Control of Hepatitis C Virus Infection; a Model that includes the Effects of Vaccination and Waning Immunity

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Dedicated

To my brothers, Ahmed Abdullah
and Ahmed Abdur Rahman.

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In the name of Allah, Most Gracious, Most Merciful.

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Abstract

This thesis considers a mathematical model for studying the transmission dynamics of hepatitis C virus (HCV) infection. In addition to the usual compartments for susceptible, exposed, and infected individuals, this model includes compartments for individuals who are under treatment and those who have had vaccination. It is assumed that the immunity provided by the vaccine fades with time. The model exhibits the phenomenon of backward bifurcation, where a stable disease-free equilibrium co-exists with a stable endemic equilibrium when the basic reproductive number $R_0 < 1$. It is shown that the use of a perfect vaccine can eliminate backward bifurcation completely. Further, the model has an endemic equilibrium, which is shown to be globally asymptotically stable under certain restrictions on the parameter values. Numerical simulation results are given to support the theoretical predictions.

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Chapter 1

Introduction

Infectious (or communicable) diseases, are those diseases which spread by means of contact between individuals of same or different species of population. Indeed, there have been great advancements in the field of medicine, new and improved antibiotics have been developed, and there is a lot of progress in creating new immunization methods, still, infectious diseases continue to be a main reason of mortality. With the fast increase in the world population, deforestation, rapid industrial growth, and environmental pollution, there has been an increase in the outbreak of new infectious diseases as well, such as Lyme disease, Legionnaires disease, hepatitis C, severe acute respiratory syndrome (SARS), avian influenza, heartland virus disease and corona virus infection [1]. Due to global warming, and changes in climatic conditions, diseases such as malaria and yellow fever have spread to almost all parts of the world. Disease causing agents mainly include viruses and bacteria, but recently, new infectious agents, named prions, have been discovered. With time, these infectious agents acquire resistance to drugs and antibiotics, and hence improved antibiotics have to be made to fight the resistant agent. The emergence of new infectious diseases has led to an increase in the need to formulate methods to help control their negative impact on the human population.

Epidemiology refers to the study of disease patterns in a population. It describes the distribution of disease, and can be used to test different theories related to the field of health sciences. It is important to analyze the modes of transmission of any disease, so that various techniques can be developed to counter its effects. Infectious diseases are a major cause of high death rate, especially in under developed countries. In developed countries, chronic diseases such as cancer, and heart diseases are a major source of attention and research. Even though there have been great breakthroughs in the field of medicine and vaccination is available for prevention of many infectious diseases, these diseases still are a major source of mortality. The transmission of disease in any population is a very complex process, it effects different individuals in different ways according to their gender,

age, occupation, geographical location, and a number of other factors. A mathematical model makes it easier to understand and predict the large scale dynamics of the disease spread.

The mathematical model developed in this thesis analyzes the transmission dynamics of hepatitis C virus (HCV) infection. Ordinary differential equations are used to model the HCV infection. The basic aim is to meticulously analyze the model and examine various parameters to explore their effect on transmission of HCV and its control. The model focuses on studying the effects of imperfect vaccines on the control of hepatitis C. This can help us achieve awareness about the spread of HCV infection and assess the effectiveness of immunization techniques.

The model compartmentalizes the total population into six classes: susceptible, exposed, acutely infectious, chronically infectious, treated, and vaccinated. Individuals are recruited into the susceptible class by birth and by waning vaccination. Those who are exposed to the HCV, enter the acutely infectious stage. If treated, they return to the susceptible class, otherwise they progress to the chronic stage of the infection. Individuals leave all classes through natural mortality. As a result of these assumptions, a mathematical model consisting of six differential equations is established, with one independent variable for every class. Disease free and endemic equilibrium solutions of the mathematical model are then calculated, and their local and global stability (and instability) is determined. Using the next generation operator method [2], the threshold quantity, R_0, is computed, which determines wether the disease will persist in the population or not. For $R_0 < 1$, HCV infection is locally eliminated, whereas for $R_0 > 1$, HCV infection persists in the population. It is seen that when $R_0 < 1$, a stable disease free equilibrium (DFE) may exist along with a stable endemic equilibrium, a phenomenon referred to as *backward bifurcation*. It is proved that backward bifurcation can be eliminated by the use of a perfect vaccine. This implies that when $R_0 < 1$ and a perfect vaccine is used, the DFE becomes globally stable, i.e, the infection is removed completely from the entire population. Also, a unique endemic equilibrium is shown to be globally stable if certain changes are made in the parameter values. Finally, these results are verified using numerical techniques.

This thesis is based on formulating a mathematical model which focuses on the spread and control of HCV infection. In Chapter 1, few basic facts about the HCV infection are given, and several ways of prevention from this disease are also provided. In Chapter 2, definitions and theorems are presented, which are later used in this thesis. Chapter 3 focuses on developing the mathematical model based on HCV infection, and some results are established, which are later proved numerically in Chapter 4.

1.1 Functions of the liver

Since the liver plays a very crucial role in the metabolism of foodstuffs, it has been aptly termed as the commissariat of the body [3]. The liver is responsible for maintaining normal blood sugar level in the body. Glucose is stored in the liver in the form of glycogen, and glycogen can be converted to glucose by the liver. It is the site of synthesis of fat, cholesterol, many fractions of serum proteins, immune factors and coagulation factors [4]. Liver is the storage site for proteins and vitamins A, C and D. The liver breaks down toxic and harmful substances, and it is the exclusive producer of urea by deamination of amino acids, that is, it converts harmful ammonia into urea. Liver produces bile, whose function is the breakdown of fats during digestion in the small intestine.

1.2 Infections of the liver-hepatitis

The liver is one of the most frequently damaged organs in the body, and it is indeed fortunate that it has a very large functional reserve. In the experimental animal, it has been shown that only 10% of the hepatic parenchyma (the functional part of the liver) is required to maintain normal liver function [5]. The liver can be infected due to a variety of infectious agents such as parasites, viruses, and bacteria, and the diseases of liver have a variety of causes such as obstructive, vascular, metabolic and toxic involvements. In most developed countries, the two major causes of hepatic failure are cirrhosis (scarring) and liver failure.

Hepatitis is the most common illness of the liver. Hepatitis is the inflammation of the liver. It is most commonly caused by viruses and is of different types such as hepatitis A, B, C, D, E and G [6]. Hepatitis can also be caused by over usage of certain drugs, very heavy alcohol use and certain bacteria.

1.2.1 Acute hepatitis

Acute hepatitis is inflammation of the liver which spans over a period of weeks to a few months, not lasting more than six months. Most of the times, acute (viral) hepatitis is asymptomatic, that is, there are no visible signs or symptoms. 80% of the cases of hepatitis A are asymptomatic, minor illness usually occurs in children. Similarly, hepatitis B and C patients usually show no symptoms, except for intravenous drug users who might show signs of jaundice (yellow color of the skin and whites of the eye) associated with hepatitis B. Acute hepatitis is characterized by moderate liver injury and if symptoms appear, they include fatigue, loss of appetite, abdominal pain, fever and jaundice. Generally, these conditions clear over a span of weeks to a few months, and rarely cause death [5].

1.2.2 Chronic hepatitis

Almost all patients who have had acute hepatitis A, and a large percentage of those with hepatitis B and C, recover completely. But, some patients develop a long term illness known as chronic hepatitis (massive necrosis of the liver). Chronic hepatitis lasts for more than six months and may span over a period of many years. In most people, it is mild and their condition may improve. But, in others, chronic hepatitis may damage the liver, cause cirrhosis, hepatic failure, and sometimes liver cancer. Necrosis (destruction of the cells) of the lobes of the liver, or even the entire liver, can be caused by viral infections and toxic chemicals. The liver damage may slowly develop in the form of chronic hepatitis, or it may be in the form of an overwhelming attack leading to death within one day [5].

1.3 HCV infection in Pakistan

HCV infection is a huge health problem worldwide, including Pakistan. About 4% of the population of Pakistan is infected with HCV. Those who are at high risk include health care workers (4-6%), hemodialysis patients (24-44%), and Thalassemia patients (24%). After the year 2000, analysis of eleven studies from different areas of Pakistan show 50-80% anti HCV positivity in hepatocellular carcinoma patients. Prevalence of HCV infection in children is 0.4-4.09%. In professional blood donors, there is 20% prevalence of anti HCV antibodies [7].

A mortality analysis carried out in 2002 in Pakistani hospitals showed that 7% of the deaths in hospitals were caused by liver disease out of which 1.53% were due to hepatitis, 0.48% were because of liver cancer, and 5.46% of the deaths were due to chronic disease of the liver [7]. Eight years data from a tertiary care hospital showed that about 20% deaths were caused by HBV and HCV infections. In different provinces of Pakistan, the prevalence of chronic liver disease due to HCV is variable. HCV virus infection is continuously increasing in Pakistan. In studies done before 1997, 16.6% of chronic liver disease patients were infected with HCV, while recent studies show that 60-70% of chronic liver disease patients are anti HCV positive [8].

1.4 HCV infection

1.4.1 Modes of transmission

HCV can be transmitted through various routes. Mostly, HCV infection occurs through parenteral transmission, i.e., to administer a substance into the body through means other than the alimentary canal, such as intra muscular, intra venous, or by subcutaneous means. Rarely, non-parenteral transmission may also occur, such as perinatal transmission, sexual

exposure and household contacts [6].

HCV is usually spread through contact with blood or contaminated needles. In the third world countries, a major cause of HCV transmission is injection drug use and treatment with unsterilized equipment. In developed countries such as United States, intravenous drug use is the most common mode of transmission of HCV. Drug addicts who administer drugs through injections are not only at a high risk of exposure to HCV, but also hepatitis B virus (HBV) and HIV. In the subcontinent, one of the major cause of transmission of chronic HCV infection is through blood transfusions. In Pakistan, 25-83% of chronic liver disease patients have a history of blood transfusions [7]. Non-sterile medical, surgical and dental practices by unqualified health care workers, tattooing, ear and nose piercing are also one of the modes of transmission of HCV virus.

1.4.2 Signs and symptoms, diagnosis and treatment

HCV infection is sometimes known as the 'silent killer' or the 'hidden disease'. This is because people infected with HCV often exhibit no symptoms at all. But if present, they may include flu like symptoms, fatigue, general weakness, dark urine, anxiety or depression, joint pain, loss of appetite and nausea [9].

HCV infection is diagnosed by certain tests known as liver function tests that are performed on a blood sample. In case of chronic hepatitis, severity of the infection is determined by liver biopsy, in which a small sample of the liver tissue is obtained and then tested. Acute HCV infection is difficult to diagnose, since most patients are asymptomatic and the exact time of acquisition is not definite. Patients who do show symptoms, should be kept under observation for about twelve weeks. Most likely, spontaneous clearing of infection will occur. Patients in whom HCV infection is not cleared out after twelve weeks should be treated with standard interferon therapy and ribavirin. Patients with HCV related cirrhosis and renal diseases are to be treated with different medications.

1.4.3 Impact on public health and economy

Today, HCV infects an estimated 170 million persons worldwide. Countries with the highest prevalence of chronic liver infection are Egypt (15%), Pakistan (4.8%) and China (3.2%) [10]. HCV infection is a public health crisis in Pakistan and most of south east Asia. At present, there is no vaccine available which can help protect against HCV infection. HCV is a highly changeable virus. Many endeavors are being made to create a vaccine against HCV infection, for example, protein vaccines, oral vaccines and epitope vaccines [11].

In Pakistan, 7.5 million people are infected with HCV. Majority of HCV infected patients are asymptomatic, more than 50% become chronically infected in about 20 years, and out

of these, 5% develop liver cancer. At mass level, it is important to create awareness about public health, and how to control the transmission of HCV. In 2005, the government of Pakistan started the 'National Program for Prevention and Control of Hepatitis' in the country [7]. The main aim of this program was to provide disposable syringes and free hepatitis B vaccination, proper waste disposal and provision of blood screening for transfusions. In Pakistan, the cost of an antibody screening test is about 1000 rupees. Six months of treatment with combined Pegylated Interferon and Ribavirin costs around 5000 US dollars, whereas conventional interferon costs 1000 dollars per patient [7]. Very few people can afford such expensive treatment, and most have to rely on government supported public hospitals, where treatment is not available for everyone.

1.4.4 Prevention of HCV infection

Prevention of hepatitis C depends essentially on preventing the transfer of infected blood. Instruments used for different medical procedures must always be sterile, for example, a separate needle and syringe should be used for each individual patient. Before transfusion of blood, blood screening must be carried out. Those persons who have a history of jaundice in the previous year must be excluded as blood donors. Whenever possible, blood products must be sterilized [12]. Sharing needles and syringes, razors and toothbrushes with an infected person must be avoided. HCV can even be contracted by accidental pricking with a contaminated needle. In health care facilities, it is essential that health care workers adhere to universal precautions for control and prevention of HCV infection. Isolation facilities should be made available in the hospitals, and patients should not be transferred to other units. Unnecessary blood transfusions should not be carried out. HCV infection is relatively common among patients who have kidney diseases and are on dialysis, as well as kidney transplant recipients. So, renal transplantation should be carried out at the earliest opportunity and patients with acute renal failure should be treated in a separate unit. Maximum use of disposable articles should be encouraged, so that they can be incinerated. Laboratory staff must take special precautions such as blood samples should be taken wearing gloves and protective clothing, cuts and abrasions should be covered with waterproof dressings.

Practitioners of alternative medical treatments should be educated about methods of minimizing blood contamination. Similarly, tattooists, and barbers should be made aware of the hazards of using contaminated instruments. People who are infected with HCV should never share tooth brushes, razors, scissors and towels. They should not donate blood or body organs. Persons with a history of blood transfusions should have their blood tested for possibility of HCV infection.

Chapter 2

Preliminaries

2.1 Introduction on compartmental modeling

Mathematical epidemiology uses mathematical methods to formulate models based on different infectious diseases. The basic aim of any mathematical model on a disease is to determine its process of transmission. In this way, various cost effective means can be developed to understand, and thereby control the spread of infection. The use of mathematical modeling in immunology and virology is growing very rapidly [13]. Epidemiological models can be used to identify the risk factors of different diseases which help to find why everyone in a particular population does not have the same disease uniformly.

One of the earliest mathematical models was given by Bernoulli in 1760, in which he studied the effect of cowpox vaccination to control smallpox. It was the first time that a mathematical model based on an infectious disease was used to determine the applicability of a vaccination programme [13]. Over the last century, a lot of work has been done by various mathematicians on disease epidemiology. In 1906, Hamer developed a mathematical model based on the epidemiology of measles. In his model, it was assumed that the rate of new infections depends upon the product of the number of susceptible and infectious individuals [1]. In 1911, Ross made models comprising of differential equations that discussed control of malaria. Anderson and May developed models on tuberculosis in the early 1990's. In 1927, 1932, and 1933, Kermack and McKendrick formulated classical mathematical models which had a great impact in the field of epidemiological modeling, and are still relevant in a large number of epidemic situations. These models opened new avenues for mathematical analysis of infectious diseases, making way for others in this field to explore and enhance knowledge and perspectives.

In classical models based on infectious diseases, the size of the total population is taken to be constant, and is partitioned into mutually exclusive compartments. Consider a simple infectious disease, which confers immunity after recovery. If the disease is lethal, it includes

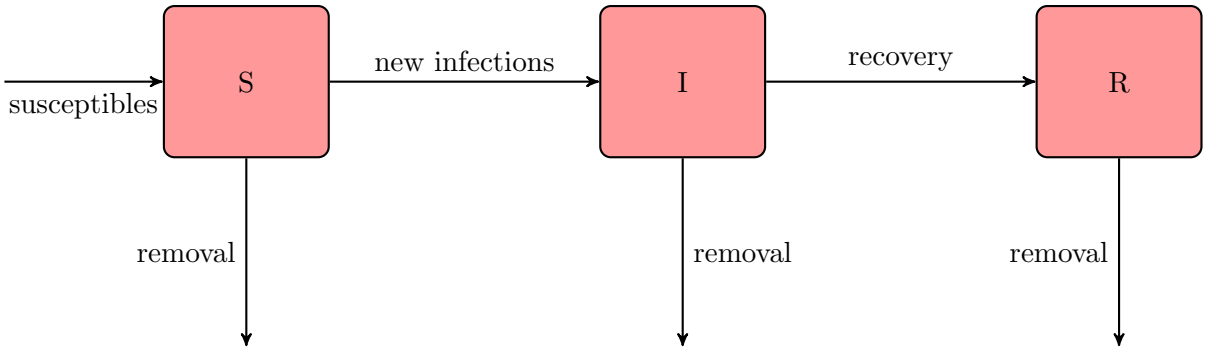

Figure 2.1: *Transfer diagram for an endemic SIR model.*

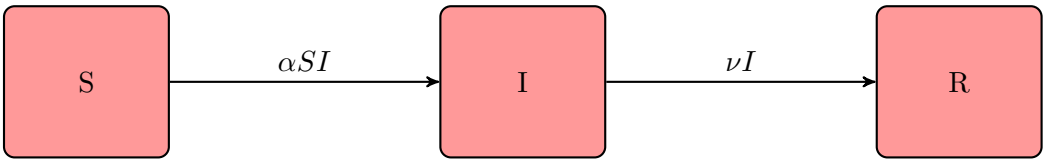

Figure 2.2: *Transfer diagram for Kermack-McKendrick model.*

death. Let the total population be divided into three mutually exclusive compartments: susceptible individuals, S, who are at risk of getting the infection; infective individuals, I, who have the infection; and the recovered individuals, R, who have had the disease and are now immune to it [13]. This model is known as the endemic SIR model (Fig. 2.1).

In the epidemic SIR model by Kermack and McKendrick, $S(t)$ is the number of individuals who are susceptible to the disease, $I(t)$ denotes the number of infected individuals, and $R(t)$ is the number of individuals who have recovered from the disease or are immune to it (Fig. 2.2). It consists of a system of three differential equations which represent the rate of change of susceptible, infected and recovered populations

$$\begin{aligned} \frac{dS}{dt} &= -\alpha SI, \qquad S(0) > 0, \\ \frac{dI}{dt} &= \alpha SI - \nu I, \quad I(0) > 0, \\ \frac{dR}{dt} &= \nu I, \qquad R(0) > 0. \end{aligned} \tag{2.1.1}$$

The rate at which individuals enter the infective class is directly proportional to the number of individuals in the infected and susceptible class, i.e., αSI, where $\alpha > 0$ is the infection rate, and is a constant parameter. The infective individuals exit the infected compartment at a rate that is directly proportional to the population of the infectives, i.e., νI, where $\nu > 0$.

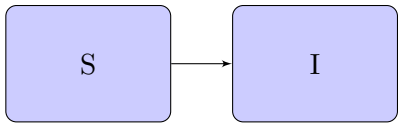

Figure 2.3: *Transfer diagram for an SI model.*

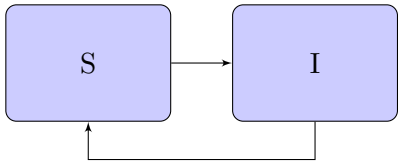

Figure 2.4: *Transfer diagram for an SIS model.*

The number of compartments in any model depends upon the disease under consideration. The SI model has only the susceptible and infected compartments. In such cases, the individuals do not recover from the disease. In SIS model, recovery does not give immunity. In SIRS model, recovery gives only temporary immunity. This means that persons who recover from the disease again become susceptible. The SEIR model has a susceptible compartment, S, a compartment in which the disease is latent, E, an infectious compartment, I, and a recovered compartment, R (Figs. 2.3, 2.4, 2.5, 2.6).

Below, some important definitions and known results are presented, which would provide a background for the research work in subsequent chapters.

Definition 2.1.1. Epidemic: An infectious disease is said to be an epidemic if it suddenly outbreaks in an area and spreads quickly in a population. Plague, smallpox, and yellow fever are major examples of epidemic diseases which have wreaked havoc in the world over the past few centuries. More recent epidemics include Avian influenza outbreaks in Egypt, Indonesia, Vietnam and Ebola hemorrhagic fever in Uganda in 2012 [14].

Definition 2.1.2. Endemic: If an infectious disease persists in a population for a long time, it is said to be an endemic, during which there is a continuous renewal in the susceptible pool by birth, ineffective or waning vaccination, and reinfection due to temporary acquired immunity. Hepatitis, AIDS (acquired immune deficiency syndrome), and malaria are endemic diseases in the world.

Definition 2.1.3. Vaccine efficacy: Vaccine efficacy refers to the ability and effectiveness of a particular vaccine to produce the desired effect, that is, the capacity of a vaccine to control an infection.

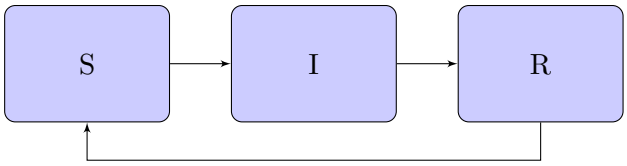

Figure 2.5: *Transfer diagram for an SIRS model.*

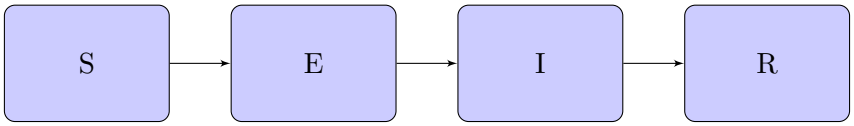

Figure 2.6: *Transfer diagram for an SEIR model.*

2.2 Disease incidence

Disease incidence is the rate at which new infections occur in a population [15]. Assume that a simple infectious disease persists in a population. Let $N(t)$ denote the total number of individuals in the host population at time t. Let $S(t)$ and $I(t)$ denote the number of hosts in the susceptible and infected compartment, respectively, at time t. Let η be the *contact* rate, that is, the average number of contacts with the infectious individuals required by the susceptible individuals for disease transmission per unit time [1]. Then, the incidence is given by

$$\frac{\eta SI}{N}. \tag{2.2.1}$$

Depending on the disease epidemiology, the disease incidence may be taken to be of many forms, two most commonly used in mathematical modeling include mass action incidence (also known as bilinear incidence) and standard incidence (or proportionate incidence).

Definition 2.2.1. Mass Action Incidence: When it is assumed that the total population size, N, is a constant, the contact rate, η, will be directly proportional to N.

$$\eta \propto N.$$

Or

$$\eta = \beta N,$$

where β is known as the *transmission coefficient*. Hence, in this case, using equation (2.2.1), the disease incidence is given by

$$\beta S(t)I(t). \tag{2.2.2}$$

Definition 2.2.2. Standard Incidence: In the case of standard incidence, $N(t)$ is assumed to vary with time, and η is taken to be independent of the population size, N [15]. Hence, the incidence is simply

$$\frac{\eta S(t)I(t)}{N(t)}. \tag{2.2.3}$$

2.3 Stability in first order systems

In this section, nonlinear, first order, ordinary differential equations (ODEs) are discussed. Stability theory and techniques useful in the analysis of systems of such differential equations are introduced. In particular, methods for determining local and global stability of equilibrium solutions are studied. The primary aim of this portion of the thesis is determining the stability of solutions using Liapunov functions.

2.3.1 Non linear systems and equilibrium solutions

An autonomous system of differential equations is a system of ODEs which does not explicitly depend on the independent variable. Mathematical models on infectious diseases usually consider autonomous systems, hence, these systems and the conditions for the existence and uniqueness of their solutions are given in detail in this subsection. Moreover, equilibrium solutions of autonomous systems are defined, and their local stability is also discussed below.

Consider an n-dimensional autonomous system of nonlinear ODEs with initial conditions:

$$\begin{aligned}
\frac{dx_1}{dt} &= g_1(x_1, x_2, ..., x_n), \qquad & x_1(t_0) = x_{10},\\
\frac{dx_2}{dt} &= g_2(x_1, x_2, ..., x_n), \qquad & x_2(t_0) = x_{20},\\
&\vdots & \\
\frac{dx_n}{dt} &= g_n(x_1, x_2, ..., x_n), \qquad & x_n(t_0) = x_{n0}.
\end{aligned}$$

The above system can be written as

$$\frac{d\mathbf{X}}{dt} = \mathbf{G}(\mathbf{X}), \qquad \mathbf{X}(t_0) = \mathbf{X}_0, \tag{2.3.1}$$

where $\mathbf{X} = (x_1, x_2, ..., x_n)^T$, $\mathbf{G}(\mathbf{X}) = (g_1(x_1, x_2, ..., x_n), g_2(x_1, x_2, ..., x_n), ..., g_n(x_1, x_2, ..., x_n))^T$, where $\mathbf{G}$ does not explicitly depend on t. It is assumed that the interval of existence of solutions is $[t_0, \infty)$, and that a unique solution exists to the initial value problem as stated in the following theorem:

Theorem 2.3.1. *Suppose that for $j = 1, 2, ..., n$, the functions $\boldsymbol{G}$ and $\dfrac{\partial \boldsymbol{G}}{\partial x_j}$ are continuous functions of $(x_1, x_2, ..., x_n)$ on $\mathbb{R}^n$. Then, for any initial value $\boldsymbol{X}_0 \in \mathbb{R}^n$, the system (2.3.1), with initial condition $\boldsymbol{X}(t_0) = \boldsymbol{X}_0$, has a unique solution.*

Definition 2.3.2. Equilibrium solution: An equilibrium solution (also known as fixed point or critical point) of the differential system (2.3.1) is a constant solution $\bar{\mathbf{X}}$ such that $\mathbf{G}(\bar{\mathbf{X}}) = 0$ [16].

An equilibrium solution $\bar{\mathbf{X}}$ of the differential system (2.3.1) is locally stable if all solutions of the system (2.3.1) which start close to $\bar{\mathbf{X}}$ (meaning that the initial conditions are in a neighborhood of $\bar{\mathbf{X}}$) always remain close to $\bar{\mathbf{X}}$ for all time, or more formally:

An equilibrium solution $\bar{\mathbf{X}}$ of (2.3.1) is said to be locally stable at $t = t_0$, if for each $\varepsilon > 0$, there exists a $\delta > 0$ with the property that

$$|\mathbf{X}(t) - \bar{\mathbf{X}}| < \varepsilon,$$

whenever

$$|\mathbf{X}_0 - \bar{\mathbf{X}}| < \delta,$$

for all $t \geq t_0$.

If the equilibrium solution is not locally stable, it is said to be unstable [16].

An equilibrium solution $\bar{\mathbf{X}}$ of the differential system (2.3.1) is locally asymptotically stable if $\bar{\mathbf{X}}$ is locally stable and all solutions starting close to $\bar{\mathbf{X}}$ converge to it when t$\to \infty$, or more formally:

An equilibrium solution $\bar{\mathbf{X}}$ is said to be locally asymptotically stable if it is locally stable, and if it is locally attractive, i.e., there exists $\xi > 0$ such that

$$|\mathbf{X}_0 - \bar{\mathbf{X}}| < \xi,$$

implies

$$\lim_{t\to\infty} |\mathbf{X}(t) - \bar{\mathbf{X}}| = 0.$$

An equilibrium solution $\bar{\mathbf{X}}$ is said to be globally asymptotically stable if it is locally asymptotically stable for all initial conditions X_0, i.e, if every solution of the differential system (2.3.1) satisfies

$$\lim_{t\to\infty} \mathbf{X}(t) = \bar{\mathbf{X}},$$

for any choice of initial conditions.

2.3.2 Routh-Hurwitz criterion

Stability of the solutions of a linear system of ODEs depends upon the roots of the characteristic equation of the Jacobian matrix, which is defined as follows:

Definition 2.3.3. Jacobian Matrix: Let $f = g(y)$ be a set of n equations in n variables $y_1, ..., y_n$, i.e.,

$$\begin{aligned} f_1 &= g_1(y_1, ..., y_n), \\ &\vdots \\ f_n &= g_n(y_1, ..., y_n), \end{aligned}$$

then, the Jacobian matrix, J, is defined as

$$J(y_1, ..., y_n) = \begin{pmatrix} \frac{\partial f_1}{\partial y_1} & \cdots & \frac{\partial f_1}{\partial y_n} \\ \vdots & \ddots & \vdots \\ \frac{\partial f_n}{\partial y_1} & \cdots & \frac{\partial f_n}{\partial y_n} \end{pmatrix}.$$

For a linear system to be stable, all roots (eigenvalues) of the characteristic polynomial of the Jacobian matrix must have negative real parts. The Routh-Hurwitz criterion is not a method to compute all the roots, it is merely a test that gives necessary and sufficient conditions for the eigenvalues of the characteristic equation to lie in the negative half of the complex plane [16].

Theorem 2.3.4. ***Routh-Hurwitz Criteria****: Consider the characteristic polynomial,*

$$p(\lambda) = \lambda^n + c_1\lambda^{n-1} + ... + c_{n-1}\lambda + c_n,$$

where, the coefficients c_i, $i = 1, 2, ...n$ are real constants. All roots of the polynomial $p(\lambda)$ have negative real parts if and only if

$$\Phi_1, \Phi_2, ..., \Phi_n > 0,$$

where

$$\Phi_k = \begin{vmatrix} c_1 & 1 & 0 & 0 & 0 & 0 & \dots & 0 \\ c_3 & c_2 & c_1 & 1 & 0 & 0 & \dots & 0 \\ c_5 & c_4 & c_3 & c_2 & c_1 & 1 & \dots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \dots & \vdots \\ c_{2k-1} & c_{2k-2} & c_{2k-3} & c_{2k-4} & c_{2k-5} & c_{2k-6} & \dots & c_k \end{vmatrix},$$

and $c_j = 0$ *if* $j > k$. Φ_k *are known as Hurwitz determinants.*

Lienard-Chipart criterion: This criterion is a modified form of the Routh-Hurwitz criterion. It is a method used to reduce the calculation of Hurwitz determinants. By using this method, it becomes necessary and sufficient to calculate only even or only odd Hurwitz determinants.

Consider a polynomial

$$p(\lambda) = \lambda^n + c_1\lambda^{n-1} + ... + c_{n-1}\lambda + c_n.$$

Let $\Phi_1, \Phi_2, ..., \Phi_n$ be its Hurwitz determinants. Then, for the given polynomial to have negative real roots, any one of the following conditions is necessary and sufficient:

1. $c_n > 0$, $c_{n-2} > 0$,...,$\Phi_1 > 0$, $\Phi_3 > 0$,...,
2. $c_n > 0$, $c_{n-2} > 0$,...,$\Phi_2 > 0$, $\Phi_4 > 0$,...,
3. $c_n > 0$, $c_{n-1} > 0$, $c_{n-3} > 0$,...,$\Phi_1 > 0$, $\Phi_3 > 0$,...,
4. $c_n > 0$, $c_{n-1} > 0$, $c_{n-3} > 0$,...,$\Phi_2 > 0$, $\Phi_4 > 0$,....

2.3.3 Determining local stability in differential equations

(1) Local asymptotic stability in first order ODEs

Let

$$\frac{dx}{dt} = g(x) \tag{2.3.2}$$

be an an autonomous differential equation with an equilibrium solution $\bar{x}$. Assume that g has two continuous derivatives in an interval containing $\bar{x}$. The function g can be expanded about $\bar{x}$ using Taylor's formula. Let $u(t) = x(t) - \bar{x}$, then

$$\frac{du}{dt} = g(\bar{x}) + g'(\bar{x})u + \frac{g''(\varsigma)u^2}{2},$$

where ς is some number between x and $\bar{x}$. The linearization of (2.3.2) is defined as

$$\frac{du}{dt} = g'(\bar{x})u, \tag{2.3.3}$$

since $g'(\bar{x}) = 0$, and second order term u^2 can be neglected.

The following theorem is then established:

Theorem 2.3.5. *Let g be continuous in an open interval containing $\bar{x}$, where $\bar{x}$ is an equilibrium solution of (2.3.2), then $\bar{x}$ is locally asymptotically stable if $g\prime(\bar{x}) < 0$, and unstable if $g\prime(\bar{x}) > 0$.*

(2) Local asymptotic stability in first order systems of ODEs

Consider the autonomous differential system

$$\frac{d\mathbf{X}}{dt} = \mathbf{G}(\mathbf{X}), \tag{2.3.4}$$

and its component form

$$\begin{aligned} \frac{dx_1}{dt} &= g_1(x_1, x_2, ..., x_n), \\ &\vdots \\ \frac{dx_n}{dt} &= g_n(x_1, x_2, ..., x_n), \end{aligned} \tag{2.3.5}$$

with an equilibrium solution $(\bar{x}_1, ..., \bar{x}_n)$. Let $\mathbf{G}(\mathbf{X})$ have continuous first order partial derivatives. Then, the system (2.3.5) can be expanded using Taylor's formula:

$$\frac{dx_1}{dt} = g_1(\bar{x}_1, ..., \bar{x}_n) + \frac{\partial g_1}{\partial x_1}(\bar{x}_1, ..., \bar{x}_n)(x_1 - \bar{x}_1) + ... + \frac{\partial g_1}{\partial x_n}(\bar{x}_1, ..., \bar{x}_n)(x_n - \bar{x}_n) + \mathbf{O}_H(\mathbf{X}),$$

$$\vdots$$

$$\frac{dx_n}{dt} = g_n(\bar{x}_1, ..., \bar{x}_n) + \frac{\partial g_n}{\partial x_1}(\bar{x}_1, ..., \bar{x}_n)(x_1 - \bar{x}_1) + ... + \frac{\partial g_n}{\partial x_n}(\bar{x}_1, ..., \bar{x}_n)(x_n - \bar{x}_n) + \mathbf{O}_H(\mathbf{X}),$$

where $\mathbf{O}_H(\mathbf{X})$ symbolizes higher order terms.

Using the fact that $g_1(\bar{x}_1, ..., \bar{x}_n)$,..., $g_n(\bar{x}_1, ..., \bar{x}_n) = 0$, the linearized system about $(\bar{x}_1, ..., \bar{x}_n)$ is defined as

$$\frac{dU}{dt} = JU, \tag{2.3.6}$$

where

$$U = \begin{pmatrix} x_1 - \bar{x}_1 \\ \vdots \\ x_n - \bar{x}_n \end{pmatrix},$$

and

$$J = \begin{pmatrix} \dfrac{\partial g_1(x_1,...,x_n)}{\partial x_1} & \cdots & \dfrac{\partial g_1(x_1,...,x_n)}{\partial x_n} \\ \vdots & \ddots & \vdots \\ \dfrac{\partial g_n(x_1,...,x_n)}{\partial x_1} & \cdots & \dfrac{\partial g_n(x_1,...,x_n)}{\partial x_n} \end{pmatrix} \Bigg|_{x_1=\bar{x}_1,...,x_n=\bar{x}_n}.$$

The following theorem is then established:

Theorem 2.3.6. *Assume that the first order partial derivatives of $g_1, ..., g_n$ are continuous in some open interval containing the equilibrium $(\bar{x}_1, ..., \bar{x}_n)$ of the system (2.3.5). Then, the equilibrium is locally asymptotically stable if all the eigenvalues of the Jacobian matrix have negative real parts.*

2.3.4 Liapunov functions

The most important and useful tool in the theory of stability is known as the *direct method of Liapunov*. A function known as a Liapunov function is formed in order to establish the asymptotic stability of an equilibrium solution in some given region.

Definition 2.3.7. A basin of attraction is a subset W in $\mathbb{R}^n$ containing the equilibrium solution with the property that all solutions which begin in W, approach the equilibrium [16].

By using this method by Liapunov, estimates for the basin of attraction of the equilibrium can be obtained. In the subsequent discussion, it is assumed that the equilibrium of interest is the origin.

Definition 2.3.8. Positive definite: Let U be an open subset of $\mathbb{R}^n$, containing the origin. A real valued C^1 function, $L : U \to \mathbb{R}$, is called a positive definite function on the set U if these conditions are satisfied:

1. $L(\mathbf{Y}) > 0$ for all $\mathbf{Y} \in U$, with $\mathbf{Y} \neq 0$.
2. $L(\mathbf{0})$=0.

L is said to be negative definite if -L is positive definite [16].

Definition 2.3.9. Liapunov function: A positive definite function L, in an open neighborhood, U, of the origin is said to be a Liapunov function for the differential system $\frac{d\mathbf{Y}}{dt} = \mathbf{G}(\mathbf{Y})$, if $\frac{dL}{dt} \leq 0$ for all $\mathbf{Y} \in U - \{\mathbf{0}\}$ [16].

Theorem 2.3.10. ***Liapunov's stability theorem****: Let* $\frac{d\,\boldsymbol{Y}}{dt} = \boldsymbol{G}(\boldsymbol{Y})$ *be an autonomous system of differential equations, where* $\boldsymbol{Y} \in \mathbb{R}^n$*. Let* $\boldsymbol{Y}^* = \boldsymbol{0}$ *be an equilibrium solution of the system, and let* $U \in \mathbb{R}^n$ *be a neighborhood of* $\boldsymbol{Y}^* = \boldsymbol{0}$*. Also, suppose that* $L : U \to \mathbb{R}$ *is a continuously differentiable positive definite function in* U*, then Liapunov's stability theorem states that:*

1. *If* $\frac{dL(\boldsymbol{Y})}{dt} \leq 0$*, for* $\boldsymbol{Y} \in U - \{\boldsymbol{0}\}$*, then* $\boldsymbol{0}$ *is stable,*

2. *If* $\frac{dL(\boldsymbol{Y})}{dt} < 0$*, for* $\boldsymbol{Y} \in U - \{\boldsymbol{0}\}$*, then* $\boldsymbol{0}$ *is asymptotically stable,*

3. *If* $\frac{dL(\boldsymbol{Y})}{dt} > 0$*, for* $\boldsymbol{Y} \in U - \{\boldsymbol{0}\}$*, then* $\boldsymbol{0}$ *is unstable.*

Definition 2.3.11. Positively invariant: A set $U \in \mathbb{R}^n$ is said to be invariant with respect to the system $\frac{d\mathbf{Y}}{dt} = \mathbf{G}(\mathbf{Y})$, if for any initial value $\mathbf{Y_0} \in U$ implies that the solution $\mathbf{Y}(\mathbf{Y_0}, t) \in U$ for all time. The set is said to be positively invariant if every solution that begins in U, stays in U, for all time $t > 0$.

Theorem 2.3.12. ***LaSalle's Invariance Principle****: Let* Φ *be a bounded, positively invariant set with respect to the system* $\frac{d\,\boldsymbol{Y}}{dt} = \boldsymbol{G}(\boldsymbol{Y})$*. Let* $L : D \in \mathbb{R}^n \to \mathbb{R}$ *be a continuously differentiable function such that* $\frac{dL(\boldsymbol{Y})}{dt} \leq 0$ *on* Φ*. Let* P *be the set of all points in* Φ *so that* $\frac{dL(\boldsymbol{Y})}{dt} = 0$ *, and* N *be the largest invariant set in* P*. Then, LaSalle's Invariance Principle states that all solutions starting in* Φ *approach* N *as* $t \to \infty$ *[17].*

2.4 Basic reproduction number, R_0

The basic reproduction number is defined as the average number of secondary infections produced in a completely susceptible population when an infectious individual is introduced into it [1]. In other words, R_0 is the threshold quantity which determines the average number of new infectious individuals generated by a single infection carrying individual in the total time span of the disease. The primary concern about any infection is wether it spreads in the population, or it may be controlled. A disease free equilibrium solution is that equilibrium solution of a mathematical model, at which the population

is free of the disease. In classical epidemiological models, if $R_0 < 1$, it implies that the one infectious person transmits infection to less than one person, hence the disease will eventually die out. On the other hand, $R_0 > 1$ means that one infectious person transmits infection to more than one person, hence the disease spreads in the population. The next generation method used for finding the basic reproduction number is given below [2].

Consider any simple epidemiological model, with m compartments. The number of people in each compartment is $z = (z_1, ..., z_m)$ with $z_j > 0$ for all $j = 1, ..., m$. Assume that the first r compartments consist of infected persons. In order to find the basic reproduction number, it is necessary to separate the infected compartments from the uninfected ones. Let Υ_a be the collection of all those compartments which do not have disease, i.e.,

$$\Upsilon_a = \{z \geq 0 | z_j = 0, j = 1, ..., r\}.$$

Now, let $\mathcal{F}_j(z)$ represent the rate at which new infections occurs in the compartment j.

Let $\mathcal{V}_{j+}(z)$ represent the rate at which persons move into compartment j.

And $\mathcal{V}_{j-}(z)$ represents the rate at which persons move out of compartment j.

Let $\mathcal{V}_j = \mathcal{V}_{j-} - \mathcal{V}_{j+}$. Suppose that the epidemiological model consists of the following system of first order ODEs.

$$\frac{dz_j}{dt} = g_j(z) = \mathcal{F}_j(z) - \mathcal{V}_j(z), \tag{2.4.1}$$

and the functions $\mathcal{F}_j$, $\mathcal{V}_{j+}$, and $\mathcal{V}_{j-}$ satisfy the following conditions:

1. For $j = 1, ..., m$, if $z \geq 0$, then $\mathcal{F}_j, \mathcal{V}_{j+}, \mathcal{V}_{j-} \geq 0$. This means that all functions are non negative because they symbolize transfer of persons between compartments.

2. $\mathcal{V}_{j-} = 0$, if $z_j = 0$, which implies that if there are no individuals in a compartment, then clearly no individuals can transfer out of it.

3. $\mathcal{F}_j = 0$ when $j > r$. This assumption implies that for those compartments which do not have infection, incidence of infection will not take place.

4. For $j = 1, ..., r$, if $z \in \Upsilon_a$, then $\mathcal{F}_j = 0$, and $\mathcal{V}_{j+} = 0$, which means that if the population is initially disease free, then it remains disease free.

5. If $\mathcal{F}(z)$ is assumed to be 0, then all eigenvalues of the Jacobian matrix, $Jg(z_0)$, evaluated at disease free equilibrium, z_0, have negative real part. This implies that in the absence of new infections, the disease free equilibrium is locally stable.

If the above conditions are satisfied, then the derivatives $J\mathcal{F}(z_0)$ and $J\mathcal{V}(z_0)$ are partitioned as

$$J\mathcal{F}(z_0) = \begin{pmatrix} M & 0 \\ 0 & 0 \end{pmatrix},$$

and

$$J\mathcal{V}(z_0) = \begin{pmatrix} N & 0 \\ J_3 & J_4 \end{pmatrix},$$

where M and N represent

$$M = \frac{\partial \mathcal{F}_j}{\partial z_j}(z_0),$$

and

$$N = \frac{\partial \mathcal{V}_j}{\partial z_j}(z_0).$$

The quantity MN^{-1} is known as the next generation matrix, and the basic reproduction number, R_0, is defined as

$$\mathcal{R}_0 = \tau(MN^{-1}), \tag{2.4.2}$$

where $\tau(H)$ stands for the spectral radius of a matrix H.

A theorem regarding the local stability of disease free equilibrium, given in [2], is reproduced below:

Theorem 2.4.1. *Consider the model given in (2.4.1), with $g(z)$ satisfying the above given conditions from 1 to 5. A disease free equilibrium, z_0, of the model is locally asymptotically stable if $R_0 < 1$, and unstable if $R_0 > 1$.*

Chapter 3

Mathematical Analysis of the HCV Model

The effects of an infectious disease on population dynamics have always been an area of great interest. Regardless of the preventive measures taken, HCV infection has made quite an impact on the general health and decline of the world population. ODEs are an important tool in the study of population dynamics. This chapter focuses on the formulation of a mathematical model based on HCV infection. The model consists of six first order ODEs, which take into account the spread of HCV infection by acutely infected as well as chronically infected individuals. The main aim of this chapter is to asses the use of imperfect immunization on the control and spread of this lethal infection. A vaccine for HCV infection has not been created yet, although many efforts to do so are under way. This model shows that an imperfect vaccine reduces the number of individuals who are exposed to HCV, and a perfect vaccine completely removes them.

Some mathematical models on HCV infection have been formulated recently, but much work has not been done yet, since HCV infection is a new disease which has been discovered only a few years ago. In contrast, more research has been carried out on HBV infection. The modes of transmission of both HCV and HBV are same, i.e., through blood, thus mathematical models on both infections are somewhat inter related. These models help in understanding the viral infections, so that they may be combated effectively. Some mathematical models, that were formed, considered infected cells, uninfected cells and viral cells in the human host. The basic aim of these models was to study the effects of liver transplant in patients with HBV and HCV infections. But, in major cases, HBV or HCV infection is not completely eliminated even after the transplant, and returns to infect the host in a few years. Thus, these models were extended to include more infected compartments [18]. However, the newer models also had a few drawbacks; they did not give an exact description of viral dynamics after liver transplantation. These models were

again modified to include the desired results, and backward bifurcation analysis was also carried out [19].

Several epidemiological models have focused on the effects of preventive measures as well as control of HBV infection [20]. These models incorporate various infectious compartments, such as acute and chronically infected individuals. These have been extended to include compartments containing individuals who have been vaccinated. This has helped in creating cost effective disease prevention techniques. Little work has been carried out on HCV infection, since it is a relatively new disease and much data is not available on account of the high variability of the HCV. The available models focus only on the infection carrying compartments, since a vaccine for HCV infection is still in testing phase. The mathematical model developed here, includes a compartment of individuals undergoing treatment, and another for vaccinated individuals. As soon as this, presently under trials, vaccine is developed, the model, given below, will provide measures to estimate the time required for total elimination of HCV infection from the population.

The following section formally introduces the HCV transmission model.

3.1 Model formulation

Let $N(t)$ be the total population at time t. $N(t)$ is partitioned into mutually exclusive compartments of susceptible persons, $S(t)$; persons who have been exposed to HCV but are not yet infectious, $E(t)$; persons who are acutely infected with HCV, $I(t)$; chronically infected persons, $C_h(t)$; persons undergoing treatment, $T(t)$; and vaccinated persons, $V(t)$, so that

$$N(t) = S(t) + E(t) + I(t) + T(t) + C_h(t) + V(t). \tag{3.1.1}$$

It assumed that the mode of transmission of HCV infection is horizontal, that is, HCV spreads through direct contact between individuals. It is further assumed that mixing of individual hosts is homogeneous (every person in the population $N(t)$ has an equal chance of getting HCV). In other words, the number of contacts between individuals of different compartments depends only on the number of individuals in each compartment.

To define the dynamics of HCV infection with waning immunity, the following system of ODEs has been formulated:

$$
\begin{aligned}
\frac{dS}{dt} &= (1-b)\Lambda + \rho T + \alpha V - (\beta_1 I + \beta_2 C_h + \beta_3 T)S + \sigma C_h - \mu S, \\
\frac{dE}{dt} &= (\beta_1 I + \beta_2 C_h + \beta_3 T)S + (1-\psi)(\beta_1 I + \beta_2 C_h + \beta_3 T)V - (\epsilon + \mu)E, \\
\frac{dI}{dt} &= \epsilon E - (\kappa + \mu)I, \\
\frac{dT}{dt} &= \pi_1 \kappa I + \pi_2 C_h - (\rho + \mu)T, \\
\frac{dC_h}{dt} &= (1-\pi_1)\kappa I - (\pi_2 + \sigma + \mu)C_h, \\
\frac{dV}{dt} &= b\Lambda - (\alpha + \mu)V - (1-\psi)(\beta_1 I + \beta_2 C_h + \beta_3 T)V.
\end{aligned}
\tag{3.1.2}
$$

The recruitment rate of susceptible humans is Λ. A proportion, b, of these susceptible individuals is vaccinated. The natural death rate is denoted by μ. The rate of progression from acute infected class to both treated and chronic infected class is given by κ. The acutely infected proportion of individuals who enter the treated class is π_1. The remaining infected proportion, $(1-\pi_1)$, progresses to chronic infectious stage. The rate of progression for treatment from chronic hepatitis is given by π_2. The term ϵ is the rate of progression from exposed class to acute infected class. The recovery rates due to treatment and naturally from the chronic group are ρ and σ, respectively.

The transmission coefficients of HCV infection by individuals with acute hepatitis C, $I(t)$, chronic hepatitis C, $C_h(t)$ and individuals undergoing treatment but not yet cured, $T(t)$ are β_1, β_2, and β_3, respectively. Following effective contact with $I(t)$, $C_h(t)$, and $T(t)$, susceptible individuals can acquire HCV at a rate $(\beta_1 I + \beta_2 C_h + \beta_3 T)$. Also, it is supposed that the vaccine is not perfect. Let ψ $(0 < \psi \leq 1)$ represent the vaccine efficacy. $\psi = 1$ represents a perfect vaccine, and $\psi \in (0, 1)$ corresponds to an imperfect vaccine which will wane with time. $(1 - \psi)$ corresponds to the decrease in disease transmission in vaccinated individuals, in contrast to susceptible individuals who are not vaccinated. Hence, vaccinated individuals acquire HCV at a reduced rate $(1 - \psi)(\beta_1 I + \beta_2 C_h + \beta_3 T)$. α is the rate at which the vaccine wanes. The variables and parameters are summarized in Tables 3.1 and 3.2, respectively.

Table 3.1: *Description of variables of the mathematical model (3.1.2).*

Variable	Description
$S(t)$	Number of susceptible persons
$E(t)$	Number of exposed persons
$I(t)$	Number of acutely infected persons
$T(t)$	Number of persons undergoing treatment
$C_h(t)$	Number of chronically infected persons
$V(t)$	Number of vaccinated persons

Table 3.2: *Description of parameters of the mathematical model (3.1.2.)*

Parameter	Description
Λ	recruitment rate
μ	natural death rate
α	waning rate of vaccine
ψ	vaccine efficacy $(0 < \psi \leq 1)$
β_i	transmission coefficients (i=1, 2, 3)
b	proportion of vaccinated individuals
κ	rate of progression from acute state
	to treated and chronic state
ϵ	rate of transfer from exposed class
	to acute infected class
π_1	proportion of individuals who enter the treated
	class from acutely infected class
π_2	rate of progression for treatment
	from chronic hepatitis
ρ	rate of recovery due to treatment
σ	rate of recovery from the chronic class

3.2 Analysis of the model

From equation (3.1.1), it can be seen that

$$\begin{aligned}\frac{dN}{dt} &= \frac{dS}{dt}+\frac{dE}{dt}+\frac{dI}{dt}+\frac{dT}{dt}+\frac{dC_h}{dt}+\frac{dV}{dt}\\ &= \Lambda-\mu N.\end{aligned}$$

Solving the first order linear differential equation

$$\frac{dN}{dt}=\Lambda-\mu N,$$

and letting $t\to\infty$, gives:

$$N=\frac{\Lambda}{\mu}. \tag{3.2.1}$$

Hence, in the proposed model (3.1.2), the total population is $S+E+I+T+C_h+V=\frac{\Lambda}{\mu}$ for all $t\geq 0$, provided that $S(0)+E(0)+I(0)+T(0)+C_h(0)+V(0)=\frac{\Lambda}{\mu}$.

Lemma 3.2.1. *The set*

$$\Omega=\left\{(S,E,I,T,C_h,V)\in R^6 : S+E+I+T+C_h+V=\frac{\Lambda}{\mu}\right\}, \tag{3.2.2}$$

is positively invariant for the mathematical model (3.1.2).

3.2.1 Disease free equilibrium (DFE) and its local stability

For the mathematical model (3.1.2), the DFE, P_0, is given by

$$(S_0,E_0,I_0,T_0,C_{h0},V_0)=\left(\frac{(1-b)\Lambda}{\mu}+\frac{\alpha b\Lambda}{\mu(\alpha+\mu)},0,0,0,0,\frac{b\Lambda}{\alpha+\mu}\right). \tag{3.2.3}$$

The basic reproduction number, R_0, is defined as the average number of secondary infections produced by an infected individual in a completely susceptible population. R_0 completely describes the dynamics of HCV infection in the proposed population. It is determined by using the next generation operator method [2] on system (3.1.2).

Using the same notation as in [2], the matrices $\mathcal{F}$ and $\mathcal{V}$ are given by

$$\mathcal{F}=\begin{pmatrix}0\\(\beta_1 I+\beta_2 C_h+\beta_3 T)S+(1-\psi)(\beta_1 I+\beta_2 C_h+\beta_3 T)V\\0\\0\\0\\0\end{pmatrix},$$

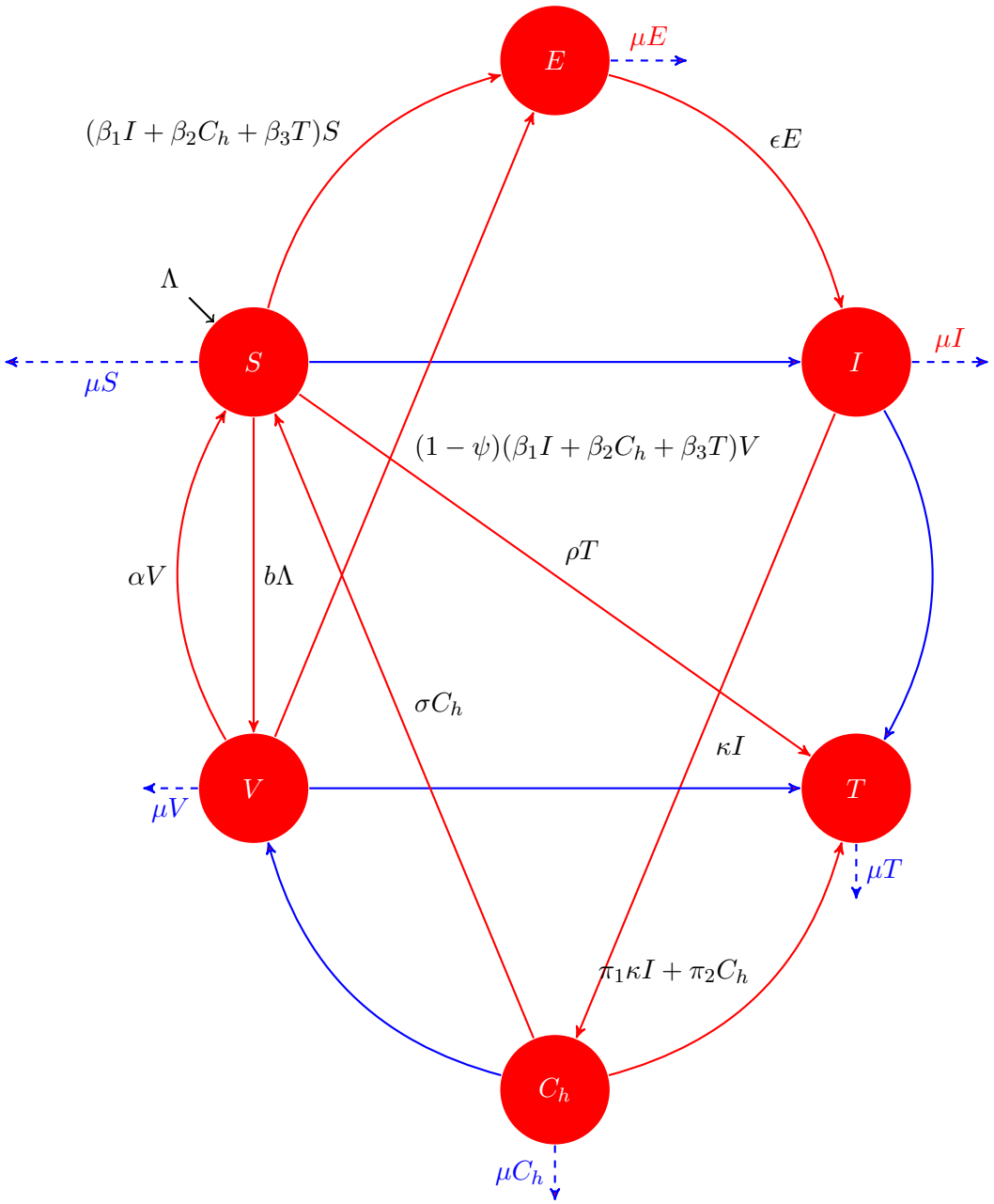

Figure 3.1: *Flow diagram for the HCV transmission model (3.1.2).*

and

$$\mathcal{V} = \begin{pmatrix} (b-1)\Lambda - \rho T - \alpha V + (\beta_1 I + \beta_2 C_h + \beta_3 T)S + \mu S \\ K_1 E \\ -\epsilon E + K_2 I \\ -\pi_1 \kappa I - \pi_2 C_h + K_3 T \\ -(1-\pi_1)\kappa I + K_4 C_h \\ -b\Lambda + K_5 V + (1-\psi)(\beta_1 I + \beta_2 C_h + \beta_3 T)V \end{pmatrix},$$

where

$$K_1 = \epsilon + \mu, \qquad K_2 = \kappa + \mu, \qquad K_3 = \rho + \mu, \qquad K_4 = \pi_2 + \sigma + \mu,$$
$$K_5 = \alpha + \mu.$$

The infected compartments are E, I, T and C_h. Hence, the matrix F, V, and V^{-1} evaluated at P_0 are given by

$$\mathrm{F} = \begin{pmatrix} 0 & \beta_1 S_0 + (1-\psi)\beta_1 V_0 & \beta_3 S_0 + (1-\psi)\beta_3 V_0 & \beta_2 S_0 + (1-\psi)\beta_2 V_0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix},$$

$$\mathrm{V} = \begin{pmatrix} K_1 & 0 & 0 & 0 \\ -\epsilon & K_2 & 0 & 0 \\ 0 & -\pi_1\kappa & K_3 & -\pi_2 \\ 0 & (\pi_1 - 1)\kappa & 0 & K_4 \end{pmatrix},$$

$$\mathrm{V}^{-1} = \begin{pmatrix} \frac{1}{K_1} & 0 & 0 & 0 \\ \frac{\epsilon}{K_1 K_2} & \frac{1}{K_2} & 0 & 0 \\ \frac{\epsilon\pi_1\kappa}{K_1K_2K_3} + \frac{\epsilon\pi_2(1-\pi_1)\kappa}{K_1K_2K_3K_4} & \frac{(1-\pi_1)\kappa\pi_2}{K_2K_3K_4} + \frac{\pi_1\kappa}{K_2K_3} & \frac{1}{K_3} & \frac{-\pi_2}{K_3K_4} \\ \frac{\epsilon(1-\pi_1)\kappa}{K_1K_2K_4} & \frac{(1-\pi_1)\kappa}{K_2K_4} & 0 & \frac{1}{K_4} \end{pmatrix}.$$

Using the definition in [2], R_0 is given by

$$R_0 = \tau\big(\mathrm{FV}^{-1}\big),$$

where $\tau\big(\mathrm{FV}^{-1}\big)$ is the spectral radius of the matrix FV^{-1}. Hence, R_0 is given as

$$R_0 = \frac{\epsilon}{K_1 K_2}\left(\frac{(1-b)\Lambda}{\mu} + \frac{\alpha b \Lambda}{\mu K_5} + (1-\psi)\frac{b\Lambda}{K_5}\right)\left[\beta_1 + \beta_2\frac{\kappa(1-\pi_1)}{K_4} + \beta_3\frac{(\pi_1\kappa K_4 + \pi_2\kappa(1-\pi_1))}{K_3 K_4}\right]. \tag{3.2.4}$$

The following result is now established:

Theorem 3.2.2. *The DFE, $P_0(S_0, 0, 0, 0, 0, V_0)$, is locally asymptotically stable if $R_0 < 1$, and unstable if $R_0 > 1$.*

Proof: To prove the local asymptotic stability of P_0, it is shown that all roots of the characteristic polynomial of the Jacobian matrix (computed at P_0) have negative real parts.

The Jacobian matrix, J, of system (3.1.2) calculated at P_0 is

$$J = \begin{pmatrix} -\mu & 0 & -\beta_1(\frac{\Lambda}{\mu} - \frac{b\Lambda}{K_5}) & \rho - \beta_3(\frac{\Lambda}{\mu} - \frac{b\Lambda}{K_5}) & \sigma - \beta_2(\frac{\Lambda}{\mu} - \frac{b\Lambda}{K_5}) & \alpha \\ 0 & -K_1 & \beta_1 A & \beta_3 A & \beta_2 A & 0 \\ 0 & \epsilon & -K_2 & 0 & 0 & 0 \\ 0 & 0 & \pi_1\kappa & -K_3 & \pi_2 & 0 \\ 0 & 0 & (1-\pi_1)\kappa & 0 & -K_4 & 0 \\ 0 & 0 & -\frac{(1-\psi)\beta_1\Lambda b}{K_5} & -\frac{(1-\psi)\beta_3\Lambda b}{K_5} & -\frac{(1-\psi)\beta_2\Lambda b}{K_5} & -K_5 \end{pmatrix},$$

where

$$A = \frac{(1-b)\Lambda}{\mu} + \frac{\alpha b\Lambda}{\mu K_5} + (1-\psi)\frac{b\Lambda}{K_5}.$$

The characteristic equation, in λ, of J is given as

$$(-\mu - \lambda)(-K_5 - \lambda)\left(\lambda^4 + D_1\lambda^3 + D_2\lambda^2 + D_3\lambda + D_4\right) = 0 \tag{3.2.5}$$

with

$$
\begin{aligned}
D_1 &= K_1 + K_2 + K_3 + K_4, \\
D_2 &= K_3K_4 + K_1K_3 + K_2K_3 + K_1K_4 + K_2K_4 + K_1K_2 - \beta_1\epsilon A, \\
D_3 &= K_1K_3K_4 + K_2K_3K_4 + K_1K_2K_3 + K_1K_2K_4 - \beta_1\epsilon A(K_3 + K_4) - \beta_3\kappa\pi_1\epsilon A \\
&\quad -(1-\pi_1)\beta_2\kappa\epsilon A, \\
D_4 &= K_1K_2K_3K_4(1 - R_0).
\end{aligned}
$$

The characteristic equation (3.2.5) has two negative roots, $-\mu$ and $-K_5$. The remaining four roots are given by the following equation in λ:

$$\lambda^4 + D_1\lambda^3 + D_2\lambda^2 + D_3\lambda + D_4 = 0. \tag{3.2.6}$$

To compute the signs of roots of (3.2.6), Routh-Hurwitz criteria is used to show that when $R_0 < 1$, all roots of (3.2.6) have negative real parts. It is necessary and sufficient to show that $D_1, D_2, D_3, D_4 > 0$ and $D_1D_2D_3 > D_3^2 + D_1^2D_4$ (using the Lienard-Chipart test). It can be seen that D_1 is always positive, and D_4 is positive when $R_0 < 1$. D_2 and D_3 can be rewritten in terms of R_0 as follows:

$$
\begin{aligned}
D_2 &= K_1K_2(1 - R_0)K_3K_4 + K_1K_3 + K_2K_3 + K_1K_4 + K_2K_4 + \frac{\beta_2(1-\pi_1)\kappa\epsilon A}{K_4} \\
&\quad +\beta_3\frac{\pi_1\kappa K_4 + \pi_2(1-\pi_1)\kappa\epsilon A}{K_3K_4}, \\
D_3 &= K_1K_2K_3(1 - R_0) + K_1K_2K_4(1 - R_0) + K_1K_3K_4 + K_2K_3K_4 + \epsilon A\Big[\frac{\beta_2(1-\pi_1)\kappa K_3}{K_4} \\
&\quad +\frac{\beta_3\pi_2(1-\pi_1)\kappa}{K_4} + \beta_3\frac{\pi_1\kappa K_4 + \pi_2(1-\pi_1)\kappa}{K_3}\Big].
\end{aligned}
$$

Clearly, D_2 and D_3 are also positive when $R_0 < 1$, and it can be verified that

$$D_1D_2D_3 > D_3^2 + D_1^2D_4. \tag{3.2.7}$$

It is obvious that $D_1D_2D_3 > 0$, since $D_1 > 0$, $D_2 > 0$, and $D_3 > 0$ when $R_0 < 1$. Similarly, $D_3^2 + D_1^2D_4 > 0$, since $D_4 > 0$ when $R_0 < 1$ Writing D_1, D_2, D_3, and D_4 in terms of β_1, β_2, and β_3 gives:

$$D_1D_2D_3 = (K_1+K_2+K_3+K_4)\Big[3K_1K_2K_3K_4^2 + 3K_1K_2K_3^2K_4 + 3K_1K_2^2K_3K_4$$

$$+3K_1^2K_2K_3K_4 + K_1K_3^2K_4 + K_2K_3^2K_4 - \beta_1\epsilon AK_3^2K_4 - \beta_1\epsilon AK_3K_4^2 - (1-\pi_1)\beta_2$$

$$\kappa\epsilon AK_3K_4 - \beta_3\kappa\pi_1\epsilon AK_3K_4 + K_1K_3^2K_4 + K_1^2K_3^2K_2 - \beta_1\epsilon AK_1K_3^2 - \beta_1\epsilon AK_1K_3K_4$$

$$-(1-\pi_1)\beta_2\kappa\epsilon AK_1K_3 - \beta_3\kappa\pi_1\epsilon AK_1K_3 + K_1K_2^2K_3^2 + K_2^2K_3^2K_4 - \beta_1\epsilon AK_3^2K_2$$

$$-\beta_1\epsilon AK_2K_3K_4 - (1-\pi_1)\beta_2\kappa\epsilon AK_2K_3 \ - \beta_3\kappa\pi_1\epsilon AK_2K_3 + K_1^2K_4^2K_3 + K_1^2K_2^2K_4$$

$$-\beta_1\epsilon AK_1K_3K_4 - \beta_1\epsilon AK_1K_4^2(1-\pi_1)\beta_2\kappa\epsilon AK_1K_4 - \beta_3\kappa\pi_1\epsilon AK_1K_4 + K_2^2K_3K_4^2$$

$$+K_1K_2^2K_4 - \beta_1\epsilon AK_2K_3K_4 - \beta_1\epsilon AK_2K_4^2 - (1-\pi_1)\beta_2\kappa\epsilon AK_2K_4 - \beta_3\kappa\pi_1\epsilon AK_2K_4$$

$$+K_1^2K_2^2K_3 + K_1^2K_2^2K_4 - \beta_1\epsilon AK_1K_2K_3 - \beta_1\epsilon AK_1K_2K_4 - (1-\pi_1)\beta_2\kappa\epsilon AK_1K_2$$

$$-\beta_3\kappa\pi_1\epsilon AK_1K_2 - K_1K_2K_4\beta_1\epsilon A - K_2K_3\beta_1\epsilon A - K_1K_2K_3\beta_1\epsilon A - K_1K_2K_4\beta_1\epsilon A$$

$$+\beta_1^2\epsilon^2A^2(K_3+K_4) + \beta_1\beta_3\epsilon^2A^2\pi_1\kappa + (1-\pi_1)\beta_1\beta_2\epsilon^2A^2\kappa\Big] > 0. \tag{3.2.8}$$

Right hand side of (3.2.7) is

$$D_3^2 + D_1^2D_4 = \underbrace{K_1^2K_3^2K_4^2 + K_2^2K_3^2K_4^2 + K_1^2K_2^2K_3^2 + K_1^2K_2^2K_4^2 + \beta_1^2\epsilon^2A^2K_3^2 + \beta_1^2\epsilon^2A^2K_4^2}$$

$$\underbrace{+2K_1K_2K_3^2K_4^2 + 2K_1^2K_2K_3K_4^2 + 2K_1^2K_2K_3^2K_4 - 2\beta_1\epsilon AK_1K_3^2K_4 - 2\beta_1\epsilon AK_1K_3K_4^2}$$

$$\underbrace{-2\beta_3\kappa\pi_1\epsilon AK_1K_3K_4 - 2\beta_2(1-\pi_1)\kappa\epsilon AK_1K_3K_4 + 2K_1K_2^2K_3^2K_4 + 2K_1K_2^2K_3K_4^2}$$

$$\underbrace{-2\beta_1\epsilon AK_2K_3^2K_4 - 2\beta_1\epsilon AK_1K_2K_3K_4^2 - 2\beta_3\kappa\pi_1\epsilon AK_2K_3K_4 - 2\beta_2(1-\pi_1)\kappa\epsilon AK_2K_3K_4}$$

$$\underbrace{+2K_1^2K_2^2K_3K_4 - 2\beta_1\epsilon AK_1K_2K_3^2 - 2\beta_1\epsilon AK_1K_2K_3K_4 - 2\beta_3\kappa\pi_1\epsilon AK_1K_2K_3}$$

$$\underbrace{-2\beta_2(1-\pi_1)\kappa\epsilon AK_1K_2K_3 - 2\beta_1\epsilon AK_1K_2K_3K_4 - 2\beta_1\epsilon AK_1K_2K_4^2 - 2\beta_3\kappa\pi_1\epsilon AK_1K_2K_4}$$

$$\underbrace{-2\beta_2(1-\pi_1)\kappa\epsilon AK_1K_2K_4 + 2\beta_1^2\epsilon^2A^2K_3K_4 + \beta_1\beta_3\epsilon^2A^2\kappa\pi_1K_3 + \beta_1\beta_2(1-\pi_1)\kappa\epsilon^2A^2K_3}$$

$$\underbrace{+\beta_1\beta_2(1-\pi_1)\kappa\epsilon^2A^2K_4} + \beta_3^2\kappa^2\pi_1^2\epsilon^2A^2 + \beta_3^2\kappa^2(1-\pi_1^2)\epsilon^2A^2 + \beta_1\beta_3\epsilon^2A^2\kappa\pi_1K_3$$

$$+\beta_1\beta_2(1-\pi_1)\kappa\epsilon^2A^2K_3 + \beta_1\beta_2(1-\pi_1)\kappa\epsilon^2A^2K_4 + 2\beta_1\beta_3\kappa\pi_1\epsilon^2A^2K_4 + 2\beta_2\beta_3\kappa^2(1-\pi_1)$$

$$\epsilon^2A^2 + (K_1+K_2+K_3+K_4)^2\Big[K_1K_2K_3K_4 - K_3K_4\epsilon A\beta_1 - \epsilon AK_3\beta_2(1-\pi_1)\kappa$$

$$-\epsilon A\beta_3[\pi_1\kappa K_4 + \pi_2(1-\pi_1)\kappa]\Big] > 0. \tag{3.2.9}$$

The terms under brace in (3.2.9) are similar to some terms of (3.2.8), and are canceled. β_1 is then replaced with R_0 in the remaining terms of (3.2.8) and (3.2.9), and similar terms are again canceled on both sides. (3.2.9) then becomes

$$\begin{aligned} D_3^2 + D_1^2D_4 \;=\; & -\frac{\epsilon^2A^2\kappa^2K_3\pi_1\beta_2\beta_3(1-\pi_1)}{K_4} - \frac{\epsilon^2A^2\kappa^2K_3\beta_2^2(1-\pi_1)}{K_4} - \frac{\epsilon^2A^2\kappa^2\pi_2\beta_3^2(1-\pi_1)}{K_4} \\ & -\epsilon^2A^2\kappa^2\pi_1\beta_2\beta_3(1-\pi_1) - \frac{\epsilon^2A^2\kappa^2\pi_2\beta_2\beta_3(1-\pi_1)^2}{K_4} - \frac{\beta_3[\pi_1\kappa K_4 + \pi_2(1-\pi_1)\kappa]}{K_3K_4}\times \\ & \Big(2\epsilon^2A^2\beta_3\kappa\pi_1K_4 + \epsilon^2A^2K_4(1-\pi_1)\beta_2\kappa\Big) - \epsilon A\Big(K_1+K_2+K_3+K_4\Big)^2\times \\ & \Big[K_3K_4\beta_1 + K_3\beta_2(1-\pi_1)\kappa + \beta_3[\pi_1\kappa K_4 + \pi_2(1-\pi_1)\kappa]\Big] < 0. \end{aligned} \tag{3.2.10}$$

Hence, $D_1D_2D_3 - D_3^2 - D_1^2D_4 > 0$. From Routh-Hurwitz criteria, all roots of (3.2.6) have negative real parts. Therefore, all eigenvalues of the Jacobian matrix of the linearized system have negative real parts only. Hence, P_0 is locally asymptotically stable when $R_0 < 1$.

When $R_0 > 1$, Descartes's rule of signs can be used to show that positive roots of (3.2.6) exist. Clearly D_1 is always positive, and D_4 is negative when $R_0 > 1$. Hence, irrespective of the signs of D_2, and D_3, equation (3.2.6) will always have at least one positive root, whenever $R_0 > 1$. Therefore, P_0 is unstable when $R_0 > 1$.

3.2.2 Determining endemic equilibria

Endemic equilibria are those equilibria where all those compartments of the model which involve infection are non-zero. To determine the endemic equilibria of system (3.1.2), and

to make calculation easier, equations (3.1.1) and (3.2.1) will be used. Putting the value of N from equation (3.2.1) into (3.1.1) gives:

$$S(t) = \frac{\Lambda}{\mu} - E - I - T - C_h - V.$$

Hence, the following reduced system of ODEs is formulated:

$$\begin{aligned}
\frac{dE}{dt} &= (\beta_1 I + \beta_2 C_h + \beta_3 T)(\frac{\Lambda}{\mu} - E - I - T - C_h - \psi V) - K_1 E, \\
\frac{dI}{dt} &= \epsilon E - K_2 I, \\
\frac{dT}{dt} &= \pi_1 \kappa I + \pi_2 C_h - K_3 T, \\
\frac{dC_h}{dt} &= (1-\pi_1)\kappa I - K_4 C_h, \\
\frac{dV}{dt} &= b\Lambda - K_5 V - (1-\psi)(\beta_1 I + \beta_2 C_h + \beta_3 T)V,
\end{aligned} \tag{3.2.11}$$

in the invariant region $\Omega_1 = \left\{ E + I + T + C_h + V \leq \frac{\Lambda}{\mu} \right\}$.

The endemic equilibrium, $P^*(E^*, I^*, T^*, C_h^*, V^*)$, for the system (3.2.11) is determined by setting the right hand side of the system equal to zero,

where

$$\begin{aligned}
E^* &= \frac{K_2 I^*}{\epsilon}, \\
T^* &= \frac{(\pi_1 \kappa K_4 + \pi_2 (1-\pi_1)\kappa) I^*}{K_4 K_3}, \\
C_h^* &= \frac{(1-\pi_1)\kappa I^*}{K_4}, \\
V^* &= \frac{b\Lambda}{K_5 + (1-\psi)\Big[\beta_1 + \beta_2 \frac{\kappa(1-\pi_1)}{K_4} + \beta_3 \frac{(\pi_1 \kappa K_4 + \pi_2 \kappa (1-\pi_1))}{K_3 K_4}\Big] I^*},
\end{aligned} \tag{3.2.12}$$

and I^* is the positive root of the quadratic equation

$$a_1 I^{*2} + a_2 I^* + a_3 = 0, \tag{3.2.13}$$

with

$$\begin{aligned} a_1 &= (1-\psi)B^2\Big[\mu K_2K_3K_4 + \epsilon\mu\ K_3K_4 \\ &\quad + (\pi_1\kappa K_4 + \pi_2\kappa(1-\pi_1))\,\epsilon\mu + \epsilon\kappa\mu(1-\pi_1)K_3\Big], \\ a_2 &= B\Big[\mu K_2K_3K_4K_5 + \epsilon\mu K_3K_4K_5 + (1-\psi)\mu K_1K_2K_3K_4 \\ &\quad + \epsilon\mu K_5(\pi_1\kappa K_4 + \pi_2(1-\pi_1)\kappa) + (1-\pi_1)\epsilon\kappa\mu K_3K_5 \\ &\quad - (1-\psi)\Lambda\epsilon B K_3K_4\Big], \\ a_3 &= \mu K_1K_2K_4K_3K_5(1-R_0), \end{aligned} \tag{3.2.14}$$

where

$$B = \left[\beta_1 + \beta_2\frac{\kappa(1-\pi_1)}{K_4} + \beta_3\frac{(\pi_1\kappa K_4 + \pi_2\kappa(1-\pi_1))}{K_3K_4}\right].$$

The endemic equilibrium of the system(3.2.11) can be then obtained by solving for I^* from the quadratic equation (3.2.13), and substituting the positive values of I^* into the expressions in (3.2.12). S^* can be determined from

$$S^* = \frac{\Lambda}{\mu} - E^* - I^* - T^* - C_h^* - V^*.$$

From (3.2.14), it can be seen that a_1 is always positive for an imperfect vaccine ($\psi \neq 1$). Also, a_3 is positive when $R_0 < 1$, and negative when $R_0 > 1$. Hence, the following cases regarding the existence of positive endemic equilibria can be discussed.

The HCV model (3.2.11) has:

Case (i): unique endemic equilibrium if $a_3 < 0 \Leftrightarrow R_0 > 1$

Let p_1 and p_2 be the roots of the quadratic equation (3.2.13). The product of the roots is $p_1p_2 = \frac{a_3}{a_1}$. Now, a_1 is always positive, and a_3 is negative when R_0 is greater than unity, hence, $p_1p_2 < 0$. Since, the product of the roots is negative, there exists only one positive root of equation (3.2.13). Therefore, a unique positive endemic equilibrium exists for $R_0 > 1$.

Case (ii): a unique endemic equilibrium if $a_2 < 0$, *and* $a_3 = 0$ *or* $a_2^2 - 4a_1a_3 = 0$

For $a_3 = 0$, the quadratic equation (3.2.13) becomes

$$a_1{I^*}^2 + a_2I^* = 0.$$

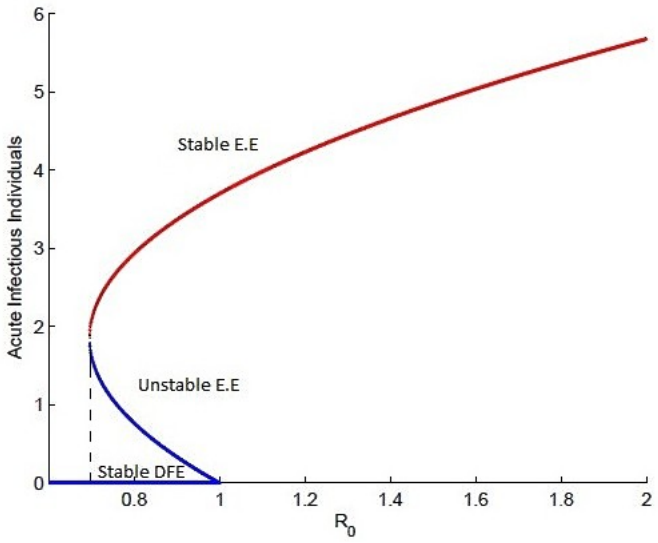

Figure 3.2: *Backward bifurcation diagram, with parameter values* $\beta_1 = 0.03$, $\beta_3 = 0.19$, $\mu = 0.00004$, $\alpha = 0.1$, $\rho = 0.152$, $\pi_1 = .001$, $\pi_2 = 0.02$, $\epsilon = 0.022$, $\kappa = 0.032$, $\Lambda = 0.0052$, $\sigma = 0.2$, $\psi = 0.95$. *Here, E.E denotes endemic equilibrium.*

Solving the above equation gives $I^* = 0$ (which corresponds to the DFE) and $I^* = -\frac{a_2}{a_1}$. Since a_2 is negative, and a_1 is always positive, $-\frac{a_2}{a_1}$ will be positive. Hence, a unique, positive endemic equilibrium exists in this case.

Case (iii): two endemic equilibria if $a_3 > 0, a_2 < 0$ *and* $a_2^2 - 4a_1a_3 > 0$

This case clearly indicates a possible chance of backward bifurcation (in which case, a locally asymptotically stable disease free equilibrium exists along with a locally asymptotically stable endemic equilibrium when $R_0 < 1$). Since, for $a_3 > 0$, $R_0 < 1$, the model will have one DFE and two endemic equilibria. To check for this, the discriminant $a_2^2 - 4a_1a_3$ is set to zero and is solved for the critical value of R_0, denoted by R_c, given by

$$R_c = 1 - \frac{a_2^2}{4a_1\mu K_1K_2K_5K_3K_4}.$$

Backward bifurcation occurs for those values of R_0 such that $R_c < R_0 < 1$. This is illustrated by simulating the model with these parameter values: $\beta_1 = 0.03$, $\beta_3 = 0.19$, $\mu = 0.00004$, $\alpha = 0.1$, $\rho = 0.152$, $\pi_1 = 0.001$, $\pi_2 = 0.02$, $\epsilon = 0.022$, $\kappa = 0.032$, $\Lambda = 0.0052$, $\sigma = 0.2$, $\psi = 0.95$. (These values are used merely for illustration purposes, and may not be realistic from epidemiological point of view.) The result is shown in Fig. 3.2. It can be seen that a locally asymptotically stable disease free equilibrium, a locally asymptotically stable endemic equilibrium, and, an unstable endemic equilibrium coexist when $R_0 < 1$.

3.3 Backward bifurcation analysis

In classical mathematical models based on disease transmission, the basic reproduction number being less than unity is a necessary as well as sufficient condition for complete disease eradication from the population under consideration. However, in some cases, backward bifurcation phenomenon may occur. From epidemiological point of view, the importance of backward bifurcation is that the classical requirement of having $R_0 < 1$ becomes necessary, but is no longer sufficient for disease elimination. Backward bifurcation refers to the effect in which a locally stable disease free equilibrium can coexist with a locally stable endemic equilibrium when $R_0 < 1$. Hence, it is crucial to study the effects of this phenomenon on disease control, since $R_0 < 1$ could mean the disease still persisting in the population. There are several mathematical models based on infectious diseases in which the effects of backward bifurcation have been discussed [21, 22].

To analyze the effects of backward bifurcation in the HCV transmission model, formulated in this thesis, the following theorem will be used. This theorem is based on the centre manifold theory and is given in [23].

Theorem 3.3.1. *Consider the following general system of ODEs with a parameter ϕ:*

$$\frac{dy}{dt} = f(y, \phi), \quad f : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R}, \quad \text{and} \quad f \in C^2(\mathbb{R} \times \mathbb{R}). \tag{3.3.1}$$

Without loss of generality, it is assumed that 0 is an equilibrium for system (3.3.1) for all values of the parameter ϕ, (that is $f(0, \phi) \equiv 0 \ \forall \ \phi$).

Assume

A1: $A = D_y f(0,0) = \left(\frac{\partial f_i}{\partial y_j}\right)$ is the linearized matrix of system (3.3.1) around the equilibrium 0 with ϕ evaluated at 0. Zero is a simple eigenvalue of A and all other eigenvalues of A have negative real parts;

A2: Matrix A has a nonnegative right eigenvector $\boldsymbol{w}$ and a left eigenvector $\boldsymbol{u}$ corresponding to the zero eigenvalue.

Let f_k be the kth component of f

and

$$a = \sum_{k,i,j=1}^{n} u_k w_i w_j \frac{\partial^2 f_k}{\partial y_i \partial y_j}(0,0),$$

$$b = \sum_{k,i=1}^{n} u_k w_i \frac{\partial^2 f_k}{\partial y_i \partial \phi}(0,0).$$

The local dynamics of system (3.3.1) around 0 are totally determined by a and b.

Case (i): $a > 0, b > 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is locally asymptotically stable and there exists a positive unstable equilibrium; when $0 < \phi \ll 1$, 0 is unstable and there exists a negative and locally asymptotically stable equilibrium;

Case (ii): $a < 0, b < 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is unstable; when $0 < \phi \ll 1$, 0 is locally asymptotically stable, and there exists a positive unstable equilibrium;

Case (iii): $a > 0, b < 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is unstable, and there exists a locally asymptotically stable negative equilibrium; when $0 < \phi \ll 1$, 0 is stable, and a positive unstable equilibrium appears;

Case (iv): $a < 0, b > 0$. When ϕ changes from negative to positive, 0 changes its stability from stable to unstable. Correspondingly, a negative unstable equilibrium becomes positive and locally asymptotically stable. Particularly, if $a > 0$ and $b > 0$, then a backward bifurcation occurs at $\phi = 0$.

To apply this method, the following change of variables is made on model (3.1.2). Let $y_1 = S, y_2 = E, y_3 = I, y_4 = T, y_5 = C_h$, and $y_6 = V$. Let $Y = (y_1, y_2, y_3, y_4, y_5, y_6)^T$. Thus, system (3.1.2) can now be written as $\frac{dY}{dt} = (f_1, f_2, f_3, f_4, f_5, f_5, f_6)^T$ given below

$$\begin{aligned}
\frac{dy_1}{dt} &= f_1 = \quad (1-b)\Lambda + \rho y_4 + \alpha y_6 - (\beta_1 y_3 + \beta_2 y_5 + \beta_3 y_4) y_1 + \sigma y_5 - \mu y_1, \\
\frac{dy_2}{dt} &= f_2 = \quad (\beta_1 y_3 + \beta_2 y_5 + \beta_3 y_4) y_1 + (1-\psi)(\beta_1 y_3 + \beta_2 y_5 + \beta_3 y_4) y_6 - K_1 y_2, \\
\frac{dy_3}{dt} &= f_3 = \quad \epsilon y_2 - K_2 y_3, \\
\frac{dy_4}{dt} &= f_4 = \quad \pi_1 k y_3 + \pi_2 y_5 - K_3 y_4, \\
\frac{dy_5}{dt} &= f_5 = \quad (1-\pi_1) k y_3 - K_4 y_5, \\
\frac{dy_6}{dt} &= f_6 = \quad b\Lambda - K_5 y_6 - (1-\psi)(\beta_1 y_3 + \beta_2 y_5 + \beta_3 y_4) y_6.
\end{aligned} \tag{3.3.2}$$

To explore the possibility of backward bifurcation, choose β_1 as the bifurcation parameter, and let R_0=1. Solving for β_1=$\bar{\beta}_1$ from R_0=1 gives

$$\beta_1 = \bar{\beta}_1 = \frac{K_1 K_2}{\epsilon A} - \frac{\beta_2(1-\pi_1)\kappa}{K_4} - \frac{\beta_3(\pi_1 k K_4 + \pi_2(1-\pi_1)\kappa)}{K_3 K_4},$$

where

$$A = \frac{(1-b)\Lambda}{\mu} + \frac{\alpha b\Lambda}{\mu K_5} + (1-\psi)\frac{b\Lambda}{K_5}.$$

The Jacobian matrix (J) of system (3.3.2) calculated at the DFE, P_0, with $\beta_1 = \bar{\beta}_1$ is given as follows:

$$J = \begin{pmatrix} -\mu & 0 & -\beta_1(\frac{\Lambda}{\mu} - \frac{b\Lambda}{K_5}) & \rho - \beta_3(\frac{\Lambda}{\mu} - \frac{b\Lambda}{K_5}) & \sigma - \beta_2(\frac{\Lambda}{\mu} - \frac{b\Lambda}{K_5}) & \alpha \\ 0 & -K_1 & \beta_1 A & \beta_3 A & \beta_2 A & 0 \\ 0 & \epsilon & -K_2 & 0 & 0 & 0 \\ 0 & 0 & \pi_1\kappa & -K_3 & \pi_2 & 0 \\ 0 & 0 & (1-\pi_1)\kappa & 0 & -K_4 & 0 \\ 0 & 0 & -\frac{(1-\psi)\beta_1\Lambda b}{K_5} & -\frac{(1-\psi)\beta_3\Lambda b}{K_5} & -\frac{(1-\psi)\beta_2\Lambda b}{K_5} & -K_5 \end{pmatrix}.$$

The characteristic equation (in λ) of the jacobian matrix, J, is given as

$$(-\mu-\lambda)(-K_5-\lambda)\big(\lambda^4 + D_1\lambda^3 + D_2\lambda^2 + D_3\lambda + D_4\big) = 0 \tag{3.3.3}$$

where

$$\begin{aligned} D_1 &= K_1 + K_2 + K_3 + K_4, \\ D_2 &= K_3K_4 + K_1K_3 + K_2K_3 + K_1K_4 + K_2K_4 + K_1K_2 - \beta_1\epsilon A, \\ D_3 &= K_1K_3K_4 + K_2K_3K_4 + K_1K_2K_3 + K_1K_2K_4 - \beta_1\epsilon A(K_3+K_4) - \beta_3\kappa\pi_1\epsilon A \\ &\quad -(1-\pi_1)\beta_2\kappa\epsilon A, \\ D_4 &= K_1K_2K_3K_4(1-R_0). \end{aligned}$$

For R_0=1, the characteristic equation (3.3.3) becomes

$$\lambda(-\mu-\lambda)(-K_5-\lambda)\big(\lambda^3 + D_1\lambda^2 + D_2\lambda + D_3\big) = 0 \tag{3.3.4}$$

Hence, the equation (3.3.4) has a zero eigenvalue and two negative eigenvalues, $-\mu$ and $-K_5$. The remaining three eigenvalues are given by the following cubic equation in λ:

$$\lambda^3 + D_1\lambda^2 + D_2\lambda + D_3 = 0. \tag{3.3.5}$$

D_1 is clearly positive, and replacing β_1 with $\bar{\beta}_1$ in D_2 and D_3 gives:

$$D_2 = K_3K_4 + K_1K_3 + K_2K_3 + K_1K_4 + K_2K_4 + \frac{\beta_2(1-\pi_1)\kappa\epsilon A}{K_4} + \beta_3\frac{\pi_1\kappa K_4 + \pi_2(1-\pi_1)\kappa\epsilon A}{K_3K_4},$$

$$D_3 = K_1K_3K_4 + K_2K_3K_4 + \epsilon A\Big[\frac{\beta_2(1-\pi_1)\kappa K_3}{K_4} + \frac{\beta_3\pi_2(1-\pi_1)\kappa}{K_4} + \beta_3\frac{\pi_1\kappa K_4 + \pi_2(1-\pi_1)\kappa}{K_3}\Big].$$

Clearly, D_2 and D_3 are also positive, and it is easy to verify that $D_1D_2 - D_3$ is positive as well. Hence, from Routh-Hurwitz criterion [16], all roots of the characteristic equation (3.3.5) have negative real parts. Therefore, the Jacobian matrix of the linearized system has a simple zero eigenvalue, with all other eigenvalues having negative real parts. Hence, the Centre Manifold Theory can be used to analyze the dynamics of system (3.3.2).

Corresponding to the zero eigenvalue, the Jacobian matrix $J\,|_{\beta_1=\bar{\beta}_1}$ can be shown to have a right eigenvector denoted by $\mathbf{w}= [w_1, w_2, w_3, w_4, w_5, w_6]^T$,

where

$$w_1 = \frac{1}{\mu}\left[\rho\left(\frac{\pi_1\kappa K_4 + \pi_2(1-\pi_1)\kappa}{K_3K_4}\right) + \sigma\frac{(1-\pi_1)\kappa}{K_4} - \frac{K_1K_2}{\epsilon A}\left(\frac{(1-b)\Lambda}{\mu} + \frac{\alpha b\Lambda}{\mu K_5} + \frac{\alpha(1-\psi)b\Lambda}{K_5^2}\right)\right]w_3,$$

$$w_2 = \frac{K_2}{\epsilon}w_3,$$

$$w_3 = w_3,$$

$$w_4 = \frac{\pi_1\kappa}{K_3}w_3 + \frac{\pi_2(1-\pi_1)\kappa}{K_3K_4}w_3,$$

$$w_5 = \frac{(1-\pi_1)\kappa}{K_4}w_3,$$

$$w_6 = \frac{-(1-\psi)b\Lambda K_1K_2}{K_5^2\epsilon A}w_3.$$

Similarly, corresponding to the zero eigenvalue, $J\,|_{\beta_1=\bar{\beta}_1}$ has a left eigenvector given by $\mathbf{u}$=$[u_1, u_2, u_3, u_4, u_5, u_6]$, where

$$u_1 = 0,$$

$$u_2 = \frac{\epsilon}{K_1}u_3,$$

$$u_3 = u_3,$$

$$u_4 = \frac{\epsilon\beta_3 A}{K_1K_3}u_3,$$

$$u_5 = \frac{\epsilon\beta_2 A}{K_1K_4}u_3 + \frac{\epsilon\beta_3\pi_2 A}{K_1K_4K_3}u_3,$$

$$u_6 = 0.$$

Calculation of a. For the system (3.3.2), the corresponding non-zero partial derivatives of f_i $(i = 1, 2, ..., 6)$ calculated at the DFE, P_0, are given by

$$\frac{\partial^2 f_1}{\partial y_1\partial y_3} = -\beta_1, \quad \frac{\partial^2 f_1}{\partial y_1\partial y_5} = -\beta_2, \quad \frac{\partial^2 f_1}{\partial y_1\partial y_4} = -\beta_3, \quad \frac{\partial^2 f_2}{\partial y_1\partial y_3} = \beta_1, \quad \frac{\partial^2 f_2}{\partial y_1\partial y_5} =$$

$$\beta_2, \quad \frac{\partial^2 f_2}{\partial y_1\partial y_4} = \beta_3, \quad \frac{\partial^2 f_2}{\partial y_3\partial y_6} = (1-\psi)\beta_1, \quad \frac{\partial^2 f_2}{\partial y_5\partial y_6} = (1-\psi)\beta_2, \quad \frac{\partial^2 f_2}{\partial y_4\partial y_6} = (1 -$$

$$\psi)\beta_3, \quad \frac{\partial^2 f_6}{\partial y_3\partial y_6} = -(1-\psi)\beta_1, \quad \frac{\partial^2 f_6}{\partial y_3\partial y_6} = -(1-\psi)\beta_2, \quad \frac{\partial^2 f_6}{\partial y_4\partial y_6} = -(1-\psi)\beta_3.$$

Consequently, the associated bifurcation coefficient, a, is given by

$$\begin{aligned} a &= \sum_{k,i,j=1}^{6} u_k w_i w_j \frac{\partial^2 f_k}{\partial y_i \partial y_j}(0,0) \\ &= \frac{\epsilon u_3 w_3^2}{K_1\mu}\left(\beta_1 + \beta_2\frac{\kappa(1-\pi_1)}{K_4} + \beta_3\frac{(\pi_1\kappa K_4 + \pi_2\kappa(1-\pi_1))}{K_3K_4}\right)\Big[\rho\left(\frac{\pi_1\kappa K_4 + \pi_2(1-\pi_1)\kappa}{K_3K_4}\right) \\ &\quad +\sigma\frac{(1-\pi_1)\kappa}{K_4} - \frac{K_1K_2}{\epsilon A}\left(\frac{(1-b)\Lambda}{\mu} + \frac{\alpha b\Lambda}{\mu K_5} + \frac{\alpha(1-\psi)b\Lambda}{K_5^2}\right) - \frac{(1-\psi)^2\mu b\Lambda K_1K_2}{K_5^2\epsilon A}\Big]. \end{aligned}$$

Calculation of b. The required partial derivative, for the computation of b, is calculated at the DFE, i.e.,

$$\frac{\partial^2 f_2}{\partial y_3\partial\beta_1} = A.$$

Hence, the associated bifurcation coefficient, b, is given as

$$b = \sum_{k,i=1}^{6} u_k w_i \frac{\partial^2 f_k}{\partial y_i\partial\phi}(0,0) = \frac{A\epsilon u_3 w_3}{K_1} > 0.$$

The coefficient b is clearly always positive, hence Theorem (3.3.1) implies that the system (3.3.2) experiences backward bifurcation if the coefficient a is positive. Hence, the following result is formulated.

Theorem 3.3.2. *The HCV transmission model (3.3.2) exhibits backward bifurcation at* $R_0 = 1$ *whenever the coefficient a is positive.*

3.3.1 Use of a perfect vaccine to eliminate backward bifurcation

The phenomenon of backward bifurcation poses a lot of problems, since it jeopardizes the possibility of total disease eradication from the population, when the basic reproduction number is less than unity. Hence, it is instructive to try to eliminate the backward bifurcation effect. Since, this effect requires the existence of at least two endemic equilibria when $R_0 < 1$ [21, 22], it may be removed by considering such a model, in which positive endemic equilibria cease to exist.

The backward bifurcation behavior of the proposed HCV infection model (3.1.2), can be eliminated by using a perfect vaccine, i.e., when ψ=1. For ψ=1, the original model now becomes

$$\begin{aligned}
\frac{dS}{dt} &= (1-b)\Lambda + \rho T + \alpha V - (\beta_1 I + \beta_2 C_h + \beta_3 T)S + \sigma C_h - \mu S,\\
\frac{dE}{dt} &= (\beta_1 I + \beta_2 C_h + \beta_3 T)S - K_1 E,\\
\frac{dI}{dt} &= \epsilon E - K_2 I,\\
\frac{dT}{dt} &= \pi_1 \kappa I + \pi_2 C_h - K_3 T,\\
\frac{dC_h}{dt} &= (1-\pi_1)\kappa I - K_4 C_h,\\
\frac{dV}{dt} &= b\Lambda - K_5 V.
\end{aligned} \tag{3.3.6}$$

The system (3.3.6) has a DFE, $P_0(S_0, 0, 0, 0, 0, V_0)$, which is the same as the original model given in equation (3.1.2). The corresponding *vaccinated reproduction number*, $\bar{R}_0$, for model (3.3.6) is given as

$$\bar{R}_0 = R_0 \mid_{\psi=1} = \frac{\epsilon}{K_1 K_2}\left(\frac{(1-b)\Lambda}{\mu} + \frac{\alpha b \Lambda}{\mu K_5}\right)\left(\beta_1 + \beta_2 \frac{\kappa(1-\pi_1)}{K_4} + \beta_3 \frac{(\pi_1 \kappa K_4 + \pi_2 \kappa(1-\pi_1))}{K_3 K_4}\right).$$

Consider the quadratic equation (3.2.13), rewritten below for convenience

$$a_1 I^{*2} + a_2 I^* + a_3 = 0.$$

For $\psi = 1$, using the values given in equation (3.2.14), the coefficients a_1, a_2, and a_3 of the above quadratic equation reduce to $a_1 = 0$, $a_2 > 0$, and $a_3 \geq 0$ (whenever $\bar{R}_0 = R_0 \mid_{\psi=1} \leq 1$). In this case, the quadratic equation (3.2.13) will have just a single non positive solution

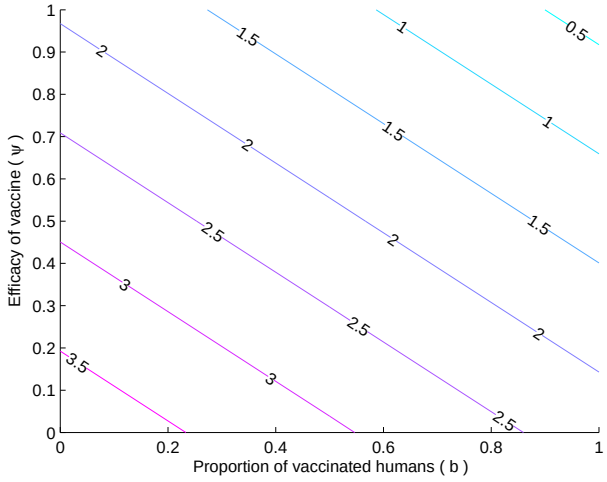

Figure 3.3: *Simulation of the model (3.3.6), showing a contour plot of $\bar{R}_0$ as a function of proportion of vaccinated humans (b) and vaccine efficacy (ψ). The parameter values used are as given in Table 4.1.*

$$I^* = -\frac{a_3}{a_2} \leq 0.$$

Hence, whenever $\bar{R}_0 \leq 1$, the model (3.3.6), with perfect vaccine, has no positive endemic equilibrium. This clearly suggests the impossibility of backward bifurcation (because for backward bifurcation to occur, there must exist at least two endemic equilibria whenever $\bar{R}_0 \leq 1$).

A contour plot of vaccinated reproduction number ($\bar{R}_0$) as a function of proportion of vaccinated humans (b) and vaccine efficacy (ψ) is shown in Fig. 3.3. The parameter values used to generate this diagram are as given in Table 4.1. The contours illustrate a significant decrease in the vaccinated reproduction number, $\bar{R}_0$, with increasing vaccine efficacy, ψ, and proportion of vaccinated humans, b. It can be seen that very high vaccine efficacy and vaccine coverage is required to control HCV infection effectively in the population. Almost all of the susceptible individuals should have had vaccination, and vaccine efficacy must be 100% for $\bar{R}_0$ to be less than one, so that the spread of HCV infection is controlled effectively.

3.4 Global stability of the DFE

The global stability of the DFE, P_0, can be proved in the region Ω defined in (3.2.2), as follows.

Theorem 3.4.1. *For a perfect vaccine ($\psi = 1$), P_0 is globally asymptotically stable in Ω*

whenever

$$\bar{R}_0 \leq \frac{S_0\mu}{\Lambda} < 1,$$

where

$$S_0 = \frac{(1-b)\Lambda}{\mu} + \frac{\alpha b\Lambda}{\mu(\alpha+\mu)}.$$

Proof: Let

$$V = A_1E + A_2I + A_3T + A_4C_h,$$

where

$$A_1 = \frac{S_0\mu}{\Lambda}, \quad A_2 = \frac{S_0K_1\mu}{\epsilon\Lambda}, \quad A_3 = \frac{\beta_3S_0}{K_3}, \quad A_4 = \frac{\beta_2S_0}{K_4} + \frac{\beta_3S_0\pi_2}{K_3K_4}.$$

Then,

$$\begin{aligned} V' &= A_1E' + A_2I' + A_3T' + A_4C_h' \\ &= A_1\Big[(\beta_1I + \beta_2C_h + \beta_3T)S - K_1E\Big] + A_2\Big[\epsilon E - K_2I\Big] + A_3\Big[\pi_1\kappa I + \pi_2C_h - K_3T\Big] \\ &\quad + A_4\Big[(1-\pi_1)\kappa I - K_4C_h\Big]. \end{aligned}$$

Now

$$S + E + I + T + C_h + V = \frac{\Lambda}{\mu},$$

implies that

$$S \leq \frac{\Lambda}{\mu}.$$

Therefore V' becomes

$$\begin{aligned} V' &\leq A_1\Big[(\beta_1I + \beta_2C_h + \beta_3T)\frac{\Lambda}{\mu} - K_1E\Big] + A_2\Big[\epsilon E - K_2I\Big] + A_3\Big[\pi_1\kappa I + \pi_2C_h - K_3T\Big] \\ &\quad + A_4\Big[(1-\pi_1)\kappa I - K_4C_h\Big] \\ &= E\Big[-K_1A_1 + \epsilon A_2\Big] + I\Big[\beta_1A_1\frac{\Lambda}{\mu} - K_2A_2 + \pi_1\kappa A_3 + A_4\kappa(1-\pi_1)\Big] + T\Big[\beta_3A_1\frac{\Lambda}{\mu} \\ &\quad - K_3A_3\Big] + C_h\Big[\beta_2A_1\frac{\Lambda}{\mu} + \pi_2A_3 - K_4A_4\Big] \end{aligned}$$

$$= I\Big[S_0\Big(\beta_1 + \beta_2\frac{\kappa(1-\pi_1)}{K_4} + \beta_3\frac{(\pi_1\kappa K_4 + \pi_2\kappa(1-\pi_1))}{K_3K_4}\Big) - \frac{S_0K_2K_1\mu}{\epsilon\Lambda}\Big]$$

$$= \frac{IK_1K_2}{\epsilon}\Big[\bar{R}_0 - \frac{S_0\mu}{\Lambda}\Big] \leq 0,$$

whenever

$$\bar{R}_0 \leq \frac{S_0\mu}{\Lambda} < 1.$$

Hence, $V' \leq 0$ for $\bar{R}_0 \leq \frac{S_0\mu}{\Lambda}$. It should also be noted that $\frac{S_0\mu}{\Lambda} = \frac{\frac{\Lambda}{\mu} - \frac{b\Lambda}{\alpha+\mu}}{\frac{\Lambda}{\mu}} < 1$. $V' = 0$ when $E = 0$, $I = 0$, $T = 0$, $C_h = 0$, which corresponds to the set $\{(E, I, T, C_h) : E = I = T = C_h = 0\}$. In this set, system (3.3.6) is given as

$$\begin{aligned}
\frac{dS}{dt} &= (1-b)\Lambda + \alpha V - \mu S, \\
\frac{dE}{dt} &= \frac{dI}{dt} = \frac{dT}{dt} = \frac{dC_h}{dt} = 0, \\
\frac{dV}{dt} &= b\Lambda - (\alpha+\mu)V.
\end{aligned} \tag{3.4.1}$$

When $t \to \infty$, the solution of the last equation in the system (3.4.1) becomes

$$V = \frac{b\Lambda}{\alpha+\mu}. \tag{3.4.2}$$

Putting this value back into the equation

$$\frac{dS}{dt} = (1-b)\Lambda + \alpha V - \mu S,$$

and letting $t \to \infty$ gives:

$$S = \frac{(1-b)\Lambda}{\mu} + \frac{\alpha b\Lambda}{\mu(\alpha+\mu)}. \tag{3.4.3}$$

This implies that solutions which started at $E = 0$, $I = 0$, $T = 0$, $C_h = 0$ approach the DFE, $P_0(S_0, 0, 0, 0, 0, V_0)$, when $t \to \infty$. Therefore, using LaSalle-Lyapunov invariance principle, P_0 is globally asymptotically stable, i.e., all solutions starting in Ω approach $P_0(S_0, 0, 0, 0, 0, V_0)$.

3.5 Global stability of the endemic equilibrium

In this section, global stability of the endemic equilibrium $P^*(S^*, E^*, I^*, T^*, C_h^*, V^*)$ is discussed. The method employed here is given in [24, 25]. At the endemic equilibrium P^*, using system (3.1.2), the following equations are satisfied:

$$\begin{cases} (1-b)\Lambda + \rho T^* + \alpha V^* - (\beta_1 I^* + \beta_2 C_h^* + \beta_3 T^*)S^* + \sigma C_h^* - \mu S^* = 0, \\ (\beta_1 I^* + \beta_2 C_h^* + \beta_3 T^*)S^* + (1-\psi)(\beta_1 I^* + \beta_2 C_h^* + \beta_3 T^*)V^* - (\epsilon + \mu)E^* = 0, \\ \epsilon E^* - (\kappa + \mu)I^* = 0, \\ \pi_1 \kappa I^* + \pi_2 C_h^* - (\rho + \mu)T^* = 0, \\ (1-\pi_1)\kappa I^* - (\pi_2 + \sigma + \mu)C_h^* = 0. \\ b\Lambda - (\alpha + \mu)V^* - (1-\psi)(\beta_1 I^* + \beta_2 C_h^* + \beta_3 T^*)V^* = 0. \end{cases} \tag{3.5.1}$$

Let

$$x_1 = \frac{S}{S^*}, \quad x_2 = \frac{E}{E^*}, \quad x_3 = \frac{I}{I^*}, \quad x_4 = \frac{T}{T^*}, \quad x_5 = \frac{C_h}{C_h^*}, \quad \text{and} \quad x_6 = \frac{V}{V^*}.$$

Then (3.1.2) can be rewritten as

$$\begin{aligned} x_1' &= x_1\Big[\frac{(1-b)\Lambda}{S^*}\Big(\frac{1}{x_1} - 1\Big) + \frac{\rho T^*}{S^*}\Big(\frac{x_4}{x_1} - 1\Big) + \frac{\alpha V^*}{S^*}\Big(\frac{x_6}{x_1} - 1\Big) - \beta_1 I^*(x_3 - 1) \\ &\quad -\beta_2 C_h^*(x_5 - 1) - \beta_3 T^*(x_4 - 1) + \frac{\sigma C_h^*}{S^*}\Big(\frac{x_5}{x_1} - 1\Big)\Big], \\ x_2' &= x_2\Big[\frac{\beta_1 I^* S^*}{E^*}\Big(\frac{x_3 x_1}{x_2} - 1\Big) + \frac{\beta_2 C_h^* S^*}{E^*}\Big(\frac{x_1 x_5}{x_2} - 1\Big) + \frac{\beta_3 T^* S^*}{E^*}\Big(\frac{x_1 x_4}{x_2} - 1\Big) \\ &\quad +(1-\psi)\frac{\beta_1 I^* V^*}{E^*}\Big(\frac{x_3 x_6}{x_2} - 1\Big) + (1-\psi)\frac{\beta_2 C_h^* V^*}{E^*}\Big(\frac{x_5 x_6}{x_2} - 1\Big) + (1-\psi)\frac{\beta_3 T^* V^*}{E^*}\Big(\frac{x_4 x_6}{x_2} - 1\Big)\Big], \\ x_3' &= x_3\Big[\frac{\epsilon E^*}{I^*}\Big(\frac{x_2}{x_3} - 1\Big)\Big], \\ x_4' &= x_4\Big[\frac{\pi_1 \kappa I^*}{T^*}\Big(\frac{x_3}{x_4} - 1\Big) + \frac{\pi_2 C_h^*}{T^*}\Big(\frac{x_5}{x_4} - 1\Big)\Big], \\ x_5' &= x_5\Big[(1-\pi_1)\frac{\kappa I^*}{C_h^*}\Big(\frac{x_3}{x_5} - 1\Big)\Big], \\ x_6' &= x_6\Big[\frac{b\Lambda}{V^*}\Big(\frac{1}{x_6} - 1\Big) - (1-\psi)\beta_1 I^*(x_3 - 1) - (1-\psi)\beta_2 C_h^*(x_5 - 1) - (1-\psi)\beta_3 T^*(x_4 - 1)\Big]. \end{aligned} \tag{3.5.2}$$

The endemic equilibrium $P^*(S^*, E^*, I^*, T^*, C_h^*, V^*)$ corresponds to the positive equilibrium $\bar{P}^*(1,1,1,1,1,1)$ of (3.5.2). Since, the global stability of $\bar{P}^*$ is the same as that of P^*, the global stability of $\bar{P}^*$ is described below instead of P^*.

The Liapunov function is defined as

$$\begin{aligned} L &= a_1 S^*(x_1 - 1 - \ln x_1) + a_2 E^*(x_2 - 1 - \ln x_2) + a_3 I^*(x_3 - 1 - \ln x_3) \\ &\quad + a_4 T^*(x_4 - 1 - \ln x_4) + a_5 C_h^*(x_5 - 1 - \ln x_5) + a_6 V^*(x_6 - 1 - \ln x_6), \end{aligned}$$

where a_1, a_2, a_3, a_4, a_5 and a_6 are positive numbers which are determined later.

The time derivative of L along the solutions of system (3.5.2) is given as

$$\begin{aligned} L' &= a_1(x_1 - 1)\Big[(1-b)\Lambda\left(\frac{1}{x_1} - 1\right) + \rho T^*\left(\frac{x_4}{x_1} - 1\right) + \alpha V^*\left(\frac{x_6}{x_1} - 1\right) - \beta_1 I^* S^*(x_3 - 1) \\ &\quad - \beta_2 C_h^* S^*(x_5 - 1) - \beta_3 T^* S^*(x_4 - 1) + \sigma C_h^*\left(\frac{x_5}{x_1} - 1\right)\Big] + a_2(x_2 - 1)\Big[\beta_1 I^* S^*\left(\frac{x_3 x_1}{x_2}\right. \\ &\quad \left. - 1\right) + \beta_2 C_h^* S^*\left(\frac{x_1 x_5}{x_2} - 1\right) + \beta_3 T^* S^*\left(\frac{x_1 x_4}{x_2} - 1\right) + (1-\psi)\beta_1 I^* V^*\left(\frac{x_3 x_6}{x_2} - 1\right) + (1-\psi) \\ &\quad \beta_2 C_h^* V^*\left(\frac{x_5 x_6}{x_2} - 1\right) + (1-\psi)\beta_3 T^* V^*\left(\frac{x_4 x_6}{x_2} - 1\right)\Big] + a_3(x_3 - 1)\Big[\epsilon E^*\left(\frac{x_2}{x_3} - 1\right)\Big] \\ &\quad + a_4(x_4 - 1)\Big[\pi_1 \kappa I^*\left(\frac{x_3}{x_4} - 1\right) + \pi_2 C_h^*\left(\frac{x_5}{x_4} - 1\right)\Big] + a_5(x_5 - 1)\Big[(1-\pi_1)\kappa I^*\left(\frac{x_3}{x_5} - 1\right)\Big] \\ &\quad + a_6(x_6 - 1)\Big[b\Lambda\left(\frac{1}{x_6} - 1\right) - (1-\psi)\beta_1 I^* V^*(x_3 - 1) - (1-\psi)\beta_2 C_h^* V^*(x_5 - 1) \\ &\quad - (1-\psi)\beta_3 T^* V^*(x_4 - 1)\Big] \\ &= a_1\big(2(1-b)\Lambda + \rho T^* + \alpha V^* - \beta_1 I^* S^* - \beta_2 C_h^* S^* - \beta_3 T^* S^* + \sigma C_h^*\big) + a_2\big(\beta_1 I^* S^* \\ &\quad + \beta_2 C_h^* S^* + \beta_3 T^* S^* + (1-\psi)\beta_1 I^* V^* + (1-\psi)\beta_2 C_h^* V^* + (1-\psi)\beta_3 T^* V^*\big) + a_3 \epsilon E^* \\ &\quad + a_4 \pi_1 \kappa I^* + a_5(1-\pi_1)\kappa I^* + a_6\big(2b\Lambda - (1-\psi)\beta_1 I^* V^* - (1-\psi)\beta_2 C_h^* V^* - (1-\psi)\beta_3 \\ &\quad T^* V^*\big) - x_1\big(a_1(1-b)\Lambda + a_1\rho T^* + a_1\alpha V^* - a_1\beta_1 I^* S^* - a_1\beta_2 C_h^* S^* - a_1\beta_3 T^* S^* + a_1\sigma \end{aligned}$$

$$C_h^*\big) + x_2\big(- a_2\beta_1 I^* S^* - a_2\beta_2 C_h^* S^* - a_2\beta_3 T^* S^* - a_2(1-\psi)\beta_1 I^* V^* - a_2(1-\psi)\beta_2 C_h^* S^*$$

$$-a_2(1-\psi)\beta_3 T^* V^* + a_3\epsilon E^*\big) + x_3\big(a_1\beta_1 I^* S^* - a_3\epsilon E^* + a_4\pi_1\kappa I^* + a_5(1-\pi_1\kappa I^*$$

$$+a_6(1-\psi)\beta_1 I^* V^*)\big) + x_4\big(a_1\rho T^* + a_1\beta_3 T^* S^* - a_4\pi_1\kappa I^* - a_4\pi_2 C_h^* + a_6(1-\psi)$$

$$\beta_3 T^* V^*\big) + x_5\big(a_1\beta_2 C_h^* S^* + a_1\sigma C_h^* + a_4\pi_2 C_h^* - a_5(1-\pi_1)\kappa I^* + a_6(1-\psi)\beta_2 C_h^* V^*\big)$$

$$-x_6\big(- a_1\alpha V^* + a_6 b\Lambda - a_6(1-\psi)\beta_1 I^* V^* - a_6(1-\psi)\beta_2 C_h^* V^* - a_6(1-\psi)\beta_3 T^* V^*\big)$$

$$+x_5 x_6\big(a_2(1-\psi)\beta_2 C_h^* V^* - a_6(1-\psi)\beta_2 C_h^* V^*\big) + x_1 x_3\big(- a_1\beta_1 I^* S^* + a_2\beta_1 I^* S^*\big)$$

$$+x_1 x_5\big(- a_1\beta_2 C_h^* S^* + a_2\beta_2 C_h^* S^*\big) + x_1 x_4\big(- a_1\beta_3 T^* S^* + a_2\beta_3 T^* S^*\big)$$

$$+x_3 x_6\big(a_2(1-\psi)\beta_1 I^* V^* - a_6(1-\psi)\beta_1 I^* V^*\big) + x_4 x_6\big(a_2(1-\psi)\beta_3 T^* V^* - a_6(1-\psi)$$

$$\beta_3 T^* V^*\big) + \frac{1}{x_1}\big(- a_1(1-b)\Lambda\big) + \frac{1}{x_6}\big(- a_6 b\Lambda\big) + \frac{x_6}{x_1}\big(- a_1\alpha V^*\big) + \frac{x_3}{x_5}\big(- a_5(1-\pi_1\kappa I^*)\big)$$

$$+\frac{x_5}{x_4}\big(- a_4\pi_2 C_h^*\big) + \frac{x_3}{x_4}\big(- a_4\pi_1\kappa I^*\big) + \frac{x_2}{x_3}\big(- a_3\epsilon E^*\big) + \frac{x_3 x_6}{x_2}\big(- a_2(1-\pi)\beta_1 I^* V^*\big)$$

$$+\frac{x_3 x_1}{x_2}\big(- a_2\beta_1 I^* S^*\big) + \frac{x_5 x_1}{x_2}\big(- a_2\beta_2 C_h^* S^*\big) + \frac{x_1 x_4}{x_2}\big(- a_2\beta_3 T^* S^*\big) + \frac{x_4 x_6}{x_2}\big(- a_2(1-\pi)$$

$$\beta_3 T^* V^*\big) + \frac{x_5 x_6}{x_2}\big(- a_2(1-\pi)\beta_2 C_h^* V^*\big) + \frac{x_4}{x_1}\big(- a_1\rho T^*\big) + \frac{x_5}{x_1}\big(- a_1\sigma C_h^*\big)$$

$$=: \quad G(x_1, x_2, x_3, x_4, x_5, x_6).$$

To make $G(x_1, x_2, x_3, x_4, x_5, x_6) \leq 0$, positive constants $a_i (i = 1, 2, ...6)$ are required to be chosen. Hence, the following function is defined:

$$H = \frac{dL}{dT} = \sum_{k=1}^{K} b_k\Big(n_k - h_{k,1} - h_{k,2} - ... - h_{k,n_k}\Big), \tag{3.5.3}$$

where $b_k \geq 0$ $(k = 1, 2, ..., K)$, and $h_{k,i}$ is an expression which involves only $x_1, x_2, ..., x_n$ and satisfies $\Pi_{i=1}^{n_k} h_{k,i} = 1$. Then, by using the property that the arithmetic mean is greater than or equal to the associated geometric mean, it can be proved that the function in (3.5.3), and hence $G(x_1, x_2, x_3, x_4, x_5, x_6)$, is less than or equal to zero.

Now, all the terms of $G(x_1, x_2, x_3, x_4, x_5, x_6)$ which satisfy $\Pi_{i=1}^{n_k} h_{k,i} = 1$ are collected.

$$\Big[x_1,\frac{1}{x_1}\Big],\quad \Big[x_6,\frac{1}{x_6}\Big],\quad \Big[x_1,\frac{1}{x_6},\frac{x_6}{x_1}\Big],\quad \Big[\frac{1}{x_1},\frac{x_1x_3}{x_2},\frac{x_2}{x_3}\Big],\quad \Big[\frac{1}{x_6},\frac{x_3x_6}{x_2},\frac{x_2}{x_3}\Big],\quad \Big[\frac{1}{x_1},\frac{x_1x_4}{x_2},\frac{x_2}{x_3},\frac{x_3}{x_4}\Big],$$

$$\Big[\frac{1}{x_6},\frac{x_4x_6}{x_2},\frac{x_3}{x_4},\frac{x_2}{x_3}\Big],\quad \Big[\frac{1}{x_6},\frac{x_5x_6}{x_2},\frac{x_3}{x_5},\frac{x_2}{x_3}\Big],\quad \Big[\frac{1}{x_6},\frac{x_1x_3}{x_2},\frac{x_6}{x_1},\frac{x_2}{x_3}\Big],$$

$$\Big[\frac{1}{x_1},\frac{x_1x_5}{x_2},\frac{x_3}{x_5},\frac{x_2}{x_3}\Big],\quad \Big[\frac{1}{x_1},\frac{x_1x_4}{x_2},\frac{x_3}{x_5},\frac{x_2}{x_3},\frac{x_5}{x_4}\Big],\quad \Big[\frac{1}{x_6},\frac{x_6x_4}{x_2},\frac{x_3}{x_5},\frac{x_2}{x_3},\frac{x_5}{x_4}\Big],$$

$$\Big[\frac{1}{x_6},\frac{x_1x_4}{x_2},\frac{x_3}{x_4},\frac{x_2}{x_3},\frac{x_6}{x_1}\Big],\quad \Big[\frac{1}{x_6},\frac{x_1x_5}{x_2},\frac{x_3}{x_5},\frac{x_2}{x_3},\frac{x_6}{x_1}\Big].$$

The function $H=\sum_{i=1}^{14}P_i$ is now defined, where $P_i(i=1,2,...,14)$ are given as

$$\begin{cases}
P_1=b_1\Big(2-x_1-\dfrac{1}{x_1}\Big),\\
P_2=b_2\Big(2-x_6-\dfrac{1}{x_6}\Big),\\
P_3=b_3\Big(3-x_1-\dfrac{1}{x_6}-\dfrac{x_6}{x_1}\Big),\\
P_4=b_4\Big(3-\dfrac{1}{x_1}-\dfrac{x_1x_3}{x_2}-\dfrac{x_2}{x_3}\Big),\\
P_5=b_5\Big(4-\dfrac{1}{x_1}-\dfrac{x_1x_4}{x_2}-\dfrac{x_3}{x_4}-\dfrac{x_2}{x_3}\Big),\\
P_6=b_6\Big(4-\dfrac{1}{x_1}-\dfrac{x_1x_5}{x_2}-\dfrac{x_3}{x_5}-\dfrac{x_2}{x_3}\Big),\\
P_7=b_7\Big(5-\dfrac{1}{x_1}-\dfrac{x_1x_4}{x_2}-\dfrac{x_5}{x_4}-\dfrac{x_2}{x_3}-\dfrac{x_3}{x_5}\Big),\\
P_8=b_8\Big(3-\dfrac{1}{x_6}-\dfrac{x_3x_6}{x_2}-\dfrac{x_2}{x_3}\Big),\\
P_9=b_9\Big(4-\dfrac{1}{x_6}-\dfrac{x_4x_6}{x_2}-\dfrac{x_3}{x_4}-\dfrac{x_2}{x_3}\Big),\\
P_{10}=b_{10}\Big(5-\dfrac{1}{x_6}-\dfrac{x_4x_6}{x_2}-\dfrac{x_5}{x_4}-\dfrac{x_2}{x_3}-\dfrac{x_3}{x_5}\Big),\\
P_{11}=b_{11}\Big(4-\dfrac{1}{x_6}-\dfrac{x_5x_6}{x_2}-\dfrac{x_3}{x_5}-\dfrac{x_2}{x_3}\Big),\\
P_{12}=b_{12}\Big(4-\dfrac{1}{x_6}-\dfrac{x_1x_3}{x_2}-\dfrac{x_6}{x_1}-\dfrac{x_2}{x_3}\Big),\\
P_{13}=b_{13}\Big(5-\dfrac{1}{x_6}-\dfrac{x_1x_5}{x_2}-\dfrac{x_6}{x_1}-\dfrac{x_2}{x_3}-\dfrac{x_3}{x_5}\Big),\\
P_{14}=b_{14}\Big(5-\dfrac{1}{x_6}-\dfrac{x_1x_4}{x_2}-\dfrac{x_6}{x_1}-\dfrac{x_2}{x_3}-\dfrac{x_3}{x_4}\Big).
\end{cases}\tag{3.5.4}$$

To determine all the coefficients, $\big(a_i > 0 \ \ (i = 1, 2, ..., 6), b_i \geq 0 \ \ (i = 1, 2, ..., 14)\big)$ let $G(x_1, x_2, x_3, x_4, x_5, x_6) = H$. Comparing coefficients of G and H, it is seen that the terms $x_2, x_3, x_4, x_5, x_5x_6, x_1x_3, x_1x_5, x_1x_4, x_3x_6, x_4x_6, \dfrac{x_4}{x_1}$ and $\dfrac{x_5}{x_1}$ of G do not appear in H. Hence their coefficients will be equal to zero, i.e.,

$$\begin{aligned} &-a_2\beta_1 I^* S^* - a_2\beta_2 C_h^* S^* - a_2\beta_3 T^* S^* - a_2(1-\psi)\beta_1 I^* V^* - a_2(1-\psi)\beta_2 C_h^* S^* \\ &-a_2(1-\psi)\beta_3 T^* V^* + a_3\epsilon E^* = 0, \end{aligned} \tag{3.5.5}$$

$$a_1\beta_1 I^* S^* - a_3\epsilon E^* + a_4\pi_1\kappa I^* + a_5(1-\pi_1)\kappa I^* + a_6(1-\psi)\beta_1 I^* V^* = 0, \tag{3.5.6}$$

$$a_1\rho T^* + a_1\beta_3 T^* S^* - a_4\pi_1\kappa I^* - a_4\pi_2 C_h^* + a_6(1-\psi)\beta_3 T^* V^* = 0, \tag{3.5.7}$$

$$a_1\beta_2 C_h^* S^* + a_1\sigma C_h^* + a_4\pi_2 C_h^* - a_5(1-\pi_1)\kappa I^* + a_6(1-\psi)\beta_2 C_h^* V^* = 0, \tag{3.5.8}$$

$$a_2(1-\psi)\beta_2 C_h^* V^* - a_6(1-\psi)\beta_2 C_h^* V^* = 0, \tag{3.5.9}$$

$$a_2(1-\psi)\beta_1 I^* V^* - a_6(1-\psi)\beta_1 I^* V^* = 0, \tag{3.5.10}$$

$$a_2(1-\psi)\beta_3 T^* V^* - a_6(1-\psi)\beta_3 T^* V^* = 0, \tag{3.5.11}$$

$$-a_1\beta_1 I^* S^* + a_2\beta_1 I^* S^* = 0, \tag{3.5.12}$$

$$-a_1\beta_2 C_h^* S^* + a_2\beta_2 C_h^* S^* = 0, \tag{3.5.13}$$

$$-a_1\beta_3 T^* S^* + a_2\beta_3 T^* S^* = 0, \tag{3.5.14}$$

$$-a_1\rho T^* = 0, \tag{3.5.15}$$

$$-a_1\sigma C_h^* = 0. \tag{3.5.16}$$

Since $a_1 \neq 0$ (from (3.5.15) and (3.5.16)), let $\rho = 0$ and $\sigma = 0$ in all subsequent calculations. With this assumption, the above equations have the following solution:

$$\begin{cases} a_1 = 1, \\ a_2 = 1, \\ a_6 = 1, \\ a_3 = \dfrac{\epsilon + \mu}{\epsilon}, \\ a_4 = \dfrac{\beta_3 S^* + (1-\psi)\beta_3 V^*}{\mu}, \\ a_5 = \dfrac{\left(S^* + (1-\psi)V^*\right)\left(\beta_2 + \frac{\beta_3 \pi_2}{\mu}\right)}{\pi_2 + \mu}. \end{cases} \tag{3.5.17}$$

With $\rho = 0$ and $\sigma = 0$, the system (3.1.2) becomes

$$\begin{aligned} \frac{dS}{dt} &= (1-b)\Lambda + \alpha V - (\beta_1 I + \beta_2 C_h + \beta_3 T)S - \mu S, \\ \frac{dE}{dt} &= (\beta_1 I + \beta_2 C_h + \beta_3 T)S + (1-\psi)(\beta_1 I + \beta_2 C_h + \beta_3 T)V - (\epsilon + \mu)E, \\ \frac{dI}{dt} &= \epsilon E - (\kappa + \mu)I, \\ \frac{dT}{dt} &= \pi_1 \kappa I + \pi_2 C_h - \mu T, \\ \frac{dC_h}{dt} &= (1-\pi_1)\kappa I - (\pi_2 + \mu)C_h, \\ \frac{dV}{dt} &= b\Lambda - (\alpha + \mu)V - (1-\psi)(\beta_1 I + \beta_2 C_h + \beta_3 T)V, \end{aligned} \tag{3.5.18}$$

and equations (3.5.1) become

$$\begin{cases} (1-b)\Lambda + \alpha V^* - (\beta_1 I^* + \beta_2 C_h^* + \beta_3 T^*)S^* - \mu S^* = 0, \\ (\beta_1 I^* + \beta_2 C_h^* + \beta_3 T^*)S^* + (1-\psi)(\beta_1 I^* + \beta_2 C_h^* + \beta_3 T^*)V^* - (\epsilon + \mu)E^* = 0, \\ \epsilon E^* - (\kappa + \mu)I^* = 0, \\ \pi_1 \kappa I^* + \pi_2 C_h^* - \mu T^* = 0, \\ (1-\pi_1)\kappa I^* - (\pi_2 + \mu)C_h^* = 0, \\ b\Lambda - (\alpha + \mu)V^* - (1-\psi)(\beta_1 I^* + \beta_2 C_h^* + \beta_3 T^*)V^* = 0. \end{cases} \tag{3.5.19}$$

Substituting the values of a_1, a_2, a_3, a_4, a_5 and a_6 into the function G gives:

$$\begin{aligned}
G(x_1,x_2,x_3,x_4,x_5,x_6) &= \Big(2\Lambda + \alpha V^* + (\epsilon+\mu)E^* + \beta_3\big(S^* + (1-\psi)V^*\big)T^* \\
&+\big(S^* + (1-\psi)V^*\big)\big(\beta_2 + \frac{\beta_3\pi_2}{\mu}\big)C_h^*\Big) - x_1\big(\mu S^*\big) - x_6\big(\mu V^*\big) - \frac{1}{x_1}\big((1-b)\Lambda\big) - \frac{1}{x_6}\big(b\Lambda\big) \\
&-\frac{x_6}{x_1}\big(\alpha V^*\big) - \frac{x_3}{x_5}\Big(\big(S^* + (1-\psi)V^*\big)\big(\beta_2 + \frac{\beta_3\pi_2}{\mu}\big)C_h^*\Big) - \frac{x_5}{x_4}\Big(\frac{\beta_3}{\mu}\big(S^* + (1-\psi)V^*\big)\pi_2 C_h^*\Big) \\
&-\frac{x_3}{x_4}\Big(\frac{\beta_3}{\mu}\big(S^* + (1-\psi)V^*\big)\pi_1\kappa I^*\Big) - \frac{x_2}{x_3}\Big((\epsilon+\mu)E^*\Big) - \frac{x_3x_6}{x_2}\big((1-\psi)\beta_1 I^*V^*\big) \\
&-\frac{x_1x_3}{x_2}\big(\beta_1 I^*S^*\big) - \frac{x_1x_5}{x_2}\big(\beta_2 C_h^*S^*\big) - \frac{x_1x_4}{x_2}\big(\beta_3 T^*S^*\big) - \frac{x_4x_6}{x_2}\big((1-\psi)\beta_3 T^*V^*\big) \\
&-\frac{x_5x_6}{x_2}\big((1-\psi)\beta_2 C_h^*V^*\big).
\end{aligned} \tag{3.5.20}$$

Comparing the remaining coefficients of G and H gives:

$$\begin{cases}
b_1 + b_3 = \mu S^*, \\
b_2 = \mu V^*, \\
b_2 + b_3 + b_8 + b_9 + b_{10} + b_{11} + b_{12} + b_{13} + b_{14} = b\Lambda, \\
b_8 = (1-\psi)\beta_1 I^*V^*, \\
b_1 + b_4 + b_5 + b_6 + b_7 = (1-b)\Lambda, \\
b_3 + b_{12} + b_{13} + b_{14} = \alpha V^*, \\
b_4 + b_{12} = \beta_1 I^*S^*, \\
b_6 + b_{13} = \beta_2 C_h^* S^*, \\
b_5 + b_7 + b_{14} = \beta_3 T^*S^*, \\
b_{11} = (1-\psi)\beta_2 C_h^* V^*, \\
b_9 + b_{10} = (1-\psi)\beta_3 T^*V^*, \\
b_4 + b_5 + b_6 + b_7 + b_8 + b_9 + b_{10} + b_{11} + b_{12} + b_{13} + b_{14} = (\epsilon+\mu)E^*, \\
b_5 + b_9 + b_{14} = \dfrac{\beta_3}{\mu}\big(S^* + (1-\psi)V^*\big)\pi_1\kappa I^*, \\
b_6 + b_7 + b_{10} + b_{11} + b_{13} = \big(S^* + (1-\psi)V^*\big)\big(\beta_2 + \dfrac{\beta_3\pi_2}{\mu}\big)C_h^*, \\
b_7 + b_{10} = \dfrac{\beta_3}{\mu}\big(S^* + (1-\psi)V^*\big)\pi_2 C_h^*.
\end{cases} \tag{3.5.21}$$

Putting values of b_2, b_8, and b_{11} in the above equations and using (3.5.19) reduces them to:

$$\begin{cases} b_1 + b_3 = \mu S^*, \\ b_3 + b_9 + b_{10} + b_{11} + b_{12} + b_{13} + b_{14} = b\Lambda - \mu V^* - (1-\psi)\big(\beta_1 I* + \beta_2 C_h^*\big)V^*, \\ b_1 + b_4 + b_5 + b_6 + b_7 = (1-b)\Lambda, \\ b_3 + b_{12} + b_{13} + b_{14} = \alpha V^*, \\ b_4 + b_{12} = \beta_1 I^* S^*, \\ b_6 + b_{13} = \beta_2 C_h^* S^*, \\ b_5 + b_7 + b_{14} = \beta_3 T^* S^*, \\ b_9 + b_{10} = (1-\psi)\beta_3 T^* V^*, \\ b_4 + b_5 + b_6 + b_7 + b_9 + b_{10} + b_{12} + b_{13} + b_{14} = (\epsilon + \mu)E^* - (1-\psi)\big(\beta_1 I* + \beta_2 C_h^*\big)V^*, \\ b_5 + b_9 + b_{14} = \dfrac{\beta_3}{\mu}\big(S^* + (1-\psi)V^*\big)\pi_1 \kappa I^*, \\ b_6 + b_7 + b_{10} + b_{13} = \dfrac{\beta_3}{\mu}\big(S^* + (1-\psi)V^*\big)\pi_2 C_h^* + \beta_2 C_h^* S^*, \\ b_7 + b_{10} = \dfrac{\beta_3}{\mu}\big(S^* + (1-\psi)V^*\big)\pi_2 C_h^*. \end{cases} \tag{3.5.22}$$

The above equations can be written equivalently as:

$$\begin{cases} b_1 = \mu S^* - \alpha V^* + b_{12} + b_{13} + b_{14}, \\ b_3 = \alpha V^* - b_{12} - b_{13} - b_{14}, \\ b_4 = \beta_1 I^* S^* - b_{12}, \\ b_5 = \beta_3 T^* S^* - \dfrac{\beta_3}{\mu}\big(S^* + (1-\psi)V^*\big)\pi_2 C_h^* + b_{10} - b_{14}, \\ b_6 = \beta_2 C_h^* S^* - b_{13}, \\ b_7 = \dfrac{\beta_3}{\mu}\big(S^* + (1-\psi)V^*\big)\pi_2 C_h^* - b_{10}, \\ b_9 = (1-\psi)\beta_3 T^* V^* - b_{10}. \end{cases} \tag{3.5.23}$$

To ensure that $b_1, b_3, b_4, b_5, b_6, b_7$ and b_9 are nonnegative, $b_{10}, b_{12}, b_{13}, b_{14}$ must satisfy the following inequalities:

$$
\begin{cases}
\alpha V^* - \mu S^* \leq b_{12} + b_{13} + b_{14} \leq \alpha V^*, \\
b_{10} \leq \min\Big((1-\psi)\beta_3 T^* V^*, \dfrac{\beta_3}{\mu}\big(S^* + (1-\psi)V^*\big)\pi_2 C_h^*\Big), \\
b_{14} - b_{10} \leq \beta_3 T^* S^* - \dfrac{\beta_3}{\mu}\big(S^* + (1-\psi)V^*\big)\pi_2 C_h^*, \\
b_{12} \leq \beta_1 I^* S^*, \\
b_{13} \leq \beta_2 C_h^* S^*.
\end{cases} \tag{3.5.24}
$$

Finally, using equations (3.5.19), the equality for the constant terms between $G(x_1, x_2, x_3, x_4, x_5, x_6)$ and H is verified, as follows:

$$
\begin{aligned}
& 2b_1 + 2b_2 + 3b_3 + 3b_4 + 4b_5 + 4b_6 + 5b_7 + 3b_8 + 4b_9 + 5b_{10} + 4b_{11} + 4b_{12} + 5b_{13} + 5b_{14} \\
= \; & 2\Big[\mu S^* - \alpha V^* + b_{12} + b_{13} + b_{14}\Big] + 2\mu V^* + 3\Big[\alpha V^* - b_{12} - b_{13} - b_{14}\Big] + 3\Big[\beta_1 I^* S^* - b_{12}\Big] \\
& + 4\Big[\beta_3 T^* S^* - \frac{\beta_3}{\mu}\big(S^* + (1-\psi)V^*\big)\pi_2 C_h^* + b_{10} - b_{14}\Big] + 4\Big[\beta_2 C_h^* S^* - b_{13}\Big] \\
& + 5\Big[\frac{\beta_3}{\mu}\big(S^* + (1-\psi)V^*\big)\pi_2 C_h^* - b_{10}\Big] + 3(1-\psi)\beta_1 I^* V^* + 4\Big[(1-\psi)\beta_3 T^* V^* - b_{10}\Big] \\
& + 5b_{10} + 4(1-\psi)\beta_2 C_h^* V^* + 4b_{12} + 5b_{13} + 5b_{14} \\
= \; & 2\mu S^* + 2\mu V^* + \alpha V^* + 3\beta_1 I^* S^* + 4\beta_2 C_h^* S^* + 4\beta_3 T^* S^* + 3(1-\psi)\beta_1 I^* V^* \\
& + 4(1-\psi)\beta_2 C_h^* V^* + 4(1-\psi)\beta_3 T^* V^* + \frac{\beta_3}{\mu}\big(S^* + (1-\psi)V^*\big)\pi_2 C_h^* \\
= \; & 4\mu S^* + 4\mu V^* + \alpha V^* + 4\beta_1 I^* S^* + 4\beta_2 C_h^* S^* + 4\beta_3 T^* S^* + 4(1-\psi)\beta_1 I^* V^* \\
& + 4(1-\psi)\beta_2 C_h^* V^* + 4(1-\psi)\beta_3 T^* V^* + \frac{\beta_3}{\mu}\big(S^* + (1-\psi)V^*\big)\pi_2 C_h^* - 2\mu S^* \\
& - \beta_1 I^* S^* - (1-\psi)\beta_1 I^* V^* - 2\mu V^*
\end{aligned}
$$

$$
\begin{aligned}
&= 4(1-b)\Lambda + 4\alpha V^* - 4(\beta_1 I^* + \beta_2 C_h^* + \beta_3 T^*)S^* + 4\mu V^* + \alpha V^* + 4\beta_1 I^* S^* + 4\beta_2 C_h^* S^* \\
&\quad + 4\beta_3 T^* S^* + 4(1-\psi)\beta_1 I^* V^* + 4(1-\psi)\beta_2 C_h^* V^* + 4(1-\psi)\beta_3 T^* V^* \\
&\quad + \frac{\beta_3}{\mu}\big(S^* + (1-\psi)V^*\big)\pi_2 C_h^* - 2\mu S^* - \beta_1 I^* S^* - (1-\psi)\beta_1 I^* V^* - 2\mu V^* \\
&= \Big[4\mu V^* - 4b\Lambda + 4\alpha V^* + 4(1-\psi)(\beta_1 I^* + \beta_2 C_h^* + \beta_3 T^*)V^*\Big] + \alpha V^* \\
&\quad + \frac{\beta_3}{\mu}\big(S^* + (1-\psi)V^*\big)\pi_2 C_h^* - 2\mu S^* - \beta_1 I^* S^* - (1-\psi)\beta_1 I^* V^* - 2\mu V^* + 4\Lambda \\
&= \alpha V^* + \frac{\beta_3}{\mu}\big(S^* + (1-\psi)V^*\big)\pi_2 C_h^* - 2\mu S^* - 2\mu V^* + 4\Lambda \ - \beta_1 I^* S^* - (1-\psi)\beta_1 I^* V^* \\
&= \alpha V^* + \frac{\beta_3}{\mu}\big(S^* + (1-\psi)V^*\big)\pi_2 C_h^* - 2\mu S^* - 2\mu V^* + 4\Lambda - (\epsilon+\mu)E^* \\
&\quad + \big(\beta_2 C_h^* + \beta_3 T^*\big)\big(S^* + (1-\psi)V^*\big) \\
&= \alpha V^* - 2\mu S^* - 2\mu V^* + 4\Lambda - (\epsilon+\mu)E^* + \beta_3\big(S^* + (1-\psi)V^*\big)T^* + \big(S^* + (1-\psi)V^*\big) \\
&\quad \Big(\beta_2 + \frac{\beta_3\pi_2}{\mu}\Big)C_h^* \\
&= \alpha V^* + 2\Lambda + (\epsilon+\mu)E^* + \beta_3\big(S^* + (1-\psi)V^*\big)T^* + \big(S^* + (1-\psi)V^*\big)\Big(\beta_2 + \frac{\beta_3\pi_2}{\mu}\Big)C_h^* \\
&\quad + 2\Big[(\Lambda - \mu S^*) - (\mu V^*) - (\epsilon+\mu)E^*\Big] \\
&= \alpha V^* + 2\Lambda + (\epsilon+\mu)E^* + \beta_3\big(S^* + (1-\psi)V^*\big)T^* + \big(S^* + (1-\psi)V^*\big)\Big(\beta_2 + \frac{\beta_3\pi_2}{\mu}\Big)C_h^* \\
&\quad + 2\Big[\big(b\Lambda - \alpha V^* + (\beta_1 I^* + \beta_2 C_h^* + \beta_3 T^*)S^*\big) - b\Lambda + \alpha V^* + (1-\psi)(\beta_1 I^* + \beta_2 C_h^* \\
&\quad + \beta_3 T^*)V^* - (\beta_1 I^* + \beta_2 C_h^* + \beta_3 T^*)S^* - (1-\psi)(\beta_1 I^* + \beta_2 C_h^* + \beta_3 T^*)V^*\Big] \\
&= \alpha V^* + 2\Lambda + (\epsilon+\mu)E^* + \beta_3\big(S^* + (1-\psi)V^*\big)T^* + \big(S^* + (1-\psi)V^*\big)\Big(\beta_2 + \frac{\beta_3\pi_2}{\mu}\Big)C_h^*,
\end{aligned}
$$

which is the same as the constant term of $G(x_1, x_2, x_3, x_4, x_5, x_6)$.

The constrained conditions (3.5.24) show that the available values of b_{10}, b_{12}, b_{13}, and b_{14} are not unique. Since, $b_1, b_3, b_4, b_5, b_6, b_7$ and b_9 depend on b_{10}, b_{12}, b_{13}, and b_{14}, their values will also be non unique. $\big(b_2, b_8, b_{11}$ have already been determined uniquely$\big)$. Therefore, the form of H in (3.5.3) will be non unique as well. Using inequalities (3.5.24), different values can be assigned to $b_i (i = 1, 3, ...14, i \neq 2, 8, 11)$, and hence H can have different forms. Cases are discussed in the following three regions.

Case 1: $\mu S > \alpha V, \qquad \frac{\beta_3}{\mu}\big(S^* + (1-\psi)V^*\big)\pi_2 C_h^* \leq (1-\psi)\beta_3 T^* V^*$

For case 1, using equations (3.5.23) and (3.5.24), choose $b_1 = \mu S^* - \alpha V^*$, $b_3 = \alpha V^*$, $b_4 = \beta_1 I^* S^*$, $b_5 = \beta_3 T^* S^*$, $b_6 = \beta_2 C_h^* S^*$, $b_7 = 0$, $b_9 = (1-\psi)\beta_3 T^* V^* - \frac{\beta_3}{\mu}\big(S^* + (1-\psi)V^*\big)\pi_2 C_h^*$, $b_{10} = \frac{\beta_3}{\mu}\big(S^* + (1-\psi)V^*\big)\pi_2 C_h^*$, $b_{12} = 0$, $b_{13} = 0$ and $b_{14} = 0$.

Using these values, and the values of b_2, b_8 and b_{11} from (3.5.21), the function $G(x_1, x_2, x_3, x_4, x_5, x_6)$ becomes

$G(x_1, x_2, x_3, x_4, x_5, x_6) =$

$$
\begin{aligned}
&(\mu S^* - \alpha V^*)\Big(2 - x_1 - \frac{1}{x_1}\Big) + \mu V^*\Big(2 - x_6 - \frac{1}{x_6}\Big) + \alpha V^*\Big(3 - x_1 - \frac{1}{x_6} - \frac{x_6}{x_1}\Big) \\
&+\beta_1 I^* S^*\Big(3 - \frac{1}{x_1} - \frac{x_2}{x_3} - \frac{x_1 x_3}{x_2}\Big) + \beta_3 T^* S^*\Big(4 - \frac{1}{x_1} - \frac{x_2}{x_3} - \frac{x_1 x_4}{x_2} - \frac{x_3}{x_4}\Big) \\
&+\beta_2 C_h^* S^*\Big(4 - \frac{1}{x_1} - \frac{x_2}{x_3} - \frac{x_1 x_5}{x_2} - \frac{x_3}{x_5}\Big) + (1-\psi)\beta_1 I^* V^*\Big(3 - \frac{1}{x_6} - \frac{x_2}{x_3} - \frac{x_3 x_6}{x_2}\Big) \\
&+\Big((1-\psi)\beta_3 T^* V^* - \frac{\beta_3}{\mu}\big(S^* + (1-\psi)V^*\big)\pi_2 C_h^*\Big)\Big(4 - \frac{1}{x_6} - \frac{x_2}{x_3} - \frac{x_4 x_6}{x_2} - \frac{x_3}{x_4}\Big) \\
&+\frac{\beta_3}{\mu}\big(S^* + (1-\psi)V^*\big)\pi_2 C_h^*\Big(5 - \frac{1}{x_6} - \frac{x_2}{x_3} - \frac{x_4 x_6}{x_2} - \frac{x_3}{x_5} - \frac{x_5}{x_4}\Big) \\
&+(1-\psi)\beta_2 C_h^* V^*\Big(4 - \frac{1}{x_6} - \frac{x_2}{x_3} - \frac{x_5 x_6}{x_2} - \frac{x_3}{x_5}\Big).
\end{aligned}
\tag{3.5.25}
$$

Case 2: $\mu S = \alpha V, \qquad \frac{\beta_3}{\mu}\big(S^* + (1-\psi)V^*\big)\pi_2 C_h^* \geq (1-\psi)\beta_3 T^* V^*$

For case 2, using equations (3.5.23) and (3.5.24), choose $b_1 = 0$, $b_3 = \alpha V^*$, $b_4 = \beta_1 I^* S^*$, $b_5 = \beta_3\big(S^*+(1-\psi)V^*\big)\dfrac{\pi_1\kappa I^*}{\mu}$, $b_6 = \beta_2 C_h^* S^*$, $b_7 = \dfrac{\beta_3}{\mu}\big(S^*+(1-\psi)V^*\big)\pi_2 C_h^* - (1-\psi)\beta_3 T^* V^*$, $b_9 = 0$, $b_{10} = (1-\psi)\beta_3 T^* V^*$, $b_{12} = 0$, $b_{13} = 0$ and $b_{14} = 0$.

Using the above values, and the values of b_2, b_8 and b_{11} from (3.5.21), the function $G(x_1, x_2, x_3, x_4, x_5, x_6)$ becomes

$G(x_1, x_2, x_3, x_4, x_5, x_6)=$

$$\mu V^*\Big(2 - x_6 - \frac{1}{x_6}\Big) + \alpha V^*\Big(3 - x_1 - \frac{1}{x_6} - \frac{x_6}{x_1}\Big) + \beta_1 I^* S^*\Big(3 - \frac{1}{x_1} - \frac{x_2}{x_3} - \frac{x_1 x_3}{x_2}\Big)$$

$$+\beta_3\big(S^* + (1-\psi)V^*\big)\frac{\pi_1\kappa I^*}{\mu}\Big(4 - \frac{1}{x_1} - \frac{x_2}{x_3} - \frac{x_1 x_4}{x_2} - \frac{x_3}{x_4}\Big) + \beta_2 C_h^* S^*\Big(4 - \frac{1}{x_1} - \frac{x_2}{x_3} - \frac{x_1 x_5}{x_2}$$

$$-\frac{x_3}{x_5}\Big) + \big(\frac{\beta_3}{\mu}\big(S^* + (1-\psi)V^*\big)\pi_2 C_h^* - (1-\psi)\beta_3 T^* V^*\big)\Big(5 - \frac{1}{x_1} - \frac{x_2}{x_3} - \frac{x_1 x_4}{x_2} - \frac{x_3}{x_5} - \frac{x_5}{x_4}\Big)$$

$$+(1-\psi)\beta_1 I^* V^*\Big(3 - \frac{1}{x_6} - \frac{x_2}{x_3} - \frac{x_3 x_6}{x_2}\Big) + (1-\psi)\beta_3 T^* V^*\Big(5 - \frac{1}{x_6} - \frac{x_2}{x_3} - \frac{x_4 x_6}{x_2} - \frac{x_3}{x_5} - \frac{x_5}{x_4}\Big)$$

$$+(1-\psi)\beta_2 C_h^* V^*\Big(4 - \frac{1}{x_6} - \frac{x_2}{x_3} - \frac{x_5 x_6}{x_2} - \frac{x_3}{x_5}\Big). \tag{3.5.26}$$

Case 3: $\mu S < \alpha V$, $\dfrac{\beta_3}{\mu}\big(S^* + (1-\psi)V^*\big)\pi_2 C_h^* \geq (1-\psi)\beta_3 T^* V^*$

For case 3, using equations (3.5.23) and (3.5.24), it is assumed that $\alpha V^* \leq \beta_3\big(S^* + (1-\psi)V^*\big)\dfrac{\pi_1\kappa I^*}{\mu}$ and choose $b_1 = \mu S^*$, $b_3 = 0$, $b_4 = \beta_1 I^* S^*$, $b_5 = \beta_3\big(S^* + (1-\psi)V^*\big)\dfrac{\pi_1\kappa I^*}{\mu} - \alpha V^*$, $b_6 = \beta_2 C_h^* S^*$, $b_7 = \dfrac{\beta_3}{\mu}\big(S^* + (1-\psi)V^*\big)\pi_2 C_h^* - (1-\psi)\beta_3 T^* V^*$, $b_9 = 0$, $b_{10} = (1-\psi)\beta_3 T^* V^*$, $b_{12} = 0$, $b_{13} = 0$ and $b_{14} = \alpha V^*$.

Using the above values, and the values of b_2, b_8 and b_{11} from (3.5.21), the function $G(x_1, x_2, x_3, x_4, x_5, x_6)$ becomes

$G(x_1, x_2, x_3, x_4, x_5, x_6)=$

$$\mu S^*\Big(2-x_1-\frac{1}{x_1}\Big)+\mu V^*\Big(2-x_6-\frac{1}{x_6}\Big)+\beta_1 I^* S^*\Big(3-\frac{1}{x_1}-\frac{x_2}{x_3}-\frac{x_1x_3}{x_2}\Big)$$

$$+\Big(\beta_3\big(S^*+(1-\psi)V^*\big)\frac{\pi_1\kappa I^*}{\mu}-\alpha V^*\Big)\Big(4-\frac{1}{x_1}-\frac{x_2}{x_3}-\frac{x_1x_4}{x_2}-\frac{x_3}{x_4}\Big)+$$

$$\beta_2 C_h^* S^*\Big(4-\frac{1}{x_1}-\frac{x_2}{x_3}-\frac{x_1x_5}{x_2}-\frac{x_3}{x_5}\Big)+\frac{\beta_3}{\mu}\big(S^*+(1-\psi)V^*\big)\pi_2 C_h^*-(1-\psi)\beta_3 T^*V^*$$

$$\Big(5-\frac{1}{x_1}-\frac{x_2}{x_3}-\frac{x_1x_4}{x_2}-\frac{x_5}{x_4}-\frac{x_3}{x_5}\Big)+(1-\psi)\beta_1 I^*V^*\Big(3-\frac{1}{x_6}-\frac{x_2}{x_3}-\frac{x_3x_6}{x_2}\Big)$$

$$+(1-\psi)\beta_3 T^*V^*\Big(5-\frac{1}{x_6}-\frac{x_2}{x_3}-\frac{x_4x_6}{x_2}-\frac{x_3}{x_5}-\frac{x_5}{x_4}\Big)+(1-\psi)\beta_2 C_h^*V^*\Big(4-\frac{1}{x_6}-\frac{x_2}{x_3}$$

$$-\frac{x_5x_6}{x_2}-\frac{x_3}{x_5}\Big)+\alpha V^*\Big(5-\frac{1}{x_6}-\frac{x_2}{x_3}-\frac{x_1x_4}{x_2}-\frac{x_3}{x_4}-\frac{x_1x_4}{x_2}-\frac{x_6}{x_1}\Big). \tag{3.5.27}$$

Since, the arithmetic mean is greater than or equal to the geometric mean, $G(x_1, x_2, x_3, x_4, x_5, x_6) \leq 0$ in each of the above three cases. The equality holds only when $x_1 = 1, x_6 = 1$, and $x_2 = x_3 = x_4 = x_5$, i.e., $\{(x_1, x_2, x_3, x_4, x_5, x_6) \in \Omega : G(x_1, x_2, x_3, x_4, x_5, x_6) = 0\} = \{(x_1, x_2, x_3, x_4, x_5, x_6) : x_1 = x_6 = 1, x_2 = x_3 = x_4 = x_5\}$. This corresponds to the set $\Delta = \{(S, E, I, T, C_h, V) : S = S^*, V = V^*, E/E^* = I/I^* = T/T^* = C_h/C_h^*\} \subset \Omega$. Hence, the maximum invariant set of (3.1.2) on the set Δ is the singleton $\{P^*\}$. Therefore, by LaSalle's Invariance principle, the endemic equilibrium P^* is globally stable in Ω when $\rho = 0$ and $\sigma = 0$.

Hence, the following theorem is established:

Theorem 3.5.1. *The endemic equilibrium, $P^*(S^*, E^*, I^*, T^*, C_h^*, V^*)$, of the system (3.1.2), with $\rho = 0$ and $\sigma = 0$, is globally asymptotically stable in Ω.*

Chapter 4

Numerical Results

In this section, numerical proofs, for all the results that are obtained in the preceding sections, are given. All numerical simulations were carried out in MATLAB. These were performed using the MATLAB ODE solver, ode45. It is first shown that when $\bar{R}_0 < 1$, the DFE is globally asymptotically stable, and hence, the HCV infection is gradually wiped out from the population. When the endemic equilibrium is globally asymptotically stable, the HCV infection persists in the population.

Figs. 4.1 to 4.6 are numerical simulations of system (3.3.6) when $\bar{R}_0 < 1$. Parameter values are described in Table 4.1, where $\psi = 1$ for perfect vaccine, $\beta_1 = 0.0009$, $\beta_2 = 0.0006$, $\beta_3 = 0.0001$ and $\bar{R}_0 = 0.654$. Since, HCV is not in the breakout epidemic phase in the world, the simulations were run until a steady state (t=100 years) was reached. It is assumed that the acute phase is more infectious than the chronic stage which is in turn more infectious than the treatment phase. So $\beta_1 > \beta_2 > \beta_3$. These simulations shows that the disease is eliminated when P_0 is globally stable.

Figs. 4.7 to 4.12 are numerical simulations of system (3.5.18) when $P^*(S^*, E^*, I^*, T^*, C_h^*, V^*)$ is globally asymptotically stable. The simulations were run until a steady state (t=140 years) was reached. Parameter values used are given in Table 4.1, with $\psi = 0.6$, $\rho = 0$, $\sigma = 0$, $\beta_1 = 0.0009$, $\beta_2 = 0.0006$, and $\beta_3 = 0.0001$. These simulations shows that the disease persists when P^* is globally stable.

Table 4.1: *Values of parameters used in the numerical simulation.*

Parameter	Value (range)	Units	Source
Λ	85	per year	[26, 27]
μ	0.085	per year	[26, 27]
β_i	(0,1)	per year	[26, 27]
π_1	0.26	per year	[26, 27]
ρ	1.992	per year	[27]
ψ	(0,1]	per year	Variable
α	0.006	per year	Assumed
b	0.4	per year	Assumed
κ	2.085	per year	Assumed
ϵ	0.269	per year	Assumed
π_2	0.25	per year	Assumed
σ	0.004	per year	Assumed

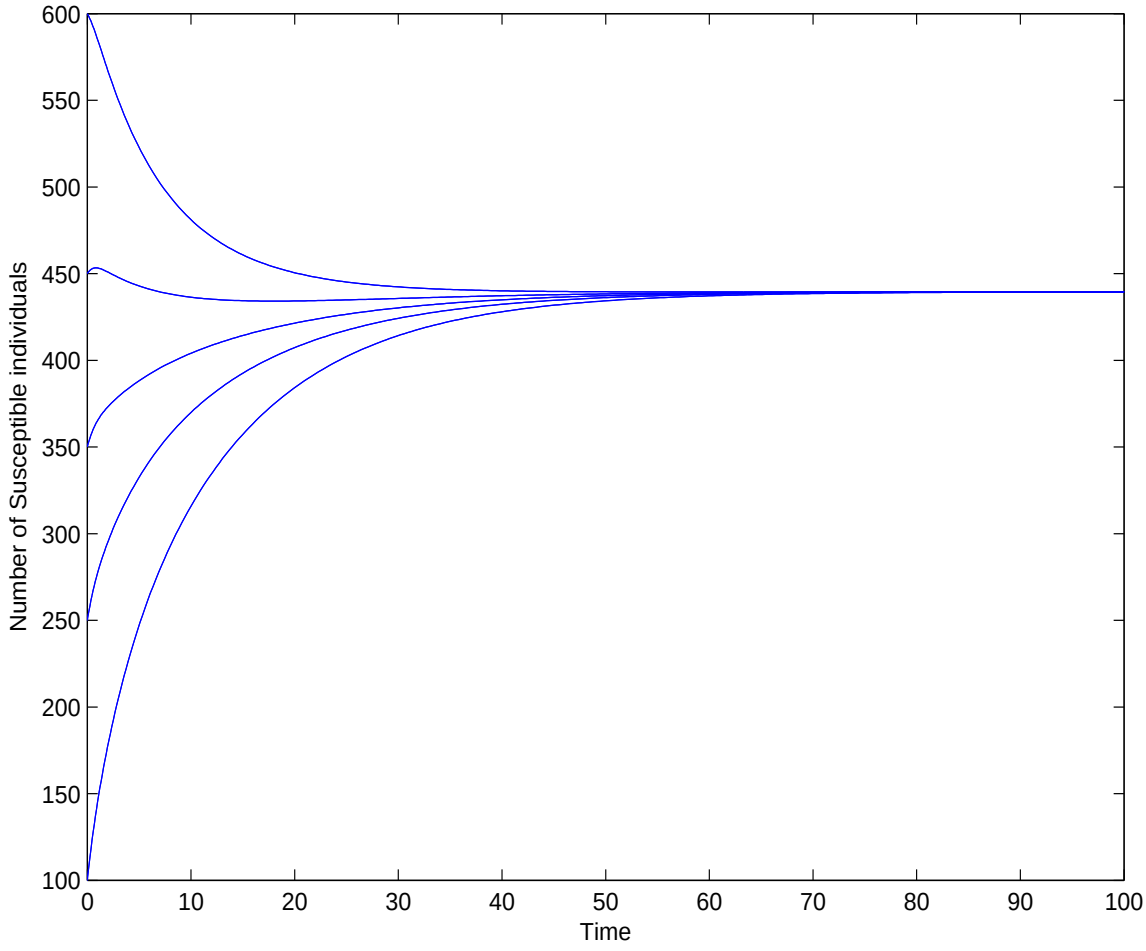

Figure 4.1: *Simulation of system (3.3.6). This figure shows the total population of susceptible individuals as a function of time (years) when* P_0 *is globally stable.*

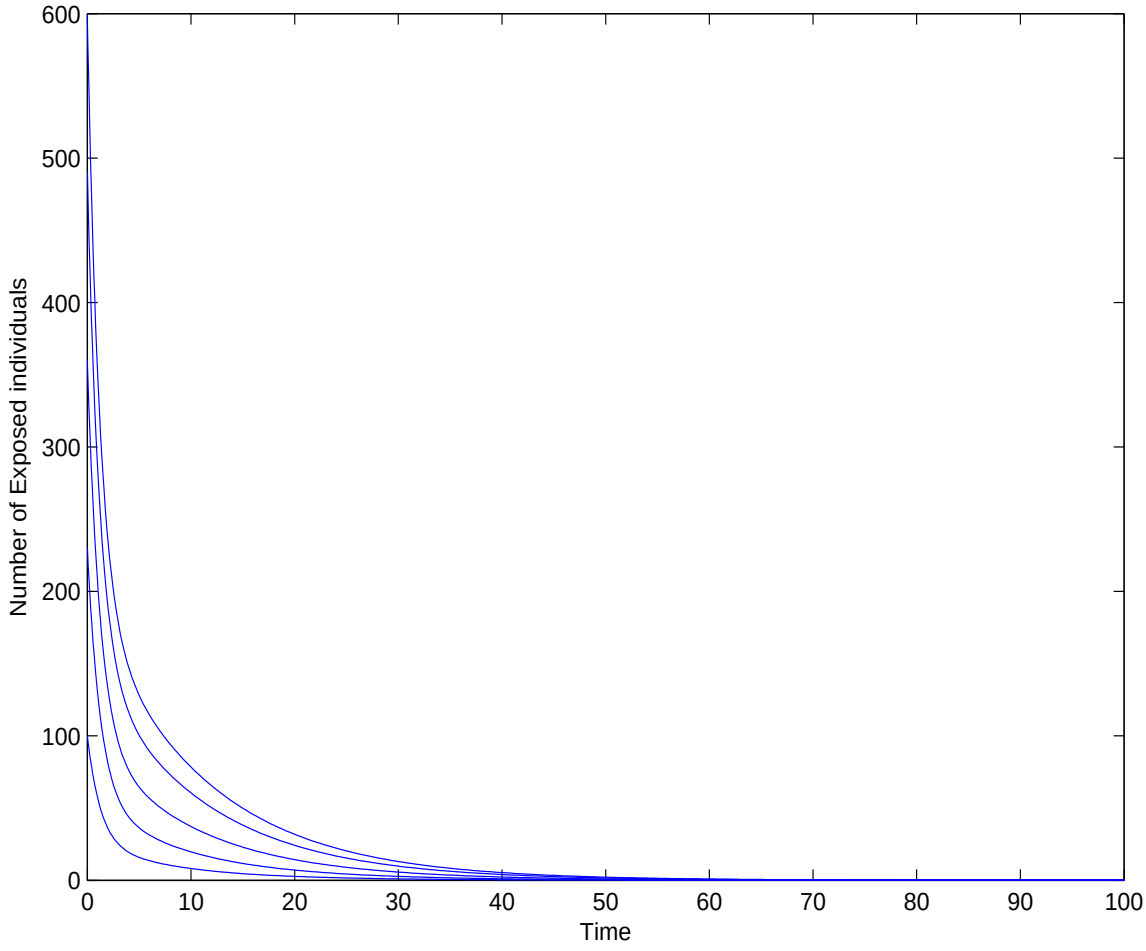

Figure 4.2: *Simulation of system (3.3.6). This figure shows the total population of exposed individuals as a function of time (years) when P_0 is globally stable.*

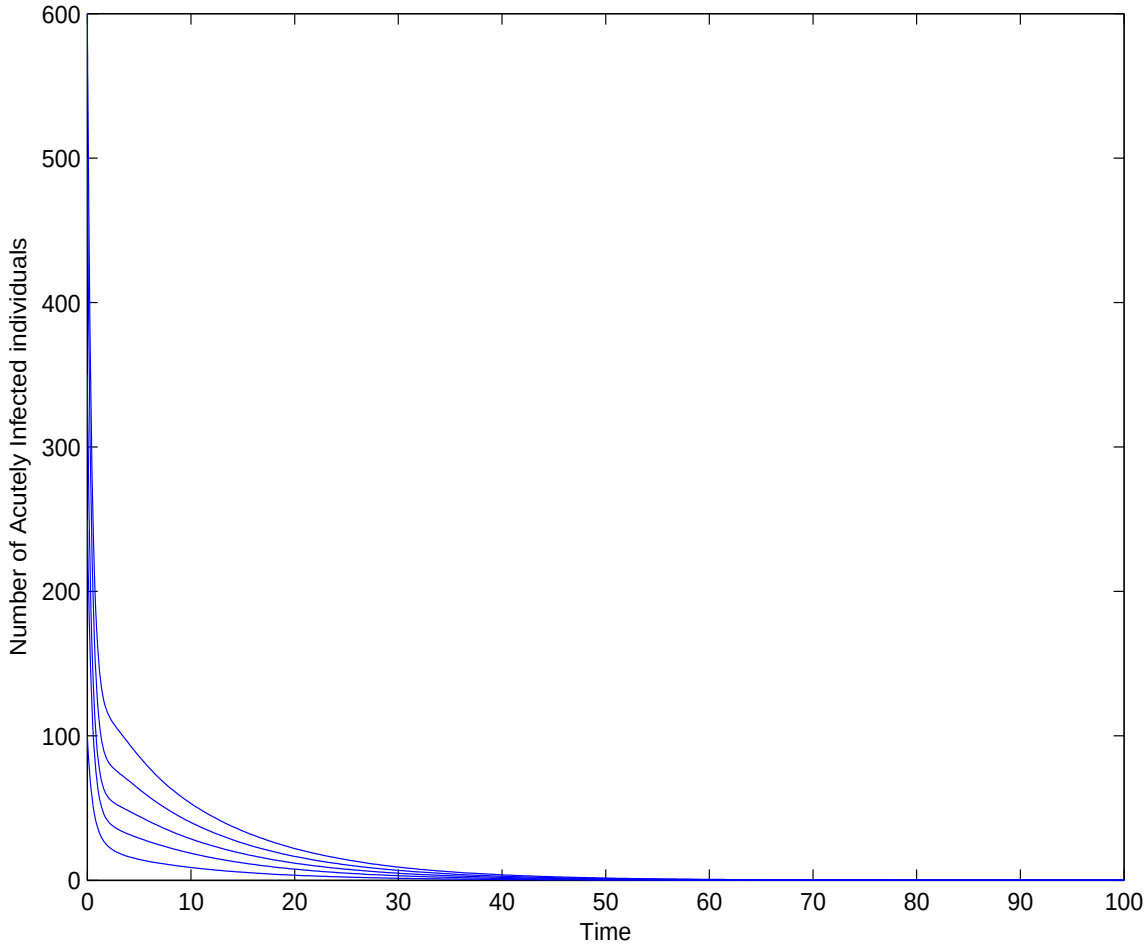

Figure 4.3: *Simulation of system (3.3.6). This figure shows the total population of acutely infected individuals as a function of time (years) when P_0 is globally stable.*

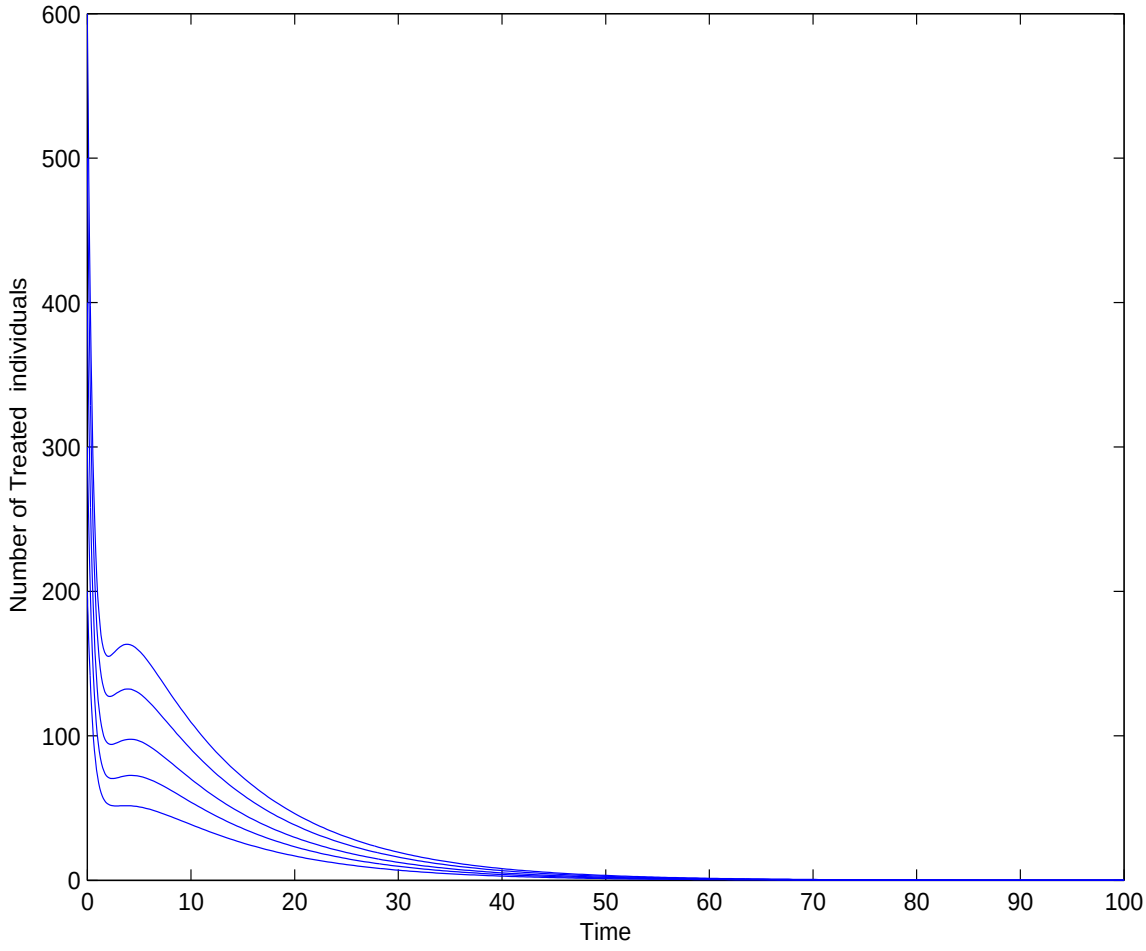

Figure 4.4: *Simulation of system (3.3.6). This figure shows the total population of individuals undergoing treatment as a function of time (years) when P_0 is globally stable.*

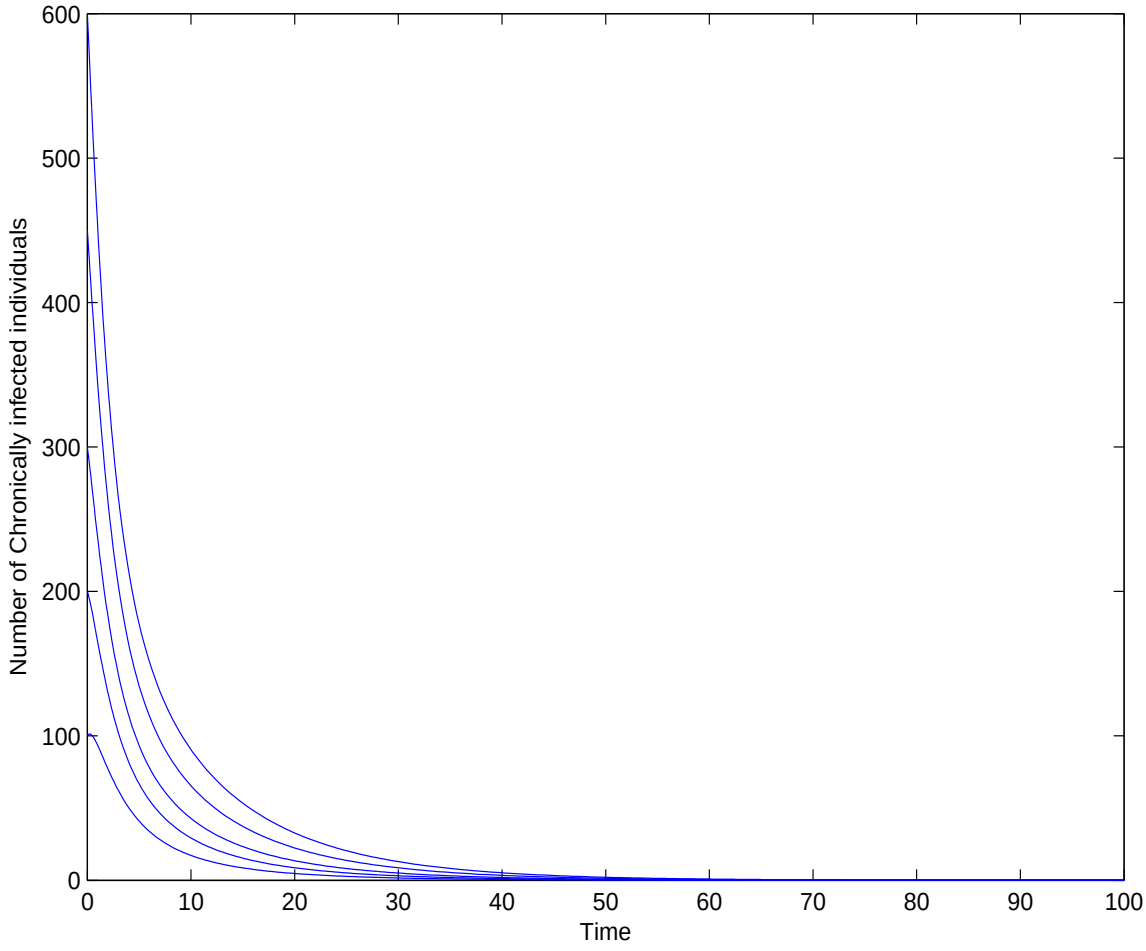

Figure 4.5: *Simulation of system (3.3.6). This figure shows the total population of chronically infected individuals as a function of time (years) P_0 is globally stable.*

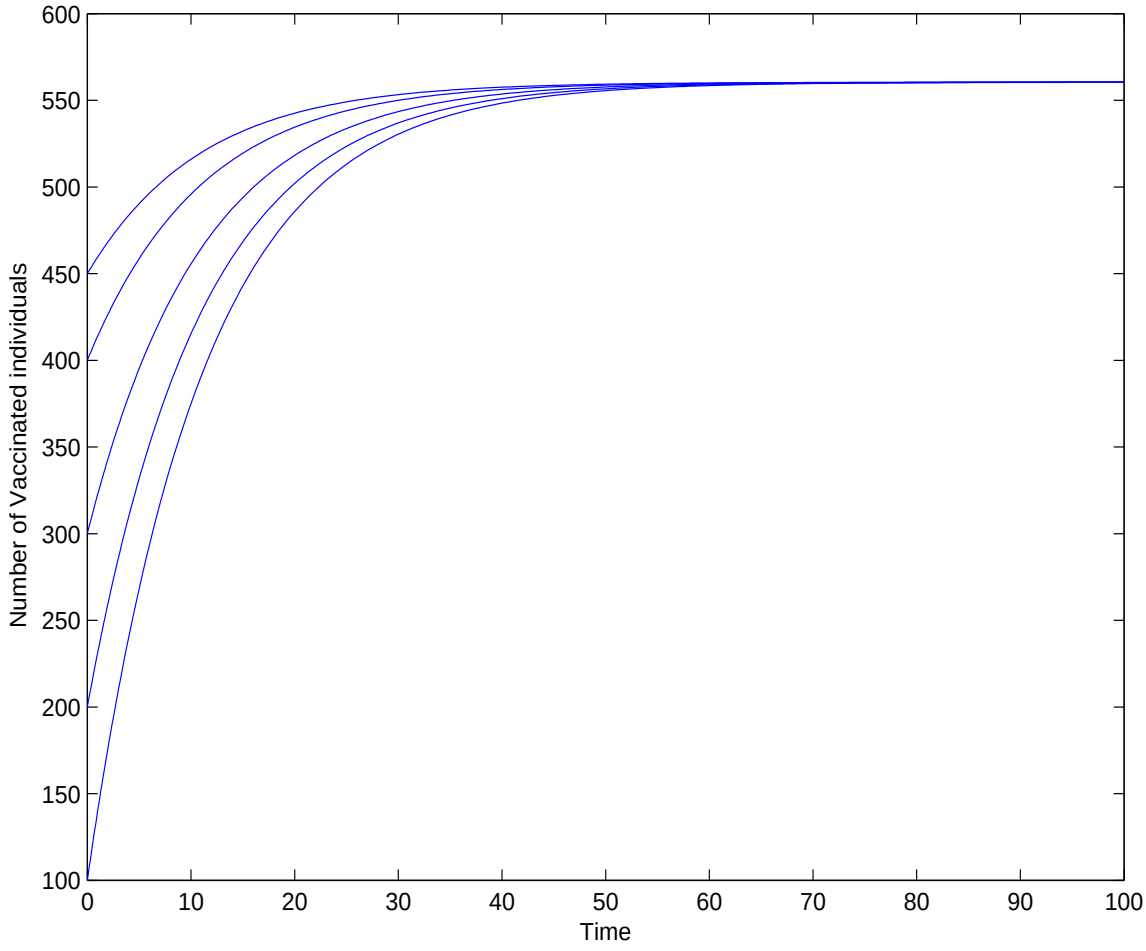

Figure 4.6: *Simulation of system (3.3.6). This figure shows the total population of vaccinated individuals as a function of time (years) when P_0 is globally stable.*

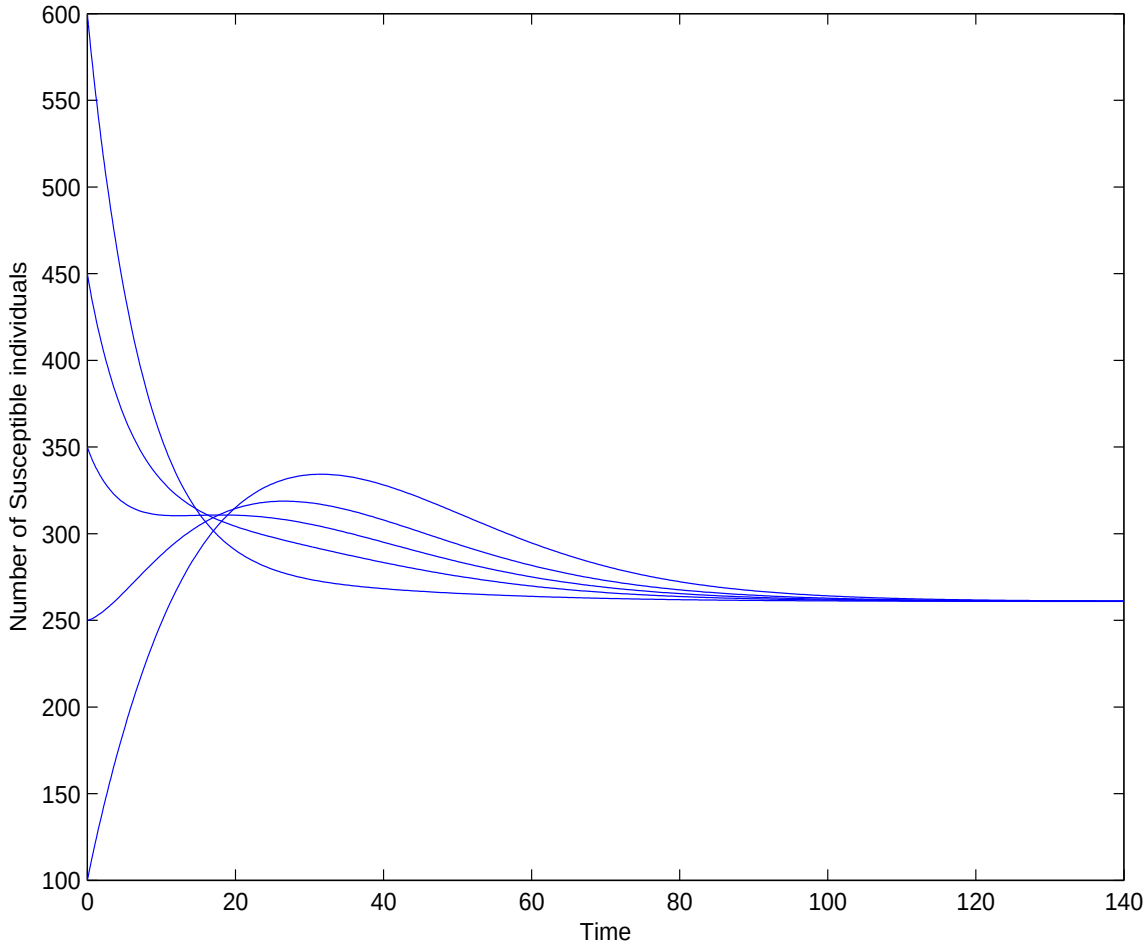

Figure 4.7: *Simulation of system (3.5.18). This figure shows the total population of susceptible individuals as a function of time (years) when P^* is globally stable.*

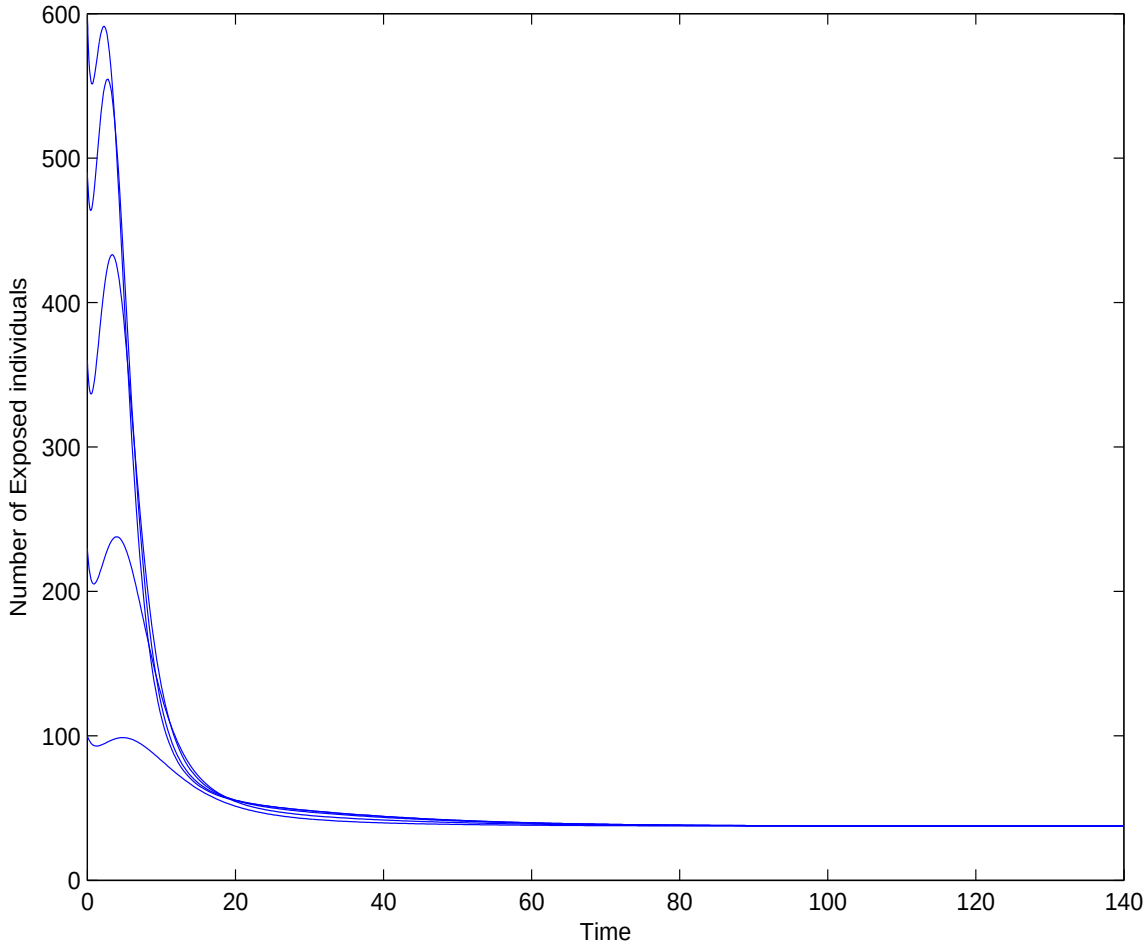

Figure 4.8: *Simulation of system (3.5.18). This figure shows the total population of exposed individuals as a function of time (years) when P^* is globally stable.*

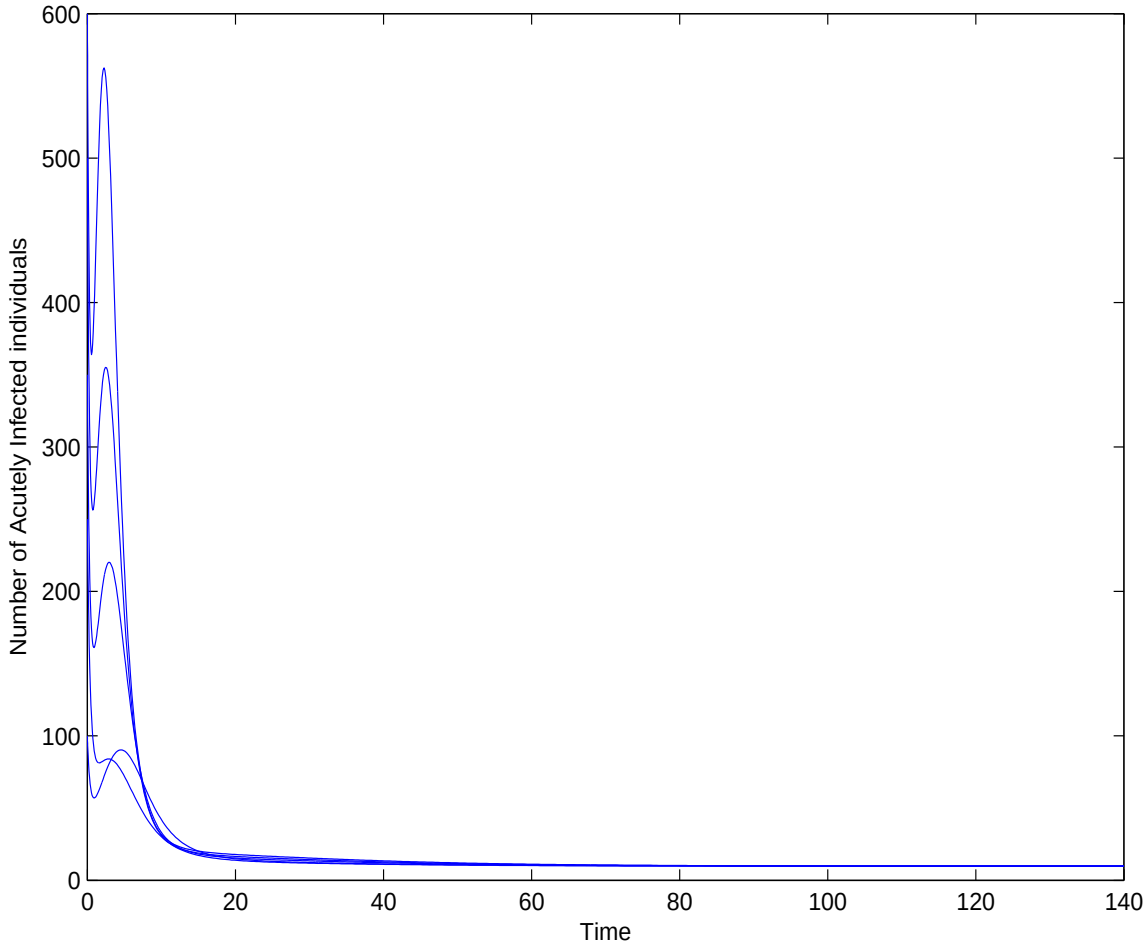

Figure 4.9: *Simulation of system (3.5.18). This figure shows the total population of acutely infected individuals as a function of time (years) when P^* is globally stable.*

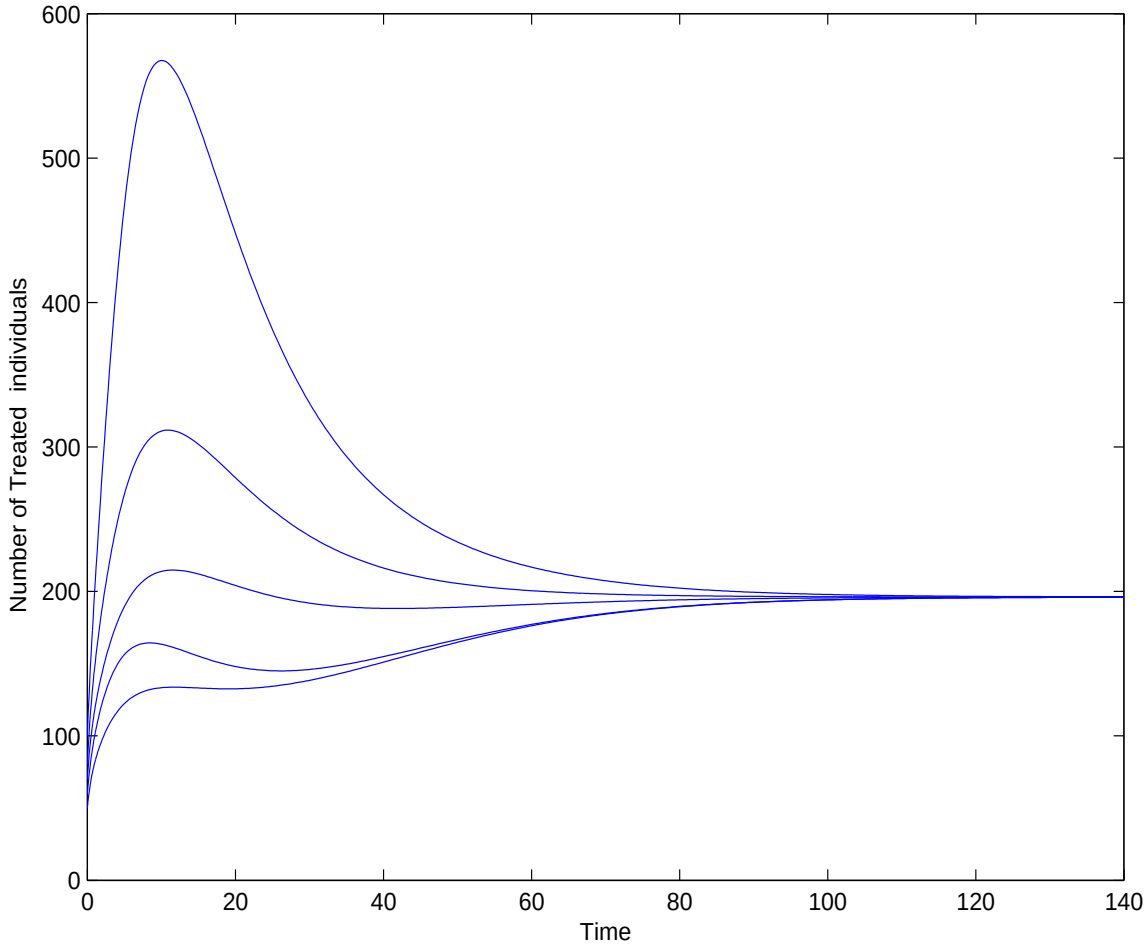

Figure 4.10: *Simulation of system (3.5.18). This figure shows the total population of individuals undergoing treatment as a function of time (years) when P^* is globally stable.*

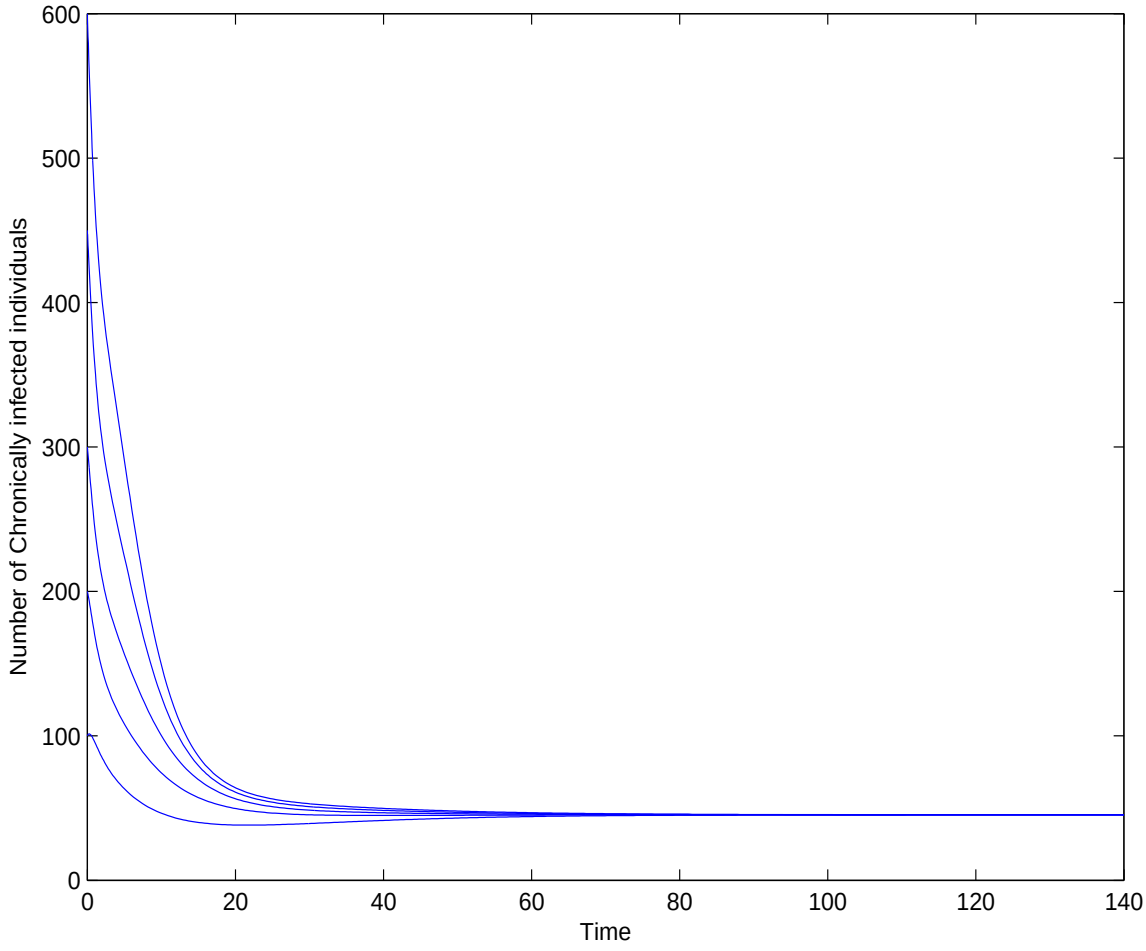

Figure 4.11: *Simulation of system (3.5.18). This figure shows the total population of chronically infected individuals as a function of time (years) when P^* is globally stable.*

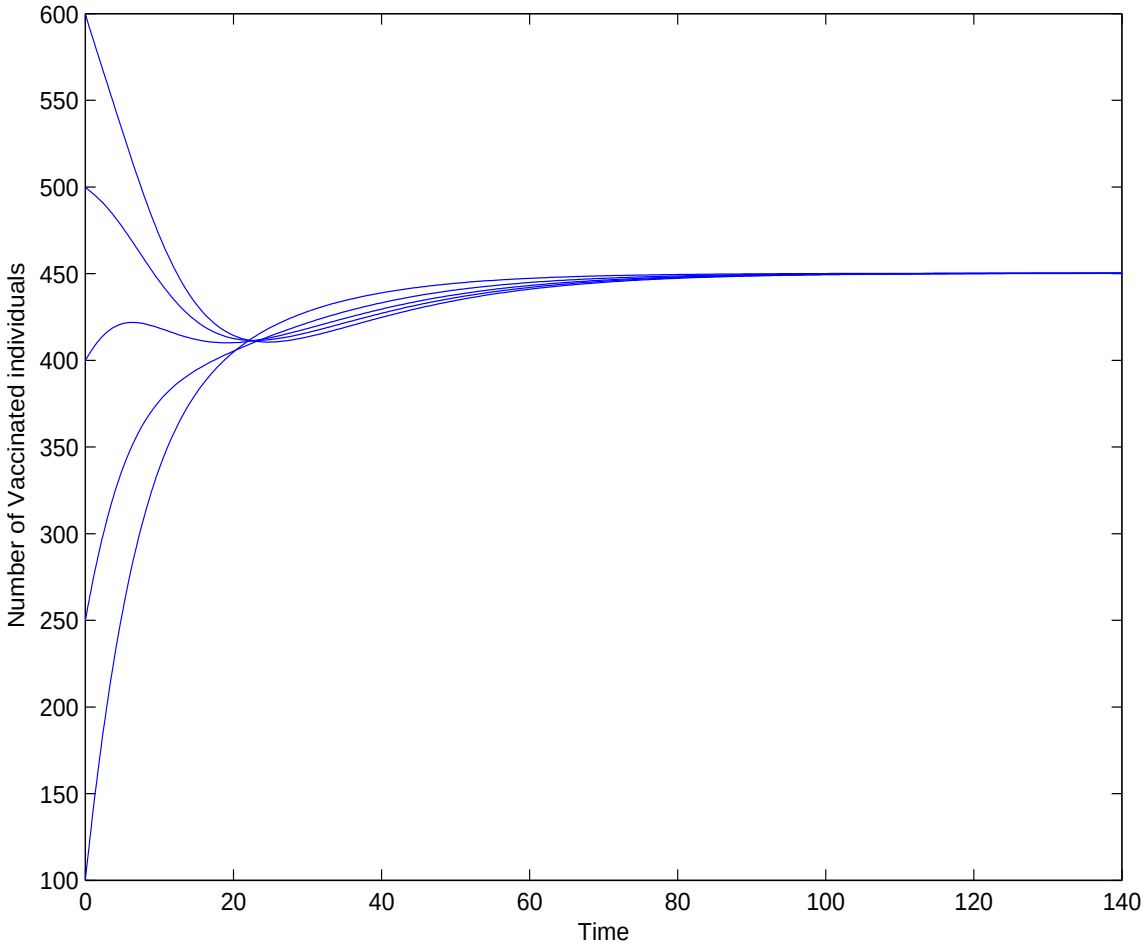

Figure 4.12: *Simulation of system (3.5.18). This figure shows the total population of vaccinated individuals as a function of time (years) when P^* is globally stable.*

Conclusion

This thesis presents a deterministic model, based on the transmission dynamics of HCV infection. The formulated model, realistically, allows HCV transmission by acutely and chronically infected individuals. Most importantly, the model includes a compartment of vaccinated individuals, and considers the effects of a waning vaccine on the transfer of individuals from one compartment to another. The model was rigorously analyzed to gain insights into its qualitative dynamics.

First, the basic reproduction number, R_0, is calculated by using the next generation operator method. The disease free equilibrium and the endemic equilibria are then found, and different cases regarding the existence of one or more endemic equilibrium solutions are discussed. It is shown that when two endemic equilibria exist, backward bifurcation may occur, which jeopardizes the possibility of total disease eradication from the population under consideration. It is established that the use of a perfect vaccine (that is, a vaccine which does not wane over time) eliminates backward bifurcation completely when the associated basic reproduction number is less than one, and hence the disease free equilibrium becomes globally asymptotically stable. This is proved by using the Liapunov stability theory. A unique endemic equilibrium is shown to exist, which is proved to be globally asymptotically stable under certain parameter restrictions. Finally, the global stability of disease free and endemic equilibrium is proved numerically.

Hence, the following results are established:

1. The model has a locally stable disease free equilibrium whenever the associated reproduction number is less than unity.

2. The model exhibits the phenomenon of backward bifurcation, suggesting a case where a stable disease-free equilibrium co-exists with a stable endemic equilibrium, whenever the basic reproduction number is less than unity.

3. Using an imperfect Hepatitis C vaccine would have no positive epidemiological impact to reduce the disease burden in a community.

4. Using a perfect vaccine can result in effective elimination of HCV infection in a community. That is, the efficacy of the vaccine should be 100% for complete removal of the disease.

Bibliography

[1] S. Ma, Y. Xia, *Mathematical Understanding of Infectious Disease Dynamics*, World Scientific Publishing Company, Singapore, 2008.

[2] P. van den Driessche, J. Watmough, *Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission*, Math. Biosci. 180 (2002) 29-48.

[3] F. C. Mann, *The role of the liver as the commissariat of the body*, Am. J. Dig. Dis. 4 (1937) 355-364.

[4] V. C. Vaughan, R. J. Mackay, W. E. Nelson, *Textbook of Pediatrics*, W.B. Saunders, Philadelphia, 1975.

[5] S. L. Robbins, *Pathologic Basis of Disease*, W. B. Saunders, Philadelphia, 1994.

[6] M. Umar, B. Khaar, *Jaundice and its types; Hepatitis A, B, and C; symptoms, precautions and cure*, brochure, Holy Family Hospital, Rawalpindi, 2012.

[7] M. Umar, B. Khaar, A. Khan, A. Mohsin, H. Shah, *Diagnosis, Management, and Prevention of Hepatitis C in Pakistan*, Pak. J. Gastroenterol. 23 (2009) 7-40.

[8] M. Umar, B. Khaar, M. Khurram, *Anti-HCV-antibodies positivety of various sections of Pakistani population*, J. Col. Phys. Surg. Pak. 19 (2009) 737-741.

[9] *What is viral hepatitis*, http://www.worldhepatitisalliance.org/AboutViralHepatitis.aspx

[10] *World Health Organization Hepatitis C Factsheet no. 164*, http://www.who.int/mediacentre/factsheets/fs164/en/ (Accessed December 2012).

[11] J-Y Chen, F. Li, *Development of hepatitis C virus vaccine using hepatitis B core antigen as immuno-carrier*, World. J. Gastroenterol. 12 (2006) 7774-7778.

[12] C. G. A. Thomas, *Medical Microbiology*, Bailliere Tindall, London, 1986.

[13] J. D. Murray, *Mathematical Biology: An Introduction*, Third edition, Springer, 2002.

[14] *World Health Organization, Global Alert and Response (GAR)*, http://www.who.int/csr/don/archive/year/2012/en/index.html (Accessed January 2013)

[15] M. Y. Li, *Mathematical Epidemiology: Models and Analysis*, unpublished lecture notes, University of Alberta, Edmonton, Alberta.

[16] L. J. S. Allen, *An Introduction to Mathematical Biology*, Pearson Education Inc., 2007.

[17] J. P. LaSalle, *The Stability of Dynamical Systems*, Regional Conference Series in Applied Mathematics, SIAM Philadelphia, PA, 1976.

[18] H. Dahari, A. Feliu, M. Garcia-Retortillo, X. Forns, A. U. Neumann, *Second hepatitis C replication compartment indicated by viral dynamics during liver transplantation*, J. Hepatol. 42 (2005) 491-498.

[19] R. Qesmi, J. Wu, J. M. Heffernan, *Influence of backward bifurcation in a model of Hepatitis B and C viruses*, Math. Biosci. 224 (2010) 118-125.

[20] S. Zhang, Y. Zhou, *The analysis and application of an HBV model*, Appl. Math. Model. 36 (2012) 1302-1312.

[21] M. A. Safi, A. B. Gumel, *Mathematical analysis of a disease transmission model with quarantine, isolation and an imperfect vaccine*, Comp. Math. Appl. 61 (2011) 3044-3070.

[22] S. M. Garba, A. B. Gumel, M. R. Abu Bakar, *Backward bifurcations in dengue transmission dynamics*, Math. Biosci. 215 (2008) 11-25.

[23] C. C. Chavez, B. Song, *Dynamical model of tuberclosis and their applications*, Math. Biosci. Eng. 1 (2004) 361-404.

[24] J. Li, Y. Yang, Y. Zhou, *Global stability of an epidemic model with latent stage and vaccination*, Non. Anal. RWA. 12 (2011) 2163-2173.

[25] J. Li, Y. Xiao, F. Zhang, Y. Yang, *An algebraic approach to proving the global stability of a class of epidemic models*, Non. Anal. RWA. 13 (2012) 2006-2016.

[26] N. K. Martin, P. Vickerman, G. R. Foster, S. J. Hutchinson, D. J. Goldberg, M. Hickman, *Can antiviral therapy for hepatitis C reduce the prevalence of HCV among injecting drug user populations? A modeling analysis of its prevention utility*, J. Hepatol. 54 (2011) 1137-1144

[27] N. K. Martin, P. Vickerman, M. Hickman, *Mathematical modelling of hepatitis C treatment for injecting drug users*, J. Theor. Biol. 274 (2011) 58-66