MATHEMATICAL MODEL OF HEPATITIS B TRANSMISSION DYNAMICS WITH OPTIMAL CONTROL

By
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A Thesis Submitted to
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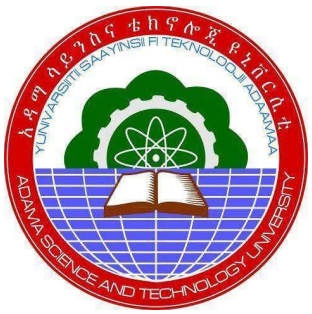

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List of Abbreviations

SLICVRS	Susceptible Exposed,Acute infective Carriers Vaccinated Recover Susceptible
OC	Optimal Control
OCP	Optimal Control Problem
PMP	Pontryagin Maximum Principle
ODE	Ordinary Differential Equation
NLP	Nonlinear Programming
RK	Runge Kutta
WHO	World Health Organization
DFE	Disease Free Equilibrium
FBS	Forward Backward Sweep
HBV	Hepatitis B Virus
STDs	Sexually Transmitted Diseases

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Abstract

In this thesis we study the dynamics of Hepatitis B virus (HBV) infection under administration of a vaccine and treatment, where the disease is transmitted directly from the parents to the offspring and also through contact with infective individuals. Initially we consider constant controls for vaccination and treatment. In the constant controls case, by determining the basic reproduction number, the basic reproductive number, R_0 of our SVLICRS model was calculated to be 2.467198, which implies that on average, each infectious individual transmits virus to 2.467198 people, we study the existence and stability of the disease-free and endemic steady-state solutions of the model. Next, we take the controls as time and formulate the appropriate optimal control problem and obtain the optimal control strategy to minimize the number of acutely infected, Chronic carriers humans and the associated costs. Finally at the end numerical simulation results show that vaccination and treatment are the most effective way to control hepatitis B virus infection.

Contents

Chapter 1

Introduction

1.1 Background of the Study

Hepatitis is an inflammation of the liver caused by certain viruses and other factors, such as alcohol abuse, some medications and trauma. Although many cases of hepatitis are not a serious threat to health, infectious with certain hepatitis viruses can become chronic and can sometimes lead to liver failure and death[15].

In [32] the author stated that hepatitis B virus (HBV) can be transmitted horizontally and vertically. Horizontal transmission occurs during adolescence or childhood, throughout sexual exposure, needle stick (both accidental or through intravenous drug use), and blood transfusion. Therefore, any person with a bad history of sexually transmitted diseases (STDs), multiple sexual partners or an injecting drug user stands a higher chance of being infected with HBV [9]. Exposure to blood is also means of open wounds in households and other close contacts and multiple transfusions in hemophiliacs. This view of exposure to risk was also shared who argued that most of the infections occur among adolescents and young adults due to exposure to high risk activities they engage in at this stage of life [6].

In the same article, the author strayed that a vertical transmission occurs when an infected mother transmits the virus directly to the neonatal during child birth. Such transmissions are usually possible when the expectant mother suffers an acute infection of hepatitis B during pregnancy or if she is a chronic carrier during that period. The mode of this vertical transmission is not clear cut, but indications are that, infection might occur through a placenta cutting during childbirth. Majority of countries in Southeast Asia, the Western pacific and Africa have high endemicity of HBV. In these settings the major mode of HBV transmission has been identified as vertical, where by mothers directly transmit virus to their infants during prenatal periods or where infected siblings, playmates,other members of different households transmit the virus to their younger ones. A cross-sectional study clarified that without prophylaxis, an estimated number of 6000 infants born to carrier mothers each year in the USA would develop chronic HBV infection as a consequence of prenatal transmission

Hepatitis B is highly endemic in developing countries with large population such as South East Asia, China, sub−Saharan Africa including Ethiopia and the Amazon Basin, where at least 8% of the population are HBV chronic carrier. In these areas, 70 - 95% of the population shows past or present serological evidence of HBV infection. Most infections occur during infancy or childhood. Since most infections in children are asymptomatic, there is little evidence of acute disease related to HBV, but the rates of chronic liver disease and liver cancer in adults are high [19].
A community-based seroepidemiological survey of Addis Ababa, Ethiopia was conducted in 1994 to inform on the transmission dynamics and control of hepatitis B virus (HBV) infection. Venous blood from 4736 individuals under 50 years of age from 1262 households, selected using stratified cluster-sampling, was screened for HBV markers using commercial ELISAs. HBsAg prevalence was 7% (95% CI 6˘8), higher in males (9%; 7−10) than females (5%; 4−6). HBeAg prevalence in HBsAg positives was 23% (18˘29), and less than 1% of women of childbearing age were HBeAg positive. Overall HBV seroprevalence (any marker), rose steadily with age to over 70% in 40−49 year olds, indicating significant childhood and adult transmission. Estimated instantaneous incidence was 3˘4% susceptibles/year, higher in males than females in 0−4 year olds, and peaking in early childhood and young adults. The age at which 50% had evidence of infection was around 20 years, and the herd immunity threshold is approximated at 63−77%. Addis Ababa is of intermediate-high HBV endemicity, with negligible perinatal transmission [1].

Causes and Symptoms of Hepatitis B

Many people infected with viral hepatitis have no symptoms. For example, about one-third of people infected with HBV have a completely ”silent” disease. When symptoms are present, they may be mild or severe.

- The most common early symptoms are mild fever, headache, muscle aches, fatigue, loss of appetite, nausea, vomiting and diarrhea.
- Later symptoms may include dark coffee-colored, rather than dark yellow, urine, clay-colored stools, abdominal pain,and yellowing of the skin and whites of the eyes (jaundice).

Testing for Hepatitis B Infection

Several blood tests can detect signs of HBV even before symptoms develop.These tests measure liver function and identify HBV antigens (certain portions of the hepatitis B virus) or antibodies (proteins produced by the body in response to the virus) in the blood.

Acute Infections

Acute HBV infections have an average incubation period of 90 days (range: 60-150 days) and can be define as an abrupt clinical, biochemical, and/or histopatho-logical manifestation of hepatic injury that occurs within six months of HBV exposure and that resolves

spontaneously, in more than 90% of cases, within six months of the onset of symptoms. Clinical symptoms include nausea,vomiting, abdominal pain, fever, jaundice, dark urine, changes in stool colour, and hepatomegaly. Acute hepatitis B refers to the first six months of exposure of the patients's body to HBV. In this stage the immune system is usually able to clear the virus from the body and the individual may completely recover within a few months [15].

Chronic Infections

Chronic hepatitis B refers to the illness that occurs when HBV remains in the body for a long time and develops serious health problem. Individuals with chronic hepatitis often do have no history of acute illness, but it can cause liver scarring that causes liver failure and may also develop liver cancer [25] .

How is the Hepatitis B Vaccine Made

People are protected against hepatitis B virus infection by making an immune response to a protein that sits on the surface of the virus. When hepatitis B virus grows in the liver, an excess amount of this surface protein is made. The hepatitis B vaccine is made by taking the part of the virus that makes surface protein ("surface protein gene") and putting it into yeast cells. The yeast cells then produce many copies of the protein that are subsequently used to make the vaccine. When the surface protein is given to children in the vaccine, their immune systems make an immune response that provides protection against infection with the hepatitis B virus. The first hepatitis B vaccine was made in the 1980s by taking blood from people infected with hepatitis B virus and separating or purifying the surface protein from the infectious virus. Because blood was used, there was a risk of contaminating the vaccine with other viruses that might be found in blood, such as HIV. Although contamination with HIV was a theoretical risk of the early, blood-derived, hepatitis B vaccine, no one ever got HIV from the hepatitis B vaccine. That is because the blood used to make vaccine was submitted to a series of chemical and treatments that inactivated any possible contaminating virus. Today, there is no risk of contaminating the vaccine with other viruses because the surface protein is manufactured in the laboratory [15].

Figure 1.1: Hepatitis B pills and vaccination:Source (gett-rf -photo pills and vaccination)

1.2 Statement of the Problem

Hepatitis B is a potentially life-threatening liver infection caused by the hepatitis B virus (HBV).Hepatitis B is the most serious types of viral hepatitis in the world. The disease has caused endemics in parts of Asia and Africa . About one third of the world population has been infected with hepatitis B, including 350 million who are chronic carriers which causes 620,000 deaths worldwide each year [15]. So far different prevention approaches and scientific methodologies have been applied to prevent and study this disease. However the epidemiology of Hepatitis B has become imperative, needing research and effort to help control the spread and eradicate this disease. So that, this study intended to answer the following basic questions:

- How,we formulate a mathematical model that describe the transmission dynamics of hepatitis B virus?
- What are the basic assumptions in developing a mathematical model which describes the HBV transmission dynamics?
- What is the biological implication of the solution of the developed mathematical model?

1.3 Objective of the Study

1.3.1 General objective

The general objective of this study is to investigate the transmission dynamics of HBV and its control strategy.

1.3.2 Specific Objectives

The Specific objectives of the study are to:

- modify the existing mathematical model for spread of Hepatitis B virus,
- investigate stability analysis of the model,
- investigate the control strategies, and
- interpret the biological meaning of the solution of the modified mathematical model.

1.4 Benefits and Beneficiaries

This study provides a reliable information on the transmission dynamics of hepatitis B virus (HBV), the control strategies of the spread of the disease, initiate further research on the dynamics of the disease and its transmission, and create awareness.

1.5 Mathematical Preliminary

1.5.1 Basic Reproduction Number

Intuitively from the epidemiological point of view, the basic reproduction number is the average number of new cases (infections), that one infected case will generate during their entire infectious lifetime [18]. The basic reproduction number, denoted <0; is the expected number of secondary cases produced, in a completely susceptible population, by a typical infective individual. If $R_0 < 1$; then on average an infected individual produces less than one new infected individual over the course of its infectious period, and the infection can not grow. Conversely, if $R_0 > 1$, then each infected individual produces, on average, more than one new infection, and the disease can invade the population. For the case of a single infected compartment, R_0 is simply the product of the infection rate and the mean duration of the infection[24]. However, for more complicated models with several infected compartments this simple heuristic definition of R_0 is insufficient. A more general basic reproduction number can be defined as the number of new infections produced by a typical infective individual in a population at a disease free equilibrium[14].

1.5.2 Next Generation Matrix

We define the next generation matrix as the square matrix G in which the ij^{th} element of G, g_{ij}, is the expected number of secondary infections of type i caused by a single infected individual of type$j$, again assuming that the population of type i is entirely susceptible. That is, each element of the matrix G is a reproduction number, but one where who

infects whom is accounted for Once we have G, we are one step away from R_0. The basic reproduction number is given by the spectral radius of G. The spectral radius is the also known as the dominant eigenvalue of G. The next generation matrix has a number of desirable properties from a mathematical standpoint. In particular, it is a non-negative matrix and, as such, it is guaranteed that there will be a single, unique eigenvalue which is positive, real, and strictly greater than all the others[14].
Consider the next generation matrix G. It is comprised of two parts: F and V^{-1}, where $F = \left[\frac{\partial F_i(x_0)}{\partial x_j}\right]$ And $V = \left[\frac{\partial V_i(x_0)}{\partial x_j}\right]$

The F_i are the new infections, while the V_i transfers of infections from one compartment to another.x_0 is the disease-free equilibrium state. R_0 is the dominant eigenvalue of the matrix $G = FV^{-1}$.

1.5.3 Numerical Methods for System of ODEs

The following numerical techniques are summarized from ([23], [24], [25], [22]). When a system of ODEs involves equations that can not be solved analytically, numerical methods are used to compute its approximate solution. For example, Euler's and fourth order Runge-Kutta methods can be used to solve initial-value problems. For example,if we want to solve the initial value problem

$$x' = \frac{dx}{dt} = f(t, x(t)), x(t_0) = x_0$$

on the interval $t_0 \leq t \leq T$, we divide the interval into N small segments of constant length h, called the step size given by

$$h = \frac{T - t_0}{N}.$$

This defines the set of equally spaced discrete times $t_0, t_1, t_2, \cdots, t_N = T$, where $t_n = t_0 + nh, n = 0, 1, 2, \cdots, N$. Note that $h = t_{n+1} - t_n$. We develop a recursive formula that gives the approximation X_{n+1} at time t_{n+1} in terms of the previous approximation X_n at time t_n.

Euler's Method

Euler's method approximates the equation $x' = \frac{dx}{dt} = f(t, x(t)), x(t_0) = x_0$ by

$$x_{n+1} = x_n + hf(t_n, x_n), n = 0, 1, 2, \cdots, N.$$

From an equivalent perspective, this method can be described by the following equation:

$$x(t + h) = x(t) + h\frac{dx}{dt},$$

where the h is the step size defined above. This method computes the value at $t + h$ with an error of order $O(h^2)$. The time step h is crucial to determine the accuracy of the approximation. Here, the smaller the value of h, the greater the accuracy of the approximation. However, the smaller the value of h, the greater the computational effort required. As such, for higher order systems of ODEs, due to its dependency on h, the Euler's method can become unstable and, consequently, does not converge to the exact solution.

Systems of equations

The numerical methods introduced for a single equation can be easily extended to systems of equations. For example, consider the two-dimensional system

$$\begin{aligned} x' &= f(t,x,y) \\ y' &= g(t,x,y) \end{aligned}$$

with initial conditions

$$x(t_0) = x_0,\ y(t_0) = y_0$$

We want to obtain a numerical solution on the interval $t_0 \le t \le T$ .The first step is to discretize the interval as before by defining the time steps by

$$t_n = t_0 + nh, n = 0, 1, 2, \cdots, N,$$

where N is the number of steps. Again, we use the notation X_n and Y_n to denote the approximate values of $x(t_n)$ and $y(t_n)$, respectively. We can summarize the methods as follows.

The Euler method

$$\begin{aligned} X_{n+1} &= X_n + hf(t_n, X_n, Y_n), \\ Y_{n+1} &= Y_n + hg(t_n, X_n, Y_n). \end{aligned}$$

The Runge-Kutta method

First we compute the values of the eight slopes:

$$\begin{aligned} k_{11} &= f(t_n, X_n, Y_n) \\ k_{21} &= g(t_n, X_n, Y_n) \\ k_{12} &= f\left(t_n + \frac{h}{2}, X_n + \frac{h}{2}k_{11}, Y_n + \frac{h}{2}k_{21}\right) \\ k22 &= g\left(t_n + \frac{h}{2}, X_n + \frac{h}{2}k_{11}, Y_n + \frac{h}{2}k_{21}\right) \\ k13 &= f\left(t_n + \frac{h}{2}, X_n + \frac{h}{2}k_{12}, Y_n + \frac{h}{2}k_{22}\right) \\ k23 &= g\left(t_n + \frac{h}{2}, X_n + \frac{h}{2}k_{12}, Y_n + \frac{h}{2}k_{22}\right) \\ k14 &= f\left(t_n + X_n + hK_{13}, Y_n + hK_{23}\right) \\ k24 &= g\left(t_n + X_n + hK_{13}, Y_n + hK_{23}\right) \end{aligned}$$

Then we compute the next approximation using weighted averages of these slopes,

$$\begin{aligned} X_{n+1} &= X_n + \frac{h}{6}\left(K_{11} + 2K_{12} + 2K_{13} + K_{14}\right) \\ Y_{n+1} &= Y_n + \frac{h}{6}\left(K_{21} + 2K_{22} + 2K_{23} + K_{24}\right) \end{aligned} \tag{1.1}$$

In such process, the continuous time model is reduced to an approximate discrete-time model that is amenable to computer simulation.
There are two major classes of numerical methods for solving Optimal control (OC) problems: indirect and direct methods. The first ones indirectly solve the problem by converting the optimal control problem to a boundary-value problem, using the Pontryagin's maximum principle-PMP. On the other hand, in a direct method, the optimal solution is found by transcribing an infinite-dimensional optimization problem to a finite-dimensional optimization problem which we do not consider in this work.

1.5.4 Indirect Method

In an indirect method, the Pontryagin's maximum principle(PMP) is used to determine the first order optimality conditions of the original optimal control problem. In the case of indirect method it is a must to explicitly get the adjoint equations, the control equations and all the transversality conditions, if they exsed to solve problems with the minimization problems , and generates numerical approximations to the optimal piece wise continuous control $u^*(t)$.The process begins with an initial guess on the control variable. Then, the state equations are first. Then we compute first-order optimality conditions using PMP from which the optimal trajectories are derived by solving a multiple-point boundary-value problem.

Backward-forward Sweep Method

For an indirect numerical approach, forward-backward sweep method (FBS) is presented in [25] and references therein. This method can be simultaneously solved forward in time and the adjoint equations are solved backward in time. The control is updated by inserting the new values of states and adjoints into its characterization, and the process is repeated until convergence occurs. It can be implemented, using the following algorithm:Considering $\mathbf{x} = (x_1, x_2), \ldots, x_{N+1}$ and $\mathbf{lambda} = (\lambda_1, \lambda_2, \ldots, \lambda_{N+1})$

the vector approximations for the state and the adjoint respectively. Hence, this algorithm can be summarized as follows.

Algorithm 1 Forward-Backward Sweep Method

1: Make an initial guess for $\mathbf{u}$ over the time interval ($\mathbf{u} \equiv 0$ is almost always sufficient)
2: Using the initial condition $x_1 = x(t_0) = a$ and the values for $\mathbf{u}$, solve $\mathbf{x}$ **forward** in time in compliance with its differential equation in the optimality system(using, e.g., RK4).
3: Using the transversality condition $\lambda_{N+1} = \lambda(t_f)$ and the values for u and x, solve λ **backward** in time according to its differential equation in the optimality system (using, e.g., RK4).
4: Update $\mathbf{u}$ using the new values for $\mathbf{x}$ and λ into the characterization of the optimal control.
5: Check convergence: if the variables are sufficiently close to the corresponding in the previous iteration, then output the current values as solutions, else return to Step 2.

Remark 1.5.1. *The convergence speed can be improved when a convex combination between the control values given by the characterization of the optimal control in step 4 and the previous ones is used.*

We make a few notes about the algorithm. When making the initial guess, **u** is almost always sufficient. For certain problems, where division by u occurs, an alternative initial guess must be used. Occasionally, our initial guess may require adjusting if the algorithm has problems converting. For step 2 and 3, any standard ODE solver can be used. In this thesis, a Runge-Kutta method of order four is used.

Chapter 2

Literature Review

Tahir Khana et al[27] presented the model for the transmission dynamic of acute and chronic HBV. They incorporated in the model acute-infected class and chronic-infected class and then modified the model with these new features. After formulating the model, they found the basic reproduction number R_0. As in epidemiological models, the model has two steady states, infected and uninfected steady states. Thus, they investigated both the disease-free state and endemic state and proved that the disease-free and endemic equilibria are both locally as well as globally stable under certain conditions. Furthermore, three time-dependent control variables are taken and a control strategy for minimizing the number of infected individuals and maximizing the number of non-infected individuals was developed.

Momoh A.A. et al[2] proposed an SVEIR model to understand the effect of detection and treatment of Hepatitis B at latent stage on the transmission dynamics of hepatitis B disease.Mathematical analysis was carried out that completely determines the global dynamics of the model. The impact of detection and treatment of Hepatitis B at latent stage on the transmission dynamics are discussed through the stability analysis of the disease free equilibrium.

Zou.L et al [33], proposed a mathematical model to understand the transmission dynamics and prevalence of HBV infection in China. Based on the data reported by the Ministry of Health of China, the model provides an approximate estimate of the basic reproduction number $R_0 = 2 : 406$. This indicates that hepatitis B is endemic in China and is approaching its equilibrium with the current immunization program and control measures. Although China made a great progress in increasing coverage among infants with hepatitis B vaccine, it has a long and hard battle to fight in order to significantly reduce the incidence and eventually eradicate the virus.

Kimbir A.R. et al [4] a mathematical model for the transmission dynamics of hepatitis B virus infection considering vaccination and treatment as control parameters in the host population is presented. First, the disease-free equilibrium state of the model was determined. The next generation method was used to determine the basic reproduction number R_0, as a threshold parameter, in terms of the given model parameters. R_0 was

analytically evaluated for its sensitivity to vaccination and treatment parameters. It was proved that the disease-free equilibrium state is locally asymptotically stable if the R_0 is below unity, otherwise, it is unstable. Local stability of the endemic equilibrium state was established using the centre manifold theory. The analytical results of the R_0 show that increasing the proportion of people who receive vaccines, either at birth or later in life, reduces it below unity. Similarly, increasing the proportion of carriers who receive treatment achieves the same purpose. The result of the local stability analysis of the disease-free equilibrium state shows that the disease can be eliminated if R_0 is below unity. The result of the centre manifold theory on the endemic equilibrium state shows that the disease can persist as the value of R_0 increases above one.The findings of this study strongly suggest a combination of effective vaccination and treatment as a control strategy is crucial to the success of HBV disease control.

In Ali Vahidian Kamyad[5], the author studied the dynamics of hepatitis B virus (HBV) infection which can be controlled by vaccination as well as treatment. Initially they considered constant controls for both vaccination and treatment. In the constant controls case, by determining the basic reproduction number, they studied the existence and stability of the disease-free and endemic steady-state solutions of the model. Next, they took the controls as time and formulate the appropriate optimal control problem and obtain the optimal control strategy to minimize both the number of infectious humans and the associated costs. Finally at the end numerical simulation results show that optimal combination of vaccination and treatment is the most efective way to control hepatitis B virus infection.

In Reza Akbari et al[25] the author studied the dynamics of Hepatitis B virus (HBV) infection under administration of a vaccine and treatment, where the disease is transmitted directly from the parents to the offspring and also through contact with infective individuals. Stability of the disease-free steady state is investigated. The basic reproductive rate, R_0, is derived. The results show that the dynamics of the model is completely determined by the basic reproductive number R_0. If $R_0 < 1$, the disease-free equilibrium is globally stable and the disease always dies out and if $R_0 > 1$, the disease-free equilibrium is unstable and the disease is uniformly persistent.

Blessing O.Emerenini and Simeon C.Inyama[7],proposed a mathematical model for the transmission dynamics of hepatitis B is considering different classes of individuals, namely immunized, susceptible, latent,infected and recovered class. The model in this study is based on the standard SEIR model. The disease-free equilibrium state of the model was established and its stability was analyzed using the Routh-Hurwitz theorem. The result of the analysis of the stability of the disease-free equilibrium state shows that hepatitis B can totally be eradicated if effort is made to ensure that the sum of the rate of recovery of the latent class, the rate at which latently infected individuals become actively infected and the rate of natural death must have a lower bound.

Sacrice Nana-Kyere et al [26] formulated and studied the transmission dynamics of hepatitis B disease that employs preventive and treatment controls for optimal control analysis of the SEIR model. The necessary conditions for the optimal control of the disease was derived and analyzed. Two types of control functions associated with the reduction of the exposed and the infective and treatment of infective strategies were considered. The control plots that were plotted showed that the number of exposed and infected human decreased in the optimality system. The control analysis indicates that the optimal control strategies have an incomparable effect for the reduction of the infected individuals as compared to the model without control and model with control . The simulation results showed that despite the vertical transmission incidence, the proposed control strategy is effective in the reduction of the number of the infective of the disease .

In this thesis, we use SVEICRS model and apply it to HBV transmission. We extended the model A.R.Kimbir.Aboiyar el at [4] by introducing the recovered individuals enter into the susceptible class again and the newborns to acutely infected mothers infected at birth proceed to the latent class.

Chapter 3

Research Methodology

3.1 Research Methodology

To study the transmission dynamics of HBV with optimal control, we use a system of non-linear ordinary differential equation.The model analysis was done using standard mathematical tools. Both local and global stability analysis was performed using linearazation and lypunov functions respectively.The optimal control was derived using Pontryagin's maximum principle (a necessary condition also known as pontryagin's principle) or by solving the Hamilton-Jacobi-Bellman equation (a sufficient condition). To supplement the analytical solution of the model equation,we were perform a numerical simulation using MATLAB software.

Chapter 4

Model Formulation and Analysis

4.1 Model Description

The population is divided in to six compartments: Susceptible (S), vaccinated (V),latent (L), acutely infected (I), Chronic carriers (C) and Recover (R). The flow between the six compartments is shown in the schematic diagram below:

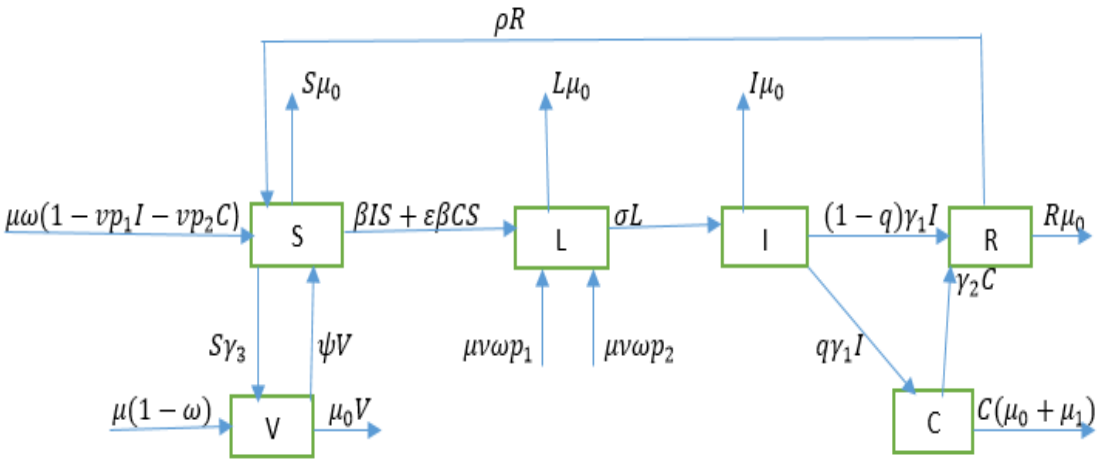

Figure 4.1: Flow diagram of the model.

Model Assumptions

- The population is compartmentalized into the proportions of susceptible individuals S(t) , latent individuals L(t), acutely infected individuals I(t), chronic carriers C(t), vaccinated individuals V(t) and the recovered individuals R(t) all at time t,
- The population is homogeneous,
- Influx into the population is by birth only,

- Exit out of the population is by natural and HBV-related mortality only,
- The vaccinated individuals do not acquire permanent immunity,
- The newborns to carrier mothers infected at birth, first, enter the latent class
- The newborns to acutely infected mothers infected at birth, first, enter the latent class,
- The treated individuals recover,
- The recovered individuals enter in to permanent immunity.

Table 4.1: Variables of the Model

variables	description
S(t)	the susceptible individuals at time t
L(t)	the latent individuals at time t
I(t)	the acutely infected individuals at time t
C(t)	the chronic carriers at time t
R(t)	the recovered individuals at time t
V(t)	the vaccinated individuals at time t

Table 4.2: parameter of the model

parameter	description
μ	birth rate
μ_0	natural mortality
μ_1	HBV-related mortality rate
ω	proportion of births without vaccination
$(1-\omega)$	proportion of births with vaccinated
υ	proportion of births vertically infected
ψ	rate of waning vaccine-induced immunity
σ	rate of moving from latent state to acute state
β	transmission coefficient
γ_1	rate of moving from acutely infected to chronic carriers and recovered class
q	average probability that an individual fails to clear I and develops to C
$q\gamma_1$	rate of moving from acute to carrier
$(1-q)\gamma_1$	rate of moving from acute to recovered class
γ_2	rate of moving from carrier to recover
γ_3	vaccination rate of susceptible individuals
ϵ	reduced transmission rate relative to acutely infection by carriers
p_1	probability of infected newborns from acutely infected mothers
p_2	probability of infected newborns from carrier infected mothers
ρ	denotes a portion that moves from compartment R to S due to loss of immunity

Based on the model assumption and the schematic diagram the governing system of equation is given as

$$\begin{cases} \dot{S}(t) = \mu\omega(1 - vp_1I - vp_2C) + \psi V + \rho R - (\mu_0 + \beta I + \epsilon\beta C + \gamma_3)S \\ \dot{L}(t) = (\beta I + \epsilon\beta C)S + (p_1I + p_2C)\mu v\omega - (\mu_0 + \sigma)L \\ \dot{I}(t) = \sigma L - (\mu_0 + \gamma_1)I \\ \dot{C}(t) = q\gamma_1 I - (\mu_0 + \mu_1 + \gamma_2)C \\ \dot{V}(t) = \mu(1 - \omega) + \gamma_3 S - (\psi + \mu_0)V \\ \dot{R}(t) = (1 - q)\gamma_1 I + \gamma_2 C - (\mu_0 + \rho)R \end{cases} \tag{4.1}$$

with initial condition $S(0) = S_0$, $V(0) = V_0$, ,$L(0) = L_0$, $I(0) = I_0$, $C(0) = C_0$ and $R(0) = R_0$

4.2 Positivity of the Solutions

Since the model deals with human population we have to show that all the solution of the system of equations should be non negative.For this we state the following theorem and prove it.

Theorem 4.2.1. *Let* $\Omega = \{(S, L, I, C, V, R) \in R_+^6 : S_0 > 0, L_0 \geq 0, I_0 \geq 0, C_0 \geq 0, V_0 \geq 0, R_0 \geq 0\}$, *then the solution* S, L, I, C, V, R *of the system of equation (4.1) are non negative.*

Proof. From the system of differential equation (4.1), let us take the second equation;

$$\frac{dL}{dt} = (\beta I + \epsilon\beta C)S + (p_1I + p_2C)\mu v\omega - (\mu_0 + \sigma)L$$
$$\frac{dL}{dt} \geq -(\mu_0 + \sigma)L$$
$$\frac{1}{L}dL \geq -(\mu_0 + \sigma)dt$$
$$L(t) \geq L_0 \exp^{-(\mu_0+\sigma)t} > 0$$

From the system of differential equation (4.1), let us take the third equation;

$$\frac{dI}{dt} = \sigma L - (\mu_0 + \gamma_1)I$$
$$\frac{dI}{dt} \geq -(\mu_0 + \gamma_1)I$$
$$\frac{1}{I}dI \geq -(\mu_0 + \gamma_1)$$
$$\int \frac{1}{I}dI \geq -\int(\mu_0 + \gamma_1)$$
$$I(t) \geq I_0 \exp^{(\mu_0+\gamma_1)t} > 0$$

From the system of differential equation (4.1), let us take the fourth equation;

$$\frac{dC}{dt} = q\gamma_1 I - (\mu_0 + \mu_1 + \gamma_2)C$$
$$\frac{dC}{dt} \geq -(\mu_0 + \mu_1 + \gamma_2)C$$
$$\frac{1}{C}dC \geq -(\mu_0 + \mu_1 + \gamma_2)dt$$

$$\int \frac{1}{C} dC \geq -\int (\mu_0 + \mu_1 + \gamma_2) dt$$
$$C(t) \geq C_0 \exp^{-(\mu_0+\mu_1+\gamma_2)} > 0$$

From the system of differential equation (4.1), let us take the first equation;

$$\frac{dS}{dt} = \mu\omega(1 - vp_1 I - vp_2 C) + \psi V + \rho R - (\mu_0 + \beta I + \epsilon\beta C + \gamma_3)S$$
$$\frac{dS}{dt} \geq -(\mu_0 + \beta I + \epsilon\beta C + \gamma_3)S$$
$$\frac{1}{S} dS \geq -(\mu_0 + \beta I + \epsilon\beta C + \gamma_3) dt$$
$$\int \frac{1}{S} dS \geq -\int (\mu_0 + \beta I + \epsilon\beta C + \gamma_3) dt$$
$$S(t) \geq S_0 \exp^{-(\mu_0+\beta I+\epsilon\beta C+\gamma_3)t} > 0$$

From the system of differential equation (4.1), let us take the fiveth equation;

$$\frac{dV}{dt} = \mu(1 - \omega) + \gamma_3 S - (\psi + \mu_0)V$$
$$\frac{dV}{dt} \geq -(\psi + \mu_0)V$$
$$\frac{1}{V} dV \geq -(\psi + \mu_0) dt$$
$$\int \frac{1}{V} dV \geq -\int (\psi + \mu_0) dt$$
$$V(t) \geq V_0 \exp^{-(\psi+\mu_0)t} > 0$$

similarly,

$$\frac{dR}{dt} = (1 - q)\gamma_1 I + \gamma_2 C - (\mu_0 + \rho)R \quad \frac{dR}{dt} \geq -(\mu_0 + \rho)R$$
$$\frac{1}{R} dR \geq -(\mu_0 + \rho) dt$$
$$\int \frac{1}{R} dR \geq -\int (\mu_0 + \rho) dt$$
$$R(t) \geq R_0 \exp^{-(\mu_0+\rho)t} > 0$$

□

For the model to be mathematical well possed and epidemiologically meaningful we will show that the solution of the system equation (4.1) is bounded. For this let the total population N is given by $N = S + L + I + C + V + R$

Then $\frac{dN}{dt} = \frac{d}{dt}(S + V + E + I + C + R) = \mu - \mu_0 N - \mu_1 C$, since $C > 0$

$\frac{dN}{dt} \leq \mu - \mu_0 N$ solving the differential inequality we obtain that we obtain that $0 \leq N \leq \frac{\mu}{\mu_0}$ for all $t \geq 0$.

Therefore, the feasible solution set of the system equation (4.1) of the model remain in the region:

$\Omega = \{(S, L, I, C, V, R) \in R_+^6 : N \leq \frac{\mu}{\mu_0}\}$

4.3 Model Analysis

In this section, we investigate the geometrical properties of the equilibrium points of the system. For simplicity, we normalize the population size to 1; that is, now $S+L+I+C+V+R=N$.We scale the equations by letting $\frac{S}{N}=s,\frac{L}{N}=l,\frac{I}{N}=i,\frac{C}{N}=c,\frac{V}{N}=w$ and $\frac{R}{N}=r$ and $\frac{S}{N}+\frac{L}{N}+\frac{I}{N}+\frac{C}{N}+\frac{V}{N}+\frac{R}{N}=s+l+i+c+w+r=1$ where s,l,i,c,w and r are susceptible, the exposed, the acute infective, the carriers,vaccinated and the recovered population respectively.Since $s(t)+l(t)+i(t)+c(t)+w(t)+r(t)=1$, we can calculate r from $r(t)=1-s-l-i-c-w$.
Then

$$\begin{cases} \dot{s}(t)=\mu\omega(1-vp_1i-vp_2c)+\psi w+\rho(1-s-l-i-c-w)-(\mu_0+\beta i+\epsilon\beta c+\gamma_3)s \\ \dot{l}(t)=(\beta i+\epsilon\beta c)s+(p_1i+p_2c)\mu v\omega-(\mu_0+\sigma)l \\ \dot{i}(t)=\sigma l-(\mu_0+\gamma_1)i \\ \dot{c}(t)=q\gamma_1 i-(\mu_0+\mu_1+\gamma_2)c \\ \dot{w}(t)=\mu(1-\omega)+\gamma_3 s-(\psi+\mu_0)w \\ \dot{r}(t)=(1-q)\gamma_1 i+\gamma_2 c-(\mu_0+\rho)r \end{cases} \tag{4.2}$$

The variable r of the system (4.2) does not appear in the first five equations in the analysis; we only consider the first five equations of the system (4.2) as:

$$\begin{cases} \dot{s(t)}=\mu\omega(1-vp_1i-vp_2c)+\psi w+\rho(1-s-l-i-c-w)-(\mu_0+\beta i+\epsilon\beta c+\gamma_3)s \\ \dot{l}(t)=(\beta i+\epsilon\beta c)s+(p_1i+p_2c)\mu v\omega-(\mu_0+\sigma)l \\ \dot{i}(t)=\sigma l-(\mu_0+\gamma_1)i \\ \dot{c}(t)=q\gamma_1 i-(\mu_0+\mu_1+\gamma_2)c \\ \dot{w}(t)=\mu(1-\omega)+\gamma_3 s-(\psi+\mu_0)w \end{cases} \tag{4.3}$$

4.4 Equilibrium Point

4.4.1 Disease-free Equilibrium

To find the equilibrium point of the system (4.3), we equate the system of differential equation (4.3) to zero and we obtain .

$$\begin{cases} \dot{s(t)}=\mu\omega(1-vp_1i-vp_2c)+\psi w+\rho(1-s-l-i-c-w)-(\mu_0+\beta i+\epsilon\beta c+\gamma_3)s=0 \\ \dot{l}(t)=(\beta i+\epsilon\beta c)s+(p_1i+p_2c)\mu v\omega-(\mu_0+\sigma)l=0 \\ \dot{i}(t)=\sigma l-(\mu_0+\gamma_1)i=0 \\ \dot{c}(t)=q\gamma_1 i-(\mu_0+\mu_1+\gamma_2)c=0 \\ \dot{w}(t)=\mu(1-\omega)+\gamma_3 s-(\psi+\mu_0)w=0 \end{cases} \tag{4.4}$$

We denote disease-free equilibrium point by $E_0 = (S_0, 0, 0, 0, V_0, 0)$.Then solving they system of differential equation simultaneously (4.4),we obtain

$$E_0 = (\frac{(\mu+\rho)(\psi+\mu_0)+\mu(1-\omega)(\mu+\rho)}{(\mu_0+\rho)(\mu_0+\gamma_3+\psi)}, 0, 0, 0, 0, \frac{\gamma_3(\mu+\rho)+\mu(1-\omega)(\rho+\mu_0)}{(\mu_0+\rho)(\mu_0+\psi+\gamma_3)})$$

4.4.2 Endemic Equilibrium

In this subsection, we consider a situation in which there is persistence of HBV in the population. We denote the endemic equilibrium point$E^* = (S^*, L^*, I^*, C^*, V^*)$.Then solving they system of differential equation simultaneously (4.4),we obtain

$S^* = \frac{(\mu_0+\sigma)(\mu_0+\gamma_1)(\mu_0+\mu_1+\gamma_2)-\sigma\mu v\omega P_1(\mu_0+\mu_1+\gamma_2)-\sigma\mu v\omega P_2 q\gamma_1}{\sigma\beta(\mu_0+\mu_1+\gamma_2+\epsilon q\gamma_1)}$,

$L^* = \frac{(\mu_0+\gamma_1)I^*}{\sigma}$,

$I^* = \frac{\rho(1-S^*-V^*)\sigma(\mu_0+\mu_1+\gamma_2)}{\gamma_1\sigma(\mu_0+\mu_1+\gamma_2)+\rho(\mu_0+\gamma_1)(\mu_0+\mu_1+\gamma_2)+\rho\sigma(\mu_0+\mu_1+\gamma_2)+\sigma\rho q\gamma_1}$,

$C^* = \frac{q\gamma_1 I^*}{\mu_0+\mu_1+\gamma_2}$ and

$V^* = \frac{\mu(1-\omega)+\gamma_3 S^*}{\psi+\mu_0}$

4.4.3 The Basic Reproduction Number,R_0

we discuss the basic reproduction number of the system (4.3) by using the next generation matrix approach.From the equations (4.3), we have the following:
The vector $F(x)$ of the rates of new infections in compartments L,I and C is given by:

$$F(x) = \begin{bmatrix} \mu v\omega(p_1 I + p_2 C) + (\beta I + \epsilon\beta C)S \\ 0 \\ 0 \end{bmatrix} \tag{4.5}$$

Also, the remaining transfer terms in compartments L, I and C are given by:

$$V(x) = \begin{bmatrix} (\mu_0+\sigma)L \\ -\sigma L + (\mu_0+\gamma_1)I \\ -q\gamma_1 I + (\mu_0+u_1+\gamma_2)C \end{bmatrix} \tag{4.6}$$

The matrix of partial derivatives of F(x) at the disease-free equilibrium state $\tilde{x} = E_0 = (S_0^*, 0, 0, 0, V_0^*)$ is given by:

$$F_x(E_0) = \begin{bmatrix} 0 & \mu v\omega p_1 + \beta S_0^* & \mu v\omega p_2 + \epsilon\beta S_0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \tag{4.7}$$

where, $S_0^* = \dfrac{(\mu+\rho)(\psi+\mu_0)-\mu(1-\omega)(\mu+\rho)}{(\mu_0+\rho)(\mu_0+\gamma_3+\psi)}$
and the matrix of partial derivatives of v(t) at the disease-free equilibrium state $\tilde{x} = E_0 = (S_0^*, 0, 0, 0, V_0^*)$ is:

$$V_x(E_0) = \begin{bmatrix} \mu_0+\sigma & 0 & 0 \\ -\sigma & \mu_0+\gamma_1 & 0 \\ 0 & -q\gamma_1 & \mu_0+\mu_1+\gamma_2 \end{bmatrix} \tag{4.8}$$

and

$$V_x^{-1}(E_0) = \begin{bmatrix} \frac{1}{\mu_0+\sigma} & 0 & 0 \\ \frac{\sigma}{(\mu_0+\gamma_1)(\sigma+\mu_0)} & \frac{1}{\mu_0+\gamma_1} & 0 \\ \frac{q\gamma_1\sigma}{(\mu_0+\mu_1+\gamma_2)(\mu_0+\gamma_1)(\sigma+\mu_0)} & \frac{q\gamma_1}{(\mu_0+\mu_1+\gamma_2)(\mu_0+\gamma_1)} & \frac{1}{\mu_0+\mu_1+\gamma_2} \end{bmatrix} \tag{4.9}$$

The eigenvalues of FV^{-1} are

$\lambda_{1,2} = 0$ and $\lambda_3 = \dfrac{\sigma(\mu v\omega p_1 + \beta S_0^*)}{(\mu_0+\gamma_1)(\sigma+\mu_0)} + \dfrac{q\gamma_1\sigma(\mu v\omega p_2 + \epsilon\beta S_0^*)}{(\mu_0+\mu_1+\gamma_2)(\mu_0+\gamma_1)(\sigma+\mu_0)}$

Since the dominant eigenvalues of FV^{-1} is

$\lambda = \dfrac{\sigma(\mu v\omega p_1 + \beta S_0^*)}{(\mu_0+\gamma_1)(\sigma+\mu_0)} + \dfrac{q\gamma_1\sigma(\mu v\omega p_2 + \epsilon\beta S_0^*)}{(\mu_0+\mu_1+\gamma_2)(\mu_0+\gamma_1)(\sigma+\mu_0)}$

then $R_0 = \lambda$.

Therefore $R_0 = \dfrac{\sigma(\mu v\omega p_1 + \beta S_0^*)}{(\mu_0+\gamma_1)(\sigma+\mu_0)} + \dfrac{q\gamma_1\sigma(\mu v\omega p_2 + \epsilon\beta S_0^*)}{(\mu_0+\mu_1+\gamma_2)(\mu_0+\gamma_1)(\sigma+\mu_0)}$

4.5 Stability Analysis

4.5.1 Local Stability of Disease-free Equilibrium

To determine the local stability of the disease free equilibrium point E_0 we use the Jacobian matrix of the system.

Theorem 4.5.1. *If $R_0 < 1$, then the disease-free equilibrium point E_0 is locally asymptotically stable.*

Proof. By considering the linearized system of equation (4.3), by taking the Jacobian matrix and obtained

$$J(E_0) = \begin{bmatrix} -(\mu_0+\gamma_3+\rho) & 0 & -\mu\omega v p_1 - \beta S_0^* & -\mu\omega v p_2 - \epsilon\beta S_0^* & \psi \\ 0 & -(\mu_0+\sigma) & \beta S_0^* + p_1\mu v\omega & \epsilon\beta S_0^* + p_2\mu v\omega & 0 \\ 0 & \sigma & -(\mu_0+\gamma_1) & 0 & 0 \\ 0 & 0 & q\gamma_1 & -(\mu_0+\mu_1+\gamma_2) & 0 \\ \gamma_3 & 0 & 0 & 0 & -(\psi+\mu_0) \end{bmatrix}$$

For ease of analysis, we perform the following operations:

- multiply row 1 by $\frac{\gamma_3}{(\mu_0+\gamma_3+\rho)}$,
- Add row 1 to row 5.

By these operations, we have the following equivalent matrix:

$$J(E_0) = \begin{bmatrix} -\gamma_3 & 0 & (-\mu\omega v p_1 - \beta S_0^*)\frac{\gamma_3}{(\mu_0+\gamma_3+\rho)} & (-\mu\omega v p_2 - \epsilon\beta S_0^*)\frac{\gamma_3}{(\mu_0+\gamma_3+\rho)} & \frac{\psi\gamma_3}{(\mu_0+\gamma_3+\rho)} \\ 0 & -(\mu_0+\sigma) & \beta S_0^* + p_1\mu v\omega & \epsilon\beta S_0^* + p_2\mu v\omega & 0 \\ 0 & \sigma & -(\mu_0+\gamma_1) & 0 & 0 \\ 0 & 0 & q\gamma_1 & -(\mu_0+\mu_1+\alpha+\gamma_2) & 0 \\ 0 & 0 & (-\mu\omega v p_1 - \beta S_0^*)\frac{\gamma_3}{(\mu_0+\gamma_3+\rho)} & (-\mu\omega v p_2 - \epsilon\beta S_0)\frac{\gamma_3}{(\mu_0+\gamma_3+\rho)} & \frac{\gamma_3\psi}{(\mu_0+\gamma_3+\rho)} - (\psi+\mu_0) \end{bmatrix}$$

The diagonal entries $-\gamma_3 < 0$ and $\frac{\gamma_3\psi}{(\mu_0+\gamma_3+\rho)} - (\psi+\mu_0) < 0$ if $\psi < \frac{\mu_0^2+\mu_0\gamma_3+\mu_0\rho}{1-\mu_0-\gamma_3-\rho}$ are the two of the eigenvalues of the characteristic equation of Jacobian matrix $J(E_0)$. Thus, excluding these columns and the corresponding rows, we calculate the remaining eigenvalues. These eigenvalues are the roots of the characteristic equation of the reduced matrix of dimension three given by

$$M = \begin{bmatrix} -(\mu_0+\sigma) & \beta S_0^* + p_1\mu v\omega & \epsilon\beta S_0^* + p_2\mu v\omega \\ \sigma & -(\mu_0+\gamma_1) & 0 \\ 0 & q\gamma_1 & -(\mu_0+\mu_1+\gamma_2) \end{bmatrix} \tag{4.10}$$

The determinant of (4.10) is given by

$$|M-\lambda I| = \begin{vmatrix} -(\mu_0+\sigma)-\lambda & \beta S_0^* + p_1\mu v\omega & \epsilon\beta S_0^* + p_2\mu v\omega \\ \sigma & -(\mu_0+\gamma_1)-\lambda & 0 \\ 0 & q\gamma_1 & -(\mu_0+\mu_1+\gamma_2)-\lambda \end{vmatrix} = 0$$

Therefore, the corresponding characteristic equation to M is

$$\lambda^3 + (a_0+a_1+a_2)\lambda^2 + (a_0a_1 + a_0a_2 + a_1a_2 - \sigma a_3)\lambda + a_0a_1a_2 - \sigma q\gamma_1 a_4 - \sigma a_2 a_3 = 0$$

where
$a_0 = (\mu_0+\sigma)$
$a_1 = (\mu_0+\gamma_1)$
$a_2 = (\mu_0+\mu_1+\gamma_2)$
$a_3 = \beta S_0^* + p_1\mu v\omega$
$a_4 = \epsilon\beta S_0^* + p_2\mu v\omega$

$$\lambda^3 + A\lambda^2 + B\lambda + C = 0 \tag{4.11}$$

where
$A = a_0 + a_1 + a_2$
$B = a_0a_1 + a_0a_2 + a_1a_2 - \sigma a_3$
$C = a_0a_1a_2 - \sigma q\gamma_1 a_4 - \sigma a_2 a_3$
By Routh-Hurwiz criteria, all the roots of the characteristic equation (4.11) have negative real parts if $A, B, C > 0$ and $AB - C > 0$
To shaw $AB - C > 0$, we apply R_0 as a threshold. observe that the basic reproduction number as show in 4.11 is $R_0 = \dfrac{\sigma(\mu v\omega p_1 + \beta S_0^*)}{(\mu_0+\gamma_1)(\sigma+\mu_0)} + \dfrac{q\gamma_1\sigma(\mu v\omega p_2 + \epsilon\beta S_0^*)}{(\mu_0+\mu_1+\gamma_2)(\mu_0+\gamma_1)(\sigma+\mu_0)}$
substituting $a_0 = (\mu_0+\sigma), a_1 = (\mu_0+\gamma_1), a_2 = (\mu_0+\mu_1+\gamma_2), a_3 = \beta S_0 + p_1\mu v\omega, a_4 = \epsilon\beta S_0^* + p_2\mu v\omega$ in R_0 gives
$R_0 = \dfrac{\sigma a_3}{a_0a_1} + \dfrac{\sigma q\gamma_1 a_4}{a_0a_1a_2}$
Let $R_1 = \dfrac{\sigma a_3}{a_0a_1}$ and $R_2 = \dfrac{\sigma q\gamma_1 a_4}{a_0a_1a_2}$
So that $R_0 = R_1 + R_2$
$R_0 < 1$ implies that $R_1 < 1$, $R_2 < 1$. R_1 and R_2 are in terms of R_0.
$AB - C = (a_0+a_1+a_2)(a_0a_1 + a_0a_2 + a_1a_2 - \sigma a_3) - a_0a_1a_2 - \sigma q\gamma_1 a_4 - \sigma a_2 a_3$
$AB - C = a_0^2a_1 + a_0^2a_2 - \sigma a_0a_3 + a_0a_1a_2 + a_0a_1^2 - \sigma a_1a_3 + a_1^2a_2 + a_0a_1a_2 + a_0a_2^2 + a_1a_2^2 + \sigma q\gamma_1 a_4$
$AB - C = a_0^2a_2 + a_0(a_0a_1)(1 - \dfrac{\sigma a_3}{a_0a_1}) + a_0a_1a_2 + a_1(a_0a_1)(1 - \dfrac{\sigma\gamma_3}{a_0a_1}) + a_1^2a_2 + a_0a_2^2 + a_1a_2^2 + \sigma q\gamma_1 a_4$

$AB-C = a_0^2a_2+a_0(a_0a_1)(1-R_1)+a_0a_1a_2+a_1(a_0a_1)(1-R_1)+a_1^2a_2+a_0a_2^2+a_1a_2^2+\sigma q\gamma_1 a_4 > 0$, iff $R_1 < 1$.

To show that $B > 0$, we also apply R_1 as a threshold as follows.

$$\begin{aligned} B &= a_0a_1 + a_0a_2 + a_1a_2 - \sigma a_3 \\ &= a_0a_2 + a_1a_2 + a_0a_1(1 - \frac{\sigma a_3}{a_0a_1}) \\ &= a_0a_2 + a_1a_2 + a_0a_1(1 - R_1) > 0 \text{ iff } R_1 < 1. \end{aligned}$$

To show that $C > 0$, we also apply R_1 as a threshold as follows

$$\begin{aligned} C &= a_0a_1a_2 - \sigma q\gamma_1 a_4 - \sigma a_2a_3 \\ C &= a_0a_1a_2(1 - R_0) > 0, \text{iff } R_0 < 1 \end{aligned}$$

Therefore, by Routh-Hurwitz criteria all the roots have negative real parts and the disease-free equilibrium state E_{0-} is locally asymptotically stable if $R_0 < 1$.Otherwise it is unstable.

□

4.5.2 Local Stability of Endemic Equilibrium

Theorem 4.5.2. *The endemic equilibrium point E^* is locally asymptotically stable if $R_0 > 1$*

Proof. The Jacobian matrix of the system of equations is given by

$$J(E^*) = \begin{bmatrix} -(\mu_0 + \beta I^* + \epsilon\beta C^* + \gamma_3 + \rho) & -\rho & -(\mu\omega vp_1 + \beta S^* + \rho) & -(\mu\omega vp_2 + \rho + \epsilon\beta S^*) & \psi - \rho \\ \beta I^* + \epsilon\beta C^* & -(\mu_0 + \sigma) & \beta S^* + p_1\mu v\omega & \epsilon\beta S^* + p_2\mu v\omega & 0 \\ 0 & \sigma & -(\mu_0 + \gamma_1) & 0 & 0 \\ 0 & 0 & q\gamma_1 & -(\mu_0 + \mu_1 + \gamma_2) & 0 \\ \gamma_3 & 0 & 0 & 0 & -(\psi + \mu_0) \end{bmatrix}$$

we make an elementary row-transformation for the Jacobian matrix at E^* and obtain the following matrix:

$$J(E^*) = \begin{bmatrix} \frac{-ar+\rho e}{fr}(\frac{-gkn+\sigma hn+\sigma q\gamma_1 i}{\sigma q\gamma_1}) + \frac{\rho kn+\sigma nc+\sigma q\gamma_1 d}{\sigma q\gamma_1} & \frac{-\rho kn-\sigma nc-\sigma q\gamma_1 d}{\sigma q\gamma_1} & \frac{-nc-d}{q\gamma_1} & -d & e \\ 0 & \frac{-gkn+\sigma hn+\sigma q\gamma_1 i}{\sigma q\gamma_1} & \frac{hn+iq\gamma_1}{q\gamma_1} & i & 0 \\ 0 & 0 & -\frac{kn}{q\gamma_1} & 0 & 0 \\ 0 & 0 & 0 & -n & 0 \\ 0 & 0 & 0 & 0 & -r \end{bmatrix}$$

The corresponding characteristic equation is given by
$(\frac{-ar+\rho e}{fr}(\frac{-gkn+\sigma hn+\sigma q\gamma_1 i}{\sigma q\gamma_1}) - \lambda_1)(\frac{-gkn+\sigma hn+\sigma q\gamma_1 i}{\sigma q\gamma_1} - \lambda_2)(-\frac{(\mu_0+\gamma_1)(\mu_0+\mu_1+\gamma_2)}{q\gamma_1} - \lambda_3(-(\mu_0 + \mu_1 + \gamma_2) - \lambda_4(-(\psi + \mu_0) - \lambda_5) = 0$
Where
$a = (\mu_0 + \beta I^* + \epsilon\beta C^* + \gamma_3 + \rho)$
$c = (\mu\omega vp_1 + \beta S^* + \rho)$
$d = (\mu\omega vp_2 + \rho + \epsilon\beta S^*$
$e = \psi - \rho$
$f = \beta I^* + \epsilon\beta C^*$
$g = (\mu_0 + \sigma)$

$h = \beta S^* + p_1\mu v\omega$
$i = \epsilon\beta S^* + p_2\mu v\omega$
$k = (\mu_0 + \gamma_1)$
$n = \mu_0 + \mu_1 + \gamma_2$
$r = (\psi + \mu_0)$
Then the eigenvalues are
$\lambda_1 = \frac{-ar+\rho e}{fr}(\frac{-gkn+\sigma hn+\sigma q\gamma_1 i}{\sigma q\gamma_1}) + \frac{\rho kn+\sigma nc+\sigma q\gamma_1 d}{\sigma q\gamma_1} < 0,$
iff $gkn < \sigma hn + \sigma q\gamma_1 i$ and $\frac{-ar+\gamma_3 e}{fr}(\frac{-gkn+\sigma hn+\sigma q\gamma_1 i}{\sigma q\gamma_1}) > \frac{\rho kn+\sigma nc+\sigma q\gamma_1 d}{\sigma q\gamma_1}$
$\lambda_2 = \frac{-gkn+\sigma hn+\sigma q\gamma_1 i}{\sigma q\gamma_1} = \frac{S^*\sigma\beta}{\sigma q\gamma_2}(1 - (\mu_0 + \mu_1 + \gamma_2)) < 0,$
iff $(\mu_0 + \mu_1 + \gamma_2) > 1$
$\lambda_3 = -\frac{(\mu_0+\gamma_1)(\mu_0+\mu_1+\gamma_2)}{q\gamma_1} < 0,$
$\lambda_4 = -(\mu_0 + \mu_1 + \gamma_2) < 0$ and
$\lambda_5 = -(\psi + \mu_0) < 0$
Therefore the disease endemic equilibrium point E^* is locally asymptotically stable. □

4.5.3 The Global Stability of the Disease-free Equilibrium

Theorem 4.5.3. *The disease-free equilibrium $E_0 = (S_0^*, 0, 0, 0, V_0^*)$ of the system (4.2) is globally asymptotically stable if $R_0 < 1$.*

Proof. Let us construct the Lyapunov function

$$F(t) = \frac{1}{2}((s(t) - S_0^*) + l(t) + i(t) + c(t) + r(t) + (w(t) - V_0^*))^2 \tag{4.12}$$

Differentiating Equation (4.12) with respect to t,we obtain

$$\begin{aligned}\frac{dF}{dt} &= ((s(t) - S_0^*) + l(t) + I(t) + c(t) + r(t) + (v(t) - V_0^*))(\frac{ds}{dt} + \frac{dl}{dt} + \frac{di}{dt} + \frac{dc}{dt} + \frac{dr}{dt} + \frac{dw}{dt}) \\ &= ((s(t) - S_0^*) + l(t) + i(t) + c(t) + r(t) + (w(t) - V_0^*))(\mu - \mu_0 - \mu_1 c(t)) \\ &= ((s(t) - S_0) + l(t) + i(t) + c(t) + r(t) + (w(t) - V_0))(-\mu_1 c(t)) \\ &= -((s(t) - S_0^*) + l(t) + i(t) + c(t) + r(t) + (w(t) - V_0^*))(\mu_1 c(t)) < 0\end{aligned}$$

Therefore $\frac{dF}{dt} < 0$. Also $\frac{dF}{dt} = 0$ at $E_0 = (S_0^*, 0, 0, 0, V_0^*))$, thus the largest compact invariant set is the singleton set $E_)$,so LaSalle's invariant principle implies that the disease-free equilibrium point $E_0 = (S_0^*, 0, 0, 0, V_0^*)$ is globally asymptotically stable. □

Chapter 5

The Optimal Control of the Hepatitis B Virus Transmission

Optimal control deals with the problem of finding a control law for a given system such that a certain optimality criterion is achieved. A control problem includes a cost functional that is a function of state and control variables. An optimal control is a set of differential equations describing the paths of the control variables that minimize the cost function. The optimal control can be derived using Pontryagin's maximum principle (a necessary condition also known as Pontryagin's minimum principle or simply Pontryagin's Principle) or by solving the HamiltonJacobi-Bellman equation (a sufficient condition)[15].

5.1 Formulation of Optimal Control Problem

If $x(t)$ represents the group of individuals to be vaccinated,treated and $u_1(t), u_2(t) \in U$ represents the control where the control sets u_1 and u_2 .A strategy for the control $u_1(t)$ and $u_2(t)$ of the virus is introduced into the model (4.2) representing the vaccination and treatment rate at time t. Precisely, the control $u_1(t)$ is the fraction of susceptible individuals being vaccinated at time t and $u_2(t)$ is the fraction of acutely infected and chronic carriers individuals being treated at time t taking values between 0 and 100%. In this section,an optimal control problem is formulated by incorporating one intervention strategies into our basic model equation (4.3). The following intervention is incorporated in to the basic model; $u_1(t)$ and $u_2(t)$ are the control which represents the vaccination ratio of susceptible individuals being vaccinated and the treatment ratio of acutely infected and chronic carriers per unit of time respectively which bounds between 0 and 1. The dynamics Hepatitis B virus transmission model with optimal control is governed by the following modified nonlinear system (state equations):

$$\begin{cases} \dot{S}(t) = \mu\omega(1 - vp_1I - vp_2C) + \psi V + \rho R - (\mu_0 + (1-u_1)(\beta I + \epsilon\beta C) + \gamma_3)S \\ \dot{L}(t) = (1-u_1)(\beta I + \epsilon\beta C)S + (p_1I + p_2C)\mu v\omega - (\mu_0 + \sigma)L \\ \dot{I}(t) = \sigma L - (\mu_0 + \gamma_1)I \\ \dot{C}(t) = (1-u_2)q\gamma_1 I - (\mu_0 + \mu_1 + \gamma_2)C \\ \dot{V}(t) = \mu(1-\omega) + \gamma_3 S - (\psi + \mu_0)V \\ \dot{R}(t) = (1 - (1-u_2)q)\gamma_1 I + \gamma_2 C - (\mu_0 + \rho)R \\ S(0) = S_0 > 0, L(0) = L_0 \geq 0, I(0) = I_0 \geq 0, \\ C(0) = C_0 \geq 0, V(0) = V_0 > 0, R(0) = R_0 \geq 0 \end{cases} \tag{5.1}$$

The optimal control problem is to minimize the objective (cost) functional J considering the costs of vaccination of susceptible and treatment of acutely infected and Chronic carries human. The goal of the adopted strategy is to reduce the infected individuals and the cost of vaccination and treatment on a fixed time interval. Precisely, the optimal control problem consists of minimizing the objective functional J,

$$J(u_1, u_2) = \int_0^T (A_1I(t) + A_2C(t) + \frac{1}{2}(B_1u_1^2(t) + B_2u_2^2(t)))dt \to min \tag{5.2}$$

Subject to the differential equations (5.1).
$\Omega_\epsilon = \{(u_1, u_2) : 0 \leq u_i \leq 1 - \epsilon = 0.999$ if we fix $\epsilon = 0.001, t \in [0, T], i = 1, 2\}$
and the A_1, A_2, B_1, B_2 are the relative weight constants which balances each term in the integrand to reduce the dominance of any of the term in the integral. The weight constants B_1 and B_2 measures the cost or effort required for the implementation of each of the two control measures adopted while A_1 and A_2 measures the relative importance of reducing the associated classes on the spread of the disease.The parameter T is the duration,in months(days) of vaccination and treatment program. The control u_1 represents the proportion of susceptible individuals that is effectively vaccinated and hence have full immunity per unit time, while u_2 is the proportion of individuals in the acute class who are currently being effectively managed so that their case do not deteriorate into the chronic stage. Thus,u_i lies between 0 and 1 while u_i will depend on the amount of resources available to implement each of the control measures. If $u_1, u_2 = 0$, then no vaccination and treatment are done this means the model (5.1) is uncontrolled which are equivalent to model equation (4.1) and $u_1 = 1$ indicates that all susceptible population is vaccinated and $u_2 = 1$ indicates that all acutely infected is treated.In the reality this case is not possible. The rate of vaccination and treatment are assumed to take values in [0, 1) to eliminate the case where the entire susceptible population is vaccinated acutely infected is treated the target here is to minimize the objective functional defined above by decreasing the number of acutely infected and chronic carries individuals and increasing the numbers of vaccinated and recover individual. This is achieved using possible minimal control variable, u_1 and u_2 at each time unit within the implementation period. Hence ,we are looking for the optimal control pair (u_1^*, u_2^*) such that
$J(u_1^*, u_2^*) = min\{J(u_1^*, u_2^*) : u_1^*, u_2^*\} \in \Omega$ where Ω is the set of admissible control defined by
$\Omega = \{(u_1^*, u_2^*) : 0 \leq u_1^*, u_2^* \leq 0.999, t \in [0, T]$, where $u_i, i = 1, 2$ are Lebesgue measurable

function.
The solution of the optimal control problem is the vector function

$$(S^*(0), L^*(0), I^*(0), C^*(0), V^*(0), R^*(0)) \in F$$

associated with an admissible control $u^* = (u_1^*, u_2^*) \in \Omega$ on the time interval [0,T] that minimize the cost functional (5.2)

5.2 Existence and Characterization of the Optimal Control

In this section, we examine conditions that can be assure the existence of a solution to the optimal control problem(5.2).

Theorem 5.2.1. *(Existence of optimal control Solution) There exists an optimal control $u^* = (u_1^*, u_2^*)$ and a corresponding solution vector x^* to the state initial value problem (5.1) to the state initial value problem (5.1) that minimizes the cost functional $J(u_1, u_2)$ of (5.2) over the set of admissible controls Ω.*

Proof. The non trivial requirement on the set of admissible controls Ω and the set of end conditions are followed by Fleming and Rishel's theorem.

i The set of all solution to system (5.1) with corresponding control functions in Ω is non empty.

ii The control set is convex and closed.

iii The integral of the objective functional is convex.

iv The integral of the Objective functional is bounded below by $-\Lambda_2+\Lambda_1|u_1, u_2|^\delta$,where $\Lambda_i > 0$ for all $i = 1, 2$ and $\delta > 1$

In order to establish condition (i), we refer to picard-lindelo'f existence theorem [8]. If $g(x, u, t)$ is bounded, continuous, and lipshitz in the state variable, then there exists a unique solution corresponding to every admissible control Ω. Hence, for any $u \in \Omega$ and the state variable, we have

$$0 \leq N(t) \leq \frac{\mu}{\mu_0} \tag{5.3}$$

and non empty by model assumption. Furthermore, the system is continuous and bounded with the established (5.3),it implies that the state system is continuous and bounded.It is possible to show the boundedness of the partial derivatives variable w.r.t the state variables [8].This establish the proof condition(i).
To prove (ii), condition $\Omega = \{u \in R^2 :\| u \|\leq 0.999\}$
Assume that $u_1, u_2 \in \Omega$ such that $\| u_1 \|\leq 0.999\}$ and $\| u_2 \|\leq 0.999\}$. then for any $\alpha \in [0, 1], \| \alpha u_1 + (1-\alpha)u_2 \|\leq\| \alpha u_1 \| + \| (1-\alpha)u_2 \|\leq 0.999$.This implies that $\Omega_{0.001}$ is convex and closed.
Next we verify condition (iii), the integral of the cost function is

$$f(x,u,t) = A_1 I(t) + A_2 C(t) + \tfrac{1}{2}(B_1 u_1^2(t) + B_2 u_2^2(t))$$

Any affine and convex function is convex and the sum of convex function is also convex [21].
Therefore, f(x,u,t) is convex on Ω. to prove the bound on the f observe from definition of Ω that $B_2 u_2^2 \leq B_2$ because $u_2 \in [0, 0.999], 0 < 0.999 << 1$.

$$\frac{B_2 u_2^2}{2} \leq \frac{B_2}{2},$$
$$\frac{B_2 u_2^2}{2} - \frac{B_2}{2} \leq 0$$

$$f(x,u,t) = A_1 I(t) + A_2 C(t) + \tfrac{1}{2}(B_1 u_1^2(t) + B_2 u_2^2(t)) \geq \frac{B_1 u_1^2}{2} + \frac{B_2 u_2^2}{2} - \frac{B_2}{2}$$

This implies

$$\begin{aligned} f(x,u,t) &\geq min(\frac{B_1}{2}, \frac{B_2}{2})|(u_1,u_2)|^2 - \frac{B_2}{2} \\ &= min(\frac{B_1}{2}, \frac{B_2}{2})|(u_1^2 + u_2^2)| - \frac{B_2}{2} \\ &= -\Lambda_2 + \Lambda_1 |u_1, u_2|^\delta \end{aligned}$$

Hence,

$$f(x,u,t) \geq -\Lambda_2 + \Lambda_1 |u_1, u_2|^\delta,$$

where $\Lambda_1 = min(\frac{B_1}{2}, \frac{B_2}{2}), \Lambda_2 = \frac{B_2}{2}$ and $\delta = 2$. with this we conclude the existence of an optimal control pair (x^*, u^*) that minimizes the coast functional of (5.3) the pontryagin's maximum principle(PMP) stated in theorem gives the required necessary optimality condition as given the following theorem.
Note since we look for minimization we use pontryagin's maximum principle. □

5.3 Optimality System

The optimal control and the state are found by solving the following optimality system,

i The state system (5.1)

ii The adjoint system

iii Tranversality conditions and

iv The characterization of the optimal control u_i^*.

1 The Hamiltonian is given by

$H = A_1 I(t) + A_2 C(t) + \frac{1}{2}(B_1 u_1^2(t) + B_2 u_2^2(t)) + \lambda_1(\mu\omega(1 - vp_1 I - vp_2 C) + \psi V + \rho R - (\mu_0 + (1-u_1)(\beta I + \epsilon\beta C) + \gamma_3)S) + \lambda_2((1-u_1)(\beta I + \epsilon\beta C)S + (p_1 I + p_2 C)\mu v\omega - (\mu_0 + \sigma)L) + \lambda_3(\sigma L - (\mu_0 + \gamma_1)I + \lambda_4((1-u_2)q\gamma_1 I - (\mu_0 + \mu_1 + \gamma_2)C + \lambda_5(\mu(1 - \omega) + \gamma_3 S - (\psi + \mu_0)V) + \lambda_6((1 - q(1-u_2)\gamma_1 I + \gamma_2 C - (\mu_0 + \rho))$

2 The minimality condition is

$$\begin{cases} \frac{\partial H}{\partial u_1} = B_1 u_1(t) + \lambda_1(\beta SI + \epsilon\beta SC) - \lambda_2(\beta SI + \epsilon\beta SC) \\ \frac{\partial H}{\partial u_2} = B_2 u_2 + \lambda_6 q\gamma_1 I - \lambda_4 q\gamma_1 I \end{cases}$$

3 The Hamiltonian System

$$\begin{cases} \dot{S}(t) = \mu\omega(1 - vp_1 I - vp_2 C) + \psi V + \rho R - (\mu_0 + (1-u_1)(\beta I + \epsilon\beta C) + \gamma_3)S \\ \dot{L}(t) = (1-u_1)(\beta I + \epsilon\beta C)S + (p_1 I + p_2 C)\mu v\omega - (\mu_0 + \sigma)L \\ \dot{I}(t) = \sigma L - (\mu_0 + \gamma_1)I \\ \dot{C}(t) = (1-u_2)q\gamma_1 I - (\mu_0 + \mu_1 + \gamma_2)C \\ \dot{V}(t) = \mu(1-\omega) + \gamma_3 S - (\psi + \mu_0)V \\ \dot{R}(t) = (1 - (1-u_2)q)\gamma_1 I + \gamma_2 C - (\mu_0 + \rho)R \\ \lambda_1' = \lambda_1(\mu_0 + (1-u_1)(\beta I + \epsilon\beta C) + \gamma_3) - \lambda_2(1-u_1)(\beta I + \epsilon\beta C) - \lambda_5\gamma_3 \\ \lambda_2' = \lambda_2(\mu_0 + \sigma) - \lambda_3\sigma \\ \lambda_3' = -A_1 + \lambda_1(\mu\omega vp_1 + (1-u_1)\beta S) - \lambda_2(u_1\beta S + p_1\mu v\omega) - \lambda_3(\mu_0 + \gamma_1) - \lambda_4(1-u_2)q\gamma_1 - \lambda_6(\\ \lambda_4' = -A_2 + \lambda_1(\mu\omega vp_2 + (1-u_1)\epsilon\beta S) - \lambda_2((1-u_1)\epsilon\beta S + p_2\mu v\omega) + \lambda_4((\mu_0 + \mu_1 + \gamma_2)) - \lambda_6\gamma_2 \\ \lambda_5' = -\lambda_1\psi + \lambda_5(\psi + \mu_0) \\ \lambda_6' = -\lambda_1\rho + \lambda_6(\mu_0 + \rho) \end{cases}$$

4 The characterization of the optimal control u_i^* Therefore, using the characterization of the optimal control, we have the following optimality system:

$$\begin{cases} \dot{S}(t) = \mu\omega(1 - vp_1 I - vp_2 C) + \psi V + \rho R - (\mu_0 + (1-u_1)(\beta I + \epsilon\beta C) + \gamma_3)S \\ \dot{L}(t) = (1-u_1)(\beta I + \epsilon\beta C)S + (p_1 I + p_2 C)\mu v\omega - (\mu_0 + \sigma)L \\ \dot{I}(t) = \sigma L - (\mu_0 + \gamma_1)I \\ \dot{C}(t) = (1-u_2)q\gamma_1 I - (\mu_0 + \mu_1 + \gamma_2)C \\ \dot{V}(t) = \mu(1-\omega) + \gamma_3 S - (\psi + \mu_0)V \\ \dot{R}(t) = (1 - (1-u_2)q)\gamma_1 I + \gamma_2 C - (\mu_0 + \rho)R \\ \lambda_1' = \lambda_1(\mu_0 + u_1(\beta I + \epsilon\beta C) + \gamma_3) - \lambda_2 u_1(\beta I + \epsilon\beta C) - \lambda_5\gamma_3 \\ S(0) = S_0 L(0) = L_0 I(0) = I_0 C(0) = C_0 V(0) = V_0 R(0) = R_0 \\ \lambda_1' = \lambda_1(\mu_0 + (1-u_1)(\beta I + \epsilon\beta C) + \gamma_3) - \lambda_2(1-u_1)(\beta I + \epsilon\beta C) - \lambda_5\gamma_3 \\ \lambda_2' = \lambda_2(\mu_0 + \sigma) - \lambda_3\sigma \\ \lambda_3' = -A_1 + \lambda_1(\mu\omega vp_1 + (1-u_1)\beta S) - \lambda_2(u_1\beta S + p_1\mu v\omega) - \lambda_3(\mu_0 + \gamma_1) - \lambda_4(1-u_2)q\gamma_1 - \lambda_6(\\ \lambda_4' = -A_2 + \lambda_1(\mu\omega vp_2 + (1-u_1)\epsilon\beta S) - \lambda_2((1-u_1)\epsilon\beta S + p_2\mu v\omega) + \lambda_4((\mu_0 + \mu_1 + \gamma_2)) - \lambda_6\gamma_2 \\ \lambda_5' = -\lambda_1\psi + \lambda_5(\psi + \mu_0) \\ \lambda_6' = -\lambda_1\rho + \lambda_6(\mu_0 + \rho) \end{cases} \tag{5.4}$$

$$\lambda_i(T) = o \text{ for i=1,2,3,4,5,6}$$

We follow the Pontryagin Minimum Principle to solve this problem manually(even though not possible)

Now we consider the bounded control case for u_1^* and u_2^* . We note that

$$\begin{cases} \frac{\partial H}{\partial u_1} = B_1 u_1(t) + \lambda_1(\beta SI + \epsilon\beta SC) - \lambda_2(\beta SI + \epsilon\beta SC) \\ \frac{\partial H}{\partial u_2} = B_2 u_2 + \lambda_6 q\gamma_1 I - \lambda_4 q\gamma_1 I \end{cases}$$

Situation 1

$$\frac{\partial H}{\partial u_1} > 0 \iff u_1^*(t) = 0 \iff \lambda_1(\beta SI + \epsilon\beta SC) - \lambda_2(\beta SI + \epsilon\beta SC) > 0 \implies \lambda_1 > \lambda_2$$

$$\frac{\partial H}{\partial u_2} > 0 \iff u_2^* = 0 \iff \lambda_6 q\gamma_1 I - \lambda_4 q\gamma_1 I > 0 \implies \lambda_6 > \lambda_4$$

Situation 2

$$\frac{\partial H}{\partial u_1} < 0 \iff u_1^*(t) = 1 \iff B_1 + \lambda_1(\beta SI + \epsilon\beta SC) - \lambda_2(\beta SI + \epsilon\beta SC) < 0$$

$$\frac{\partial H}{\partial u_2} < 0 \iff u_2^* = 1 \iff B_2\lambda_6 q\gamma_1 I - \lambda_4 q\gamma_1 I < 0$$

Situation 3

$$\frac{\partial H}{\partial u_1} = 0 \iff B_1 u_1(t) - \lambda_1(\beta SI + \epsilon\beta SC) + \lambda_2(\beta SI + \epsilon\beta SC) = 0$$
$$\iff u_1^*(t) = \frac{\lambda_1(\beta SI+\epsilon\beta SC)-\lambda_2(\beta SI+\epsilon\beta SC)}{B_1}$$

$$\frac{\partial H}{\partial u_2} = 0 \iff B_2 u_2 - \lambda_6 q\gamma_1 I + \lambda_4 q\gamma_1 I = 0 \iff u_2^*(t) = \frac{\lambda_6 q\gamma_1 I - \lambda_4 q\gamma_1 I}{B_2}$$

combining these three cases in a compact form we get

$$\begin{cases} u_1^*(t) = max\{min\{\frac{\lambda_2(\beta SI+\epsilon\beta SC)-\lambda_1(\beta SI+\epsilon\beta SC)}{B_1}, 0.999\}, 0\} \\ u_2^*(t) = max\{min\{\frac{\lambda_4 q\gamma_1 I-\lambda_6 q\gamma_1 I}{B_2}, 0.999\}, 0\} \end{cases}$$

Theorem 5.3.1. *(Necessary Conditions for the existence of an optimal Control pair) Let $u_1^*, u_2^* \in U$ be an optimal control pair with the corresponding states $(S^*, L^*, I^*, C^*, V^*, R^*)$, then there exists the adjoint variables λ_i for i = 1, 2, 3,4,5 satisfying*

$$\begin{cases} \lambda_1' = \lambda_1(\mu_0 + (1-u_1)(\beta I + \epsilon\beta C) + \gamma_3) - \lambda_2(1-u_1)(\beta I + \epsilon\beta C) - \lambda_5\gamma_3 \\ \lambda_2' = \lambda_2(\mu_0 + \sigma) - \lambda_3\sigma \\ \lambda_3' = -A_1 + \lambda_1(\mu\omega v p_1 + (1-u_1)\beta S) - \lambda_2(u_1\beta S + p_1\mu v\omega) - \lambda_3(\mu_0 + \gamma_1) - \lambda_4(1-u_2)q\gamma_1 - \lambda_6((1-q \\ \lambda_4' = -A_2 + \lambda_1(\mu\omega v p_2 + (1-u_1)\epsilon\beta S) - \lambda_2((1-u_1)\epsilon\beta S + p_2\mu v\omega) + \lambda_4((\mu_0 + \mu_1 + \gamma_2)) - \lambda_6\gamma_2 \\ \lambda_5' = -\lambda_1\psi + \lambda_5(\psi + \mu_0) \\ \lambda_6' = -\lambda_1\rho + \lambda_6(\mu_0 + \rho) \end{cases} \tag{5.5}$$

and the transversality conditions

$$\lambda_1(T) = \lambda_2(T) = \lambda_3(T) = \lambda_4(T) = \lambda_5(T) = \lambda_6(T) = 0 \tag{5.6}$$

as the terminal conditions at the final time t_f while the optimal control variables are defined as:

$$u_1^*(t) = max\{min\{\frac{\lambda_1(\beta SI+\epsilon\beta SC)-\lambda_2(\beta SI+\epsilon\beta SC)}{B_1}, 0.999\}, 0\}$$

$$u_2^*(t) = max\{min\{\frac{\lambda_6 q\gamma_1 I-\lambda_4 q\gamma_1 I}{B_2}, 0.999\}, 0\}$$

Proof. Using the Pontryagin's maximum principle (PMP), we obtain equation (5.2.1) from

$$\lambda_1' = -\frac{\partial H}{\partial S}$$
$$\lambda_2' = -\frac{\partial H}{\partial L}$$
$$\lambda_3' = -\frac{\partial H}{\partial I}$$
$$\lambda_4' = -\frac{\partial H}{\partial C}$$
$$\lambda_5' = -\frac{\partial H}{\partial V}$$
$$\lambda_6' = -\frac{\partial H}{\partial R}$$

where the Hamiltonian H is given by

$$H = A_1 I(t) + A_2 C(t) + \tfrac{1}{2}(B_1 u_1^2(t) + B_2 u_2^2(t)) + \lambda_1(\mu\omega(1 - vp_1 I - vp_2 C) + \psi V + \rho R - (\mu_0 + (1-u_1)(\beta I + \epsilon\beta C) + \gamma_3)S) + \lambda_2((1-u_1)(\beta I + \epsilon\beta C)S + (p_1 I + p_2 C)\mu v\omega - (\mu_0 + \sigma)L) + \lambda_3(\sigma L - (\mu_0 + \gamma_1)I + \lambda_4((1-u_2)q\gamma_1 I - (\mu_0 + \mu_1 + \gamma_2)C + \lambda_5(\mu(1-\omega) + \gamma_3 S - (\psi + \mu_0)V) + \lambda_6((1 - q(1-u_2)\gamma_1 I + \gamma_2 C - (\mu_0 + \rho))$$

$$u_2^*(t) = max\{min\{\frac{\lambda_6 q\gamma_1 I-\lambda_4 q\gamma_1 I}{B_2}, 0.999\}, 0\}$$

By imposing the bounds $0 \le u_1 \le 1$, $0 \le u_2 \le 1$ on the control variables, we have

$$\begin{cases} u_1^*(t) = max\{min\{\frac{\lambda_1(\beta SI+\epsilon\beta SC)-\lambda_2(\beta SI+\epsilon\beta SC)}{B_1}, 0.999\}, 0\} \\ u_2^*(t) = max\{min\{\frac{\lambda_6 q\gamma_1 I-\lambda_4 q\gamma_1 I}{B_2}, 0.999\}, 0\} \end{cases} \tag{5.7}$$

Thus, the required optimality system consists of the state variables system of equations (5.1) with its initial conditions and the adjoint variables system of equations (5.5) with its terminal conditions which incorporates the optimal control variables characterization in dynamics. □

Chapter 6

Simulation Results and Discussion

Numerical solutions to the optimal system (5.7) are executed using MATLAB.The considered control u_1 and u_2 depends on the adjoints $\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5$ and λ_6 of the state variables S, L, I, C, V and R respectively. We simulate the model without control and with control and then we compare the results. We considered the numerical value of the control u_i in between (0,1) as they are not 100 percent effective. We solve numerically using the forward-backward sweep method given in [26]. In this formulation, there exist initial conditions for the state variables and terminal conditions for the adjoint variables. That is, the optimality system is a two-point boundary value problem, with separated boundary conditions at times t_0 and T .
The twelve ordinary differential equations in (5.4) comprising the optimality system are numerically solved together with the control characterization which is used to simulate the Hepatitis B virus vaccination and treatment strategies.The processes begin with an initial guess on the control variable. Then, the state equations are solved simultaneously forward in time, and next the adjoint equations are simultaneously solved backward in time. The control is updated by inserting the new values of states and adjoints into its characterization, and the process is repeated until convergence occurs. The ODE solver used for the state and adjoint systems is a Runge-Kutta fourth order procedure implemented with MATLAB.

6.1 Data

The table (6.2) specifies the parameter values and table (6.1) indicates the initial conditions for each of the state variables used in carrying out our simulation.

Table 6.1: variables values for HBV model.

variables	value	source
S_0	0.5	Assume
L_0	0.2	Assume
I_0	0.1	Assume
C_0	0.05	Assume
V_0	0.05	Assume
R_0	0.1	Assume

Table 6.2: Parameter values for HBV model.

parameter	value	source
μ	0.0121	[33]
μ_0	0.00693	[33]
μ_1	0.2%	[33]
ω	0-100%%	[33]
υ	0.11	[33]
ψ	0.1	[33]
σ	6 per year	[33]
β	0.95-20.49%	[33]
γ_1	4 per year	[33]
q	0.885	[33]
γ_2	0.025 per yer	[33]
γ_3	0-100%	[33]
ϵ	0.16	[33]
p_1	0.72	Assume
p_2	0.3	Assume
ρ	0.2-0.06	[5]

It is important to emphasize here that the set of parameter values above yields $R_0 = 2.467198 > 1$ which implies that HBV is endemic in the scenario under consideration. Also, the initial condition for the state variables is a realistic hypothetic one. We simulate the optimality system with parameter values from Table (6.2) using the weight constants $B_1 = 5, B_2 = 2$ $A_1 = 5, A_2 = 3$ and $A_3 = 2$.

6.2 Numerical results

The control variables u_1, u_2 are used to optimize the objective function. Using u_1, u_2 that means number of acutely infected and chronic carriers individuals minimize with small time interval.

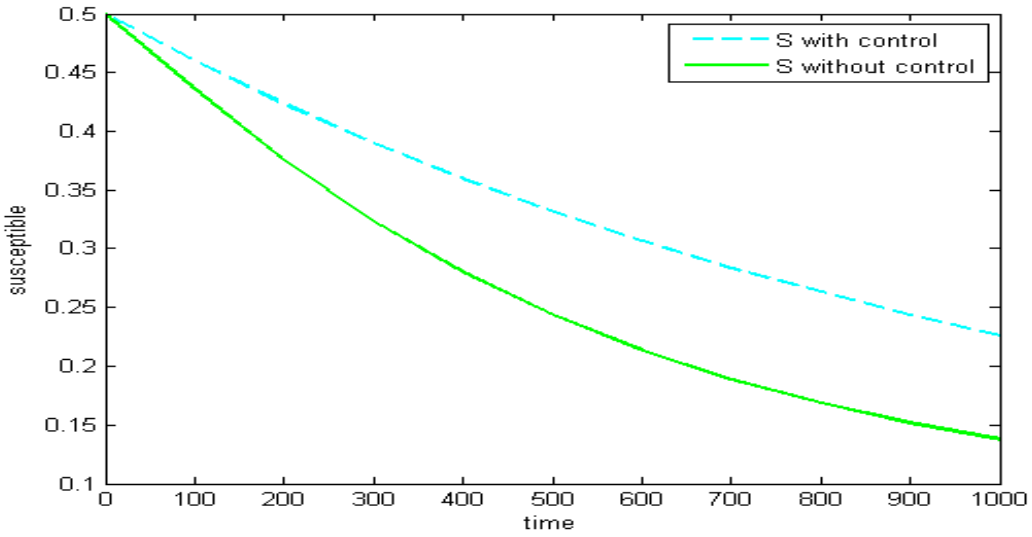

Figure 6.1: Comparison of susceptible populations

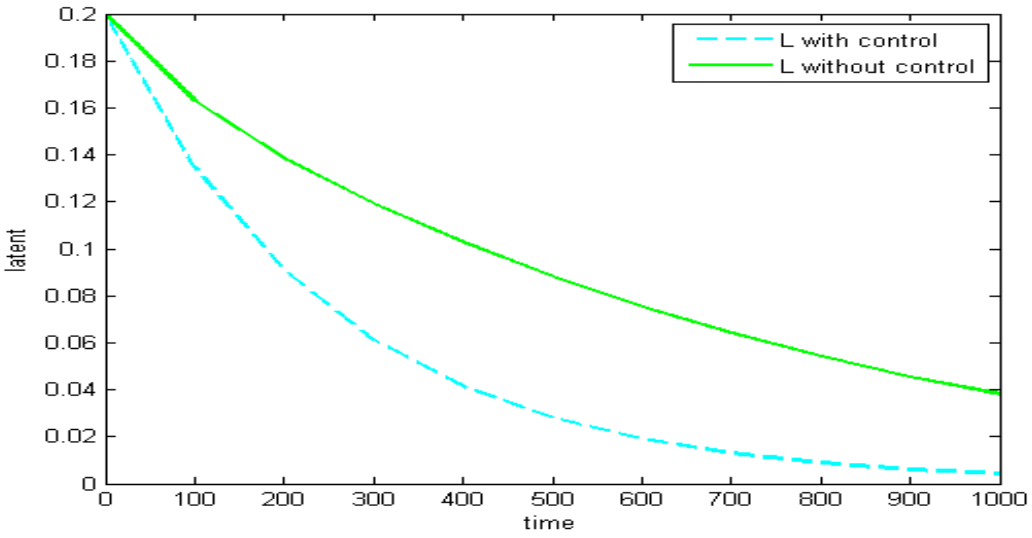

Figure 6.2: Comparison of latent population

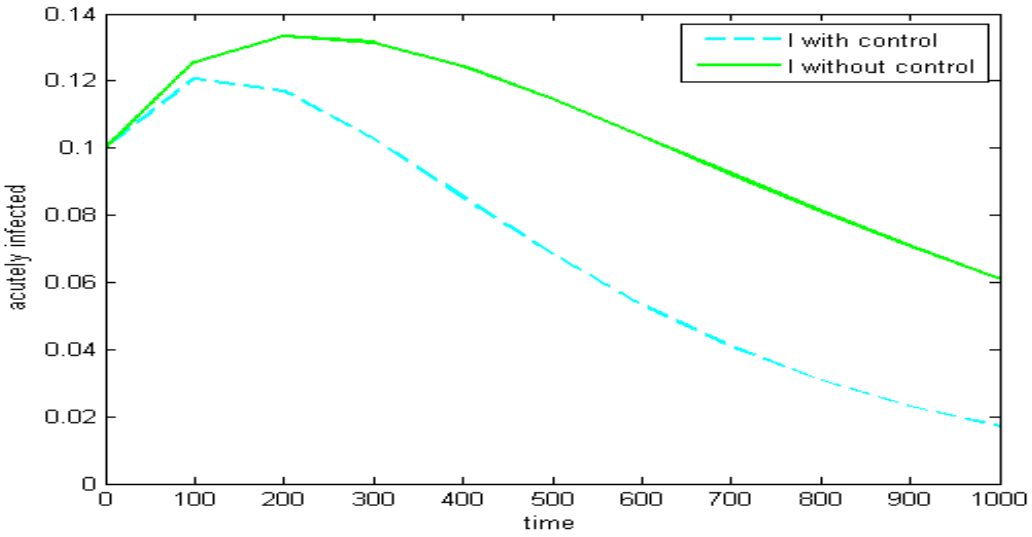

Figure 6.3: Comparison of acutely infected population

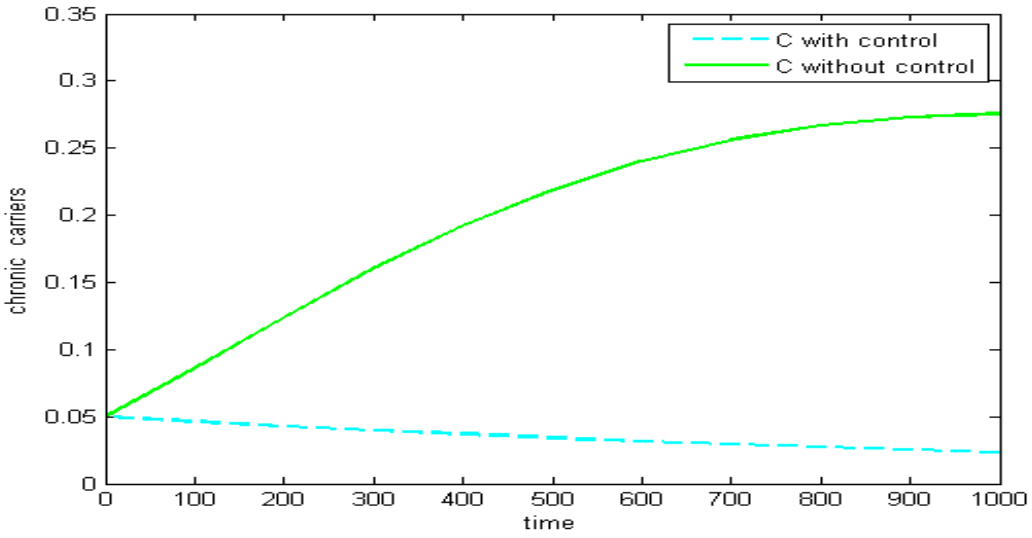

Figure 6.4: Comparison of chronic carriers population

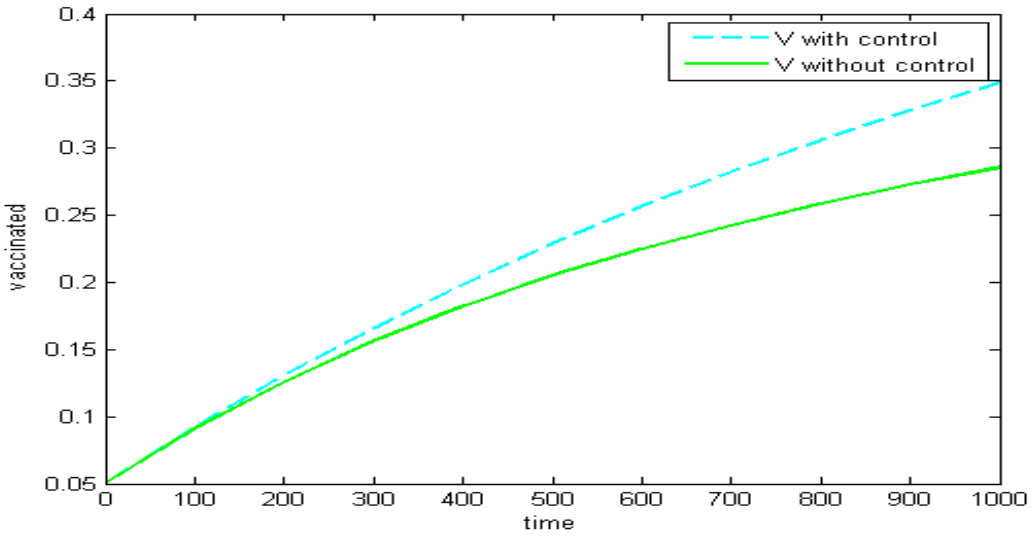

Figure 6.5: Comparison of vaccinated population

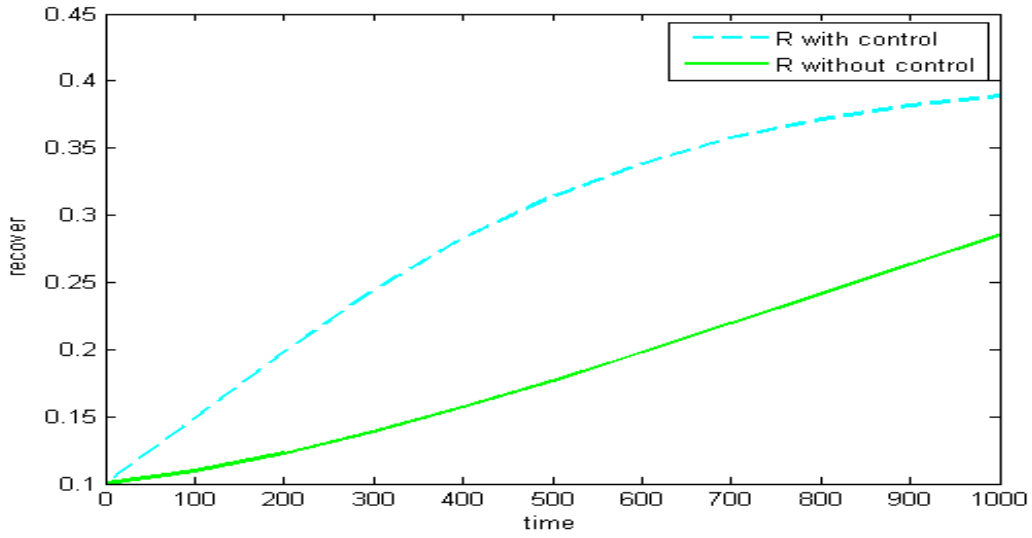

Figure 6.6: Comparison of recover population

Figures 6.1- 6.6 show the numerical solution of controlled and uncontrolled susceptible, latent, acutely infected, chronic carriers,vaccinated and recover individuals. From this figure we observe that the latent , acutely infected and chronic carriers individuals decrease significantly when control strategies are implemented and both go to stable states at the end of the control period. The results clearly show vaccination and treatment given the result to minimize acutely infected and chronic carriers individual significantly of infective individuals on the dynamics of the population than minimize numbers population.

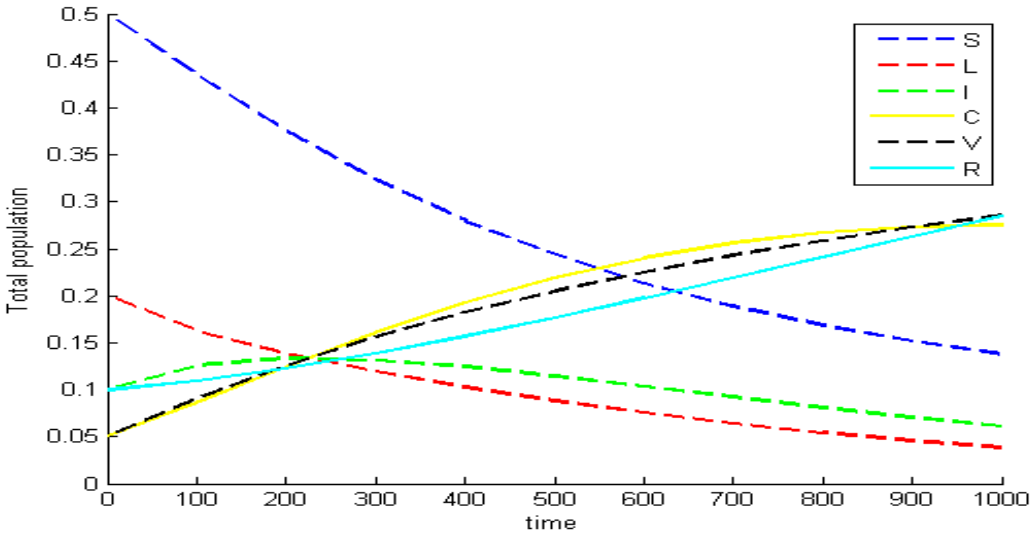

Figure 6.7: SLICVRS model without control

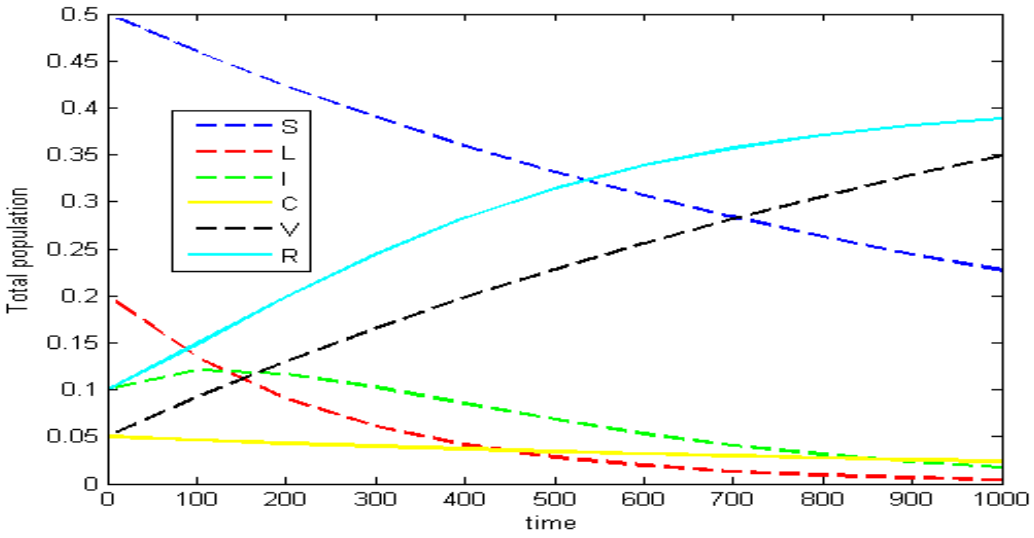

Figure 6.8: SLICVRS model with control

Figure 6.7 and 6.8 show the numerical solution of controlled and uncontrolled SLICVRS model. From these figure latent, acutely infected and chronic carriers individuals were minimize slowly.This mean hepatitis B with out any control increasing acutely infected and chronic carriers individuals.But on the other figure 6.8 show the numerical solution of controlled SLICVRS model we observe that the latent, acutely infected and chronic carriers individuals decrease significantly when control strategies are implemented and susceptible,vaccinated, recovered individuals increasing at the end of the control period. The results clearly show using different controlling methods given to the susceptible, acutely infected and chronic carriers individual. Indirectly the controlling methods also affect latent population to be reduced.

Chapter 7

Conclusion and Recommendations

7.1 Conclusion

In this thesis, we propose an $SLICVRS$ model of hepatitis B virus infection with two controls: vaccination and treatment. First we analyze the dynamic behavior of the system for constant controls. In the constant controls case, we calculate the basic reproduction number and investigate the existence and stability of equilibria. There are two non negative equilibria of the system, namely, the disease-free and endemic. We see that the disease-free equilibrium which always exists and is locally asymptotically stable if $R_0 < 1$, endemic equilibria which exists and is locally asymptotically stable if $R_0 > 1$ and disease-free equilibrium of the system is globally asymptotically stable.The basic reproductive number, R_0 of our SVLICRS model was calculated to be 2.467198, which implies that on average, each infectious individual transmits virus to 2.467198 people.After investigating the dynamic behavior of the system with constant controls we formulate an optimal control problem if the controls become time dependent and solve it by using Pontryagin's maximum principle. Different possible combinations of controls are used and their effectiveness is compared by simulation works.

7.2 Recommendations

It is highly recommended that besides the attempts being made by Minister of Health Service to fight HBV , there are other effective measures that can be implemented to reduce drastically the burden of HBV on the health of the people.

- take drug when HBV infected recommend by doctors.
- All unvaccinated adults at risk for HBV infection should be vaccinated. This includes:Sex partners of people uninfected with HBV, People who inject street drugs, People with more than one sex partner, People with chronic liver or kidney disease, People with jobs that expose them to human blood and Household contacts of people infected with HBV.

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Appendices

MATLAB CODES

SLICVRS model without control

function y = gab1(t,x1,x2,x3,x4,x5,x6) test = -1; delta = 0.001; N = 1000; mu=0.014; mu0=0.0003; mu1=0.000071; omega=0.05; v=0.005; phsi=0.0001; sigima=4; beta=6; gamma1=0.99; q=0.7; gamma2=0.72; gamma3=3.85; p1=1.072; p2=1.003; rho=0.061; epsilon=4; t=linspace(0,1000,N+1); h=1/N; h2=h/2; x1=zeros(1,N+1); x2=zeros(1,N+1); x3=zeros(1,N+1); x4=zeros(1,N+1); x5=zeros(1,N+1); x6=zeros(1,N+1); x1(1)=0.5; x2(1)=0.2; x3(1)=0.1; x4(1)=0.05; x5(1)=0.05; x6(1)=0.1; while(test < 0) oldx1=x1; oldx2=x2; oldx3=x3; oldx4=x4; oldx5=x5; oldx6=x6; for i = 1:N k11=mu*omega*(1-v*p1*x3(i)-v*p2*x4(i))+phsi*x5(i)+rho*x6(i)-(mu0+beta*x3(i)+epsilon*0*x4(i)+gamma3)*x1(i); k12=(beta*x3(i)+epsilon*beta*x4(i))*x1(i)+(p1*x3(i)+p2*x4(i))*mu*v*omega-(mu0+sigima)*x2(i); k13=sigima*x2(i)-(mu0+gamma1)*x3(i); k14=q*gamma1*x3(i)-(mu0+mu1+gamma2)*x4(i); k15=mu*(1-omega)+gamma3*x1(i)-(phsi+mu0)*x5(i); k16=(1-q)*gamma1*x3(i)+gamma2*x4(i)-(mu0+rho)*x6(i);

k21=mu*omega*(1-v*p1*(x3(i)+h2*k13)-v*p2*(x4(i)+h2*k14))+phsi*(x5(i)+h2*k15)+rho*(x6(i)+
(mu0+beta*(x3(i)+h2*k13)+epsilon*0*(x4(i)+h2*k14)+gamma3)*(x1(i)+h2*k11); k22=(beta*(x3(i)+
(mu0+sigima)*(x2(i)+h2*k12); k23=sigima*(x2(i)+h2*k12)-(mu0+gamma1)*(x3(i)+h2*k13);
k24=q*gamma1*(x3(i)+h2*k13)-(mu0+mu1+gamma2)*(x4(i)+h2*k14); k25=mu*(1-omega)+gamma3
(phsi+mu0)*(x5(i)+h2*k15); k26=(1-q)*gamma1*(x3(i)+h2*k13)+gamma2*(x4(i)+h2*k14)-
(mu0+rho)*(x6(i)+h2*k16);

k31=mu*omega*(1-v*p1*(x3(i)+h2*k23)-v*p2*(x4(i)+h2*k24))+phsi*(x5(i)+h2*k25)+rho*(x6(i)+
(mu0+beta*(x3(i)+h2*k23)+epsilon*0*(x4(i)+h2*k24)+gamma3)*(x1(i)+h2*k21); k32=(beta*(x3(i)+
(mu0+sigima)*(x2(i)+h2*k22); k33=sigima*(x2(i)+h2*k22)-(mu0+gamma1)*(x3(i)+h2*k23);
k34=q*gamma1*(x3(i)+h2*k23)-(mu0+mu1+gamma2)*(x4(i)+h2*k24); k35=mu*(1-omega)+gamma3
(phsi+mu0)*(x5(i)+h2*k25); k36=(1-q)*gamma1*(x3(i)+h2*k23)+gamma2*(x4(i)+h2*k24)-
(mu0+rho)*(x6(i)+h2*k26);

k41=mu*omega*(1-v*p1*(x3(i)+h*k33)-v*p2*(x4(i)+h*k34))+phsi*(x5(i)+h*k35)+rho*(x6(i)+h*
(mu0+beta*(x3(i)+h*k33)+epsilon*0*(x4(i)+h*k34))*(x1(i)+h*k31); k42=(beta*(x3(i)+h*k33)+epsil
(mu0+sigima)*(x2(i)+h*k32); k43=sigima*(x2(i)+h*k32)-(mu0+gamma1)*(x3(i)+h*k33);
k44=q*gamma1*(x3(i)+h*k33)-(mu0+mu1+gamma2)*(x4(i)+h*k34); k45=mu*(1-omega)+gamma3*(
(phsi+mu0)*(x5(i)+h*k35); k46=(1-q)*gamma1*(x3(i)+h*k33)+gamma2*(x4(i)+h*k34)-
(mu0+rho)*(x6(i)+h*k36);

x1(i+1) = x1(i) + (h/6)*(k11 + 2*k21 + 2*k31 + k41); x2(i+1) = x2(i) + (h/6)*(k12 + 2*k22 + 2*k32 + k42); x3(i+1) = x3(i) + (h/6)*(k13 + 2*k23 + 2*k33 + k43); x4(i+1)

= x4(i) + (h/6)*(k14 + 2*k24 + 2*k34 + k44); x5(i+1) = x5(i) + (h/6)*(k15 + 2*k25 + 2*k35 + k45); x6(i+1) = x6(i) + (h/6)*(k16 + 2*k26 + 2*k36 + k46);
end
temp1 = delta*sum(abs(x1)) - sum(abs(oldx1 - x1)); temp2 = delta*sum(abs(x2)) - sum(abs(oldx2 - x2)); temp3 = delta*sum(abs(x3)) - sum(abs(oldx3 - x3)); temp4 = delta*sum(abs(x4)) - sum(abs(oldx4 - x4)); temp5 = delta*sum(abs(x5)) - sum(abs(oldx5 - x5)); temp6 = delta*sum(abs(x6)) - sum(abs(oldx6 - x6)); test= min(temp1, min(temp2,min(temp3,mi
end y(1,:) = t; y(2,:) = x1; y(3,:) = x2; y(4,:) = x3; y(5,:) = x4; y(6,:) = x5; y(7,:) = x6; hold off plot(y(1,:),y(2,:),'b',y(1,:),y(3,:),'g',y(1,:),y(4,:),'y',y(1,:),y(5,:),'r',y(1,:),y(6,:),'c',y(1,:),y(7,:)
xlabel('time') ylabel('Total population') legend('S','L','I','C','V','R') hold off

SLICVRS model with control

function y = su2(t,A1,A2,B1,B2,x1,x2,x3,x4,x5,x6) test = -1; delta = 0.001; N = 100;
A1=3; A2=2; B1=5; B2=2; mu=0.014; mu0=0.0003; mu1=0.000071; omega=0.05; v=0.005;
phsi=0.0001; sigma=4; beta=6; gamma1=0.99; q=0.7; gamma2=0.72; gamma3=3.85;
p1=1.072; p2=1.003; rho=0.061; epsilon=4; M1=0; M2=1; t=linspace(0,1000,N+1);
h=1/N; h2=h/2; u1=zeros(1,N+1); u2=zeros(1,N+1); x1=zeros(1,N+1); x2=zeros(1,N+1);
x3=zeros(1,N+1); x4=zeros(1,N+1); x5=zeros(1,N+1); x6=zeros(1,N+1); lambda1=zeros(1,N+1);
lambda2=zeros(1,N+1); lambda3=zeros(1,N+1); lambda4=zeros(1,N+1); lambda5=zeros(1,N+1);
lambda6=zeros(1,N+1); x1(1)=0.5; x2(1)=0.2; x3(1)=0.1; x4(1)=0.05; x5(1)=0.05; x6(1)=0.1;
while(test < 0) oldu1=u1; oldu2=u2; oldx1=x1; oldx2=x2; oldx3=x3; oldx4=x4; oldx5=x5;
oldx6=x6; oldlambda1=lambda1; oldlambda2=lambda2; oldlambda3=lambda3; oldlambda4=lambda4;
oldlambda5=lambda5; oldlambda6=lambda6; for i = 1:N k11=mu*omega*(1-v*p1*x3(i)-v*p2*x4(i))+phsi*x5(i)+rho*x6(i)-(mu0+u1(i)*(beta*x3(i)+epsilon*0*x4(i))+gamma3)*x1(i);
k12=u1(i)*(beta*x3(i)+epsilon*beta*x4(i))*x1(i)+(p1*x3(i)+p2*x4(i))*mu*v*omega-(mu0+sigma)*x
k13=sigma*x2(i)-(mu0+gamma1)*x3(i); k14=u2(i)*q*gamma1*x3(i)-(mu0+mu1+gamma2)*x4(i);
k15=mu*(1-omega)+gamma3*x1(i)-(phsi+mu0)*x5(i)+u1(i)*x1(i); k16=(1-u2(i)*q)*gamma1*x3(i)+g
(mu0+rho)*x6(i);
k21=mu*omega*(1-v*p1*(x3(i)+h2*k13)-v*p2*(x4(i)+h2*k14))+phsi*(x5(i)+h2*k15)+rho*(x6(i)-
(mu0+0.5*(u1(i)+u1(i+1))*(beta*(x3(i)+h2*k13)+epsilon*0*(x4(i))+h2*k14)+gamma3)*(x1(i)+h2*k
k22=0.5*(u1(i)+u1(i+1))*(beta*(x3(i)+h2*k13)+epsilon*beta*(x4(i)+h2*k14))*(x1(i)+h2*k11)+(p1*
(mu0+sigma)*(x2(i)+h2*k12); k23=sigma*(x2(i)+h2*k12)-(mu0+gamma1)*(x3(i)+h2*k13);
k24=0.5*(u2(i)+u2(i+1))*q*gamma1*(x3(i)+h2*k13)-(mu0+mu1+gamma2)*(x4(i)+h2*k14);
k25=mu*(1-omega)+gamma3*(x1(i)+h2*k11)-(phsi+mu0)*(x5(i)+h2*k15); k26=(1-0.5*(u2(i)+u2(i+
(mu0+rho)*(x6(i)+h2*k16);
k31=mu*omega*(1-v*p1*(x3(i)+h2*k23)-v*p2*(x4(i)+h2*k24))+phsi*(x5(i)+h2*k25)+rho*(x6(i)-
(mu0+0.5*(u1(i)+u1(i+1))*(beta*(x3(i)+h2*k23)+epsilon*0*(x4(i)+h2*k24))+gamma3)*(x1(i)+h2*k
k32=(0.5*(u1(i)+u1(i+1))*beta*(x3(i)+h2*k23)+epsilon*beta*(x4(i)+h2*k24))*(x1(i)+h2*k21)+(p1*
(mu0+sigma)*(x2(i)+h2*k22); k33=sigma*(x2(i)+h2*k22)-(mu0+gamma1)*(x3(i)+h2*k23);
k34=0.5*(u2(i)+u2(i+1))*q*gamma1*(x3(i)+h2*k23)-(mu0+mu1+gamma2)*(x4(i)+h2*k24);
k35=mu*(1-omega)+gamma3*(x1(i)+h2*k21)-(phsi+mu0)*(x5(i)+h2*k25); k36=(1-0.5*(u2(i)+u2(i+
(mu0+rho)*(x6(i)+h2*k26);
k41=mu*omega*(1-v*p1*(x3(i)+h*k33)-v*p2*(x4(i)+h*k34))+phsi*(x5(i)+h*k35)+rho*(x6(i)+h*
(mu0+u1(i+1)*(beta*(x3(i)+h*k33)+epsilon*0*(x4(i)+h*k34))+gamma3)*(x1(i)+h*k31);
k42=u1(i+1)*(beta*(x3(i)+h*k33)+epsilon*beta*(x4(i)+h*k34))*(x1(i)+h*k31)+(p1*(x3(i)+h*k33)+
(mu0+sigma)*(x2(i)+h*k32); k43=sigma*(x2(i)+h*k32)-(mu0+gamma1)*(x3(i)+h*k33);
k44=u2(i+1)*q*gamma1*(x3(i)+h*k33)-(mu0+mu1+gamma2)*(x4(i)+h*k34); k45=mu*(1-

omega)+gamma3*(x1(i)+h*k31)-(phsi+mu0)*(x5(i)+h*k35); k46=(1-u2(i+1)*q)*gamma1*(x3(i)+h*k
(mu0+rho)*(x6(i)+h*k36);

x1(i+1) = x1(i) + (h/6)*(k11 + 2*k21 + 2*k31 + k41); x2(i+1) = x2(i) + (h/6)*(k12
+ 2*k22 + 2*k32 + k42); x3(i+1) = x3(i) + (h/6)*(k13 + 2*k23 + 2*k33 + k43); x4(i+1)
= x4(i) + (h/6)*(k14 + 2*k24 + 2*k34 + k44); x5(i+1) = x5(i) + (h/6)*(k15 + 2*k25
+ 2*k35 + k45); x6(i+1) = x6(i) + (h/6)*(k16 + 2*k26 + 2*k36 + k46);

end for i=1:N j=N+2-i; k11=lambda1(j)*(mu0+u1(i)*(beta*x3(j)+epsilon*beta*x4(j))+gamma3)-
lambda2(j)*u1(i)*(beta*x3(j)+epsilon*beta*x4(j))-lambda5(j)*gamma3; k12=lambda2(j)*(mu0+sigma
lambda3(j)*sigma; k13=-A1+lambda1(j)*(mu*omega*v*p1+(mu0+u1(i)*beta)*x1(j))-lambda2(j)*(u1
lambda3(j)*(mu0+gamma1)+lambda4(j)*u2(i)*q*gamma1-lambda6(j)*(1-u2(i)*q)*gamma1;
k14=-A2+lambda1(j)*(mu*omega*v*p2+u1(i)*epsilon*beta*x1(j))-lambda2(j)*(epsilon*beta*x1(j)+p
lambda6(j)*gamma2; k15=lambda1(j)*phsi+lambda5(j)*(phsi+mu0); k16=-lambda1(j)*rho*x6(j)+lam

k21=(lambda1(j)-h2*k11)*(mu0+0.5*(u1(i)+u1(i+1))*(beta*0.5*(x3(j)+x3(j-1))+epsilon*beta*0.5
1)))+gamma3)-(lambda2(j)-h2*k12)*0.5*(u1(i)+u1(i+1))*((beta*0.5*(x3(j)+x3(j-1))+epsilon*beta*0.
1))))-(lambda5(j)-h2*k15)*gamma3; k22=(lambda2(j)-h2*k12)*(mu0+sigma)-(lambda3(j)-
h2*k13)*sigma; k23=-A1+(lambda1(j)-h2*k11)*(mu*omega*v*p1+(mu0+0.5*(u1(i)+u1(i+1))*beta)*
1))-(lambda2(j)-h2*k12)*(0.5*(u1(i)+u1(i+1))*beta*0.5*(x1(j)+x1(j-1))+mu*omega*v*p1)-
(lambda3(j)-h2*k13)*(mu0+gamma1)+(lambda4(j)-h2*k14)*0.5*(u2(i)+u2(i+1))*q*gamma1-
(lambda6(j)-h2*k16)*(1-0.5*(u1(i)+u1(i+1))*q)*gamma1; k24=-A2+(lambda1(j)-h2*k11)*(mu*omega
1)))-(lambda2(j)-h2*k12)*(0.5*(u1(i)+u1(i+1))*epsilon*beta*0.5*(x1(j)+x1(j-1))+p2*mu*omega*v)+
h2*k14)*(mu0+mu1+gamma2)-(lambda6(j)-h2*k16)*gamma2; k25=(lambda1(j)-h2*k11)*phsi+(lambd
h2*k15)*(phsi+mu0); k26=-(lambda1(j)-h*k11)*rho*0.5*(x6(j)+x6(j-1))+(lambda6(j)-h*k16)*(mu0+r

k31=(lambda1(j)-h2*k21)*(mu0+0.5*(u1(i)+u1(i+1))*(beta*0.5*(x3(j)+x3(j-1))+epsilon*beta*0.5
1)))+gamma3)-(lambda2(j)-h2*k22)*0.5*(u1(i)+u1(i+1))*(beta*0.5*(x3(j)+x3(j-1))+epsilon*beta*0.5
1)))-(lambda5(j)-h2*k25)*gamma3; k32=(lambda2(j)-h2*k22)*(mu0+sigma)-(lambda3(j)-
h2*k23)*sigma; k33=-A1+(lambda1(j)-h2*k21)*(mu*omega*v*p1+(mu0+0.5*(u1(i)+u1(i+1))*beta)*
1))-(lambda2(j)-h2*k22)*(0.5*(u1(i)+u1(i+1))*beta*0.5*(x1(j)+x1(j-1))+mu*omega*v*p1)-
(lambda3(j)-h2*k23)*(mu0+gamma1)+(lambda4(j)-h2*k24)*0.5*(u1(i)+u1(i+1))*q*gamma1-
(lambda6(j)-h2*k26)*(1-0.5*(u1(i)+u1(i+1))*q)*gamma1; k34=-A2+(lambda1(j)-h2*k21)*(mu*omega
1)))-(lambda2(j)-h2*k22)*(0.5*(u1(i)+u1(i+1))*epsilon*beta*0.5*(x1(j)+x1(j-1))+p2*mu*omega*v)+
h2*k24)*(mu0+mu1+gamma2)-(lambda6(j)-h2*k26)*gamma2; k35=(lambda1(j)-h2*k21)*phsi+(lambd
h2*k25)*(phsi+mu0); k36=-(lambda1(j)-h*k21)*rho*0.5*(x6(j)+x6(j-1))+(lambda6(j)-h*k26)*(mu0+r

k41=(lambda1(j)-h*k31)*(mu0+u1(i+1)*(beta*x3(j-1))+epsilon*beta*x4(j-1))+gamma3-
(lambda2(j)-h*k32)*u1(i+1)*(beta*x3(j-1)+epsilon*beta*x4(j-1))-(lambda5(j)-h*k35)*(gamma3);
k42=(lambda2(j)-h*k32)*(mu0+sigma)-(lambda3(j)-h*k33)*sigma; k43=-A1+(lambda3(j)-
h*k31)*(mu*omega*v*p1+(mu0+u1(i+1)*beta)*x1(j-1))-(lambda2(j)-h*k32)*(u1(i+1)*beta*x1(j-
1)+mu*omega*v*p1)-(lambda3(j)-h*k33)*(mu0+gamma1)+(lambda4(j)-h*k34)*u2(i+1)*q*gamma1-
(lambda6(j)-h*k36)*(1-u2(i+1)*q)*gamma1; k44=-A2+(lambda4(j)-h*k31)*(mu*omega*v*p2+u1(i+1
1))-(lambda2(j)-h*k32)*(u1(i+1)*epsilon*beta*x1(j-1)+p2*mu*omega*v)+(lambda4(j)-h*k34)*(mu0+
(lambda6(j)-h*k36)*gamma2; k45=(lambda5(j)-h*k31)*phsi+(lambda5(j)-h*k35)*(phsi+mu0);
k46=-(lambda6(j)-h*k31)*rho*x6(j-1)+(lambda6(j)-h*k36)*(mu0+rho);

lambda1(j-1)=lambda1(j)-(h/6*(k11+2*k21+2*k31+k41)); lambda2(j-1)=lambda2(j)-
(h/6*(k12+2*k22+2*k32+k42)); lambda3(j-1)=lambda3(j)-(h/6*(k13+2*k23+2*k33+k43));
lambda4(j-1)=lambda4(j)-(h/6*(k14+2*k24+2*k34+k44)); lambda5(j-1)=lambda5(j)-(h/6*(k15+2*k2
lambda6(j-1)=lambda6(j)-(h/6*(k16+2*k26+2*k36+k46));

end

u1=min(M2,max(M1,(lambda1(j-1)*(x1(i+1)*x3(i+1)+epsilon*beta*x1(i+1)*x3(i+1))-
lambda2(j-1)*(x1(i+1)*x3(i+1)+epsilon*beta*x1(i+1)*x3(i+1)))/B1)); u1=0.5*(u1+oldu1);

```
u2=min(M2,max(M1,(lambda6(j-1)*(q*gamma1*x3(i+1))+-lambda4(j-1)*(q*gamma1*x3(i+1)))/B2))
u2=0.5*(u2+oldu2); temp1 = delta*sum(abs(x1)) - sum(abs(oldx1 - x1)); temp2 =
delta*sum(abs(x2)) - sum(abs(oldx2 - x2)); temp3 = delta*sum(abs(x3)) - sum(abs(oldx3
- x3)); temp4 = delta*sum(abs(x4)) - sum(abs(oldx4 - x4)); temp5 = delta*sum(abs(x5))
- sum(abs(oldx5 - x5)); temp6 = delta*sum(abs(x6)) - sum(abs(oldx6 - x6)); temp7=delta*sum(abs(u1))
sum(abs(oldu1-u1)); temp8=delta*sum(abs(u2))-sum(abs(oldu2-u2)); temp9=delta*sum(abs(lambda1)
sum(abs(oldlambda1-lambda1)); temp10=delta*sum(abs(lambda2))-sum(abs(oldlambda2-
lambda2)); temp11=delta*sum(abs(lambda3))-sum(abs(oldlambda3-lambda3)); temp12=delta*sum(ab
sum(abs(oldlambda4-lambda4)); temp13=delta*sum(abs(lambda5))-sum(abs(oldlambda5-
lambda5)); temp14=delta*sum(abs(lambda6))-sum(abs(oldlambda6-lambda6)); test= min(temp1,
min(temp2,min(temp3,min(temp4,min(temp5,min(temp6,min(temp7, min(temp8,min(temp9,min(temp
    end y(1,:) = t; y(2,:) = x1; y(3,:) = x2; y(4,:) = x3; y(5,:) = x4; y(6,:) =
x5; y(7,:) = x6; y(8,:) = u1; y(9,:) = u2; y(10,:) = lambda1; y(11,:) = lambda2;
y(12,:) = lambda3; y(13,:) = lambda4; y(14,:) = lambda5; y(15,:) = lambda6; hold off
plot(y(1,:),y(2,:),'b',y(1,:),y(3,:),'g',y(1,:),y(4,:),'y',y(1,:),y(5,:),'r',y(1,:),y(6,:),'c',y(1,:),y(7,:),'m','linewi
xlabel('time') ylabel('Total population') legend('S','L','I','C','V','R' ) hold off
```