisition per contact, while λ is the rate of infection, and is given by

$$\lambda = \beta(A + \eta_n C_n + \eta_s C_s + \eta_c D_c). \tag{5.2}$$

Here η_n, η_s, η_c are the modification parameters which account for differences in transmission rates from the infected individuals with respect to the acutely infected individuals. Since the infectiousness of symptomatic chronic carriers is higher relative to that of asymptomatic chronic carriers, we assume that $\eta_s > \eta_n$. Similarly, we consider that the individuals with

disease complications are more infectious than the acutely infected individuals, so that, $\eta_c > 1$. The population of vaccinated individuals, V, increases with the vaccination rate ψ and decreases due to infection acquisition (at a reduced rate $r\lambda$, where, $0 < r < 1$ is the vaccine efficacy), vaccine waning (at the rate ω) and by natural death.

f is a fraction of the newly infected individuals to show no disease symptoms initially. The other fraction $(1-f)$, of the newly infected individuals who are assumed to display immediate disease symptoms. The population of acutely infected individuals is generated at the rate λ (for unvaccinated susceptible individuals) and $r\lambda$ (for the vaccine dose recipients). This class of population is decreased by progression to the chronic carriers (at a rate ϕ) and by natural death.

The chronic carrier with no clinical disease symptoms is increased by transferred fraction f of individuals from $A(t)$ and reduced by recovery (at the rate γ) and the progression to the symptomatic chronic carriers (at the rate ξ) and natural death (at the rate μ). Similarly, the chronic carrier with symptoms is increased by transferred individuals from $A(t)$ and $C_n(t)$ and decreased by recovery rate due to effective treatment (at the rate θ_t) where, $\theta_t > 1$ and progression to disease complications (at the rate ν), natural death (at the rate μ) and disease induced death (at the rate δ).The individuals of complicated disease symptoms is increased by the transferred individuals from $C_s(t)$ at the rate ν and decreased by natural death rate, μ and disease related death rate, δ. The population of recovered individuals, $R(t)$ is generated by the recovered asymptomatic and symptomatic chronic carriers (at the rate γ) and the population is decreased by natural death (at the rate μ), (it is assumed that recovered individuals do not lose their immunity and become susceptible to HBV infection). We assume two control variables, u_1 and u_2. The two control strategies are : (i) cost of vaccination and (ii) cost of awareness. Generally, it is evident that the vaccines are not 100% effective, so only a portion of vaccinated individuals are protected by the vaccine and individuals in this class can be infected by the contact with infected individuals and move to the infectious classes. The control function $u_1(t)$, with $0 \leq u_1(t) \leq 1$ represents the proportion of susceptible individuals that requires vaccination. When $u_1(t)$ is close to 1, the failure rate of vaccination is very low but then the implementation costs are high. Similarly, $u_2(t)$ is the proportion of susceptible that is aware of the transmission probability of HBV per unit time.

After applying control strategy, the differential equations of the HBV model are given below:

$$\begin{aligned}
\frac{dS}{dt} &= \Pi(1-p) + \omega V - \lambda S - \psi S - \mu S - u_1 S - u_2 S \\
\frac{dV}{dt} &= \Pi p + \psi S - r\lambda V - \omega V - \mu V + u_1 S \\
\frac{dA}{dt} &= \lambda S + r\lambda V - \phi A - \mu A \\
\frac{dC_n}{dt} &= \phi f A - \gamma C_n - \xi C_n - \mu C_n \\
\frac{dC_s}{dt} &= \phi(1-f)A + \xi C_n - \theta_t \gamma C_s - \nu C_s - \mu C_s - \delta C_s \\
\frac{dD_c}{dt} &= \nu C_s - \mu D_c - \delta D_c \\
\frac{dR}{dt} &= \gamma C_n + \theta_t \gamma C_s - \mu R + u_2 S
\end{aligned} \tag{5.3}$$

with initial conditions,

$$\begin{aligned}
&S(0) = S_0 \geq 0,\ V(0) = V_0 \geq 0,\ A(0) = A_0 \geq 0,\ C_n(0) = C_{n_0} \geq 0,\ C_s(0) = C_{s_0} \geq 0, \\
&D_c(0) = D_{c_0} \geq 0,\ \textit{and}\ R(0) = R_0 \geq 0.
\end{aligned} \tag{5.4}$$

We consider the following objective function [78]:

$$Minimize\ J(u_1(t), u_2(t)) = \int_0^T a_0 A(t) + a_1 C_n(t) + a_2 C_s(t) + a_3 D_c(t) + \frac{1}{2}(B_1 {u_1}^2 + B_2 {u_2}^2) dt$$

where, $a_0, a_1, a_2, a_3, b_1, b_2 > 0$. We want to minimize the infected individuals $(A(t), C_n(t), C_s(t), D_c(t))$ by keeping the cost of vaccination$(u_1(t))$ and cost of awareness$(u_2(t))$ low. The terms $a_0 A(t), a_1 C_n(t), a_2 C_s(t), a_3 D_c(t)$ represents the infected individuals with the positive weight parameters, while the terms $\frac{b_1 u_1^2(t)}{2}$ and $\frac{b_2 u_2^2(t)}{2}$ represents the cost of vaccination and awareness at the time t.

The aim of our study is to find out the optimal controls, u_1^* and u_2^*, such that

$$J(u_1^*, u_2^*) = \min_{u_1, u_2 \in U} J(u_1, u_2) \tag{5.5}$$

where, $U = \{(u_1(t), u_2(t)) : 0 \leq u_1(t) \leq 1\ , 0 \leq u_2(t) \leq 1,\ t \in [0, T]\}$

5.4 Equilibria of the System

The disease free equilibrium point (DFE) of the model is

$$\varepsilon_0^* = (S^*, V^*, A^*, C_n^*, C_s^*, D_c^*, R^*) = (S^*, V^*, 0, 0, 0, 0, R^*) \tag{5.6}$$

with, $S^* = \dfrac{\Pi(p\omega + k_3(1-p))}{k_1k_3 - \omega k_2}$, $V^* = \dfrac{\Pi(k_2(1-p) + k_1p)}{k_1k_3 - \omega k_2}$ and $R^* = \dfrac{\Pi u_2(\omega p + k_3(1-p))}{\mu(k_1k_3 - \omega k_2)}$ where, $k_1 = \psi + \mu + u_1 + u_2$, $k_2 = \psi + u_1$,$k_3 = \omega + \mu$,$k_4 = \phi + \mu$, $k_5 = \gamma + \xi + \mu$, $k_6 = \theta_t\gamma + \mu + \delta$, $k_7 = \mu + \delta$ and $k_1k_3 - \omega k_2 > 0$. Considering the new infection terms from the model equations, the matrix P and the non-singular matrix Q are respectively as

$$P = \begin{bmatrix} \beta(S^* + rV^*) & \beta\eta_n(S^* + rV^*) & \beta\eta_s(S^* + rV^*) & \beta\eta_c(S^* + rV^*) \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix},$$

$$Q = \begin{bmatrix} k_4 & 0 & 0 & 0 \\ -\phi f & k_5 & 0 & 0 \\ -\phi(1-f) & -\xi & k_6 & 0 \\ 0 & 0 & -\nu & k_7 \end{bmatrix},$$

The associated reproduction threshold is given by $\mathcal{R}_0 = \rho PQ^{-1})$,
where,

$$\mathcal{R}_0 = \frac{\beta(S^* + rV^*)\{(1-f)(\nu\phi\eta_c k_5 + \phi\eta_s k_5 k_7)(f\nu\phi\xi\eta_c + f\phi\xi\eta_s k_7 + f\phi\eta_n k_6 k_7 + k_5 k_6 k_7)\}}{k_4 k_5 k_6 k_7}$$

Hence, we have the following lemma [49].

Lemma 5.1. *If $\mathcal{R}_0 < 1$ then the disease free equilibrium point (DFE) of the model (5.3) is locally asymptotically stable (LAS) and otherwise unstable (i.e. if $\mathcal{R}_0 > 1$).*

5.5 Existence of the Optimal Control

5.5.1 Existence of the State

Here we consider the following control system:

$$\min J(u_1, u_2) = \int_0^T \{a_0 A(t) + a_1 C_n(t) + a_2 C_s(t) + a_3 D_c(t) + \frac{1}{2}(b_1 {u_1}^2 + b_2 {u_2}^2)\} dt$$

$$\begin{aligned}
\frac{dS}{dt} &= \Pi(1-p) + \omega V(t) - (\lambda + \psi + \mu + u_1 + u_2) S(t) \\
\frac{dV}{dt} &= \Pi p + (\psi + u_1) S(t) - (r\lambda + \omega + \mu) V(t) \\
\frac{dA}{dt} &= \lambda S(t) + r\lambda V(t) - (\phi + \mu) A(t) \\
\frac{dC_n}{dt} &= \phi f A(t) - (\gamma + \xi + \mu) C_n(t) \\
\frac{dC_s}{dt} &= \phi(1-f) A(t) + \xi C_n(t) - (\theta_t \gamma + \nu + \mu + \delta) C_s(t) \\
\frac{dD_c}{dt} &= \nu C_s(t) - (\mu + \delta) D_c(t) \\
\frac{dR}{dt} &= \gamma C_n(t) + \theta_t \gamma C_s(t) - \mu R(t) + u_2 S(t)
\end{aligned} \tag{5.7}$$

with initial conditions,

$$S(0) = S_0 \geq 0,\ V(0) = V_0 \geq 0,\ A(0) = A_0 \geq 0,\ C_n(0) = C_{n0} \geq 0,\ C_s(0) = C_{s0} \geq 0,$$
$$D_c(0) = D_{c0} \geq 0,\ \textit{and}\ R(0) = R_0 \geq 0.$$

Theorem 5.1. Given initial conditions are $S(0) = S_0 \geq 0,\ V(0) = V_0 \geq 0,\ A(0) = A_0 \geq 0,\ R(0) = R_0 \geq 0,$ and the solutions $(S(t), V(t), A(t), C_n(t), C_s(t), D_c(t), R(t))$ are positively invariant $\forall\ t > 0$.

Let $Z = Sup(t > 0 \mid S > 0, V > 0, A > 0, C_n > 0, C_s > 0, D_c > 0, R > 0)$
for the first equation,

$$\frac{dS}{dt} = \Pi(1-p) + \omega V - \lambda S - \psi S - \mu S - u_1 S - u_2 S$$

From the above equation we have,

$$\frac{ds}{dt} + (\lambda + \psi + \mu + u_1 + u_2)S \geq \Pi(1-p) + \omega V$$

The integrating factor is,

$$exp(\lambda + \psi + \mu + u_1 + u_2)t$$

Multiplying the above expression by the integrating factor we have

$$\frac{dS}{dt}\left(exp(\lambda + \psi + \mu + u_1 + u_2)t\right) \geq \left(\Pi(1-p) + \omega V\right) exp(\lambda + \psi + \mu + u_1 + u_2)t$$

Solving this inequality,we obtain

$$S(t) \times exp(\lambda+\psi+\mu+u_1+u_2)t - S(0) \geq \int_0^T (\Pi(1-p) + \omega V) \times exp(\lambda+\psi+\mu+u_1+u_2)tdt$$

Therefore, $S(t)$ becomes

$$\begin{aligned} S(t) \geq S(0) \times exp\left(-(\lambda + \psi + \mu + u_1 + u_2)t\right) + exp\left(-(\lambda + \psi + \mu + u_1 + u_2)t\right) \\ \times \int_0^T (\Pi(1-p) + \omega V) \times exp(\lambda + \psi + \mu + u_1 + u_2)tdt > 0. \end{aligned}$$

Similarly, it can be shown for the other states that they all are positive respectively.

5.5.2 Boundedness of the solution of the model

Theorem 5.2. All solutions $(S(t), V(t), A(t), C_n(t), C_s(t), D_c(t), R(t)$ of the model are bounded.

Proof. The model refers that the total population $N(t) = S(t) + V(t) + A(t) + C_n(t) + C_s(t) + D_c(t) + R(t)$. Adding all the states we have $S^{'} + V^{'} + A^{'} + C_n^{'} + C_s^{'} + D_c^{'} + R^{'} = \Pi - \mu(S + V + A + C_n + C_s + D_c + R) - \delta(C_s + D_c)$

implies

$$S^{'} + V^{'} + A^{'} + C_n^{'} + C_s^{'} + D_c^{'} + R^{'} \leq \Pi - \mu(S + V + A + C_n + C_s + D_c + R)$$

and so

$$\frac{dN(t)}{dt} \leq \Pi - \mu N(t)$$

Then we have,

$$N(t) \leq \frac{\Pi}{\mu} + N(0)e^{-t}; t \in [0, T]$$

Thus it follows from above that as $t \to \infty$, then $N(t) \leq \frac{\Pi}{\mu}$. Therefore all the solutions of the model are bounded.

Hence all the feasible solutions enter into the region $U = ((S, V, A, C_n, C_s, D_c, R) \in R_+^7 : N \leq \frac{\Pi}{\mu}, as \ \ t \to \infty)$. □

5.5.3 Existence of the objective Functional

To prove the existence of the optimal control technique we have to reveal the existence of the objective functional which is obtained by using a result of Fleming and Rishel in [44].

Theorem 5.3. Cosider the control problem with system (5.5). Then there exists optimal controls (u_1^*, u_2^*) that minimize $J(u_1, u_2)$ over the control set U. i.e.,

$$J(u_1^*, u_2^*) = \min_{u_1, u_2 \in U} J(u_1, u_2) \tag{5.8}$$

To use an existence result in [44], we must follow the following properties from [77].

1. The set of controls and state variables is nonempty.
2. The control set U is convex and closed.
3. The right side of the state system is bounded by a linear function in the state and control variables.
4. The integrand of the objective functional is convex on U and is bounded below by $-k_2 + k_1 |\ (u_1, u_2)\ |^{\eta}$ with $k_1 > 0$, $k_2 > 0$ and $\eta > 1$.

Proof of (i): Consider

$$\frac{dS}{dt} = F_1(t, S, V, A, C_n, C_s, D_c, R)$$

$$\frac{dV}{dt} = F_2(t, S, V, A, C_n, C_s, D_c, R)$$

$$\frac{dA}{dt} = F_3(t, S, V, A, C_n, C_s, D_c, R)$$

$$\frac{dC_n}{dt} = F_4(t, S, V, A, C_n, C_s, D_c, R)$$

$$\frac{dC_s}{dt} = F_5(t, S, V, A, C_n, C_s, D_c, R)$$

$$\frac{dD_c}{dt} = F_6(t, S, V, A, C_n, C_s, D_c, R)$$

$$\frac{dR}{dt} = F_7(t, S, V, A, C_n, C_s, D_c, R)$$

where, F_1, F_2, F_3 ,F_4 , F_5 , F_6 and F_7 are expressed the right side of the model equation. Let $u_1(t) = C_1$ and $u_2(t) = C_2$ where C_1 and C_2 are constants. F_1, F_2, F_3 ,F_4 ,F_5, F_6 and F_7 are linear and continuous everywhere. Moreover, the partial derivatives of F_i, (for $i = 1, 2, \ldots, 7$) with respect to the states are constants and continuous everywhere.

So by using the theorem 5.4, we can say that a unique solution exists of the form $S = \sigma_1(t)$, $V = \sigma_2(t)$, $A = \sigma_3(t)$, $C_n = \sigma_4(t)$, $C_s = \sigma_5(t)$, $D_c = \sigma_6(t)$, $R = \sigma_7(t)$ satisfies the initial conditions. Hence, the set of control parameters and associated state variables is non-empty. therefore condition (i) is satisfied.

Proof of (ii): Let U is closed. Take any controls $u_1, u_2 \in U$, $\theta \in [0, 1]$ and observed that $\theta u_1 \leq \theta$, $(1 - \theta)u_2 \leq (1 - \theta)$. Then

$$\theta u_1 + (1 - \theta)u_2 \leq \theta + (1 - \theta) = 1.$$

Hence, $0 \leq \theta u_1 + (1 - \theta)u_2 \leq 1$ for all $u_1, u_2 \in U$ and $\theta \in [0, 1]$. Therefore, U is convex, and condition (ii) of the Theorem 5.4 is satisfied.

Proof of (iii):

Let us consider,

$$F_1 \leq \omega V - u_1 S - u_2 S$$

$$F_2 \leq \psi S + u_1 S$$

$$F_3 \leq \phi A$$

$$F_4 \leq \phi f A$$

$$F_5 \leq \phi(1-f)A + \xi C_n$$

$$F_6 \leq \nu C_s$$

$$F_7 \leq \gamma C_n + \theta_t \gamma C_s + u_2 S$$

The state system is given below:

$$\frac{dS}{dt} = F_1(t, S, V, A, C_n, C_s, D_c, R)$$

$$\frac{dV}{dt} = F_2(t, S, V, A, C_n, C_s, D_c, R)$$

$$\frac{dA}{dt} = F_3(t, S, V, A, C_n, C_s, D_c, R)$$

$$\frac{dC_n}{dt} = F_4(t, S, V, A, C_n, C_s, D_c, R)$$

$$\frac{dC_s}{dt} = F_5(t, S, V, A, C_n, C_s, D_c, R)$$

$$\frac{dD_c}{dt} = F_6(t, S, V, A, C_n, C_s, D_c, R)$$

$$\frac{dR}{dt} = F_7(t, S, V, A, C_n, C_s, D_c, R)$$

we can rewrite the system in matrix form:

$$\bar{F}(t, \bar{X}, u_1, u_2) \leq \bar{m}\left(t, \begin{bmatrix} S \\ V \\ A \\ C_n \\ C_s \\ D_c \\ R \end{bmatrix}\right)\bar{X}(t) + \bar{n}\left(t, \begin{bmatrix} S \\ V \\ A \\ C_n \\ C_s \\ D_c \\ R \end{bmatrix}\right)\begin{pmatrix} u_1(t) \\ u_2(t) \end{pmatrix} \tag{5.9}$$

where,

$$\bar{m}\left(t,\begin{bmatrix} S \\ V \\ A \\ C_n \\ C_s \\ D_c \\ R \end{bmatrix}\right) = \begin{bmatrix} 0 & \omega & 0 & 0 & 0 & 0 & 0 \\ \psi & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \phi & 0 & 0 & 0 & 0 \\ 0 & 0 & \phi f & 0 & 0 & 0 & 0 \\ 0 & 0 & \phi(1-f) & \xi & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \nu & 0 & 0 \\ 0 & 0 & 0 & \gamma & \theta_t\gamma & 0 & 0 \end{bmatrix} \tag{5.10}$$

and

$$\bar{n}\left(t,\begin{bmatrix} S \\ V \\ A \\ C_n \\ C_s \\ D_c \\ R \end{bmatrix}\right) = \begin{bmatrix} -(S+S) \\ +S \\ 0 \\ 0 \\ 0 \\ 0 \\ +S \end{bmatrix} \tag{5.11}$$

which gives us a linear function of the controls u_1 and u_2 with coefficients determined by time and state variables. So we can write,

$$\mid \bar{F}(t,\bar{X},u_1,u_2) \mid \leq \Big| \mid \bar{m} \mid \Big| \mid \bar{X} \mid + \mid \bar{S} \mid \mid (u_1(t),u_2(t)) \mid$$

$$\leq p\Big(\mid \bar{X} \mid + \mid (u_1(t),u_2(t)) \mid \Big)$$

where, $\bar{S}$ is bounded above and p is upper bound of the above constant matrix. Hence, the right side of the system is bounded by a sum of controls and the state variables. Therefore, condition (iii) is also satisfied.

Proof of (iv):

To proof the condition (iv) of the Theorem 5.4 we use the result of [44]. It is clear that the state variables and controls are positive and non-empty. For the minimization problem, the convexity of the objective functional in U is satisfied and the control variables u_1,$u_2 \in U$ are convex and closed.

Now we want to prove $J(u_1, u_2) \geq -k_2 + k_1 |\ (u_1, u_2)\ |^{\eta}$ with $k_1 > 0$, $k_2 > 0$ and $\eta > 1$.
Here,

$$J(u_1, u_2) = \int_0^T \left(a_0 A(t) + a_1 C_n(t) + a_2 C_s(t) + a_3 D_c(t) + b_1 \frac{u_1^2}{2} + b_2 \frac{u_2^2}{2} \right) dt$$

To verify the convexity of the integrand of the objective functional, J, we need to reveal that

$$J(t, X, (1-\epsilon)u + \epsilon v) \geq (1-\epsilon) J(t, X, u) + \epsilon J(t, X, v)$$

for arbitrarily small ϵ such that $0 < \epsilon < 1$ and

$$J(t, X, u) = a_0 A(t) + a_1 C_n(t) + a_2 C_s(t) + a_3 D_c(t) + b_1 \frac{u_1^2}{2} + b_2 \frac{u_2^2}{2}$$

Now,

$$\begin{aligned}
&a_0 A + a_1 C_n + a_2 C_s + a_3 D_c + \frac{b_1}{2}((1-\epsilon)u_1 + \epsilon v_1)^2 + \frac{b_2}{2}((1-\epsilon)u_2 + \epsilon v_2)^2 \\
&- (1-\epsilon)\left[a_0 A + a_1 C_n + a_2 C_s + a_3 D_c + \frac{b_1}{2} u_1^2 + \frac{b_2}{2} u_2^2 \right] \\
&- \epsilon \left[a_0 A + a_1 C_n + a_2 C_s + a_3 D_c + \frac{b_1}{2} v_1^2 + \frac{b_2}{2} v_2^2 \right] \\
&= \frac{b_1}{2}\left[((1-\epsilon)u_1 + \epsilon v_1)^2 - (1-\epsilon)u_1^2 - \epsilon v_1^2 \right] + \frac{b_2}{2}\left[((1-\epsilon)u_2 + \epsilon v21)^2 - (1-\epsilon)u_2^2 - \epsilon v_2^2 \right] \\
&= -\frac{b_1}{2}\left[(1-\epsilon)u_1^2 + \epsilon v_1^2 - ((1-\epsilon)u_1 + \epsilon v_1)^2 \right] - \frac{b_2}{2}\left[(1-\epsilon)u_2^2 + \epsilon v_2^2 - ((1-\epsilon)u_2 + \epsilon v_2)^2 \right] \\
&= \frac{b_1}{2}(\sqrt{\epsilon(1-\epsilon)}u_1 - \sqrt{\epsilon(1-\epsilon)v_1})^2 - \frac{b_2}{2}(\sqrt{\epsilon(1-\epsilon)}u_2 - \sqrt{\epsilon(1-\epsilon)v_2})^2 \\
&= -\frac{b_1}{2}\epsilon(1-\epsilon)(u_1 - v_1)^2 - \frac{b_2}{2}\epsilon(1-\epsilon)(u_2 - v_2)^2 \leqslant 0 \\
&\Rightarrow -\left(\frac{b_1}{2}\epsilon(1-\epsilon)(u_1 - v_1)^2 + \frac{b_2}{2}\epsilon(1-\epsilon)(u_2 - v_2)^2 \right) \leqslant 0 \\
&\Rightarrow \frac{b_1}{2}\epsilon(1-\epsilon)(u_1 - v_1)^2 + \frac{b_2}{2}\epsilon(1-\epsilon)(u_2 - v_2)^2 \geqslant 0
\end{aligned}$$

Since b_1 and b_2 both are positive, $J(t, X, u)$ is convex.
We need to show that

$$J(u_1, u_2) \geqslant -k_1 + k_2 |(u_1, u_2)|^{\eta}$$

where, $k_1, k_2 > 0$ and $\eta > 1$. Now

$$
\begin{aligned}
&J(u_1,u_2) = a_0A + a_1C_n + a_2C_s + a_3D_c + \frac{b_1}{2}u_1^2 + \frac{b_2}{2}u_2^2\\
&\Rightarrow J(u_1,u_2) \geqslant -\left(a_0A + a_1C_n + a_2C_s + a_3D_c + \frac{b_1}{2}u_1^2 + \frac{b_2}{2}u_2^2\right)\\
&J(u_1,u_2) \geqslant -\left(a_0A + a_1C_n + a_2C_s + a_3D_c\right) - \left(\frac{b_1}{2}u_1^2 + \frac{b_2}{2}u_2^2\right)\\
&\Rightarrow J(u_1,u_2) \geqslant -\left(a_0A + a_1C_n + a_2C_s + a_3D_c\right) + \frac{b_1+b_2}{2}|-(u_1,u_2)|^2\\
&\Rightarrow J(u_1,u_2) \geqslant -\left(a_0A + a_1C_n + a_2C_s + a_3D_c\right) + \frac{B}{2}|(u_1,u_2)|^2
\end{aligned}
$$

where, $k_2 = b_1 + b_2 = B > 0$ that is constant and depends on upper bounds of the infected classes and $\eta = 2 > 1,\ k_1 > 0$. Hence, condition (iv) is satisfied. Therefore, the existence of the objective functional is established.

Theorem 5.4. Let $x_i = F_i(t, x_1, \ldots, x_n)$ for $i \in [1, n]$ is a $n - th$ order differential equation with initial conditions $x_i(t_0) = x_{i0}$ for $i \in [1, n]$. If $F_1, \ldots, F_n$ and their partial derivatives $\frac{\partial F_1}{\partial x_1}, \ldots \frac{\partial F_1}{\partial x_n}, \ldots, \frac{\partial F_n}{\partial x_1}, \ldots, \frac{\partial F_n}{\partial x_n}$ are continuous in $\mathcal{R}^{n+1}$, then $\exists$ a unique solution of the form $x_1 = \sigma_1(t), \ldots, x_n = \sigma_n(t)$, satisfies the given initial conditions.

5.5.4 Characterization of the Optimal Cotrol

The following Hamiltonian is derived by using Pontraygin's Maximum principle [43]

$$
\begin{aligned}
H = {} & a_0A + a_1C_n + a_2C_s + a_3D_c + b_1\frac{u_1^2}{2} + b_2\frac{u_2^2}{2} + \lambda_s[\Pi(1-p) + \omega V - \lambda S - (\psi + \mu +\\
& u_1 + u_2)S] + \lambda_V[\Pi p + (\psi + u_1)S - (r\lambda + \omega + \mu)V] + \lambda_A[\lambda S + r\lambda V - (\phi + \mu)A)\\
& + \lambda_{C_n}(\phi f A - (\gamma + \xi + \mu)C_n] + \lambda_{C_s}[\phi(1-f)A + \xi C_s - (\theta_t\gamma + \nu + \mu\\
& + \delta)C_s] + \lambda_{D_c}[\nu C_s - (\mu + \delta)D_c] + \lambda_R[\gamma C_n + \theta_t\gamma C_s + u_2 S - \mu R]
\end{aligned}
$$

Where, λ_S, λ_V, λ_A , λ_{C_n}, λ_{C_s}, λ_{D_c} and λ_R are the associated adjoints for the respective states. The adjoints are obtained by differentiating the Hamiltonian H with respect to the

respective state variables. Therefore, the given adjoint system is,

$$\begin{aligned}
\lambda_S^{'} &= (\lambda + \psi + \mu + u + 1 + u_2)\lambda_S - (\psi + u_1)\lambda_V - \lambda\lambda_A - u_2\lambda_R \\
\lambda_V^{'} &= -\omega\lambda_S + (r\lambda + \omega + \mu)\lambda_V - r\lambda\lambda_A \\
\lambda_A^{'} &= -a_0 + \beta S\lambda_S + r\beta V\lambda_V - \beta S\lambda_A - r\beta V\lambda_A + (\phi + \mu)\lambda_A - \phi f\lambda_{C_n} - \phi(1-f)\lambda_{C_s} \\
\lambda_{C_n}^{'} &= -a_1 + \beta\eta_n S\lambda_S + r\beta\eta_n V\lambda_V - \beta\eta_n S\lambda_A - r\beta\eta_n V\lambda_A + (\gamma + \xi + \mu)\lambda_{C_n} - \xi\lambda_{C_s} - \gamma\lambda_R \\
\lambda_{C_s}^{'} &= -a_2 + \beta\eta_s S\lambda_S + r\beta\eta_s V\lambda_V - \beta\eta_s S\lambda_A - r\beta\eta_s V\lambda_A + (\theta_t\gamma + \nu + \mu + \delta)\lambda_{C_s} - \nu\lambda_{D_c} - \theta_t\gamma\lambda_R \\
\lambda_{D_c}^{'} &= -a_3 + \beta\eta_c S\lambda_S + r\beta\eta_c V\lambda_V - \beta\eta_c S\lambda_A - r\beta\eta_c V\lambda_A + (\mu + \delta)\lambda_{D_c} \\
\lambda_R^{'} &= \mu\lambda_R
\end{aligned} \tag{5.12}$$

and the transversality conditions,
$\lambda_i(T) = 0, i = 1, 2, 3, \cdots, 7$ and $\lambda = \beta(A + \eta_n C_n + \eta_s C_s + \eta_c D_c)$

For the control u_1 we have from, $\frac{\partial H}{\partial u_1}|_{u_1 = u_1^*} = 0$
$\implies b_1 u_1^* - S\lambda_S + S\lambda_V = 0$
$\implies u_1^* = \frac{S(\lambda_S - \lambda_V}{b_1}$
Again, for the control u_2 we have from,
$\frac{\partial H}{\partial u_2}|_{u_2 = u_2^*} = 0$
$\implies b_2 u_2^* - S\lambda_S + S\lambda_R = 0$
$\implies u_2^* = \frac{S(\lambda_S - \lambda_R)}{b_2}$
Thus the controls u_1^* and u_2^* satisfies the following optimality conditions

$$\begin{aligned}
u_1^* &= min\left(max\left(0, \frac{S^*(\lambda_S - \lambda_V)}{b_1}\right), 1\right) \\
u_2^* &= min\left(max\left(0, \frac{S^*(\lambda_S - \lambda_R)}{b_2}\right), 1\right)
\end{aligned}$$

5.6 Numerical Simulations and Discussion

The optimality is formed by the system (5.5) with the adjoints (5.12) with corresponding time conditions. At first, we solve the model for the optimal system and represent the diagrams of the state variables without and with controls separately. Then we observe how the result changes after imposing a control strategy. Here, we also consider that the two controls will not be 100% effective. So the upper bounds for the two controls u_1 and u_2 is

between 0 and 1. The weight parameters in the objective function are $a_0, a_1, a_2, a_3, b_1, b_2$. For varying weight parameters, we can find how the controls are related to the respective weight parameters. Here, the values of the paremeters in the simulations are given in Table 5.2.

Variables	Description
$S(t)$	unvaccinated susceptible individuals
$V(t)$	vaccine dose recipients
$A(t)$	acutely infected individuals
$C_n(t)$	asymptomatic chronic carriers
$C_s(t)$	symptomatic chronic carriers
$D_c(t)$	individuals with disease complications
$R(t)$	recovered individuals

TABLE 5.1: Variable's description of the HBV model (5.3)

Parameters	Description	Baseline values
π	Birth rate	0.0121 [28]
p	Proportion of newborns vaccinated	0.3 [variable]
β	Transmission rate	0.8-20.49 [28]
ω	vaccine waning rate	0.1 [28]
ψ	Rate of administration of vaccine dose	0.885 [varialbe]
μ	Natural death rate	0.00693 [28]
δ	HBV related mortality rate	0.002 [28]
f	The fraction of acutely-infected people become asymptomatic chronically infected	0.7 [variable]
r	Efficacy of vaccine dose	0.09 [variable]
ϕ	the rate at which acutely-infected people become chronically-infected	0.885 [28]
γ	Recovery rate of chronically-infected individuals	0.06 [79]
ξ	Rate at which asymptomatic chronically-infected individuals become symptomatic chronically-infected	0.12 [Variable]
θ_t	Modified parameter for the assumed decrease of the recovery rate of symptomatic chronically-infected individuals in comparison to non-symptomatic chronically-infected individuals	0.0936 [79]
ν	Rate at which symptomatic chronically-infected individuals develop disease complications	0.2323 [79]

TABLE 5.2: Parameter's description of the HBV model (5.3)

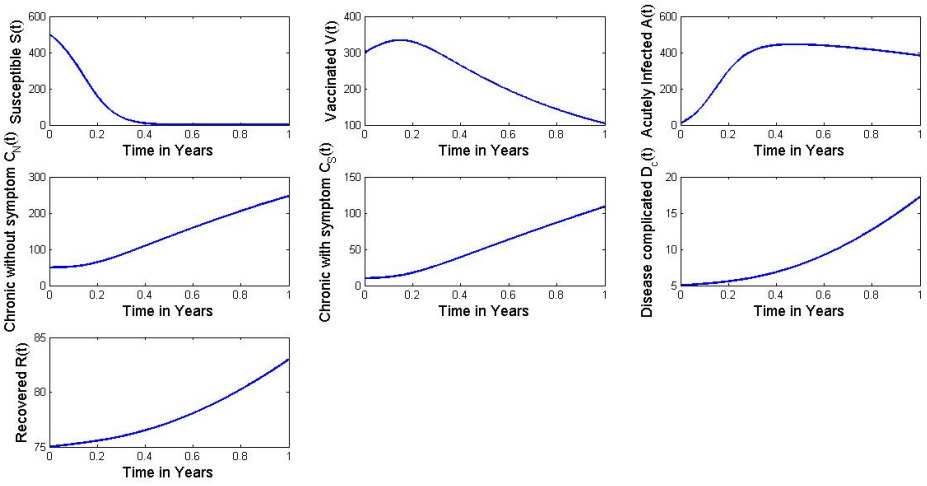

FIGURE 5.1: HBV basic model without control parameters

From Figure 5.1, we can see that before applying any control strategy, the infected individuals start to grow up. Since the acutely infected individuals can recovered by their own immunity response, so recovered individuals grow up at a consistent rate.

We subsequently solve the optimality system with two controls. The two controls are vaccination and creating awareness. Then we show how these controls affect the recovery rate of the infected individuals. Since HBV acutely infected individuals may be recovered

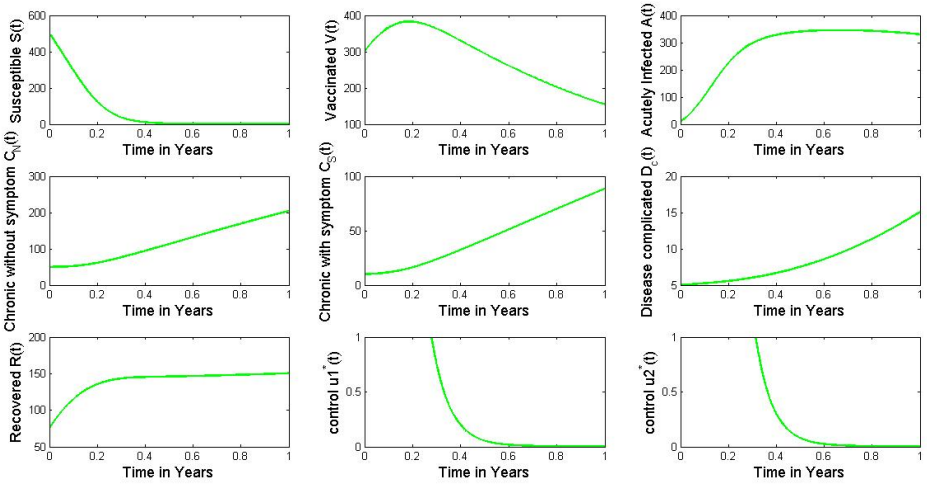

FIGURE 5.2: HBV model with control parameters

within 6 months, so here we consider the time period for 1 year. We observed from Figure

5.2 that for the first three months the controls are so much effective. As a result, the recovered individuals increases for the first 3 months. After that, the change of recovery rate is in a stable situation. After 3 months the effectiveness of the controls start to decrease and for this, the infectious individuals start to increase gradually. Because of this control strategy, the increasing rate of infected individuals is smaller than those who are not using controls.

Now for with and without control, we will monitor the effectiveness of controls of the model by placing the graphs on the identical co-ordinate axes. From the comparison Figure

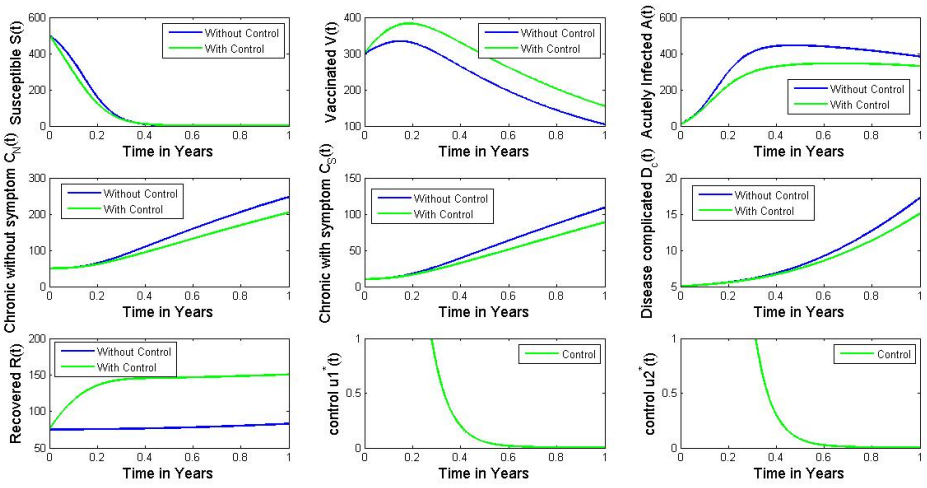

FIGURE 5.3: HBV model with and without control

5.3, it is seen that using optimal control we are able to control the disease over the finite time interval. It is also clear from the figure that the growth rate of recovered individuals is smooth after using control. The acutely infected population is also decreased after introducing control strategies. Since the chronic carriers carry the virus for life long, so after applying controls their increasing rate is smaller than without control.

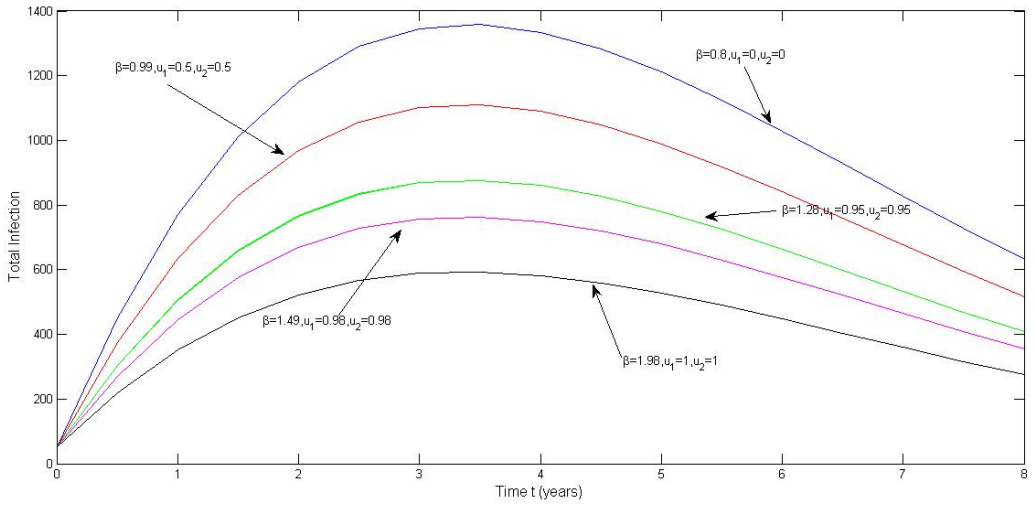

FIGURE 5.4: Total infection with different transmission rate using different controls

From the Figure 5.4, for a long time interval, we see that for different transmission rate ($\beta = 0.8, 0.99, 1.28, 1.49, 1.98$) and the use of controls ($u_1 = 0, 0.5, 0.95, 0.98, 1 = u_2$), the total infected individuals eventually decreases. For a high transmission rate with $\mathcal{R}_0 > 1$, the infection can be controlled by using different values of controls.

Numerically, we examine the impact of the controls u_1 and u_2 on the basic reproduction number. We choose u_1 and u_2 in such a way that $\mathcal{R}_0$ is less than unity. We demonstrate this situation by a surface plot and a contour plot in the following figure.

We can see from Figure 5.5 that for $u_1 = 0$ and $u_2 = 0$ the value of $\mathcal{R}_0$ attains its maximum

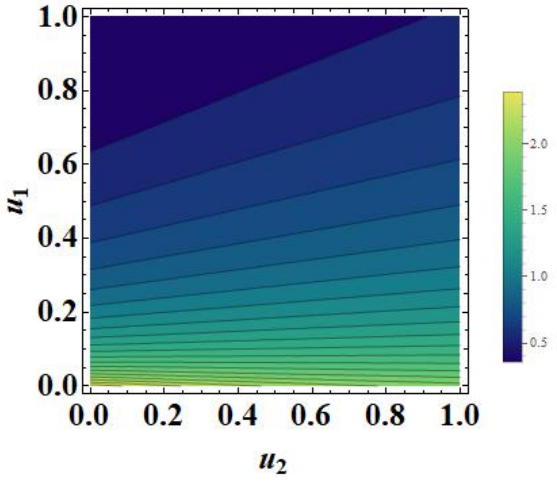

FIGURE 5.5: Contour plot of $\mathcal{R}_0$

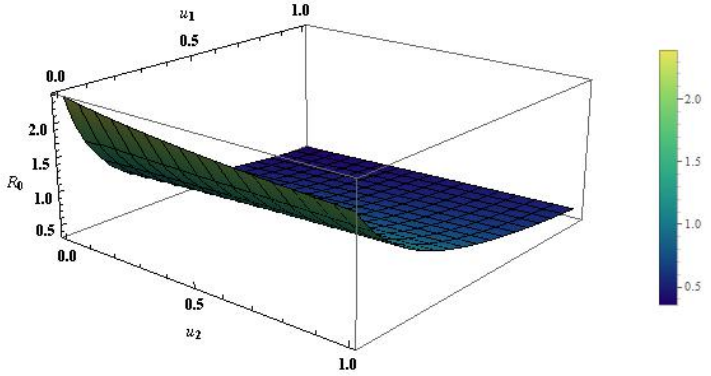

FIGURE 5.6: Surface plot of $\mathcal{R}_0$

value, which is $\mathcal{R}_0 = 2.39$. We choose the value from 0 to 1 for u_1 and u_2 and also observed the value of $\mathcal{R}_0$, which is gradually decrease. From Figure 5.6 of the surface plot, it is clear that u_1 is a more effective control than u_2 to reduce the value of $\mathcal{R}_0$ as well as the disease burden. This, in reality, reflects the effect of the efficacies of the control to clear the infection.

5.7 Conclusion

There are some numerical findings such as:

(i) Combination of with and without control strategy is consodered. The control parameters are much more effective to reduce the infected individuals and control the disease dynamics.

(ii) The controls are needed to be effective for a long time interval with a high transmission rate.

(iii) The optimal control is also effective for minimizing the infected individuals as well as the cost of the two controls.

(iv) From the simulation, it is monitored that vaccination is very prominent for disease elimination.

Chapter 6

Qualitative Dynamics of HBV Vaccination Model

6.1 Introduction

The liver is an essential part of the human body. Infections in the liver can arise through distinct diseases. Hepatitis B is a liver infection causing an eruption of the liver. The virus can not do direct damage to the epithelial cell, however, the immune mechanism leads to the eruption of the liver. [80]. At the same time as hepatitis B virus enters the human body and infects the cells of the liver, then it is known as hepatocytes. [81]. Hepatitis B infection has two stages namely acute phase and chronic phase. The acute hepatitis B phase is the first six months of the disease after the respective virus enters the human body of an infected person [82]. At the acute phase, the immunity response is generally responsible for removing a virus from the human body and for which that person may be completely cured of the disease within a few months. Chronic infection of hepatitis B refers to the infection when the virus remains in the human body for a long time interval and progress to critical physical problems. People with persistent hepatitis frequently do not have any history of acute symptoms. But at the late stage, it can cause liver failure and liver cancer [83]. Most HBV carriers are asymptomatic during the stage of acute infection, but some people have experience of acute illness that can last for several days.

Hepatitis B vaccine can prevent hepatitis B infection. Usually, three-dose Hepatitis B

vaccine series is recommended to the individuals intramuscularly. The successive doses are given during the birth time within 24 hours, then by the age of 1 month and six months. Successful timely completion of three doses vaccine may ensure protection against infection and reduce the risk of liver cancer. More than 90% of infants and approximately 50% of unvaccinated young children who are infected with Hepatitis B will have lifelong infections (by the reference of Hepatitis B foundation). Around the age of 40, after 1st dose, the protective antibody response is approximately $30\% - 55\%$, after 2nd dose, it is approximately 75% and after 3rd dose, it increases $> 90\%$ [85]. It is evident that there is no major effect on immunogenicity if the minimum spacing of the first two doses is 4 weeks, the second and third doses is 8 weeks and the first and booster doses is 16 weeks. But if the interval between the first 2 doses is increased then there is a little affect on immunogenicity or antibody concentration [86]. After the third dose, the maximum level of protection is appeared for getting optimal long-term protection [87].
In this chapter, we construct a model with vaccination administered at three different stages at different times for describing the dynamics of HBV transmission. The model can also be used for predicting the long-term effectiveness of the immunization.

6.2 Formulation of the Model

The model is constracted by splitting the total population $N(t)$ at time t into didderent compartments of individuals such as unvaccinated susceptible $(S(t))$, vaccinated susceptible who received the first dose of vaccine $(V_1(t))$, vaccinated susceptible who received the 2nd dose of vaccine $(V_2(t))$ and vaccinated susceptible who received the 3rd dose as a booster dose of vaccine $(V_3(t))$, acutely infected individuals $(A(t))$, chronically infected individuals with no clinical disease symptoms of HBV$(C_n(t))$, chronically infected individuals with clinical disease symptoms of HBV$(C_S(t))$, individuals with disease complications $(D_C(t))$and recovered individuals $(R(t))$, so that

$$N(t) = S(t) + V_1(t) + V_2(t) + V_3(t) + A(t) + C_n(t) + C_S(t) + D_C(t) + R(t).$$

Here, we consider acutely infected individuals are moved to the two chronic classes with clinical symptoms and without clinical symptoms. Approximately 0.5% adults of

unvaccinated susceptible individuals and a smaller number of children with chronic HBV infection will clear the infection and develop anti-HBs annually [54]. Many patients do not develop symptoms, particularly when the infection occurs in both infants and children.

The population of unvaccinated susceptible individuals is increased by the constant recruitment at the rate $\Pi(1-p)$ into the community, where Π is the birth rate and p is the proportion of children born with maternal immunity and also by waning of first vaccine dose (at a rate ω_1). It is decreased by the administration of the first vaccine dose (at a rate ψ_1), natural death (at a rate μ) and by the force of infection λ, where λ is given by,

$$\lambda = \frac{\beta(A + \eta_n C_n + \eta_S C_S + \eta_C D_C)}{N} \tag{6.1}$$

β is the effective contact rate, η_n, η_S and η_C are the modification parameters, the infectiousness of chronic carriers relative to acute infection. We assume that $0 < \eta_n < 1$ and $\eta_S > 1$, $\eta_C > 1$. The population of individuals who received the first vaccine dose increases by the administration of the first vaccine dose (at a rate ψ_1) and waning of the second vaccine dose (at the rate ω_2). The class of population is further decreased by infection (at a rate $r_1\lambda$, where, $0 < r_1 < 1$ is the vaccine efficacy of the first vaccine dose), vaccine waning (at the rate ω_1) and administration of second vaccine dose of the individuals (at a rate ψ_2) and natural death. The second vaccine dose recipients is increased at a rate ψ_2, due to lack of immune protection in the V_3 class (for taking booster dose of vaccine in the appropriate time interval) move back to the V_2 class (at a rate ω_3). The population is decreased by infection (at a reduced rate $r_2\lambda$; with $0 < r_2 < 1$ is the efficacy of second vaccine dose) and administration of booster dose (at a rate ψ_3) and natural death.

The population of individuals who received the booster dose in V_3 class increases at a rate ψ_3 and decreased by infection (at a rate $r_3\lambda$; with $0 < r_3 < 1$ is the efficacy of booster dose), reverted individuals to V_2 class (at the rate ω_3) and natural death.

The population of acutely infected individuals is generated at the rate λS (for unvaccinated susceptible individuals), $r_1\lambda$ (for the 1st vaccine dose recipients), $r_2\lambda$ (for the 2nd vaccine dose recipients) and $r_3\lambda$ (for the booster dose vaccine recipients). This population is decreased by the progression rate of the asymptomatic chronic infectious phase (at a rate ϕ) and the symptomatically chronic infection carrier phase and natural death. At the stage of acute infection, treatment is not needed and the patient will get

cure normally. But individuals with chronic hepatitis B need treatment to reduce the risk of liver disease and to prevent from passing the infection to others [88].

The chronic carrier with no clinical disease symptoms is increased by transferred individuals from $A(t)$ and decreased by recovery (at the rate γ) and the progression rate (at the rate ξ) of symptomatic chronic carriers and natural death. Similarly, The chronic carrier with symptoms is increased by transferred individuals from $A(t)$ and $C_n(t)$ and decreased by recovery rate due to effective treatment (at the rate $\theta_t > 1$), due to the progression (at the rate ν) of disease complications, natural death and disease related death (at the rate δ). The individuals of complicated disease symptoms is increased by the transferred individuals from $C_S(t)$ at the rate ν and decreased by natural death and disease related death (at the rate δ). The recovered individuals is generated at the rate γ and the population is decreased by natural death (it is assumed that recovered individuals become completely susceptible to HBV infection).

Combining all the assumptions in the model for the transmission disease dynamics of HBV at population level and considering dose-dependent vaccination and treatment, a deterministic model of non-linear differential equations, a flow diagram of the model in Figure 6.1 and the description of variables and parameters are in Table 6.1 and Table 6.2 are given below:

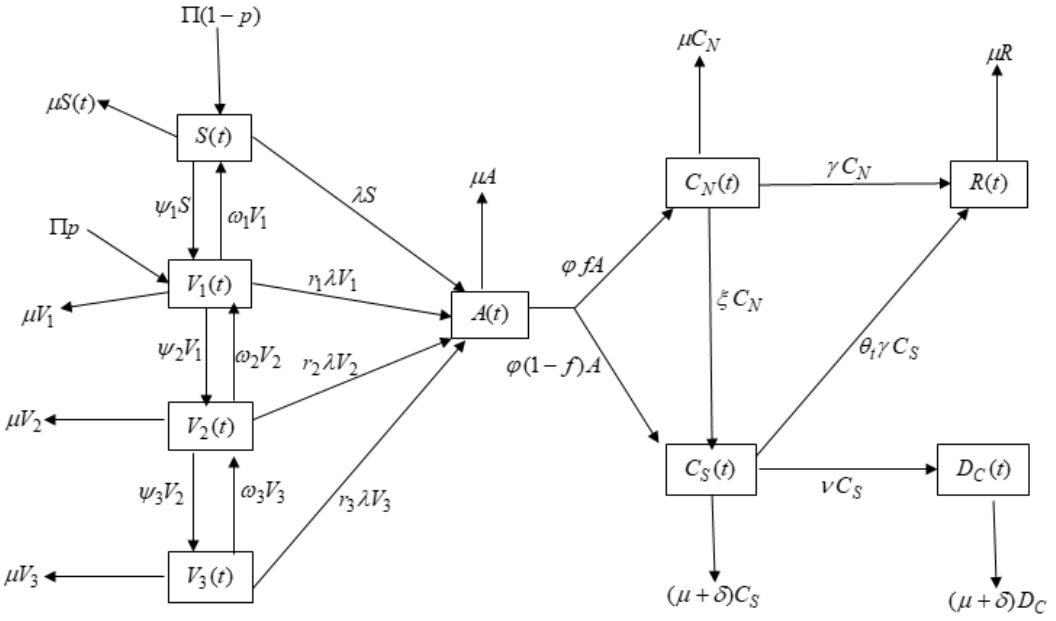

FIGURE 6.1: Model diagram of HBV vaccination model.

Variables	Description
$S(t)$	unvaccinated susceptible individuals
$V_1(t)$	first vaccine dose recipients
$V_2(t)$	second vaccine dose recipients
$V_3(t)$	booster dose recipients
$A(t)$	acutely infected individuals
$C_n(t)$	Population of chronic carriers with no clinical disease symptoms of HBV
$C_S(t)$	Population of chronic carriers with clinical disease symptoms of HBV
$D_C(t)$	individuals with disease complications
$R(t)$	Population of recovered individuals

TABLE 6.1: Variable's description of the HBV vaccination model (6.2)

$$\begin{aligned}
\frac{dS}{dt} &= \Pi(1-p) + \omega_1 V_1 - \lambda S - k_1 S \\
\frac{dV_1}{dt} &= \Pi p + \psi_1 S + \omega_2 V_2 - r_1 \lambda V_1 - k_2 V_1 \\
\frac{dV_2}{dt} &= \psi_2 V_1 + \omega_3 V_3 - r_2 \lambda V_2 - k_3 V_2 \\
\frac{dV_3}{dt} &= \psi_3 V_2 - r_3 \lambda V_3 - k_4 V_3 \\
\frac{dA}{dt} &= \lambda S + r_1 \lambda V_1 + r_2 \lambda V_2 + r_3 \lambda V_3 - k_5 A \\
\frac{dC_n}{dt} &= \phi f A - k_6 C_n \\
\frac{dC_S}{dt} &= \phi(1-f)A + \xi C_n - k_7 C_S \\
\frac{dD_C}{dt} &= \nu C_S - k_8 D_C \\
\frac{dR}{dt} &= \nu C_n + \theta_t \gamma C_S - \mu R
\end{aligned} \tag{6.2}$$

where,

$$k_1 = \psi_1 + \mu,\ k_2 = \omega_1 + \psi_2 + \mu,\ k_3 = \omega_2 + \psi_3 + \mu,\ k_4 = \omega_3 + \mu,\ k_5 = \phi + \mu,$$
$$k_6 = \gamma + \xi + \mu,\ k_7 = \theta_t \gamma + \nu + \mu + \delta \text{ and } k_8 = \mu + \delta.$$

Parameters	Description	Baseline values
Π	Birth rate	0.0121 [89]
p	Proportion of newborns vaccinated	[0,1] [variable]
β	Transmission rate	0.95-20.49 [89]
ω_1	first dose vaccine waning rate	0.1 [89]
ψ_1	Rate of administration of first vaccine dose	0.885 y^{-1} [90]
μ	Natural (continuous) mortality rate	0.00693 [89]
δ	HBV- related mortality rate	0.002 [89]
f	Fraction of the acutely infected individuals who become chronically infected	[0,1] [variable]
r_1	the first vaccine dose efficacy	[0,1] [variable]
r_2	the second vaccine dose efficacy	[0,1] [variable]
r_3	the booster vaccine dose efficacy	[0,1] [variable]
ψ_2	administration rate of the second vaccine dose	0.925 y^{-1} [90]
ω_2	second vaccine dose waning rate (and reversion of V_1)	[0,1] [variable]
ω_3	the booster vaccine dose waning rate (and reversion of V_2)	[0,1] [variable]
ψ_3	administration rate of the booster dose	0.879 y^{-1} [90]
ϕ	The rate at which acutely-infected people become chronically infected	4 [89]
ξ	Rate at which asymptomatic chronically-infected individuals become symptomatic chronically-infected	0.12 [variable]
γ	Recovery rate of chronically-infected individuals	0.06 [91]
θ_t	Modified parameter for the assumed decrease of the recovery rate of symptomatic chronically-infected individuals in complication to non-symptomatic chronically-infected individuals	0.0936 y^{-1} [91]
ν	Rate at which symptomatic chronically-infected individuals develop disease complications	0.2323 y^{-1} [91]

TABLE 6.2: Parameter's description of the HBV vaccination model (6.2)

6.3 Analysis of the Vaccination Model

6.3.1 Basic Properties of the Vaccination Model

Here we prove the positivity and boundedness of the solutions to the model (6.2).

Lemma 6.1. *The closed set* $\Omega = \left\{(S, V_1, V_2, V_3, A, C_n, C_S, D_C, R) \in \mathbb{R}^9_+ : N \leq \frac{\Pi}{\mu}\right\}$ *is positively-invariant and attracting with respect to the model* (6.2).

Proof. At first consider the biologically–feasible region, Ω. To establish the positive invariance of Ω (which means for $t > 0$ all solutions in Ω remain in Ω) here we follow the

following steps. Adding all the equations of the model (6.2) we get the rate of change of total population

$$\frac{dN}{dt} = \Pi - \mu N - \delta C_S - \delta D_C \tag{6.3}$$

If $N > \frac{\Pi}{\mu}$ then $\frac{dN}{dt} < 0$. Further, since $\frac{dN}{dt} \leq \Pi - \mu N$ from (6.3), a standard Comparison theorem [72] can be used to show that $N(t) \leq N(0)e^{-\mu t} + \frac{\Pi}{\mu}(1 - e^{-\mu t})$. From which we find that $N(t) \leq \frac{\Pi}{\mu}$ if $N(0) \leq \frac{\Pi}{\mu}$. Again, if $N > \frac{\Pi}{\mu}$ then either the solution enters Ω in finite time, or $N(t)$ approaches to $\frac{\Pi}{\mu}$ and the respective variables $V_1(t), V_2(t), V_3(t), A(t), C_n(t), C_S(t), D_C(t)$ and $R(t)$ approaches to zero. Hence, all solutions of the model in Ω for $t > 0$. Therefore, Ω is attracting and positively-invariant. Thus the model within the region Ω is mathematically and epidemiologically well-proposed [62]. □

6.3.2 The Disease Free Equilibrium (DFE) of the model

The model (6.2) has a positive DFE, is defined by

$$\mathcal{E}_0^* = (S^*, V_1^*, V_2^*, V_3^*, A^*, C_n^*, C_S^*, D_C^*, R^*) = (S^*, V_1^*, V_2^*, V_3^*, 0, 0, 0, 0, 0) \tag{6.4}$$

with,

$$\begin{aligned}
S^* &= \frac{\Pi[\mu\psi_2(1-p)b_{11} + a_{11}(\mu(1-p)+\omega_1)]}{\mu a_{11}(\mu+\omega_1+\psi_1) + \mu\psi_2(\mu+\psi_1)b_{11}},\\
V_1^* &= \frac{\Pi a_{11}(p\mu+\psi_1)}{\mu a_{11}(\mu+\omega_1+\psi_1) + \mu\psi_2(\mu+\psi_1)b_{11}},\\
V_2^* &= \frac{\Pi\psi_2(\mu+\omega_3)(p\mu+\psi_1)}{\mu a_{11}(\mu+\omega_1+\psi_1) + \mu\psi_2(\mu+\psi_1)b_{11}},\\
V_3^* &= \frac{\Pi\psi_2\psi_3(p\mu+\psi_1)}{\mu a_{11}(\mu+\omega_1+\psi_1) + \mu\psi_2(\mu+\psi_1)b_{11}}.
\end{aligned}$$

where, $a_{11} = \mu^2 + \mu\omega_3 + \mu\psi_3 + \mu\omega_2 + \omega_2\omega_3$, $b_{11} = \mu + \omega_3 + \psi_3$.

6.3.3 Stability analysis of DFE

To show the stability of the DFE, ε_0^*, here we consider the next generation method [49]. The positive matrix F and the non-singular matrix V are as follows:

$$F = \begin{pmatrix} \frac{\beta T}{N^*} & \frac{\beta \eta_n T}{N^*} & \frac{\beta \eta_S T}{N^*} & \frac{\beta \eta_C T}{N^*} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

where, $T = S^* + r_1 V_1^* + r_2 V_2^* + r_3 V_3^*$ and S^*, V_1^*, V_2^*, V_3^* are at DFE.
and

$$V = \begin{pmatrix} k_5 & 0 & 0 & 0 \\ -\phi f & k_6 & 0 & 0 \\ -\phi(1-f) & -\xi & k_7 & 0 \\ 0 & 0 & -\nu & k_8 \end{pmatrix}$$

where,

$k_5 = \phi + \mu, k_6 = \xi + \gamma + \mu, k_7 = \delta + \nu + \mu + \theta_t \gamma, k_8 = \delta + \mu.$

The associated basic reproduction threshold is given by $\mathcal{R}_0 = \rho(FV^{-1})$, where ρ represents the dominant eigenvalue of the next generation matrix. It follows that

$$R_0 = \frac{\beta T}{N^* k_5 k_6 k_7 k_8}[(1-f)(\eta_C \nu \phi k_6 + \eta_S \phi k_6 k_8) + \eta_n \phi f k_7 k_8 + \eta_S \phi k_8 \xi f + \eta_C \phi \nu \xi f + k_6 k_7 k_8].$$

Therefore, the following result is established from Theorem 2 of [49].

Lemma 6.2. *If $\mathcal{R}_0 < 1$, then the disease free equilibrium (DFE) of the model (6.2) is locally asymptotically stable (LAS), and otherwise unstable.*

For disease elimination, we need to check the global stability of the *DFE* whenever $\mathcal{R}_0 < 1$. Which is done below.

6.3.4 The Global stability of the DFE of the model

Theorem 6.1. If we assume $S(t) \leq S^*$, $V_1(t) \leq V_1^*$, $V_2(t) \leq V_2^*$, $V_3(t) \leq V_3^*$ for all $t > 0$ then the DFE, $\mathcal{E}_0^*$ of the model (6.2) is globally-asymptotically stable (GAS) whenever $\mathcal{R}_0 < 1$.

Proof. Consider the following Lyapunov function

$$\mathcal{F} \quad = \quad f_1 A + f_2 C_n + f_3 C_S + f_4 D_C$$

where,

$$f_1 = \frac{f\eta_C\nu\phi\xi - f\eta_C\nu\phi k_6 + f\eta_S\phi\xi k_8 + f\eta_n\phi k_7 k_8 - f\eta_S\phi k_8 k_6 + \eta_C\phi\nu k_6 + \phi\eta_S k_6 k_8 + k_6 k_7 k_8}{\eta_C k_5 k_6 k_7},$$

$$f_2 = \frac{\eta_C\nu\xi + \eta_S\xi k_8 + \eta_n k_7 k_8}{\eta_C k_6 k_7},$$

$$f_3 = \frac{\eta_C\nu + \eta_S k_8}{\eta_C k_7},$$

$$f_4 = 1.$$

Now Lyapunov derivative with respect to t is given by

$$\begin{aligned}
\dot{\mathcal{F}} &= f_1\dot{A} + f_2\dot{C_n} + f_3\dot{C_S} + f_4\dot{D_C}, \\
&= \frac{f\eta_C\nu\phi\xi - f\eta_C\nu\phi k_6 + f\eta_S\phi\xi k_8 + f\eta_n\phi k_7 k_8 - f\eta_S\phi k_8 k_6 + \eta_C\phi\nu k_6 + \phi\eta_S k_6 k_8 + k_6 k_7 k_8}{\eta_C k_5 k_6 k_7}(\lambda S + r_1\lambda V_1 \\
&+ r_2\lambda V_2 + r_3\lambda V_3 - k_5 A) + \frac{\eta_C\nu\xi + \eta_S\xi k_8 + \eta_n k_7 k_8}{\eta_C k_6 k_7}(\phi f A - k_6 C_n) \\
&+ \frac{\eta_C\nu + \eta_S k_8}{\eta_C k_7}(\phi(1-f)A + \xi C_n - k_7 C_S) + 1(\nu C_S - k_8 D_C).
\end{aligned}$$

For simplification, we first consider the coefficient of A:

$\frac{1}{\eta_C k_5 k_6 k_7 N}\beta(S+r_1V_1+r_2V_2+r_3V_3)[(1-f)(\eta_C\nu\phi k_6+\eta_S\phi k_6 k_8)+f\eta_C\phi\nu\xi+f\eta_S\phi k_8\xi+f\eta_n\phi k_7 k_8+ k_6 k_7 k_8] - N k_5 k_6 k_7 k_8$

$= \frac{N k_5 k_6 k_7 k_8}{\eta_C k_5 k_6 k_7 N}\left[\frac{\beta(S+r_1V_1+r_2V_2+r_3V_3)[(1-f)(\eta_C\nu\phi k_6+\eta_S\phi k_6 k_8)+f\eta_C\phi\nu\xi+f\eta_S\phi k_8\xi+f\eta_n\phi k_7 k_8+k_6 k_7 k_8]}{N k_5 k_6 k_7 k_8} - 1\right]$

$\leq \frac{N k_5 k_6 k_7 k_8}{\eta_C k_5 k_6 k_7 N}\left[\frac{\beta T[(1-f)(\eta_C\nu\phi k_6+\eta_S\phi k_6 k_8)+f\eta_C\phi\nu\xi+f\eta_S\phi k_8\xi+f\eta_n\phi k_7 k_8+k_6 k_7 k_8]}{N^* k_5 k_6 k_7 k_8} - 1\right]$ where,

$T = S^* + r_1V_1^* + r_2V_2^* + r_3V_3^*.$

$\leq \frac{k_8}{\eta_C}[\mathcal{R}_0 - 1],$

and the similar expressions come for the coefficients of $\eta_n C_n$, $\eta_S C_S$ *and* $\eta_C D_C$. Thus we have,

$$\dot{\mathcal{F}} \leq \frac{k_8}{\eta_C}(\mathcal{R}_0 - 1)(A + \eta_n C_n + \eta_S C_S + \eta_C D_C)$$

Since $S(t) \leq S^*$, $V_1(t) \leq V_1^*$, $V_2(t) \leq V_2^*$, $V_3(t) \leq V_3^*$ for all $t > 0$. If $\mathcal{R}_0 < 1$, then $\dot{F} < 0$. If $\dot{F} = 0$ if and only if $A = C_n = C_S = D_C = 0$(note that $k_8 = \mu + \delta > 0$). Thus by Lasalle Invariance Principle it follows that $A \to 0$, $C_n \to 0$,$C_S \to 0$,$D_C \to 0$ as $t \to \infty$. Further, substituting $A = C_n = C_S = D_C = 0$ in the model equation we get the DFE $(S^*, V_1^*, V_2^*, V_3^*)$. This established that the disease free equilibrium point (DFE) is globally stable for $\mathcal{R}_0 < 1$. □

The epidemiological aspect shows that if $\mathcal{R}_0 < 1$ then the disease will be eliminated from the community . Using various initial conditions the result of Theorem 6.1 is simulated numerically for $\mathcal{R}_0 < 1$. The solution trajectories converges to the DFE $(\mathcal{E}_0^*)$,as depicted in Figure 6.2, which is GAS when $\mathcal{R}_0 < 1$.

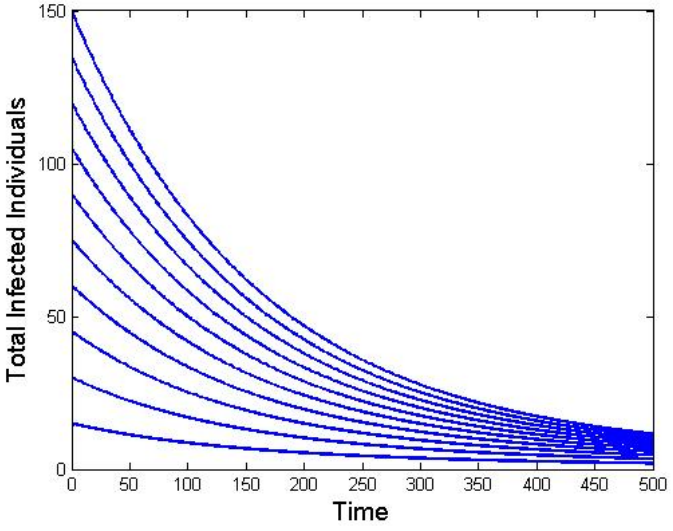

FIGURE 6.2: Figure 6.2 illustrates Theorem 6.1 and represents the total number of infected individuals for $\mathcal{R}_0 = 0.8479 < 1$, where, $\beta = 0.49$ and other parameter values are given in Table 6.2.

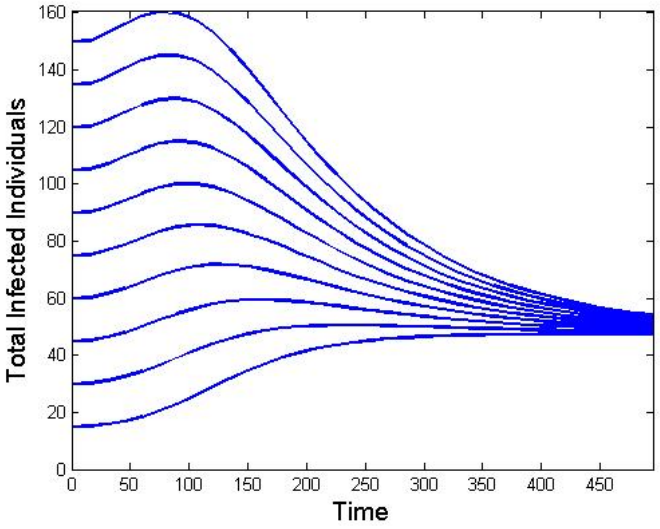

FIGURE 6.3: Figure 6.3 illustrates Theorem 6.3 and represents the total number of infected individuals for $\mathcal{R}_0 = 1.8385 > 1$, where, $\beta = 1.49$ and other parameter values are given in Table 6.2.

6.3.5 Existence of the EEP of the model

Here, we can find possible existence of positive EEP of (6.2) (where, at least one of the infected components is non-zero).

Let $\mathcal{E}_1 = (S^{**}, V_1^{**}, V_2^{**}, V_3^{**}, A^{**}, C_n^{**}, C_S^{**}, D_C^{**}, R^{**})$ be any arbitrary endemic equilibrium point (EEP) of the model (6.2). Then we have from (6.2)

$$
\begin{aligned}
S^{**} &= \frac{\Pi(1-p) + \omega_1 V_1^{**}}{\lambda^{**} + k_1} \\
V_1^{**} &= \frac{\Pi p + \psi_1 S^{**} + \omega_2 V_2^{**}}{r_1\lambda^{**} + k_2} \\
V_2^{**} &= \frac{\psi_2 V_1^{**} + \omega_3 V_3^{**}}{r_2\lambda^{**} + k_3} \\
V_3^{**} &= \frac{\psi_3 V_2^{**}}{r_3\lambda^{**} + k_4} \\
A^{**} &= \frac{\lambda^{**}S^{**} + r_1\lambda^{**}V_1^{**} + r_2\lambda^{**}V_2^{**} + r_3\lambda^{**}V_3^{**}}{k_5} \\
C_N^{**} &= \frac{\phi f[\lambda^{**}S^{**} + r_1\lambda^{**}V_1^{**} + r_2\lambda^{**}V_2^{**} + r_3\lambda^{**}V_3^{**}]}{k_5k_6} \\
C_S^{**} &= \frac{[k_6\phi(1-f) + \xi\phi f]A^{**}}{k_6k_7} \\
D_C^{**} &= \frac{[\nu k_6\phi(1-f) + \nu\xi\phi f]A^{**}}{k_6k_7k_8} \\
R^{**} &= \frac{\gamma C_N^{**} + \theta_t\gamma C_S^{**}}{\mu}
\end{aligned}
$$

where, $k_1 = \psi_1 + \mu, k_2 = \omega_1 + \psi_2 + \mu, k_3 = \omega_2 + \psi_3 + \mu, k_4 = \omega_3 + \mu, k_5 = \phi + \mu,$
$k_6 = \gamma + \xi + \mu, k_7 = \theta_t\gamma + \nu + \mu + \delta, k_8 = \mu + \delta.$

Existence of EEP: From $\lambda^{**} = \frac{\beta(A^{**} + \eta_n C_n^{**} + \eta_S C_S^{**} + \eta_C^{**} D_C)}{N^{**}}$ we have the following polynomial:

$$G(\lambda^{**}) = a_0(\lambda^{**})^5 + a_1(\lambda^{**})^4 + a_2(\lambda^{**})^3 + a_3(\lambda^{**})^2 + a_4\lambda^{**} = 0$$

$$\implies \lambda^{**}\{a_0(\lambda^{**})^4 + a_1(\lambda^{**})^3 + a_2(\lambda^{**})^2 + a_3\lambda^{**} + a_4\} = 0$$

If $\lambda^{**} = 0$ then we get the DFE, otherwise

$$a_0(\lambda^{**})^4 + a_1(\lambda^{**})^3 + a_2(\lambda^{**})^2 + a_3\lambda^{**} + a_4 = 0$$

It should be noted that a_0 is always positive but the signs of a_1, a_2, a_3 and a_4 are unknown. So the possible real roots of the above polynomial depends on the signs of $a_1, a_2, a_3,$ and a_4 and possible combinations of the coefficients are explored below in Table 6.3.

Thus we have the following statement:

Cases	a_0	a_1	a_2	a_3	a_4	Possible or NOT	Number of Sign Change
1	+	+	+	+	+	N	-
2	+	+	+	+	−	Y	1
3	+	+	+	−	+	N	-
4	+	+	−	+	+	N	-
5	+	−	+	+	+	N	-
6	+	+	+	−	−	Y	1
7	+	+	−	−	+	N	-
8	+	−	−	+	+	N	-
9	+	+	−	+	−	N	-
10	+	−	+	+	−	N	-
11	+	−	+	−	+	N	-
12	+	+	−	−	−	Y	1
13	+	−	+	−	−	N	-
14	+	−	−	+	−	N	-
15	+	−	−	−	+	N	-
16	+	−	−	−	−	Y	1

TABLE 6.3: Sign of the coefficients of the polynomial.

Theorem 6.2. If there is at least one sign change occurs in the coefficients then the model has a unique EEP and otherwise no EEP.

6.3.6 Local Stability analysis of EEP

Theorem 6.3. If $B_1 > B_2$ and $\mathcal{R}_0 > 1$ then the model has a unique endemic equilibrium point, $\mathcal{E}_1$, which is LAS.

Proof. The proof of the local stability of the unique EEP, $\mathcal{E}_1$, using central manifold theory [56] will now be explored below. Let $\mathcal{R}_0 > 1$. For convenience let change of variables: $S = x_1$, $V_1 = x_2$, $V_2 = x_3$, $V_3 = x_4$, $A = x_5$, $C_n = x_6$,$C_S = x_7$, $D_C = x_8$ and $R = x_9$ and also use the vector notation $\mathrm{X} = (x_1, x_2, x_3, x_4, x_5, x_6, x_7, x_8, x_9)^T$. Thus the model (6.2) can be reduced by the form $\frac{d\mathrm{X}}{dt} = F(\mathrm{X})$, where $F = (f_1, f_2, f_3, f_4, f_5, f_6, f_7, f_8, f_9)^T$.

$$
\begin{aligned}
\frac{dx_1}{dt} &= f_1 = \Pi(1-p) + \omega_1 x_2 - \frac{\beta(x_5+\eta_n x_6+\eta_S x_7+\eta_C x_8)x_1}{N} - k_1 x_1 \\
\frac{dx_2}{dt} &= f_2 = \Pi p + \psi_1 x_1 + \omega_2 x_3 - \frac{r_1\beta(x_5+\eta_n x_6+\eta_S x_7+\eta_C x_8)x_2}{N} - k_2 x_2 \\
\frac{dx_3}{dt} &= f_3 = \psi_2 x_2 + \omega_3 x_4 - \frac{r_2\beta(x_5+\eta_n x_6+\eta_S x_7+\eta_C x_8))x_3}{N} - k_3 x_3 \\
\frac{dx_4}{dt} &= f_4 = \psi_3 x_3 - \frac{r_3\beta(x_5+\eta_n x_6+\eta_S x_7+\eta_C x_8)x_4}{N} - k_4 x_4 \\
\frac{dx_5}{dt} &= f_5 = \frac{\beta(x_5+\eta_n x_6+\eta_S x_7+\eta_C x_8)x_1}{N} + \frac{r_1\beta(x_5+\eta_n x_6+\eta_S x_7+\eta_C x_8)x_2}{N} \\
&\quad + \frac{r_2\beta(x_5+\eta_n x_6+\eta_S x_7+\eta_C x_8)x_3}{N} + \frac{r_3\beta(x_5+\eta_n x_6+\eta_S x_7+\eta_C x_8)x_4}{N} - k_5 x_5 \\
\frac{dx_6}{dt} &= f_6 = \phi f x_5 - k_6 x_6 \\
\frac{dx_7}{dt} &= f_7 = \phi(1-f)x_5 + \xi x_6 - k_7 x_7 \\
\frac{dx_8}{dt} &= f_8 = \nu x_7 - k_8 x_8 \\
\frac{dx_9}{dt} &= f_9 = \gamma x_6 + \theta_t \gamma x_7 - \mu x_9
\end{aligned}
\tag{6.5}
$$

The Jacobian matrix of the reduced system (6.5) evaluated at the DFE ($\mathcal{E}_0^*$), which is

$$
J = \begin{pmatrix}
-k_1 & \omega_1 & 0 & 0 & -m_1 & -m_1\eta_n & -m_1\eta_S & -m_1\eta_C & 0 \\
\psi_1 & -k_2 & \omega_2 & 0 & -n_1 & -n_1\eta_n & -n_1\eta_S & -n_1\eta_C & 0 \\
0 & \psi_2 & -k_3 & \omega_3 & -m_2 & -m_2\eta_n & -m_2\eta_S & -m_2\eta_C & 0 \\
0 & 0 & \psi_3 & -k_4 & -n_2 & -n_2\eta_n & -n_2\eta_S & -n_2\eta_C & 0 \\
0 & 0 & 0 & 0 & n_1+m_2+m_1+n_2+k_5 & m\eta_n & m\eta_S & m\eta_C & 0 \\
0 & 0 & 0 & 0 & \phi f & -k_6 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & \phi(1-f) & \xi & -k_7 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & \nu & -k_8 & 0 \\
0 & 0 & 0 & 0 & 0 & \nu & \theta_t\gamma & 0 & -\mu
\end{pmatrix}.
$$

with

$m_1 = \frac{\beta^* x_1^*}{x_1^*+x_2^*+x_3^*+x_4^*}$, $n_1 = \frac{\beta^* r_1 x_2^*}{x_1^*+x_2^*+x_3^*+x_4^*}$ $m_2 = \frac{\beta^* r_2 x_3^*}{x_1^*+x_2^*+x_3^*+x_4^*}$, $n_2 = \frac{\beta^* r_3 x_4^*}{x_1^*+x_2^*+x_3^*+x_4^*}$

$m = m_1 + m_2 + n_1 + n_2$.

Assume that the bifurcation parameter is β and solving from $\mathcal{R}_0 = 1$ we get

$$\beta^* = \frac{N^* \prod_{i=5}^{8} k_i}{\beta(S^*+V_1^*+V_2^*+V_3^*)[(1-f)(\eta_C\nu\phi k_6+\eta_S\phi k_6 k_8)+\eta_n\phi f k_7 k_8+\eta_S\phi k_8\xi f+\eta_C\phi\nu\xi f+k_6k_7k_8]}$$

where, S^*, V_1^*, V_2^*, V_3^* are the DFE.
The transformed system (6.5) with $\beta = \beta^*$ has a simple eigenvalue with zero real part, and all other eigenvalues have negative real part. Hence, for analysing the dynamics of the system near $\beta = \beta^*$ we can use the Centre Manifold theory.

Eigenvectors of $J(\epsilon_0^*)|_{\beta=\beta^*} = J_{\beta^*}$:

The Jacobian of (6.5) at $\beta = \beta^*$ has a right eigenvector (correlated with the zero eigenvalues) which is considered by $w = (w_1,\ w_2,\ w_3,\ w_4,\ w_5,\ w_6,\ w_7,\ w_8,\ w_9)^T$, where

$$w_1 = -\frac{1}{k_6k_7k_8[k_3k_4(k_1k_2-\omega_1\psi_1)-\omega_3\psi_3(k_1k_2-\omega_1\psi_1)-k_1k_4\omega_2\psi_2]}$$
$$\times[(k_2k_3k_4m_1-k_2m_1\omega_3\psi_3+k_3k_4n_1\omega_1-k_4m_1\omega_2\psi_2+k_4m_2\omega_1\omega_2-n_1\omega_1\omega_3\psi_3+n_2\omega_1\omega_2\omega_3)(f\eta_C\phi\nu\xi$$
$$-f\eta_C\nu\phi k_6+f\eta_S\phi k_8\xi+f\eta_n\phi k_7k_8-f\eta_S\phi k_6k_8+\eta_C\nu\phi k_6+\eta_S\phi k_6k_8+k_6k_7k_8)]w_5<0$$

$$w_2 = -\frac{1}{[k_1k_2k_3k_4-k_1k_2\omega_3\psi_3-k_1k_4\omega_2\psi_2-k_3k_4\omega_1\psi_1)+\omega_1\psi_1\omega_3\psi_3]}$$
$$\times[(k_1k_3k_4n_1+k_1k_4m_2\omega_2-k_1n_1\omega_3\psi_3+k_1n_2\omega_2\omega_3+k_3k_4m_1\psi_1-m_1\omega_3\psi_1\omega_3)(f\eta_C\phi\nu\xi-f\eta_C\nu\phi k_6$$
$$+f\eta_S\phi k_8\xi+f\eta_n\phi k_7k_8-f\eta_S\phi k_6k_8+\eta_C\nu\phi k_6+\eta_S\phi k_6k_8+k_6k_7k_8))]w_5<0$$

$$w_3 = -\frac{1}{k_6k_7k_8[k_1k_2k_3k_4-k_1k_2\omega_3\psi_3-k_1k_4\omega_2\psi_2-k_3k_4\omega_1\psi_1)+\omega_1\psi_1\omega_3\psi_3]}$$
$$\times[(k_1k_2k_4m_2+k_1k_2n_2\omega_3+k_1k_4n_1\psi_2+k_4m_1\psi_1\psi_2-k_4m_2\omega_1\psi_1-n_2\omega_1\psi_1\omega_3)(f\eta_C\phi\nu\xi-f\eta_C\nu\phi k_6$$
$$+f\eta_S\phi k_8\xi+f\eta_n\phi k_7k_8-f\eta_S\phi k_6k_8+\eta_C\nu\phi k_6+\eta_S\phi k_6k_8+k_6k_7k_8)]w_5<0$$

$$w_4 = -\frac{1}{k_6k_7k_8[k_1k_2k_3k_4-k_1k_2\omega_3\psi_3-k_1k_4\omega_2\psi_2-k_3k_4\omega_1\psi_1+\omega_1\psi_1\omega_3\psi_3]}$$
$$\times[(k_1k_2k_3n_2+k_1k_2m_2\psi_3+k_1n_1\psi_2\psi_3-k_1n_2\omega_2\psi_2-k_3n_2\omega_1\psi_1+m_1\psi_1\psi_2\psi_3+m_2\omega_1\psi_1\psi_3)(f\eta_C\phi\nu\xi$$
$$-f\eta_C\nu\phi k_6+f\eta_S\phi k_8\xi+f\eta_n\phi k_7k_8-f\eta_S\phi k_6k_8+\eta_C\nu\phi k_6+\eta_S\phi k_6k_8+k_6k_7k_8)]w_5<0$$

$w_5 = \text{free}$
$w_6 = \frac{\phi f w_5}{k_6}$
$w_7 = \frac{\phi(1-f)K_6+\zeta\phi f}{k_6 k_7} w_5$
$w_8 = \frac{\nu\phi(1-f)k_6+\nu\xi\phi f}{k_6 k_7 k_8} w_5$
$w_9 = \frac{\nu\phi f k_7+\theta_t\nu\phi(1-f)k_6+\theta_t\nu\xi\phi f}{\mu k_6 k_7} w_5.$

Additionally, the Jacobian J_{β^*}, has a left eigenvector (correlated with the zero eigenvalue) which is considered by $v = (v_1,\ v_2,\ v_3,\ v_4,\ v_5,\ v_6,\ v_7,\ v_8,\ v_9)^T$

$$v_1 = \frac{\psi_1\psi_2\psi_3 v_4}{k_1k_2k_3 - k_1\omega_2\psi_2 - k_3\omega_1\psi_1}$$
$$v_2 = \frac{v_4\psi_2\psi_3 k_1}{k_1k_2k_3 - k_1\omega_2\psi_2 - k_3\omega_1\psi_1}$$
$$v_3 = \frac{\psi_3(k_1k_2 - \omega_1\psi_1)v_4}{k_1k_2k_3 - k_1\omega_2\psi_2 - k_3\omega_1\psi_1}$$

$v_4 = free$

$$v_5 = \frac{1}{k_5k_6k_7k_8(k_1k_2k_3 - k_1\omega_2\psi_2 - k_3\omega_1\psi_1)(m\mathcal{R}_0 - 1)} \times [v_4(n_2(k_1k_2k_3 - k_1\omega_2\psi_2 - k_3\omega_1\psi_1) + m_2\psi_3(k_1k_2 - \omega_1\psi_1) + k_1n_1\psi_2\psi_3 + m_1\psi_1\psi_2\psi_3)((1-f)(\eta_C\nu\phi k_6 + \eta_S\phi k_6k_8) + f\nu\phi\xi\eta_C + f\phi\xi\eta_s k_8 + f\phi\eta_n k_7k_8 + k_6k_7k_8)]$$

$$v_6 = \frac{1}{k_5k_6k_7k_8(k_1k_2k_3 - k_1\omega_2\psi_2 - k_3\omega_1\psi_1)(m\mathcal{R}_0 - 1)} \times [k_5v_4(\nu\xi\eta_C + \xi\eta_S k_8 + \eta_n k_7k_8)(n_2(k_1k_2k_3 - k_1\omega_2\psi_2 - k_3\omega_1\psi_1) + m_2\psi_3(k_1k_2 - \omega_1\psi_1) + k_1n_1\psi_2\psi_3 + m_1\psi_1\psi_2\psi_3)]$$

$$v_7 = \frac{k_5k_6\nu_4(\nu\eta_C + \eta_S k_8)[\eta_2(k_1k_2k_3 - k_1\omega_2\psi_2 - k_3\omega_1\psi_1) + m_2\psi_3(k_1k_2 - \omega_1\psi_1) + k_1\eta_1\psi_2\psi_3 + m_1\psi_1\psi_2\psi_3]}{k_5k_6k_7k_8(k_1k_2k_3 - k_1\omega_2\psi_2 - k_3\omega_1\psi_1)(m\mathcal{R}_0 - 1)}$$

$$v_8 = \frac{k_5k_6k_7\eta_C v_4[\eta_2(k_1k_2k_3 - k_1\omega_2\psi_2 - k_3\omega_1\psi_1) + m_2\psi_3(k_1k_2 - \omega_1\psi_1) + k_1\eta_1\psi_2\psi_3 + m_1\psi_1\psi_2\psi_3]}{k_5k_6k_7k_8(k_1k_2k_3 - k_1\omega_2\psi_2 - k_3\omega_1\psi_1)(m\mathcal{R}_0 - 1)}$$

$v_9 = 0$

Computation of b:

$b = \frac{x_2^* r_1(v_5-v_2)+x_3^* r_2(v_5-v_3)+x_4^* r_3(v_5-v_4)+x_1^*(v_5-v_1)(\eta_c w_8+\eta_n w_6+\eta_S w_7+w_5)}{x_1^*+x_2^*+x_3^*+x_4^*}$

The coefficient b is positive provided $v_5 > v_1, v_2, v_3, v_4$.

Computation of a:

$a = \frac{-2\beta(\eta_c w_8+\eta_n w_6+\eta_S w_7+w_5)}{(x_1+x_2+x_3+x_4)^2}[-x_1 r_1 w_2(v_5 - v_2) - x_1 r_2 w_3(v_5 - v_3) - x_1 r_3 w_4(v_5 - v_4) + (w_1 + w_2 + w_3 + w_4 + w_5 + w_6 + w_7 + w_8 + w_9)x_2 r_1(v_5 - v_2) - x_3 r_1 w_2(v_5 - v_2) - x_2 r_2 w_3(v_5 - v_3) - x_2 r_3 w_4(v_5 - v_4) + (w_1 + w_2 + w_3 + w_4 + w_5 + w_6 + w_7 + w_8 + w_9)x_3 r_2(v_5 - v_3) - x_4 r_1 w_2(v_5 - v_2) - x_4 r_2 w_3(v_5 - v_3) - x_3 r_3 w_4(v_5 - v_4) + (w_1 + w_2 + w_3 + w_4 + w_5 + w_6 + w_7 + w_8 + w_9)x_4 r_3(v_5 - v_4) - w_1(v_5 - v_1)(x_2 + x_3 + x_4)]$

$$
\begin{aligned}
\Rightarrow a = \frac{-2\beta(\eta_c w_8 + \eta_n w_6 + \eta_S w_7 + w_5)}{(x_1 + x_2 + x_3 + x_4)^2}[&-x_1 r_1 w_2(v_5 - v_2) - x_1 r_2 w_3(v_5 - v_3) - \\
&x_1 r_3 w_4(v_5 - v_4) + (w_5 + w_6 + w_7 + w_8 + w_9)x_2 r_1(v_5 - v_2) - x_3 r_1 w_2(v_5 - v_2) - \\
&x_2 r_2 w_3(v_5 - v_3) - x_2 r_3 w_4(v_5 - v_4) + (w_5 + w_6 + w_7 + w_8 + w_9)x_3 r_2(v_5 - v_3) - \\
&x_4 r_1 w_2(v_5 - v_2) - x_4 r_2 w_3(v_5 - v_3) - x_3 r_3 w_4(v_5 - v_4) + \\
&(w_5 + w_6 + w_7 + w_8 + w_9)x_4 r_3(v_5 - v_4) + x_1(w_5 + w_6 + w_7 + w_8 + w_9)(v_5 - v_1) - \\
&w_1(v_5 - v_1)(x_2 + x_3 + x_4) + ((w_1 + w_3 + w_4)x_2 r_1(v_5 - v_2) + (w_1 + w_2 + w_4)x_3 r_2(v_5 - v_3) + \\
&(w_1 + w_2 + w_3)x_4 r_3(v_5 - v_4) + x_1(w_2 + w_3 + w_4)(v_5 - v_1))]
\end{aligned}
$$

if $a < 0$ and $b > 0$ then the EEP of the model will be locally asymptotically stable.
From the above expression it can be shown that $a < 0$ if

$$B_1 > B_2 \tag{6.6}$$

where $B_1 = -x_1 r_1 w_2(v_5 - v_2) - x_1 r_2 w_3(v_5 - v_3) - x_1 r_3 w_4(v_5 - v_4)$
$+ (w_5 + w_6 + w_7 + w_8 + w_9)x_2 r_1(v_5 - v_2) - x_3 r_1 w_2(v_5 - v_2) - x_2 r_2 w_3(v_5 - v_3)$
$- x_2 r_3 w_4(v_5 - v_4) + (w_5 + w_6 + w_7 + w_8 + w_9)x_3 r_2(v_5 - v_3) - x_4 r_1 w_2(v_5 - v_2)$

$- x_4r_2w_3(v_5 - v_3) - x_3r_3w_4(v_5 - v_4) + (w_5 + w_6 + w_7 + w_8 + w_9)x_4r_3(v_5 - v_4) +$
$x_1(w_5 + w_6 + w_7 + w_8 + w_9)(v_5 - v_1) - w_1(v_5 - v_1)(x_2 + x_3 + x_4)$ and
$B_2 = (w_1 + w_3 + w_4)x_2r_1(v_5 - v_2) + (w_1 + w_2 + w_4)x_3r_2(v_5 - v_3)$
$+ (w_1 + w_2 + w_3)x_4r_3(v_5 - v_4) + x_1(w_2 + w_3 + w_4)(v_5 - v_1).$
Thus, using Central Manifold theory, the endemic equilibrium point is LAS under some condition ($B_1 > B_2$). □

6.4 Vaccination Impact

In this section, the impact of the HBV vaccine is analysed on the threshold, $\mathcal{R}_{01}$. First of all, let us consider $\mathcal{R}_0$ as a function of susceptible individuals vaccinated at steady-state (i.e. at $P_1 = \frac{V^*}{N^*}$). For mathematical simplification, we assume that $V^* = V_1^* + V_2^* + V_3^*$ and their efficacy are equal. That is,

$$\mathcal{R}_0 = \mathcal{R}_0(P_1) = \frac{\beta((1-P_1) + rP_1)[(1-f)(\eta_C\nu\phi k_6 + \eta_S\phi k_6k_8) + \eta_n\phi f k_7k_8 + \eta_S\phi k_8\xi f + \eta_C\phi\nu\xi f + k_6k_7k_8]}{k_5k_6k_7k_8}$$
$$= \frac{\beta((1-P_1) + rP_1)A_{11}}{k_5k_6k_7k_8}$$

where, $A_{11} = (1-f)(\eta_C\nu\phi k_6 + \eta_S\phi k_6k_8) + \eta_n\phi f k_7k_8 + \eta_S\phi k_8\xi f + \eta_C\phi\nu\xi f + k_6k_7k_8$. Differentiating $\mathcal{R}_0(P_1)$ partially with respect to P_1 gives

$$\mathcal{R}_{01} = \frac{\partial\mathcal{R}_0(P_1)}{\partial P_1} = -\frac{\beta A_{11}}{k_5k_6k_7k_8}(1 - \nabla) \tag{6.7}$$

with $\nabla = \frac{r\beta A_{11}}{A_{11}\beta}$.

It follows from (6.7), if $\nabla < 1$ then $\frac{\partial\mathcal{R}_{01}}{\partial P_1} < 0$. That is $\mathcal{R}_0$ is a decreasing function of P_1, when $\nabla < 1$. Moreover, reduction in reproduction number means reduction in disease burden. So, the analysis shows that an imperfect HBV vaccine has a positive effect in reducing the burden of disease if $\nabla < 1$, and has no impact for other cases. The is summarized as:

Lemma 6.3. *The imperfect vaccine will have*

(i) a positive impact in reducing disease burden if $\nabla < 1$ *;*

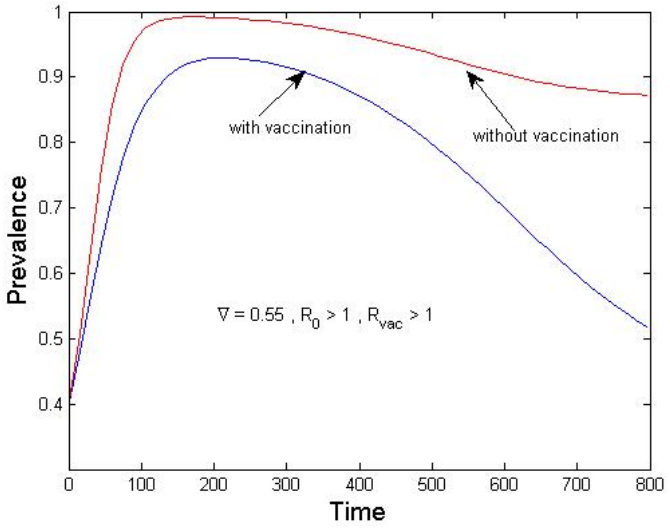

FIGURE 6.4: The prevelance considering the presence and absence of a vaccine, where, $\beta = 3.09$ (so that $\nabla = 0.55$, $\mathcal{R}_0 = 2.34 > 1$ and $\mathcal{R}_{01} = 2.68 > 1$) and the parameter values are given in Table 6.2.

(ii) no impact in reducing disease burden if $\nabla = 1$ *;*

(iii) increase disease burden if $\nabla > 1$.

The above result is done by simulating the vaccination model (6.2) using the value of the parameters in Table 6.2. The above Figure 6.4 illustrate that prevalence as a function of time. From the figure we see that with $\nabla = 0.55 < 1$ (corresponding to the vaccine efficacy of 65%, 55%, 87%, where, $r_1 = 0.65, r_2 = 0.55, r_3 = 0.87$ respectively) vaccine has a positive impact, since it reduces disease burden than that of the case when vaccine is not used.

A contour plot of $\mathcal{R}_0$, as a function of the first vaccine dose efficacy and administration rate of first dose. Figure 6.5 shows that with the expected minimum 65% efficacy of the first vaccine dose, administrating 75% to the susceptible population with the first vaccine dose may be sufficient to control the spread of Hepatitis B infection. However, form Figure 6.6, it is clear that same effective control may also be obtained if 60% of the first vaccine dose recipients take the second dose.

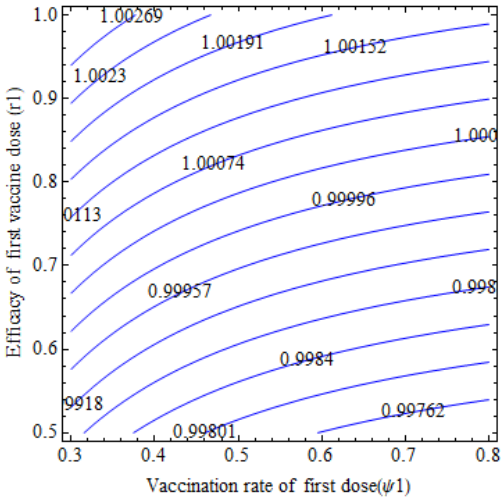

FIGURE 6.5: Contour plots of $\mathcal{R}_0$ as a function of the first dose of vaccination rate (ψ_1) and vaccine efficacy (r_1) with $\beta = 0.93$.

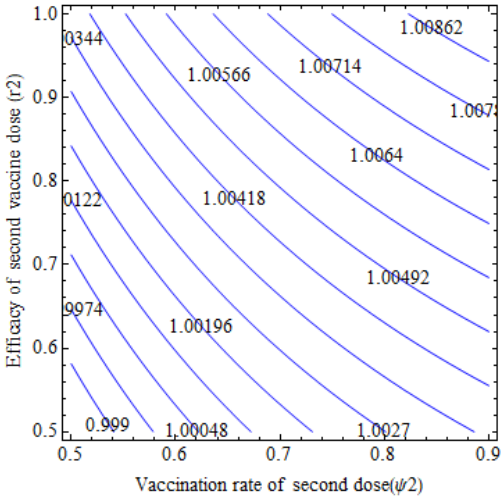

FIGURE 6.6: Contour plots of $\mathcal{R}_0$ as a function of the second dose of vaccination rate (ψ_2) and vaccine efficacy (r_2) with $\beta = 0.85$.

6.5 Sensitivity Analysis of the parameters

The analysis of the sensitive parameters is done to decide which of the parameters have vital importance in the disease transmission dynamics. We calculate the sensitivity indices of the threshold, $\mathcal{R}_0$, to the parameters defined in (6.2), to decide which of the parameters have an essential effect on $\mathcal{R}_0$ and consequently responsible for the transmission of disease among the population. Here we use the method described in [92, 93]. Sensitivity indices estimate the relative change in the state while a parameter is also changed. The normalized forward

sensitivity index of a variable to a parameter is the ratio of the relative change of the variable to the relative change of the respective parameter.

6.5.1 Definition

The normalized sensitivity index of a variable, v, that depends differentiably on a parameter, r, is given by:

$$\chi_r^v = \frac{r}{v} \times \frac{\partial v}{\partial r}$$

6.5.2 Sensitivity Indices of Effective Reproduction Number ($\mathcal{R}_0$)

Since we have a formula for $\mathcal{R}_0$, we can derive an analytical expression for the sensitivity of $\mathcal{R}_0$,

$$\chi_r^{\mathcal{R}_0} = \frac{r}{\mathcal{R}_0} \times \frac{\partial \mathcal{R}_0}{\partial r}$$

We can see from the Table 6.4 that all the parameters of the model have either positive or negative impact on $\mathcal{R}_0$. We observed from the Table 6.4 that the parameters β, r_3 and η_C are the most positively sensitive parameters with vaccine effect. This implies that the increased values of those parameters, $\mathcal{R}_0$ will also increase.

Again we can see that the parameters, p, ψ_1, ψ_2, ω_3 and δ are the most negatively sensitive parameters. This implies that if the values of these parameters increased then $\mathcal{R}_0$ will be decreased and vice versa.

Further, the parameters β, η_S and η_C are positively sensitive when vaccine is not used and the parameters p , f, μ, δ and θ_t are the most negative sensitive parameters for the same case.

Therefore, Local sensitivity analysis (LAS) shows that the negatively influential parameters are the proportion of the newborn's vaccination rate (p), fraction of the acutely infected individuals who become chronically infected (f), natural death rate (μ), HBV- related mortality rate (δ) and modification parameter for the assumed decrease of the recovery rate of symptomatic chronically-infected individuals in complication to non-symptomatic chronically-infected individuals (θ_t) and positively sensitive parameters are the

Parameter	Base value	Sensitivity index of $\mathcal{R}_0$ with vaccine	Sensitivity index of $\mathcal{R}_0$ without vaccine
Π	0.0121	too small (positive)	too small (positive)
p	[0,1]	-0.000773	-1.85714
β	$0.95 - 20.49$	0.9999	≈ 1
ω_1	0.1	0.000131	$-$
ω_2	[0,1]	0.00001183	-
ω_3	[0,1]	-0.0008107	-
f	[0,1]	-0.036512	-0.006965
ψ_1	0.885 y^-1	-0.000543	-
ψ_2	0.925 y^-1	-0.0004195	-
ψ_3	0.879 y^-1	0.003619	-
μ	0.00693	-0.7855	-0.782081
δ	0.002	-0.224904	-0.225013
r_1	[0,1]	0.007909	-
r_2	[0,1]	0.006305	-
r_3	[0,1]	0.98167	-
ϕ	4	0.0001416	0.0001868
ξ	0.12	0.023439	0.006476
γ	0.06	-0.044202	-0.028612
θ_t	0.0936 y^-1	-0.022703	-0.022713
ν	0.2323 y^-1	0.029029	0.0290437
η_n	(0,1)	0.0005437	0.000137
η_S	1.2	0.029772	0.029787
η_C	1.5	0.968096	0.968567

TABLE 6.4: Sensitivity index of $\mathcal{R}_0$ to some parameters of the HBV vaccination model (6.2)

infectiousness of symptomatic chronic carriers (η_S), infectiousness of the disease complicated individuals (η_C)and disease transmission rate (β). However, LAS does not accurately assess the uncertainty and sensitivity of the parameters in the system. To avoid this difficulty Latin Hypercube sampling-partial rank correlation coefficient (PRCC) technique is the most popular method for global sensitivity analysis.

6.5.3 PRCC Analysis for Global Sensitivity

A statittical technique for sensitivity analysis named PRCC, which calculates the partial rank correlation coefficient for the parameters of the model (with the help of Latin hypercube sampling technic)[94, 95]. The calculated values of PRCC for parameters lies are between -1 and 1 and they are comparable between distinct model inputs. The positive or negative sign of the PRCC values of parameters gives the relationship between the model input and output. A positive value of PRCC means that if the corresponding model input parameters increase then the output will also increase. Similarly, the negative value of PRCC indicates a negative correlation. The constant value of PRCC measures the significant change of the model input and contribute to the associated model output[94, 95].

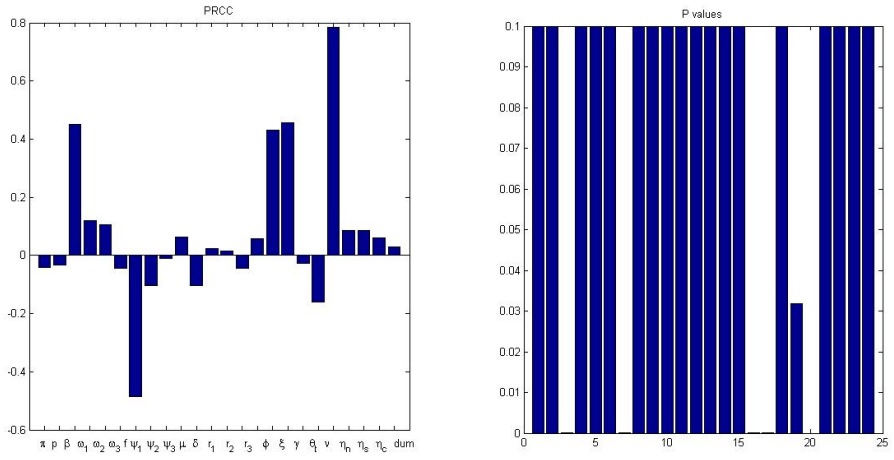

FIGURE 6.7: Sensitivity of some parameters of HBV vaccination model as indicated by the PRCC

For the HBV vaccination model (6.2), the PRCC index illustrates that disease transmission rate (β), fraction of the acutely infected individuals who are gradually chronically infected (f), at the rate when acutely-infected people become chronically infected (ϕ), rate at which asymptomatic chronically-infected individuals become symptomatic chronically-infected (ξ) and rate at which symptomatic chronically-infected individuals develop disease complications (ν) and the respective PRCC indices are 0.5305, -0.5870, 0.5318, 0.5612, 0.7865 respectively, and their p-values are illustrated in Figure 6.7. The entire result illustrates that if the transmission rate (β) increases unexpectedly, then the spread of the disease is unbounded and it is very difficult to control. In comparison, the proportion of acutely infected individuals

who become chronically infected (f) can be the most sensitive parameter for controlling the spread of infectious disease transmission.

6.5.4 Contour Plot Analysis

In this section, we find the correlation between the most sensitive parameters through some contour plot analysis. Figure 6.8 illustrates that there is a positive correlation between the transmission rate (β) and the reproduction number, $\mathcal{R}_0$, similarly, the same correlation occurs between the infectiousness of disease complications (η_C) and $\mathcal{R}_0$.

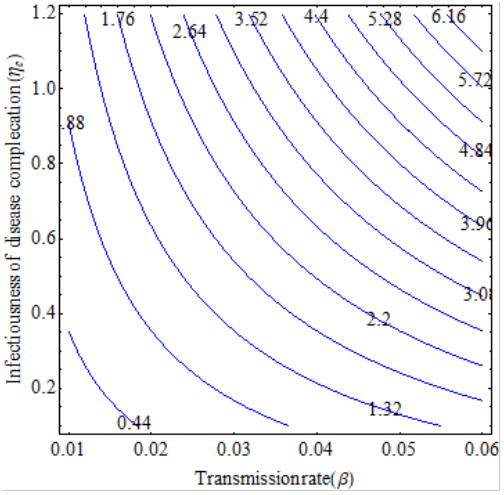

FIGURE 6.8: Figure of contour plot in terms of the two sensitive parameters: β (transmission rate)and η_C(infectiousness of disease complications).

Figure 6.9 illustrates that there is a negative relation between the recovery rate of symptomatic chronic carriers (θ_t) and $\mathcal{R}_0$, whereas there is a positive correlation between the rate of symptomatic chronic carriers (ξ) and $\mathcal{R}_0$.

6.6 Conclusions

A deterministic model, assessing imperfect dose-dependent vaccination of HBV transmission dynamics at the population level, is constructed and analysed (mathematically and numerically). Some mathematical and epidemiological findings are given below:

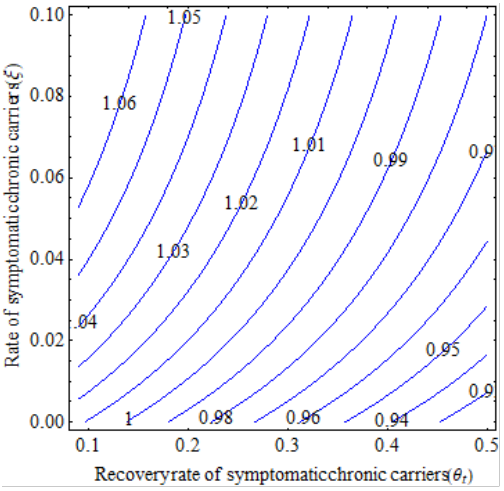

FIGURE 6.9: Figure of contour plot in terms of the two sensitive parameters: θ_t(recovery rate of symptomatic chronic carriers) and ξ (rate of symptomatic chronic carriers).

(i) The HBV vaccination model has a locally and globally asymptotically stable disease free equilibrium (DFE) when the corresponding threshold quantity, known as, $\mathcal{R}_0 < 1$.

(ii) The model has also a locally asymptotically stable unique endemic equilibrium point (EEP) under some condition.

(iii) An imperfect HBV vaccine have positive, negative and no effect on population depending on ∇.

(iv) Local sensitivity analysis of the parameters show that disease transmission rate (β), infectious rate of disease complication (η_C), the development rate of disease complication (ν) are the positive sensitive parameters and proportion of the newborns vaccination rate (p), recovery rate of chronically infected individuals (γ) are the negative sensitive parameters of the model on threshold quantity.

(v) Using Latin hypercube sampling for partial rank correlation coefficient (PRCC) of global sensitive parameters shows that disease transmission rate (β), fraction of the acutely infected individuals who developed chronic infection (f), the rate at which acutely-infected people become chronically infected (ϕ), development rate of the asymptomatic chronic carriers to be symptomatic (ξ),the development rate of disease complication (ν) are highly sensitive parameters that effect the disease dynamics of HBV among individuals.

(vi) Furthermore, contour plot analysis between the sensitive parameters show that disease can be controlled if the disease burden is reduced.

Chapter 7

Contributions of the Thesis

In this thesis, a number of deterministic mathematical models related to HBV transmission disease dynamics are formulated and analyzed rigorously (mathematically and numerically) and presented in different chapters. Some mathematical and epidemiological findings are as follows:

(i) In ***Chapter 3***, a new deterministic model for the transmission disease dynamics of HBV among the population is formulated numerical simulations is rigorously analyzed. The model has a locally-asymptotically stable (LAS) DFE for $\mathcal{R}_0 < 1$. By Lyapunov function and LaSalle Invariance Principle, the model has a globally-asymptotically stable DFE whenever $\mathcal{R}_0 < 1$. The model has a unique endemic equilibrium (EEP) for $\mathcal{R}_0 > 1$. Sublinearity trick is used for stability analysis of EEP and using nonlinear Lyapunov function the global stability of EEP is shown, whenever, the threshold $\mathcal{R}_0 > 1$. If re-infection is considered then backward bifurcation occurs, where an asymptotic stable DFE and an unstable EEP co-exists when $\mathcal{R}_0 < 1$.

(ii) In ***Chapter 4***, a new basic (without immune response) deterministic model for the transmission disease dynamics of HBV *in vivo* is constructed and numerically analysed. Then the model is extended for immune responses namely cell-mediated and humoral against HBV *in vivo*. The basic model (4.3) has a GAS VFE and also

has at least one locally asymptotically positive virus present equilibrium (VPE), $\mathcal{E}_1$ whenever $\mathcal{R}_0 > 1$. The reduced model of the immune system has a GAS VFE if $\mathcal{R}_{01} < 1$ and a positive unique locally asymptotically stable VPE whenever $\mathcal{R}_{01} > 1$. Due to vaccine impact, the humoral immune response such as antibody level is always more effective than the cell-mediated immune response in reducing HBV infection. The high effective level of immune response with a low contact rate can reduce the HBV burden *in vivo*.

(iii) In ***Chapter 5***, the dynamics of hepatitis B virus infection, subject to optimal control strategies with vaccination and creating awareness as controls are designed and analysed. The numerical simulations show that the optimal strategies of vaccination and awareness are much more effective not only to minimize the infection as well as to control hepatitis B virus infection. A combination of with and without control strategies is considered. The control parameters are much more effective to reduce the infected individuals and controlling the disease dynamics. The controls are needed to be effective for a long time interval with a high transmission rate. The control strategy is also effective in minimising the infection of infected individuals and the cost of the two controls. The numerical results illustrate that vaccination plays an essential role in disease elimination.

(iv) In ***Chapter 6***, A deterministic model, assessing imperfect dose-dependent vaccination of HBV transmission dynamics at the population level, is considered and analysed (mathematically and numerically). The HBV vaccination model has a disease free equilibrium (DFE) which is locally and globally asymptotically stable when the associated threshold quantity, known as $\mathcal{R}_0$, is less than unity. The model has a unique endemic equilibrium point (EEP) which is LAS under certain conditions. An imperfect HBV vaccine could have positive or negative or no population-level impact depending on ∇, which is either less than or equal to or greater than unity. Local sensitivity analysis of the parameters shows that disease transmission rate (β), infectious rate of disease complication (ν) are the most positively sensitive parameters. On the other hand, the proportion of the newborn's vaccination rate (p), the recovery rate of chronically infected individuals (γ) are the

most negatively sensitive parameters on the epidemic threshold. For evaluating the partial rank correlation coefficient (PRCC) of global sensitive parameters we use Latin hypercube sampling, which shows that disease transmission rate (β), fraction of the acutely infected individuals who developed chronic infection (f), the rate of the acutely-infected people who become chronically infected (ϕ), development rate of the asymptomatic chronic carriers to be symptomatic (ξ), the development rate of disease complication (ν) are highly influential sensitive parameters that affect the disease dynamics of HBV among individuals. Furthermore, contour plot analysis between the sensitive parameters shows that disease can be controlled if the disease burden is reduced.

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