Stability Analysis and Simulation of Deterministic Models in Epidemiology and Immunology

THESIS

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by

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Under the Supervision of
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&

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To my parents*, for making it possible to commence this journey*

To my husband*, for making it possible to complete it*

BIRLA INSTITUTE OF TECHNOLOGY AND SCIENCE, PILANI

CERTIFICATE

This is to certify that the thesis entitled "**Stability Analysis and Simulation of Deterministic Models in Epidemiology and Immunology**" and submitted by **Preeti Dubey, ID No. 2011PHXF033P** for award of Ph.D. Degree of the institute embodies original work done by her under our supervision.

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The proactive approach to a mistake is to acknowledge it instantly, correct and learn from it.

Stephen Covey

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Abstract

Communicable diseases have been prevalent and affecting the health of populations since very early times and remain to be a matter of global concerns. Communicable diseases and associated outbreaks deeply affect the mortality and morbidity rate and are responsible for billions of deaths across the globe every years. The most common diseases caused by infectious agents are diarrhea, AIDS, TB, Influenza and malaria. These diseases have very high mortality rate and propagate due to poor sanitation, lack of awareness, dearth of treatment and paucity of medical resources. These aspects are a matter of serious concern among the health care providers and public health professionals. It is important to take the issue forward and take the initiative to repress the pandemic by using multiple approaches. This has led to development of numerous mathematical epidemic models to understand the dynamics of viral infection at population level as well as at cellular level.

This thesis aims at understanding the dynamics of transmission of communicable diseases at two different levels (i) population level i.e. the transmission of infection among individuals, and (ii) the transmission of infection among cells within an individual at cellular level. The former is associated with epidemiology whereas the later includes the study of virus dynamics models. During the onset and spread of an epidemic, the rate of transmission of infection among individuals plays a significant role. In an epidemic model the rate of transmission of infection is defined as the number of individuals getting infected per unit time and is known as the *incidence rate*. In classical epidemic models, the incidence rate has been taken as law of mass action i.e. bilinear incidence rate which is directly proportional to product of the number of susceptible and the number of infected individuals. In case of an epidemic with large number of infection, use of bilinear incidence rate is not suitable to address the same. The nonlinear incidence rate gives a better insight of infection in case of large number of infectives due to its saturated nature.

Epidemic model analysis is a primary tool which helps in eradicating the pervasive infection among the populations. Many researchers incorporated treatment rate either as a constant or as a linear function. In our thesis, it has been found that a saturated treatment gives a better alternative due to its saturated behavior. It is a well known fact that infection in the community can not be controlled com-

pletely by treatments only due to limited availability of medical resources. The dissemination of awareness about prevention, spread and treatment modalities of infectious diseases through public/social media and health care workers is also an important tool to control and restrain further infection.

Further, in virus dynamics models, the pathogen-immune interaction has been modeled, analyzed and interpreted to understand the dynamics of infection at cellular level. Immune response plays a key role in prevention and reduction of infection. This study is further supplemented by the use of suitable drug therapy to eliminate the infection from the body.

Acknowledging the above assertions, we have proposed and analyzed some epidemic models incorporating all the aforesaid epidemic tools and interventions to control the spread of infection. This thesis is comprised of deterministic epidemic models which are analyzed at population level (population dynamics) as well as cellular level (virus dynamics). Our goal here is to study the analytical behavior (stability analysis) of these models and provide an intricate details of infections with the help of numerical simulations.

In this thesis, we investigated the dynamics of some epidemiological models both at population level and cellular level. This thesis is organized as follows:

Chapter 1 of the thesis provides a brief introduction about the problem. It addresses three main important questions (i) Why, (ii) What and finally (iii) How of the thesis. Introduction comprises of background of the problem, objective of the thesis, a brief history of mathematical models and the terminology used throughout thesis followed by mathematical tools to analyze analytical behavior of mathematical models. We have also provided some biological definitions and basic terms used in epidemiology, which are required for the forthcoming chapters.

Chapter 2 of the thesis is devoted to understand the dynamics of susceptible-infected-recovered (SIR) epidemic model incorporating nonlinear transmission rate and nonlinear treatment rate. The global dynamics of an SIR model is investigated in which the incidence rate is being considered as Beddington-DeAngelis type and the treatment rate as Holling type II (saturated). Analytical study of this model shows that the model has two equilibrium points (disease-free equilibrium (DFE) and endemic equilibrium (EE)). The disease-free equilibrium (DFE) is locally asymptotically stable when the reproduction number (R_0) is less than unity. The uniform persistence of the model has been shown under certain conditions. This implies that infection will persist in an endemic zone and will not lead to

its eradication if it is present initially. Some conditions on the model parameters are obtained to show the existence as well as nonexistence of limit cycle. Some sufficient conditions for global stability of the endemic equilibrium using Lyapunov function are obtained. The existence of Hopf bifurcation of model is investigated by using Andronov-Hopf bifurcation theorem. Furthermore, Numerical simulations are performed to exemplify the analytical studies.

Chapter 3 is a modified version of Chapter 2. We propose a mathematical model with different nonlinear incidence and treatment rates to study the dynamics of an SIR model. The nonlinear incidence rate is assumed as Crowley-Martin type and nonlinear treatment rate as Holling type III (saturated treatment function). The global stability analysis of disease-free equilibrium point and endemic equilibrium point has been investigated using Lasalle's invariance principle and Lyapunov function. A threshold value has been found to ensure either the elimination or persistence of infection. Uniform permanence of the model has also been examined. The nonexistence of periodic solutions has been shown using Dulac's criterion. This ensures non-reoccurrence of infection in future under the mentioned condition. Numerical simulations are performed to illustrate analytical findings. Through simulations, it is observed that the number of infected individuals can be decreased faster in case of Holling type III treatment rate in comparison to that of Holling type II treatment rate (from Chapter 2). When there is low availability of treatment, infection is high. When the ample quantity of treatment is available in the community the infection almost dies out. Infection increases with the increase in limitation to the availability of treatment.

In Chapter 4, we considered an SIR epidemic model involving the behavioral changes among the population. The impact of awareness programs as well as treatment on an SIR model has been investigated. We assume that the whole population is divided into four compartments, named as susceptible (S), infected (I), aware susceptible (S_a) and recovered (R). Analytical findings and numerical simulations of the model show that if the exposure to the awareness program is high and adequate treatment is available, then the infection can be eradicated from the population. Analysis of the model also depicts that if treatment is not available, then infection is high even if enough awareness is present. But in the absence of awareness an infection can not be eliminated inspite of adequate treatment. Effective treatment can led to a diminished level of infection. Further, numerical simulations are carried out to illustrate the analytical results.

Chapter 5 is devoted to the study of a virus dynamics model at cellular level. Virus dynamics models are an important source of information for research in emerging diseases like SARS, Ebola, Influenza, HIV/AIDS, hepatitis B & C etc. In this chapter, we studied the role of immune response and therapeutic drug to understand the dynamics of uninfected cells, infected cells and free viruses. A threshold value of basic reproduction number of infection in the presence of immune response (R_I) is established. Further, the global stability of virus-free equilibrium and interior equilibrium is discussed analytically using LaSalle's principle and Lyapunov's Direct method. The global stability of virus-free equilibrium ensures the clearance of virus from the body which is independent of initial status of subpopulations. Central manifold theory is used to study the dynamics of equilibrium points when the basic reproductive number in the presence of immune response is one i.e. $R_I = 1$. It is observed that the virus-free equilibrium loses its stability from the stable state to unstable state.

A special case, when the immune response is not present, has also been studied. We found that basic reproductive number in the absence of immune response R_0 is greater than basic reproductive number in the presence of immune response R_I i.e. $R_0 > R_I$. This implies that in the presence of immune response the number of secondary infections will be less. It suggests that infection may be eradicated if $R_I < 1$. It is observed that the number of secondary infections decreases with the enhancement of immune response and drug efficacy. This shows that R_I may be made less than one by increasing drug efficacy and improving the immune conditions. Thus, increase in treatment is effective in controlling the number of infected cells and free viruses. In addition, action of immune response also reduces the virus load. Numerical simulations are performed to illustrate the analytical results using MatLab and Mathematica.

In Chapter 6, we studied pathogen-immune interaction considering four different models incorporating biological features (absorption of pathogens and therapeutic drug) step by step. Many common and emergent infectious diseases like Influenza, SARS, Hepatitis etc. are caused by viral pathogens. These can be controlled or prevented by understanding the dynamics of pathogen-immune interaction *in vivo*. In this chapter, interaction of pathogens with uninfected and infected cells in the presence or absence of immune response are considered in four different cases. In the first case, the model considers saturated nonlinear infection rate and linear cure rate without absorption of pathogens and without immune

responses. The next model considers the effect of absorption of pathogens into uninfected cells while all other terms are same as in the first case. The third model incorporates innate immune response, humoral immune response and Cytotoxic T lymphocytes (CTL) mediated immune response with cure rate and without absorption of pathogens into uninfected cells. The last model is an extension of the third model in which the effect of absorption of pathogens into uninfected cells has been considered. Positivity and boundedness of the solutions are established to ensure the well-posedness of the problem.

It has been found that all the four models have two equilibria, namely, pathogen-free equilibrium and pathogen-present equilibrium. In each case, stability analysis of each equilibrium point is investigated. Pathogen-free equilibrium is globally asymptotically stable when basic reproduction number is less or equal to unity. This implies that control or prevention of infection is independent of initial concentrations of uninfected cells, infected cells, pathogens and immune responses in the body. The proposed models show that introduction of immune response and cure rate strongly affects the stability behavior of the system. Further, on computing basic reproduction number, it has been found to be minimum for the fourth model vis-a-vis other models. The analytical findings of each model have been exemplified by numerical simulations.

Chapter 7 deals with the dynamics of HIV infection, which is the most catastrophic one among newly emerging infections. The emphasis has been given to antiretroviral therapy and combination of such therapy during primary HIV infection. In order to get better insights of dynamics of HIV infection, a virus dynamics model incorporating combination of therapy (reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs)) has been investigated. RTIs prevent viral integration within the genome of the infected $CD4^+$ T cells. PIs defend against the virus by blocking the synthesis of new virus. This further prevents propagation of virus to other cells. Both of the drugs inhibit different steps of the viruses life cycle. They ultimately inhibit its proliferation thus drastically reduce the infection in the individual. The proliferation of uninfected $CD4^+$ T cells has been assumed to be as full logistic growth term.

The model has also considered two important component of immune response, namely the CTL and antibody. We found the critical efficacy of the combination of therapy as a threshold for the existence of virus-free equilibrium and immune-free equilibrium. In a real world scenario, $CD4^+$ T cells count is used to assess the

clinical state of an HIV patient. So we have used cell count of uninfected $CD4^+$ T cells as measure of critical value for the existence of equilibrium points. It is observed during the study of this chapter that antibody immune response helps in reducing the viral load and further clearing the infection. It is also observed that the combination of therapy reduces viral load and enhances the lifespan of HIV infected patients. Numerical simulations are performed to illustrate the analytical results.

Finally, the main findings of the thesis are summarized in concluding remarks section. The future scope of the thesis is also outlined in this section. References are provided in bibliography section.

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Chapter 1

Introduction

I simply wish that, in a matter which so closely concerns the wellbeing of the human race, no problem shall be made without all the knowledge which a little analysis and calculation provide.

Daniel Bernoulli 1760

1.1 Background of the Problem

Communicable diseases have been a cause of global concern throughout the history of mankind. Its outbreak severely affects the morbidity and the mortality rates across the globe. World Health Organization (WHO, 2008) has revealed that approximately twenty percent of global deaths happened due to infectious diseases. There are several causes of these deaths like the lack of prophylactic interventions, lack of trained medicinal personnel and hospitals, inappropriate treatment, limited resources and insufficient health awareness. Lower respiratory infections, Diarrhoeal diseases, HIV/AIDS and Tuberculosis were among the most pervasive infectious diseases which caused myriad of deaths (WHO, 2008).

Last few decades have seen an emergence of new infectious diseases such as Acquired Immunodeficiency Syndrome (AIDS), Severe Acute Respiratory Syndrome (SARS), Ebola, etc. Furthermore, the major outbreak of AIDS has led to the re-emergence in the incidence of infectious diseases (e.g tuberculosis and Candida Albicals infection in AIDS patients) which had been earlier brought into control by vaccination and effective medication. Most of these diseases have reoccurred due to the weakened immune response caused by the HIV virus in AIDS patient. Therefore, it has become the immediate concern of all countries to bolster the global initiative to combat HIV and other infectious diseases. It was earlier thought that most infectious diseases could be eradicated with the help of vaccines, antibiotics, medicare and proper sanitation. But infectious diseases remain a perennial problem and a major cause of concern. The sustenance is due to many causes such as resistance to antibodies, lack of hygiene, insufficient healthcare, natural calamities and continuous evolution of pathogens in a changing environment. There is a continuous competitive interaction between the immune system and the pathogen present in the environment (Dubey and Mittal, 2013).

WHO statistics on infectious diseases shows that it is essential to control the spread of infections through public health policies. It is very important to either prevent or cure them through active interventions. It is also reported by WHO that emerging infectious diseases mostly affected the developing countries zones as shown in figure 1.1.

These very important issues related to health in general and infectious diseases in particular have led to the development of mathematical modeling to make future predictions on the outbreak and further propagation of epidemics. It is well understood that the mathematical models would be helpful in making health decisions which are more cost effective and accurate in comparison to the experimental studies. It is not possible to conduct direct experiments in all situations, actually real data pertaining to epidemics are available only after the event. Furthermore conducting corresponding experiments has various practical limitations of dealing with complicated and expensive experiments which may take a very long time.

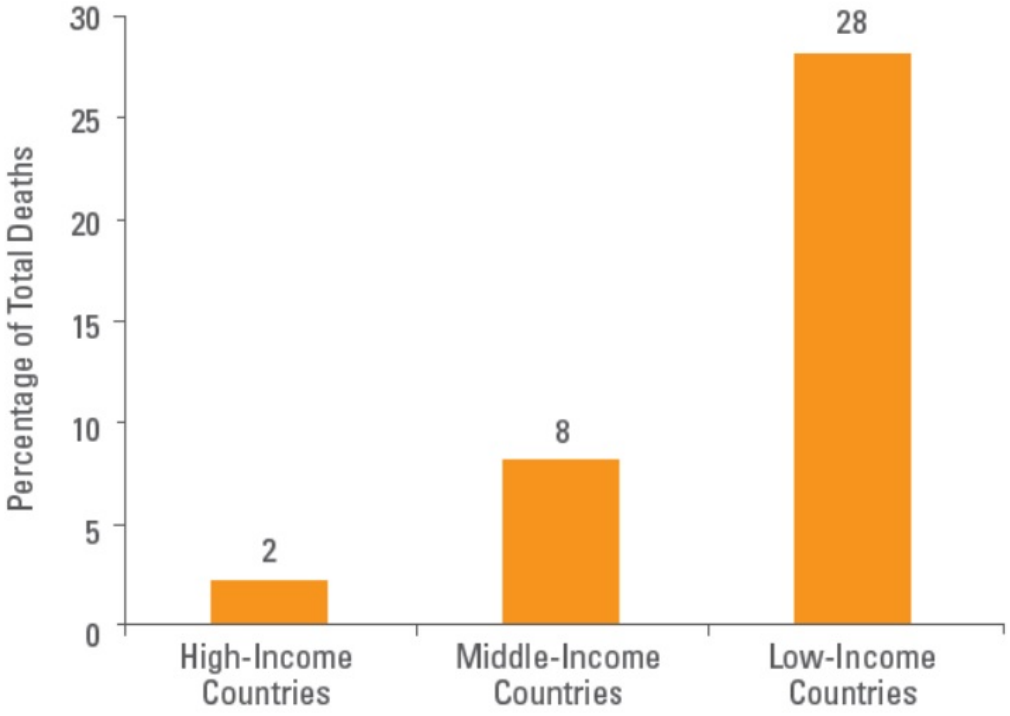

Figure 1.1: Percentage of deaths from infectious diseases among countries, (source: WHO (2008)).

Mathematical models are capable to capture both qualitative and quantitative aspects of complex systems. Mathematical models are very effective tool to understand dynamics of the transmission of infection *in vitro* and *in vivo*. Many researchers have developed mathematical models in epidemiology to facilitate the formation of public health policies (Bailey, 1975; Brauer and Castillo-Chavez, 2001; Heesterbeek, 2000; Anderson et al., 1992; Hethcote, 2000; Kermack and McKendrick, 1927; Capasso and Serio, 1978; Castillo-Chavez and Song, 2004). The basic tenet of these mathematical models was to investigate the underlying factors causing the disease, its progression and to predict the future course of action. Thus information can be used to effectively deal with diseases by using appropriate preventive and treatment measures.

1.2 Objective of the Thesis

Considering the above aspects in view, we have proposed and analyzed some epidemiological models which comprises of both population dynamics and virus dy-

namics (at a cellular level). The population dynamics models investigated in this thesis are motivated from the basic susceptible-infected-recovered (SIR) model (introduced by Kermack and McKendrick (1927)). The mathematical models studied at cellular level are motivated from the basic virus dynamics model (Nowak and Bangham, 1996). The main focus of modeling is to involve biological features like appropriate transmission, treatment, immune responses and social awareness in order to reduce the mortality and morbidity of the population. Some important objectives to develop epidemic models which are addressed in this thesis are:

- Nonlinearity of incidence and treatment rates to understand the dynamics of infection and to provide the important modalities in controlling the disease transmission.
- Stability analysis (local and global) of the epidemic models in order to determine the behavior of outbreak subjected to large perturbations.
- Role of pharmaceutical interventions (treatment) and non-pharmaceutical interventions (social/public media awareness) on an SIR model.
- Effect of therapeutic drug applied to both (infected cells and virus) in presence of immune response on a virus dynamics model.
- Effect of non-cytolytic cure and absorption of pathogens in pathogen-immune interaction models.
- Effect of RTI and PI in presence of acquired immune response to understand the dynamics of HIV infection.
- To visualize the analytical findings through computer simulations using Matlab 7.10 and Mathematica 7.

The basic definitions of epidemiology and mathematical tools required to analyze the epidemic mathematical models are discussed in the following section.

1.3 What is Epidemiology?

> *As a matter of fact, all epidemiology, concerned as it is with the variation of disease from time to time or from place to place, must be considered mathematically, however many variables as implicated, if it is to be considered scientifically at all.*
>
> Sir Ronald Ross, MD

Epidemiology is the study of occurrence, transmission and control of diseases in a population. It identifies risk factors, evaluates treatment modalities and health services, provides opportunities for prevention, treatment, planing and improving the effectiveness and efficiency of health services. The ultimate aim of any epidemiological study is to eliminate or reduce health problems thereby promoting the health and well being of the society as a whole. The scope of epidemiology is enormously vast and includes aspects such as the measurement of (i) Birth rate (natality), (ii) Death rate (mortality), (iii) Morbidity or disability, (iv) Prevalence, (v) Distribution of disease, (vi) Medical needs and health care facilities, (vii) Utilization of health services and other health related events, (viii) Role of social media in increasing public awareness, (ix) Demographical variables are all included within the bounds of epidemiology. Epidemiological studies are useful for the following reasons:

- It provides relevant information on the rise and fall of disease in a given population.
- Facilitates diagnosis of disease at a community level.
- Promotes planing and evaluation of health care facilities and programs.
- Risk assessment of individual.

- Identification of new diseases and syndromes.
- Elucidate natural course of disease.
- Helps in the search of cause and risk factors for a disease.

Epidemiology provides a framework to endure the basic tenet of addressing the determinants of infectious diseases and its distribution in specified population and helps in the control of health related problems. The important factors relevant for communicable diseases are mainly the infecting agent, host and the environment. The interaction of all these processes are important in determining the initiation and progression of a disease and can be understand from figure 1.2.

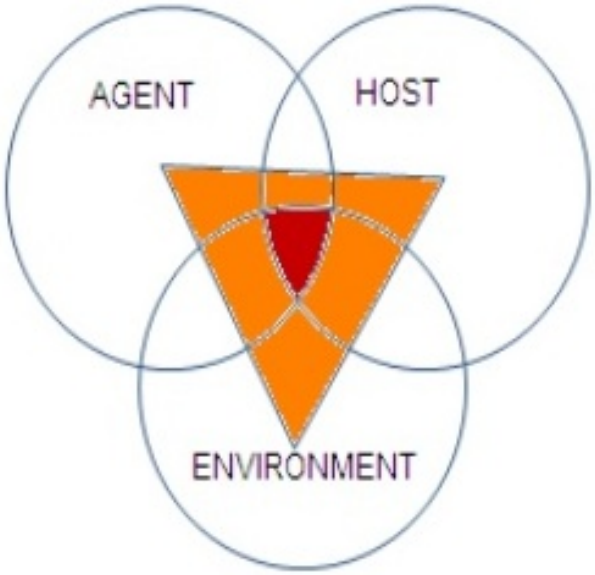

Figure 1.2: Epidemiologic concept of disease causation, (source: Park (2013)).

Epidemiology also provides tools to study and control the outbreaks of diseases such as Ebola virus, Human immunodeficiency virus (HIV) through mathematical models. Communicable diseases infect the population (man or animal) through person to person contact or through environmental factors such as dust particles, water, food, soil, and air. The infecting pathogens may be of various types like bacteria, viruses, parasites, protozoa, prions etc. The probability of infection increases

because of overcrowding, unhealthy living conditions, paucity of safe drinking water, climate change, natural calamities etc.

Communicable diseases are transmitted from the source of infection to a susceptible host. The mode of transmission may either be direct or indirect. Various forms of direct transmission include direct contact, droplet infection, contact with soil, inoculation into skin or transplacental from mother to neonate. The mode of transmission of indirect contact include the traditional 5 F's - Flies, fingers, fomites, food and fluid. The essential requirement of indirect transmission is that the infectious organism should be capable of surviving outside the human host in an external environment and retain its pathogenesis.

Populations have been suffering from infectious diseases all over the world. It is very necessary to analyze the dynamics of disease progression to control or to eradicate a disease. The dynamics of infectious diseases has been investigated using mathematical models at both population level (Beretta and Takeuchi, 1997; Shulgin et al., 1998; Li et al., 1999; Brauer and Castillo-Chavez, 2001; d'Onofrio, 2005; Zaman et al., 2008) and cellular level or virus dynamics models (Herz et al., 1996; Bonhoeffer et al., 1997; Perelson and Nelson, 1999; Nowak and May, 2000; Perelson, 2002; Zhu and Zou, 2009). Mathematical models can be categorized into two types depending on the technical approach applied; deterministic and stochastic models.

Deterministic model: It is a model in which every set of variable states is uniquely determined by parameters in the model and by sets of previous states of these variables; therefore, a deterministic model always performs the same way for a given set of initial conditions.

Stochastic model: It is a model in which randomness is present, and variable states are not described by unique values, but rather by probability distributions. Deterministic models provide the same outcome for the same set of parameters with the same initial conditions. Whereas stochastic models show randomness and provide different set of outcomes for the same set of parameters with same initial conditions.

In the next section we provide brief literature survey of epidemiological models both at population level and cellular level .

1.4 A Brief Literature Survey of Mathematical Models

Mathematical model, which describes the dynamics of diseases, has been playing an important role in better understanding of epidemiological patterns and disease control for a long time. After a certain density of infected agent, the health equilibrium or its state of activity is disturbed and the disease becomes overt. Mathematical models are useful in decision making policies for public health. Dynamics at population level have been analyzed considering the uniform mixing of demographic population as a whole. The basic mathematical models have been studied to describe directly transmitted diseases like Influenza flu, Mumps, and Tuberculosis etc. The role of mathematical epidemiology is to model the establishment and spread of disease under a given set of conditions.

Epidemiological models are also known as compartmental models. Since these models are based on the assumption that the entire host population can be divided into a number of compartments. The basic compartmental model, Susceptible-Infected-Recovered (SIR) model (Kermack and McKendrick, 1927), comprises of three compartments:

- ***Susceptible individuals***, those who are healthy and can contract disease under appropriate conditions. The size of this class is denoted by S.
- ***Infected individuals*** (I), the ones who have contracted the disease and are now infected with it. These are capable of transferring the disease to susceptibles via contact. As time progresses, infectious individuals loose the infectivity, and move to either removed compartment (by death) or recovered compartment (by appropriate treatment or autorecovery by the immune system).

- ***Recovered individuals*** (R), these recovered individuals are immune to infectious microbes and thus do not acquire the infection again in case of permanent immunity.

SIR models can be further categorised depending on the immunity against the infection; (i) SIS model without immunity against the infection, is the model in which the recovered individual will get infection again and will become susceptible, (ii) SIR model with immunity, is the model in which the recovered individual will not get infection again in future. The dynamics of these models has been investigated by Hethcote (1976). He has made the following assumptions to study the epidemic models:

(i) For sufficiently large population, the total size of the population is constant and therefore the sub-populations have been considered as continuous variable. In case of vital dynamics, the death and birth rates are assumed to be equal.

(ii) The population is uniform. The interaction of sub-populations assumed to be homogeneous.

(iii) It is assumed that the infection begins immediately after the infectious individual contract to a susceptible host (i.e. latent period is zero.)

Based on the quantitative analysis of the models, he attained the following observations:

Case (1): SIS model i.e. It is the case of the disease without immunity, the eradication of the infection is possible if the infectious contact number is less than or equal to 'one' and infection will persist if the said number exceeds one. This is independent of initial concentration of infectives. This model is useful in eradication of plague and malaria.

Case (2): SIRS model, It is the case of the disease with temporary immunity, if the infectious contact number is grater than 'one' then the infection will persists in the endemic zone for longer time otherwise the infected population approaches to zero until the total population becomes susceptible. This model is suitable for smallpox, cholera, typhoid fever, tetanus and influenza. He has further involved several biological features (disease fatalities, carriers, migration, transmission by vectors) in his SIR models to understand the asymptotic behavior of endemic equi-

librium points. He has involved the biological features in the models step by step to get a better insight of dynamics of infections.

In last few decades, classical epidemiological models with add-on of certain new factors such as different nonlinear transmission rate, treatment plans, quarantine, vaccination, awareness programs through media as well as health care workers etc. have been investigated (Shulgin et al., 1998; Wang and Ruan, 2004; Hu et al., 2008; Zhonghua and Yaohong, 2010; Li et al., 2009; Funk et al., 2009; Laskowski et al., 2015; Alexander and Moghadas, 2004). As these factors are related to reduction in transmission of infection and eventually lead to elimination of infection.

Alexander and Moghadas (2004) developed a mathematical model introducing generalized incidence rate to study the transmission dynamics of infectious diseases. The nonlinearity of the incidence rate establishes rich dynamics of the infection and describe the behavioral changes. They have described their model with examples using two different nonlinear incidence rates. Analysis of the model observed two important factors:
(i) *Bistability* is the existence of multiple equilibria in case of $R_0 < 1$. It suggests that the model exhibits backward bifurcation. This also confirms that controlling the spread of infection may not be possible by reducing R_0 to values less than unity. They have cited a study of measles during an epidemic in Poland. This study shows that there were 2255 reported cases in between November 1997 and July 1998, irrespective of high vaccination coverage (95%) (Janaszek et al., 2003).
(ii) *Periodicity*, the model exhibits Hopf bifurcation under given conditions and limit cycles exist. The periodic behavior has also been observed in case of studies on the dynamics of some infectious diseases such as measles, whooping cough, rubella, etc. (Earn et al., 2000; Keeling et al., 2001; Lin et al., 1999). They have suggested that the application of the model using the realistic data for the infections on which the model is based on, can be used to make future predictions.

Consideration of the treatment modalities in mathematical modeling has been an important step to describe the real situations during an epidemic. Wang and Ruan (2004) analyzed an SIR epidemic model with bilinear incidence rate and constant treatment rate of infectious individuals to understand the effect of the

treatment capacity on disease transmission. Here the treatment rate is taken to be dependent on the capacity of treatment of infected individuals. The optimal capacity of treatment is determined depending on their outcomes. They observed that the inclusion of constant treatment rate exhibits periodic oscillations in diseases while the model without the treatment is globally stable. They have shown that the model is more realistic and useful since the ultimate behavior of the equilibria depends on the initial positions. This model is suitable for measles, AIDS, flu, etc. The quantitative analysis carried out can be adapted to an SI model, which is useful for sexually transmitted diseases or bacterial infections. The SIR models involving the treatment of infectives are numerous in the literature (Cai et al., 2009; Cui, Mu and Wan, 2008; Hu et al., 2008).

Further, Zhonghua and Yaohong (2010) modified the model of Wang and Ruan (2004) to incorporate the saturated treatment rate in place of constant treatment rate along with the eternal immunity. They argued that this treatment rate is a better alternative for new emerging diseases such as SARS. On the onset of an outbreak, the treatment will be less and this will increase with the improvement in hospital's condition, supply of drugs etc. and approaches to maximum capacity with limited resources available in the community. Here coexistence of disease free equilibrium and endemic equilibrium has been shown. This suggests that not only the reduction of threshold value (R_0) to the values less than unity is always effective to control the spread of disease but also there is a need to eliminate such diseases, to restrict the initial value of each sub-population to the domain of attraction of the disease free equilibrium. They have shown that the model exhibits Hopf bifurcation.

In above discussed models, nonlinearity of the incidence rate and treatment was the major factor to control the epidemic. Authors have emphasized that apart from incidence rate, public awareness about the preventive and treatment is also an important tool to reduce the occurrence of infection. Nevertheless, the awareness programs driven by media is very much needed in case of such infections like AIDS for which no treatment is available. Funk et al. (2009) studied a model to get insight of impacts of dissemination of awareness on the spread of an epidemic. The

first mode of information dissemination is word of mouth, person to person. They observed that awareness may slower the incidence of epidemic or may control an infection to become epidemic in case of small number of infections. But in case of large number of infection awareness can slowdown the incidence but can not eradicate the infection. It is also supported by recent reports of National AIDS Control Organization (NACO, 2015) that there has been significant decline in HIV prevalence among female sex workers at national level (5.06% in 2007 to 2.67% in 2011) and in most of the states where long standing targeted interventions have focused on behavioral change and increased use of condom.

1.4.1 Models in Virus Dynamics

Virus dynamics is the study of dynamics of infection at cellular level. Unlike the study of spread of infection at population level, virus dynamics models study the progression of viral infection within the host organism. Some basic models of virus dynamics are discussed ahead to get the better insight of viral infections like HIV/AIDS, HBV, Ebola, SARS etc. Basic models of virus dynamics was introduced by Nowak and Bangham (1996) and Bonhoeffer et al. (1997). A very simple model of virus dynamics can be read as

$$\begin{cases} \dot{x} = \lambda - \delta_0 x - \alpha x v, \\ \dot{y} = \alpha x v - \delta_1 y, \\ \dot{v} = k y - k_0 v. \end{cases}$$

In the above model, $x(t)$ is the number of uninfected cells, $y(t)$ the number of infected cells and $v(t)$ the number of free virus at any time $t \geq 0$. λ is the constant growth rate of uninfected cells and δ_0 is its death rate. When free virus interacts with uninfected cells, it produces infected cells at the rate of α. δ_1 is the natural death rate of infected cells. Virus is produced at the rate k by infected cells and k_0 is the natural clearance rate of virus. In this model they have studied the dynamics of the above system and tried to get the answer of an awaited question, " Whether or not the virus can grow and establish an infection that depends on the basic reproductive ratio (R_0) of the infection" (Nowak and May, 2000). Further,

this model has been extended by several researchers (Wodarz and Nowak, 2000; Rosenberg et al., 2000; Smith and De Leenheer, 2003; Dubey et al., 2011; **?**; Zhuo, 2012; Kirschner, 1996) to introduce other biological features like immune response, antiretroviral therapy, therapeutic drugs etc.

Nowak and Bangham (1996) proposed a mathematical model to study the dynamics of immune response of the host to an infectious agent. This model is just the extension of the above basic virus dynamics model and is given by the following differential equations:

$$\begin{cases} \dot{x} = \lambda - \delta_0 x - \alpha x v, \\ \dot{y} = \alpha x v - \delta_1 y - p y z, \\ \dot{v} = k y - k_0 v, \\ \dot{z} = c y z - b z. \end{cases}$$

Here $z(t)$ is the density of CTL mediated immune response. This immune response proliferates in presence of virus with the rate c and decays at the rate b. The parameter p is the rate at which CTLs kill infected cells. The interaction between infected cells and CTL responses has been explored. Nevertheless, the results are also applicable for antibody or cytokine-mediated immune response. The findings has been applied to real data on CTL responses and viral diversity in infections with the human T cell leukemia virus (HTLV-1) and HIV-1. It has been shown that the viral load is high in the patients with weak immune response while this reduces to a low level in patients with strong immune response.

Perelson and Nelson (1999) studied a few models to understand the dynamics of HIV primary infection *in vivo*. They considered the single ordinary differential equation model which consists of virus compartment only. They applied clinical data to this model and analyzed production and clearance of HIV in an infected person. Furthermore, they considered the interaction between uninfected CD4+ T cells, productively infected cells and virus. In this model, the proliferation of T cells has been considered by logistic growth function and the infection rate is assumed to be "mass-action" since the concentration of HIV virus never gets high in comparison to the number of T cells. They suggested that the equilibrium can differ from one patient to the another, depending upon the parameters characteristic

of the virus and host. Further, they incorporated the combination of drug therapy into their model to reduce the concentration of virus in the body of infected person. Reverse Transcriptase Inhibitor (RTI) blocks viral infection, while Protease Inhibitor prevents viral replication and blocks the production of infectious virus particles. They have shown that combination of these therapies helps in reducing viral load and providing an early treatment to the patients. It is assumed that there may be other cells susceptible to the HIV virus. One type of these cells is the macrophage. These macrophages may serve as production factories for the virus and continue to produce the virus continuously. Another alternative model was introduced, in the same article, considering latently infected cells (these cells do not produce virus initially but upon activation they may start producing the virus). These models provided a better insight of infection biological mechanisms. The use of combination treatment therapy leads to an important and subtle tool to reduce the infection. The only main important component, which was not covered in their models, was immune response.

The viral pathogen models also considers one of important biological feature, decline in the number of pathogens because of being absorbed into uninfected cells during infection. This mechanism was used to get a better insight of dynamics of deadly viruses (Murase et al., 2005; Tian and Xu, 2012; Kajiwara and Sasaki, 2010; Wang et al., 2013). Murase et al. (2005) proposed a mathematical model with immune response and absorption of pathogens into uninfected cells. They studied the local stability of equilibria to get an insight of the persistence of infection and considered different cases in their models. Firstly they considered the basic virus dynamics model and then in the next model they incorporated immune response and ignored the effect of absorption. Further, in third case they incorporated the effect of absorption of pathogens into uninfected cells and found that absorption of pathogens may disturb the stability of interior equilibrium point.

It was assumed in earlier studies that the viral load can be reduced by killing of infected cells or destruction of infected cells by either therapeutic drugs or immune response. However, in recent viral dynamics models, authors (Ciupe et al., 2007; Zhou et al., 2008; Guidotti et al., 1999) developed an innovative approach to cure

the infected cells without destruction of infected cells i.e. using non-cytolytic processes. It is biologically proved that sometimes instead of killing, the infected cells can be cured or recovered into uninfected cells. Ciupe et al. (2007) have shown in their model that in case of hepatitis B virus infection the covalently closed circular (ccc) DNA can be removed from the nucleus of infected cells and in turn the cell become uninfected cell. The detailed mechanism of the non-cytolytic process can be explored from (Ciupe et al., 2007; Guidotti et al., 1999) and the references cited therein. Zhou et al. (2008) introduced an HIV dynamics model in which they established that the infected cells can be removed by two ways, either through death (mostly immune-mediated killing) or via cure (loss of cccDNA). They suggested that inclusion of both cytolytic and non-cytolytic mechanisms of infected cell loss is more realistic and accurate. The next section provides definitions of the terminology used throughout the thesis.

1.5 Basic Definition of Terms Involved in this Thesis

In this section, we will explore the basic biological terminology used throughout this thesis.

Infectious Disease: It is the illness due to an infectious agent or its product capable of direct or indirect transmission from man to man or from environment to man through air, dust, soil, water, food, etc.

Epidemic: It is the "unusual" occurrence in a community or region of a disease in excess of "expected occurrence". Often the term "outbreak" is used for a small, usually localized epidemic in the interest of minimizing public alarm.

Endemic: It refers to the constant presence of a disease or infectious agent within a given geographic area or population group, without importation from outside. It is also referred to as the "usual" expected frequency of the disease in the area/population. Endemic diseases when conditions are favorable burst into an epidemic.

Pandemic: It is an epidemic affecting large proportion of the population occurring over a wide geographical area such as a continent, nation or a large part of it.

Eradication: It is the total elimination of a disease in a given population. It is an absolute process. Till now only one disease has been eradicated, that is small pox.

1.5.1 Baseline Transmission Rate or Infection Rate

In epidemiological models, the disease transmission process plays an important role in determining the incidence rate. The transmission rate is the product of the rate of contact among individuals and the probability that a susceptible individual coming in contact with an infectious individual will become infected (Park, 2013). This is also called bilinear incidence rate αSI. The standard incidence rate $\alpha SI/N$ has been considered in most of the epidemic models, here S is the density of susceptible individuals, I the density of infected individuals, N the density of total population and α the baseline transmission rate. Several other nonlinear and saturated forms of incidence rate have been proposed by researchers. We will explore a few of them here.

Holling Type II: This incidence rate is also known as the saturated incidence rate and was proposed by C. S. Holling (Holling, 1959). The expression is $f(S,I) = \left(\frac{\alpha I}{1+\beta I}\right) S$, $\alpha, \beta > 0$. In Holling type II, for any outbreak of the disease its incidence is first very low and then grows slowly with increase in infection. Further, when number of infected individuals is very large, the infection reaches to its maximum due to crowding effect.

Holling Type III: The expression for Holling type III incidence rate is given by $f(S,I) = \left(\frac{\alpha I^2}{1+\beta I^2}\right) S$, $\alpha, \beta > 0$. Holling type III defines the condition in which incidence of infection first grows very fast initially with increase in infective and then it grows slowly and finally settles down to maximum saturated value. After this any increase in infective will not affect the infection rate.

Beddington-DeAngelis Type: This functional response was introduced by DeAngelis and Beddingtoan in 1975 (Beddington, 1975; DeAngelis et al., 1975)

independently and is given by the term

$$f(S,I) = \frac{\alpha S}{1+\beta S+\gamma I}.$$

Here α is the transmission rate, β is a measure of inhibition effect, such as preventive measure taken by susceptible individuals and γ is a measure of inhibition effect such as treatment with respect to infectives.

Crowley Martin Type: The Crowley-Martin type of functional response was introduced by P. H. Crowley and E. K. Martin in 1989 (Crowley and Martin, 1989) and is denoted by the term

$$f(S,I) = \frac{\alpha S}{(1+\beta S)(1+\gamma I)},$$

where α, β, γ are positive constants. From the expression, we observe that similar to the Beddington-DeAngelis type incidence rate, one can easily derive other forms of incidence rates. The important difference between the Beddington-DeAngelis type and the Crowley-Martin type incidence rate is that the latter considers the effect of inhibition among infectives even in case of high density of susceptible populations while the former neglects the aforesaid effect. This can be seen as follows:

Beddington-DeAngelis type incidence rate for $S \to \infty$,

$$\lim_{S\to\infty} f(S,I) = \frac{\alpha}{\beta},$$

and Crowley-Martin type incidence rate for $S \to \infty$,

$$\lim_{S\to\infty} f(S,I) = \frac{\alpha}{\beta(1+\gamma I)}.$$

1.5.2 Immune Response

The immune system protects our body from infection by recognizing and responding to foreign antigens. The immune system is a complex network of various type

of lymphatic organs and blood cells, their secreted product and the interaction of above. The immune system is characterized by its ability to differentiate between self and non self. The inability to differentiate between self and non self leads to autoimmunity. Rheumatoid arthritis and diabetes mellitus Type I, celiac disease are some examples of autoimmune diseases.

On the other hand immunodeficiency is the inability to mount an immune response against any foreign antigen. Severe combined immunodeficiency syndrome and AIDs are examples of immunodeficiency diseases. The lymphocytes are white blood cells which play an important role in immune system. Lymphocytes are mainly of two types: ***B cells*** and ***T cells***, besides this a small fraction of lymphocytes comprises of the Natural killer cells that are active against cancers and virally infected cells.

Innate immune response is inherent which remains unchanged in its action and is independent of the type of pathogens. This form of immunity does not possess immunological memory and therefore does not improve against repeated exposure to infections. It comprises of physical epithelial barriers macrophages, phagocytic leukocytes, dendritic cells, the natural killer (NK) cell, circulating plasma proteins etc. It includes physical defense such as hair in nostrils, cilia in respiratory tract, enzymes in tears, skin oils, mucus (which traps bacteria and small particles), stomach acid etc. It gets stimulated when any pathogen invades the host cell and protect us from infection.

Acquired immune response sets into action after the antigen has breached the innate or natural defense barrier. It takes about a week or so to develop and is highly specific in its action. It gets stimulated with the exposure to various antigens. There are two fundamental types of adaptive immune responses:

(1) ***Humoral immune response*** is generated by B-cells which are produced in the bone marrow. These B cells produce antibodies. Theses antibodies are specific to the same antigen which elicit its response.

(2) ***Cell-mediated immune response*** is mediated by the T lymphocytes. T lymphocytes are of 2 types: the cytotoxic T cells (CTLs) and the helper T

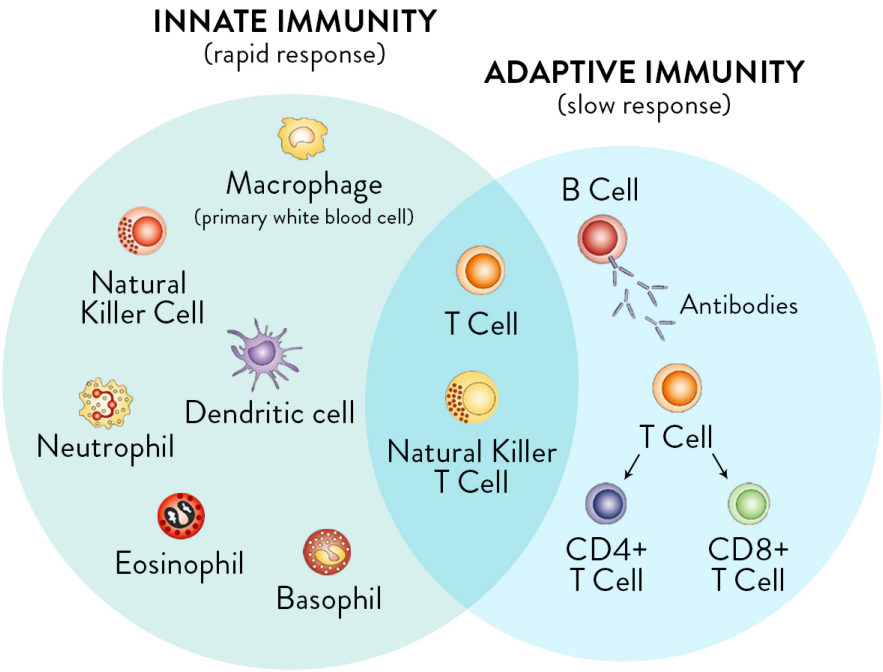

Figure 1.3: Components of immune system of the body.

cells (T_H cells or the CD4$^+$ cells). Cytotoxic T cells cause lysis of the target cells whereas helper T cells secrete lymphokines and help in regulating the immune response (Nowak and May, 2000). Lymphokines stimulation perform wide range of functions such as cytotoxic T cells and B cells to grow and divide, attract neutrophils, enhance the ability of macrophages to engross and kill microbes, etc. The gross schematic diagram of immune system has been shown in figure 1.3.

1.5.3 Threshold to Determine Epidemic: Basic Reproduction Number

The persistence of infection in mathematical epidemic models depends upon the threshold. This threshold is known as basic reproduction number and denoted by R_0. It is understood that when R_0 is less than one then infection dies out and if R_0 is greater than one then infection will persist and this state is called endemic state. The basic reproduction number R_0 in case of population models is defined as follows:

The number of newly infected individuals produced by a single infected individual when introduced into a completely susceptible population.

Further in case of cellular models of virus dynamics, the basic reproduction number is defined as

The average number of newly infected cells that arise from a single infected cell when almost all cells are uninfected or healthy (Nowak and May, 2000).

There are several techniques to compute the basic reproduction number R_0 (Diekmann et al., 1990). In this thesis we have applied next generation matrix method (Van den Driessche and Watmough, 2002) to determine the basic reproduction number R_0.

Next generation matrix method: We define the next generation matrix as the square matrix G in which the ij^{th} element of G, g_{ij} , is the expected number of secondary infections of type i caused by a single infected individual of type j, again assuming that the population of type i is entirely susceptible. That is, each element of the matrix G is a reproduction number, but one where who infects whom is accounted for (Jones, 2007). One can easily found the basic reproduction number R_0, once next generation matrix G is determined. Spectral radius of G gives the basic reproduction number. Spectral radius is also known as the dominant eigenvalue of G. The next generation matrix has a number of desirable properties from a mathematical standpoint. In particular, it is a non-negative matrix and, as such, it is guaranteed that there will be a single, unique eigenvalue which is positive, real, and strictly greater than all the others. Consider the next generation matrix G. It is comprised of two parts; F and V^{-1}, where

$$F = \left[\frac{\partial F_i(x_0)}{\partial x_j}\right],$$

$$V = \left[\frac{\partial V_i(x_0)}{\partial x_j}\right],$$

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

1.6 Mathematical Tools used in Analysis of Epidemic Models

In the deterministic analysis of evolution and stability of the system described above, many mathematical approaches have been adopted. We will adopt the following methods. Let us provide here some basic definitions of methods used. We consider nonlinear time-invariant system

$$\frac{dx}{dt} = f(x), \tag{1.1}$$

where $f \in C[R^n, R^n]$. Assume that f is smooth enough to ensure the existence and uniqueness of the solution of (1.1). We assume that $f(0) = 0$ so that the system (1.1) admits the zero solution and $x = 0$ is an equilibrium point of system (1.1).

Definition 1.6.1. (Stability) *The equilibrium point $x = 0$ of (1.1) is **locally stable** if, for each time t_0, and for every constant $R > 0$, there exists some $r(R, t_0) > 0$ such that*

$$\|x(t_0)\| < r \Rightarrow \|x(t)\| < R, \quad \forall t > t_0.$$

The equilibrium point $x = 0$ is locally stable if any solution initiating in $S_r(0)$ will always remain in $S_R(0)$. The equilibrium is unstable if it is not stable.

Definition 1.6.2. (Asymptotic stability) *The equilibrium point $x = 0$ of (1.1) is **asymptotically stable** if; (a) it is stable, and (b) for each time t_0 there exists some $r(t_0) > 0$ such that*

$$\|x(t_0)\| < r \Rightarrow \|x(t)\| \to 0 \quad as \quad t \to \infty.$$

Thus the equilibrium is asymptotically stable if the trajectories initiating from any point in $S_r(0)$ remain within the sphere $S_R(0)$ and will converge asymptotically to the equilibrium point (see figure 1.4).

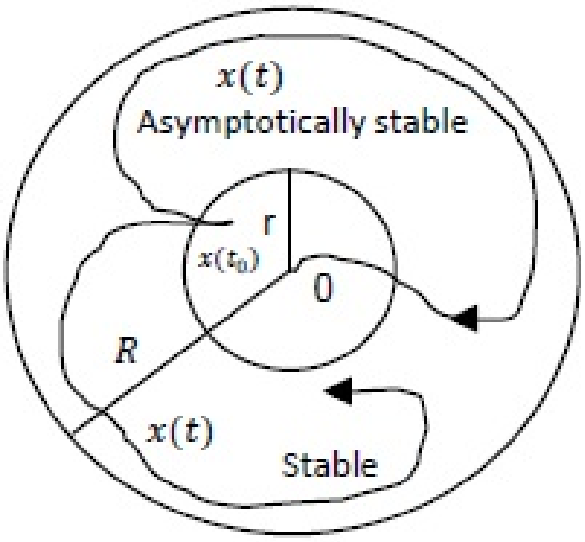

Figure 1.4: Stability of an equilibrium point.

If the trajectories initiating from any point in a finite region converge to the equilibrium $x = 0$, then the equilibrium $x = 0$ is called ***globally asymptotically stable***. In fact, if $x = 0$ is globally asymptotically stable, then the region of asymptotic stability is the whole space R^n.

Definition 1.6.3. (Invariant Set) *A set $\Omega \in R^n$ is said to be invariant if for every trajectory x, $x(t_0) \in \Omega \Rightarrow x(t) \in \Omega \ \forall t \geq t_0$, i.e. if a trajectory starts in Ω, this stays in Ω for all time $t \geq 0$.*

Theorem 1.6.4. (LaSalle's Invariance Principle) *Let $\Omega \subset R^n$ be a compact set that is positively invariant with respect to* (1.1)*. Let $L : R^n \to R$ be a continuously differentiable function such that $L(x)$ is positive definite and $\dot{L}(x) \leq 0 \in \Omega$. Define*

$$M = \left\{ x \in \Omega | \dot{L}(x) = 0 \right\}.$$

For $t \to \infty$, the trajectory tends to the largest invariant set inside M. In particular, if M contains no invariant sets other than $x = 0$, for all t then the origin is globally asymptotically stable (Khalil, 2002; LaSalle, 1976).

(For further details on stability theory we refer to LaSalle and Lefschetz (1961); Perko (2013); Guckenheimer and Holmes (1983); LaSalle (1976))

1.6.1 Eigenvalue Method

The conclusion, regarding asymptotic stability of the systems very much lie in the eigenvalues of the variational matrix, a Jacobian matrix of first order derivatives of interaction functions. As this Jacobian is determined by Taylor expansion of the interaction function and neglecting nonlinear higher order terms, this method studies only the local stability of the system in vicinity of its equilibrium state. Being a straight forward method, based purely on the sign of real parts of eigenvalues, we shall use the Routh-Hurwitz criterion (Gantmacher, 1959) to study the local stability of wide range of systems in homogeneous environment.

Routh-Hurwitz Stability Criterion: According to this criterion, the necessary and sufficient condition for the negativity of the real parts of all the roots of the polynomial

$$\lambda^n + a_1\lambda^{n-1} + a_2\lambda^{n-2} + a_3\lambda^{n-3} + \ + a_n = 0,$$

with real coefficients is the positivity of all the principal diagonals of the minors of the Hurwitz matrix

$$H_n = \begin{bmatrix} a_1 & 1 & 0 & \dots & 0 \\ a_3 & a_2 & a_1 & \dots & 0 \\ a_5 & a_4 & a_3 & \dots & 0 \\ \dots & \dots & \dots & \dots & 0 \\ 0 & 0 & 0 & \dots & a_n \end{bmatrix}.$$

The alternate columns in this matrix consist of coefficients with only odd indices or with only even indices (including the coefficient $a_0 = 1$). Hence the elements of the Hurwitz matrix $H_n = b_{ik}$ are given by $b_{ik} = a_{2i-k}$, the missing coefficients (i.e., the coefficients with indices greater than n or less than zero being replaced by zeros.

$$D_1 = a_1 > 0,\ D_2 = \begin{bmatrix} a_1 & 1 \\ a_3 & a_2 \end{bmatrix} > 0,\ D_3 = \begin{bmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ a_5 & a_4 & a_3 \end{bmatrix},\ D_n = det(H_n).$$

The Routh-Hurwitz criterion (Gantmacher, 1959) for particular values of $n = 2$ and 3 is stated below

(i) $n = 2$, $a_1 > 0$, $a_2 > 0$.

(ii) $n = 3$, $a_1 > 0$, $a_3 > 0$, $a_1 a_2 > a_3$.

The above method is useful to check the local stability of an equilibrium point. The local stability describes the qualitative behavior of the solution in a certain neighborhood. It does not give any information about the behavior of the solution out of that neighborhood. The Lyapunov's direct method can be useful to study the stability behavior of nonlinear systems.

1.6.2 Lyapunov's Direct Method

The physical validity of this method is contained in the fact that stability of the system depends on the energy of the system which is a function of system variables. Lyapunov's direct method consists in finding out such energy functions termed as Lyapunov functions which need not be unique. The major role in this process is played by positive or negative definite functions which can be obtained in general by trial of some particular functions of state variables, and in some cases with a planned procedure. We shall use the following important results for the stability analysis of our models.

Let us consider the system (1.1) and $f(0) = 0$ i.e. $x = 0$ is an equilibrium point of the system.

Definition 1.6.5. *Let $V(x)$ be a real valued scalar function belonging to Ω for some region $\Omega \in R^n$. Assume that $V(0) = 0$, Then,*
(i) $V(x)$ is positive definite on the set Ω if $V(x) > 0$ for $x \neq 0$ and $x \in \Omega$
(ii) $V(x)$ is negative definite on the set Ω if $V(x) < 0$ for $x \neq 0$ and $x \in \Omega$
(iii) $V(x)$ is positive and negative semi-definite if the inequalities are not strict, respectively or $V(x)$ is positive (negative) semi-definite on the set Ω when $V(x)$ has the positive (negative) sign throughout Ω except at certain points (including the origin) where it is zero.

Theorem 1.6.6. *If there exists a positive definite scalar function $V(x)$ such that $\dot{V}(x) \leq 0$, i.e. $\dot{V}(x)$ is negative semi-definite on Ω then the zero solution of* (1.1) *is stable.*

Theorem 1.6.7. *If there exists a positive definite scalar function $V(x)$ such that $\dot{V}(x) < 0$, i.e. $\dot{V}(x)$ is negative definite on Ω then zero solution of* (1.1) *is asymptotically stable.*

Theorem 1.6.8. *If there exists a scalar function $V(x)$, $V(0) = 0$ such that $\dot{V}(x)$ is positive definite on Ω and if in every neighborhood N of the origin, there is a point x_0, where $V(x_0) > 0$, then the zero solution of* (1.1) *is unstable.*

1.7 Bifurcations

The change in stability behavior or dynamics of equilibrium points is called bifurcation and the equilibrium point at which bifurcation occur is called bifurcation point (Strogatz, 2014). Poincarè (Guckenheimer and Holmes, 1983) has defined the bifurcation term to describe the "splitting" of equilibrium solutions in a family of differential equations. There are several additional type of bifurcations, here we discuss two types of bifurcations: transcritical and Hopf bifurcation.

1.7.1 Transcritical Bifurcation

There are certain scientific situations where a fixed point must exist for all values of a parameter and can never be destroyed. For instance, in the logistic equation and other simple models for the growth of a single species, there is a fixed point at zero population, regardless of the value of the growth rate. However, such a fixed point may change its stability as the parameter is varied. The transcritical bifurcation is the standard mechanism for such changes in stability. The normal form for a transcritical bifurcation is

$$\dot{x} = rx - x^2. \tag{1.2}$$

For $r < 0$, there is an unstable fixed point at $x^* = r$ and a stable fixed point at $x^* = 0$. As r increases, the unstable fixed point approaches to the origin, and

coincide with it when $r = 0$. Finally, when $r > 0$, the origin has become unstable, and $x^* = r$ is now stable. The change in stability behavior of equilibrium points from stable to unstable is called *transcritical bifurcation*. This is also known as forward bifurcation.

1.7.2 Hopf Bifurcation

In case of two-dimensional system, the stability behavior of the system changes with the change in sign of real part of the eigenvalues of Jacobian matrix. If both the eigenvalues have negative real part then the system is stable and if eigenvalues have positive real part then system is unstable. If the system has purely imaginary eigenvalues then the system exhibits *Hopf bifurcation*.

Theorem 1.7.1 (Poincarè-Andronov-Hopf)**.** *Let*

$$\dot{x} = A(\alpha)x + f(\alpha, x), \tag{1.3}$$

where $A \in \mathbb{M}^{2\times 2}$ *and* $f : (\alpha, x) \in \mathbb{R} \times \mathbb{R}^2 \to \mathbb{R}^2$ *is a thrice continuously differentiable vector field depending on a scalar parameter* α *such that* $f(\alpha, 0) = 0$ *and* $Df(\alpha, 0) = 0$ *for all sufficiently small* $|\alpha|$*. Assume that the linear part* $A(\alpha)$ *at the origin has eigenvalues* $a(\alpha) \pm ib(\alpha)$ *with* $a(0) = 0$ *and* $b(0) \neq 0$*. Furthermore, suppose that the eigenvalues cross the axis with non-zero speed, that is*

$$\frac{da}{d\alpha}(0) \neq 0.$$

Then in any neighborhood U *of the origin in* R^2 *and any given* $\alpha_0 > 0$*, there is a* $\bar{\alpha}$ *with* $\bar{\alpha} < \alpha_0$ *such that the differential equation*

$$\dot{x} = A(\bar{\alpha})x + f(\bar{\alpha}, x)$$

has a nontrivial periodic orbit in U*. The bifurcation is supercritical if the periodic orbit is stable otherwise it is subcritical (Glendinning, 1994).*

For further details on bifurcations see (Guckenheimer and Holmes, 1983; Strogatz, 2014; Hale and Kocak, 2012).

1.7.3 Limit cycle

A limit cycle is an isolated closed trajectory. Isolated means that neighboring trajectories are not closed; they spiral either toward or away from the limit cycle. Limit cycles can be stable, unstable, or half-stable according to whether the nearby trajectories spiral towards the limit cycle, away from the limit cycle, or both.

Stable limit cycles are very important scientifically-they model systems that exhibit self-sustained oscillations (Strogatz, 2014). In other words, these systems oscillate even in the absence of external periodic forcing. Few examples of limit cycles are the beating of a heart; the periodic firing of a pacemaker neuron; daily rhythms in human body temperature and hormone secretion; etc. In each case, there is a standard oscillation of some preferred period, waveform, and amplitude. If the system is perturbed slightly, it always returns to the standard cycle. Limit cycles are inherently nonlinear phenomena; they can not occur in linear systems.

The non-existence of limit cycles can be determined by using the following theorem.

Let us consider the planar system

$$\dot{x} = f(x) \tag{1.4}$$

where $f = (f_1, f_2)^T$ and $x = (x_1, x_2)^T \in R^2$.

Theorem 1.7.2. (Dulac's Criterion) *Let $f \in C^1(D)$ where D is a simply connected region in R^2. If there exists a function $h \in C^1(D)$ such that $\nabla.(hf) = \frac{\partial(f_1 h)}{\partial x_1} + \frac{\partial(f_2 h)}{\partial x_2}$ is not identically zero and does not change sign in D, then* (1.4) *does not have any closed orbit lying entirely in D.*

Further, the existence of limit cycles can be ensured using the following theorem.

Theorem 1.7.3. (Poincarè-Bendixson Theorem) *Suppose that:*

(i) R is a closed, bounded subset of the plane;

(ii) R does not contain any fixed points; and

(iii) There exists a trajectory C that is "confined" in R, in the sense that it starts

in R and stays in R for all future time. Then either C is a closed orbit, or it spirals toward a closed orbit as $t \to \infty$. Then the system (1.4) *has a closed trajectory lying inside R (Strogatz, 2014).*

1.8 Thesis Organization

In this thesis, we proposed and analyzed mathematical models to understand dynamics of infectious diseases. The effect of various biological features has been examined in step by step modeling which helps in prediction of future course of action to stabilize the epidemic. The thesis is organized as follows: **Chapter 1** describes the brief introduction of the problem and provides the objectives of thesis as well as literature survey. In **Chapter 2**, we discussed an SIR model with nonlinear incidence and treatment rates. The stability analysis of the model is investigated and validated through numerical simulations. In **Chapter 3**, we extended the model studied in **Chapter 2** which involves different type of nonlinear incidence and treatment rates. Furthermore in **Chapter 4**, we studied the effect of awareness programs run by media on a compartmental model which comprises of four compartments namely susceptible (S), infected (I), aware susceptible (S_a) and recovered (R). The dynamics of interaction of uninfected cells, infected cells and virus has been explored in **Chapter 5**. We examined the effect of therapeutic drugs on infected cells as well as virus on the model proposed in **Chapter 5**. The impact of non-cytolytic cure and absorption of pathogens into uninfected cells has been studied on the pathogen-immune interaction models in **Chapter 6**. Further, we developed a model to study the dynamics of HIV infection in **Chapter 7**. Finally, the main outcomes and future scope of the thesis are summarized in **Chapter 8**.

Chapter 2

Dynamics of an SIR Model with Nonlinear Incidence Rate and Holling Type II Treatment Rate

Models should be as simple as possible, but not more so.

Einstein

The incidence of infection and eventually the treatment of infection are necessary tools to analyze any epidemic. This chapter deals with the basic compartmental model i.e. susceptible-infected-recovered (SIR) model involving nonlinear incidence rate and treatment rate. The dynamics of infection among homogeneous population has been studied. The baseline transmission rate is being considered as Beddington-DeAngelis type. Further, we assumed the treatment given to the infected population is governed by the Holling type II function. To study the analytical behavior of the model theory of ordinary differential equations has been used. Numerical simulations has been performed to exemplify the analytical outcomes.

2.1 Introduction

Epidemiological models have been recognized as valuable tools in analyzing the spread and control of infectious diseases. In epidemiological models, incidence rate as well as treatment rate play an important role while analyzing the transmission of diseases. The number of individuals who become infected per unit of time in epidemiology is called incidence rate. Incidence rate has been defined in multiple ways. Firstly, the bilinear incidence rate (Anderson et al., 1992; Bailey, 1975; Brauer and Castillo-Chavez, 2001; Hethcote, 2000; Kermack and McKendrick, 1927; Shulgin et al., 1998; Zhonghua and Yaohong, 2010; Ghosh et al., 2004; Shukla et al., 2011) is based on the law of mass action (βSI, where β is infection rate and S & I denote the susceptible and infected individuals respectively) which is unreasonable for large population. As we can infer from the term βSI that if the number of susceptibles increases, the number of individuals who become infected per unit of time increases, which is not realistic. So there is a need to modify the classical linear incidence rate to study the dynamics of infection among large population.

Several authors (May and Anderson, 1978; Wei and Chen, 2008; Zhang et al., 2008; Li et al., 2009; Li and Muldowney, 1995; Korobeinikov and Maini, 2005; Xu and Ma, 2009; Capasso and Serio, 1978) suggested different type of nonlinear incidence rates. Like, the saturated incidence rate $\frac{\alpha SI}{(1+\beta S)}$, was introduced by Anderson and May in 1978. The effect of saturation factor β stems from epidemical control. Further, many authors (Mondal and Kar, 2013; Agarwal and Verma, 2012; Wei and Chen, 2008; Zhang et al., 2008) incorporated this incidence rate into their models.

Li et al. (2009) proposed an SIR model with nonlinear incidence rate given by $\frac{\alpha SI}{(1+\gamma I)}$. In this incidence rate the number of effective contacts between infective and susceptible individuals may saturate at high infective levels due to crowding of infective individuals. Beddington (1975) and DeAngelis (1975) independently, introduced nonlinear incidence rate known as Beddington-DeAngelis type incidence rate ($\frac{\alpha SI}{1+\beta S+\gamma I}$). Later, some authors (Kaddar, 2009, 2010; Huang et al., 2011; Elaiw and Azoz, 2013) used this incidence rate to describe epidemiological models.

We are aware of the fact that the treatment is an important method to reduce the spread of diseases. In classical epidemic models, the treatment rate of infected individuals is assumed to be either constant or proportional to the number of the infected individuals. But we know that there are limited treatment resources available in community. Therefore, this is very important to choose a suitable treatment rate of a disease. In the absence of effective therapeutic treatment and vaccine, the epidemical control strategies are based on taking appropriate preventive measures. Wang and Ruan (2004) considered an SIR epidemic model with constant treatment rate (i.e., the recovery from infected sub-population per unit time) as given below:

$$h(I) = \begin{cases} r, & I > 0 \\ 0, & I = 0 \end{cases},$$

where r is a positive constant and I is the number of infected individuals. They studied stability analysis and showed that this model exhibits various bifurcations. Further, Zhou and Fan (2012) modified the treatment rate to Holling type II

$$h(I) = \frac{\beta I}{(1+\gamma I)}, \quad I \geq 0, \quad \gamma \geq 0, \quad \beta \geq 0.$$

They have shown that, with varying amount of medical resources and their supply efficiency, the target model admits both backward bifurcation and Hopf bifurcation. Dubey et al. (2013) have also used Holling type II, III and IV treatment rates to study their model.

To the best of the knowledge of authors an SIR model with Beddington-DeAngelis type incidence rate and the saturated treatment rate has not been considered. Taking these important facts into account and getting motivated from Kaddar's work (Kaddar, 2009, 2010), we propose an SIR model with Beddington-DeAngelis type incidence rate and the saturated treatment rate.

This chapter is organized as follows. After introduction, Section 2.2 discusses the formulation of the mathematical model and well-posedness of the model. In Section 2.3, we discuss about the equilibrium points of the model, stability of

equilibrium points and existence of Hopf bifurcation. Further, in Section 2.4, numerical simulations are performed to validate the analytical studies. Finally, Section 2.5 concludes this chapter.

2.2 The Mathematical Model

We assume that the entire population is divided into three classes; susceptible individuals (S), infected individuals (I) and removed or recovered individuals (R). Susceptible individuals are those who are healthy and can contract disease under appropriate conditions. Infected individuals are the one who have contracted the disease and now infected with it. These are capable to transfer the disease to susceptible via contacts. As time progresses, infected individuals loose the infectivity, and move to removed or recovered compartment (by auto recovery due to immune response of the body or by treatment). These recovered individuals are immune to infectious microbes and thus do not acquire the disease again. The model is given by following differential equations:

$$\begin{cases} \frac{dS}{dt} = A - \delta_0 S - \frac{\alpha SI}{1+\beta S+\gamma I}, \\ \frac{dI}{dt} = \frac{\alpha SI}{1+\beta S+\gamma I} - \delta_0 I - \delta_1 I - \delta_2 I - \frac{aI}{1+bI}, \\ \frac{dR}{dt} = \delta_2 I - \delta_0 R + \frac{aI}{1+bI}, \end{cases} \tag{2.1}$$

$$S(0) > 0, \quad I(0) \geq 0, \quad R(0) \geq 0.$$

The interaction among the sub-populations can be understood from the schematic diagram (figure 2.1).

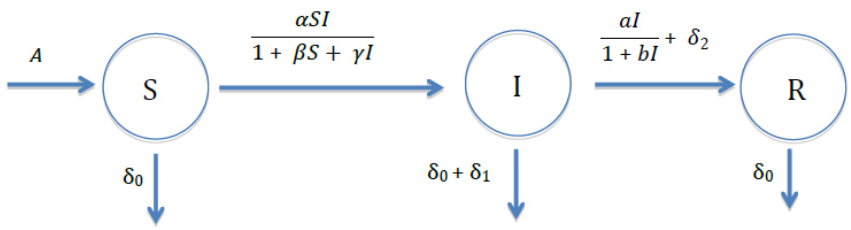

Figure 2.1: Interaction of sub-populations: a flow diagram.

Let the susceptibles be recruited at a constant rate A and δ_0 be the natural death rate of the population in each class. δ_1 be the death rate of infected individuals due to infection and δ_2 be natural recovery rate of infected individuals due to immunity. In model (2.1), we take the incidence rate as Beddington-DeAngelis type:

$$f(S,I) = \frac{\alpha SI}{1+\beta S+\gamma I}. \tag{2.2}$$

Here α is the transmission rate, β is a measure of inhibition effect, such as preventive measure taken by susceptible individuals and γ is a measure of inhibition effect such as treatment with respect to infectives. It is interesting to note that the following three types of incidence rates can be derived from the incidence rate proposed in this chapter:

1. If we set $\beta = \gamma = 0$, then $f(S,I) = \alpha SI$ which is bilinear incidence rate (Anderson et al., 1992; Bailey, 1975; Brauer and Castillo-Chavez, 2001; Hethcote, 2000; Kermack and McKendrick, 1927; Shulgin et al., 1998; Zhonghua and Yaohong, 2010).

2. If we set $\gamma = 0$, then $f(S,I) = \frac{\alpha SI}{(1+\beta S)}$, which is saturated incidence rate with the susceptible individuals. The inhibition effect due to the saturation factor β, results due to the preventive measure to control the spread of epidemic (Korobeinikov and Maini, 2005; Xu and Ma, 2009; Capasso and Serio, 1978).

3. If we set $\beta = 0$, then $f(S,I) = \frac{\alpha SI}{(1+\gamma I)}$, which is saturated incidence rate with the infected individuals. In such a case, the contact between infective and susceptible individuals may saturate at high infection level due to crowding of infective individuals or due to protection taken by susceptible individuals (May and Anderson, 1978; Wei and Chen, 2008; Zhang et al., 2008; Li et al., 2009; Li and Muldowney, 1995; Korobeinikov and Maini, 2005; Xu and Ma, 2009; Capasso and Serio, 1978).

The term $h(I) = \frac{aI}{(1+bI)}$ in system (2.1), represents the treatment term, where a is a positive constant whereas b is a constant taking into account resource limitation (Zhonghua and Yaohong, 2010; Zhou and Fan, 2012). From the above system (2.1)

we can infer that S and I are free from the effect of R. Thus it is enough to consider the following reduced system for the study:

$$\begin{cases} \frac{dS}{dt} = A - \delta_0 S - \frac{\alpha SI}{1+\beta S+\gamma I}, \\ \frac{dI}{dt} = \frac{\alpha SI}{1+\beta S+\gamma I} - \delta_3 I - \frac{aI}{1+bI}, \end{cases} \tag{2.3}$$

where $\delta_3 = \delta_0 + \delta_1 + \delta_2$ and $S(0) > 0$, $I(0) \geq 0$.

2.2.1 Positivity of the Model

For the above system (2.3), we find a region of attraction which is given by Lemma 2.2.1.

Lemma 2.2.1. *The set* $\Omega = \{(S, I) \in R_+^2 : 0 < S + I \leq \frac{A}{\delta_0}\}$ *is a positively invariant region of system (2.3).*

Proof. Let $N = S + I$, then $\dot{N} = \dot{S} + \dot{I} = A - \delta_0 N - (\delta_1 + \delta_2)I - \frac{aI}{1+bI}$
Then,

$$N(t) \leq N(0)e^{-\delta_0 t} + \frac{A}{\delta_0}(1 - e^{-\delta_0 t}).$$

Thus,

$$\lim_{t\to\infty} \sup N(t) \leq \frac{A}{\delta_0}.$$

Furthermore, $\dot{N} < 0$ if $N > \frac{A}{\delta_0}$. This shows that solutions of system (2.3) point towards Ω. Hence Ω is positively invariant and solutions of (2.3) are bounded. □

The above lemma shows that all solutions of the model are non-negative and bounded. Thus the model is biologically well behaved. In the next section, first we find the equilibrium points of system (2.3), then discuss the existence and stability of equilibrium points of system (2.3).

2.3 Equilibrium and Stability Analysis

System (2.3) has only two equilibria: (i) the disease-free equilibrium (DFE) $E_0(S_0, I_0)$, i.e., there is no infection and (ii) the endemic equilibrium $E_1(S^*, I^*)$, i.e., infection persists. We can infer from system (2.3) that the disease-free equilibrium E_0 is trivial equilibrium point and given by $E_0(S_0, I_0) = E_0(\frac{A}{\delta_0}, 0)$.

To compute the basic reproduction number and to study the local stability of the DFE, we use the next generation matrix method (Diekmann et al., 1990; Van den Driessche and Watmough, 2002). Using the same notation as in (Van den Driessche and Watmough, 2002), we define $\dot{x} = F(x) - V(x)$, where $x = [I, S]^T$, $F(x)$ is the matrix of new infection terms and $V(x)$ is the matrix of transfer terms into compartment and out of compartment. The Jacobian of matrices $F(x)$ and $V(x)$ at DFE $E_0(\frac{A}{\delta_0}, 0)$ is given by

$$F = \begin{bmatrix} \frac{\alpha A}{\delta_0 + A\beta} & 0 \\ 0 & 0 \end{bmatrix}, \quad \text{and} \quad V = \begin{bmatrix} (\delta_3 + a) & 0 \\ \frac{\alpha A}{\delta_0 + A\beta} & \delta_0 \end{bmatrix}.$$

Then the spectral radius of new generation matrix (Van den Driessche and Watmough, 2002) (FV^{-1}) gives R_0 i.e.,

$$R_0 = \rho(FV^{-1}) = \frac{A\alpha}{(\delta_3 + a)(\delta_0 + A\beta)},$$

where R_0 is basic reproduction number, the number of newly infected individuals produced by a single infected person when introduced into a completely susceptible population. We conclude the following result using the above computation for R_0 and from Theorem 2 of the paper (Van den Driessche and Watmough, 2002).

Theorem 2.3.1. *The disease-free equilibrium E_0 is locally asymptotically stable if $R_0 < 1$, and is a saddle point with stable manifold locally in the S-direction and unstable manifold locally in the I-direction if $R_0 > 1$.*

Epidemiologically, the above result depicts that small inflow of infected individuals will not be able to spread infection if $R_0 < 1$. In this case the spread of infection is dependent on initial sizes of sub-population. To ensure that the spread of infection is independent of initial sizes of sub-population, we study the global stability of the DFE in the next theorem.

Theorem 2.3.2. *(i) When $b = 0$, then the disease-free equilibrium E_0 is globally asymptotically stable if $R_0 \leq 1$ and (ii) when $b \neq 0$, then the disease-free equilibrium E_0 is globally asymptotically stable if $R_1 = \frac{\alpha A}{(\delta_0 + A\beta)\delta_3} \leq 1$.*

Proof. Let L be the Lyapunov function defined as

$$L = \frac{1}{1+\beta S_0}\left(S - S_0 - S_0 ln\frac{S}{S_0}\right) + I, \quad \text{where} \quad S_0 = \frac{A}{\delta_0}.$$

Differentiating L along the solutions of (2.3) and after simplification, we have

$$\dot{L}(t) = -\left[\frac{\delta_0(S-S_0)^2}{S(1+\beta S_0)} + \frac{\alpha\gamma S_0 I^2}{(1+\beta S+\gamma I)(1+\beta S_0)}\right] + \frac{(\delta_3+a)I}{(1+\gamma I)}[R_0 - 1] + PI^2,$$

where $P = \frac{b}{1+bI}\left(\frac{\alpha S_0}{(1+\beta S_0)} - \delta_3\right)$.

Case I: $b = 0$

Then clearly $P = 0$ and

$$\dot{L}(t) < 0 \text{ if } R_0 \leq 1 \text{ and } \dot{L}(t) = 0 \text{ iff } S = S_0 = \tfrac{A}{\delta_0} \text{ and } I = I_0 = 0.$$

Case II: $b \neq 0$

Then

$$\dot{L}(t) < 0 \text{ if } P < 0 \text{ i.e., } \tfrac{\alpha A}{(\delta_0 + A\beta)} < \delta_3 \text{ and } \dot{L}(t) = 0 \text{ iff } S = S_0 = \tfrac{A}{\delta_0} \text{ and } I = I_0 = 0.$$

This implies that the largest compact invariant set in $\{(S, I) \in \Omega : \dot{L}(t) = 0\}$ is the singleton set $\{E_0\}$. From Lasalle's invariance principle (LaSalle, 1976) disease-free equilibrium is globally asymptotically stable. Hence the theorem follows. □

Remark 2.3.1. *(i) We observe that $R_0 < R_1$ (if $a > 0$) and $R_0 = R_1$ (if $a = 0$). (ii) When $R_1 \leq 1$, then $R_0 \leq 1$.*

This implies that the threshold value for the disease eradication is less if there is no limitation on the medical resources availability in the community ($b = 0$). However, this threshold increases as the availability of the medical resources limits in the community ($b > 0$).

2.3.1 Analysis at $R_0 = 1$

In this section, we analyze the behaviour of system (2.3) when basic reproduction number is equal to one. We notice that the Jacobian matrix of system (2.3) evaluated at $R_0 = 1$ and $\alpha = \alpha^* = \frac{(\delta_3+a)(\delta_0+A\beta)}{A}$ has a simple zero eigenvalue

and another eigenvalue with negative real part. Stability behaviour of equilibrium points at $R_0 = 1$ can not be determined using linearization so we use Center manifold theory (Sastry, 1999). In order to apply center manifold theorem to system (2.3), we made following assumptions:
Let $S = x_1$ and $I = x_2$, then system (2.3) can be rewrite as

$$\begin{cases} \frac{dx_1}{dt} = A - \delta_0 x_1 - \frac{\alpha x_1 x_2}{1+\beta x_1+\gamma x_2}, \\ \frac{dx_2}{dt} = \frac{\alpha x_1 x_2}{1+\beta x_1+\gamma x_2} - \delta_3 x_2 - \frac{a x_2}{1+b x_2}, \end{cases} \tag{2.4}$$

Let J be the Jacobian matrix at $R_0 = 1$ and $\alpha = \alpha^*$. Then

$$J = \begin{bmatrix} -\delta_0 & -\frac{\alpha^* A}{(\delta_0+A\beta)} \\ 0 & \frac{\alpha^* A}{(\delta_0+A\beta)} - \delta_3 - a \end{bmatrix}.$$

Let $w = [w_1, w_2]$ and $u = [u_1, u_2]^T$ be the left eigenvector and right eigenvector of J corresponding to the zero eigenvalue. Then we have

$$w_1 = 0, \quad w_2 = 1 \quad \text{and} \quad u_1 = -\frac{\alpha^* A}{(\delta_0 + A\beta)\delta_0}, \quad u_2 = 1.$$

The nonzero partial derivatives associated with the functions of system (2.4) evaluated at $R_0 = 1$ and $\alpha = \alpha^*$ are

$$\left(\frac{\partial^2 f_2}{\partial x_1 \partial x_2}\right)_{E_0} = \frac{\alpha^*}{(1+\beta S_0)^2}, \quad \left(\frac{\partial^2 f_2}{\partial x_2^2}\right)_{E_0} = -\frac{2\alpha^*\gamma S_0}{(1+\beta S_0)^2},$$

$$\left(\frac{\partial^2 f_2}{\partial x_2 \partial \alpha^*}\right)_{E_0} = \frac{S_0}{(1+\beta S_0)^2}.$$

Then from Theorem 4.1 of (Castillo-Chavez and Song, 2004), the bifurcation constants a_1 and b_1 are

$$a_1 = \sum_{k,i,j=1}^{2} w_k u_i u_j \left(\frac{\partial^2 f_k}{\partial x_i \partial x_j}\right)_{E_0} = w_2 \left(u_1 u_2 \frac{\alpha^*}{(1+\beta S_0)^2} + u_2^2 \left(-\frac{2\alpha^*\gamma S_0}{(1+\beta S_0)^2}\right)\right)$$

$$= -\frac{\alpha^*}{(1+\beta S_0)^2}\left(\frac{\alpha^* A}{(\delta_0 + A\beta)\delta_0} + 2\gamma S_0\right) < 0,$$

and

$$b_1 = \sum_{k,i=1}^{2} w_k u_i \left(\frac{\partial^2 f_k}{\partial x_i \partial \alpha^*} \right)_{E_0} = w_2 \left(u_2 \frac{S_0}{(1+\beta S_0)^2} \right) = \frac{S_0}{(1+\beta S_0)^2} > 0.$$

Thus from Theorem 4.1(iv) of (Castillo-Chavez and Song, 2004), we conclude the following result.

Theorem 2.3.3. *The disease-free equilibrium changes its stability from stable to unstable at $R_0 = 1$ and there exists a positive equilibrium as R_0 exceeds one. Hence system (2.3) undergoes transcritical bifurcation at $R_0 = 1$.*

2.3.2 Existence of Endemic Equilibrium $E_1(S^*, I^*)$

Equating the second equation of system (2.3) to zero, we have

$$\frac{\alpha S^* I^*}{1+\beta S^* + \gamma I^*} - \delta_3 I^* - \frac{a I^*}{1+bI^*} = 0. \tag{2.5}$$

After solving the above equation (2.5), we get S^* in terms of I^* as follows:

$$S^* = \frac{(\delta_3 + a + \delta_3 b I^*)(1+\gamma I^*)}{(\alpha - \delta_3\beta - a\beta) + (\alpha - \delta_3\beta) b I^*}. \tag{2.6}$$

S^* is positive if

$$\alpha > (\delta_3 + a)\beta. \tag{2.7}$$

Now equating the first equation of system (2.3) to zero and solving we get the following quadratic equation in S^*:

$$\delta_0 \beta S^{*2} + (\delta_0 - A\beta + (\delta_0\gamma + \alpha) I^*) S^* - A(1+\gamma I^*) = 0. \tag{2.8}$$

Substituting the value of S^* from equation (2.6) into equation (2.8), we get the following cubic equation in I^*:

$$A_1 I^{*3} + A_2 I^{*2} + A_3 I^* + A_4 = 0, \tag{2.9}$$

where

$$A_1 = \delta_0\beta\gamma{\delta_3}^2b^2 + \delta_3b^2pl,$$

$$A_2 = \delta_0\beta{\delta_3}^2b^2 + 2\delta_0\delta_3(\delta_3+a)\beta\gamma b + b\delta_3ql + bp((\delta_3+a)l + \delta_3bm - Abp),$$

$$A_3 = 2\delta_0\delta_3(\delta_3+a)\beta b + \delta_0\beta\gamma(\delta_3+a)^2 + (\delta_3+a)bmp + q((\delta_3+a)l + \delta_3bm - 2Abp),$$

$$A_4 = \delta_0\beta(\delta_3+a)^2 + (\delta_3+a)mq - Aq^2,$$

and

$$p = (\alpha - \delta_3\beta), \quad q = (\alpha - \delta_3\beta - a\beta), \quad l = (\delta_0\gamma + \alpha), \quad m = (\delta_0 - A\beta).$$

It may be noted that p, $q > 0$ under condition (2.7). Now using Descartes' rule of sign, the cubic equation (2.9) has unique positive real root I^* if anyone of the following holds:

(i) $A_2 > 0$, $A_3 > 0$ and $A_4 < 0$,

(ii) $A_2 > 0$, $A_3 < 0$ and $A_4 < 0$,

(iii) $A_2 < 0$, $A_3 < 0$ and $A_4 < 0$.

We consider first two cases from which we have the following inequalities

$$(\delta_3+a)l + \delta_0\delta_3b > A\alpha b, \tag{2.10}$$

$$R_0 > 1. \tag{2.11}$$

After finding the value of I^*, we can find the value of S^* from equation (2.6). This implies that there exists a unique endemic equilibrium $E_1(S^*, I^*)$ if inequalities (2.7), (2.10) and (2.11) are satisfied.

In the next theorem, we show the uniform persistence of system (2.3). Biologically persistence implies that the sub-populations exist always and will not lead to extinction if initially they are present.

Theorem 2.3.4. *Assume that Lemma 2.2.1 holds and the following inequality is satisfied:*

$$\max\left\{\frac{\alpha A}{\delta_0(\delta_0 + (\beta+\gamma)A)}, \frac{a}{\delta_0 + bA}\right\} < 1.$$

Then system (2.3) *is uniformly persistent.*

Proof. In order to define permanence (uniformly persistence) of the system, we assume that $S(0) > 0$ and $I(0) > 0$. Then we say that system (2.3) is uniformly persistence (Sarwardi et al., 2014; Wang et al., 2001) if there exists positive constants M_1 and M_2 such that

$$M_1 \leq \liminf_{t\to\infty} S(t) \leq \limsup_{t\to\infty} S(t) \leq M_2,$$

$$M_1 \leq \liminf_{t\to\infty} I(t) \leq \limsup_{t\to\infty} I(t) \leq M_2.$$

From Lemma 2.2.1, it follows that

$$\limsup_{t\to\infty} S(t) \leq \frac{A}{\delta_0}, \quad \text{and} \quad \limsup_{t\to\infty} I(t) \leq \frac{A}{\delta_0}.$$

$\Rightarrow$ For any $\epsilon > 0$, $\exists$ a $T > 0$ such that

$$S(t) < \frac{A}{\delta_0} + \epsilon = S_m(say),$$

$$I(t) < \frac{A}{\delta_0} + \epsilon = S_m, \quad \forall t \geq T.$$

From the first equation of model (2.3), we have

$$\frac{dS}{dt} \geq A - \delta_0 S - \frac{\alpha S_m^2}{(1 + (\beta + \gamma)S_m},$$

This implies that

$$\liminf_{t\to\infty} S(t) \geq \frac{1}{\delta_0}\left(A - \frac{\alpha S_m^2}{(1 + (\beta + \gamma)S_m)}\right),$$

which is true for every sufficiently small $\epsilon > 0$. Hence for large t, it follows that

$$\liminf_{t\to\infty} S(t) \geq \frac{A}{\delta_0}\left(1 - \frac{\alpha A}{\delta_0(\delta_0 + (\beta + \gamma)A)}\right) = S_a(say)$$

and

$$S_a > 0 \quad \text{if} \quad \frac{\alpha A}{\delta_0(\delta_0 + (\beta + \gamma)A)} < 1.$$

Again from model (2.3), we have

$$\frac{d}{dt}(S+I) \geq A - \delta_m(S+I) - \frac{aA}{\delta_0 + bA},$$

where $\delta_m = max\{\delta_0, \delta_3\}$.

$$\Rightarrow \liminf_{t\to\infty}(S(t)+I(t)) \geq \frac{A}{\delta_m}\left(1 - \frac{a}{\delta_0 + bA}\right) = I_a(say),$$

We note that $I_a > 0$ if $\frac{a}{\delta_0+bA} < 1$. Hence the theorem follows. □

Theorem 2.3.5. *The endemic equilibrium $E_1(S^*, I^*)$ is locally asymptotically stable iff the following inequalities hold true:*

$$\frac{\alpha S^*(1+\beta S^*)}{(1+\beta S^* + \gamma I^*)^2} < L_1, \tag{2.12}$$

$$\frac{\delta_0 \alpha S^*(1+\beta S^*)}{(1+\beta S^* + \gamma I^*)^2} < L_2, \tag{2.13}$$

where

$$L_1 = \delta_0 + \delta_3 + \frac{a}{(1+bI^*)^2} + \frac{\alpha I^*(1+\gamma I^*)}{(1+\beta S^* + \gamma I^*)^2},$$

$$L_2 = \left(\delta_3 + \frac{a}{(1+bI^*)^2}\right)\left(\delta_0 + \frac{\alpha I^*(1+\gamma I^*)}{(1+\beta S^* + \gamma I^*)^2}\right).$$

Proof. The variational matrix corresponding to endemic equilibrium $E_1(S^*, I^*)$ is

$$M_{E_1} = \begin{bmatrix} -\delta_0 - \frac{\alpha I^*(1+\gamma I^*)}{(1+\beta S^*+\gamma I^*)^2} & -\frac{\alpha S^*(1+\beta S^*)}{(1+\beta S^*+\gamma I^*)^2} \\ \frac{\alpha I^*(1+\gamma I^*)}{(1+\beta S^*+\gamma I^*)^2} & \frac{\alpha S^*(1+\beta S^*)}{(1+\beta S^*+\gamma I^*)^2} - \delta_3 - \frac{a}{(1+bI^*)^2} \end{bmatrix}.$$

The characteristic polynomial of the above matrix is given by the following equation

$$\lambda^2 + a_1\lambda + a_2 = 0, \tag{2.14}$$

where

$$a_1 = \delta_0 + \frac{\alpha I^*(1+\gamma I^*)}{(1+\beta S^* + \gamma I^*)^2} - \frac{\alpha S^*(1+\beta S^*)}{(1+\beta S^* + \gamma I^*)^2} + \delta_3 + \frac{a}{(1+bI^*)^2},$$

$$a_2 = \left(\delta_3 + \frac{a}{(1+bI^*)^2}\right)\left(\delta_0 + \frac{\alpha I^*(1+\gamma I^*)}{(1+\beta S^*+\gamma I^*)^2}\right) - \frac{\delta_0 \alpha S^*(1+\beta S^*)}{(1+\beta S^*+\gamma I^*)^2}.$$

Using the Routh-Hurwitz criteria, it follows that eigenvalues of the above variational matrix have negative real parts iff $a_1 > 0$ and $a_2 > 0$. This implies that the endemic equilibrium $E_1(S^*, I^*)$ is locally asymptotically stable iff inequalities (2.12) and (2.13) hold true. Hence the theorem follows. □

Remark 2.3.2. *If $\alpha = 0$, then condition (2.12) and (2.13) are satisfied. This shows that if the transmission rate of infection is zero or very small, then endemic equilibrium E_1 is locally asymptotically stable.*

Remark 2.3.3. *If α is very large, then condition (2.12) and (2.13) may not hold true, This implies that if the transmission rate of infection is large enough, then the endemic equilibrium may be unstable.*

Remark 2.3.4. *It may be noted that condition (2.12) and (2.13) hold true if*

$$\frac{\alpha S^*(1+\beta S^*)}{(1+\beta S^*+\gamma I^*)^2} < \delta_3 + \frac{a}{(1+bI^*)^2}.$$

From equation (2.14), noticing the sign of real parts of the eigenvalues λ, we can state the following two theorems (2.3.6) and (2.3.7).

Theorem 2.3.6. *Let the following inequality hold true:*

$$\frac{\delta_0 \alpha S^*(1+\beta S^*)}{(1+\beta S^*+\gamma I^*)^2} > L_2, \tag{2.15}$$

then $E_1(S^*, I^*)$, whenever it exists, is a saddle point.

Theorem 2.3.7. *If inequality (2.13) and the following inequality hold true:*

$$\frac{\alpha S^*(1+\beta S^*)}{(1+\beta S^*+\gamma I^*)^2} > L_1, \tag{2.16}$$

then $E_1(S^*, I^*)$, whenever it exists, is unstable.

In the following theorem, we are able to show the existence of a Hopf bifurcation under certain conditions.

Theorem 2.3.8. *Assume that:*

$$\frac{\alpha S^*(1+\beta S^*)}{(1+\beta S^*+\gamma I^*)^2} = L_1, \tag{2.17}$$

and (2.13) hold true, then system (2.3) exhibits Hopf bifurcation near $E_1(S^*, I^*)$.

Proof. Condition (2.17) implies that $a_1 = 0$ in equation (2.14) and condition (2.13) implies that $a_2 > 0$. Thus, equation (2.14) has purely imaginary roots. From Theorem 2.3.5 and Theorem 2.3.7, it follows that the positive equilibrium $E_1(S^*, I^*)$ changes its behavior from stability to instability as the parameter α passes through its critical value $\alpha = \alpha^*$, where

$$\alpha^* = \frac{(1+\beta S^*+\gamma I^*)^2}{S^*(1+\beta S^*) - I^*(1+\gamma I^*)} \left(\delta_0 + \delta_3 + \frac{a}{(1+bI^*)^2}\right).$$

Again we have

$$\begin{aligned}\frac{d}{d\alpha}[tr(M_{E_1})]_{\alpha=\alpha^*} &= \frac{S^*(1+\beta S^*) - I^*(1+\gamma I^*)}{(1+\beta S^*+\gamma I^*)^2} \\ &= \frac{1}{\alpha^*}\left(\delta_0 + \delta_3 + \frac{a}{(1+bI^*)^2}\right) \neq 0.\end{aligned}$$

Hence the system (2.3) shows a Hopf bifurcation near the positive equilibrium E_1 when $\alpha = \alpha^*$. Hence the theorem follows. □

In the following theorem, we show the nonexistence of limit cycle under certain condition.

Theorem 2.3.9. *If* $b(1 + \frac{\beta A}{\delta_0}) < \gamma$, *then model (2.3) does not have any periodic solution in the interior of the positive quadrant of the* SI*-plane.*

Proof. We define a real valued function in the interior of positive quadrant of the SI-plane as follows:

$$H(S, I) = \frac{1+\beta S+\gamma I}{SI} > 0.$$

Let us consider,

$$h_1(S,I) = A - \delta_0 S - \frac{\alpha SI}{1+\beta S+\gamma I},$$
$$h_2(S,I) = \frac{\alpha SI}{1+\beta S+\gamma I} - \delta_3 I - \frac{aI}{1+bI}.$$

Then we have,

$$\begin{aligned} div(Hh_1, Hh_2) &= \frac{\partial}{\partial S}(Hh_1) + \frac{\partial}{\partial I}(Hh_2) \\ &= -\frac{A(1+\gamma I)}{IS^2} - \frac{\delta_0\beta}{I} - \frac{\delta_3\gamma}{S} - \frac{a(\gamma - b(1+\beta S))}{S(1+bI)^2}. \end{aligned}$$

We can see that the above expression is not equal zero and this will not change sign in the positive quadrant of the SI-plane if the inequality $b(1+\frac{\beta A}{\delta_0}) < \gamma$ holds. Then from Dulac's criterion (Sastry, 1999), we can say that model (2.3) does not have any periodic solution in the interior of the positive quadrant of the the SI-plane. Hence the theorem follows. □

Epidemiologically the above theorem refers that if the given inequality hold true then disease will not reoccur.

Since the set Ω defined in Lemma 2.2.1 is a positively invariant set, hence the following theorem is a direct consequence of the Poincare-Bendixon theorem (Sastry, 1999) showing the existence of a limit cycle about the interior equilibrium E_1.

Theorem 2.3.10. *Assume that either (2.13) and (2.16) or (2.15) are satisfied, then model (2.3) has at least one limit cycle in the interior of the positive quadrant of the SI-plane.*

This theorem depicts that if the positive equilibrium point E_1 is a saddle point or unstable then disease may reoccur in future.

In the following theorem, we show that the endemic equilibrium $E_1(S^*, I^*)$ is globally asymptotically stable.

Theorem 2.3.11. *Let the following inequality holds in Ω:*

$$\frac{\alpha^2\gamma S^* I^*(1+\gamma I^*)}{(1+\beta S^*+\gamma I^*)^2} < X_1 X_2, \tag{2.18}$$

where

$$X_1 = \delta_0 + \frac{\alpha I^*(1+\gamma I^*)\delta_0}{(\delta_0+(\beta+\gamma)A)(1+\beta S^*+\gamma I^*)},$$

$$X_2 = \frac{\alpha\gamma S^*\delta_0}{(\delta_0+(\beta+\gamma)A)(1+\beta S^*+\gamma I^*)} - \frac{ab}{1+bI^*}.$$

Then $E_1(S^*, I^*)$ is globally asymptotically stable with respect to all solutions in the interior of the positive quadrant Ω.

Proof. We consider the following positive definite scalar function about E_1:

$$V = \frac{1}{2}(S-S^*)^2 + k\left(I - I^* - I^* ln\frac{I}{I^*}\right),$$

where k is a positive constant to be chosen suitably.

Now differentiating V with respect to time t along the solutions of model (2.3), we get

$$\dot{V} = (S-S^*)\dot{S} + k\frac{(I-I^*)}{I^*}\dot{I}.$$

Substituting the values of $\dot{S}$ and $\dot{I}$ from model (2.3) into the above equation, we get

$$\dot{V} = -a_{11}(S-S^*)^2 + a_{12}(S-S^*)(I-I^*) - a_{22}(I-I^*)^2,$$

where

$$a_{11} = \delta_0 + \frac{\alpha I^*(1+\gamma I^*)}{(1+\beta S+\gamma I)(1+\beta S^*+\gamma I^*)},$$

$$a_{12} = \frac{(\alpha\gamma S^* I^* + k\alpha(1+\gamma I^*))}{(1+\beta S+\gamma I)(1+\beta S^*+\gamma I^*)} - \frac{\alpha S}{(1+\beta S+\gamma I)},$$

$$a_{22} = \frac{k\alpha\gamma S^*}{(1+\beta S+\gamma I)(1+\beta S^*+\gamma I^*)} - \frac{kab}{(1+bI)(1+bI^*)}.$$

Sufficient conditions for $\dot{V}$ to be negative definite are given as follows:

$$a_{11} > 0 \text{ and } a_{12}^2 < 4a_{11}a_{22}.$$

Here, we can see that a_{11} is positive for all values of (S^*, I^*) and another condition for global stability $a_{12}^2 < 4a_{11}a_{22}$ is satisfied if the inequality (2.18) holds true. Hence the theorem follows. □

2.4 Numerical Simulations

In this section, we present computer simulation results for system (2.3) using MatLab 7.10. We choose the set of parameters given in Table 2.1. For these values of parameters, conditions (2.7), (2.10) and (2.11) for the existence of $E_1(S^*, I^*)$ are satisfied and $E_1(S^*, I^*)$ is given by $S^* = 301.0107$, $I^* = 3.7996$. We further note that inequalities (2.12) and (2.13) in Theorem 2.3.5 are satisfied for E_1 to be locally asymptotically stable. The trajectories of S and I with initial conditions $S(0) = 245$, $I(0) = 45$, approach to the endemic equilibrium $E_1(301.0107, 3.7996)$ as shown in figure 2.2.

Table 2.1: List of parameters for model (2.3): dataset 1.

Parameter	Value (Unit)
Recruitment rate (A)	7 $(person\ (d)^{-1})$
Natural death rate of each sub-population (δ_0)	0.02 $(d)^{-1}$
Disease induced death rate of infected (δ_1)	0.05 $(d)^{-1}$
Recovery rate of infected due to auto immunity (δ_2)	0.002 $(d)^{-1}$
Treatment rate (a)	0.2 $(d)^{-1}$
Limitation rate in treatment availability (b)	0.02 $(d)^{-1}$
Transmission rate (α)	0.003 $(person)^{-1}$ $(d)^{-1}$
Inhibition rate due to susceptible (β)	0.002 $(person)^{-1}$
Inhibition rate due to infected (γ)	0.5 $(person)^{-1}$

In figure 2.2, the number of infected population decreases with time due to treatment and these individuals once recovered have become immunized to the infection and will not get reinfected in future. Furthermore, the susceptible population increases to attain a steady state. This increase may be due to decrease in the number of infected individuals because of treatment. Further, we choose the set of parameters as given in Table 2.2.

For these values of parameters given in Table 2.2, we see that the endemic equilibrium $E_1(7.0861, 1.9796)$ exists and all conditions of Theorem 2.3.5 and Theorem 2.3.6 are satisfied. From these simulations and following figure 2.3, we conclude that the endemic equilibrium E_1 is globally asymptotically stable. This implies that for the given set of parameters the trajectories of S and I will converge to

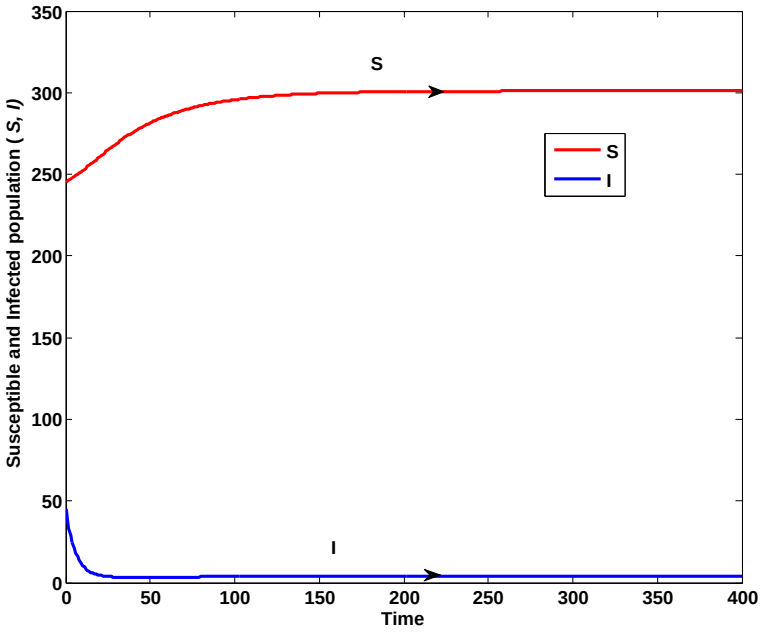

Figure 2.2: Susceptible (S) and infected (I) population vs time.

Table 2.2: List of parameters for model (2.3): dataset 2.

Parameter	Value (Unit)
Recruitment rate (A)	1.97 $(person\ (d)^{-1})$
Natural death rate of each sub-population (δ_0)	0.2 $(d)^{-1}$
Disease induced death rate of infected (δ_1)	0.03 $(d)^{-1}$
Recovery rate of infected due to auto immunity (δ_2)	0.03 $(d)^{-1}$
Treatment rate (a)	0.02 $(d)^{-1}$
Limitation rate in treatment availability (b)	0.02 $(d)^{-1}$
Transmission rate (α)	0.05 $(person)^{-1}$ $(d)^{-1}$
Inhibition rate due to susceptible (β)	0.01 $(person)^{-1}$
Inhibition rate due to infected (γ)	0.1 $(person)^{-1}$

the same value (steady state) E_1 irrespective of the initial value of S and I. This implies that for the given set of parameters the disease will restrict itself to a given endemic zone, no matter what the magnitude of infection and susceptibility is.

In figure 2.3, we considered five different initial values of the susceptible and infected populations. All trajectories starting from different initial values approach to the endemic equilibrium $E_1(7.0861, 1.9796)$. All the details related to initial values (IV) are shown in the legend.

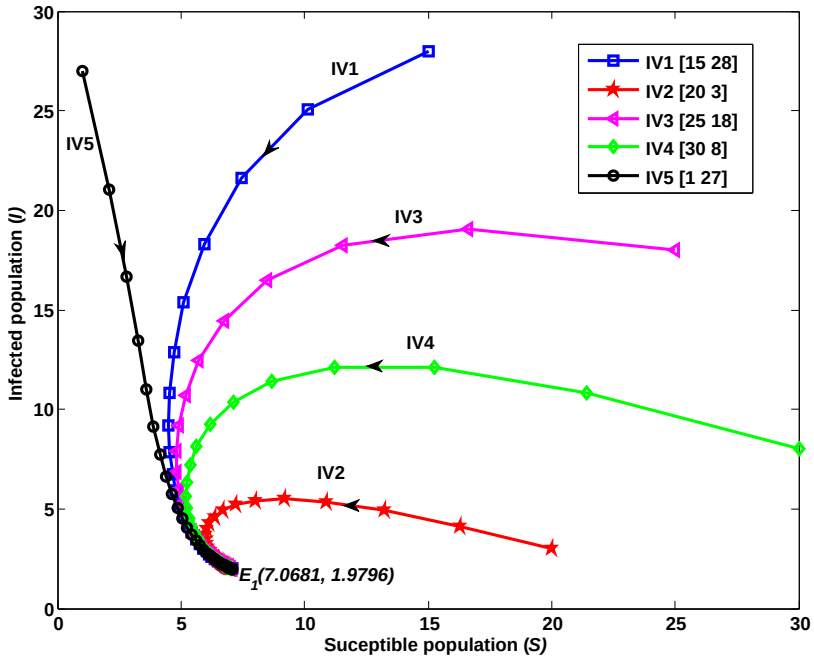

Figure 2.3: Global stability of endemic equilibrium point.

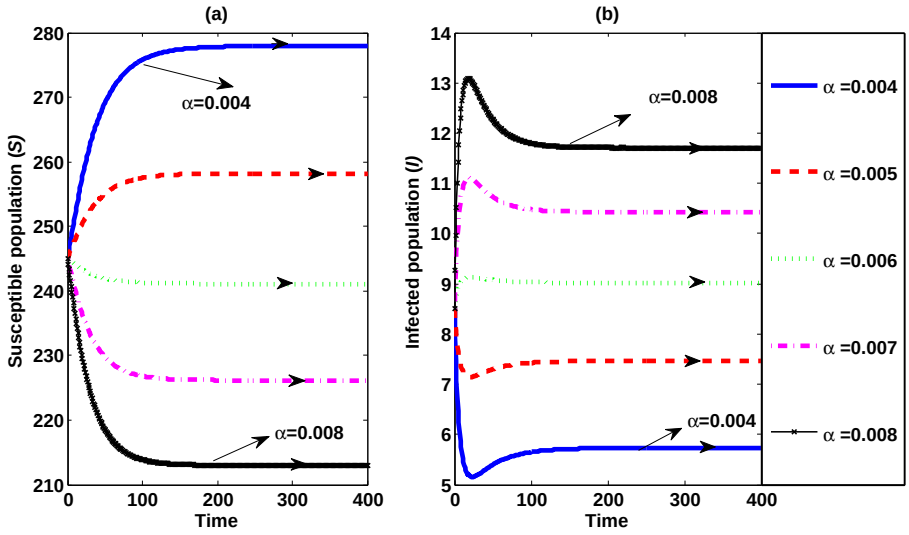

Figure 2.4: Effect of α on S and on I population respectively.

In figures 2.4(a) and 2.4(b), we plotted the effect of incidence rate α on S and I population (respectively) for the set of parameters given in Table 2.1. In figure 2.4(a) we see that as α increases, the susceptible population S shows sharp decline initially and after a threshold value of α (say α=0.006) S decreases slowly and get settled to the its equilibrium point. From figure 2.4(b), we note that when the incidence rate is high then more people will be infected and only the remaining

noninfected people will be susceptible. Whereas when the incidence rate is low then less people are infected and the noninfected i.e., susceptible population is larger. We further note that for a larger incidence rate, the number of infected individuals increases initially, then decreases and finally settles down at its steady state. This decrease is possibly due to immunity and the treatments. When the incidence rate is below a threshold value, then the number of infected individuals first decreases, then increases and finally gets stabilized at its steady state. This increase may be due to the fact that the infection is not removed completely but will persist in the endemic zone due to inability of treatment to eradicate the infection. The details of different trajectories and different values of α used in figures 2.4(a) and 2.4(b) are shown in the legend, which is same for both figures.

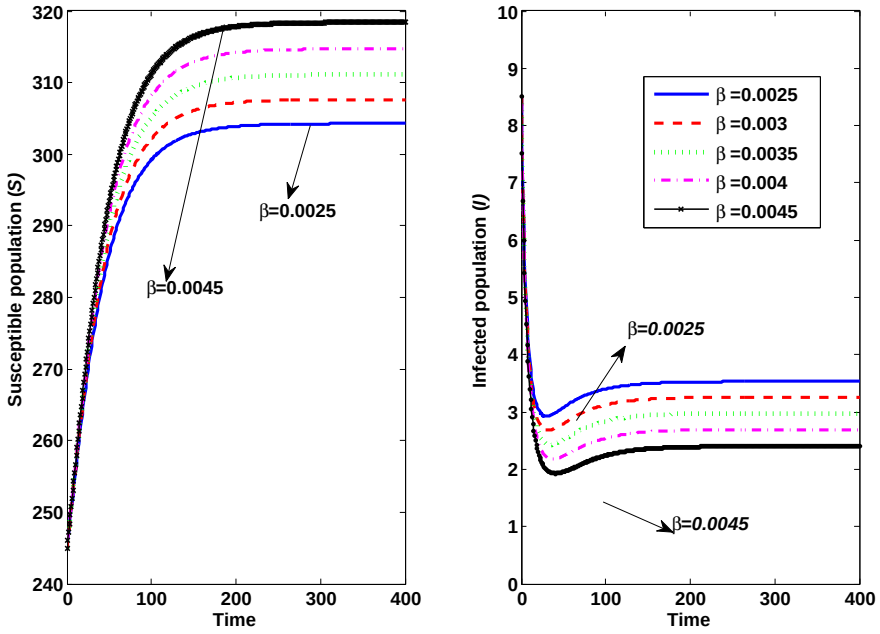

Figure 2.5: Effect of β on S on I population respectively.

In figures 2.5(a) and 2.5(b), we plotted the effect of measure of inhibition β (preventive measure taken by susceptible individuals) on the susceptible and infected populations respectively, with respect to time. From figures 2.5(a) and 2.5(b), we observe that the number of infected individuals decreases as β increases and consequently the susceptible population increases with increase in β . The trajectories of S and I settle down at their respective equilibrium levels. Figure 2.5(b) also shows that initially the number of infected individuals decreases, then increases for

some time and finally obtains its equilibrium level. The initial decrease in number of infectives may be due to the prevention measures taken by susceptibles and the treatments recieved. However, these preventive measures and treatments may not be adequate, thus number of infectives increases slightly and gets stabilized at the steady state. This overall implies that when the inhibition is less then more people are infected and less people are susceptible whereas when the inhibition is more then more people are susceptible and less are infected.

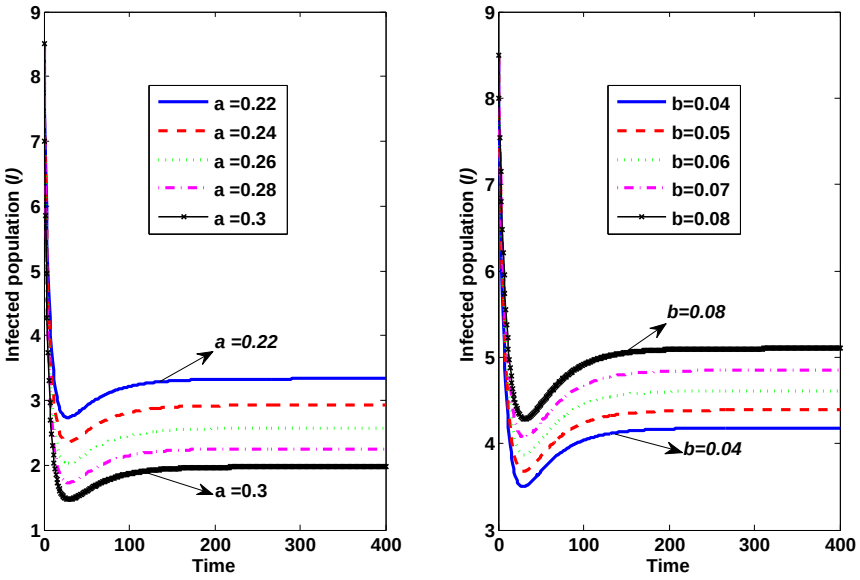

Figure 2.6: Effect of a and b on I population.

Figures 2.6(a) and 2.6(b) show the effect of treatment rate 'a' and limitation to treatment rate 'b' on infected population. Figure 2.6(a) shows a decrease in infected population as treatment rate a increases and it settles down at its steady state. But the disease is not getting totally eradicated it will persist at a much lower level. And figure 2.6(b) shows increase in infected population as b increases which is due to limited availability of resources in community.

Next, we choose another set of parameters for model (2.3) as given in Table 2.3. In addition to the values of parameters given in Table 2.3, we chose $\alpha = 0.15$ $(person)^{-1}$ $(d)^{-1}$. Then it is noted that all the conditions of Theorem 2.3.5 are satisfied. Hence E_1 is locally asymptotically stable. For $\alpha = 0.06$ $(person)^{-1}$ $(d)^{-1}$ (keeping other values of parameters same as in Table 2.3), condition (2.16)

Table 2.3: List of parameters for model (2.3): dataset 3.

Parameter	Value (Unit)
Recruitment rate (A)	7 $person$ $(d)^{-1}$
Natural death rate of each sub-population (δ_0)	0.002 $(d)^{-1}$
Disease induced death rate of infected (δ_1)	0.005 $(d)^{-1}$
Recovery rate of infected due to auto immunity (δ_2)	0.01 $(d)^{-1}$
Treatment rate (a)	2 $(d)^{-1}$
Limitation rate in treatment availability (b)	0.02 $(d)^{-1}$
Inhibition rate due to susceptible (β)	0.02 $(person)^{-1}$
Inhibition rate due to infected (γ)	0.005 $(person)^{-1}$

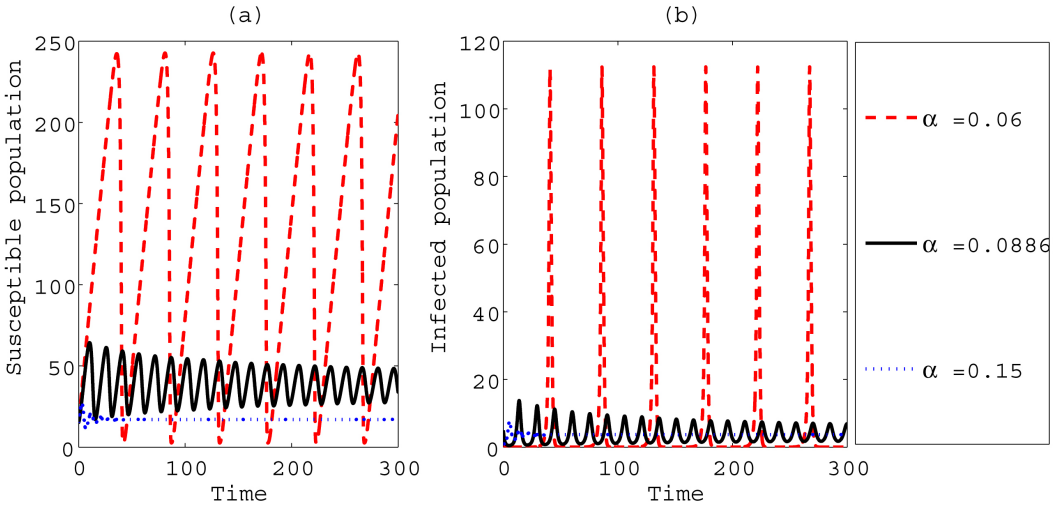

Figure 2.7: Plot of S and I population vs time for different values of α.

in Theorem 2.3.7 is satisfied. Hence E_1 is unstable. Further, for $\alpha = \alpha^* = 0.08863$ $(person)^{-1}$ $(d)^{-1}$ and other values of parameters are same as in Table 2.3, all conditions in Theorem 2.3.8 are satisfied, which shows the existence of Hopf bifurcation near the interior equilibrium E_1. These three different behavior are shown in figures 2.7(a) and 2.7(b) for susceptible and infected populations respectively.

Time series analysis of susceptible and infected population are represented in figure 2.8 and figure 2.9, respectively. Figure 2.8 represents a stable limit cycle for $\alpha = 0.08863$ $(person)^{-1}$ $(d)^{-1}$ and other parameters are same as given in Table 2.3. In figure 2.9, trajectories represent unstable endemic equilibrium for $\alpha = 0.06$ $(person)^{-1}$ $(d)^{-1}$ and other parameters are same as given in Table 2.3.

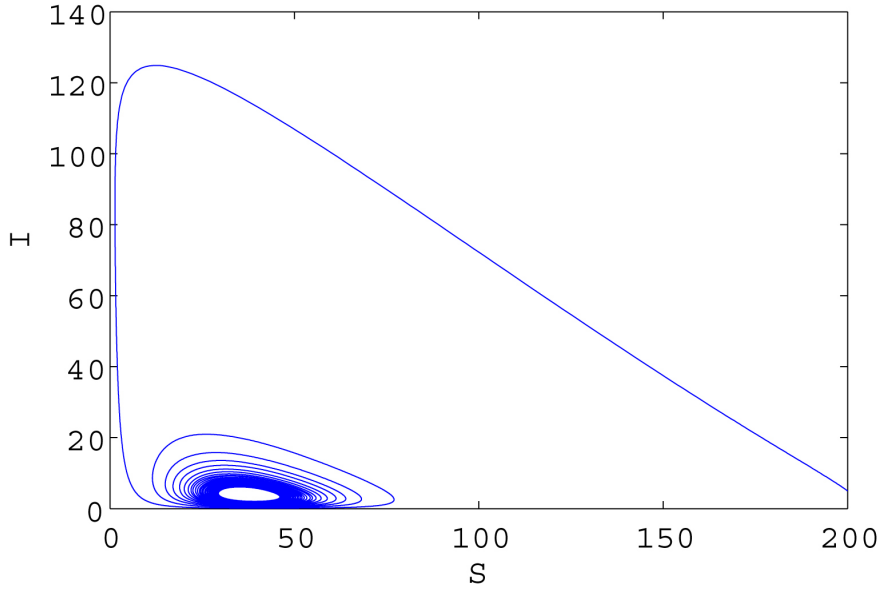

Figure 2.8: Limit cycle in the SI-plane.

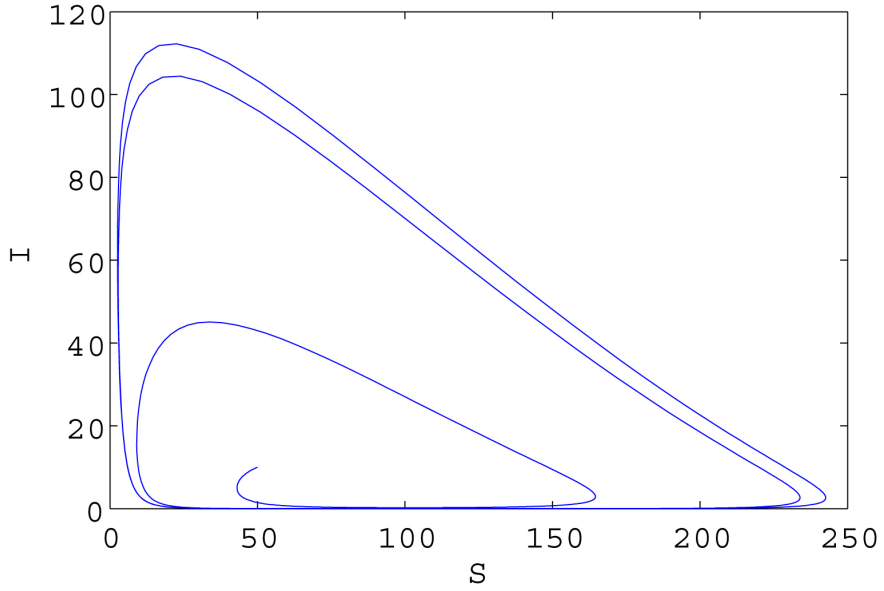

Figure 2.9: Phase portrait of model (2.3) in the SI-plane.

2.5 Conclusions

In this chapter, we have introduced an SIR model with Beddington-DeAngelis type incidence rate and saturated treatment rate. The local and global dynamics of this model has been studied. The analysis of the proposed model shows that there exists only two non-negative equilibrium points; the disease-free equilibrium $E_0(\frac{A}{\delta_0}, 0)$

i.e., when there is no infection (as $I = 0$) and the endemic equilibrium $E_1(S^*, I^*)$ i.e., when infection is present in the community. The DFE is locally asymptotically stable when the basic reproductive number $R_0 < 1$ and globally asymptotically stable when $R_1 = \frac{\alpha A}{(\delta_0 + A\beta)} \leq 1$. It is also noted that the value of the threshold R_1 can be made less than or equal to one by decreasing the incidence rate (α) and by increasing the preventive measures (β) adopted by susceptibles. We have also shown that system (2.3) undergoes transcritical bifurcation at $R_0 = 1$ and there exists an endemic equilibrium when R_0 exceeds one. Biologically this depicts that if the average number of newly infected individuals is more than one then infection will persist. The endemic equilibrium is locally asymptotically stable for $R_0 > 1$ and under conditions stated in Theorem 2.3.5. We observed that the system changes its stability behavior around the endemic equilibrium from stable to unstable as bifurcation parameter α changes and system (2.3) exhibits Hopf bifurcation near endemic equilibrium E_1 for $\alpha = \alpha^*$ (defined in the proof of Theorem 2.3.8). We have found that system (2.3) has periodic solution if inequalities as stated in Theorem 2.3.10 hold true and there is no periodic solution if $b(1 + \frac{\beta A}{\delta_0}) < \gamma$ holds true. The existence of periodic solution shows that the infection may reoccur in future.

The proposed model depicts the presence of endemic equilibrium point that is not only globally asymptotically stable but also independent of the initial values of the susceptible and infected individuals. This indicates the restriction of the disease within endemic zone. This model shows a decrease in infected individuals with both decline in incidence rate α and an enhancement of inhibition rate (preventive measures) i.e., β. It has also been observed that number of infected individuals decreases as the treatment rate (a) increases. However it increases as the limitation on resource (b) increases. This shows that for effective treatment the resource limitation should be minimized.

Chapter 3

An SIR Model with Nonlinear Incidence Rate and Holling Type III Treatment Rate

An approximate answer to the right problem is worth a good deal more than an exact answer to an approximate problem.

John Tukey

In continuation with Chapter 2, we try to explore the transmission dynamics of an SIR model using Crowley-Martin type incidence rate which gives rich dynamics in case of large population. The treatment given to the infected population is given by the Holling type III function (saturated treatment function). Qualitative analysis of the model has been shown using stability theory of ordinary differential equations which has been verified using the numerical simulations.

3.1 Introduction

In the field of epidemiology, interventions (e.g. treatment, vaccination, quarantine etc.) play an important role in controlling the disease spread. The diseases for which treatment is available like flu, tuberculosis, measles (Earn et al., 2002; Rohani et al., 2002); treatment is an useful tool to eradicate them. Several researchers (Hethcote, 2000; Ma et al., 2004; Sun and Yang, 2010; Qiu and Feng, 2010; Moghadas and Alexander, 2006) have studied the effect of treatment using different type of treatment rates. In classical models treatment rate is considered to be proportional to the number of infectives. This treatment rate is not suitable in case of large number of infectives due to availability of limited resources in a community. To study this effect of limited resources, Wang and Ruan (2004) developed the constant removal rate (i.e. recovery per unit time), which is given by:

$$h(I) = \begin{cases} r, & \text{if} \quad I > 0 \\ \\ 0, & \text{if} \quad I = 0 \end{cases}.$$

This removal rate is further improved by taking the following removal rate function (Wang, 2006):

$$h(I) = \begin{cases} rI, & \text{if} \quad 0 \leq I \leq I_0 \\ \\ rI_0, & \text{if} \quad I > I_0 \end{cases},$$

where r and I_0 are positive constants. This removal rate shows that when the capacity of treatment is not reached then the removal rate is proportional to the number of infectives otherwise it takes the maximum capacity. Several authors (Hu et al., 2008; Li et al., 2009) used this removal rate to study the dynamics of their models. Further there was a scope to improve this removal rate. Zhang and Liu (2008) introduced the improved treatment rate as a continuous differentiable function which saturates at its maximum value. This removal rate is given by the term $h(I) = \frac{rI}{1+\alpha I}$, where r is positive constant which denotes the cure rate and α is nonnegative constant which measures the effect of delay in treatment. The term $\frac{1}{1+\alpha I}$ represents inverse of the effect of delay in treatment. This saturated removal

rate is recently studied by Zhou and Fan (2012) with little modification. This saturated removal rate also named as Holling type II removal rate and considered by several authors (Zhonghua and Yaohong, 2010; Dubey et al., 2013, 2015) to study the dynamics of their models.

Dubey et al. (2013) proposed an SEIR model with three different types of removal rates: (i) Holling type II removal rate, (as explained above) (ii) Holling type III removal rate, this is given by the term $h(I) = \frac{\beta I^2}{1+\alpha I^2}$, where β is positive constant and α is nonnegative constant, $h(I)$ is a continuous differentiable function and approaches to its peak or maximum value when the number of infectives is large, and (iv) Holling type IV removal rate, which is given by $h(I) = \frac{\beta I}{\frac{I^2}{a}+I+b}$, where β and a are positive constants and b is nonnegative constant.

In population dynamics, transmission of infection is the process in which susceptibles are getting infected via infected population through the various channels. Transmission plays an important role to study the dynamical behaviour of epidemic models. Recently, several researchers (Li et al., 2009; Capasso and Serio, 1978; Liu et al., 1987; Zhang et al., 2008; Gao et al., 2006; Mukhopadhyay and Bhattacharyya, 2008; Korobeinikov and Maini, 2005; Alexander and Moghadas, 2004; Xu and Ma, 2009) have focused on nonlinear type incidence rate whereas in standard models the incidence rate was defined by law of mass action i.e. bilinear incidence rate (Hethcote, 2000; Zhonghua and Yaohong, 2010; Anderson et al., 1992; Bailey, 1975; Brauer and Castillo-Chavez, 2001; Kermack and McKendrick, 1927; McKendrick, 1925; Shulgin et al., 1998; Ghosh et al., 2004; Shukla et al., 2011).

Different type of nonlinear incidence rates (Dubey et al., 2013, 2015; Beddington, 1975; DeAngelis et al., 1975; Kaddar, 2010; Elaiw and Azoz, 2013) (e.g. Holling type II, DeAngelis-beddington type, etc.) have already been implemented by the authors in their models to study the dynamics of infectious diseases. Considering these facts, we proposed a mathematical model incorporating Crowley-Martin type incidence rate and saturated treatment rate (Holling type III) in SIR model to analyze the cited epidemic situation to control the spread of infection.

In the next section, we present SIR model with nonlinear incidence rate and Holling type III treatment rate.

3.2 The Mathematical Model

We considered compartmental SIR model divided into three compartments; susceptible S, infected I and recovered R compartments respectively. The model is given by the following system of differential equations:

$$\begin{cases} \frac{dS}{dt} = A - \delta_0 S - \frac{\alpha SI}{(1+\beta S)(1+\gamma I)}, \\ \frac{dI}{dt} = \frac{\alpha SI}{(1+\beta S)(1+\gamma I)} - \delta_0 I - \delta_1 I - \delta_2 I - \frac{aI^2}{1+bI^2}, \\ \frac{dR}{dt} = \delta_2 I - \delta_0 R + \frac{aI^2}{1+bI^2}, \end{cases} \tag{3.1}$$

$$S(0) > 0, \quad I(0) \geq 0, \quad R(0) \geq 0.$$

The interaction of the sub-populations can be visualized from the flow diagram as shown in figure (2.1) (Chapter 2). For this chapter, the transmission of susceptiblles to infected individuals is defined through different functional response (Crowley-Martin type) and the recovery of infectives via treatment is also defined by different function (Holling type III) as compared to previous model studied in Chapter 2.

In model equations $\frac{d}{dt}$, represent the rate of change in corresponding compartment. Let A be the recruitment rate of the susceptible and δ_0 be the natural death rate of the population in each class. We assume that the infected individuals die out at the rate δ_1 due to infection. Infected individuals may get recover with auto immunity with the rate δ_2 and join the recovered class. We have also considered the treatment of infected individuals as saturated removal rate. The term $h(I) = \frac{aI^2}{(1+bI^2)}$ represents Holling type III treatment rate (continuously differentiable function), where a and b are nonnegative constants and can be understood as treatment given to the infected individuals and limitation to the treatment availability, respectively (Lamontagne et al., 2008; Hethcote and Van den Driessche, 1991).

Unlike the Holling type II, Holling type III treatment rate grows first very fast and later on increases slowly with increase in number of infection and gets satu-

rated to its maximum level $\frac{a}{b}$ (treatment capacity of community) due to limited availability of resources in the community (Dubey et al., 2013, 2015). The term $\frac{\alpha SI}{(1+\beta S)(1+\gamma I)}$ denotes the monotone nonlinear incidence rate, where α is incidence rate of infection, β and γ are the effects of inhibition due to susceptible individuals and due to infected individuals or γ may also be understood as the crowding effect due to infected individuals. This functional response was introduced by P.H. Crowley and E.K. Martin in 1989 (Crowley and Martin, 1989; Shi et al., 2011) and is known as Crowley-Martin type incidence rate. We notice that other forms of nonlinear incidence rates can be derived from this incidence rate (Dubey et al., 2015):

(i) If we put $\beta = \gamma = 0$, then αSI which is bilinear incidence rate (Zhonghua and Yaohong, 2010; Anderson et al., 1992; Bailey, 1975; Brauer and Castillo-Chavez, 2001; Kermack and McKendrick, 1927; McKendrick, 1925; Shulgin et al., 1998).

(ii) If $\gamma = 0$, then $\frac{\alpha SI}{(1+\beta S)}$, which is saturated incidence rate with the susceptible individuals (Zhang et al., 2008; Gao et al., 2006).

(iii) For $\beta = 0$, we get $\frac{\alpha SI}{(1+\gamma I)}$, which is again saturated incidence rate but with the infected individuals. In such a case, the contact between infective and susceptible individuals may saturate at high infection level due to crowding of infective individuals or due to protection taken by susceptible individuals (Li et al., 2009; Alexander and Moghadas, 2004; Xu and Ma, 2009).

Unlike the Beddington-DeAngelis type incidence rate, the Crowley-Martin type incidence rate considers the effect of inhibition among infectives even in case of high density of susceptible populations (Edwin, 2010). This can be seen as follows:
Beddington-DeAngelis type incidence rate for $S \to \infty$,

$$\lim_{S\to\infty} \frac{\alpha S}{1+\beta S+\gamma I} = \frac{\alpha}{\beta},$$

and Crowley-Martin type incidence rate for $S \to \infty$,

$$\lim_{S\to\infty} \frac{\alpha S}{(1+\beta S)(1+\gamma I)} = \frac{\alpha}{\beta(1+\gamma I)}.$$

From the above system (3.1) we can infer that S and I are free from the effect of R. Thus it is enough to consider the following reduced system for the study:

$$\begin{cases} \frac{dS}{dt} = A - \delta_0 S - \frac{\alpha SI}{(1+\beta S)(1+\gamma I)}, \\ \frac{dI}{dt} = \frac{\alpha SI}{(1+\beta S)(1+\gamma I)} - \delta_3 I - \frac{aI^2}{1+bI^2}, \end{cases} \tag{3.2}$$

where $\delta_3 = \delta_0 + \delta_1 + \delta_2$ and $S(0) > 0$, $I(0) \geq 0$.

3.3 Positivity and Boundedness of the System

For system (3.2), we found that all the solutions initiating in the region defined in Lemma 3.3.1 will eventually lie in the same region even after a long time say for $t \to \infty$ or will always stay in the same region. This can be observed as follows:
Let $N = S + I$, then

$$\dot{N} = \dot{S} + \dot{I} = A - \delta_0 N - (\delta_1 + \delta_2)I - \frac{aI^2}{1+bI^2}.$$

From elementary calculus we have,

$$N(t) \leq N(0)e^{-\delta_0 t} + \frac{A}{\delta_0}(1 - e^{-\delta_0 t}).$$

Thus,

$$\limsup_{t\to\infty} N(t) \leq \frac{A}{\delta_0}.$$

Furthermore, $\dot{N} < 0$ if $N > \frac{A}{\delta_0}$. This shows that solutions of system (3.2) point towards Ω the region defined in Lemma 3.3.1. Hence Ω is positively invariant and solutions of (3.2) are bounded. Thus, we can state the following Lemma.

Lemma 3.3.1. *The set* $\Omega = \{(S, I) : 0 < S + I \leq \frac{A}{\delta_0}\}$ *is a positively invariant region of system (3.2).*

The above lemma shows that all solutions of the model are nonnegative and bounded. Thus the model is biologically well behaved.

In the next section, we discuss the existence of equilibrium points of system (3.2).

3.4 Equilibrium and Stability Analysis

We see that system (3.2) has only two equilibria: (i) the disease-free equilibrium (DFE) $E_0(\frac{A}{\delta_0}, 0)$, the state when infection dies out i.e. $(I = 0)$ and (ii) the endemic equilibrium $E_1(S^*, I^*)$ i.e. state when infection persists $(I \neq 0)$. We can infer from system (3.2) that the disease-free equilibrium E_0 always exists and its existence is trivial.

We compute the basic reproduction number using next generation matrix method and describe the stability behaviour of DFE, which is independent of initial status of sub-populations.

3.4.1 Computation of R_0

Model (3.2) can be rewritten as $\dot{x} = F(x) - V(x)$, where $x = [I, S]^T$ and $F(x)$ be the rate of appearance of new infections and $V(x)$ be the the rate of transfer of individuals into compartment and out of compartment by all other means. Jacobian of $F(x)$ at E_0 is

$$F = \begin{bmatrix} \frac{\alpha A}{(\delta_0 + A\beta)} & 0 \\ 0 & 0 \end{bmatrix},$$

and Inverse of Jacobian of $V(x)$ at E_0 is

$$V^{-1} = \begin{bmatrix} \frac{1}{\delta_3} & 0 \\ \frac{\alpha A}{(\delta_0 + A\beta)\delta_3\delta_0} & \frac{1}{\delta_0} \end{bmatrix}.$$

Then $\rho(FV^{-1})$ gives the spectral radius (largest eigenvalue) of the next generation matrix (FV^{-1}) (Van den Driessche and Watmough, 2002). The spectral radius gives the basic reproduction number, thus

$$R_0 = \rho(FV^{-1}) = \frac{\alpha A}{(\delta_0 + A\beta)\delta_3},$$

where R_0 is basic reproduction number.

Theorem 3.4.1. *(i) The disease-free equilibrium E_0 is locally asymptotically stable if $R_0 < 1$ and is a saddle point with stable manifold locally in the S-direction and*

unstable manifold locally in the I-direction if $R_0 > 1$.

(ii) The disease-free equilibrium E_0 is globally asymptotically stable if $R_0 \leq 1$.

Proof. (i) We find the general variational matrix and then compute the variational matrices corresponding to each equilibrium point. The variational matrix corresponding to DFE $E_0(\frac{A}{\delta_0}, 0)$ is given by

$$J_{E_0} = \begin{bmatrix} -\delta_0 & -\frac{\alpha A}{(\delta_0 + A\beta)} \\ 0 & \frac{\alpha A}{(\delta_0 + A\beta)} - \delta_3 \end{bmatrix}.$$

The above matrix is upper-triangular matrix and has two eigenvalues: $e_1 = -\delta_0$ and $e_2 = \frac{\alpha A}{(\delta_0 + A\beta)} - \delta_3$. We note that $e_1 < 0$ and $e_2 < 0$ if $R_0 < 1$. Again $e_2 > 0$ if $R_0 > 1$. Hence first part of theorem follows.

(ii) To show the global stability of DFE, we use Lasalle's invariance principle (LaSalle, 1976). Let us define positive definite function

$$L = \frac{1}{1 + \beta S_0}\left(S - S_0 - S_0 ln\frac{S}{S_0}\right) + I, \quad \text{where} \quad S_0 = \frac{A}{\delta_0}.$$

Differentiating L along the solutions of (3.2) and simplifying, we get

$$\dot{L}(t) = -\left[\frac{\delta_0(S - S_0)^2}{S(1 + \beta S_0)} + \left(\frac{a}{1 + bI^2} + \frac{\delta_3\gamma}{1 + \gamma I}\right) I^2\right] + \frac{\delta_3 I}{(1 + \gamma I)}[R_0 - 1],$$

$\dot{L}(t) < 0$ if $R_0 \leq 1$ and $\forall\ S, I > 0$, $\dot{L}(t) = 0$ iff $S = S_0 = \frac{A}{\delta_0}$ and $I = I_0 = 0$.

Then let M be the largest invariant set in the set $E = \{(S, I) | \dot{L}(t) = 0\}$ for each element of M, we have $I = 0$. Thus $M = \{E_0\}$ is the singleton set. Thus from Lasalle's invariance principle disease-free equilibrium is globally asymptotically stable. □

3.4.2 Analysis at $R_0 = 1$

In this section, we state and prove the following theorem which characterizes the behavior of the DFE at $R_0 = 1$.

Theorem 3.4.2. *The disease-free equilibrium changes its stability from stable to unstable at* $R_0 = 1$ *and system* (3.2) *exhibits transcritical bifurcation.*

Proof. Linearization matrix of system (3.2) at E_0 and bifurcation parameter $\alpha = \alpha^* = \frac{\delta_3(\delta_0+A\beta)}{A}$ is given by

$$J = \begin{bmatrix} -\delta_0 & -\frac{\alpha^* A}{(\delta_0+A\beta)} \\ 0 & \frac{\alpha^* A}{(\delta_0+A\beta)} - \delta_3 \end{bmatrix}.$$

The matrix J has a simple zero eigenvalue at $R_0 = 1$ and other eigenvalue of the matrix has negative real part. At this stage linearization techniques fail to conclude the behaviour of system (3.2). Centre Manifold Theory is used to study the behaviour of non-hyperbolic equilibrium. Then from Theorem 4.1 of Castillo-Chavez and Song (2004), the bifurcation constants a_1 and b_1 are given by

$$a_1 = \sum_{k,i,j=1}^{2} w_k u_i u_j \left(\frac{\partial^2 f_k}{\partial x_i \partial x_j}\right)_{E_0},$$

and

$$b_1 = \sum_{k,i=1}^{2} w_k u_i \left(\frac{\partial^2 f_k}{\partial x_i \partial \alpha^*}\right)_{E_0},$$

where $u = [\frac{-\alpha^* A}{\delta_0(\delta_0+A\beta)}, 1]^T$ and $w = [0, 1]$ are right eigenvector and left eigenvector of the matrix J corresponding to zero eigenvalue, respectively. Nonzero partial derivatives associated with the system at E_0 and $\alpha = \alpha^*$ are

$$\frac{\partial^2 f_2}{\partial x_1 \partial x_2} = \frac{\alpha^* {\delta_0}^2}{(\delta_0 + A\beta)^2}, \quad \frac{\partial^2 f_2}{\partial x_2^2} = -2\left(a + \frac{\alpha^* \gamma A}{(\delta_0 + A\beta)}\right), \quad \frac{\partial^2 f_2}{\partial x_2 \partial \alpha^*} = \frac{A}{(\delta_0 + A\beta)}.$$

Hence,

$$a_1 = -\frac{{\alpha^*}^2 \delta_0 A}{(\delta_0 + A\beta)^3} - 2\left(a + \frac{\alpha^* \gamma A}{(\delta_0 + A\beta)}\right) < 0 \quad \text{and} \quad b_1 = \frac{A}{(\delta_0 + A\beta)} > 0.$$

This shows that at $R_0 = 1$, DFE changes its stability from stable to unstable and positive equilibrium exists when R_0 exceeds the threshold value i.e. 'one'. This emphasizes that the system exhibits transcritical bifurcation at $R_0 = 1$. □

3.4.3 Existence of Endemic Equilibrium $E_1(S^*, I^*)$

Now we show the existence of endemic equilibrium $E_1(S^*, I^*)$ using isocline method under certain threshold value or conditions. Let us assume that

$$f(S,I) = A - \delta_0 S - \frac{\alpha SI}{(1+\beta S)(1+\gamma I)} = 0, \tag{3.3}$$

$$g(S,I) = \frac{\alpha S}{(1+\beta S)(1+\gamma I)} - \delta_3 - \frac{aI}{1+bI^2} = 0. \tag{3.4}$$

From first isocline (3.3), we observe the following:

(i) when $I = 0$, then $S = \frac{A}{\delta_0} = S_0$.

(ii)
$$\frac{dS}{dI} = -\frac{\partial f/\partial I}{\partial f/\partial S},$$

where

$$\frac{\partial f}{\partial I} = -\frac{\alpha S}{(1+\beta S)(1+\gamma I)^2}, \quad \frac{\partial f}{\partial S} = -\delta_0 - \frac{\alpha I}{(1+\gamma I)(1+\beta S)^2}.$$

This implies that

$$\frac{dS}{dI} = -\frac{\alpha S/(1+\beta S)(1+\gamma I)^2}{\delta_0 + \frac{\alpha I}{(1+\gamma I)(1+\beta S)^2}} < 0.$$

Hence first isocline (3.3) is decreasing function of I.

From second isocline (3.4), we have the following observations:

(i) when $I = 0$, then $S = \frac{\delta_3}{\alpha - \delta_3\beta} = S_1(say)$ and $S_1 > 0$ if

$$\alpha > \delta_3\beta. \tag{3.5}$$

(ii)
$$\frac{dS}{dI} = -\frac{\partial g/\partial I}{\partial g/\partial S},$$

where

$$\frac{\partial g}{\partial I} = -\frac{\alpha\gamma S}{(1+\beta S)(1+\gamma I)^2} - \frac{a(1-bI^2)}{(1+bI^2)^2}, \quad \frac{\partial g}{\partial S} = \frac{\alpha I}{(1+\gamma I)(1+\beta S)^2},$$

This implies

$$\frac{dS}{dI} = \frac{\frac{\alpha\gamma S}{(1+\beta S)(1+\gamma I)^2} + \frac{a(1-bI^2)}{(1+bI^2)^2}}{\frac{\alpha I}{(1+\gamma I)(1+\beta S)^2}}.$$

It can be noted from the above expression that the denominator is always positive and the numerator is positive if $1 - bI^2 > 0$ i.e. $bI^2 < 1$.
After substituting the maximum value of I (i.e. $\frac{A}{\delta_0}$), we get the inequality $bA^2 < \delta_0^2$. Thus, $\frac{dS}{dI}$ is positive if $bA^2 < \delta_0^2$ and $g(S, I)$ is increasing function of I. This implies that the two isoclines (3.3) and (3.4) intersects at a unique point $E^*(S^*, I^*)$ if $S_0 > S_1$ i.e. if $R_0 = \frac{\alpha A}{\delta_3(\delta_0 + A\beta)} > 1$. Thus the endemic equilibrium exists if the following inequalities hold true.

$$bA^2 < \delta_0^2, \tag{3.6}$$

$$R_0 = \frac{\alpha A}{\delta_3(\delta_0 + A\beta)} > 1. \tag{3.7}$$

Remark 3.4.1. *It may be noted that if condition* (3.7) *holds, then condition* (3.5) *is satisfied by default.*

The graphical representation of existence of endemic equilibrium, using the set of parameters given in Table 3.1, is shown in figure 3.1.

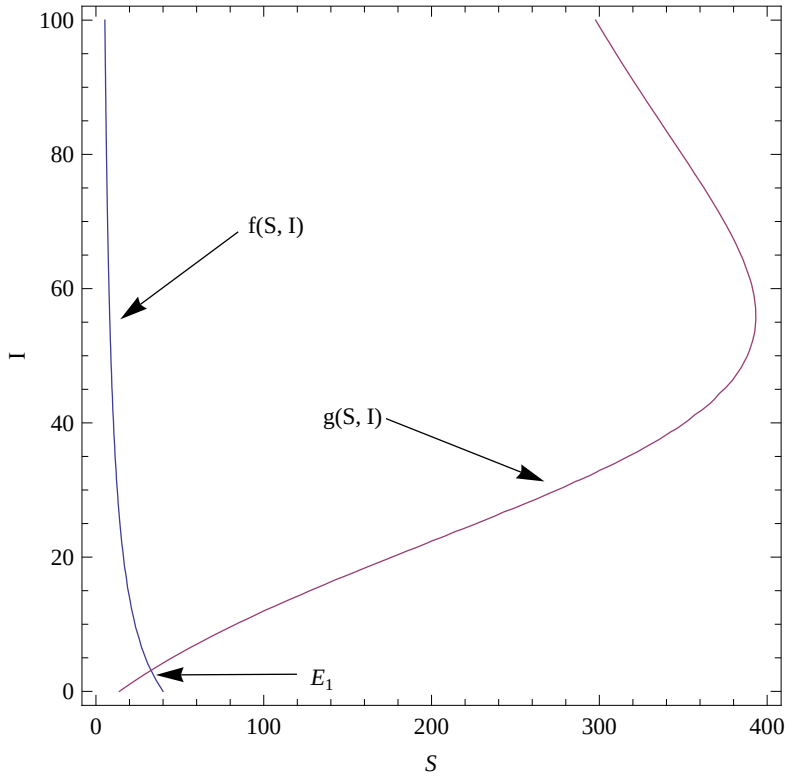

Figure 3.1: Plot of two isoclines showing existence of endemic equilibrium (E_1).

The next theorem shows uniform persistence of system (3.2). Biologically persistence implies that the sub-populations exist always and will not lead to extinction if initially they are present.

Theorem 3.4.3. *Assume that Lemma 3.3.1 holds. Let the following inequality is satisfied:*

$$\max\left\{\frac{\alpha A}{(\delta_0+\beta A)(\delta_0+\gamma A)}, \frac{aA}{\delta_0^2+bA^2}\right\} < 1.$$

Then system (3.2) *is uniformly persistent.*

The proof of theorem is similar to the proof of Theorem 2.3.4 discussed in Chapter 2, hence omitted. Further, we discuss the local and global stability of the endemic equilibrium point $E_1(S^*, I^*)$. We state and prove the following results:

Theorem 3.4.4. *The endemic equilibrium $E_1(S^*, I^*)$ is locally asymptotically stable iff the following inequalities hold true:*

$$\frac{\alpha S^*}{(1+\beta S^*)(1+\gamma I^*)^2} < L_1, \tag{3.8}$$

$$\frac{\delta_0 \alpha S^*}{(1+\beta S^*)(1+\gamma I^*)^2} < L_2, \tag{3.9}$$

where

$$L_1 = \delta_0 + \delta_3 + \frac{2aI^*}{(1+bI^{*2})^2} + \frac{\alpha I^*}{(1+\gamma I^*)(1+\beta S^*)^2},$$

$$L_2 = \left(\delta_3 + \frac{2aI^*}{(1+bI^{*2})^2}\right)\left(\delta_0 + \frac{\alpha I^*}{(1+\gamma I^*)(1+\beta S^*)^2}\right).$$

Proof. The variational matrix corresponding to endemic equilibrium $E_1(S^*, I^*)$ is given as follows:

$$J_{E_1} = \begin{bmatrix} -\delta_0 - \frac{\alpha I^*}{(1+\gamma I^*)(1+\beta S^*)^2} & -\frac{\alpha S^*}{(1+\beta S^*)(1+\gamma I^*)^2} \\ \\ \frac{\alpha I^*}{(1+\gamma I^*)(1+\beta S^*)^2} & \frac{\alpha S^*}{(1+\beta S^*)(1+\gamma I^*)^2} - \delta_3 - \frac{2aI^*}{(1+bI^{*2})^2} \end{bmatrix}.$$

The characteristic polynomial of the above matrix is given by the following equation

$$\lambda^2 + a_1\lambda + a_2 = 0, \tag{3.10}$$

where

$$a_1 = \delta_0 + \frac{\alpha I^*}{(1+\gamma I^*)(1+\beta S^*)^2} - \frac{\alpha S^*}{(1+\beta S^*)(1+\gamma I^*)^2} + \delta_3 + \frac{2aI^*}{(1+bI^{*2})^2},$$

$$a_2 = \left(\delta_3 + \frac{2aI^*}{(1+bI^{*2})^2}\right)\left(\delta_0 + \frac{\alpha I^*}{(1+\gamma I^*)(1+\beta S^*)^2}\right) - \frac{\delta_0\alpha S^*}{(1+\beta S^*)(1+\gamma I^*)^2}.$$

Using the Routh-Hurwitz criteria, it follows that eigenvalues of the above variational matrix have negative real parts iff $a_1 > 0$ and $a_2 > 0$. This implies that the endemic equilibrium $E_1(S^*, I^*)$ is locally asymptotically stable iff inequalities (3.8) and (3.9) hold true. Hence the theorem follows. □

Remark 3.4.2. *It may be noted that conditions (3.8) and* (3.9) *hold if*

$$\frac{\alpha S^*}{(1+\beta S^*)(1+\gamma I^*)^2} < \delta_3 + \frac{2aI^*}{(1+bI^{*2})^2}.$$

Remark 3.4.3. *If $\alpha = 0$, then conditions (3.8) and* (3.9) *in Theorem 3.4.4 and condition mentioned in Remark 3.4.2 are always true. This shows that the decline in the transmission rate of infection increases the feasibility of the stability of the system.*

We note that in characteristic equation (3.10) if $a_2 < 0$, then one eigenvalue is positive and other eigenvalue is negative. Also if $a_1 < 0$ and $a_2 > 0$, then both eigenvalues have positive real parts. Hence we can state the following results.

Theorem 3.4.5. *(i) Let the following inequality holds true:*

$$\frac{\delta_0\alpha S^*}{(1+\beta S^*)(1+\gamma I^*)^2} > L_2.$$

Then $E_1(S^*, I^*)$ is a saddle point.

(ii) Let the following inequality holds true:

$$L_1 < \frac{\alpha S^*}{(1+\beta S^*)(1+\gamma I^*)^2} < \frac{L_2}{\delta_0}.$$

Then $E_1(S^*, I^*)$ is always unstable.

In the following theorem, we show that the endemic equilibrium $E_1(S^*, I^*)$ is globally asymptotically stable.

Theorem 3.4.6. *Let the following inequality holds in the region Ω:*

$$\frac{\alpha^2 \gamma S^* I^*}{(1+\gamma I^*)(1+\beta S^*)^2} < X_1 X_2, \tag{3.11}$$

where

$$X_1 = \delta_0 + \frac{\alpha I^* \delta_0^2}{(1+\beta S^*)(\delta_0+\beta A)(\delta_0+\gamma A)},$$

$$X_2 = \frac{\alpha\gamma\delta_0^2 S^*}{(\delta_0+\beta A)(1+\gamma I^*)(\delta_0+\gamma A)} + \frac{a{\delta_0}^2}{({\delta_0}^2+bA^2)(1+bI^{*2})} - \frac{aI^*\sqrt{b}}{2(1+bI^{*2})^2}.$$

Then the positive equilibrium $E_1(S^*, I^*)$ is globally asymptotically stable with respect to all solutions in the interior of the positive quadrant Ω.

Proof. We take a positive definite scalar function V as follows:

$$V(S,I) = \frac{1}{2}(S-S^*)^2 + \frac{1}{2}k_1\left(I - I^* - I^* ln\frac{I}{I^*}\right).$$

Differentiating V w.r.t. time t along the solutions of model (3.2), we get

$$\dot{V} = -a_{11}(S-S^*)^2 + a_{12}(S-S^*)(I-I^*) - a_{22}(I-I^*)^2$$

where

$$a_{11} = \delta_0 + \frac{\alpha I^*}{PP^*L} > 0,$$

$$a_{12} = -\frac{\alpha S}{PL} + \frac{\alpha\gamma S^* I^*}{P^*LL^*} + \frac{\alpha k_1}{PP^*L},$$

$$a_{22} = k_1\left(\frac{\alpha\gamma S^*}{P^*LL^*} + \frac{a(1-bII^*)}{(1+bI^{*2})(1+bI^2)}\right),$$

$$P = 1 + \beta S,\ P^* = 1 + \beta S^*,\ L = 1 + \gamma I,\ L^* = 1 + \gamma I^*.$$

Sufficient conditions for $\dot{V}$ to be negative definite are $a_{11} > 0$ and $a_{12}^2 < 4a_{11}a_{22}$. The second condition for $\dot{V}$ to be negative definite leads to the inequality (3.11) for $k_1 = \frac{\gamma S^* I^*}{1+\gamma I^*}$. Hence the theorem follows. □

In the following theorem, we show the nonexistence of limit cycle under certain condition.

Theorem 3.4.7. *If $bA^2 < {\delta_0}^2$, then model (3.2) does not have any periodic solution in the interior of the positive quadrant of the SI-plane.*

Proof. We define a real valued function in the interior of positive quadrant of the SI-plane as follows:

$$H(S, I) = \frac{(1 + \beta S)(1 + \gamma I)}{SI} > 0.$$

Let us consider,

$$h_1(S, I) = A - \delta_0 S - \frac{\alpha SI}{(1 + \beta S)(1 + \gamma I)},$$

$$h_2(S, I) = \frac{\alpha SI}{(1 + \beta S)(1 + \gamma I)} - \delta_3 I - \frac{aI^2}{1 + bI^2}.$$

Then we have,

$$div(Hh_1, Hh_2) = \frac{\partial}{\partial S}(Hh_1) + \frac{\partial}{\partial I}(Hh_2)$$

$$= -\frac{A(1 + \gamma I)}{IS^2} - \frac{\delta_0\beta(1 + \gamma I)}{I} - \frac{\delta_3\gamma(1 + \beta S)}{S} - \frac{a(1 - bI^2 + 2\gamma I)(1 + \beta S)}{S(1 + bI^2)^2}.$$

We can see that the above expression is not zero and this will not change sign in the positive quadrant of the SI-plane if the inequality $bA^2 < {\delta_0}^2$ holds. Then by Dulac's criterion (Sastry, 1999), it is apparent that model (3.2) does not have any periodic solution in the interior of the positive quadrant of the SI-plane. □

3.5 Numerical Simulations

In this section, we present simulation results for model (3.2) using Mathematica and MatLab 7.10. Mathematica has been used for calculation of symbolic mathematical expressions while Matlab is used to plot the figures.

Table 3.1: Parameter values and units for model (3.2)

Parameters	Value (Unit)
Recruitment rate (A)	2 $(person\ (d)^{-1})$
Natural death rate of each sub-population (δ_0)	0.05 $(d)^{-1}$
Disease induced death rate of infected (δ_1)	0.001 $(d)^{-1}$
Recovery rate of infected due to auto immunity (δ_2)	0.002 $(d)^{-1}$
Treatment rate (a)	0.02 $((d)^{-1})$
Limitation rate in treatment availability (b)	0.0004 $(person)^{-1}$
Transmission rate (α)	0.004 $(person)^{-1}$ $(d)^{-1}$
Inhibition rate due to susceptible (β)	0.004 $(person)^{-1}$ $(d)^{-1}$
Inhibition rate due to infected (γ)	0.002 $(person)^{-1}$ $(d)^{-1}$

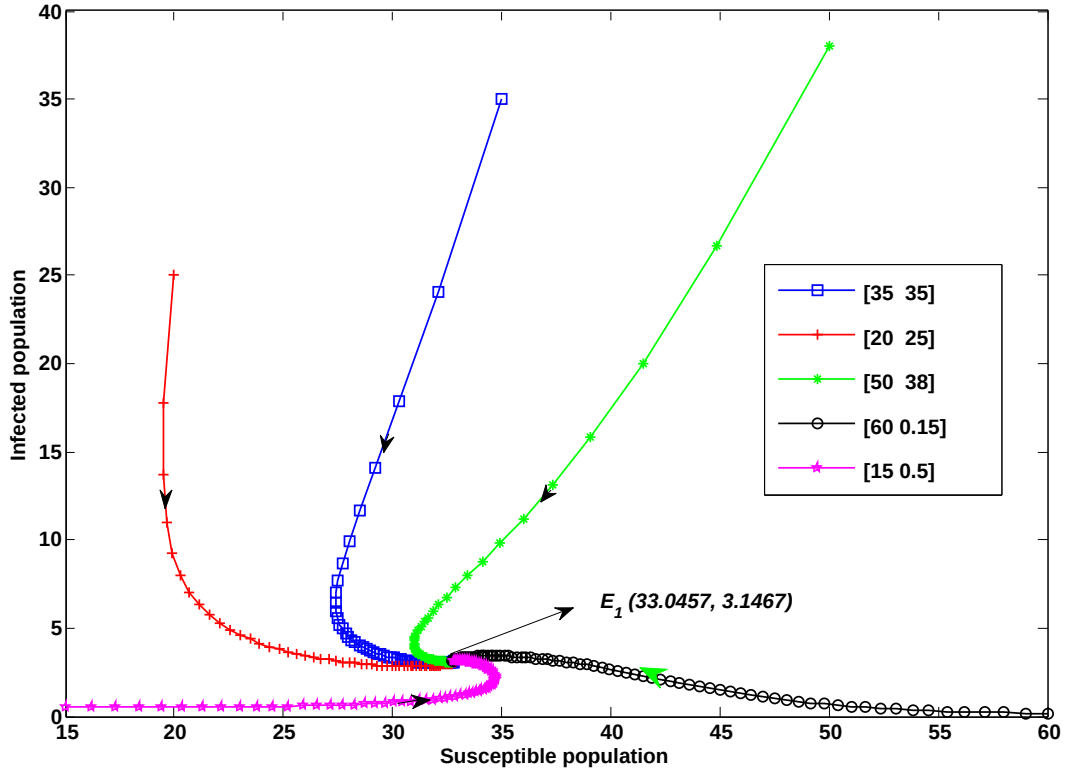

Figure 3.2: Phase portrait of endemic equilibrium point E_1.

We chose the dataset of parameters as given in Table 3.1 for model (3.2). For this set of parameters, the basic reproduction number R_0 is $2.6025 > 1$ and other conditions for the existence of endemic equilibrium are satisfied. Endemic equilibrium point $E_1(S^*, I^*)$ is given by $S^* = 33.0457$ and $I^* = 3.1467$. The phase portrait of susceptible population and infected population (figure 3.2) shows that the trajectories initiating from different initial points (initial values are given in the legend) approach to the unique equilibrium point $E_1(33.0457, 3.1467)$. This is

evident from figure 3.2 that the endemic equilibrium point is globally asymptotically stable for this dataset. Thus the stability of the endemic equilibrium point is independent of initial status of susceptibles and infectives. In figures 3.3(a)

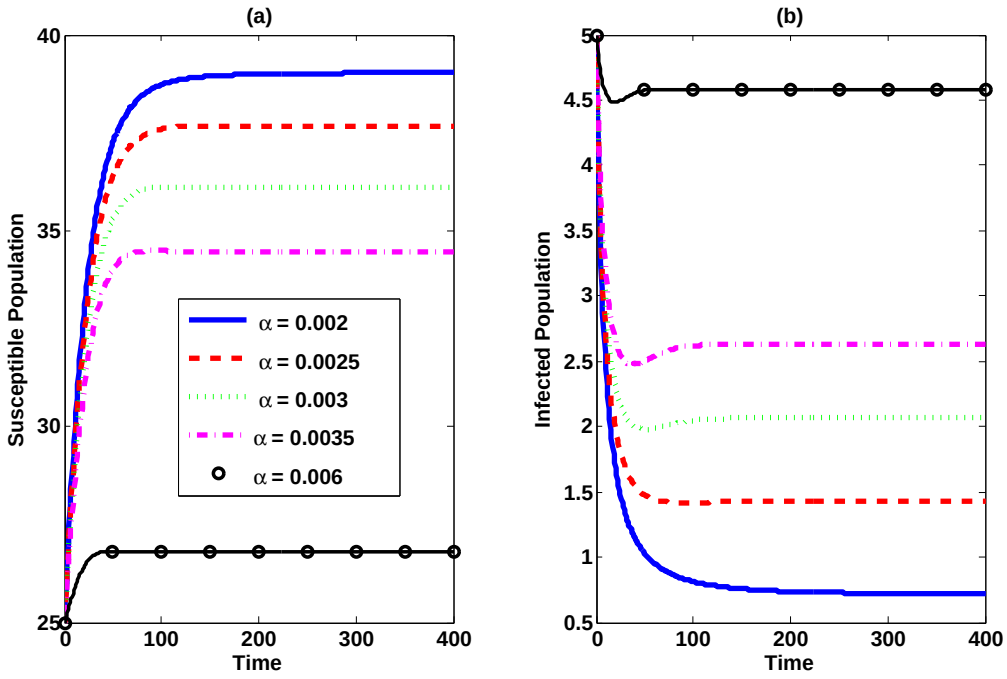

Figure 3.3: Effect of incidence rate (α) on S and I.

and 3.3(b), we plotted the effect of variation of incidence rate α on susceptible S and infected population I for the values of parameters given in Table 3.1. For higher values of α the trajectory corresponding to susceptible population settles down at low level while trajectory for infected population first decreases and then attains its steady state at high level of infection. The initial decrease in infection is due to treatment available in the community. The number of infectives decreases with decrease in incidence of infection which can be controlled by treatment. We have considered Crowley-Martin type nonlinear incidence rate so the effect of the constant β (involved in the incidence expression) i.e. measure of inhibition with respect to susceptible is plotted in figures 3.4(a) and 3.4(b). When β is low the trajectory corresponding to susceptible population settles at a lower level and the trajectory corresponding to infected population settles at high level of infection. This shows that the number of susceptible can be increased and the number of in-

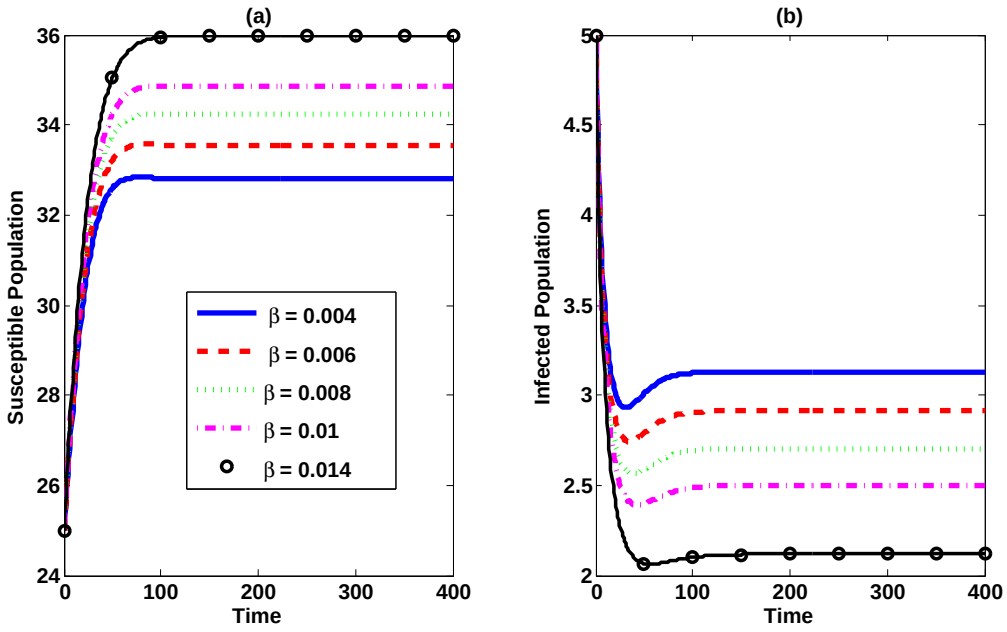

Figure 3.4: Effect of β on S and I.

fectives can be decreased by increasing the value of β i.e. by increasing the density of preventive measures taken by susceptible individuals.

The effect of treatment given to the community is shown in figures 3.5(a) - 3.5(d) using different treatment rates. It may be noted here that the legend for figures 3.5(a) and 3.5(c) is same and the legend for figures 3.5(b) and 3.5(d) is same. Figure 3.5(a) shows the effect of treatment on the infected population and figure 3.5(b) shows the effect of limitation to the treatment resources on infected population with Holling type III treatment rate while the same has been shown in figures 3.5(c) and 3.5(d) using Holling type II treatment rate for comparison purposes. In absence of treatment ($a = 0$) the infection increases very rapidly and settles to its steady state (figure 3.5(a)), on the contrary, when there is no restriction to availability of treatment ($b = 0$) the infection decreases sharply and get settled to its steady state (figure 3.5(b)). Figures 3.5(a) and 3.5(c) show that the number of infected individuals can be decreased faster in the case of Holling type III treatment rate in comparison to that of Holling type II treatment rate (from Chapter 2). When there is low availability of treatment, infection is high.

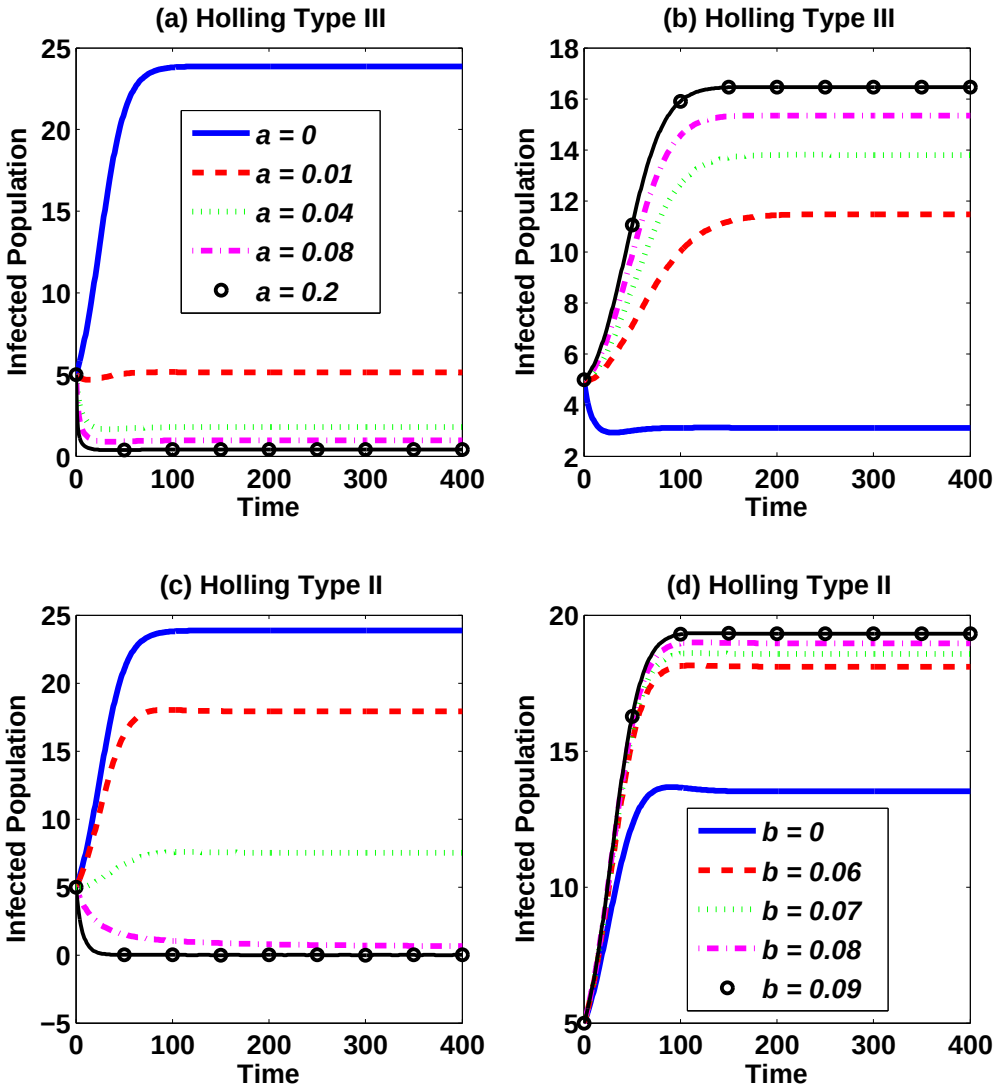

Figure 3.5: Effect of a and b on I with HTIII and HTII treatment rates.

When the ample quantity of treatment is available in the community the infection almost dies out. Infection gets increase with increase in limit to the availability of treatment.

3.6 Conclusions

In this chapter, we addressed the pharmaceutical intervention to control the infection and a monotone nonlinear incidence rate to get the better insight of spread of infection among the populations. We found that the model has two equilibria: disease-free equilibrium E_0 and endemic equilibrium E_1. It has been shown that the infection persists along with the low availability of treatment when basic

reproduction number is greater than one. The local and global stability of each equilibria has been studied and found that persistence or eradication of infection is independent of initial status of the sub-populations and system is uniformly persistence under the condition stated in Theorem 3.4.3.

This is also evident from numerical simulations that the infection increases with increase in incidence but settles at a lower level due to availability of treatment. Further infection will decrease with the increase in measure of inhibition taken by susceptibles. It is also found that the eradication of infection is possible only when the treatment given to the population managed according to the availability of resources. It has also been observed that the equilibrium point changes its stability from stable to unstable at $R_0 = 1$ i.e. model exhibits transcritical bifurcation at $R_0 = 1$. Nonexistence of periodic solution under the condition defined in Theorem 3.4.7 ensures that the infection will not reoccur in future under mentioned condition.

Chapter 4

Role of Media and Treatment on an SIR Model

Health is not mainly an issue of doctors, social service and hospitals, it is an issue of social justice.

Park

"*Prevention is better than cure*" is a proven fact. This advises us to take necessary preventive measures to be away from any kind of infection or to reduce the further spread of any outbreak. But this is also an important fact that ultimately cure is needed to eliminate the infection or to complete eradication of epidemic. In this chapter, we try to model the aforesaid phenomenon in real world i.e. the proposed model deal with the effect of dissemination of awareness through media as well as treatment. The model is simple SIR model which is assumed to be divided into four classes depending on the modeling requirement. Stability analysis of the model has been performed which has been validated using simulations.

4.1 Introduction

World Health Organization report (WHO, 2008) has shown that approximately 15 million people die each year due to infectious diseases. When an epidemic spreads in a society, there is a need for effective treatment to control the epidemic. Moreover, vaccination is a prophylactic measure to control the spread of the disease among susceptible individuals. Medical facilities and subsequent therapies may require some time to be developed and implemented. If individuals are familiar with the disease and have knowledge about the transmission modality of infection then they can take necessary preventive measures to avoid infection. The susceptible individuals may isolate themselves from infected individuals or they can take necessary prophylactic measures. Infection can be reduced by awareness among susceptibles but will not be eradicated. To control the spread of further infection and to eradicate the infection from the society, there is a requirement of not only the awareness programs but also treatment.

Literature shows that several SIR models have been studied with different type of nonlinear incidence rates. Authors (Pathak et al., 2010; Kaddar, 2010; Xu, 2013; Buonomo and Lacitignola, 2011) analyzed the dynamics of SIR models with different type of nonlinear incidence rates. Pathak et al. (2010) proposed an SIR model with an asymptotic homogeneous transmission function and concluded that the spread of disease decreases as the social or psychological protection measures for the infection increases. Kaddar (2010) studied the role of incubation period on the dynamics of an SIR model. Further, Xu (2013) investigated the global stability dynamics of an SEIR epidemic model with disease relapse, a saturated incidence rate and a time delay describing the latent period of the disease. Buonomo and Lacitignola (2011) studied an SIR model with vaccination and treatment and obtained threshold on the basic reproduction number to control the spread of disease.

Surveys indicate that people who watch television (Khanam et al., 1997; Rahman and Rahman, 2007) or read article or magazine related to the public health on daily basis are more aware about the ways of spread of infection as compared to those who do not do so. Awareness programs run by media campaigns induce

the behavioral changes in the susceptibles towards infection. These campaigns of awareness through media and education focus on individual's knowledge about the disease transmission and facilitate measures that can reduce the chances of being infected. Annual report of NACO (2010) shows that the awareness campaigns about the HIV/AIDS driven by government are very helpful in controlling the epidemic. Many authors (Liu and Cui, 2008; Cui, Tao, Zhu et al., 2008; Cui, Sun and Zhu, 2008) have introduced models showing the effect of awareness programs run by media to control the spread of epidemic. Liu et al. (2007) have studied the psychological impact on epidemic. They have postulated that an increase in infection level reduces the effective contacts but they did not take into account factors of mandatory quarantine and isolation. Funk et al. (2009) studied the impact of awareness programs on the spread of epidemic using mathematical modeling and showed that awareness programs play a vital role in reducing the spread of epidemic. Further, Kiss et al. (2010) proposed an SIS type compartmental model for Sexually Transmitted Infections with the assumption that the whole population is aware of risk but only a certain proportion chooses to respond by limiting their contact with infectives and seeking faster treatment. They have assumed that the total number of susceptibles remains relatively unchanged. The demographic factors such as natural birth rate, death rate, immigration were ignored. However, in all these studies, the density of awareness programs is considered to be a constant which need not be true in real life.

Misra, Sharma and Shukla (2011) proposed a non-linear mathematical model for the effects of awareness programs on the spread of infectious diseases, like flu. They have shown that awareness programs through the media campaigning are helpful in decreasing the spread of infectious diseases. This is done by isolating a fraction of susceptibles from infectives. Further, Misra, Sharma and Singh (2011) proposed a non-linear mathematical model with delay to study the dynamics of the effects of awareness programs on prevalence of any epidemic. In this study, they have shown that though awareness programs can not eradicate the infection but they can help in controlling disease prevalence. They have also shown that time delay in execution of awareness programs destabilizes the system and periodic

solutions may arise through Hopf bifurcation. Recently, Samanta et al. (2013) proposed a mathematical model to assess the effect of awareness programs by media on the prevalence of infectious diseases. They have shown that if the rate of implementation of awareness programs through the media increases, the number of individuals getting infected decline and the system remains stable up to a threshold value of implementation of awareness program. But, the system becomes unstable above that threshold. They have also observed that for moderate range of value of immigration rate the system shows unstable dynamics, but for lower and higher values the system becomes stable. Further, Cai et al. (2009) studied the effect of treatment on HIV/AIDS epidemic in their model and showed that the disease may persist or die out depending on treatment parameter values. They have also considered time delay in their model to study the effect of time on dynamics of endemic equilibrium. Recently, Sharma and Misra (2014) studied the impact of awareness program on the coverage of vaccination of hepatitis B. They showed that vaccination coverage can be increased and prevalence of the disease can be decreased by taking appropriate steps by media.

Since awareness programs alone can not eradicate the disease, treatment of the disease in infected population must go along with awareness programs for the susceptible. The effect of treatment has not been considered in the models studied by Misra, Sharma and Shukla (2011); Misra, Sharma and Singh (2011). Keeping this aspect in view, we present here an SIR model to study the impact of two important parameters: (i) awareness programs (run by media) and (ii) treatment on the spread of an infectious disease.

4.2 The Mathematical Model

We assume that the whole population is first divided into three compartments, namely susceptible population (S), infected population (I) and recovered population (R). Next, we assume that a part of the susceptible population forms another class called susceptible aware population (S_a). This class develops due to awareness programs driven by social/electronic media of density M at any time t. When the media interacts with the susceptible population, it starts influencing them to

take appropriate measures so that they should not be infected by the pathogens. This media influence is initially low and increases as the infection increases. But media can influence susceptible population only upto a certain level after that it gets saturated due to the resource limitation (Liu et al., 2007; Misra, Sharma and Singh, 2011).

Generally media sources do not deal with the same topic for a very long time. Their emphasis changes with changing social/political issues. Moreover, their impact may not reach to the entire population due to factors like time shortage, illiteracy and financial limitation of population as well as resources required to propagate information. Thus, neither media nor its impact can go on increasing forever and therefore attains saturation. Hence we assume that the impact of media on susceptible populations is governed by Holling Type II functional response (Liu et al., 2007; Misra, Sharma and Singh, 2011). It is also considered that the growth rate of the cumulative density of awareness programs driven by the media is proportional to the number of infectives present in the population. Further, the awareness about the disease will alert susceptibles to isolate themselves from infectives and avoid being infected by forming a separate class. The effect of depletion of awareness programs has also been considered. We also consider the treatment rate as saturated treatment rate due to limited availability of resources in community. The model is given by the following system of differential equations:

$$\begin{cases} \frac{dS}{dt} = A - \delta_0 S - \alpha SI - \frac{\beta SM}{1+\gamma M} + \delta_3 S_a, \\ \frac{dI}{dt} = \alpha SI - \delta_0 I - \delta_1 I - \delta_2 I - \frac{aI}{1+bI}, \\ \frac{dS_a}{dt} = \frac{\beta SM}{1+\gamma M} - \delta_0 S_a - \delta_3 S_a, \\ \frac{dM}{dt} = \mu I - \mu_0 M, \\ \frac{dR}{dt} = \delta_2 I - \delta_0 R + \frac{aI}{1+bI}, \end{cases} \tag{4.1}$$

$$S(0) > 0, \quad I(0) > 0, \quad S_a(0) \geq 0, \quad M(0) \geq 0, \quad R(0) \geq 0.$$

Let the susceptibles be recruited at a constant rate A and δ_0 be the natural death rate of the population in each class. δ_1 be the death rate of infected individuals due to infection and δ_2 be natural recovery rate of infected individuals due to immu-

nity. Realistically speaking, the whole aware population may not keep themselves isolated. Due to negligence or loss of memory, a part of the aware population may become susceptible to the disease. Let δ_3 be the rate of transfer of aware individuals to susceptible class and μ be the implementation rate of awareness programs. The awareness programs may be slowed down due to treatment of the disease or due to the diversion caused by other hot topics of high priority coming in the media. Let μ_0 be the depletion rate of awareness programs, α is the incidence rate which is the number of persons getting infected per unit of time.

For any outbreak of the disease, its treatment initially is slow due to non-availability of the treatment techniques and appropriate drugs. After some time, the treatment grows with the improvement in hospitals' conditions, effective drugs and skillful techniques. Thus, it is better to use saturated treatment rate which is given by

$$h(I) = \frac{aI}{1 + bI},$$

where a and b are positive constants. In the above treatment function, $\frac{a}{b}$ ($\frac{a}{b} = \lim_{I\to\infty} h(I)$) denotes the maximum supply of medical resources per unit time and $\frac{1}{1+bI}$ denotes the reverse effect of infected individuals being delayed for treatment (Zhou and Fan, 2012).

Similar interpretation may be given for the term $f(M) = \frac{\beta M}{1+\gamma M}$, which denotes the effect of media coverage on susceptible population. β can be thought of as the dissemination rate of awareness programs among susceptibles and γ limits the effect of awareness programs on susceptibles, $\frac{\beta}{\gamma}$ is the maximum effect that media can put on susceptibles.

From the above system (4.1) we can infer that S, I, S_a and M are free from the effect of R as we assume immunity in recovered individuals. Thus, it is enough to consider the following sub-system:

$$\begin{cases} \frac{dS}{dt} = A - \delta_0 S - \alpha SI - \frac{\beta SM}{1+\gamma M} + \delta_3 S_a, \\ \frac{dI}{dt} = \alpha SI - \delta_0 I - \delta_1 I - \delta_2 I - \frac{aI}{1+bI}, \\ \frac{dS_a}{dt} = \frac{\beta SM}{1+\gamma M} - \delta_0 S_a - \delta_3 S_a, \\ \frac{dM}{dt} = \mu I - \mu_0 M. \end{cases} \tag{4.2}$$

Let $S + I + S_a = N$, then system (4.2) reduces to

$$\begin{cases} \frac{dI}{dt} = \alpha(N - I - S_a)I - \delta I - \frac{aI}{1+bI}, \\ \frac{dS_a}{dt} = \frac{\beta(N-I-S_a)M}{1+\gamma M} - \delta_0 S_a - \delta_3 S_a, \\ \frac{dN}{dt} = A - \delta_0 N - (\delta_1 + \delta_2)I - \frac{aI}{1+bI}, \\ \frac{dM}{dt} = \mu I - \mu_0 M, \end{cases} \tag{4.3}$$

where $\delta = \delta_0 + \delta_1 + \delta_2$.

For the above system (4.3), a region of attraction has been found and it is given in Lemma 4.2.1.

Lemma 4.2.1. *The set* $\Omega = \{(I, S_a, N, M) \in \Re^4_+ : 0 < I + S_a \leq N \leq \frac{A}{\delta_0}, 0 \leq M \leq \frac{\mu A}{\delta_0 \mu_0}\}$ *is a positively invariant region of system (4.3).*

Proof. Let $W(t) = (N(t), M(t))$,then

$$\frac{dW}{dt} = \left(\frac{dN}{dt}, \quad \frac{dM}{dt}\right) = \left(A - \delta_0 N - (\delta_1 + \delta_2)I - \frac{aI}{1+bI}, \quad \mu I - \mu_0 M\right), \tag{4.4}$$

We note that $\frac{dN}{dt} \leq A - \delta_0 N \leq 0$ if $N \geq \frac{A}{\delta_0}$ and $\frac{dM}{dt} \leq \frac{\mu A}{\delta_0} - \mu_0 M \leq 0$ if $M \geq \frac{\mu A}{\mu_0 \delta_0}$. From equation (4.4), $\frac{dW}{dt} \leq 0$ for $N \geq \frac{A}{\delta_0}$ and $M \geq \frac{\mu A}{\mu_0 \delta_0}$.

This shows that the set Ω is a positively invariant set.

From the third equation of model (4.3), we have

$$\frac{dN}{dt} \leq A - \delta_0 N,$$

which implies that

$$\limsup_{t \to \infty} N(t) \leq \frac{A}{\delta_0}.$$

From the last equation of model (4.3) it follows that

$$\frac{dM}{dt} \leq \frac{\mu A}{\delta_0} - \mu_0 M,$$

and hence

$$\limsup_{t\to\infty} M(t) \leq \frac{\mu A}{\delta_0 \mu_0}.$$

This completes the proof of Lemma 4.2.1. □

The above lemma shows that all solutions of the model are nonnegative and bounded. Thus, the model is biologically well behaved. In the next section, we discuss the existence of equilibrium points of system (4.3).

4.3 Equilibrium Analysis

We see that system (4.3) has only two equilibria:
(i) the disease-free equilibrium (DFE) $E_0(0, 0, \frac{A}{\delta_0}, 0)$, and
(ii) the endemic equilibrium (EE) $E_1(I^*, S_a^*, N^*, M^*)$.
We can infer from system (4.3) that the disease-free equilibrium E_0 exists without any condition. Now we need to check the existence of endemic equilibrium E_1.

4.3.1 Existence of Endemic Equilibrium $E_1(I^*, S_a^*, N^*, M^*)$

We note that I^*, ${S_a}^*$, N^*, and M^* are the positive solutions of the following system of algebraic equations:

$$\alpha(N^* - I^* - S_a^*) - \delta - \frac{a}{1 + bI^*} = 0,$$

$$\frac{\beta(N^* - I^* - S_a^*)M^*}{1 + \gamma M^*} - \delta_0 S_a^* - \delta_3 S_a^* = 0,$$

$$A - \delta_0 N^* - (\delta_1 + \delta_2)I^* - \frac{aI^*}{1 + bI^*} = 0,$$

$$\mu I^* - \mu_0 M^* = 0.$$

After solving the above equations, we get

$$S_a^* = \frac{\beta\mu(\delta + a + \delta bI^*)I^*}{\alpha(\delta_0 + \delta_3)(1 + bI^*)(\mu_0 + \mu\gamma I^*)},$$

$$N^* = I^* + S_a^* + \frac{(\delta + a + \delta bI^*)}{\alpha(1 + bI^*)}, \quad M^* = \frac{\mu I^*}{\mu_0},$$

and the cubic polynomial in I^* is given as

$$A_1 I^{*3} + A_2 I^{*2} + A_3 I^* + A_4 = 0, \tag{4.5}$$

where

$$\begin{aligned}
A_1 &= b\delta\alpha\mu\gamma(\delta_0 + \delta_3),\\
A_2 &= \alpha(\delta_0 + \delta_3)(\mu_0\delta b + \gamma\mu(\delta + a)) + \beta\mu\delta\delta_0 b + \delta_0(\delta_0 + \delta_3)\delta b\mu\gamma - \alpha A(\delta_0 + \delta_3)b\mu\gamma,\\
A_3 &= \alpha(\delta_0 + \delta_3)\mu_0(\delta + a) + \beta\mu\delta_0(\delta + a) + \delta_0(\delta_0 + \delta_3)(\delta b\mu_0 + (\delta + a)\mu\gamma)\\
&\quad - \alpha A(\delta_0 + \delta_3)(b\mu_0 + \mu\gamma),\\
A_4 &= \delta_0(\delta_0 + \delta_3)(\delta + a)\mu_0 - \alpha A(\delta_0 + \delta_3)\mu_0.
\end{aligned}$$

By Descartes' rule of sign, one can see that the cubic equation (4.5) has unique positive real root I^* if the following inequality hold:

$$1 < R_0 < \frac{\alpha}{b\delta_0}, \tag{4.6}$$

where $R_0 = \frac{A\alpha}{(\delta+a)\delta_0}$ is the basic reproductive number. After finding the value of I^*, we can find the values of N^*, S_a^* and M^*. This implies that there exists a unique endemic equilibrium $E_1(I^*, S_a^*, N^*, M^*)$ if the inequality (4.6) is satisfied.

Remark 4.3.1. *Equation (4.6) shows a threshold on the basic reproduction number R_0 which depends upon α, δ_0 and b. We note that if the parameter b (delay in the treatment) is large, then equation (4.6) may not be satisfied and thus more than one positive equilibrium may exist.*

4.4 Stability Analysis

In this section, we discuss the local and global stability of the equilibrium points, $E_0(0, 0, \frac{A}{\delta_0}, 0)$ and $E_1(I^*, S_a^*, N^*, M^*)$. By calculating the Jacobian matrix at E_0, we note that three eigenvalues are always negative and the fourth one is negative if $R_0 < 1$ and positive if $R_0 > 1$. Thus, we state the following theorem.

Theorem 4.4.1. *The disease-free equilibrium $E_0(0, 0, \frac{A}{\delta_0}, 0)$ is locally asymptotically stable if $R_0 < 1$ and is unstable if $R_0 > 1$.*

Remark 4.4.1. *If $R_0 = 1$, then one eigenvalue of the Jacobian matrix evaluated at E_0 is zero with multiplicity one (simple zero) and other three eigenvalues are $-(\delta_0 + \delta_3), -\delta_0$ and $-\mu_0$, which are real and negative. Thus, E_0 is linearly locally stable. If $R_0 > 1$, then E_0 is unstable. This shows that transcritical bifurcation occurs at $R_0 = 1$, which is shown in figure 4.1.*

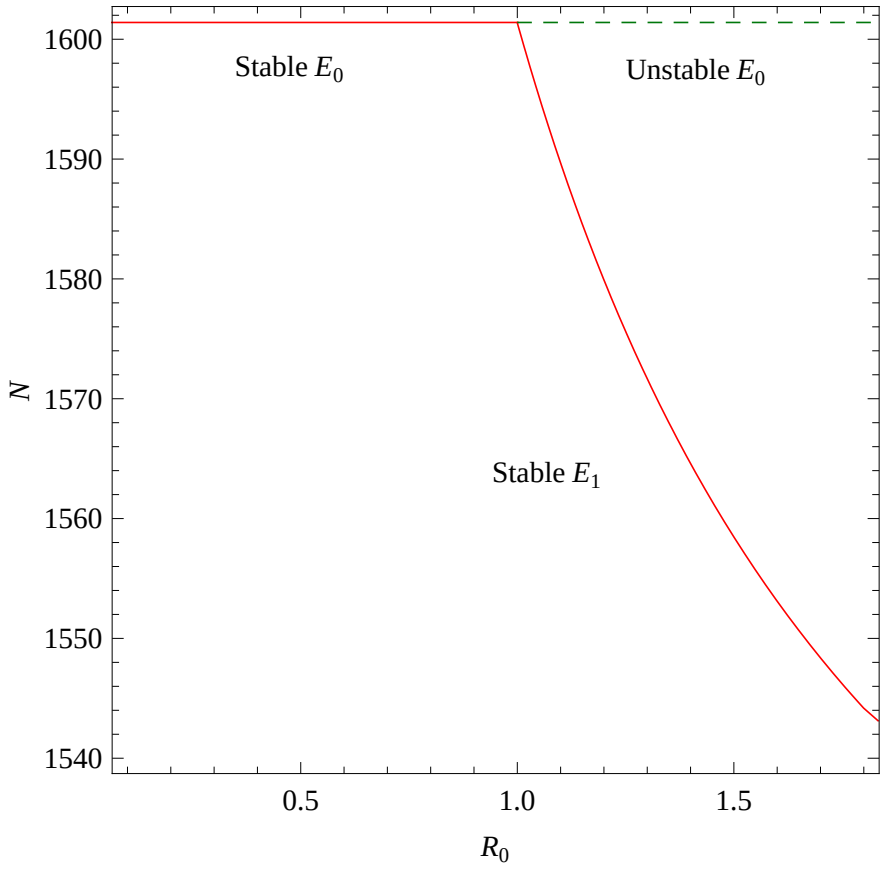

Figure 4.1: Plot of N vs R_0 showing the transcritical bifurcation at $R_0 = 1$

In the following theorem, we have found conditions for E_1 to be locally asymptotically stable.

Theorem 4.4.2. *The endemic equilibrium $E_1(I^*, S_a^*, N^*, M^*)$ is locally asymptotically stable if the following inequalities hold true:*

$$\alpha > \frac{ab}{(1+bI^*)^2}, \tag{4.7}$$

$$\left(\alpha + c_1\frac{\beta M^*}{1+\gamma M^*}\right)^2 < c_1\frac{4}{9}\left(\alpha - \frac{ab}{(1+bI^*)^2}\right)p, \tag{4.8}$$

where

$$c_1 < min\left\{\frac{2}{9}\frac{(1+\gamma M^*)^4}{(\beta(N^*-I^*-S_a^*))^2}\frac{\mu_0^2}{\mu^2}\left(\alpha - \frac{ab}{(1+bI^*)^2}\right)p, \quad \frac{2}{3}\frac{\alpha p}{q}\delta_0\frac{(1+\gamma M^*)^2}{(\beta M^*)^2}\right\},$$

$$p = \left(\delta_0 + \delta_3 + \frac{\beta M^*}{1+\gamma M^*}\right), \quad q = \left(\delta_1 + \delta_2 + \frac{a}{(1+bI^*)^2}\right).$$

Proof. Let $x = I - I^*$, $y = S_a - S_a^*$, $n = N - N^*$, $m = M - M^*$ be the small perturbations about the endemic equilibrium E_1. Using the above new variables, we linearize model system (4.3) around the endemic equilibrium E_1. Then in the linear model, we consider the following positive definite function:

$$V_1 = \frac{1}{2I^*}x^2 + \frac{c_1}{2}y^2 + \frac{c_2}{2}n^2 + \frac{c_3}{2}m^2, \tag{4.9}$$

where c_1, c_2 and c_3 are positive constants to be chosen suitably.
Now differentiating V_1 with respect to time t along the solutions of model (4.3), a little algebraic manipulation yields

$$\begin{aligned}\frac{dV_1}{dt} = &-\frac{1}{2}a_{11}x^2 + a_{12}xy - \frac{1}{2}a_{22}y^2\\ &-\frac{1}{2}a_{11}x^2 + a_{13}xn - \frac{1}{2}a_{33}n^2\\ &-\frac{1}{2}a_{11}x^2 + a_{14}xm - \frac{1}{2}a_{44}m^2\\ &-\frac{1}{2}a_{22}y^2 + a_{23}yn - \frac{1}{2}a_{33}n^2\\ &-\frac{1}{2}a_{22}y^2 + a_{24}ym - \frac{1}{2}a_{44}m^2,\end{aligned}$$

where

$$a_{11} = \frac{2}{3}\left(\alpha - \frac{ab}{(1+bI^*)^2}\right), \quad a_{22} = \frac{2}{3}c_1 p, \quad a_{33} = c_2\delta_0, \quad a_{44} = c_3\mu_0,$$

$$a_{14} = c_3\mu, \quad a_{12} = -\left(\alpha + c_1\frac{\beta M^*}{1+\gamma M^*}\right), \quad a_{13} = \alpha - c_2 q,$$

$$a_{23} = c_1\frac{\beta M^*}{1+\gamma M^*}, \quad a_{24} = c_1\frac{\beta(N^* - I^* - S_a^*)}{(1+\gamma M^*)^2}.$$

Sufficient conditions for $\frac{dV_1}{dt}$ to be negative definite are given as follows:

$$a_{11} > 0, \tag{4.10}$$

$$a_{12}^2 < a_{11}a_{22}, \tag{4.11}$$

$$a_{13}^2 < a_{11}a_{33}, \tag{4.12}$$

$$a_{14}^2 < a_{11}a_{44}, \tag{4.13}$$

$$a_{23}^2 < a_{22}a_{33}, \tag{4.14}$$

$$a_{24}^2 < a_{22}a_{44}. \tag{4.15}$$

By choosing $c_2 = \frac{\alpha}{q}$ and $c_3 = \frac{\mu_0}{3\mu^2}\left(\alpha - \frac{ab}{(1+bI^*)^2}\right)$, we note that conditions (4.12) and (4.13) are satisfied. If we choose c_1 as given in Theorem 4.4.2, then conditions (4.14) and (4.15) are satisfied. Finally, we note that (4.7) $\Rightarrow$ (4.10) and (4.8) $\Rightarrow$ (4.11). Hence the theorem follows. □

In the following theorem, we show that the endemic equilibrium $E_1(I^*, S_a^*, N^*, M^*)$ is globally asymptotically stable.

Theorem 4.4.3. *Let the following inequalities hold in Ω:*

$$\alpha > \frac{ab}{(1+bI^*)}, \tag{4.16}$$

$$\left(\alpha + k_1\frac{\beta M^*}{1+\gamma M^*}\right)^2 < k_1\frac{4}{9}\left(\alpha - \frac{ab}{(1+bI^*)}\right)p, \tag{4.17}$$

where

$$k_1 < min\left\{\frac{2}{9}\left(\frac{\delta_0(1+\gamma M^*)}{\beta A}\right)^2\frac{\mu_0^2}{\mu^2}\left(\alpha-\frac{ab}{(1+bI^*)}\right)p,\quad \frac{2}{3}\frac{\alpha\delta_0 p}{r}\left(\frac{(1+\gamma M^*)}{\beta M^*}\right)^2\right\},$$

$$r=\left(\delta_1+\delta_2+\frac{a\delta_0}{(1+bI^*)(\delta_0+Ab)}\right).$$

Then $E_1(I^*, S_a^*, N^*, M^*)$ is globally asymptotically stable with respect to all solutions initiating in the interior of the positive octant Ω.

Proof. We consider the following positive definite function about E_1:

$$V_2=\left(I-I^*-I^*\ln\frac{I}{I^*}\right)+\frac{k_1}{2}(S_a-S_a^*)^2+\frac{k_2}{2}(N-N^*)^2+\frac{k_3}{2}(M-M^*)^2,$$

where k_1, k_2 and k_3 are positive constants to be chosen suitably.
Now differentiating V_2 with respect to time t along the solutions of model (4.3), we get

$$\begin{aligned}\frac{dV_2}{dt}=&-\frac{1}{2}b_{11}(I-I^*)^2+b_{12}(I-I^*)(S_a-S_a^*)-\frac{1}{2}b_{22}(S_a-S_a^*)^2\\&-\frac{1}{2}b_{11}(I-I^*)^2+b_{13}(I-I^*)(N-N^*)-\frac{1}{2}b_{33}(N-N^*)^2\\&-\frac{1}{2}b_{11}(I-I^*)^2+b_{14}(I-I^*)(M-M^*)-\frac{1}{2}b_{44}(M-M^*)^2\\&-\frac{1}{2}b_{22}(S_a-S_a^*)^2+b_{23}(S_a-S_a^*)(N-N^*)-\frac{1}{2}b_{33}(N-N^*)^2\\&-\frac{1}{2}b_{22}(S_a-S_a^*)^2+b_{24}(S_a-S_a^*)(M-M^*)-\frac{1}{2}b_{44}(M-M^*)^2,\end{aligned}$$

where

$$b_{11}=\frac{2}{3}\left(\alpha-\frac{ab}{(1+bI^*)(1+bI)}\right),\quad b_{22}=\frac{2}{3}k_1p,\quad b_{33}=k_2\delta_0,\quad b_{44}=k_3\mu_0,$$

$$b_{12}=-\left(\alpha+k_1\frac{\beta M^*}{1+\gamma M^*}\right),\quad b_{13}=\alpha-k_2\left(\delta_1+\delta_2+\frac{a}{(1+bI)(1+bI^*)}\right),$$

$$b_{14}=k_3\mu,\quad b_{23}=k_1\frac{\beta M^*}{1+\gamma M^*},\quad b_{24}=k_1\frac{\beta(N-I-S_a)}{(1+\gamma M^*)(1+\gamma M)}.$$

Sufficient conditions for $\frac{dV_2}{dt}$ to be negative definite are given as follows:

$$b_{11} > 0, \tag{4.18}$$

$$b_{12}^2 < b_{11}b_{22}, \tag{4.19}$$

$$b_{13}^2 < b_{11}b_{33}, \tag{4.20}$$

$$b_{14}^2 < b_{11}b_{44}, \tag{4.21}$$

$$b_{23}^2 < b_{22}b_{33}, \tag{4.22}$$

$$b_{24}^2 < b_{22}b_{44}. \tag{4.23}$$

For the given value of k_1 in Theorem 4.4.3, we note that conditions (4.22) and (4.23) are satisfied. Again (4.16) $\Rightarrow$ (4.18) and (4.17) $\Rightarrow$ (4.19). If we choose $k_2 = \frac{\alpha}{r}$ and $k_3 = \frac{\mu_0}{3\mu^2}\left(\alpha - \frac{ab}{(1+bI^*)}\right)$, then (4.20) and (4.22) are satisfied. This implies that V_2 is a Liapunov's function with respect to the endemic equilibrium $E_1(I^*, S_a^*, N^*, M^*)$. Hence the theorem follows. □

4.5 Numerical Simulations

In this section, we present computer simulation results for model system (4.3) by using MatLab 7.10. The dataset used for simulation is given in Table 4.1. For these values of parameters, we see that the endemic equilibrium $E_1(I^*, S_a^*, N^*, M^*)$ exists and (I^*, S_a^*, N^*, M^*) are given as follows:

$I^* = 223.42, \quad S_a^* = 20.4951, \quad N^* = 1032.8$ and $M^* = 4.6546$.

We also note that all conditions of Theorem 4.4.2 and Theorem 4.4.3 are satisfied. This implies that E_1 is locally as well as globally asymptotically stable for the set of values of parameters in Table 4.1.

In figure 4.2, we considered the five different initial values of the infected and aware susceptible populations. All trajectories starting from different initial values approach to (I^*, S_a^*). The endemic equilibrium point (E_1) is independent of the initial status of sub-populations. This shows that (I^*, S_a^*) is globally asymptotically stable in the IS_a- plane. All the details related to initial values are shown

Table 4.1: List of parameters for model (4.3).

Parameter	Value (Unit)
Recruitment rate of susceptible (A)	250 $person$ $(d)^{-1}$
Natural death rate of each sub-population (δ_0)	0.2 $(d)^{-1}$
Disease induced death rate of infected (δ_1)	0.005 $(d)^{-1}$
Recovery rate of infected due to auto immunity (δ_2)	0.002 $(d)^{-1}$
Conversion rate of S_a into S (δ_3)	0.18 $(d)^{-1}$
Treatment rate (a)	0.2 $(d)^{-1}$
Limitation rate in treatment availability (b)	0.0003 $(d)^{-1}$
Transmission rate (α)	0.0005 $(person)^{-1}$ $(d)^{-1}$
Dissemination rate (β)	0.0022 $(person)^{-1}$
Limitation rate to awareness programs (γ)	0.008 $(person)^{-1}$
Implementation rate of awareness programs (μ)	0.005 $(person)^{-1}(d)^{-1}$
Depletion rate of awareness programs (μ_0)	0.24 $(d)^{-1}$

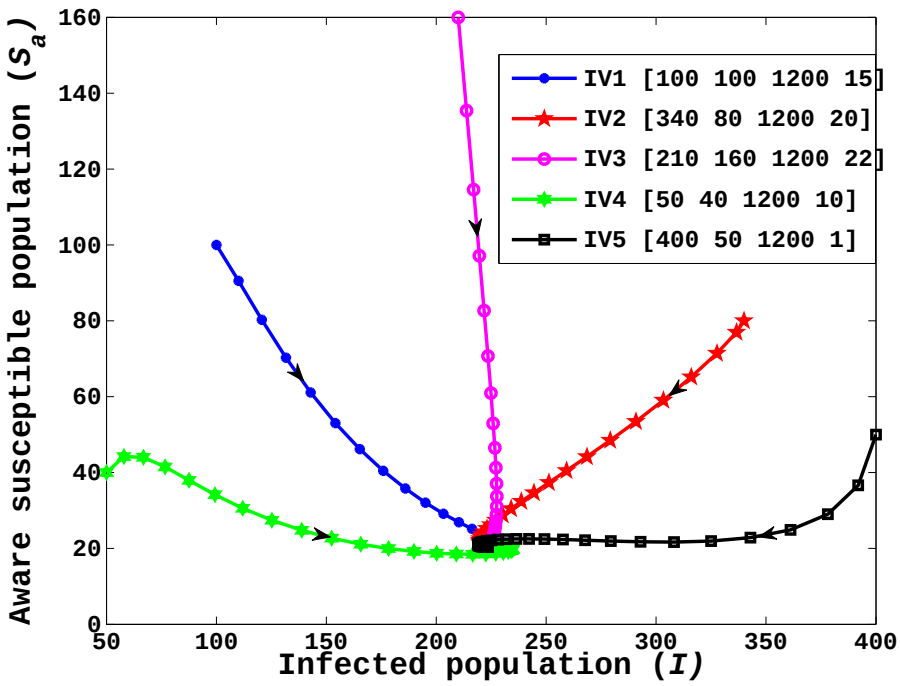

Figure 4.2: Global stability of (I^*, S_a^*) in the IS_a-plane.

in the legend of figure 4.2. Similarly in figure 4.3, we have shown that trajectories initiating from different initial points converge to the same equilibrium point (I^*, M^*). This shows that (I^*, M^*) is globally asymptotically stable in the IM-plane. When awareness programs are delivered to susceptible population then too the stabilization of infected population takes place and it gets restricted to an

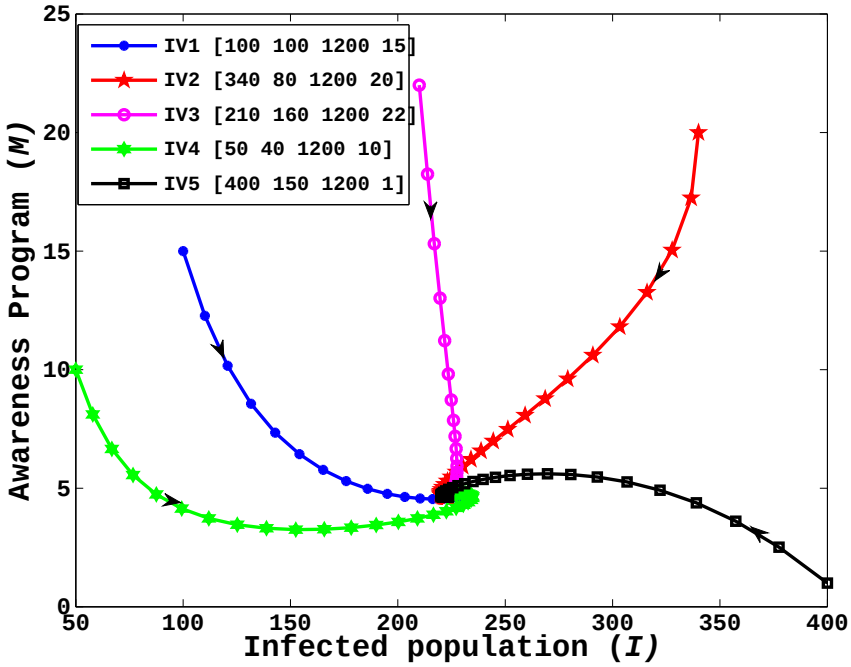

Figure 4.3: Global stability of (I^*, M^*) in the IM-plane.

equilibrium point which is again independent of the initial level of awareness or infection. All the details related to initial values are shown in the legend. This implies that for the given set of parameters the disease will restrict itself to a given endemic zone/population, irrespective of parameters like, the magnitude of infected population, aware susceptible population, total population and awareness programs.

In figures 4.4(a) and 4.4(b), we have shown the effect of information dissemination rate (β) on (i) infected population (I) and (ii) aware susceptible population (S_a), respectively. From figures 4.4(a) and 4.4(b), we observe that when there is no spread of awareness programs among susceptibles i.e. dissemination rate (β) is zero, then the number of infected population is high and the aware susceptible is zero. Further the infection decreases with increase in information dissemination rate (β). This shows that by increasing the dissemination rate of the awareness program, the number of infected individuals decreases but the number of aware susceptibles increases. Some of the susceptible individuals can keep themselves isolated and will not be infected.

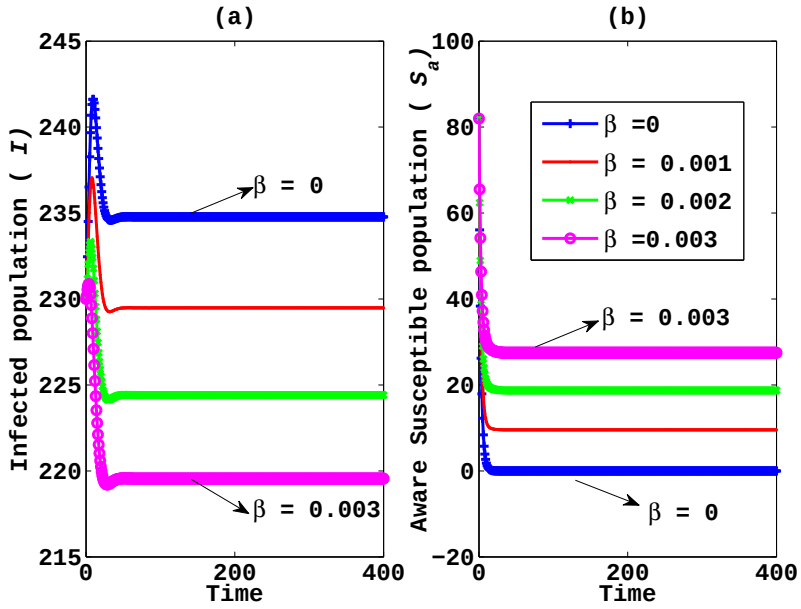

Figure 4.4: Effect of β on I and S_a, respectively.

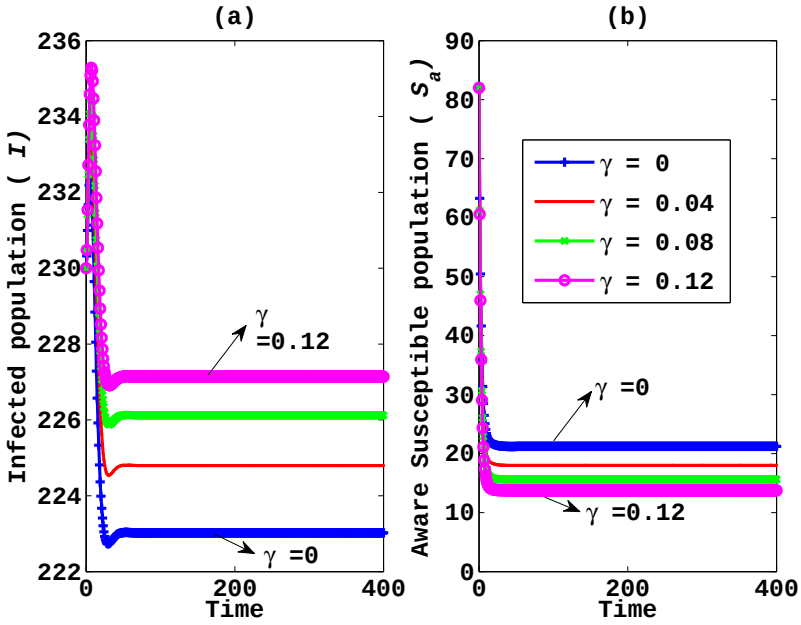

Figure 4.5: Effect of γ on I and S_a, respectively.

Figures 4.5(a) and 4.5(b) represent the effect of γ on infected population and aware susceptible population. We note from figure 4.5(a) that infected population increases as we increase γ, limitations on awareness program and is lowest when there is no limitation on dissemination of awareness ($\gamma = 0$). The transient kink settling down at a high infection level in former case can be explained by

the behavioural slackness with time as information spreads. Whereas the kink when ($\gamma = 0$) can be explained by immunity. In figure 4.5(b), we observe that the aware susceptible population decreases with an increase in γ (limitation to the dissemination of awareness). When there is no limitation to dissemination of awareness, people are maximally aware but as limitations increase the aware susceptible population declines as more people remain ignorant of the disease.

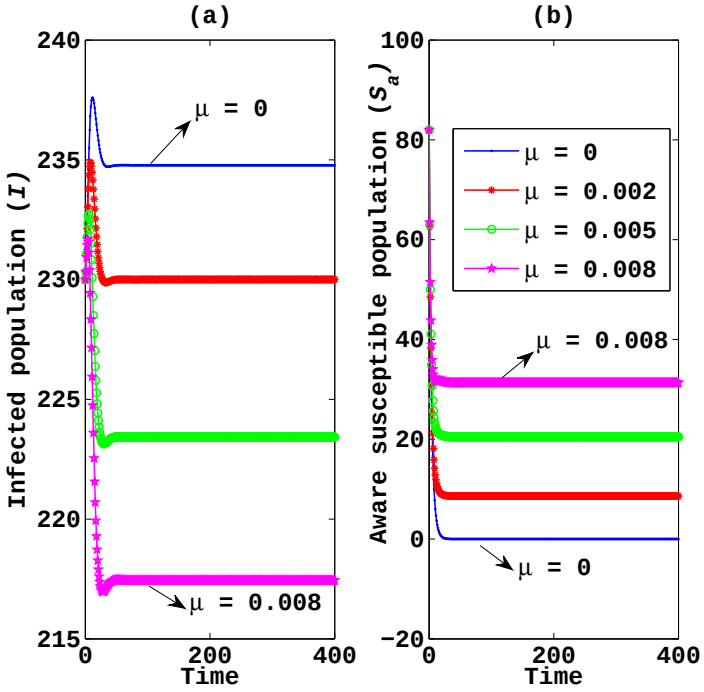

Figure 4.6: Effect of μ on I and S_a, respectively.

In figures 4.6(a) and 4.6(b), we have shown the effect of implementation rate of awareness program on infected population and aware suceptible population. From figures 4.6(a) and 4.6(b), we can see that when there is no awareness program run by media then aware susceptible population is zero and infection is high. As we increase the implementation rate of awareness program (μ), aware susceptible population is increasing and infection is decreasing very rapidly. This implies that awareness programs may reduce the susceptibility to infection but will not eradicate the infection. The transient increase in infectives at high infection level (as observed by the kink in graph) may be due to continued infection till adequate life style modification is made to prevent or overcome the infection. At a lower level

of infection the downward kink may be explained by noncompliance or resistance to making long term life style modification inspite of information. When $\mu = 0$, then the same can be explained by virtue of immunity in the population.

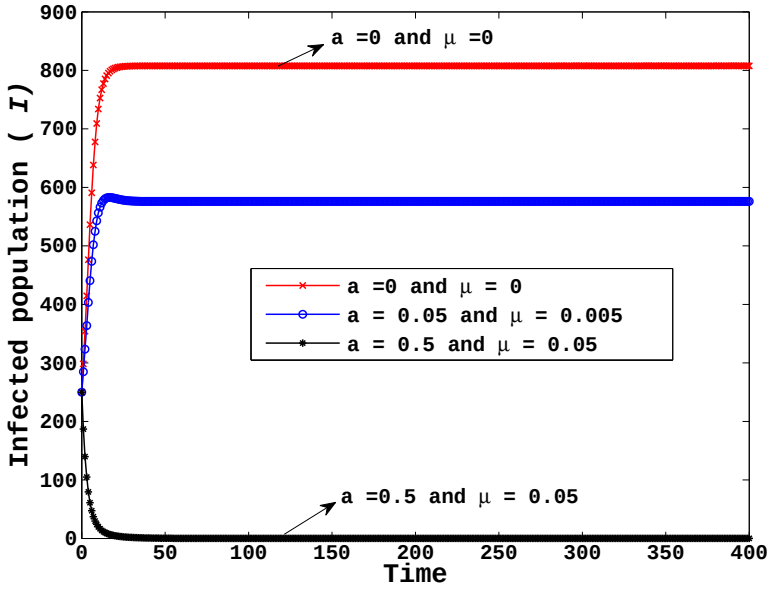

Figure 4.7: Effect of a and μ on infected population I.

In figure 4.7, we have shown the effect of treatment rate a and awareness program implementation rate μ on infected population simultaneously. We observe that when there is neither treatment nor an awareness program available then the rate of infection increases and gets saturated at high level. Further, if we increase the treatment and awareness then we observe the decrease in infection. And finally, when the treatment and awareness program both are at high level, we observe the decrease in infected population and it settles down to zero level. This shows that the disease can be eradicated if treatment availability is high and if we are able to provide enough awareness to the susceptible population about the disease. Thus highlighting the fact that not only treatment but awareness too is a prerequisite for disease eradication.

4.6 Conclusions

In this Chapter, we introduced a mathematical model to study the effect of awareness programs (run by media) and treatment on infectious diseases. The global

dynamics of this model has been studied. We have shown that there exists only two equilibrium points: the disease-free equilibrium $E_0(0, 0, \frac{A}{\delta_0}, 0)$ i.e. total elimination of infection (as $I = 0$) and the endemic equilibrium $E_1(I^*, S_a^*, N^*, M^*)$ i.e. disease will persist. The DFE is locally asymptotically stable for reproductive number $R_0 < 1$ and the endemic equilibrium exists for $R_0 > 1$ and is globally asymptotically stable under the conditions stated in Theorem 4.4.3. When optimal treatment and awareness is provided then the former refers to total eradication of the infectious disease from the population whereas the later refers to the case when disease is localized to an endemic zone.

We have also carried out numerical simulations to validate the analytical results. We have shown that the infected population decreases as we increase the information dissemination rate (β) as some of the susceptibles keep themselves isolated and did not get infected. Thus, the aware susceptibles increase with increase in dissemination rate (β). Further, we have shown that if awareness programs are not available in the society then the infection is very high and if we introduce awareness programs run by media into society infection decreases and this can be further reduced by treatment. We have also shown that when there is enough awareness among the susceptibles and enough treatment is available then disease can be eradicated completely. But if either treatment or awareness is lacking then the disease can not be eradicated.

It may be noted that small pox is the only disease that has been totally eradicated but the eradication has been taken place by virtue of vaccination and awareness since treatment of small pox was not available. Further, diseases like Polio have been brought under control and largely eradicated from most of the countries in the world. This disease too can not be treated but vaccination and awareness regarding the disease has led to its near eradication. There are no known diseases yet which have been eradicated by only treatment. Thus, sufficient emphasis must be given to awareness programs to ensure total eradication of treatable emerging infectious diseases.

Chapter 5

Analysis of a Virus Dynamics Model with Saturated Infection Rate and Immune Response in Presence of Therapeutic Drug

A cell is regarded as the true biological atom.

George Henry Lewes

Human body is composed of different type of cells, which are smallest unit of life also known as "building blocks of life". This chapter presents a mathematical model to understand the dynamics of infection at cellular level. The proposed model is based on the basic virus dynamics model involving the effect of total immune response (innate immune response and adaptive immune response). We describe the interaction of virus with uninfected cells using Holling type II function, which is defined in Chapter 2. The effectiveness of the therapeutic drugs given to virus producing cells and viruses has been studied.

5.1 Introduction

Diseases caused by viral infections have had a major impact on populations. Viruses may be present in the body either in a free state or as an intracellular parasite. Free viruses enter a cell in a receptor specific manner and infect the cell. Viral replication is possible only within a cell. The virus replicates within the cell by utilizing the cells own machinery. Inside the cell a virus may either exist in a latent (inactive) form for a prolonged period or it may immediately adopt the host replication machinery and start producing multiple copies of itself. Once large number of virus particles have been produced they come out of the cell by destroying it. Now these viruses are free to infect other healthy cells. Within the body virus encounters an immune response which prevents its spread from an infected cell to adjacent uninfected cells. The present model is being proposed to understand the dynamics of interaction between uninfected cells, infected cells, latently infected cells, free virus and immune response.

Various virus dynamics models have been developed to understand the dynamics of HIV infection *in vivo* (Anderson and May, 1981; Dubey and Dubey, 2007; Huang et al., 2011; Huo et al., 2012; Nowak and Bangham, 1996; Nowak et al., 1997; Perelson and Nelson, 1999; Roy et al., 2013; Wang and Liu, 2013; Zhou et al., 2009). Anderson and May (1981) proposed a class of epidemic models to describe the dynamics of host-parasite interaction. These were the basic models to understand the dynamics of viral infection in the presence of immune response.

Immune response plays an important role to control viral infection. Immune response fights against the virus and reduces virus load. Nowak and Bangham (1996) proposed virus dynamics model using CTL (Cytotoxic T lymphocyte) component of immune response. They concluded that an active CTL immune response may reduce virus load. Wang and Liu (2013) proposed a class of delayed viral models with saturation infection rate and immune response. In their models, they considered the CTL response (which kills infected cells) and antibody response (which facilitates removal of viruses) separately to study the analytical behavior of systems. Roy et al. (2013) studied the effect of CTL immune response on the

dynamics of infected $CD4^+$T cells, virus producing $CD4^+$T cells and virus by introducing a positive feedback parameters in the model. They also investigated an optimal control therapy using reverse transcriptase inhibitors (RTIs) that block new infection. Huo et al. (2012) proposed a virus dynamics model with saturated incidence rate and humoral immunity. They studied the stability behaviour of the nonnegative equilibria of the model.

The spread of infectious diseases, especially virus mediated is a matter of great concern. Control of epidemics may be achieved by media (Misra, Sharma and Shukla, 2011; Misra, Sharma and Singh, 2011; Samanta et al., 2013) and by treatment with appropriate therapeutic drugs. In earlier decades, researchers have paid attention to drug therapy or treatment (cure) of targeted cells in virus dynamics models (Gumel and Moghadas, 2004; Hattaf et al., 2012; Liu et al., 2011; Srivastava et al., 2009; Srivastava and Chandra, 2010; Tian and Liu, 2014; Wang et al., 2010; Zhou et al., 2008). Liu et al. (2011) developed an HIV pathogenesis dynamics model considering cure rate. They incorporated the full logistic proliferation term for uninfected cells as well as infected cells in the model. In their study they obtained a critical number (the smallest virus number released by per infected $CD4^+$T cells) and have shown that this critical number increases with increase in cure rate. This shows that the HIV infection can be controlled by increasing cure rate.

Hattaf et al. (2012) proposed and analyzed a virus dynamics model with general incidence rate and linear cure rate of the infected cells to uninfected cells. They have shown that the virus can be cleared and the disease dies out if the basic reproduction number is less than one. The model and results in Hattaf et al. (2012) were further extended by Tian and Liu (2014). Srivastava et al. (2009) proposed a mathematical model to study the effect of RT inhibitors on the dynamics of HIV infection. They obtained a critical value of the efficacy of the RT inhibitor beyond which the infection level decreases. Further, Srivastava and Chandra (2010) proposed a model to introduce the effect of time delay for the infected $CD4^+$T cells to become actively infected cell. They observed that time delay does not have any significant effect on the activation of $CD4^+$ T cells. Further, Gumel and Moghadas

(2004) studied the role of anti-retroviral therapy in controlling the HIV infection. They investigated the immunological and therapeutic control of HIV and found the optimal level of anti-retroviral therapy to eradicate HIV. In these models, treatment for free virus has not been incorporated.

Considering the above points in view, we propose a five-dimensional virus dynamics model with saturated infection rate and immune response with treatment of infected cells and free virus. The main aim of this chapter is to study the control of the replication of infected cells and free virus by considering appropriate immune response and suitable treatment therapy for infected cells and free virus.

5.2 The Mathematical Model

Let $x(t)$ be the number of uninfected cells, $y(t)$ be the number of infected cells and $v(t)$ be the number of free virus at any time $t \geq 0$. Then the following virus dynamics model has been studied in detail by several researchers (Anderson and May, 1981; Nowak and Bangham, 1996):

$$\begin{cases} \frac{dx}{dt} = \lambda - \delta_0 x - \alpha x v, \\ \frac{dy}{dt} = \alpha x v - \delta_1 y, \\ \frac{dv}{dt} = k y - k_0 v. \end{cases} \tag{5.1}$$

In the above model, λ is the constant growth rate of uninfected cells and δ_0 is its death rate. When free virus interacts with uninfected cells, it produces infected cells at the rate of α. δ_1 is the natural death rate of infected cells. Virus is produced at the rate k by infected cells and k_0 is clearance rate of virus.

Model (5.1) is generalized and studied by Dubey et al. (2011) by considering the effect of appropriate immune response on the infected cells. The model of Dubey et al. (2011) reads as follows:

$$\begin{cases} \frac{dx}{dt} = \lambda - \delta_0 x - \alpha x v, \\ \frac{dy}{dt} = \alpha x v - \delta_1 y - \gamma y z, \\ \frac{dv}{dt} = k y - k_0 v, \\ \frac{dz}{dt} = \mu - \mu_0 z + b y z - \eta \gamma y z. \end{cases} \tag{5.2}$$

In the above model, $z(t)$ is the density of immune response of the body, μ is the inherent growth rate of immune response, and μ_0 is its natural decay rate. Here b is the stimulating growth rate of the immune response due to the infected cells, γ is the decay rate of infected cells due to immune response of the body and in this process immune response also decays at the rate η. The incidence rate $f(t) = \alpha x(t) v(t)$ increases linearly with x or with v which may not be realistic in real life. If we take the saturated incidence rate

$$f(t) = \frac{\alpha x v}{1 + \alpha_1 v}, \qquad \alpha > 0, \alpha_1 \geq 0,$$

then it gives a rich dynamics of the system (Huo et al., 2012; Song and Neumann, 2007; Wang et al., 2015).

It has also been found that all virally infected cells may not produce virus. A fraction of the infected cells may be in latent state and thus do not take part in producing virus (see Nowak and May (2000); Wang et al. (2015)). However latently infected cells may become active upon stimulation and then join the other group of actively virus producing infected cells. Thus, we divide infected cells $y(t)$ into two parts: (i) $y_1(t)$, the number of infected cells, which are capable of producing virus, and (ii) $y_2(t)$, the number of infected cells in latent state, which are not capable of producing virus, but upon reactivation it start producing virus, similar to $y_1(t)$.

In most of the previous work, it has been observed that immune response increases due to infected cells. The virus is activating the immune system. But infected cells are produced by virus when it interacts with uninfected cells. We assume that the immune response increases due to infected cells as well as virus. Keeping the above aspects in view, the virus dynamics of the system can be gov-

erned by the system of five differential equations.

$$\begin{cases} \frac{dx}{dt} = \lambda - \delta_0 x - \frac{\alpha x v}{1+\alpha_1 v}, \\ \frac{dy_1}{dt} = \frac{q\alpha x v}{1+\alpha_1 v} - \delta_1 y_1 + \beta y_2 - \gamma_1 y_1 z - \theta_1 y_1, \\ \frac{dy_2}{dt} = \frac{(1-q)\alpha x v}{1+\alpha_1 v} - \delta_1 y_2 - \beta y_2, \\ \frac{dv}{dt} = k y_1 - k_0 v - \gamma_2 v z - \theta_2 v, \\ \frac{dz}{dt} = \mu - \mu_0 z + \mu_1 y_1 z + \mu_2 v z, \end{cases} \tag{5.3}$$

$$x(0) > 0,\ y_1(0) \geq 0,\ y_2(0) \geq 0,\ v(0) \geq 0,\ z(0) \geq 0.$$

The schematic diagram of model (5.3) is shown in figure 5.1.

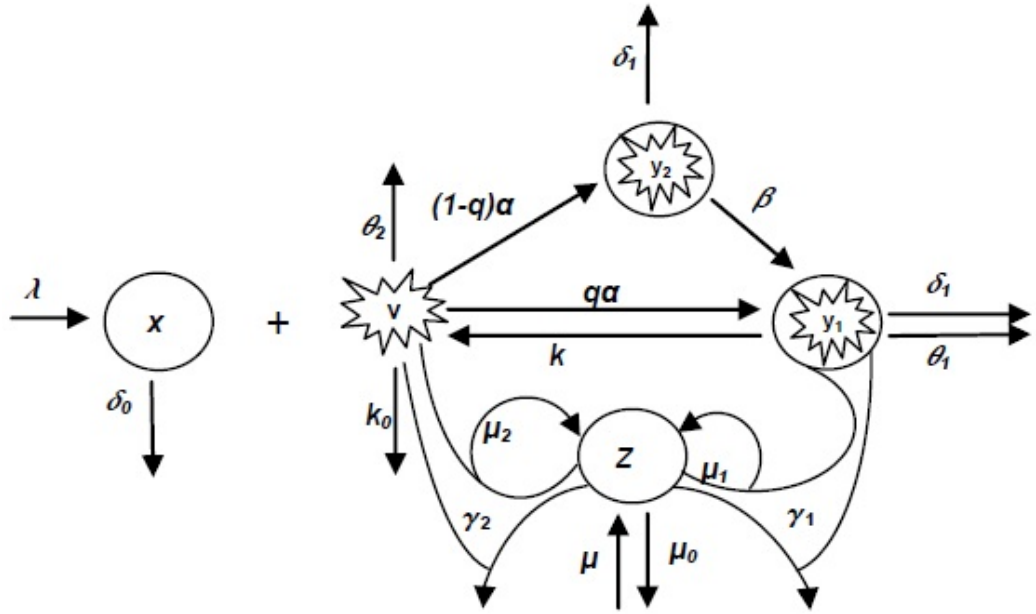

Figure 5.1: Schematic diagram of model (5.3).

Here $x(t)$, $y_1(t)$, $y_2(t)$, $v(t)$ and $z(t)$ represent the uninfected cells, infected cells, latently infected cells, free virus and immune response respectively. The uninfected cells grow from the sources inside the body (thymus) at the rate λ and die out at the rate δ_0. We assume that the free virus infects the uninfected cells with the saturated infection rate which is given by Holling type II functional response ($\frac{\alpha x v}{1+\alpha_1 v}$, where α and α_1 are positive constants) (Huo et al., 2012). We also considered two states of infected cells (Nowak and May, 2000; Wang et al., 2015): virus producing state (y_1), in this state infected cells produce new virions; latently

infected state (y_2), in this state infected cells do not contribute in producing new virions but can be reactivated to produce new virions. q is the probability that upon infection a cell enters to the virus producing state and $(1-q)$ is the probability that upon infection a cell enters to the latently infected state. δ_1 is death rate of these infected cells.

We assume that the latently infected cells are getting reactivated at the rate β and join the virus producing infected cells to contribute in production of virus. Free virions are produced by infected cells at the rate k and k_0 is the clearance rate of free virions. μ is the inherent growth rate of immune response and μ_0 is its natural decay rate. The immune response interacts with the infected cells and free virus and the increase in immune response due to infected cells and free virus is given by the rate μ_1 and μ_2, respectively. The immune response kills the infected cells and free virus at the rates γ_1 and γ_2, respectively. θ_1 and θ_2 denote clearance rates of the infected cells and free virus due to therapeutic drugs.

Remark 5.2.1. *In the absence of immune response ($z = 0$) and drug therapy ($\theta_1 = \theta_2 = 0$), model (5.3) reduces to the model proposed by Wang et al. (2015).*

In the next section, we show that all the solutions of system (5.3) are positively invariant and bounded.

5.3 Positivity and Boundedness of the Model

Let $(x(t), y_1(t), y_2(t), v(t), z(t)) \in \Re^5_+$ be a solution of model (5.3) with the initial conditions given in (5.3). Let $T = x + y_1 + y_2$, then

$$\dot{T} = \dot{x} + \dot{y_1} + \dot{y_2} \leq \lambda - \delta(x + y_1 + y_2),$$

where $\delta = min\{\delta_0, \delta_1\}$. From elementary calculus, we have

$$T(t) \leq T(0)e^{-\delta t} + \frac{\lambda}{\delta}(1 - e^{-\delta t}).$$

Thus,

$$\lim_{t\to\infty} \sup T(t) \leq \frac{\lambda}{\delta}.$$

Again we have, $\dot{v} = ky_1 - k_0 v - \gamma_2 vz - \theta_2 v \leq \frac{k\lambda}{\delta} - (k_0 + \theta_2)v$. This implies that

$$\limsup_{t\to\infty} v(t) \leq \frac{k\lambda}{\delta(k_0 + \theta_2)}.$$

The last equation of model (5.3) gives

$$\dot{z} = \mu - \mu_0 z + \mu_1 y_1 z + \mu_2 vz \leq \mu - \left(\mu_0 - \frac{\mu_1\lambda}{\delta} - \frac{\mu_2 k\lambda}{\delta(k_0 + \theta_2)}\right) z,$$

and hence

$$\limsup_{t\to\infty} z(t) \leq \frac{\mu}{\eta},$$

where $\eta = \left(\mu_0 - \frac{\mu_1\lambda}{\delta} - \frac{\mu_2 k\lambda}{\delta(k_0+\theta_2)}\right) > 0$.
Furthermore, $\dot{T} < 0$ if $T > \frac{\lambda}{\delta}$, $\dot{v} < 0$ if $v > \frac{k\lambda}{\delta(k_0+\theta_2)}$ and $\dot{z} < 0$ if $z > \frac{\mu}{\eta}$. This shows that solutions of system (5.3) point towards the region Ω defined in Lemma (5.3.1). Hence Ω is positively invariant and solutions of (5.3) are bounded. Thus, we can state the following lemma.

Lemma 5.3.1. *The set* $\Omega = \{(x, y_1, y_2, v, z) \in \Re^5_+ : 0 < x + y_1 + y_2 \leq \frac{\lambda}{\delta}, 0 < v \leq \frac{k\lambda}{\delta(k_0+\theta_2)}, 0 < z \leq \frac{\mu}{\eta}\}$ *is positively invariant region of system (5.3).*

This proves that the model is biologically well behaved.

In the next section, first we find equilibrium points of system (5.3). Then determine the basic reproduction number of system (5.3). Afterwards, the local and global stability of the equilibrium points has been studied.

5.4 Stability Analysis

From model (5.3), it is clear that the system has two non-negative equilibria: (i) Virus-free equilibrium (VFE) $E_0(x_0, 0, 0, 0, z_0)$, the point where infection is not present, (ii) Interior equilibrium (IE) $E_1(x^*, y_1^*, y_2^*, v^*, z^*)$, the equilibrium point where infection persists.
VFE is trivial and given by $E_0(x_0, 0, 0, 0, z_0) = E_0(\frac{\lambda}{\delta_0}, 0, 0, 0, \frac{\mu}{\mu_0})$.
We use the next generation operator method (Diekmann et al., 1990; Van den Driessche and Watmough, 2002) to determine the basic reproduction number. We

are considering y_1, y_2 and v to be the infection compartments. Let $X = (y_1, y_2, v)^T$, $F_1(X)$ is the nonnegative infection matrix (gain in infection terms) and $V_1(X)$ (the matrix for transfer terms between compartments) associated with system (5.3). Then we can rewrite system (5.3) as

$$\dot{X} = F_1(X) - V_1(X)$$

where

$$F_1(X) = \begin{bmatrix} \frac{q\alpha xv}{1+\alpha_1 v} + \beta y_2 \\ 0 \\ 0 \end{bmatrix} \quad \text{and} \quad V_1(X) = \begin{bmatrix} (\delta_1 + \theta_1 + \gamma_1 z)y_1 \\ (\delta_1 + \beta)y_2 - \frac{(1-q)\alpha xv}{1+\alpha_1 v} \\ (k_0 + \theta_2 + \gamma_2 z)v - ky_1 \end{bmatrix}.$$

The Jacobian of matrices $F_1(X)$ and $V_1(X)$ evaluated at virus-free equilibrium $E_0(\frac{\lambda}{\delta_0}, 0, 0, 0, \frac{\mu}{\mu_0})$ is given by

$$F_1 = \begin{bmatrix} 0 & \beta & \frac{q\alpha\lambda}{\delta_0} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \quad \text{and} \quad V_1 = \begin{bmatrix} (\delta_1 + \theta_1 + \gamma_1 \frac{\mu}{\mu_0}) & 0 & 0 \\ 0 & (\delta_1 + \beta) & -\frac{(1-q)\alpha\lambda}{\delta_0} \\ -k & 0 & (k_0 + \theta_2 + \gamma_2 \frac{\mu}{\mu_0}) \end{bmatrix}.$$

Then $\rho(F_1 V_1^{-1})$ gives the spectral radius (largest eigenvalue) of the next generation matrix $(F_1 V_1^{-1})$ as defined in (Van den Driessche and Watmough, 2002). Thus,

$$R_I = \rho(F_1 V_1^{-1}) = \frac{\alpha\lambda k(q\delta_1 + \beta)}{(\delta_1 + \beta)(\delta_0)(\delta_1 + \theta_1 + \frac{\gamma_1\mu}{\mu_0})(k_0 + \theta_2 + \frac{\gamma_2\mu}{\mu_0})},$$

where R_I is the basic reproduction number in the presence of immune response. This can be defined as the average number of newly infected cells produced by single infected cell, when introduced into a completely healthy cells. In the present model, we consider immune response so the given basic reproduction is determined in the presence of immune response. Further we can state the following theorem using the above results and Theorem 2 of (Van den Driessche and Watmough, 2002).

Theorem 5.4.1. *The virus-free equilibrium E_0 is locally asymptotically stable if $R_I < 1$, and unstable if $R_I > 1$.*

Local stability of virus-free equilibrium shows that the infection will die out if basic reproduction number is less than one and infection will further go on if basic reproduction number is more than one. To ensure that the virus-free equilibrium is independent of initial concentration of cells, there is a need to study the global stability, which is shown in the next theorem.

Theorem 5.4.2. *The virus-free equilibrium E_0 is globally asymptotically stable in Ω if $R_I \leq 1$.*

Proof. Let us define the following Lyapunov function

$$L = y_1 + \frac{\beta}{\delta_1 + \beta} y_2 + \frac{\delta_1 + \theta_1 + \gamma_1 \frac{\mu}{\mu_0}}{k} v.$$

Differentiating $L(t)$ w.r.t. t along all solutions of model (5.3), we get

$$\dot{L}(t) = \left[\frac{(q\delta_1 + \beta)\alpha x v}{(\delta_1 + \beta)(1 + \alpha_1 v)} - \frac{(\delta_1 + \theta_1 + \gamma_1 \frac{\mu}{\mu_0})(k_0 + \theta_2 + \gamma_2 z)}{k} v - \gamma_1 \left(z - \frac{\mu}{\mu_0} \right) y_1 \right].$$

After further simplification we have

$$\dot{L}(t) \leq P[R_I - 1]v - P\alpha_1 v^2,$$

where $P = \frac{(\delta_1 + \theta_1 + \gamma_1 \frac{\mu}{\mu_0})(k_0 + \theta_2 + \gamma_2 \frac{\mu}{\mu_0})}{k(1 + \alpha_1 v)}$.
Thus, $\dot{L}(t) < 0$ for $R_I \leq 1$ and $\dot{L}(t) = 0$ iff $x = x_0$, $y_1 = y_2 = v = 0$ and $z = z_0$. This implies that the largest compact invariant set in $\{(x, y_1, y_2, v, z) \in \Omega : \dot{L}(t) = 0\}$ is the singleton set $\{E_0\}$. From LaSalle's invariance principle (LaSalle, 1976) this implies that every solution of model (5.3) with initial conditions in Ω approaches $E_0(\frac{\lambda}{\delta_0}, 0, 0, 0, \frac{\mu}{\mu_0})$ as $t \to \infty$. Hence E_0 is globally asymptotically stable in Ω if $R_I \leq 1$. □

Biologically this theorem depicts that infection is cleared from the body if the number of newly infected cells is less than or equal to one which is independent of initial concentration of cells.

5.4.1 Existence of Interior Equilibrium $E_1(x^*, y_1^*, y_2^*, v^*, z^*)$

Equating equations of system (5.3) to zero, we note that x^*, y_1^*, y_2^*, v^*, and z^* are the positive solutions of the following algebraic equations:

$$\lambda - \delta_0 x - \frac{\alpha x v}{1 + \alpha_1 v} = 0, \tag{5.4}$$

$$\frac{q\alpha x v}{1 + \alpha_1 v} - \delta_1 y_1 - \gamma_1 y_1 z + \beta y_2 - \theta_1 y_1 = 0, \tag{5.5}$$

$$\frac{(1-q)\alpha x v}{1 + \alpha_1 v} - \delta_1 y_2 - \beta y_2 = 0, \tag{5.6}$$

$$k y_1 - k_0 v - \gamma_2 v z - \theta_2 v = 0, \tag{5.7}$$

$$\mu - \mu_0 z + \mu_1 y_1 z + \mu_2 v z = 0. \tag{5.8}$$

After solving equations (5.4, 5.6, 5.7) we get,

$$x = \frac{\lambda(1 + \alpha_1 v)}{\delta_0 + (\delta_0 \alpha_1 + \alpha v)},$$

$$y_1 = \frac{k_0 + \theta_2 + \gamma_2 z}{k} v,$$

$$y_2 = \frac{(1-q)\alpha\lambda v}{(\delta_1 + \beta)(\delta_0 + (\delta_0\alpha_1 + \alpha)v)}.$$

Now substituting these values of x, y_1, y_2 in equations (5.5) and (5.8), we get the following equations:

$$\left(\frac{\mu_1\gamma_2}{k}\right) v z^2 + \left(\frac{\mu_1(k_0 + \theta_2)}{k} + \mu_2\right) v z - \mu_0 z + \mu = 0, \tag{5.9}$$

$$\gamma_1\gamma_2 z^2 + Bz + (\delta_1 + \theta_1)(k_0 + \theta_2) - \frac{\alpha\lambda k(q\delta_1 + \beta)}{(\delta_1 + \beta)(\delta_0 + (\delta_0\alpha_1 + \alpha)v)} = 0, \tag{5.10}$$

where $B = ((\delta_1 + \theta_1)\gamma_2 + (k_0 + \theta_2)\gamma_1) > 0$.

We solve equations (5.9) and (5.10) using isocline method. Let us consider

$$f_1(z, v) = \left(\frac{\mu_1\gamma_2}{k}\right) vz^2 + \left(\frac{\mu_1(k_0 + \theta_2)}{k} + \mu_2\right) vz - \mu_0 z + \mu = 0, \tag{5.11}$$

$$f_2(z, v) = \gamma_1\gamma_2 z^2 + Bz + (\delta_1 + \theta_1)(k_0 + \theta_2) - \frac{\alpha\lambda k(q\delta_1 + \beta)}{(\delta_1 + \beta)(\delta_0 + (\delta_0\alpha_1 + \alpha)v)} = 0. \tag{5.12}$$

From equation (5.11), when $v = 0$, $z = \frac{\mu}{\mu_0} = z_1(say)$.

When $v \to \infty$, we have either $z = 0$ or $z = -\frac{\mu_1(k_0+\theta_2)+\mu_2 k}{\mu_1\gamma_2}$. Now

$$\begin{aligned}\frac{dz}{dv} &= -\frac{\partial f_1/\partial v}{\partial f_1/\partial z} \\ &= -\frac{\mu_1\gamma_2 z^2 + (\mu_1(k_0 + \theta_2) + \mu_2 k)z}{(2\mu_1\gamma_2 z + \mu_1(k_0 + \theta_2))v + (\mu_2 v - \mu_0)k}\end{aligned}$$

This implies that $\frac{dz}{dv} < 0$ if, $v > \frac{\mu_0}{\mu_2}$.

Now from equation (5.12), when $v = 0$, we have

$$\gamma_1\gamma_2 z^2 + Bz + (\delta_1 + \theta_1)(k_0 + \theta_2) - \frac{\alpha\lambda k(q\delta_1 + \beta)}{(\delta_1 + \beta)(\delta_0)} = 0, \tag{5.13}$$

which gives $z = \frac{-B+\sqrt{B^2-4AC}}{2A} = z_2(say)$,

where $A = \gamma_1\gamma_2$, $B = ((\delta_1+\theta_1)\gamma_2+(k_0+\theta_2)\gamma_1)$ and $C = (\delta_1+\theta_1)(k_0+\theta_2) - \frac{\alpha\lambda k(q\delta_1+\beta)}{(\delta_1+\beta)(\delta_0)}$.

The above polynomial (5.13) has unique positive root if $C < 0$, this implies that $R_0 > 1$. R_0 is the basic reproduction number in absence of immune response.

Now when $z = 0$ in equation (5.12), we have

$$v = \left(\frac{1}{\delta_0\alpha_1 + \alpha}\right)\left(\frac{\alpha\lambda k(q\delta_1 + \beta)}{(\delta_1 + \beta)(\delta_1 + \theta_1)(k_0 + \theta_2)} - \delta_0\right) = \left(\frac{\delta_0}{\delta_0\alpha_1 + \alpha}\right)(R_0 - 1),$$

which is positive if $R_0 > 1$.

$$\frac{dz}{dv} = -\frac{\partial f_2/\partial v}{\partial f_2/\partial z} = -\frac{\frac{\alpha\lambda k(q\delta_1+\beta)(\delta_0\alpha_1+\alpha)}{(\delta_1+\beta)(\delta_0+(\delta_0\alpha_1+\alpha)v)^2}}{(2\gamma_1\gamma_2 z + B)} < 0.$$

The above analysis shows that the two isoclines (5.11) and (5.12) intersects each other in the positive quadrant if $z_2 > z_1$, i.e. $R_I > 1$. Thus the interior equilibrium

exists if

$$v > \frac{\mu_0}{\mu_2} \quad \text{and} \quad R_I > 1. \tag{5.14}$$

This shows that if the number of newly infected cells produced by a single infected cell, when all other cells are healthy is more than one then infection persists and interior equilibrium exists.

5.4.2 Analysis at $R_I = 1$

To study the behaviour of the equilibrium points at $R_I = 1$, we use the center manifold theorem (Castillo-Chavez and Song, 2004), as at $R_I = 1$, linearization has a simple zero eigenvalue, hence linearization is inconclusive (Sastry, 1999). We made following assumptions to apply center manifold theorem to system (5.3).
Let $x = x_1$, $y_1 = x_2$, $y_2 = x_3$, $v = x_4$ and $z = x_5$, then system (5.3) can be rewrite as

$$\begin{cases} \dot{x_1} = \lambda - \delta_0 x_1 - \frac{\alpha x_1 x_4}{1+\alpha_1 x_4} = f_1, \\ \dot{x_2} = \frac{q\alpha x_1 x_4}{1+\alpha_1 x_4} - \delta_1 x_2 + \beta x_3 - \gamma_1 x_2 x_5 - \theta_1 x_2 = f_2, \\ \dot{x_3} = \frac{(1-q)\alpha x_1 x_4}{1+\alpha_1 x_4} - \delta_1 x_3 - \beta x_3 = f_3, \\ \dot{x_4} = k x_2 - k_0 x_4 - \gamma_2 x_4 x_5 - \theta_2 x_4 = f_4, \\ \dot{x_5} = \mu - \mu_0 x_5 + \mu_1 x_2 x_5 + \mu_2 x_4 x_5 = f_5, \end{cases} \tag{5.15}$$

At $R_I = 1$, we have α as bifurcation parameter and this is given by

$$\alpha = \alpha^* = \frac{(\delta_1 + \beta)(\delta_0)(\delta_1 + \theta_1 + \frac{\gamma_1 \mu}{\mu_0})(k_0 + \theta_2 + \frac{\gamma_2 \mu}{\mu_0})}{\lambda k (q\delta_1 + \beta)}.$$

The linearization of the above system (5.15) at E_0 and for $\alpha = \alpha^*$ gives one simple zero eigenvalue and other eigenvalues have negative real part so central manifold theory can be applied. We find the right eigenvector u of the Jacobian matrix at E_0 and $\alpha = \alpha^*$ corresponding to the zero eigenvalue, which is given by $u = [u_1, u_2, u_3, u_4, u_5]^T$, where, $u_1 = -\frac{\alpha^* x_0}{\delta_0}$, $u_2 = \frac{k_0+\theta_2+\gamma_2 z_0}{k}$, $u_3 = \frac{(1-q)\alpha^* x_0}{\delta_0}$, $u_4 = 1$, $u_5 = \frac{z_0(\mu_1(k_0+\theta_2+\gamma_2 z_0)+\mu_2 k)}{k}$. And the Jacobian matrix at E_0 and $\alpha = \alpha^*$ has a left eigenvector $w = [w_1, w_2, w_3, w_4, w_5]$, where, $w_1 = 0$, $w_2 = 1$, $w_3 = \frac{\beta}{\delta_1+\beta}$, $w_4 = \frac{\delta_1+\theta_1+\gamma_1 z_0}{k}$, $w_5 = 0$. Further, the associated nonzero partial derivatives of the

functions associated with the system (5.15) at VFE E_0 and $\alpha = \alpha^*$ are:

$$\frac{\partial^2 f_2}{\partial x_1 \partial x_4} = \frac{\partial^2 f_2}{\partial x_4 \partial x_1} = q\alpha^*, \quad \frac{\partial^2 f_2}{\partial x_4^2} = -2q\alpha^*\alpha_1 x_0, \quad \frac{\partial^2 f_2}{\partial x_2 \partial x_5} = \frac{\partial^2 f_2}{\partial x_5 \partial x_2} = -\gamma_1,$$

$$\frac{\partial^2 f_3}{\partial x_1 \partial x_4} = \frac{\partial^2 f_3}{\partial x_4 \partial x_1} = (1-q)\alpha^*, \quad \frac{\partial^2 f_3}{\partial x_4^2} = -2(1-q)\alpha^*\alpha_1 x_0,$$

$$\frac{\partial^2 f_4}{\partial x_4 \partial x_5} = \frac{\partial^2 f_4}{\partial x_5 \partial x_4} = -\gamma_2, \quad \frac{\partial^2 f_2}{\partial x_4 \partial \alpha^*} = qx_0, \quad \frac{\partial^2 f_3}{\partial x_4 \partial \alpha^*} = (1-q)x_0.$$

From Theorem 4.1 of (Castillo-Chavez and Song, 2004), the bifurcation constants a and b are given by

$$a = \sum_{k,i,j=1}^{5} w_k u_i u_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(E_0) = -\frac{(q\delta_1+\beta)}{\delta_0(\delta_1+\beta)}(\alpha^*+2\delta_0\alpha_1)\alpha^* x_0 - w_2 u_2 u_5 \gamma_1 - w_4 u_4 u_5 \gamma_2.$$

For the given values of w_k's, k =2, 3, 4 and u_i, u_j's i, j=1 to 5, $a < 0$, and

$$b = \sum_{k,i=1}^{5} w_k u_i \frac{\partial^2 f_k}{\partial x_i \partial \alpha^*}(E_0) = w_2(u_4 q x_0) + w_3(u_4(1-q)x_0) = \frac{(q\delta_1+\beta)x_0}{(\delta_1+\beta)} > 0.$$

Thus from Theorem 4.1(iv) of (Castillo-Chavez and Song, 2004), we conclude the following result.

Theorem 5.4.3. *At $R_I = 1$ virus-free equilibrium changes its stability from stable to unstable and interior equilibrium becomes positive and locally asymptotically stable. Hence system (5.3) undergoes a transcritical bifurcation at $R_I = 1$.*

The transcritical bifurcation at $R_I = 1$ has been demonstrated in figure 5.2.

In the next theorem, we show that E_1 is locally asymptotically stable under certain conditions.

Theorem 5.4.4. *The interior equilibrium $E_1(x^*, y_1^*, y_2^*, v^*, z^*)$ is locally asymptotically stable in $\Re_+^5$, if the following inequalities hold true:*

$$9(\alpha v^*)^2 x^* < 4\lambda(1+\alpha_1 v^*)^2, \tag{5.16}$$

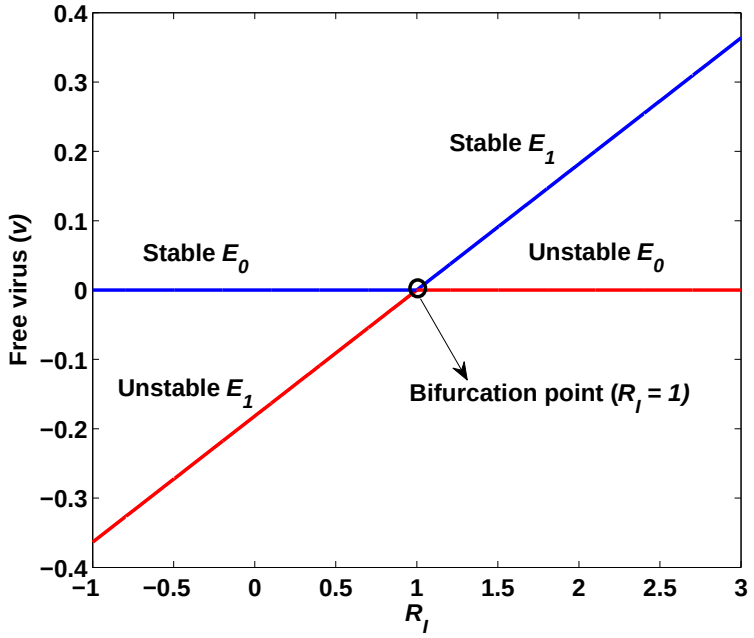

Figure 5.2: Plot of free virus vs basic reproduction number.

$$\left(\frac{\mu_2 k}{\gamma_2 v^*} + \frac{\mu_1 q\alpha x^*}{\gamma_1 y_1^*(1+\alpha_1 v^*)^2}\right)^2 < \frac{1}{4}\frac{\mu_1\mu_2 P(k_0+\theta_2+\gamma_2 z^*)}{\gamma_1\gamma_2 y_1^* v^*}, \tag{5.17}$$

$$3\gamma_2\alpha^2 x^{*3} v^* < c_4\lambda\mu_2 z^*(k_0+\theta_2+\gamma_2 z^*)(1+\alpha_1 v^*)^4, \tag{5.18}$$

where

$$c_4 < min\left\{\frac{1}{3}\frac{\lambda\gamma_1(1+\alpha_1 v^*)^2 P y_1^*}{\mu_1 x^* z^* q^2\alpha^2 v^{*2}}, \frac{1}{3}\frac{x^* P(\delta_1+\beta)^2\gamma_1 y_1^*}{\lambda\mu_1 z^*(1-q)^2\beta^2}\right\}, \quad P = (\delta_1+\theta_1+\gamma_1 z^*).$$

Proof. Let $X = x - x^*$, $Y_1 = y_1 - y_1^*$, $Y_2 = y_2 - y_2^*$, $V = v - v^*$ and $Z = z - z^*$ be the small perturbations about the interior equilibrium E_1. Using the above new variables, we linearize system (5.3) around the interior equilibrium E_1. Then in the linear model, we consider the following positive definite function:

$$W_1 = \frac{1}{2}X^2 + \frac{1}{2}c_1 {Y_1}^2 + \frac{1}{2}c_2 {Y_2}^2 + \frac{1}{2}c_3 V^2 + \frac{1}{2}c_4 Z^2,$$

where c_1, c_2 c_3 and c_4 are positive constants to be chosen suitably.
Now differentiating W_1 with respect to time t along the solutions of model (5.3), we get

$$\begin{aligned}\dot{W}_1 = &-\frac{1}{2}a_{11}X^2 + a_{12}XY_1 - \frac{1}{2}a_{22}Y_1^2 \\ &- \frac{1}{2}a_{11}X^2 + a_{13}XY_2 - \frac{1}{2}a_{33}Y_2^2 \\ &- \frac{1}{2}a_{11}X^2 + a_{14}XV - \frac{1}{2}a_{44}V^2 \\ &- \frac{1}{2}a_{22}Y_1^2 + a_{23}Y_1Y_2 - \frac{1}{2}a_{33}Y_2^2 \\ &- \frac{1}{2}a_{22}Y_1^2 + a_{24}Y_1V - \frac{1}{2}a_{44}V^2 \\ &- \frac{1}{2}a_{22}Y_1^2 + a_{25}Y_1Z - \frac{1}{2}a_{55}Z^2 \\ &- \frac{1}{2}a_{33}Y_2^2 + a_{34}Y_2V - \frac{1}{2}a_{44}V^2 \\ &- \frac{1}{2}a_{44}V^2 + a_{45}VZ - \frac{1}{2}a_{55}Z^2,\end{aligned}$$

where

$$a_{11} = \frac{2}{3}\left(\frac{\lambda}{x^*}\right), \quad a_{22} = \frac{1}{2}c_1P, \quad a_{33} = \frac{2}{3}c_2(\delta_1+\beta), \quad a_{44} = \frac{1}{2}c_3(k_0+\theta_2+\gamma_2 z^*),$$

$$a_{55} = c_4\frac{\mu}{z^*}, \quad a_{12} = \frac{c_1q\alpha v^*}{(1+\alpha_1 v^*)}, \quad a_{13} = \frac{c_2(1-q)\alpha v^*}{(1+\alpha_1 v^*)}, \quad a_{14} = -\frac{\alpha x^*}{(1+\alpha_1 v^*)^2},$$

$$a_{23} = c_1\beta, \quad a_{24} = \left(\frac{c_1q\alpha x^*}{(1+\alpha_1 v^*)^2} + c_3k\right), \quad a_{25} = (c_4\mu_1 z^* - c_1\gamma_1 y_1^*),$$

$$a_{34} = \frac{c_2(1-q)\alpha x^*}{(1+\alpha_1 v^*)^2}, \quad a_{45} = (c_4\mu_2 z^* - c_3\gamma_2 v^*).$$

Sufficient conditions for $\dot{W}_1$ to be negative definite are given as follows:

$$a_{12}^2 < a_{11}a_{22}, \tag{5.19}$$

$$a_{13}^2 < a_{11}a_{33}, \tag{5.20}$$

$$a_{14}^2 < a_{11}a_{44}, \tag{5.21}$$

$$a_{23}^2 < a_{22}a_{33}, \tag{5.22}$$

$$a_{24}^2 < a_{22}a_{44}, \tag{5.23}$$

$$a_{25}^2 < a_{22}a_{55}, \tag{5.24}$$

$$a_{34}^2 < a_{33}a_{44}, \tag{5.25}$$

$$a_{45}^2 < a_{44}a_{55}. \tag{5.26}$$

By choosing $c_1 = \frac{c_4\mu_1 z^*}{\gamma_1 y_1^*}$ and $c_3 = \frac{c_4\mu_2 z^*}{\gamma_2 v^*}$, we note that conditions (5.24) and (5.26) are satisfied. Let us choose $c_2 = \frac{x^*(\delta_1+\beta)}{(1-q)^2\lambda}$, then conditions (5.21) and (5.25) are equivalent and we see that (5.18)⇒(5.21) and (5.25). Further, if we choose c_4 in such a manner that it satisfies the following inequality:

$$c_4 < min\left\{\frac{1}{3}\frac{\lambda\gamma_1(1+\alpha_1 v^*)^2 P y_1^*}{\mu_1 x^* z^* q^2\alpha^2 v^{*2}}, \frac{1}{3}\frac{x^* P(\delta_1+\beta)^2\gamma_1 y_1^*}{\lambda\mu_1 z^*(1-q)^2\beta^2}\right\},$$

then we note that (5.16)⇒(5.17) and (5.22)⇒(5.23). Hence the theorem follows. □

In the next theorem, we are able to find sufficient conditions for E_1 to be globally asymptotically stable.

Theorem 5.4.5. *Let the following inequalities hold in the interior of the positive octant Ω:*

$$9(\alpha v^*)^2 x^* < 4\lambda(1+\alpha_1 v^*)^2, \tag{5.27}$$

$$\left(\frac{\mu_2 k}{\gamma_2 v^*} + \frac{\mu_1 q\alpha x^*}{\gamma_1 y_1^*(1+\alpha_1 v^*)}\right)^2 < \frac{1}{4}\frac{\mu_1\mu_2 P(k_0+\theta_2+\gamma_2 z^*)}{\gamma_1\gamma_2 y_1^* v^*}, \tag{5.28}$$

$$2\mu_1\gamma_1\mu y_1^* < \eta^2 P, \tag{5.29}$$

$$2\mu_2\gamma_2\mu v^* < \eta^2(k_0+\theta_2+\gamma_2 z^*), \tag{5.30}$$

$$3\gamma_2\alpha^2\lambda^2 x^* v^* < m_4\lambda\mu_2 z^*(k_0+\theta_2+\gamma_2 z^*){\delta_0}^2(1+\alpha_1 v^*)^2, \tag{5.31}$$

where

$$m_4 < min\left\{\frac{1}{3}\frac{\gamma_1 y_1^*(\delta(k_0+\theta_2)+\alpha_1 k\lambda)^2 P}{\mu_1 x^* z^*\lambda q^2\alpha^2 k^2}, \frac{1}{3}\frac{x^* P(\delta_1+\beta)^2\gamma_1 y_1^*}{\lambda\mu_1 z^*(1-q)^2\beta^2}\right\}.$$

Then $E_1(x^*, y_1^*, y_2^*, v^*, z^*)$ is globally asymptotically stable with respect to all solutions in the interior of the positive octant Ω.

Proof. We consider the following positive definite function about E_1:

$$W_2 = \frac{1}{2}(x-x^*)^2 + \frac{m_1}{2}(y_1-y_1^*)^2 + \frac{m_2}{2}(y_2-y_2^*)^2 + \frac{m_3}{2}(v-v^*)^2 + \frac{m_4}{2}(z-z^*)^2,$$

where m_1, m_2, m_3 and m_4 are positive constants to be chosen suitably.
Now differentiating W_2 with respect to time t along the solutions of model (5.3),

we get

$$\begin{aligned}\dot{W}_2 = &-\frac{1}{2}b_{11}(x-x^*)^2 + b_{12}(x-x^*)(y_1-y_1^*) - \frac{1}{2}b_{22}(y_1-y_1^*)^2\\ &-\frac{1}{2}b_{11}(x-x^*)^2 + b_{13}(x-x^*)(y_2-y_2^*) - \frac{1}{2}b_{33}(y_2-y_2^*)^2\\ &-\frac{1}{2}b_{11}(x-x^*)^2 + b_{14}(x-x^*)(v-v^*) - \frac{1}{2}b_{44}(v-v^*)^2\\ &-\frac{1}{2}b_{22}(y_1-y_1^*)^2 + b_{23}(y_1-y_1^*)(y_2-y_2^*) - \frac{1}{2}b_{33}(y_2-y_2^*)^2\\ &-\frac{1}{2}b_{22}(y_1-y_1^*)^2 + b_{24}(y_1-y_1^*)(v-v^*) - \frac{1}{2}b_{44}(v-v^*)^2\\ &-\frac{1}{2}b_{22}(y_1-y_1^*)^2 + b_{25}(y_1-y_1^*)(z-z^*) - \frac{1}{2}b_{55}(z-z^*)^2\\ &-\frac{1}{2}b_{33}(y_2-y_2^*)^2 + b_{34}(y_2-y_2^*)(v-v^*) - \frac{1}{2}b_{44}(v-v^*)^2\\ &-\frac{1}{2}b_{44}(v-v^*)^2 + b_{45}(v-v^*)(z-z^*) - \frac{1}{2}b_{55}(z-z^*)^2,\end{aligned}$$

where

$$b_{11} = \frac{2}{3}\left(\frac{\lambda}{x^*}\right), \quad b_{22} = \frac{1}{2}m_1P, \quad b_{33} = \frac{2}{3}m_2(\delta_1+\beta), \quad b_{44} = \frac{1}{2}m_3(k_0+\theta_2+\gamma_2 z^*),$$

$$b_{55} = m_4\frac{\mu}{z^*}, \quad b_{12} = \frac{m_1 q\alpha v}{(1+\alpha_1 v)}, b_{13} = \frac{m_2(1-q)\alpha v^*}{(1+\alpha_1 v^*)}, \quad b_{14} = -\frac{\alpha x}{(1+\alpha_1 v^*)(1+\alpha_1 v)},$$

$$b_{23} = m_1\beta, \quad b_{24} = \left(\frac{m_1 q\alpha x^*}{(1+\alpha_1 v^*)(1+\alpha_1 v)} + m_3 k\right), \quad b_{25} = (m_4\mu_1 z - m_1\gamma_1 y_1),$$

$$b_{34} = \frac{m_2(1-q)\alpha x}{(1+\alpha_1 v^*)(1+\alpha_1 v)}, \quad b_{45} = (m_4\mu_2 z - m_3\gamma_2 v).$$

Sufficient conditions for $\dot{W}_2$ to be negative definite are given as follows:

$$b_{12}^2 < b_{11}b_{22}, \tag{5.32}$$

$$b_{13}^2 < b_{11}b_{33}, \tag{5.33}$$

$$b_{14}^2 < b_{11}b_{44}, \tag{5.34}$$

$$b_{23}^2 < b_{22}b_{33}, \tag{5.35}$$

$$b_{24}^2 < b_{22}b_{44}, \tag{5.36}$$

$$b_{25}^2 < b_{22}b_{55}, \tag{5.37}$$

$$b_{34}^2 < b_{33}b_{44}, \tag{5.38}$$

$$b_{45}^2 < b_{44}b_{55}. \tag{5.39}$$

Let us choose $m_2 = \frac{x^*(\delta_1+\beta)}{(1-q)^2\lambda}$, then conditions (5.34) and (5.38) are same and (5.27)⇒(5.33), (5.31)⇒(5.34) and (5.38). Further, if we choose $m_1 = \frac{m_4\mu_1 z^*}{\gamma_1 y_1^*}$, then (5.29)⇒(5.37) and for $m_3 = \frac{m_4\mu_2 z^*}{\gamma_2 v^*}$, condition (5.30)⇒(5.39) and for the above values of m_1 and m_3 condition (5.28)⇒(5.36). Hence the theorem follows. □

5.5 A Special Case of the Model without Immune Response

In the absence of immune response, model (5.3) reduces to the following model:

$$\begin{cases} \frac{dx}{dt} = \lambda - \delta_0 x - \frac{\alpha x v}{1+\alpha_1 v}, \\ \frac{dy_1}{dt} = \frac{q\alpha x v}{1+\alpha_1 v} - \delta_1 y_1 + \beta y_2 - \theta_1 y_1, \\ \frac{dy_2}{dt} = \frac{(1-q)\alpha x v}{1+\alpha_1 v} - \delta_1 y_2 - \beta y_2, \\ \frac{dv}{dt} = k y_1 - k_0 v - \theta_2 v. \end{cases} \tag{5.40}$$

Similar to model (5.3), this model (5.40) also exhibits two equilibria: (i) the virus-free equilibrium (VFE) $e_0(\frac{\lambda}{\delta_0}, 0, 0, 0)$ and (ii) the interior equilibrium (IE) $e_1(\bar{x}, \bar{y_1}, \bar{y_2}, \bar{v})$.

Using next generation operator method, as discussed in the previous section, the basic reproduction number R_0 can be computed, and we note that R_0 is given by

$$R_0 = \frac{\alpha\lambda k(q\delta_1 + \beta)}{(\delta_1+\beta)(\delta_0)(\delta_1+\theta_1)(k_0+\theta_2)}.$$

Under an analysis similar to the previous section, one can prove the following theorem easily.

Theorem 5.5.1. *(i) The virus-free equilibrium e_0 is locally asymptotically stable if $R_0 < 1$, and e_0 is unstable if $R_0 > 1$.*
(ii) The virus-free equilibrium e_0 is globally asymptotically stable in Ω if $R_0 \leq 1$.
(iii) Model (5.40) undergoes a transcritical bifurcation at $R_0 = 1$.

5.5.1 Existence of Interior Equilibrium $e_1(\bar{x}, \bar{y_1}, \bar{y_2}, \bar{v})$

In case of interior equilibrium $e_1(\bar{x}, \bar{y_1}, \bar{y_2}, \bar{v})$, we note that $\bar{x}$, $\bar{y_1}$, $\bar{y_2}$ and $\bar{v}$ are given by

$$\bar{x} = \frac{\lambda(1+\alpha_1\bar{v})}{\delta_0 + (\delta_0\alpha_1 + \alpha\bar{v})}, \quad \bar{y_1} = \frac{k_0+\theta_2}{k}\bar{v},$$

$$\bar{y_2} = \frac{(1-q)\alpha\lambda\bar{v}}{(\delta_1+\beta)(\delta_0 + (\delta_0\alpha_1+\alpha)\bar{v})},$$

$$\bar{v} = \left(\frac{1}{\delta_0\alpha_1+\alpha}\right)\left(\frac{\alpha\lambda k(q\delta_1+\beta)}{(\delta_1+\beta)(\delta_1+\theta_1)(k_0+\theta_2)} - \delta_0\right).$$

It is clear that $\bar{v}$ is positive if

$$R_0 = \frac{\alpha\lambda k(q\delta_1+\beta)}{\delta_0(\delta_1+\beta)(\delta_1+\theta_1)(k_0+\theta_2)} > 1.$$

This shows that the interior equilibrium in absence of immune response exists if $R_0 > 1$. The stability behaviour of the interior equilibrium e_1 can be studied in a similar manner as done in previous section.

By comparing R_0 and R_I, we note that $R_I < R_0$. This shows that rate of infection will be slow in the presence of immune response.

5.6 Numerical Simulations

In this section, we present the numerical simulations to validate the analytical findings. MatLab 7.10 and Mathematica 7.0 are used for simulation purposes. We note that the interior equilibrium $E_1(x^*, y_1^*, y_2^*, v^*, z^*)$ exists for the set of values of parameters given in Table 5.1, and $(x^*, y_1^*, y_2^*, v^*, z^*)$ are given as follows:
$x^* = 948.6799$, $y_1^* = 1.2014$, $y_2^* = 0.5565$, $v^* = 0.2357$ and $z^* = 0.1260$.
We observe that all conditions given in Theorem 5.4.4 and Theorem 5.4.5 are satisfied. This shows that E_1 is locally as well as globally asymptotically stable for the set of values of parameters in Table 5.1.

The phase plane analysis of the sub-system of model (5.3) in the xy_1, xy_2, xv and xz planes are shown in figures 5.3(a)-5.3(d). From these figures, we note

Table 5.1: List of parameters for model (5.3)

Parameters	Values (Unit)
Source rate of uninfected cells (λ)	10 ($mm^{-3}d^{-1}$)
Death rate of uninfected cells (δ_0)	0.01 (d^{-1})
Death rate of infected & latently infected cells (δ_1)	0.015 (d^{-1})
Virus production rate (k)	0.08 (d^{-1})
Clearance rate of virus (k_0)	0.02 (d^{-1})
Infection rate (α)	0.005 ($mm^{-3}d^{-1}$)
Inhibition rate to infection (α_1)	5 ($mm^{-3}d^{-1}$)
Killing rate of infected cells by CTL-mediated IR (γ_1)	0.2 (d^{-1})
Blocking rate of virus by humoral IR (γ_2)	0.3 (d^{-1})
Source rate of IR (μ)	0.25 (d^{-1})
Depletion rate of IR (μ_0)	2 (d^{-1})
Activation rate of CTL-mediated IR (μ_1)	0.0035 (d^{-1})
Activation rate of humoral IR (μ_2)	0.052 (d^{-1})
Activation rate of latently infected cells (β)	0.4 (d^{-1})
Drug effectiveness for infected cells (θ_1)	0.38 (d^{-1})
Drug effectiveness for virus (θ_2)	0.35 (d^{-1})
Probability of infected cell joining y_1 compartment (q)	0.55

that all the trajectories initiating from different initial values converge to the same equilibrium point. The initial values are shown in the legend can be read as IV1 $\rightarrow$ [800, 2, 1, 0.2, 0.04], IV2 $\rightarrow$ [1100, 2.5, 0.5, 0.3, 0.03], IV3 $\rightarrow$ [920, 3, 1.5, 0.04, 0.05] and IV4 $\rightarrow$ [850, 0.05, 0.2, 0.05, 0.01]. Since the system is globally asymptotically stable therefore it is independent of initial status of the sub-populations.

Figures 5.4(a) and 5.4(b) represent the effect of α on uninfected cells and infected cells, respectively. We observe that the concentration of uninfected cells is high (fig 5.4(a)) and that of infected cells is low (at zero level) for $\alpha = 0.001$ and in this case $R_I = 0.4598 < 1$. This shows that infection is no more at this stage. Further the number of uninfected cells decreases with increase in α which is obvious for real world scenarios when infection increases the number of uninfected or healthy cells declines. In figure 5.4(b), the number of infected cells increases with increase in infection rate α, which is also usual in real situations. Thus, infection can be controlled by controlling the spread of infection within the cells with the help of immune response and appropriate drugs. Figures 5.4(c) and 5.4(d) show the effect of α_1, whereas α_1 changes reversibly with infection rate. In figure 5.4(c), we observe oscillations for small value of $\alpha_1 = 0.005$. In the expression for infection

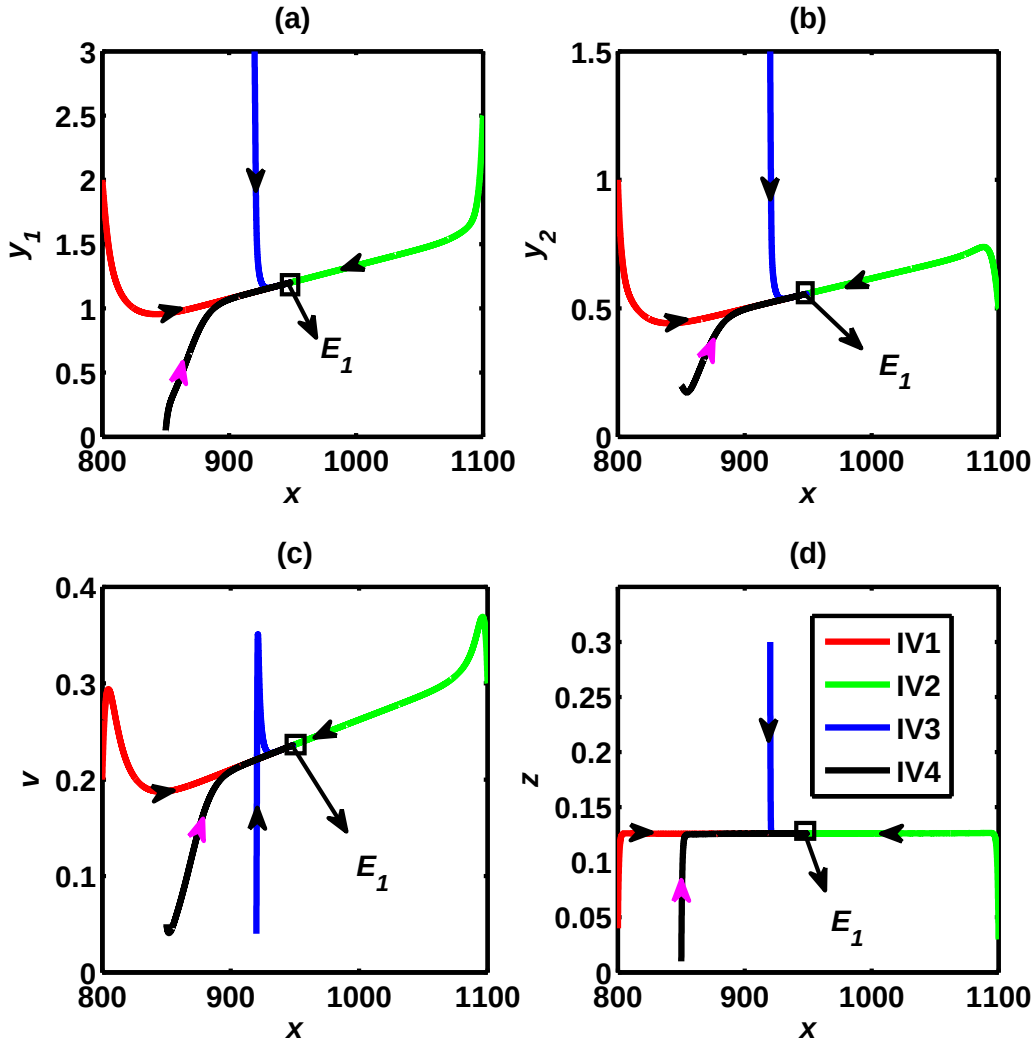

Figure 5.3: Global stability of the sub-system.

rate, when α_1 approaches zero then this infection rate term $\frac{\alpha x v}{(1+\alpha_1 v)}$ becomes bilinear, which is not realistic in case of large number of infected cells. It may be noted that behavior of infected cells is complementary to the behavior of uninfected cells so similar explanation can be given for the oscillations in fig 5.4(d).

The effect of drug therapy θ_1 and θ_2 on infected cells y_1 and free virus v are shown in figures 5.5(a) and 5.5(b), respectively. From these figures it follows that in the absence of treatment ($\theta_1 = \theta_2 = 0$), the number of infected cells and free virus are high. As efficacy of therapeutic drugs θ_1 and θ_2 increases, the number of infected cells and free virus decreases and settles down at their respective equilibrium levels.

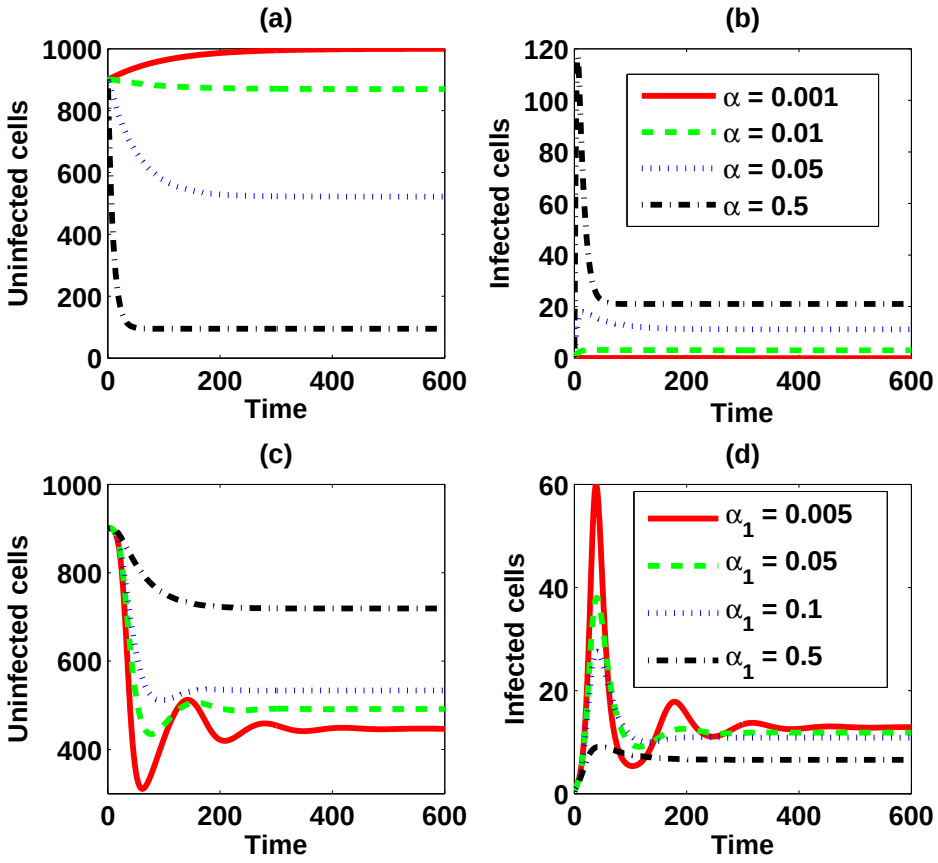

Figure 5.4: Effect of α and α_1 on x and y_1, respectively.

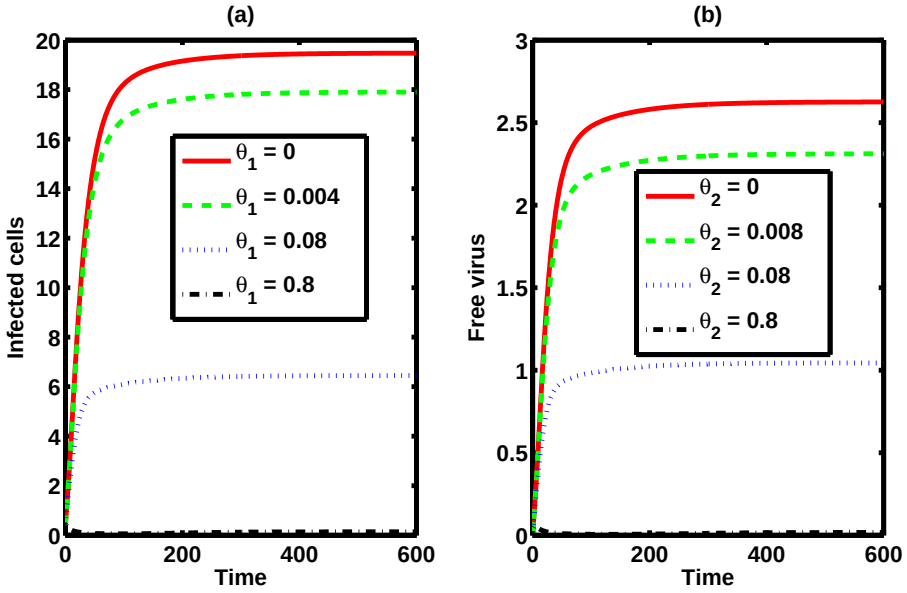

Figure 5.5: Effect of θ_1 on y_1 and effect of θ_2 on v, respectively.

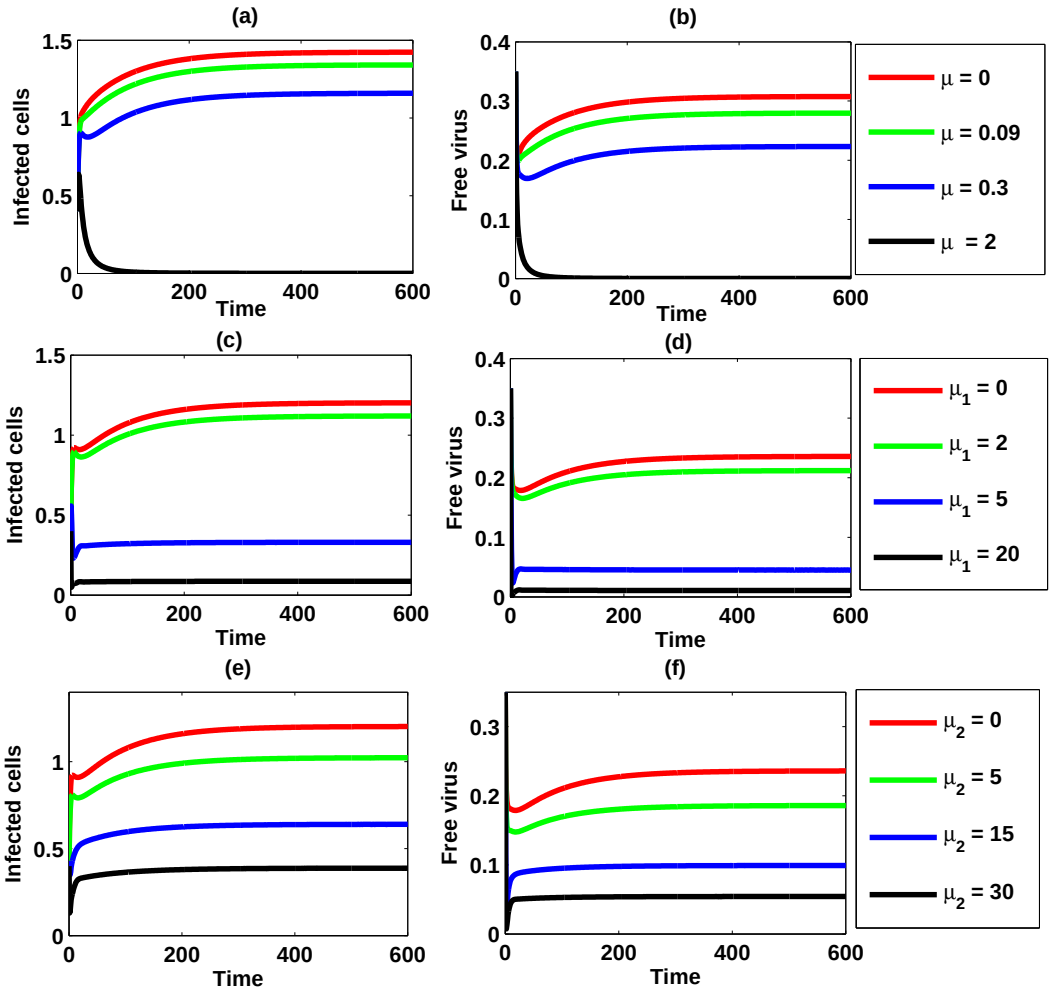

Figure 5.6: Effect of μ, μ_1, μ_2 on y_1 and v, respectively.

This highlights the efficacy of the drug in controlling the concentration of infected cells and free virus, respectively.

Figures 5.6(a) and 5.6(b) show that when immune response is not present then trajectories settle at higher concentration of infected cells and free virus while the concentration of the infected cells and free virus decreases with increase in immune response (μ) and approaches to zero for higher values of μ. In figures 5.6(c) and 5.6(d), the trajectories settle at high level for $\mu_1 = 0$ and for higher values of μ_1 these trajectories are settled down at lower concentration of infected cells and free virus but not approaching to zero as μ_1 is the increase in immune response due to stimulation from infected cells. Similar explanation can be given for figures 5.6(e) and 5.6(f), where μ_2 is the increase in immune response due to stimulation from free virus. It is interesting to note that if immune responses are at high levels,

then infected cells and free virus can be brought back to zero level with adequate drugs and thus the infection can be cured.

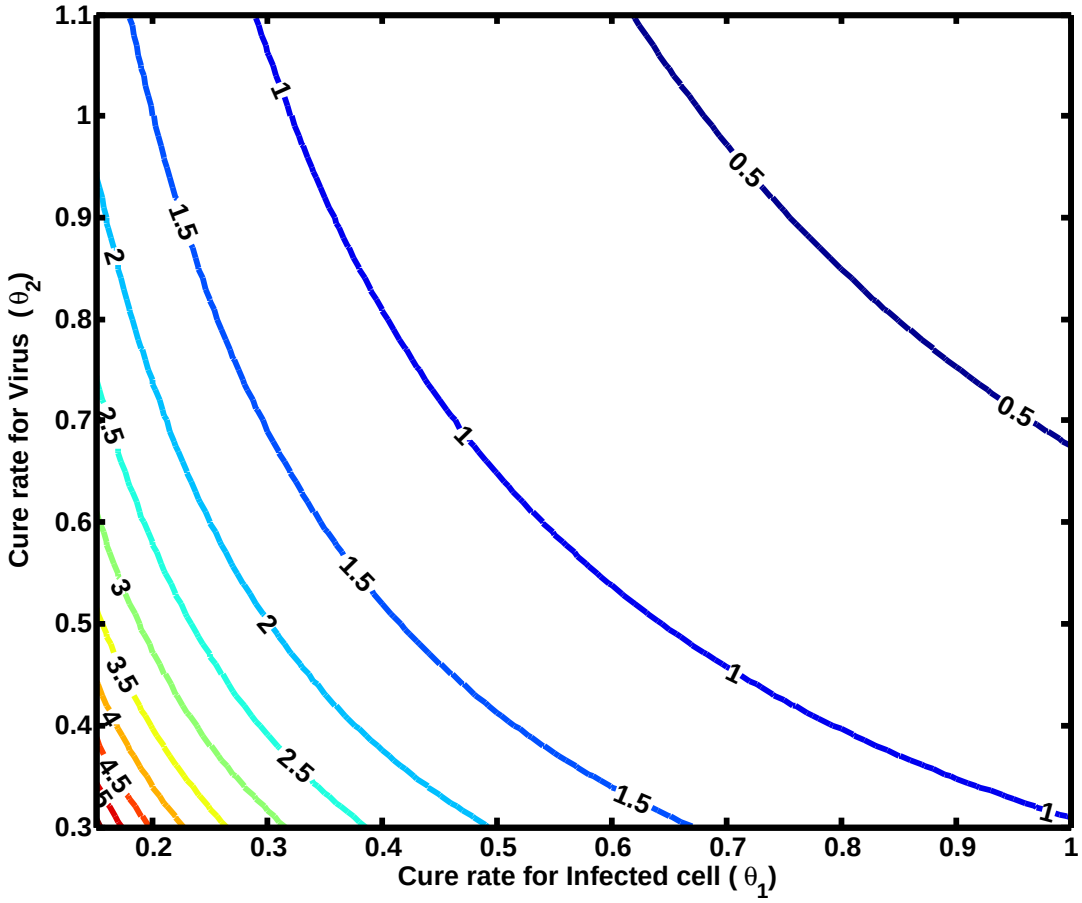

Figure 5.7: Variation of therapeutic drugs (θ_1 and θ_2) on R_I.

In the last figure 5.7, we have shown the variation of R_I with respect to therapeutic drugs given to infected cells (θ_1) and virus (θ_2) respectively. We observe that for the less values of the therapeutic drug given to the infected cells ($\theta_1 = 0.15$) and that of to viruses ($\theta_2 = 0.3$) the corresponding value of R_I is 5. And it is apparent from the figure 5.7 that if we increase the amount of therapeutic drug given to the infected cells ($\theta_1 = 1$) and virus ($\theta_2 = 1.1$) the corresponding value of R_I decreases i.e. $R_I = 0.5$. This emphasize that combination of therapy is useful in reducing the viral load and ultimately to eradicate the infection.

5.7 Conclusions

In this chapter, we examined the effect of immune response and drug therapy on virus dynamics model. We studied global stability of virus-free equilibrium and interior equilibrium. Global stability of the interior equilibrium has also been shown numerically which suggests that the infection will persist in the endemic zone. We found a threshold value, which is defined as basic reproductive number R_I. The infection will further increase if $R_I > 1$ and infection will be eradicated if $R_I < 1$. The global stability of virus-free equilibrium ensures the clearance of virus from the body which is independent of initial status of sub-populations (Theorem 5.4.2). From the analysis of the model at $R_I = 1$, it is observed that the virus-free equilibrium loses its stability from the stable state to unstable state. It further ensures the existence of interior equilibrium and the model exhibits transcritical bifurcation.

A special case of the model in absence of immune response has also been investigated. Similar to model (5.3), the analysis of model (5.40) has been performed and we found that the virus-free equilibrium is globally asymptotically stable if $R_0 \leq 1$. We found that basic reproductive number in absence of immune response R_0 is greater than basic reproductive number in the presence of immune response R_I i.e. $R_0 > R_I$. This implies that in the presence of immune response the number of secondary infections will be less. It suggests that infection may be eradicated if $R_I < 1$. From the expression of R_I, it is observed that the number of secondary infections decreases with the enhancement of immune response and drug efficacy. This shows that R_I may be made less than one by increasing drug efficacy and improving the immune conditions. Thus, increase in treatment is effective in controlling the number of infected cells and free viruses. In addition, action of immune response also reduces the virus load. It has also been shown in figure 5.7 that the reproduction number can be reduced by applying adequate combination of therapeutic drugs which helps in reduction of viral load and finally to combat the infection.

Chapter 6

Modeling the Intracellular Pathogen-Immune Interaction with Cure Rate

Simple laws can very well describe complex structures. The miracle is not the complexity of our world, but the simplicity of the equations describing that complexity.

B. Sander Bais

Pathogens are infectious agents which cause diseases into hosts. This chapter addresses the infections caused by viral pathogens. We proposed a class of mathematical models to study the pathogen-immune interaction *in vivo*. Main aim of this chapter is to explore the effect of biological features i.e. non-cytolytic cure, absorption of pathogens and immune response. Out of the four proposed models, first and third models involve non-cytolytic cure rate without absorption of pathogens in absence of immune response and in presence of immune response, respectively. On the contrary, second and fourth model deals with the aforesaid phenomenon in presence of absorption of pathogens. Stability analysis of the models has been analyzed and ratified with the help of numerical simulations.

6.1 Introduction

Many devastating diseases are caused by intracellular viral pathogens within a human cell. These pathogens use the host's machinery for its own growth and reproduction. When pathogen enters the body, this encounter the first line of defense mechanism which is largely the innate/natural immune response subsequently the acquired or specific immune response develops. This includes the cell mediated (Cytotoxic T cell mediated) immune response and humoral (antibody mediated) immune response. The presence of immune response along with the absorption/uptake of pathogens into uninfected cells and the presence of appropriate treatment modality play a significant role in determining the outcome and stability of the given system.

In the last few decades some mathematical models have been developed to understand the dynamics of interactions of pathogens with host's immune response in vivo (Anderson and May, 1981; Nowak and Bangham, 1996; Covert and Kirschner, 2000; Pugliese and Gandolfi, 2008; Zhou et al., 2009; Dubey and Dubey, 2007; Dubey et al., 2011; Murase et al., 2005; Nuraini et al., 2009; Kajiwara and Sasaki, 2010; Tian and Xu, 2012). This has helped us to predict reduction of viral load and to get a better insight of spread of infection within the body. The mechanisms of immune response and pathogen interaction are discussed by Denise and the references cited therein (Covert and Kirschner, 2000). The loss of pathogens or effect of absorption has not been considered in pathogen-immune interaction models (Anderson and May, 1981; Nowak and Bangham, 1996; Covert and Kirschner, 2000; Pugliese and Gandolfi, 2008; Zhou et al., 2009; Dubey and Dubey, 2007; Dubey et al., 2011). Murase et al. (2005) proposed a mathematical model with immune response and absorption of pathogens into uninfected cells. They studied the local stability of equilibria to get an insight of the persistence of infection and considered different cases in their models. Firstly, they considered the basic virus dynamics model and then in the next model they incorporated immune response and ignored the effect of absorption. Further, in third case they incorporated the effect of absorption of pathogens into uninfected cells and found that absorption of

pathogens may disturb the stability of interior equilibrium point. Further, authors (Nuraini et al., 2009; Kajiwara and Sasaki, 2010; Tian and Xu, 2012; Wang et al., 2013) considered the virus dynamics model with loss of pathogens into uninfected cells and extended their models to incorporate the effect of immune responses. For instance, Tian and Xu (2012) studied the delayed model with CTL immune response and saturated infection rate considering the effect of absorption to describe the dynamics of HIV-1 infection. They have shown that infection becomes chronic in both cases (i) when CTL immune response is absent and (ii) when CTL immune response is present. Nuning et al. (2009) studied a viral infection model for Dengue virus. They assumed that the inclusion of immune response may eradicate the infection and virus load decreases with increase in immune response. Wang et al. (2013) studied viral dynamics model considering CTL immune response and antiretroviral therapy together with loss of virus into uninfected cells. They argued that the inclusion of absorption of virus term is important to get the better insight of the infection in-host.

In recent viral dynamics models, authors (Ciupe et al., 2007; Zhou et al., 2008; Srivastava et al., 2009; Liu et al., 2011; Tian and Liu, 2014; Hattaf and Yousfi, 2011; Hattaf et al., 2012) developed an innovative approach to cure the infected cells using non-cytolytic processes (the removal of virus without destruction of infected cell). It is assumed and biologically proved that instead of killing, the infected cells can be cured or recovered into uninfected cells. Cuipe et. al. (2007) have shown in their model that in case of hepatitis B virus infection the covalently closed circular (ccc) DNA can be removed from the nucleus of infected cells and in turn the cell become uninfected cell. The detailed mechanism of the non-cytolytic process can be explored from (Ciupe et al., 2007; Guidotti et al., 1999) and the references cited therein. Zhou et al. (2008) considered in their HIV dynamics model that the infected cells can be removed by two ways, either through death (mostly immune-mediated killing) or via cure (loss of cccDNA). The approach of inclusion of both cytolytic and non-cytolytic mechanisms of infected cell loss is more realistic and accurate. After that, Srivastava et al. (2009) argued that the

infected cells revert back to uninfected cells class due to non-completion of reverse transcription process i.e drug will not be 100% effective.

Getting motivated from the work of (Murase et al., 2005; Zhou et al., 2008), we propose a class of mathematical models to study the effect of non-cytolytic cure process without and with absorption of pathogens into uninfected cells in the absence of immune response. Further, we extend our model to study aforesaid effect in the presence of immune response. We incorporated the biological features in above models step by step to understand that which biological term affects prominently the behavior of infection. Besides this, we have also considered the infection rate as saturated infection rate, which is more realistic approach for modeling the dynamics of the system under consideration.

6.2 The Mathematical Model

Let $x(t)$ be the concentration of uninfected cells, $y(t)$ be the concentration of infected cells, $p(t)$ be the concentration of pathogens in blood cells. We assume that the uninfected cells are recruited at a constant rate λ from the source within the body such as bone marrow and has a natural life expectancy of $\frac{1}{\delta_0}$ days. In general, the interaction of pathogens with uninfected cells are considered to be as "mass-action" which suggests that rate of infection is directly proportional to the product of concentrations of uninfected cells and pathogens. But this principle is not always true in real life. For example, the law of mass-action will not be followed if the concentration of pathogens is greater than that of concentration of uninfected cells. In such case, increase in concentration of pathogens will not increase infection. Taking this into consideration, we suggest that infection rate can be taken as nonlinear infection rate. Here in the proposed model we have considered saturated infection rate, also known as Holling type II infection rate and represented by the term $\frac{\beta xp}{1+\alpha p}$; $\beta > 0$, $\alpha \geq 0$. We assumed that infected cells die out at a rate δ_1 and r is the total number of pathogens produced by an infected cell due to its death. Let ρ be the cure rate of pathogens using the non-cytolytic processes. If we ignore the loss of pathogens due to absorption (Nowak and Bangham, 1996; Dubey and Dubey, 2007), then the dynamics of uninfected cells, infected cells

and pathogen can be governed by the following system of ordinary differential equations:

$$\begin{cases} \frac{dx}{dt} = \lambda - \delta_0 x - \frac{\beta xp}{1+\alpha p} + \rho y, \\ \frac{dy}{dt} = \frac{\beta xp}{1+\alpha p} - \delta_1 y - \rho y, \\ \frac{dp}{dt} = r\delta_1 y - \delta_2 p, \end{cases} \tag{6.1}$$

$$x(0) > 0, \quad y(0) \geq 0, \quad p(0) \geq 0.$$

Remark 6.2.1. *If we take $\alpha = 0$ and $\rho = 0$, then model (6.1) is well studied in (Murase et al., 2005).*

The interaction of sub-populations can be understood from the schematic diagram of model (6.1) as shown in figure (6.1).

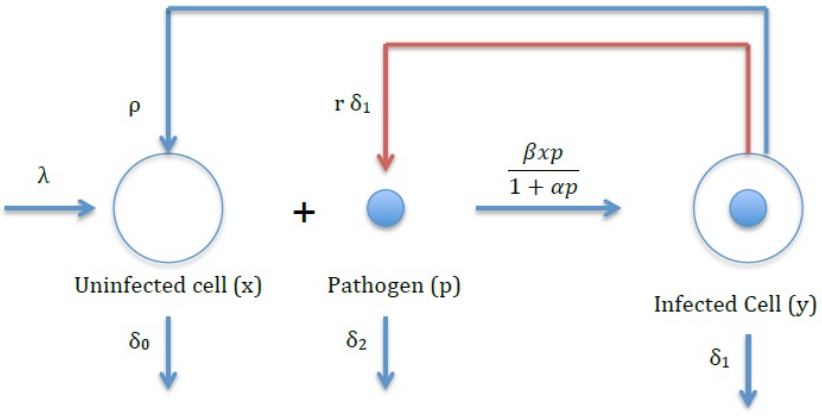

Figure 6.1: Schematic diagram of model (6.1).

6.3 Positivity and Boundedness of Model (6.1)

Adding first two equations of model (6.1), we get

$$\dot{x} + \dot{y} = \lambda - \delta_0 x - \delta_1 y \leq \lambda - \delta_m (x + y),$$

where $\delta_m = \min\{\delta_0, \delta_1\}$. Using elementary calculus,

$$\limsup_{t\to\infty} x(t) \leq \frac{\lambda}{\delta_m}.$$

Similarly

$$\limsup_{t\to\infty} p(t) \leq \frac{r\delta_1\lambda}{\delta_m\delta_2}.$$

This proves the boundedness of the solutions of model (6.1). To show the positive invariance of the solutions, let $N = x + y$ and $\dot{N} < 0$ if $N > \frac{\lambda}{\delta_m}$ and $\dot{p} < 0$ if $p > \frac{r\delta_1\lambda}{\delta_2\delta_m}$. This shows that all solutions of system (6.1) point towards the region Ω_1 defined in Lemma 6.3.1. The above calculation leads to the following lemma:

Lemma 6.3.1. *The set* $\Omega_1 = \{(x, y, p) \in \Re^3_+ : 0 \leq x + y \leq \frac{\lambda}{\delta_m}, 0 \leq p \leq \frac{r\delta_1\lambda}{\delta_2\delta_m}\}$ *is positively invariant region of system (6.1).*

The above lemma shows mathematically and epidemiologically the well-posedness of model (6.1).

6.4 Equilibrium and Stability Analysis

It can be observed easily that model (6.1) has two equilibria; (i) pathogen-free equilibrium $E_{01}(x_0, 0, 0)$ and (ii) pathogen-present equilibrium point $E_1(x^*, y^*, p^*)$. Pathogen-free equilibrium exists trivially and is given by $E_{01}(x_0, 0, 0) = E_{01}(\frac{\lambda}{\delta_0}, 0, 0)$. The basic reproduction number R_1 for model (6.1) is given by

$$R_1 = \frac{\beta\lambda r\delta_1}{\delta_0\delta_2(\delta_1 + \rho)}.$$

The basic reproduction number is the number of newly infected cells produced by a single infected cell when introduced into completely healthy cells.
From the model equations, it is easy to find the equilibrium point $E_1(x^*, y^*, p^*)$, where

$$x^* = \frac{(\lambda r\alpha + \delta_2)(\delta_1 + \rho)}{r(\alpha(\delta_1 + \rho)\delta_0 + \beta\delta_1)},$$

$$y^* = \frac{\delta_0\delta_2(\delta_1 + \rho)(R_1 - 1)}{r\delta_1(\alpha(\delta_1 + \rho)\delta_0 + \beta\delta_1)},$$

$$p^* = \frac{\delta_0(\delta_1 + \rho)(R_1 - 1)}{(\alpha(\delta_1 + \rho)\delta_0 + \beta\delta_1)}.$$

We can easily observe from above equations that pathogen-present equilibrium E_1 exists if $R_1 > 1$. Using the Routh-Hurwitz criteria, one can notice that the

pathogen-free equilibrium E_{01} is locally asymptotically stable for $R_1 < 1$ and unstable if $R_1 > 1$.

Further, taking $L = \frac{r\delta_1}{\delta_1+\rho}y + p$ as a positive definite function and using LaSalle's invariance principle (LaSalle, 1976), it has been found that E_{01} is globally asymptotically stable if $R_1 \leq 1$. This shows that the infection will be controlled if basic reproduction number is less than one and this is independent of initial concentrations of sub-populations. Further, one can easily prove that pathogen-present equilibrium $E_1(x^*, y^*, p^*)$ is locally asymptotically stable if $R_1 > 1$. This shows that infection may spread if $R_1 > 1$ and infection will die out if $R_1 < 1$.

The global stability of the pathogen-present equilibrium point $E_1(x^*, y^*, p^*)$ is discussed in the next theorem.

Theorem 6.4.1. *The pathogen-present equilibrium $E_1(x^*, y^*, p^*)$ is globally asymptotically stable if following inequalities hold true in Ω_1:*

$$\left(\rho + \frac{\beta p^*}{1+\alpha p^*}\right)^2 < \left(\delta_0 + \frac{\beta p^*}{1+\alpha p^*}\right)(\delta_1 + \rho), \tag{6.2}$$

$$\left(\frac{\beta\lambda}{\delta_m(1+\alpha p^*)}\right)^2 < \delta_2\left(\delta_0 + \frac{\beta p^*}{1+\alpha p^*}\right), \tag{6.3}$$

$$\left(\frac{\beta\lambda}{\delta_m(1+\alpha p^*)} + r\delta_1\right)^2 < \delta_2(\delta_1 + \rho). \tag{6.4}$$

Proof. We consider the positive definite function about E_1 as

$$W_1 = \frac{1}{2}(x - x^*)^2 + \frac{1}{2}(y - y^*)^2 + \frac{1}{2}(p - p^*)^2.$$

After differentiating W_1 w.r.t t along all positive solutions of (6.1) and manipulating the calculation, we get

$$\begin{aligned}\dot{W}_1 = &-\frac{1}{2}a_{11}(x - x^*)^2 + a_{12}(x - x^*)(y - y^*) - \frac{1}{2}a_{22}(y - y^*)^2 \\ &- \frac{1}{2}a_{11}(x - x^*)^2 + a_{13}(x - x^*)(p - p^*) - \frac{1}{2}a_{33}(p - p^*)^2 \\ &- \frac{1}{2}a_{22}(y - y^*)^2 + a_{23}(y - y^*)(p - p^*) - \frac{1}{2}a_{33}(p - p^*)^2,\end{aligned}$$

where

$$a_{11} = \frac{1}{2}\left(\delta_0 + \frac{\beta p^*}{(1+\alpha p^*)}\right), \quad a_{22} = \frac{1}{2}(\delta_1+\rho), \quad a_{33} = \frac{2}{3}\delta_2, \quad a_{12} = \left(\rho + \frac{\beta p^*}{(1+\alpha p^*)}\right),$$

$$a_{13} = -\frac{\beta x}{(1+\alpha p)(1+\alpha p^*)}, \quad a_{23} = \left(\frac{\beta x}{(1+\alpha p)(1+\alpha p^*)} + r\delta_1\right).$$

We know from Sylvester's criterion, sufficient conditions for $\dot{W}_1$ to be negative definite are

$$a_{12}^2 < a_{11}a_{22}, \tag{6.5}$$

$$a_{13}^2 < a_{11}a_{33}, \tag{6.6}$$

$$a_{23}^2 < a_{22}a_{33}. \tag{6.7}$$

The above equations represent to the conditions given in Theorem 6.4.1. Hence the theorem follows. □

The above result shows that if pathogen-present equilibrium exists and if the above inequalities hold true then the pathogen-present equilibrium will persist and approach to its steady state irrespective of concentration of their sub-populations.

6.5 Effect of Absorption of Pathogens in Model (6.1)

It is known that when a pathogen interacts with uninfected cells, the number of pathogens reduces by one in blood. This process is known as absorption of pathogens (Tian and Xu, 2012). It results in uptake of the pathogens into uninfected cells. Presently we consider the absorption of pathogens into uninfected cells, in this case model (6.1) reduces as follows:

$$\begin{cases} \frac{dx}{dt} = \lambda - \delta_0 x - \frac{\beta xp}{1+\alpha p} + \rho y, \\ \frac{dy}{dt} = \frac{\beta xp}{1+\alpha p} - \delta_1 y - \rho y, \\ \frac{dp}{dt} = r\delta_1 y - \delta_2 p - \frac{\beta xp}{1+\alpha p}, \end{cases} \tag{6.8}$$

$$x(0) > 0, \quad y(0) \geq 0, \quad p(0) \geq 0.$$

From Lemma 6.3.1 we observe that all the solutions of the model initiating in the positive orthant will remain positive. This shows that the loss of pathogens does not alter the positive invariance and boundedness of the solutions. Similar to model 6.1, we found two equilibria for this model. The pathogen-free equilibrium $E_{02}(\frac{\lambda}{\delta_0}, 0, 0)$ and pathogen-present equilibrium $E_2(\bar{x}, \bar{y}, \bar{p})$. The basic reproduction number for this model is given by

$$R_2 = \frac{\beta\lambda r\delta_1}{(\delta_1+\rho)(\delta_0\delta_2+\beta\lambda)}.$$

Equating RHS of equations of model (6.8) to zero and manipulating equations, we get

$$\bar{x} = \frac{\delta_2(\delta_1+\rho)(1+\alpha\bar{p})}{\beta(r\delta_1-\delta_1-\rho)},$$

$$\bar{y} = \frac{\delta_2}{(r\delta_1-\delta_1-\rho)}\bar{p},$$

$$\bar{p} = \frac{(\delta_1+\rho)(\delta_0\delta_2+\beta\lambda)(R_2-1)}{\delta_2(\beta\delta_1+\alpha\delta_0(\delta_1+\rho))}.$$

Here $\bar{x}$ and $\bar{y}$ are positive if $r\delta_1 > \delta_1+\rho$. Hence the pathogen-present equilibrium exists if $r\delta_1 > (\delta_1+\rho)$ and $R_2 > 1$. Using the Routh-Hurwitz criteria, we note the following results.

(i) The pathogen-free equilibrium is locally asymptotically stable if $R_2 < 1$ and unstable if $R_2 > 1$.

(ii) The pathogen-present equilibrium E_2, whenever it exists, is locally asymptotically stable.

It can also be seen that E_{02} is globally asymptotically stable for $R_2 \leq 1$. To show the global stability of E_{02}, we have taken the Lyapunov function same as for E_{01}.

In the next theorem, we have shown the global asymptotic stability of pathogen-present equilibrium when absorption of pathogens is taken into account.

Theorem 6.5.1. *The pathogen-present equilibrium $E_2(\bar{x}, \bar{y}, \bar{p})$ is globally asymptotically stable if following inequalities hold true in Ω_1:*

$$\left(\rho + \frac{\beta\bar{p}}{1+\alpha\bar{p}}\right)^2 < \left(\delta_0 + \frac{\beta\bar{p}}{1+\alpha\bar{p}}\right)(\delta_1 + \rho), \tag{6.9}$$

$$\left(\frac{\beta\lambda}{\delta_m(1+\alpha\bar{p})} + \frac{\beta\bar{p}}{1+\alpha\bar{p}}\right)^2 < \delta_2\left(\delta_0 + \frac{\beta\bar{p}}{1+\alpha\bar{p}}\right), \tag{6.10}$$

$$\left(\frac{\beta\lambda}{\delta_m(1+\alpha\bar{p})} + r\delta_1\right) < \delta_2(\delta_1 + \rho). \tag{6.11}$$

The proof of Theorem 6.5.1 is similar to that of Theorem 6.4.1 and hence omitted.

From Theorem 6.4.1 and Theorem 6.5.1, we note that conditions (6.2) and (6.9) are similar, conditions (6.4) and (6.11) are similar except the equilibrium level of pathogens. However, conditions (6.3) and (6.10) are different, which shows that stability behavior of the pathogen-present equilibrium may be altered due to absorption of pathogens into uninfected cells.

6.6 Effect of Immune Response on Infected Cells and Pathogens

Let $z(t)$ be the concentration of immune response at any time $t \geq 0$. Let μ be the innate immune response of the body. When pathogens enter into the body and attacks the uninfected cells to get it infected, then the infected cell-specific lymphocytes proliferate with the rate $\mu_1 yz$ and the pathogen-specific lymphocytes proliferate with the rate $\mu_2 pz$. The corresponding decrease in the number of infected cells and pathogens are $k_1 yz$ and $k_2 pz$, respectively. The immune response decays at the rate $\mu_0 z$. Keeping this in view, model (6.1) can be modified and written as

$$\begin{cases} \frac{dx}{dt} = \lambda - \delta_0 x - \frac{\beta xp}{1+\alpha p} + \rho y, \\ \frac{dy}{dt} = \frac{\beta xp}{1+\alpha p} - \delta_1 y - \rho y - k_1 yz, \\ \frac{dp}{dt} = r\delta_1 y - \delta_2 p - k_2 pz, \\ \frac{dz}{dt} = \mu - \mu_0 z + \mu_1 yz + \mu_2 pz, \end{cases} \tag{6.12}$$

$$x(0) > 0, \quad y(0) \geq 0, \quad p(0) \geq 0, \quad z(0) \geq 0.$$

First of all, we state the following Lemma to show the positivity and boundedness of the solutions of model (6.12). The proof of this Lemma is similar to that of Lemma 6.3.1 and hence omitted.

Lemma 6.6.1. *The set* $\Omega_2 = \{(x, y, p, z) \in \Re^4_+ : 0 \leq x+y \leq \frac{\lambda}{\delta_m}, 0 \leq p \leq \frac{r\delta_1\lambda}{\delta_2\delta_m}, 0 \leq z \leq \frac{\mu}{\eta}\}$ *is positively invariant region of system (6.12), where* $\delta_m = \min\{\delta_0, \delta_1\}$ *and* $\eta = \mu_0 - \frac{u_1\lambda}{\delta_m} - \frac{\mu_2 r\delta_1\lambda}{\delta_2\delta_m} > 0$.

This lemma proves well-posedness of model (6.12) and hence model is biologically well behaved.

6.6.1 Equilibrium Analysis of Model (6.12)

For this model, we see that there exists two equilibrium points; pathogen-free equilibrium point E_{03} and pathogen-present equilibrium point E_3. These equilibrium points are $E_{03}(x_0, 0, 0, z_0) = E_{03}(\frac{\lambda}{\delta_0}, 0, 0, \frac{\mu}{\mu_0})$ and $E_3(\tilde{x}, \tilde{y}, \tilde{p}, \tilde{z})$.
The pathogen-free equilibrium exists trivially. We show the existence of pathogen-present equilibrium point using the Isocline method. The equation $\dot{p} = 0$ of model (6.12) gives

$$y = \left(\frac{\delta_2 + k_2 z}{r\delta_1}\right) p.$$

Substituting the value of y in the equation $\dot{y} = 0$ of model (6.12), we get

$$x = \left(\frac{(\delta_1 + \rho + k_1 z)(\delta_2 + k_2 z)}{r\delta_1\beta}\right)(1 + \alpha p).$$

$\dot{x} + \dot{y} = 0$ of model (6.12) yields

$$x = \frac{\lambda}{\delta_0} - \left(\frac{(\delta_1 + k_1 z)(\delta_2 + k_2 z)}{r\delta_1\delta_0}\right) p.$$

Comparing these two values of x, we get following equation:

$$[k_1k_2\delta_0 + k_1k_2(\alpha\delta_0 + \beta)p]z^2 + [(k_1\delta_2 + (\delta_1 + \rho)k_2)(1 + \alpha p)\delta_0 + (k_1\delta_2 + k_2\delta_1)\beta p]z$$
$$+ \delta_0\delta_2(\delta_1 + \rho)(1 + \alpha p) + \beta\delta_1\delta_2 p - \lambda r\delta_1\beta = 0.$$

After some algebraic calculation, last equation of model (6.12) gives another equation in p and z

$$(\mu_1 k_2 p)z^2 + (r\delta_1\mu_2 p + \mu_1\delta_2 p - \mu_0 r\delta_1)z + \mu r\delta_1 = 0.$$

Let us assume

$$f_1(p,z) = (\mu_1 k_2 p)z^2 + (r\delta_1\mu_2 p + \mu_1\delta_2 p - \mu_0 r\delta_1)z + \mu r\delta_1 = 0, \tag{6.13}$$

$$\begin{aligned} f_2(p,z) = {} & [k_1k_2\delta_0 + k_1k_2(\alpha\delta_0+\beta)p]z^2 + [(k_1\delta_2 + (\delta_1+\rho)k_2)(1+\alpha p)\delta_0 \\ & + (k_1\delta_2 + k_2\delta_1)\beta p]z + \delta_0\delta_2(\delta_1+\rho)(1+\alpha p) + \beta\delta_1\delta_2 p - \lambda r\delta_1\beta = 0. \end{aligned} \tag{6.14}$$

From equation (6.13), we observe the following:

(i) When $p = 0$, then $z = \frac{\mu}{\mu_0} = z_1(say)$.

(ii) When $p \to \infty$, either $z \to 0$ or $z \to -\left(\frac{\mu_1\delta_2+\mu_2 r\delta_1}{\mu_1 k_2}\right)$.

(iii) $\frac{dz}{dp} = -\frac{\partial f_1/\partial p}{\partial f_1/\partial z} = -\frac{(\mu_1 k_2 z^2 + (\mu_2 r\delta_1 + \mu_1\delta_2)z)}{(2\mu_1 k_2 pz + (\mu_2 r\delta_1 p + \mu_1\delta_2 p - \mu_0 r\delta_1))}$,

$$\Rightarrow \frac{dz}{dp} < 0 \quad \text{if} \quad p > \frac{\mu_0}{\mu_2}.$$

This implies that z is decreasing function of p.

From equation (6.14), we note the following:

(i) When $z = 0$, then $p = \frac{\lambda r\delta_1\beta - \delta_0\delta_2(\delta_1+\rho)}{(\alpha(\delta_1+\rho)\delta_0\delta_2 + \beta\delta_1\delta_2)}$, and $p > 0$ if $R_1 > 1$.

(ii) When $p = 0$, equation (6.14) gives a quadratic equation in z

$$(k_1k_2\delta_0)z^2 + ((k_1\delta_2 + (\delta_1+\rho)k_2)\delta_0)z - (\lambda r\delta_1\beta - \delta_0\delta_2(\delta_1+\rho)) = 0.$$

From the above equation, we found two roots (one is positive and another one is negative) if $R_1 > 1$. For $R_1 < 1$ there is no positive real root.

Let us say $z = z_2 = \frac{-B+\sqrt{B^2+4AC}}{2A}$, where $A = k_1k_2\delta_0$, $B = (k_1\delta_2 + (\delta_1+\rho)k_2)\delta_0$ and $C = (\lambda r\delta_1\beta - \delta_0\delta_2(\delta_1+\rho))$.

(iii)

$$\frac{dz}{dp} = -\frac{\partial f_2/\partial p}{\partial f_2/\partial z} = -\frac{F_1}{F_2},$$

where

$$F_1 = k_1k_2(\alpha\delta_0+\beta)z^2+((k_1\delta_2+k_2(\delta_1+\rho)\alpha\delta_0)+\beta(k_1\delta_2+k_2\delta_1))z+(\beta\delta_1\delta_2+\alpha\delta_0\delta_2(\delta_1+\rho)),$$

$$F_2 = 2k_1k_2(\delta_0 + (\alpha\delta_0 + \beta)p)z + (k_1\delta_2 + k_2(\delta_1 + \rho))(1 + \alpha p)\delta_0 + \beta(k_1\delta_2 + k_2\delta_1)p.$$

$\Rightarrow \frac{dz}{dp} < 0$. Hence z is decreasing function of p.

We notice that the two isoclines intersects at $(\bar{p}, \bar{z})$ if

$$z_2 > z_1,$$

i.e.

$$\frac{-B + \sqrt{B^2 + 4AC}}{2A} > \frac{\mu}{\mu_0}.$$

Simple manipulation leads to the condition

$$R_3 = \frac{\lambda r\delta_1\beta}{\delta_0(\delta_1 + \rho + k_1\frac{\mu}{\mu_0})(\delta_2 + k_2\frac{\mu}{\mu_0})} > 1,$$

where R_3 is the basic reproduction number of model (6.12) in presence of immune response. The above analysis shows that the pathogen-present equilibrium exists if

$$R_3 > 1 \quad \text{and} \quad p > \frac{\mu_0}{\mu_2}.$$

This implies persistence of infection within the body under the above mentioned condition.

6.6.2 Stability Analysis of Model (6.12)

In this section, we examine the local and global stability of pathogen-present equilibrium point using Lyapunov function in the following two theorems.

Theorem 6.6.1. *The pathogen-present equilibrium E_3 is locally asymptotically stable if the following inequalities hold true:*

$$\rho^2 < \frac{1}{3}m_3\left(\delta_0 + \frac{\beta\tilde{p}}{(1 + \alpha\tilde{p})}\right)(\delta_1 + \rho + k_1\tilde{z})\frac{\mu_1\tilde{z}}{k_1\tilde{y}}, \tag{6.15}$$

$$\frac{\beta\tilde{x}^2}{(1+\alpha\tilde{p})^4} < \frac{4}{9}m_3\left(\delta_0+\frac{\beta\tilde{p}}{(1+\alpha\tilde{p})}\right)(\delta_2+k_2\tilde{z})\frac{\mu_2\tilde{z}}{k_2\tilde{p}}, \tag{6.16}$$

$$\left(\frac{\mu_1\beta\tilde{x}}{(1+\alpha\tilde{p})^2k_1\tilde{y}}+\frac{\mu_2 r\delta_1}{k_2\tilde{p}}\right)^2 < \frac{1}{3}(\delta_1+\rho+k_1\tilde{z})(\delta_2+k_2\tilde{z})\frac{\mu_1\mu_2}{k_1k_2\tilde{y}\tilde{p}}, \tag{6.17}$$

where $m_3 < \frac{1}{3}\left(\delta_0+\frac{\beta\tilde{p}}{(1+\alpha\tilde{p})}\right)(\delta_1+\rho+k_1\tilde{z})\frac{k_1\tilde{y}}{\mu_1\tilde{z}}\left(\frac{1+\alpha\tilde{p}}{\beta\tilde{p}}\right)^2$.

Proof. Let us assume that $X = x-\tilde{x}$, $Y = y-\tilde{y}$, $V = p-\tilde{p}$ and $Z = z-\tilde{z}$ be the small perturbations about the pathogen-present equilibrium E_3. We first linearize model (6.12) around E_3 and then consider the following positive definite function about E_3:

$$V_1 = \frac{1}{2}X^2+\frac{1}{2}m_1Y^2+\frac{1}{2}m_2P^2+\frac{1}{2}m_3Z^2,$$

where m_1, m_2 and m_3 are positive constants to be chosen suitably.

Differentiating V_1 w.r.t t along all positive solutions of the linearized version of model (6.12) and manipulating the calculation, we get

$$\begin{aligned}\dot{V_1} = &-\frac{1}{2}c_{11}X^2+c_{12}XY-\frac{1}{2}c_{22}Y^2\\ &-\frac{1}{2}c_{22}Y^2+c_{21}YX-\frac{1}{2}c_{11}X^2\\ &-\frac{1}{2}c_{11}X^2+c_{13}XP-\frac{1}{2}c_{33}P^2\\ &-\frac{1}{2}c_{22}Y^2+c_{23}YP-\frac{1}{2}c_{33}P^2\\ &-\frac{1}{2}c_{22}Y^2+c_{24}YZ-\frac{1}{2}c_{44}Z^2\\ &-\frac{1}{2}c_{33}P^2+c_{34}PZ-\frac{1}{2}c_{44}Z^2,\end{aligned}$$

where

$$c_{11} = \frac{2}{3}\left(\delta_0+\frac{\beta\tilde{p}}{(1+\alpha\tilde{p})}\right), \quad c_{22} = \frac{1}{2}m_1(\delta_1+\rho+k_1\tilde{z}), \quad c_{33} = \frac{2}{3}m_2(\delta_2+k_2\tilde{z}), \quad c_{12} = \rho,$$

$$c_{21} = \frac{m_1\beta\tilde{x}}{(1+\alpha_1\tilde{p})^2}, \quad c_{13} = -\frac{m_1\beta\tilde{x}}{(1+\alpha_1\tilde{p})^2}, \quad c_{23} = \left(\frac{m_1\beta\tilde{x}}{(1+\alpha_1\tilde{p})^2}+m_2r\delta_1\right),$$

$$c_{44} = \frac{1}{2}m_3\frac{\mu}{\tilde{z}}, \quad c_{24} = (m_3\mu_1\tilde{z}-m_1k_1\tilde{y}), \quad c_{34} = (m_3\mu_2\tilde{z}-m_2k_2\tilde{p}).$$

Sufficient conditions for $\dot{V}_1$ to be negative definite are

$$c_{12}^2 < c_{11}c_{22}, \tag{6.18}$$

$$c_{21}^2 < c_{22}c_{11}, \tag{6.19}$$

$$c_{13}^2 < c_{11}c_{33}, \tag{6.20}$$

$$c_{23}^2 < c_{22}c_{33}, \tag{6.21}$$

$$c_{24}^2 < c_{22}c_{44}, \tag{6.22}$$

$$c_{34}^2 < c_{33}c_{44}. \tag{6.23}$$

Now let us choose $m_1 = \frac{m_3\mu_1\tilde{z}}{k_1\tilde{y}}$ and $m_2 = \frac{m_3\mu_2\tilde{z}}{k_2\tilde{y}}$, then conditions (6.22) and (6.23) are satisfied. For the value of m_3 as given in Theorem 6.6.1, condition (6.19) is satisfied. We further note that (6.15) $\Rightarrow$ (6.18), (6.16) $\Rightarrow$ (6.20), and (6.17)$\Rightarrow$ (6.21). Hence the theorem follows. □

Theorem 6.6.2. *Let the following inequalities hold in octant Ω_2:*

$$\left(\rho + \frac{\beta\tilde{p}}{1+\alpha\tilde{p}}\right)^2 < \frac{2}{3}\left(\delta_0 + \frac{\beta\tilde{p}}{1+\alpha\tilde{p}}\right)(\delta_1 + \rho + k_1\tilde{z}) \tag{6.24}$$

$$\left(\frac{\beta\lambda}{\delta_m(1+\alpha\tilde{p})}\right)^2 < \frac{2}{3}(\delta_2 + k_2\tilde{z})\left(\delta_0 + \frac{\beta\tilde{p}}{1+\alpha\tilde{p}}\right) \tag{6.25}$$

$$\left(\frac{\beta\lambda}{\delta_m(1+\alpha\tilde{p})} + r\delta_1\right)^2 < \frac{4}{9}(\delta_2 + k_2\tilde{z})(\delta_1 + \rho + k_1\tilde{z}) \tag{6.26}$$

and $m_4 < \min\left\{\frac{2}{3}(\delta_1 + \rho + k_1\tilde{z})\left(\frac{\eta}{\mu_1^2\tilde{z}^2}\right), \frac{2}{3}(\delta_2 + k_2\tilde{z})\left(\frac{\eta}{\mu_1^2\tilde{z}^2}\right)\right\}$. Then $E_3(\tilde{x}, \tilde{y}, \tilde{p}, \tilde{z})$ is globally asymptotically stable with respect to all solutions in the interior of the positive octant Ω_2.

Proof. Let us define the positive definite function

$$W_2 = \frac{1}{2}(x-\tilde{x})^2 + \frac{1}{2}(y-\tilde{y})^2 + \frac{1}{2}(p-\tilde{p})^2 + m_4\frac{1}{2}(z-\tilde{z})^2.$$

Differentiating W_2 along the solutions of nonlinear model (6.12), after some algebraic calculations, we get

$$\begin{aligned}\dot{W}_2 = &-\frac{1}{2}d_{11}(x-\tilde{x})^2 + d_{12}(x-\tilde{x})(y-\tilde{y}) - \frac{1}{2}d_{22}(y-\tilde{y})^2\\ &-\frac{1}{2}d_{11}(x-\tilde{x})^2 + d_{13}(x-\tilde{x})(p-\tilde{p}) - \frac{1}{2}d_{33}(p-\tilde{p})^2\\ &-\frac{1}{2}d_{22}(y-\tilde{y})^2 + d_{23}(y-\tilde{y})(p-\tilde{p}) - \frac{1}{2}d_{33}(p-\tilde{p})^2\\ &-\frac{1}{2}d_{22}(y-\tilde{y})^2 + d_{24}(y-\tilde{y})(z-\tilde{z}) - \frac{1}{2}d_{44}(z-\tilde{z})^2\\ &-\frac{1}{2}d_{33}(p-\tilde{p})^2 + d_{34}(p-\tilde{p})(z-\tilde{z}) - \frac{1}{2}d_{44}(z-\tilde{z})^2,\end{aligned}$$

where

$$d_{11} = \frac{1}{2}\left(\delta_0 + \frac{\beta\tilde{p}}{(1+\alpha\tilde{p})}\right), \quad d_{22} = \frac{2}{3}(\delta_1 + \rho + k_1\tilde{z}), \quad d_{33} = \frac{2}{3}(\delta_2 + k_2\tilde{z}),$$

$$d_{44} = m_4\frac{\mu}{\tilde{z}}, \quad d_{13} = -\frac{\beta x}{(1+\alpha p)(1+\alpha\tilde{p})}, \quad d_{23} = \left(\frac{\beta x}{(1+\alpha p)(1+\alpha\tilde{p})} + r\delta_1\right),$$

$$d_{12} = \left(\rho + \frac{\beta\tilde{p}}{(1+\alpha\tilde{p})}\right), \quad d_{24} = (m_4\mu_1\tilde{z} - k_1 y), \quad d_{34} = (m_4\mu_2\tilde{z} - k_2 p).$$

Sufficient conditions for $\dot{W}_3$ to be negative definite are

$$d_{12}^2 < d_{11}d_{22}, \tag{6.27}$$

$$d_{13}^2 < d_{11}d_{33}, \tag{6.28}$$

$$d_{23}^2 < d_{22}d_{33}, \tag{6.29}$$

$$d_{24}^2 < d_{22}d_{44}, \tag{6.30}$$

$$d_{34}^2 < d_{33}d_{44}. \tag{6.31}$$

It may be noted here that for the chosen value of m_4 as given in Theorem 6.6.2, conditions (6.30) and (6.33) are satisfied. Further, (6.24)⇒(6.27), (6.25)⇒(6.28) and (6.26)⇒(6.29). Hence the theorem follows. □

In the next section, we present the last case in which effect of absorption of pathogens has been incorporated in previous model (6.12).

6.7 Model Involving the Effect of Absorption in Model (6.12)

We consider the absorption of pathogens into uninfected cells. Then model (6.12) can be re-read as

$$\begin{cases} \frac{dx}{dt} = \lambda - \delta_0 x - \frac{\beta xp}{1+\alpha p} + \rho y, \\ \frac{dy}{dt} = \frac{\beta xp}{1+\alpha p} - \delta_1 y - \rho y - k_1 yz, \\ \frac{dp}{dt} = r\delta_1 y - \delta_2 p - k_2 pz - \frac{\beta xp}{1+\alpha p}, \\ \frac{dz}{dt} = \mu - \mu_0 z + \mu_1 yz + \mu_2 pz, \end{cases} \tag{6.32}$$

$$x(0) > 0, \quad y(0) \geq 0, \quad p(0) \geq 0, \quad z(0) \geq 0.$$

Similar to model (6.12), we observe that the inclusion of the absorption of pathogens into uninfected cells does not alter the positivity and boundedness of the solutions of model (6.32). Thus model (6.32) is biologically well behaved and the set Ω_2 is the positive invariant region for model (6.32) too. The basic reproduction number R_4 for model (6.32) is given by

$$R_4 = \frac{\beta\lambda r\delta_1}{(\delta_1 + \rho + k_1\frac{\mu}{\mu_0})(\delta_0(\delta_2 + k_2\frac{\mu}{\mu_0}) + \beta\lambda)}.$$

As usual, model system (6.32) has two equilibria; pathogen-free equilibrium $E_{04}(\frac{\lambda}{\delta_0}, 0, 0, \frac{\mu}{\mu_0})$ and pathogen-present equilibrium $E_4(\hat{x}, \hat{y}, \hat{p}, \hat{z})$. One can notice that $\hat{x}$, $\hat{y}$, $\hat{p}$, $\hat{z}$ are positive solutions of $\dot{x} = 0$, $\dot{y} = 0$, $\dot{p} = 0$ and $\dot{z} = 0$. From these equations, we get

$$x = \left(\frac{(\delta_1 + \rho + k_1 z)(\delta_2 + k_2 z)}{(r\delta_1 - \delta_1 - \rho - k_1 z)\beta}\right)(1 + \alpha p),$$

$$y = \left(\frac{\delta_2 + k_2 z}{(r\delta_1 - \delta_1 - \rho - k_1 z)}\right)p.$$

Here x and y are positive if $r\delta_1 > \delta_1 + \rho + k_1 z$. After some algebraic manipulations, we further get

$$f_1(p,z) = [\mu_0 k_1 + \mu_1 k_2 p - \mu_2 k_1 p]z^2 + [((r\delta_1 - \delta_1 - \rho)\mu_2 + \mu_1\delta_2)p - \mu k_1 - \mu_0(r\delta_1 - \delta_1 - \rho)]z + \mu(r\delta_1 - \delta_1 - \rho) = 0, \tag{6.33}$$

$$f_2(p,z) = [k_1k_2\delta_0 + k_1k_2(\alpha\delta_0 + \beta)p]z^2 + [(k_1\delta_2 + (\delta_1 + \rho)k_2)(1 + \alpha p)\delta_0 + (k_1\delta_2 + k_2\delta_1)\beta p]z + \delta_0\delta_2(\delta_1 + \rho)(1 + \alpha p) + \beta\delta_1\delta_2 p + \beta\lambda(\delta_1 + \rho) - \beta\lambda r\delta_1 = 0. \tag{6.34}$$

For $p = 0$, equation (6.33) gives

$$z = \frac{-B_1 + \sqrt{{B_1}^2 - 4A_1C_1}}{2A_1} = \frac{\mu}{\mu_0} = z_1(say),$$

where $A_1 = \mu_0 k_1, \quad B_1 = -(\mu k_1 + \mu_0(r\delta_1 - \delta_1 - \rho)), \quad C_1 = \mu(r\delta_1 - \delta_1 - \rho)$.
Equation (6.33), for $p \to \infty$ gives either $z \to 0$ or $z \to -\left(\frac{\mu_1\delta_2 + \mu_2(r\delta_1 - \delta_1 - \rho)}{(\mu_1 k_2 - \mu_2 k_1}\right)$.

$$\frac{dz}{dp} = -\frac{\partial f_1/\partial p}{\partial f_1/\partial z} = -\frac{F_3}{F_4}$$

where $F_3 = (\mu_1 k_2 - \mu_2 k_1)z^2 + (\mu_2(r\delta_1 - \delta_1 - \rho) + \mu_1\delta_2)z$,
$F_4 = (2(\mu_1 k_2 - \mu_2 k_1)p + \mu_0 k_1)z + (\mu_2(r\delta_1 - \delta_1 - \rho)p + \mu_1\delta_2 p - \mu_0(r\delta_1 - \delta_1 - \rho) - \mu k_1)$.
$\Rightarrow \frac{dz}{dp} < 0$ if $\mu_1 k_2 > \mu_2 k_1$ and $p > \frac{\mu_0}{\mu_2} + \frac{\mu k_1}{\mu_2(r\delta_1 - \delta_1 - \rho)}$.
This implies z is decreasing function of p.
Further, when $z = 0$, equation (6.34) gives $p = \frac{\lambda r\delta_1\beta - (\delta_1 + \rho)(\delta_0\delta_2 + \beta\lambda)}{(\alpha(\delta_1 + \rho)\delta_0\delta_2 + \beta\delta_1\delta_2)}$, $p > 0$ if $R_2 > 1$.
When $p = 0$, equation (6.34) reduces to

$$(k_1k_2\delta_0)z^2 + ((k_1\delta_2 + (\delta_1 + \rho)k_2)\delta_0 + \beta\lambda k_1)z - (\beta\lambda r\delta_1 - (\delta_1 + \rho)(\delta_0\delta_2 + \beta\lambda) = 0.$$

From the above equation, we found two roots (one is positive and another one is negative) if $R_2 > 1$. For $R_2 < 1$ there is no positive real root.
Let us say $z = z_2 = \frac{-B_2 + \sqrt{B_2^2 + 4A_2C_2}}{2A_2}$, be a positive real root of the above equation, where $A_2 = k_1k_2\delta_0$, $B_2 = (k_1\delta_2 + (\delta_1 + \rho)k_2)\delta_0 + \beta\lambda k_1$, and $C_2 = (\beta\lambda r\delta_1 - (\delta_1 +$

$\rho)(\delta_0\delta_2 + \beta\lambda))$. Then

$$\frac{dz}{dp} = -\frac{\partial f_2/\partial p}{\partial f_2/\partial z} = -\frac{F_5}{F_6} < 0,$$

where

$$F_5 = k_1k_2(\alpha\delta_0+\beta)z^2+((k_1\delta_2+k_2(\delta_1+\rho)\alpha\delta_0)+\beta(k_1\delta_2+k_2\delta_1))z+(\beta\delta_1\delta_2+\alpha\delta_0\delta_2(\delta_1+\rho)),$$

$$F_6 = 2k_1k_2(\delta_0 + (\alpha\delta_0 + \beta)p)z + (k_1\delta_2 + k_2(\delta_1 + \rho))(1 + \alpha p)\delta_0 + \beta(k_1\delta_2 + k_2\delta_1)p.$$

We notice that the two isoclines intersects at pathogen-present equilibrium point if

$$z_2 > z_1,$$

i.e.

$$\frac{-B_2 + \sqrt{B_2^2 + 4A_2C_2}}{2A_2} > \frac{\mu}{\mu_0}.$$

After some manipulations, we get the condition

$$R_4 = \frac{\beta\lambda r\delta_1}{(\delta_1 + \rho + k_1\frac{\mu}{\mu_0})(\delta_0(\delta_2 + k_2\frac{\mu}{\mu_0}) + \beta\lambda)} > 1.$$

Thus the pathogen-present equilibrium point exists if

$$R_4 > 1, \quad r\delta_1 > \delta_1 + \rho + k_1z, \quad \mu_1k_2 > \mu_2k_1 \quad \text{and} \quad p > \frac{\mu_0}{\mu_2} + \frac{\mu k_1}{\mu_2(r\delta_1 - \delta_1 - \rho)}.$$

6.7.1 Stability Analysis of Model (6.32)

Jacobian of model (6.32) at $E_{04}(\frac{\lambda}{\delta_0}, 0, 0, \frac{\mu}{\mu_0})$ is

$$J = \begin{bmatrix} -\delta_0 & \rho & -\frac{\beta\lambda}{\delta_0} & 0 \\ 0 & -(\delta_1 + \rho + k_1\frac{\mu}{\mu_0}) & \frac{\beta\lambda}{\delta_0} & 0 \\ 0 & r\delta_1 & -(\delta_2 + k_2\frac{\mu}{\mu_0} + \frac{\beta\lambda}{\delta_0}) & 0 \\ 0 & \frac{\mu\mu_1}{\mu_0} & \frac{\mu\mu_2}{\mu_0} & -\mu_0 \end{bmatrix}.$$

The above Jacobian matrix has two eigenvalues namely $-\delta_0$ and $-\mu_0$ and rest two eigenvalues of the matrix are given by the following characteristic equation

$$Q^2 + (q_1 + q_2)Q + q_1 q_2 - \frac{\beta\lambda r\delta_1}{\delta_0} = 0,$$

where $q_1 = \delta_1 + \rho + k_1\frac{\mu}{\mu_0}$ and $q_2 = \delta_2 + k_2\frac{\mu}{\mu_0} + \frac{\beta\lambda}{\delta_0}$. Eigenvalues have negative real part if $R_4 < 1$. This shows that E_{04} is locally asymptotically stable if $R_4 < 1$ and unstable if $R_4 > 1$.

In the following two theorems, local and global stability of E_4 have been discussed.

Theorem 6.7.1. *The pathogen-present equilibrium E_4 is locally asymptotically stable if the following inequalities hold true:*

$$\rho^2 < \frac{1}{4}n_3\left(\delta_0 + \frac{\beta\hat{p}}{(1+\alpha\hat{p})}\right)(\delta_1 + \rho + k_1\hat{z})\frac{\mu_1\hat{z}}{k_1\hat{y}}, \tag{6.35}$$

$$\frac{\beta\hat{x}^2}{(1+\alpha\hat{p})^4} < \frac{1}{4}n_3\left(\delta_0 + \frac{\beta\hat{p}}{(1+\alpha\hat{p})}\right)(\delta_2 + k_2\hat{z} + \xi)\frac{\mu_2\hat{z}}{k_2\hat{p}}, \tag{6.36}$$

$$\left(\frac{\mu_1\xi}{k_1\hat{y}} + \frac{\mu_2 r\delta_1}{k_2\hat{p}}\right)^2 < \frac{1}{4}(\delta_1 + \rho + k_1\hat{z})(\delta_2 + k_2\hat{z} + \xi)\frac{\mu_1\mu_2}{k_1k_2\hat{y}\hat{p}}, \tag{6.37}$$

where $n_3 < \frac{1}{4}\left(\delta_0 + \frac{\beta\hat{p}}{(1+\alpha\hat{p})}\right)\left(\frac{1+\alpha\hat{p}}{\beta\hat{p}}\right)^2 L$, $\xi = \frac{\beta\hat{x}}{(1+\alpha\hat{p})^2}$ *and* $L = \min\{L_1, L_2\}$,
$L_1 = \frac{k_1y_1}{\mu_1\hat{z}}\left(\delta_1 + \rho + k_1\hat{z}\right)$, $L_2 = \frac{k_2\hat{p}}{\mu_2\hat{z}}\left(\delta_2 + k_2\hat{z} + \frac{\beta\hat{p}}{(1+\alpha\hat{p})^2}\right)$.

Proof. Similar to the proof of local stability of E_3, we assume that $X = x - \hat{x}$, $Y = y - \hat{y}$, $V = p - \hat{p}$ and $Z = z - \hat{z}$ be the small perturbations about the pathogen-present equilibrium E_4 and define a positive definite function

$$V_2 = \frac{1}{2}(x-\hat{x})^2 + \frac{1}{2}n_1(y-\hat{y})^2 + \frac{1}{2}n_2(p-\hat{p})^2 + \frac{1}{2}n_3(z-\hat{z})^2.$$

After differentiating V_2 w.r.t t along all positive solutions of the linear version of model (6.32) and manipulating the calculation, we get

$$\begin{aligned}\dot{V}_2 = &-\frac{1}{2}e_{11}X^2 + e_{12}XY - \frac{1}{2}e_{22}Y^2\\ &-\frac{1}{2}e_{22}Y^2 + e_{21}YX - \frac{1}{2}e_{11}X^2\\ &-\frac{1}{2}e_{11}X^2 + e_{13}XP - \frac{1}{2}e_{33}P^2\\ &-\frac{1}{2}e_{33}P^2 + e_{31}PX - \frac{1}{2}e_{11}X^2\\ &-\frac{1}{2}e_{22}Y^2 + e_{23}YP - \frac{1}{2}e_{33}P^2\\ &-\frac{1}{2}e_{22}Y^2 + e_{24}YZ - \frac{1}{2}e_{44}Z^2\\ &-\frac{1}{2}e_{33}P^2 + e_{34}PZ - \frac{1}{2}e_{44}V^2,\end{aligned}$$

where

$$e_{11} = \frac{1}{2}\left(\delta_0 + \frac{\beta\hat{p}}{(1+\alpha\hat{p})}\right), \quad e_{22} = \frac{1}{2}n_1(\delta_1 + \rho + k_1\hat{z}), \quad e_{33} = \frac{1}{2}n_2(\delta_2 + k_2\hat{z} + \beta\xi),$$

$$e_{44} = n_3\frac{\mu}{\hat{z}}, \quad e_{12} = \rho, \quad e_{21} = \frac{n_1\beta\hat{p}}{(1+\alpha_1\hat{p})}, \quad e_{13} = -\xi, \quad e_{31} = \frac{n_2\beta\hat{p}}{(1+\alpha_1\hat{p})},$$

$$e_{23} = (n_1\beta + n_2 r\delta_1), \quad e_{24} = (n_3\mu_1\hat{z} - n_1k_1\hat{y}), \quad e_{34} = (n_3\mu_2\hat{z} - n_2k_2\hat{p}).$$

If we choose $n_1 = \frac{n_3\mu_1\hat{z}}{k_1\hat{y}}$, $n_2 = \frac{n_3\mu_2\hat{z}}{k_2\hat{y}}$ and $n_3 < \frac{1}{3}\left(\delta_0 + \frac{\beta\hat{p}}{(1+\alpha\hat{p})}\right)(\delta_1+\rho+k_1\hat{z})\frac{k_1\hat{y}}{\mu_1\hat{z}}\left(\frac{1+\alpha\hat{p}}{\beta\hat{p}}\right)^2$ then we can see that $\dot{V}_2$ is negative definite under conditions (6.35) - (6.37). Hence the theorem follows. □

Theorem 6.7.2. *Let the following inequalities hold true in the region Ω_2:*

$$\left(\rho + \frac{\beta\hat{p}}{1+\alpha\hat{p}}\right)^2 < \frac{2}{3}\left(\delta_0 + \frac{\beta\hat{p}}{1+\alpha\hat{p}}\right)(\delta_1 + \rho + k_1\hat{z}), \tag{6.38}$$

$$\left(\frac{\beta\lambda}{\delta_m(1+\alpha\hat{p})}\right)^2 < \frac{2}{3}(\delta_2 + k_2\hat{z})\left(\delta_0 + \frac{\beta\hat{p}}{1+\alpha\hat{p}}\right), \tag{6.39}$$

$$\left(\frac{\beta\lambda}{\delta_m(1+\alpha\hat{p})} + r\delta_1\right)^2 < \frac{4}{9}(\delta_2 + k_2\hat{z})(\delta_1 + \rho + k_1\hat{z}), \tag{6.40}$$

and $n_4 < \min\left\{\frac{2}{3}(\delta_1+\rho+k_1\hat{z})\left(\frac{\eta}{\mu_1^2\hat{z}^2}\right), \frac{2}{3}(\delta_2+k_2\hat{z})\left(\frac{\eta}{\mu_1^2\hat{z}^2}\right)\right\}$. *Then* $E_4(\hat{x},\hat{y},\hat{p},\hat{z})$ *is globally asymptotically stable with respect to all solutions in the interior of the positive octant* Ω_2.

Proof of Theorem 6.7.2 is similar to that of Theorem 6.6.2 and hence omitted.

6.8 Numerical Simulations

In this section, we performed simulations to validate the analytical results of each model using MatLab 7.10.

Table 6.1: List of parameters for model (6.1) and (6.8)

Parameters	Values (Unit)
Source rate of uninfected cells (λ)	10 ($d^{-1}mm^{-3}$)
Death rate of uninfected cells (δ_0)	0.01 (d^{-1})
Death rate of infected cells (δ_1)	0.0693 (d^{-1})
Death rate of pathogen (δ_2)	0.67 (d^{-1})
Infection rate (β)	0.0018 (mm^3d^{-1})
Inhibition to infection (α)	1 (mm^3d^{-1})
Cure rate (noncytolytic loss of infected cells) (ρ)	0.01 (d^{-1})
Burst size (r)	12 (mm^3d^{-1})

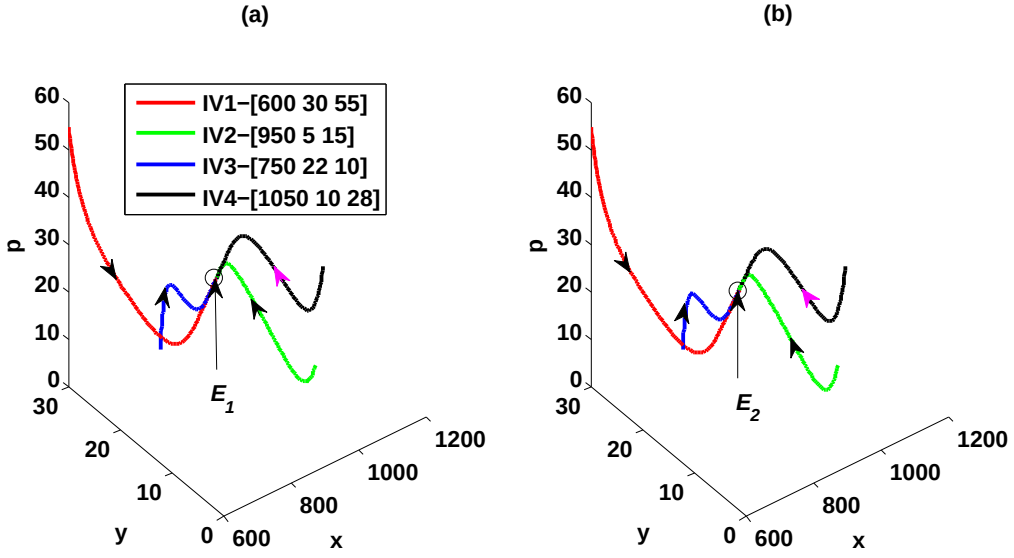

Figure 6.2: Phase portrait of model (6.1) and (6.8) in the *xyp*-space.

We chose the parameters given in Table 6.1 for model (6.1) without absorption and immune response. We found that all conditions for existence and stability of E_1 stated in Theorem 6.4.1 are satisfied. Thus the pathogen-present equilibrium exists and is globally asymptotically stable (fig 6.2(a)). The trajectories initiating from different initial points approach to the same steady state point $E_1(860.3563, 18.6882, 23.2034)$. This implies that system (6.1) is globally asymptotically stable in the xyp -space. This figure 6.2(a) indicates that the uninfected cells, infected cells and pathogen exist in a steady state in absence of immune response and uptake of pathogens into uninfected cells. This shows that under such conditions the infection will persist in the body. Arrows in figure 6.2 represent the direction of motion of trajectories and in legend IV stands for initial values of sub-populations of model (6.1) and values are given in the legend. Phase portrait of model (6.8) with absorption has been shown in figure 6.2(b). Keeping all the parameters same as given in Table 6.1, we found that conditions for existence of E_2 are satisfied and is given by $E_2(860.8709, 18.6146, 20.8957)$. We observe the similar behavior of the trajectories as in figure 6.2(a). This shows that the system is globally asymptotically stable in the xyp -space. The initial values of the sub-populations of model (6.8) in figure 6.2(b) are same as given in the legend of figure 6.2(a). Figure 6.2(b) too does not show any remarkable variation from this pattern. Thus even when uptake of pathogen by uninfected cells is considered, it will not alter the situation very much although the equilibrium point is different and have less concentration of pathogens and a very less increase in uninfected cells.

Further, we simulated model (6.12) with immune response and in absence of absorption of pathogens, by choosing the parameters given in Table 6.2. We found that E_3 exists and is given by $E_3(870.6360, 18.6082, 21.2756, 1.1565)$. In fig 6.3, trajectories for different initial points has been plotted. Figures 6.3(a) and 6.3(b) represent the global stability of the subsystem of model (6.12) in the xyp-space and xyz-space respectively. In the legend IV stands for initial value of the sub-populations of model (6.12) and are given as $IV1 \rightarrow [600, 30, 55, 2]$, $IV2 \rightarrow [950, 5, 15, 0.5]$, $IV3 \rightarrow [750, 22, 10, 0.05]$, and $IV4 \rightarrow [1050, 10, 28, 5]$. The

Table 6.2: List of parameters for model (6.12) and (6.32)

Parameters	Values (Unit)
Source rate of uninfected cells (λ)	10 ($d^{-1}mm^{-3}$)
Death rate of uninfected cells (δ_0)	0.01 (d^{-1})
Death rate of infected cells (δ_1)	0.0693 (d^{-1})
Death rate of pathogen (δ_2)	0.67 (d^{-1})
Infection rate (β)	0.0018 (mm^3d^{-1})
Inhibition to infection (α)	1 (mm^3d^{-1})
Cure rate (non-cytolytic loss of infected cells) (ρ)	0.01 (d^{-1})
Burst size (r)	12 (mm^3d^{-1})
Source rate of innate immune response (μ)	0.265 (d^{-1})
Killing rate of infected cells by CTL-mediated IR (k_1)	0.001 (d^{-1})
Blocking rate of pathogens by humoral IR (k_2)	0.05 (d^{-1})
Activation rate of CTL-mediated IR (μ_1)	0.03 (d^{-1})
Activation rate of humoral IR (μ_2)	0.01 (d^{-1})
Depletion rate of IR (μ_0)	1 (d^{-1})

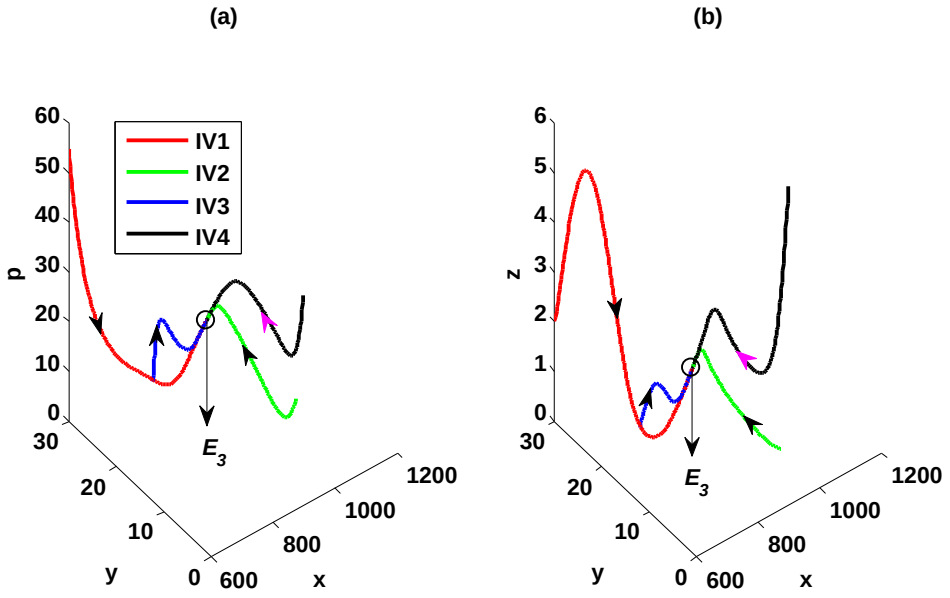

Figure 6.3: Phase portrait of sub-populations of model (6.12) in xyp-space and xyz-space, respectively.

behaviour of uninfected and infected cells for different values of β is shown in figures 6.4(a) and 6.4(b) respectively. From these two figures, we notice that when there is no transmission of infection i.e. ($\beta = 0$), then $y(t) \to 0$ i.e. infected cells tend to its zero equilibrium level, and uninfected cells settle down at higher density of its equilibrium level. This is the normal healthy state of an individual when he

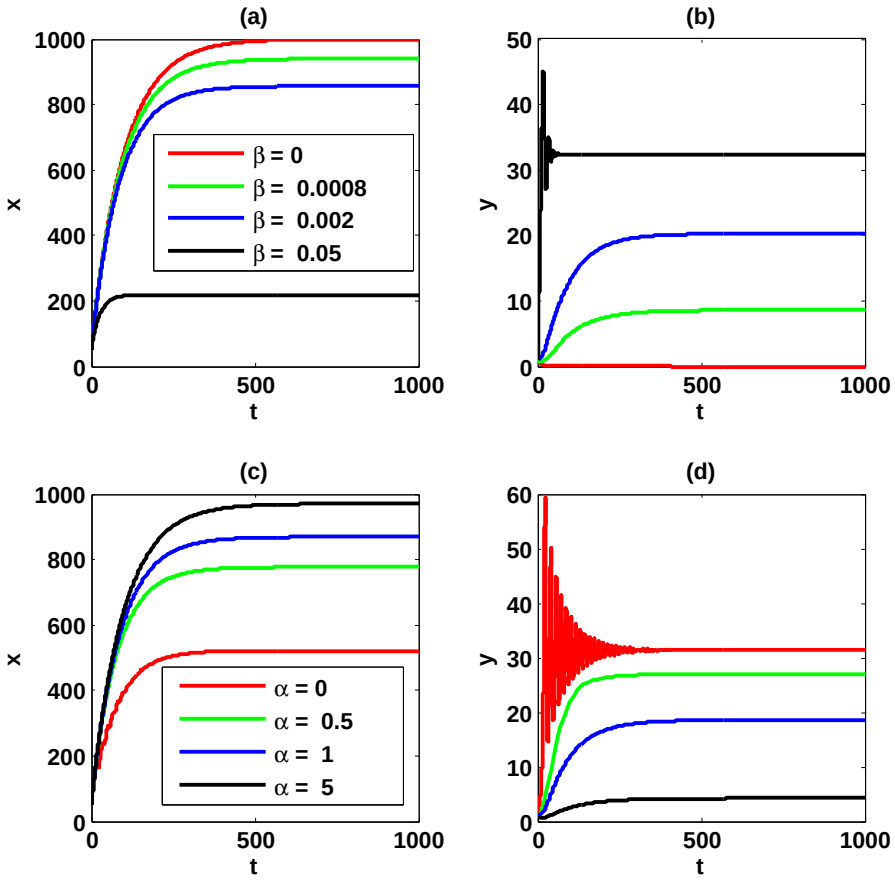

Figure 6.4: Effect of β and α on uninfected cells (x) and infected cells (y), respectively in model (6.12).

has not been infected by a pathogen. As the incidence of infection increases the concentration of uninfected cells falls down and that of infected cells increases. When infection rate is high ($\beta = 0.05$), we observe a sharp increase in infected cells at initial stage and after some time it settles at a higher level of steady state, whereas the number of uninfected cells decline to a lower steady state.

The effect of inhibition to infection α on uninfected cells and infected cells is shown in figures 6.4(c) and 6.4(d) respectively. In case of $\alpha = 0$, initially, we observed oscillations with small period in uninfected cells and with high period in infected cells and after some time trajectories for both populations traversed to approach its steady state. When α increases, we notice that infection decreases and settles down to its steady state. The oscillatory behaviour of the graph at initial stage can be explained by the presence of immune response in this model

(6.12). The immune response will counter the infected cells leading to their decline. When the infected cells decline the immune response itself slows down resulting in an subsequent increase in infection.

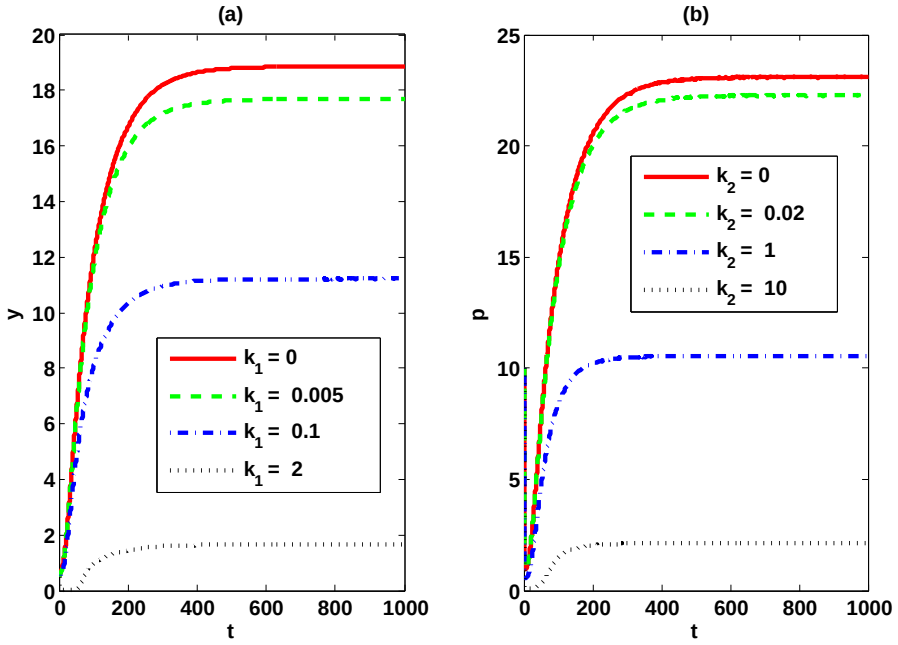

Figure 6.5: Effect of immune responses on infected cells (y) and pathogens (p) in model (6.12).

Effect of immune response on infected cells (y) and on pathogens (p) has been shown in fig 6.5. When $k_1 = k_2 = 0$ i.e. when there is no killing or blocking of infected cells and pathogens due to immune responses then the trajectories in figures 6.5(a) and 6.5(b) are settling at their peak level. We observe reduction in concentration of infected cells as well as that of pathogens with increase in CTL-mediated immune response (k_1) and humoral immune response (k_2). If immune responses act adequately then the concentrations of infected cells and that of pathogens can be lowered.

We plotted here the effect of cure rate (ρ) on uninfected and infected cells in figures 6.6(a) and 6.6(b) respectively. In absence of therapeutic drugs (cure) the concentration of uninfected cells is less and that of infected cells is high. When supply of therapeutic drugs or treatment increases the concentration of infected cells decreases and this enhances the concentration of uninfected cells. This is possible

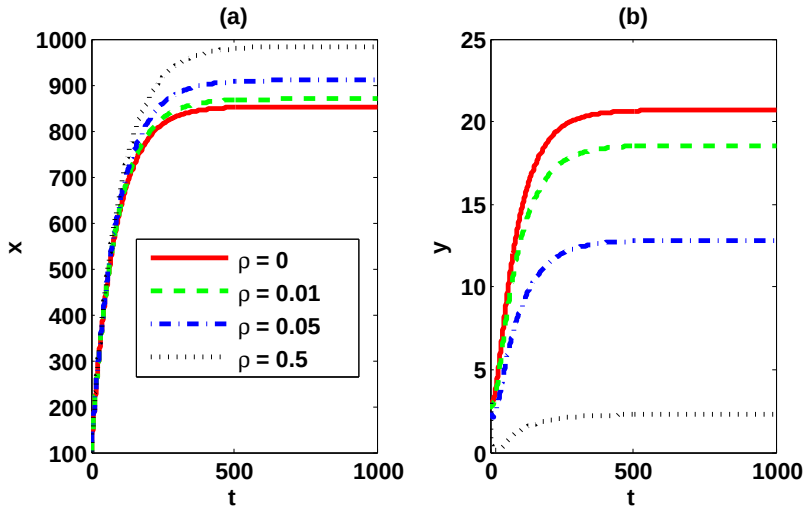

Figure 6.6: Effect of cure rate (ρ) on uninfected (x) and infected cells (y), respectively in model (6.12).

because of two reasons; (i) as infected cell is getting cured through non-cytolytic process and become the susceptible or uninfected cell again, (ii) the uninfected cells are no longer getting infected due to blocking of infection through immune response. Also it can be observed that concentration of uninfected cell change significantly with subsequent increase in therapeutic drug.

Simulation parameters for fourth case (model (6.32)), in which loss of pathogens is considered together with immune response, are same as given in Table 6.2. Similar to figures 6.3(a) and 6.3(b), phase portrait of sub-populations have been shown in the xyp-space and xyz-space in figures 6.7(a) and 6.7(b) respectively. Initial values of the sub-populations has been taken same as for fig 6.3. The pathogen-present equilibrium point E_4 exists and given as $(871.3486, 18.5624, 19.2906, 1.0593)$. It is observed from fig 6.7 that the pathogen-present equilibrium E_4 is globally asymptotically stable. Figure 6.8 represents the effect of β and α on uninfected cells (x) and infected cells (y) respectively. When there is no transmission of infection i.e. ($\beta = 0$), the concentration of uninfected cells are at their peak and infected cells are stabilizing at zero level. It is evident from figure 6.8 that the behavior of the trajectories of the sub-populations is similar as in the earlier case (figure 6.4). It is clear that the absorption of pathogens will not significantly affect the uninfected cell and infected cell sub-population. Further, the effect of immune

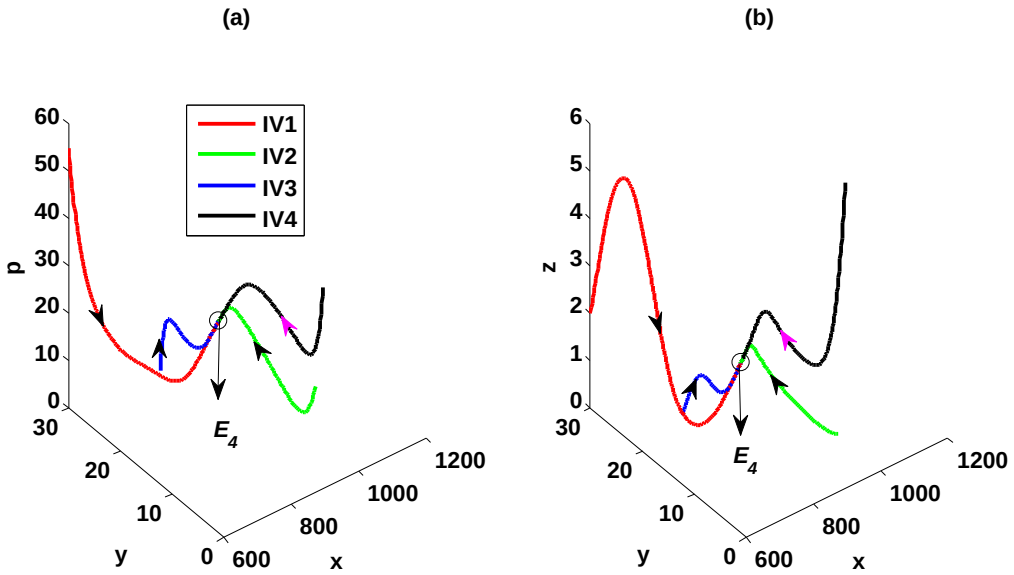

Figure 6.7: Phase portrait of model (6.32) in xyp-space and xyz-space respectively.

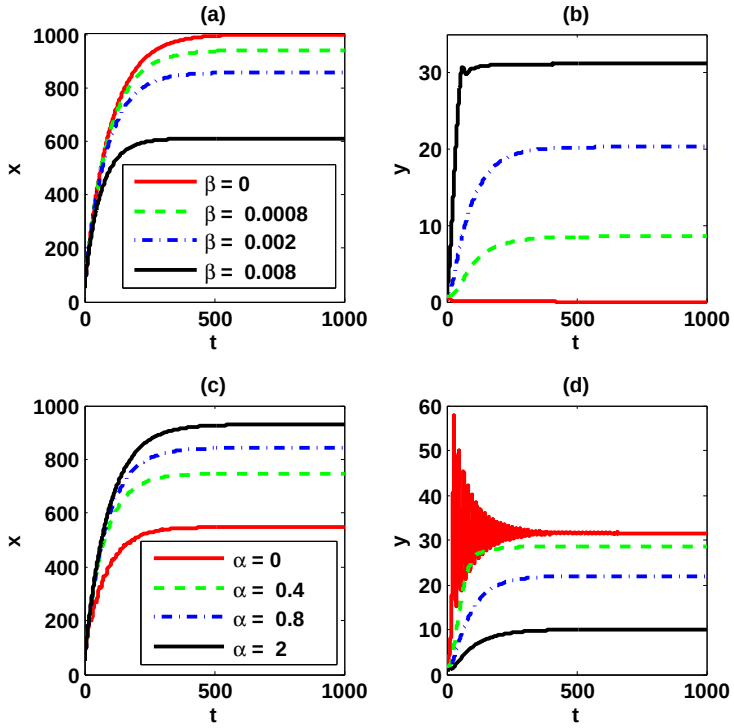

Figure 6.8: Effect of β and α on uninfected cells (x) and infected cells (y), respectively in model (6.32).

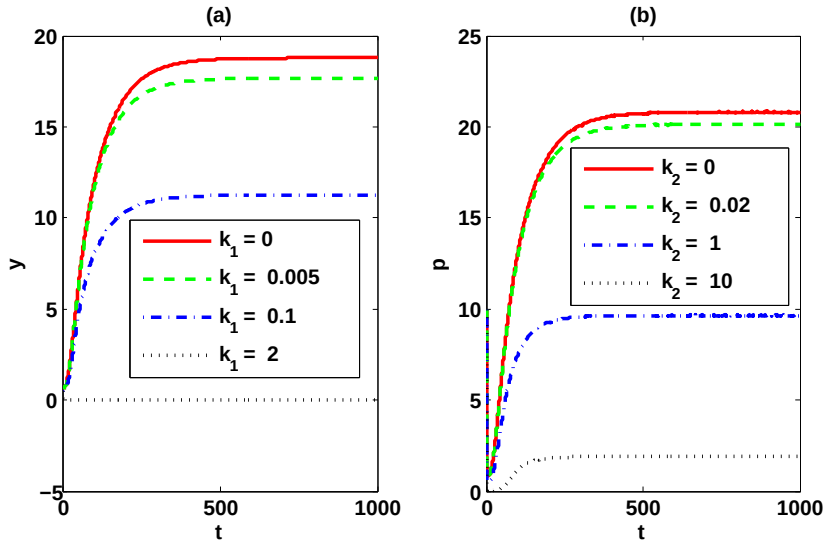

Figure 6.9: Effect of immune responses on infected cells (y) and pathogens (p), respectively in model (6.32).

response on infected cells and pathogens has been studied in figures 6.9(a) and 6.9(b) respectively in presence of absorption. We observed almost similar behavior of the trajectories as in fig 6.5. But in this case we found that infected cells approach to zero level for $k_1 = 2$, whereas for the same value of k_1 this does not attain zero level (figure 6.5(a)). Similarly for the same value of $k_2 = 10$, the concentration of pathogens is less (1.922) in the case of absorption (model (6.32)) as compared to the case when absorption of pathogens into pathogens is not considered (model (6.12)).

Furthermore, we notice that the basic reproduction number is dependent on various parameters. To understand the effect of most sensitive parameters on the basic reproduction number, we present fig 6.10. The effect of infection rate (β) and of cure rate (ρ) on basic reproduction number R_4 for model (6.32) has been shown in fig 6.10. It is evident from the figure that basic reproduction number ($R_4 = 6$) is high when cure rate is less ($\rho = 0.05$) and infection rate is high ($\beta = 0.005$). Further, R_4 decreases with increase in cure rate and decrease in infection rate and can be made less than one, which blocks the existence of pathogen-present equilibrium.

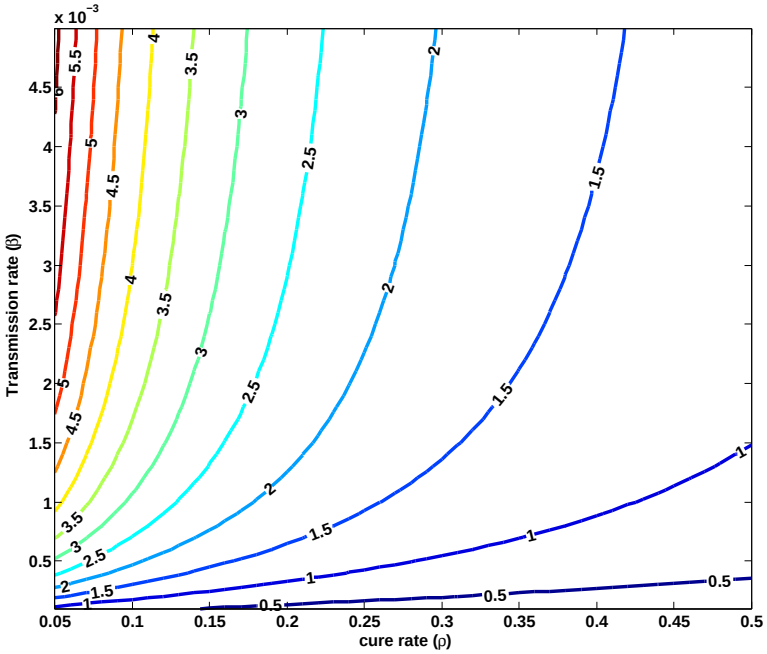

Figure 6.10: Variation of ρ and β on R_4 for model (6.32).

6.9 Conclusions

In this problem, we formulated four basic models to get an insight of host-pathogen interaction and pathogen-immune interaction *in vivo*. In the first case, we studied the interaction between uninfected cells, infected cells and pathogens with cure rate. This case has been well studied in literature by Murase et al. (2005) with incidence rate following mass-action law and without cure rate. We have shown the global stability of the pathogen-free equilibrium point in each case. This study suggests that the elimination of infection does not depend on the initial size of sub-populations. First model is extended to take into account the case of absorption of pathogens into uninfected cells. It has been observed that loss of pathogens can alter the stability of pathogen-present equilibrium point. Furthermore, first model is again extended to investigate the effect of innate, humoral and cellular immune response on the system under consideration. In absence of immune response ($k_1 = k_2 = 0$), it has been noted that the density of infected cells and that of pathogens both get stabilized at high equilibrium level. However, in presence of immune response, density of infected cells and that of pathogens both can be brought back to a lower equilibrium level, as shown in figures 6.5(a)-6.5(d). Fourth

model is extension of the third model with absorption of pathogens into uninfected cells. It has been observed here that the concentration of infected cells and that of pathogens approaches towards zero equilibrium level faster in comparison to third case. Stability behavior of the equilibrium points are studied in third case (without absorption with immune response) and fourth case (with absorption and immune response). Here, also we noticed that the equilibrium points are globally asymptotically stable in each case and the stability behavior gets altered in presence of immune response along with absorption of pathogens. The effect of cure in infected cells through non-cytolytic process has also been observed and found a decrease in infected cells and subsequent increase in uninfected cells (figure 6.6).

Basic reproduction number in each case has been computed. It is apparent from the expression of basic reproduction numbers in each case (R_1, R_2, R_3 and R_4) that there is a relation between these reproduction numbers which is given as (i) $R_1 > R_2$ and (ii) $R_1 > R_3 > R_4$, i.e. the basic model (6.1) involving only cure rate (without absorption and immune response) will have greater basic reproduction number in comparison to other models (6.8, 6.12, 6.32) comprising absorption and immune response. Which in turn emphasizes the importance of absorption and immune response. Another relation is given as (iii) $R_2 > R_4$ and $R_3 > R_4$. This indicates that when absorption is considered along with immune response then the basic reproduction number is least. However, the basic reproduction number of model (6.12) with immune response and without absorption may or may not be less than that of model (6.8) (with absorption and without immune response) depending on the effectiveness of the immune response. Thus the consideration of both biological features (absorption and immune response) together with non-cytolytic cure is most suitable for effective control of infection.

Chapter 7

Modeling the Role of Acquired Immune Response and Antiretroviral Therapy in the Dynamics of HIV Infection

Inferior doctors treat the full-blown disease, Mediocre doctors treat the disease before it is manifested, Superior doctors prevent the disease.

Ancient Chinese proverb

Human immunodeficiency virus (HIV) acts by weakening the immune system and thus making its host susceptible to many forms of infectious diseases and cancers. It is a matter of grave concern that no effective cure for HIV is available yet. The prevalence of HIV in an individual can be minimized by the use of proper treatment and he/she may be able to live longer life. This chapter studies the effect of combination of antiretroviral therapy on the dynamics of HIV infection. The proposed model also involves the effect of acquired immune response.

7.1 Introduction

The most recent global disease burden report of WHO (2013) proclaims that around 78 million people have been infected with the HIV virus and about 39 million people have died of HIV virus. In the current scenario around 35.0 million people are living with HIV globally. Nevertheless, the HIV burden may vary depending upon the geographical region, e.g. Like Sub-Saharan Africa is the most affected region which contributes nearly 70% of the global HIV burden (WHO, 2013). The number of people dying from AIDS-related causes has been reduced with the increasing availability of antiretroviral therapy in low and middle-income countries. This emphasizes the importance of treatment of HIV through antiretroviral therapy.

The human immunodeficiency virus (HIV) is a retrovirus that infects immune systems's $CD4^+$ T cells and macrophages of the immune system. It deteriorates the person's immune system as infection progresses. The primary stage of infection takes around 10-15 years to develop into a full blown case of acquired immunodeficiency syndrome (AIDS). HIV is transmitted through various process involving mixing of body fluids like transfusion of contaminated blood, sharing of contaminated needles, unprotected sexual intercourse, childbirth and breastfeeding.

Being a retrovirus, HIV virus's genetic information is not encoded as DNA but instead as RNA. The HIV virus can not reproduce on its own. The reproduction of the HIV virus takes place in a cell of the infected host. Here the HIV virus inserts its RNA into the cell, and makes a DNA copy (called provirus) of its RNA by the process of reverse transcription. This proviral DNA integrates itself into the hosts DNA and is later transcribed and translated into viral proteins in non-latent cells. These viral proteins develop into the fully functional virus and are released by bursting open the cell. This process of replication of $CD4^+$ T cells is known as the HIV life cycle. The stages of HIV life cycle can be understood from figure 7.1. These changes impair the immune system which further leads to reduction in number of $CD4^+$ T cells count. The $CD4^+$ T cells count in healthy individual is 1000 cells per μl of blood. The decline in the $CD4^+$ T cell below a critical level (i.e.

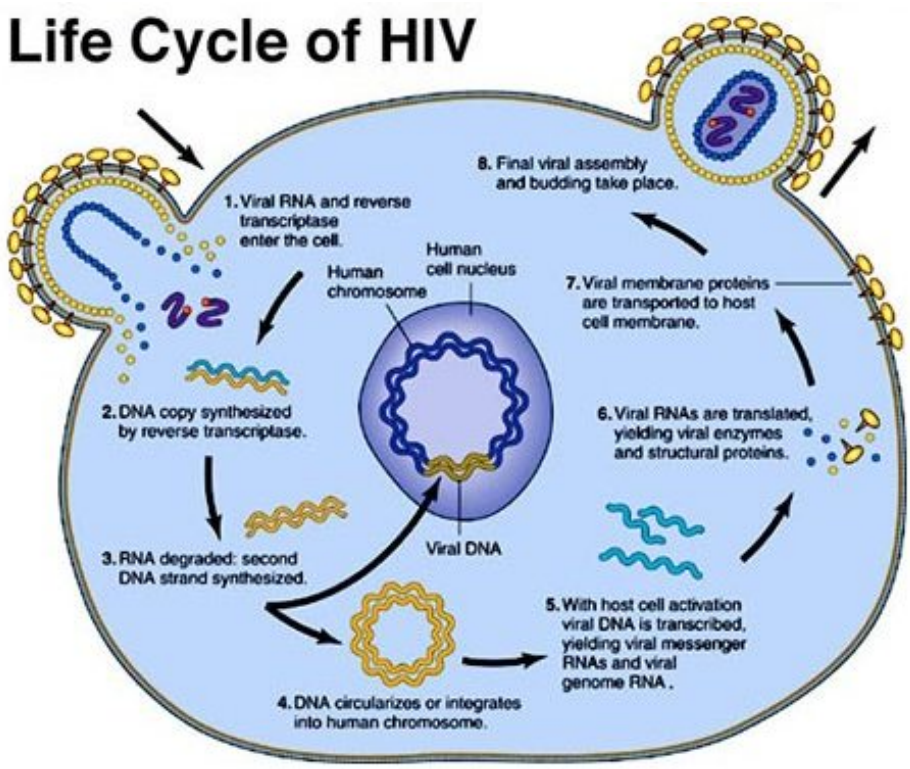

Figure 7.1: Stages of HIV life cycle (Source: Byer et al. (1999)).

200 cells per μl of blood), accentuates the immune system weakening and causes full blown acquired immune deficiency syndrome (AIDS) (Nowak and May, 2000). Till now there is no treatment for this infection but preventive measures may help in controlling its prevalence. Antiretroviral drugs can control the infection and help in increasing the life span of the infected person. Both of these drugs act on different stages of the viral life cycle. The ultimate consequence of both is to block viral replication but in a different manner.

In early literature, several basic mathematical models have been studied to understand the dynamics of primary HIV infection (McLean and Nowak, 1992; Perelson et al., 1993; Wodarz and Nowak, 2002; Wang and Li, 2006; Song and Neumann, 2007; Zhou et al., 2008; Burg et al., 2009; Srivastava and Chandra, 2010; Liu et al., 2011; Buonomo and Vargas-De-León, 2012; Culshaw et al., 2004; Perelson et al., 1996; Wang et al., 2007; Nuraini et al., 2009; Zhou et al., 2009). These models do not involve the effect of treatment of HIV using therapeutic drugs or antiretroviral therapy. The mathematical models incorporating antiretroviral therapy to reduce

HIV viral load have been studied by some researchers (Kirschner and Perelson, 1995; Perelson and Nelson, 1999; Landi et al., 2008; Srivastava et al., 2009; Gao et al., 2011; Srivastava et al., 2012; Wang et al., 2013). Two commonly known drugs are reverse transcriptase inhibitors and protease inhibitors. Reverse transcriptase inhibitors block the new infection by inhibiting the reverse transcription of HIV RNA into its proviral DNA. While protease inhibitors inhibit the production of new infectious virus particles by disabling enzymes required for viral protein production and assembly. The combination of protease inhibitors and retroviral drugs is more suitable for patient treatment. The effect of combination of these therapies has been studied by authors (Kirschner and Perelson, 1995; Perelson and Nelson, 1999; Landi et al., 2008; Srivastava et al., 2009, 2012; Wang et al., 2013).

Perelson and Nelson (1999) studied a few models to understand the dynamics of HIV primary infection *in vivo*. They considered the single ordinary differential equation model which consists of virus compartment only. They applied clinical data to this model and analyzed production and clearance of HIV in an infected person. Furthermore, they considered the interaction between uninfected $CD4^+$ T cells, productively infected cells and virus. In this model, the proliferation of T cells has been considered to be a logistic growth function and the infection rate is assumed to be "mass-action", since the concentration of HIV virus never gets high in comparison to the number of $CD4^+$ T cells. They suggested that the equilibrium can differ from one patient to the another, depending upon the parameters characteristic of the virus and host. Further, they incorporated the combination of drug therapy into their model to reduce the concentration of virus in the body of infected person. They have shown that combination of therapy helps in reducing viral load and providing the early treatment to the patients. It is assumed that there may be other cells susceptible to the HIV virus. One cell of this type is macrophages. These macrophages were introduced as productively infected long-lived cells that produce virus continuously. Another alternative model is considered in the same article. Here latently infected cells have been considered. Latently infected cells do not produce viruses without activation, but upon activation they may do so. These models provided a better insight of HIV infection's biological

mechanisms. The use of combination treatment therapy leads to an important and subtle tool to reduce the infection. The only main important component, which was not considered in their models was immune response.

Recently, Wang et al. (2013) investigated the dynamics of viral infection incorporating the immune response along with the combination of therapy. They proposed two models, involving CTL immune response as well as effect of RTI and PI (i) without absorption of virus and (ii) with absorption of virus into uninfected cells. They found the critical threshold value (dependent on the number of $CD4^+$ T cells which is easy to count in patients blood) and studied the stability behavior of equilibrium points. They have performed Latin hypercube sampling analysis to investigate the existence of multiple infected equilibria. This study suggests that the combination of therapy reduces viral load rapidly and increases the count of $CD4^+$ T cells.

The limitation of their model was the ignorance of humoral immune response which is important factor in case of HIV infection. Considering all the above aspects, we propose a mathematical model to investigate the behavior of HIV infection. This model involves the interaction of HIV virus, acquired immune response and the effect of combination of reverse transcriptase and protease inhibitors therapy. The aquired immune response is inclusive of both the cell mediated immune response as well as the humoral immune response.

7.2 The Mathematical Model

The proposed model involves the interaction between uninfected $CD4^+$ T cells $x(t)$, infected cells $y(t)$, free virus $v(t)$ and both the components of acquired immune response i.e. cytotoxic T lymphocytes (CTLs) $C(t)$ and antibody $A(t)$. We have considered here the control strategy of infection through combination therapy i.e. reverse transcriptase inhibitor (RTI) and protease inhibitor (PI). The five dimensional ordinary differential equation model is given as

$$\begin{cases} \frac{dx}{dt} = \lambda + rx\left(1 - \frac{x}{x_m}\right) - \lambda_0 x - \beta(1-\eta_r)xv, \\ \frac{dy}{dt} = \beta(1-\eta_r)xv - \delta_0' y - k_1 C y, \\ \frac{dv}{dt} = N\delta_0'(1-\eta_p)y - \delta_1 v - k_2 A v, \\ \frac{dC}{dt} = \alpha_0 + \alpha_1' y + \mu_1 C y - \mu_{10} C, \\ \frac{dA}{dt} = \mu_2 v A - \mu_{20} A, \end{cases} \tag{7.1}$$

$$x(0) > 0, \quad y(0) \geq 0, \quad v(0) \geq 0, \quad C(0) \geq 0, \quad A(0) \geq 0.$$

Here λ is the inflow of CD4$^+$ T cells and λ_0 is natural death rate of uninfected CD4$^+$ T cells. The logistic term $rx(1 - \frac{x}{x_m})$ in first equation represents the growth of T-cells by proliferation of existing CD4$^+$ T cells. In this function r is the maximum proliferation rate and $x_m = x_{max}$ is the CD4$^+$ T cell population density at which proliferation shuts off. We assume that virus $v(t)$ meets the uninfected CD4$^+$ T cells and infects them with the infection rate β. This leads to loss of uninfected cells $x(t)$ at the rate βxv and generation of infected cells $y(t)$ at the rate βxv. η_r is the reverse transcriptase inhibitor therapy to kill the infected cells and η_p is protease inhibitor therapy to block infection or to inhibit the production of new virions. δ_0' is the death rate of infected cells and these infected cells produce new virus at rate $N\delta_0' y(t)$ via lysis, where N is the total number of virus particles produced by an infected cell. δ_1 is the virus clearance rate of the virus due to natural factors.

In last two equations of model (7.1), we consider both the component of acquired immune response CTLs and the antibody. The CTLs are produced at constant rate α_0 and deplete at the rate μ_{10}. Moreover, we assume that CTLs get stimulated at the rate α_1' due to the increase of infected cells, as well as from the interactions with infected cells at the rate μ_1. CTLs interact with the infected cells and remove the infected cells at the rate k_1. Further the antibody also gets stimulated at the rate μ_2 due to increase in virus and it depletes at the rate μ_{20}. Antibody acts against the virus when comes into contact with the virus and reduces the number of virus at the rate k_2.

This model can easily be transformed to the following model using the transformation $\bar{C} = C - \frac{\alpha_0}{\mu_{10}}$ and the transformed model (after dropping bar) is given

as follows:

$$\begin{cases} \frac{dx}{dt} = \lambda + rx\left(1 - \frac{x}{x_m}\right) - \lambda_0 x - \beta(1-\eta_r)xv, \\ \frac{dy}{dt} = \beta(1-\eta_r)xv - \delta_0 y - k_1 Cy, \\ \frac{dv}{dt} = N\delta_0(1-\eta_p)y - \delta_1 v - k_2 Av, \\ \frac{dC}{dt} = \alpha_1 y + \mu_1 Cy - \mu_{10} C, \\ \frac{dA}{dt} = \mu_2 vA - \mu_{20} A, \end{cases} \tag{7.2}$$

where $\delta_0 = \delta_0' + \frac{k_1\alpha_0}{\mu_{10}}$ and $\alpha_1 = \alpha_1' + \frac{\mu_1\alpha_0}{\mu_{10}}$.

In the next section, we will discuss the well-posedness of model (7.2).

7.3 Boundedness and Positivity of the Model

From the first equation of model (7.2), we have

$$\dot{x} \leq \lambda + rx\left(1 - \frac{x}{x_m}\right) - \lambda_0 x,$$

Using elementary calculus we get

$$\limsup_{t\to\infty} x(t) \leq x_0,$$

where $x_0 = \frac{x_m}{2r}[(r-\lambda_0) + \sqrt{(r-\lambda_0)^2 + \frac{4r\lambda}{x_m}}]$.
Further, $\dot{x} + \dot{y} \leq \lambda + rx\left(1 - \frac{x}{x_m}\right) - \delta_a(x+y)$ and $\delta_a = \min\{\lambda_0, \delta_0\}$.
This implies

$$\limsup_{t\to\infty}(x(t) + y(t)) \leq \frac{1}{\delta_a}\left(\lambda + \frac{rx_m}{4}\right) = M_a(say).$$

We have $\dot{v} \leq N_1\delta_0 M_a - \delta_1 v$, this implies

$$\limsup_{t\to\infty} v(t) \leq \frac{N_1\delta_0 M_a}{\delta_1} = v_a(say),$$

where $N_1 = N(1-\eta_p)$.

Let us assume $L_1 = y + \frac{k_1}{\mu_1}C$, differentiating L_1 w.r.t. 't' we get

$$\dot{L}_1 \leq \beta_1 M_a v_a + \frac{\alpha_1 k_1}{\mu_1} M_a - \delta_b \left(y + \frac{k_1}{\mu_1} C \right),$$

where $\beta_1 = \beta(1 - \eta_r)$ and $\delta_b = \min\{\delta_0, \mu_{10}\}$. Then

$$\limsup_{t \to \infty} L_1(t) \leq \frac{\beta_1 M_a v_a + \frac{\alpha_1 k_1}{\mu_1} M_a}{\delta_b} = C_a(say).$$

Further let us assume that $L_2 = v + \frac{k_2}{\mu_2}A$. Then

$$\dot{L}_2 \leq N_1 \delta_0 M_a - \delta_c \left(v + \frac{k_2}{\mu_2} A \right),$$

where $\delta_c = \min\{\delta_1, \mu_{20}\}$. This implies

$$\limsup_{t \to \infty} L_2(t) \leq \frac{N_1 \delta_0 M_a}{\delta_c} = A_a.$$

Furthermore, we observe that $\dot{x} < 0$ if $x > x_0$, $\dot{y} < 0$ if $y > M_a$, $\dot{v} < 0$ if $v > v_a$, $\dot{C} < 0$ if $C > C_a$, and $\dot{A} < 0$ if $A > A_a$. It is noticeable that all the solutions of model system (7.2) point towards the set Ω defined in Lemma 7.3.1. The above results can be summarized in the following lemma.

Lemma 7.3.1. *The set* $\Omega = \{(x, y, v, C, A) \in \Re^5_+ : 0 \leq x \leq x_0, 0 \leq y \leq M_a, 0 \leq v \leq v_a, 0 \leq C \leq C_a, 0 \leq A \leq A_a\}$ *is positively invariant region of system* (7.2).

The above lemma shows that model (7.2) is mathematically and biologically well behaved.

In the next section, we will study the analytical behaviour (stability analysis of equilibrium points) of model (7.2).

7.4 Equilibrium and Stability Analysis

It is observed that model (7.2) has following three nonnegative equilibrium points.
(i) Virus-free equilibrium point (VFE), $E_0(x_0, 0, 0, 0, 0)$,

(ii) Immune-free equilibrium (IFE), $E_1(\bar{x}, \bar{y}, \bar{v}, 0, 0)$,

(iii) Positive equilibrium (PE), $E_2(x^*, y^*, v^*, C^*, A^*)$.

It is clear from model (7.2) that the virus-free equilibrium exists trivially and is given by $E_0(x_0, 0, 0, 0, 0)$, where $x_0 = \frac{x_m}{2r}[(r - \lambda_0) + \sqrt{(r - \lambda_0)^2 + \frac{4r\lambda}{x_m}}]$.

7.4.1 Basic Reproduction Number

We computed the basic reproduction number of model (7.2) using next generation matrix method and is given as

$$R_0 = \frac{\beta N(1 - \eta)}{\delta_1} x_0, \tag{7.3}$$

where $\eta = 1 - (1 - \eta_r)(1 - \eta_p)$. It is apparent from the expression (7.3) that the basic reproduction number is independent of immune response parameters. It can be understood as the basic reproduction number is the number of newly infected cells produced by a single infected cell when introduced into completely healthy cells. We have considered in this model acquired immune response which is highly specific and takes time to get activated. Therefore at initial stage this immune response is not active.

In the next theorem, we will examine the local stability of the VFE E_0.

Theorem 7.4.1. *The virus-free equilibrium E_0 is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.*

Proof. The linearization of system (7.2) gives the following Jacobian matrix J_{E_0}

$$J_{E_0} = \begin{bmatrix} -j_{11} & 0 & -\beta_1 x_0 & 0 & 0 \\ 0 & -\delta_0 & \beta_1 x_0 & 0 & 0 \\ 0 & N_1\delta_0 & -\delta_1 & 0 & 0 \\ 0 & 0 & 0 & -\mu_{10} & 0 \\ 0 & 0 & 0 & 0 & -\mu_{20} \end{bmatrix}.$$

where $j_{11} = \left(\frac{2r}{x_m}x_0 - (r-\lambda_0)\right) = \sqrt{(r-\lambda_0)^2 + \frac{4r\lambda}{x_m}} > 0$.
The characteristic equation of the above Jacobian matrix at E_0 is given as

$$(\psi_1 + j_{11})(\psi_1 + \mu_{20})(\psi_1 + \mu_{10})[\psi_1^2 + (\delta_0 + \delta_1)\psi_1 + (\delta_0\delta_1 - \beta_1 N_1 \delta_0 x_0)] = 0. \quad (7.4)$$

We note that the characteristic equation (7.4) has three real and negative eigenvalues and the rest two eigenvalues have negative real part if $R_0 < 1$. Thus the virus free equilibrium is locally asymptotically stable if $R_0 < 1$. □

Biologically, it is observable from the above result that on the onset of infection if $R_0 < 1$, (i.e. number of new infections on average is less than one) then the infection will not keep on increasing further and the system will settle to virus-free equilibrium point.

In the next theorem, we will study the global stability of VFE E_0.

Theorem 7.4.2. *The virus-free equilibrium is globally asymptotically stable if* $R_0 \leq 1$.

Proof. Let us consider the positive definite function

$$W = N(1-\eta_p)y + v,$$

Differentiating the above function with respect to the solutions of model (7.2), we get

$$\dot{W} = N(1-\eta_p)\dot{y} + \dot{v},$$

Some simple manipulations lead to

$$\dot{W} \leq \delta_1(R_0 - 1)v,$$

This implies that $\dot{W} \leq 0$ if $R_0 \leq 1$. We found that maximum invariant set in $\{(x, y, v, C, A) \in \Omega | \dot{W} = 0\}$ is the singleton set $\{E_0\}$, Hence by Lassale's invariance principle E_0 is globally asymptotically stable. □

It is apparent from the above result that the virus can be cleared from the blood if the basic reproduction number is less than one which is independent of the initial concentrations of sub-populations. In case of HIV the virus continues to persist in internal tissues.

7.4.2 Existence of Immune-Free Equilibrium $E_1(\bar{x}, \bar{y}, \bar{v}, 0, 0)$

Equating the right hand side of equations (7.2) equal to zero, we have

$$\dot{x} = 0 \Rightarrow \lambda + rx_1\left(1 - \frac{\bar{x}}{x_m}\right) - \lambda_0\bar{x} - \beta(1-\eta_r)\bar{x}\bar{v} = 0, \tag{7.5}$$

$$\dot{y} = 0 \Rightarrow \beta(1-\eta_r)\bar{x}\bar{v} - \delta_0\bar{y} = 0, \tag{7.6}$$

$$\dot{v} = 0 \Rightarrow N\delta_0(1-\eta_p)\bar{y} - \delta_1\bar{v} = 0, \tag{7.7}$$

Simple calculations lead to

$$\bar{x} = \frac{\delta_1 x_0}{\beta N(1-\eta)x_0} = \frac{x_0}{R_0},$$

$$\bar{y} = \frac{1}{\delta_0}\left(\lambda + \frac{x_0}{R_0}\left((r-\lambda_0) - \frac{rx_0}{R_0 x_m}\right)\right),$$

$$\bar{v} = \frac{N\delta_0(1-\eta_p)\bar{y}}{\delta_1}.$$

Here $\bar{y}$ is positive if $R_0 > \frac{rx_0}{(r-\lambda_0)x_m}$. After substituting the value of x_0 in this inequality and simplifying, we get to the usual threshold for the existence of infected equilibrium i.e. $R_0 > 1$. Thus the immune-free equilibrium exists if $R_0 > 1$ i.e. if the inequality $x_0 > \bar{x}$ holds.

Remark 7.4.1. *It is easy to check that* $R_0 > 1 \Rightarrow \eta < 1 - \frac{\delta_1}{\beta N}x_0 = \eta_{crit}(say)$. *This shows that the inequality for the existence of immune-free equilibrium point gives the critical value of the combination of therapies* η *which is given by*

$$\eta_{crit} = 1 - \frac{\delta_1}{\beta N}x_0.$$

Thus, the immune-free equilibrium exists if $\eta < \eta_{crit}$. When $\eta > \eta_{crit}$, then the immune-free equilibrium does not exists but the virus-free equilibrium exists and it is locally asymptotically stable.

In the next theorem, we will explore the local stability of immune-free equilibrium E_1.

Theorem 7.4.3. *The immune-free equilibrium E_1 is locally asymptotically stable if $\bar{v} < \frac{\mu_{20}}{\mu_2}$ and $n_1 > 0$, $n_2 > 0$, $n_3 > 0$, $n_4 > 0$ and $n_1 n_2 n_3 - n_3^2 - n_1^2 n_4 > 0$, where n_i's are defined in the proof of this theorem.*

Proof. The variational matrix of model system (7.2) corresponding to the equilibrium E_1 is given by

$$J_{E_1} = \begin{bmatrix} -a_{11} & 0 & -\beta_1\bar{x} & 0 & 0 \\ \beta_1\bar{v} & -\delta_0 & \beta_1\bar{x} & -k_1\bar{y} & 0 \\ 0 & N_1\delta_0 & -\delta_1 & 0 & -k_2\bar{y} \\ 0 & \alpha_1 & 0 & -(\mu_{10} - \mu_1\bar{y}) & 0 \\ 0 & 0 & 0 & 0 & -(\mu_{20} - \mu_2\bar{v}) \end{bmatrix}.$$

where $a_{11} = \beta_1\bar{v} + \frac{2r}{x_m}\bar{x} - (r - \lambda_0) = \frac{r}{x_m}\bar{x} + \frac{\beta_1 N_1}{\delta_1}\lambda > 0$.
The characteristic equation of the matrix J_{E_1} at immune-free equilibrium E_1 is

$$(\psi_2 + (\mu_{20} - \mu_2\bar{v}))(\psi_2^4 + n_1\psi_2^3 + n_2\psi_2^2 + n_3\psi_2 + n_4) = 0, \tag{7.8}$$

where

$n_1 = a_{11} + \delta_0 + \delta_1 + \mu_{10} - \mu_1\bar{y}$,

$n_2 = a_{11}\delta_0 + (a_{11} + \delta_0 + \delta_1)(\mu_{10} - \mu_1\bar{y}) + \delta_1(a_{11} + \delta_0) + \alpha_1 k_1\bar{y} - N_1\beta_1\delta_0\bar{x}$,

$n_3 = (\mu_{10} - \mu_1\bar{y})(a_{11}\delta_0 + \delta_1(a_{11} + \delta_0) - N_1\beta_1\delta_0\bar{x}) + N_1\beta_1\bar{x}\delta_0(\bar{v}\beta_1 - a_{11}) + a_{11}\delta_0\delta_1$
$+ \alpha_1 k_1\bar{y}(a_{11} + \delta_1)$,

$n_4 = (a_{11}\delta_0\delta_1 + N_1\beta_1\bar{x}\delta_0(\beta_1\bar{v} - a_{11}))(\mu_{10} - \mu_1\bar{y}) + \alpha_1 k_1\bar{y}\delta_1 a_{11}$,

From equation (7.8), it is clear that one eigenvalue of the matrix J_{E_1} is negative under the condition $\bar{v} < \frac{\mu_{20}}{\mu_2}$.

Using the Routh-Hurwitz criteria, we found that if the aforesaid inequalities in Theorem 7.4.3 hold true then equation (7.8) has all the eigenvalues with negative real part. Hence the theorem follows. □

From the local stability of immune-free equilibrium, one can easily depict that the infection persists in the endemic zone in stable state under the conditions stated in Theorem 7.4.3.

7.4.3 Existence of Positive Equilibrium $E_2(x^*, y^*, v^*, C^*, A^*)$

We found the coordinates of the positive equilibrium E_2 by performing the same algebraic calculation as for the existence of immune-free equilibrium. The coordinates of positive equilibrium are as follows:

$$x^* = \frac{x_m}{2r}\left[e + \sqrt{e^2 + \frac{4r\lambda}{x_m}}\right],$$

$$y^* = \frac{\mu_{10}C^*}{\alpha_1 + \mu_1 C_*},$$

$$v^* = \frac{\mu_{20}}{\mu_2},$$

$$C^* = \frac{m_2 + \sqrt{m_2^2 + m_1 m_3}}{2m_1},$$

$$A^* = \frac{N_1\delta_0\mu_2 y^* - \delta_1\mu_{20}}{\mu_{20}k_2},$$

where $e = r - \lambda_0 - \frac{\beta_1\mu_{20}}{\mu_2}$, $m_1 = \mu_{10}\mu_2 k_1$, $m_2 = \beta_1\mu_{20}\mu_1 x^* - \delta_0\mu_{10}\mu_2$ and $m_3 = \beta_1\mu_{20}\alpha_1 x^*$.

We note that $A^* > 0$ if $y^* > \frac{\mu_{20}\delta_1}{k_2\delta_0 N_1\mu_2}$. After some calculation, the above inequality reduces to

$$0 < C^* < \frac{\delta_0}{k_1}\left(\frac{x^*}{\bar{x}} - 1\right) = \frac{\delta_0}{k_1}(x_{crit} - 1),$$

where $x_{crit} = \frac{x^*}{\bar{x}}$. Thus, when $R_0 > x_{crit} > 1$, then $\bar{x} < x^* < x_0$. This implies that count of uninfected $CD4^+$ T cells in the presence of immune response is greater than that of uninfected $CD4^+$ T cells in the absence of immune response. Also it

is less than that of the uninfected CD4$^+$ T cells in case of virus-free equilibrium point when there is no infection in the body.

In the next theorems, we will discuss the local and global stability of positive equilibrium point.

Theorem 7.4.4. *The positive equilibrium E_2 is locally asymptotically stable if $y^* < \frac{\mu_{10}}{\mu_1}$, $s_3(s_1s_2-s_3) > s_1(s_1s_4-s_5)$ and $s_3s_4(s_1s_2-s_3) > s_2s_5(s_1s_2-s_3)+(s_1s_4-s_5)^2$.*

Proof. The Jacobian matrix of system (7.2) corresponding to E_2 is given as follows

$$J_{E_2} = \begin{bmatrix} -b_{11} & 0 & -\beta_1 x^* & 0 & 0 \\ \beta_1 v^* & -b_{22} & \beta_1 x^* & -k_1 y^* & 0 \\ 0 & N_1\delta_0 & -b_{33} & 0 & -k_2 y^* \\ 0 & b_{42} & 0 & -b_{44} & 0 \\ 0 & 0 & \mu_2 A^* & 0 & 0 \end{bmatrix}.$$

where $b_{11} = \frac{2r}{x_m}x^*+\beta_1 v^*-(r-\lambda_0) = \sqrt{e^2+\frac{4r\lambda}{x_m}} > 0$, $b_{22} = \delta_0+k_1C^*$, $b_{33} = \delta_1+k_2A^*$, $b_{44} = \mu_{10}-\mu_1 y^*$ which is positive if $y^* < \frac{\mu_{10}}{\mu_1}$ and $b_{42} = \mu_1 C^*+\alpha_1$. The characteristic equation of the Jacobian matrix at E_2 is

$$\psi_3^5 + s_1\psi_3^4 + s_2\psi_3^3 + s_3\psi_3^2 + s_4\psi_3 + s_5 = 0, \tag{7.9}$$

where

$s_1 = b_{11} + b_{22} + b_{33} + b_{44}$,

$s_2 = b_{11}b_{22} + (b_{11} + b_{22} + b_{33})b_{44} + (b_{11} + b_{22})b_{33} + b_{42}k_1y^* - N_1\beta_1\delta_0x^* + A^*k_2\mu_2y^*$,

$s_3 = b_{44}(b_{11}b_{22} + b_{33}(b_{11} + b_{22}) - N_1\beta_1\delta_0x^*) + N_1\delta_0x^*\beta_1(v^*\beta_1 - b_{11}) + b_{11}b_{22}b_{33}$
$- b_{22}b_{44}k_1y^* + a_{42}k_1y^*(b_{11} + b_{22} + b_{33}) + A^*k_2\mu_2y^*(b_{11} + b_{22} + b_{44})$,

$s_4 = N_1\delta_0\beta_1x^*(v^*\beta_1 - b_{11}) + b_{11}b_{22}b_{33} - b_{22}b_{42}k_1y^* + b_{44}k_1y^*(b_{11} + b_{22} + b_{33})$
$+ b_{44}(N_1\delta_0\beta_1x^*(v^*\beta_1 - b_{11}) + b_{11}b_{22}b_{33}) + b_{42}k_1y^*(b_{22}^2 + b_{11}b_{22} + b_{33}(b_{11} + b_{22}))$
$+ A^*\mu_2k_2y^*(b_{11}b_{22} + b_{44}(b_{11} + b_{22}) + b_{42}k_1y^*) - b_{22}b_{44}k_1y^*(b_{11} + b_{22} + b_{33})$,

$s_5 = A^*k_2\mu_2((b_{44} + b_{33})b_{11}b_{22} + b_{42}k_1y^*(b_{11} + b_{33}) - N_1\beta_1\delta_0x^*b_{11})$
$- A^*k_2\mu_2y^*b_{33}(b_{11}b_{22} + b_{33}b_{22} + b_{42}k_1y^* - N_1\beta_1\delta_0x^*)$.

By the Routh-Hurwitz criteria, it follows that all roots of the equation (7.9) have negative real parts if $s_1 > 0$, $s_3(s_1s_2 - s_3) > s_1(s_1s_4 - s_5)$ and $s_3s_4(s_1s_2 - s_3) > s_2s_5(s_1s_2 - s_3) + (s_1s_4 - s_5)^2$. Hence the theorem follows. □

Theorem 7.4.5. *Let the following inequalities hold true in region Ω:*

$$y^* < \frac{\mu_{10}}{\mu_1}, \tag{7.10}$$

$$R_0 < \min\left\{\frac{p_1X_1}{\delta_0}, \frac{(\delta_0 + k_1C^*)}{6}\right\}. \tag{7.11}$$

where $X_1 = \frac{r}{x_m}x^* + \beta_1v^* - (r - \lambda_0) = \frac{1}{2}\left[\sqrt{e^2 + \frac{4r\lambda}{x_m}} - e\right] > 0$. *Then* $E_2(x^*, y^*, p^*, z^*)$ *is globally asymptotically stable with respect to all solutions in the interior of the positive octant* Ω.

Proof. Let us consider the positive definite function about E_2:

$$V = \frac{1}{2}(x - x^*)^2 + \frac{1}{2}p_1(y - y^*)^2 + \frac{1}{2}p_2(v - v^*)^2 + \frac{1}{2}p_3(C - C^*)^2$$

$$+\frac{1}{2}p_2\frac{k_2v^*}{\mu_2}\left(A - A^* - A^*\ln\frac{A}{A^*}\right)^2.$$

Differentiating V w.r.t t along all positive solutions of model (7.2) and manipulating the calculation, we get

$$\begin{aligned}\dot{V} = &-\frac{1}{2}c_{11}(x - x^*)^2 + c_{12}(x - x^*)(y - y^*) - \frac{1}{2}c_{22}(y - y^*)^2\\ &-\frac{1}{2}c_{11}(x - x^*)^2 + c_{13}(x - x^*)(v - v^*) - \frac{1}{2}c_{33}(v - v^*)^2\\ &-\frac{1}{2}c_{22}(y - y^*)^2 + c_{23}(y - y^*)(v - v^*) - \frac{1}{2}c_{33}(v - v^*)^2\\ &-\frac{1}{2}c_{22}(y - y^*)^2 + c_{24}(y - y^*)(C - C^*) - \frac{1}{2}c_{44}(C - C^*)^2,\end{aligned}$$

where

$$c_{11} = \left(\frac{r}{x_m}(x + x^*) + \beta_1v^* - (r - \lambda_0)\right), \quad c_{22} = \frac{2}{3}p_1(\delta_0 + k_1C^*),$$

$$c_{33} = p_2(\delta_1 + k_2A), \quad c_{44} = 2p_3(\mu_{10} - \mu_1y^*), \quad c_{12} = p_1\beta_1v^*, \quad c_{13} = -\beta_1x,$$

$$c_{23} = (p_1\beta_1x + p_2N_1\delta_0), \quad c_{24} = (p_3(\mu_1C + \alpha_1) - p_1k_1y).$$

We have following sufficient conditions for $\dot{V}$ to be negative definite

$$c_{44} > 0, \tag{7.12}$$

$$c_{12}^2 < c_{11}c_{22}, \tag{7.13}$$

$$c_{13}^2 < c_{11}c_{33}, \tag{7.14}$$

$$c_{23}^2 < c_{22}c_{33}, \tag{7.15}$$

$$c_{24}^2 < c_{22}c_{44}, \tag{7.16}$$

It is clear that (7.10)⇒(7.12). Now let us choose $p_1 = \frac{X_1(\delta_0+k_1C^*)}{3\beta_1^2 v^{*2}}$, then inequality (7.13) is satisfied. Further inequality (7.16) is satisfied for the value of $p_3 < \frac{4}{3}\frac{p_1(\delta_0+k_1C^*)(\mu_{10}-\mu_1 y^*)}{(\alpha_1+\mu_1 C_a)^2}$. Again (7.14) and (7.15) hold under condition (7.11). Hence the theorem follows. □

7.5 Numerical Simulations

In this section, we illustrate some simulation results performed to validate the analytical results of model (7.2) using MatLab. We have selected parameters of model system (7.2) as given in Table 7.1.

The time series analysis of sub-populations of model (7.2) using parameters given in Table 7.1 is shown in figure 7.2. In figure 7.2(a) the trajectory of uninfected cells show sharp decline at initial stage, then it increases with small oscillations with increase in time. Finally the trajectory saturates to maximum level and settles to its equilibrium point. The decline in initial stage of uninfected cells can be explained by the onset of infection and then the subsequent increase can be due to immune response and combination of therapy given. The small oscillations may be due to the counteracting interaction between infected cells and the immune system along with the combination therapy. The delay in implementing the therapy and activation of immune response may also play a role in eliciting an oscillatory behavior. The trajectory for infected cells shows oscillatory behavior with decreasing its amplitude and settle down to its equilibrium point for similar reasons. Also since the virus is not entirely eliminated from the body there will always be residual number of infected cells (figure 7.2(b)). The trajectory for virus

Table 7.1: List of parameters for model (7.2)

Parameters	Values (Unit)
Recruitment rate of uninfected cells (λ)	10 ($mm^{-3}d^{-1}$)
Death rate of uninfected cells (λ_0)	0.055 (d^{-1})
Death rate of infected cells (δ_0')	0.24 (mm^3d^{-1})
Clearance rate of Virus (δ_1)	3 (mm^3d^{-1})
Infection rate (β)	0.002 (mm^3d^{-1})
Activation rate of CTLs (α_0)	0.265 (mm^3d^{-1})
Stimulation of CTLs due to infected cells (α_1')	0.01 (mm^3d^{-1})
Depletion rate of CTLs (μ_{10})	0.755 (d^{-1})
Depletion rate of antibody (μ_{20})	0.1 (d^{-1})
CTLs responsiveness (μ_1)	0.03 (d^{-1})
Antibody responsiveness (μ_2)	0.01 (d^{-1})
RTI (η_r)	0.57 (d^{-1})
PI (η_p)	0.38 (d^{-1})
CTL effectiveness (k_1)	0.05 (d^{-1})
Antibody Effectiveness (k_2)	0.5 (d^{-1})
Burst size (N)	100 (d^{-1})
Carrying capacity of T-cells (x_m)	1500
Growth rate of T-cells (r)	0.3 (mm^3d^{-1})

shows rapid increase in the population at initial stage and then it decreases to a low level and then again increases and oscillates for small period of time and then gets settle to its equilibrium point (figure 7.2(c)), respectively. These few oscillations in the trajectory behavior can be due to the intra-cellular viral growth and its counteraction mediated by antibody produced, CTLs and antiretroviral therapy. The trajectories of immune responses (CTLs and antibody) are shown in figures 7.2(d) and 7.2(e), respectively. The CTLs increase with increase in infection and then start declining as infection reduces. The pattern followed here too is oscillatory. Here the oscillations are caused due to counteraction between generation of CTLs in response to virus and its decline owing to effective therapy and immune response. The antibodies show oscillatory behavior initially and then settles to equilibrium point at a higher level. The counteracting interactions in this case is the antibody produced by B cells and its utilization mechanisms associated with viral blocking. The antibodies persist in the body, at a higher level because the virus does not get eliminated.

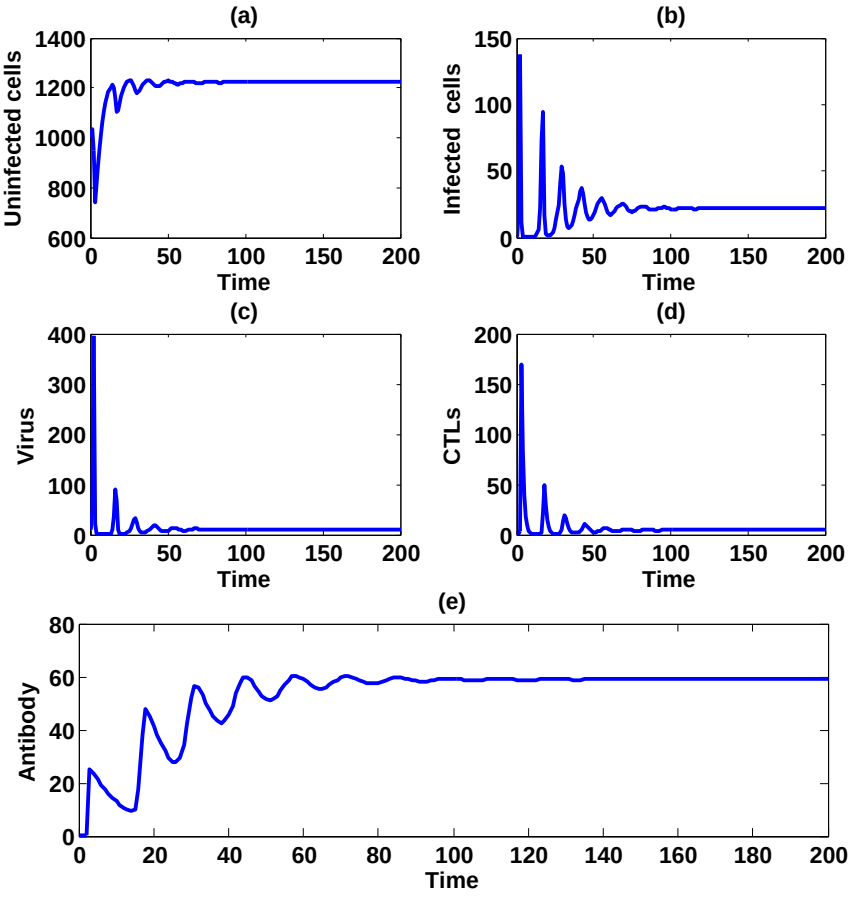

Figure 7.2: Solution trajectories of model (7.2).

In model system (7.2), we have considered effect of varying doses in the combination of therapy (RTIs and PIs) to reduce the viral load. The effect of combination of therapy on sub-populations has been shown in figures 7.3(a)-7.3(e). It is observed that in the absence of therapy the cell count of uninfected $CD4^+$ T cells is lesser than that of with therapy and the trajectory corresponding to this sub-population settles to its equilibrium with small oscillations (figure 7.3(a)). This is because a large fraction of uninfected cells have got converted into infected cells. While the level of trajectories for the rest sub-populations (infected cells, virus, CTLS and antibody) is high in absence of therapy. When combination therapy is started, we observed the increase in the cell count of uninfected cells (figure 7.3(a)) and decrease in infected cells, CTLs and antibody (figures 7.3(b), 7.3(d) and 7.3(e). While the equilibrium level of the virus does not alter with the small amount of

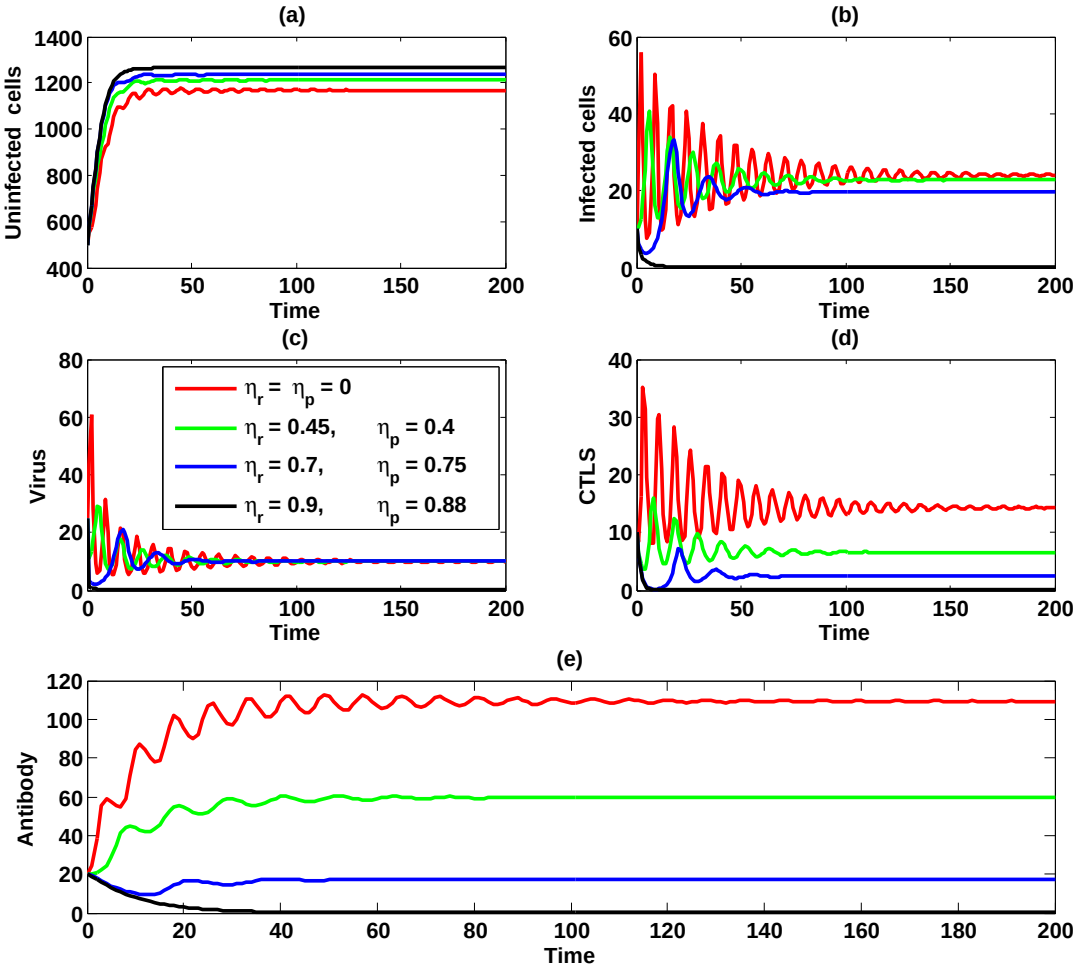

Figure 7.3: Effect of RTI (η_r) and PI (η_p) on sub-populations of model (7.2).

therapy given, nonetheless the decline in the peak of oscillations is observed (figure 7.3(c)). As we keep increasing the magnitude of therapy given, the decrease in infected cells, virus, CTLs and antibody and the corresponding increase in uninfected cells is observed. The level of infected cells and virus can be effectively reduced with the high amount of combination of therapy ($\eta_r = 0.9$ and $\eta_p = 0.88$) given. This indicates the efficacy of using a combination of protease inhibitors and RT inhibitors in reducing the infection. The level of CTLs and antibody also declines substantially with the corresponding decrease in infection.

In figures 7.4(a)-7.4(d), we have shown the effect of CTLs and antibody on the infected cells and virus sub-populations. In absence of CTLs the trajectory for infected cells first increases sharply and then decreases to get settle its high equilibrium level (figure 7.4(a)). This decrease is due to the combination of therapy

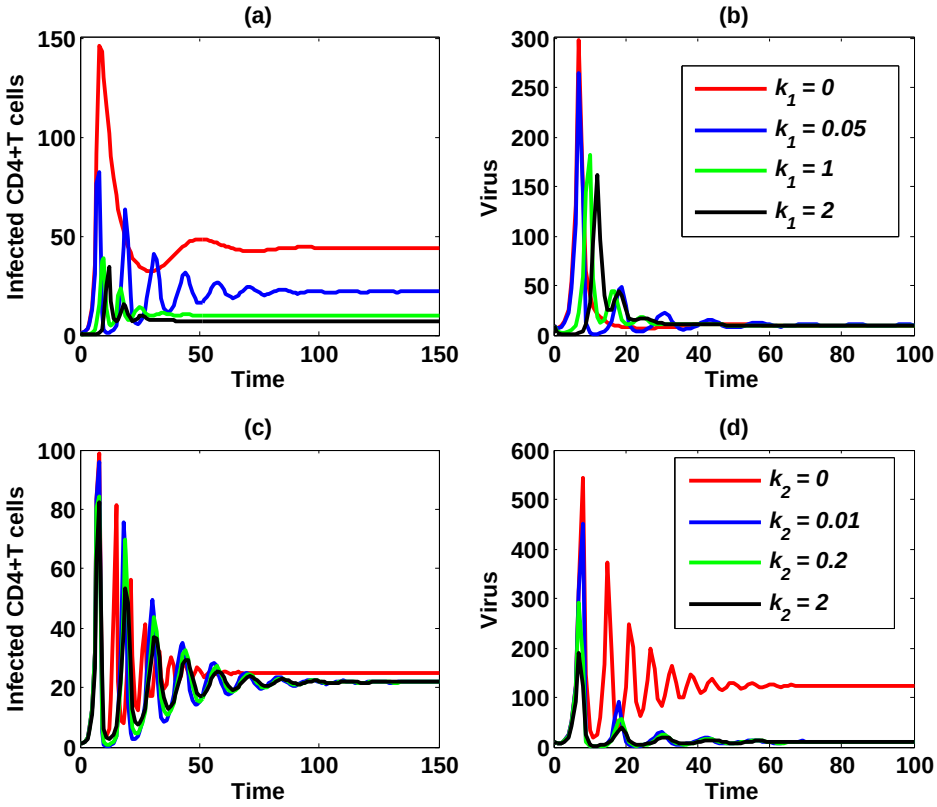

Figure 7.4: Effect of CTLs (k_1) and antibody (k_2) on infected cells and virus, respectively.

given to the sub-populations. The level of infected cells decreases with enhancement of CTLs. The trajectories corresponding to virus population does not show significant change (figure 7.4(b)). This is due to the fact that CTLs does not work directly against the virus but it kills virally infected cells. On the contrary, when we examine the effect of antibody then the infected cells population does not alter significantly (figure 7.4(c)). The reason behind this is that antibody on its own not able to kill an infected cell. While the virus population in absence of antibody is at high level and the level of virus population can be brought down with increase in the density of antibody (figure 7.4(d)). The antibody neutralizes the virus and block further viral production by blocking its entry. Therefore it counteracts the viral growth and shows oscillatory behaviour initially. At high concentration of antibody the virus settles at a very low residual value. The legend for figures 7.4(a) and 7.4(b) are same and the legend for figures 7.4(c) and 7.4(d) are same.

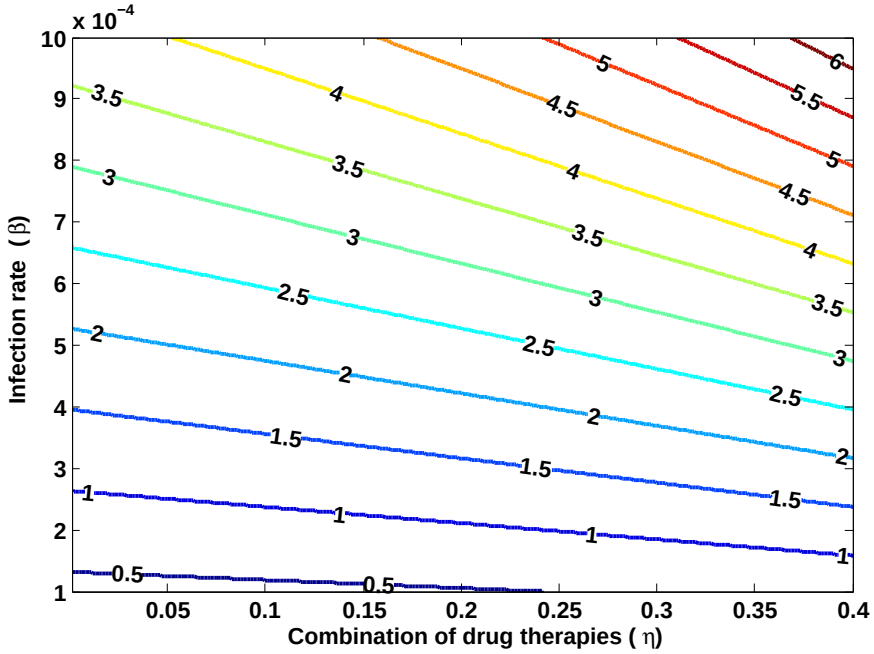

Figure 7.5: Effect of infection rate (β) and combination therapy (η) on R_0.

The basic reproduction number is dependent on the combination of components of antiretroviral therapy, number of virus produced and infection rate. We tried to understand the effect of infection rate (β) and combination of therapy (η) on basic reproduction number (R_0). The values of the other parameters are same as given in Table 7.1. We observed from figure 7.5 that the basic reproduction number is high when infection rate is high and combination therapy is low. This can be reduced and brought to less than one by reducing the infection rate and increasing the amount of combination of therapy applied, which in turn implies that the infection can be minimized by making the value of $R_0 < 1$.

7.6 Conclusions

In this Chapter, we proposed a mathematical model to study the effect of combine therapy along with two major components of acquired immune responses, namely the CTLs and antibodies. We found that model (7.2) exhibits three non-negative equilibria, (i) Virus free equilibrium, $E_0(x_0, 0, 0, 0, 0)$, (ii) Immune free equilibrium, $E_1(\bar{x}, \bar{y}, \bar{v}, 0, 0)$ and (iii) Positive equilibrium, $E_2(x^*, y^*, v^*, C^*, A^*)$. We found the critical efficacy of the combination of therapy (η) as a threshold for the existence

of virus free equilibrium and immune free equilibrium. These two equilibria will coexist if $\eta < \eta_{crit}$. Normally $CD4^+$ count is used to evaluate the criticality of AIDS patients and the effect of drugs on them. We have used cell count of uninfected $CD4^+$ T cells as measure of critical value for the existence of equilibrium points. We have shown that if $x_0 > x^* > \bar{x}$, then the immune free equilibrium and positive equilibrium points coexist. The novelty of model (7.2) lies in the inclusion of antibody mediated immune response which is an important factor in HIV infection and counteracts the virus. It is observed during the study of this research work that antibody immune response helps in reducing the viral load and clearing the infection. This Chapter also exemplifies the fact that counteracting interactions among various vital parameters lead to a oscillatory behavior. The effect of combination of therapy on the sub-populations has been shown analytically and numerically (figure 7.3(a)-7.3(e)). It is also observed that the combination of therapy reduces viral load and enhances the lifespan of HIV infected patients. The combination of drugs is more effective than individually because each drug acts on a different stage of the HIV life cycle.

Chapter 8

Conclusions and Future Work

As far as the laws of mathematics refer to reality, they are not certain; as far as they are certain, they do not refer to reality.

Albert Einstein

In this chapter, we encapsulate the main outcomes of the thesis. And further, we provide a few research directions that may be studied in future course of research work.

8.1 Conclusions

In this thesis, we have proposed and analyzed the mathematical models and established the mechanism to control the transmission of infectious diseases. This information may further help to reduce the overall disease burden. This study provides better insights primarily in two different aspects of transmission of infection. Firstly, the study of disease transmission at population level (basic SIR model) and secondly the spread of infection within an individual.

In first case, the main focus of the thesis is to emphasize on pharmaceutical and non-pharmaceutical interventions to eradicate the infection at population level. It

is assumed that the incidence of infection is nonlinear and saturated type which provides desired dynamics of transmission of infection in case of myriad populations. We have studied the effect of awareness programs run by media as well as the treatment given to infected individuals on a compartmental model. It is shown that proposed models are biologically well-behaved. Equilibrium analysis of the models proves and emanates the existence and uniqueness of equilibrium points. Local and global stability analysis of the equilibrium points have been investigated and further validated through numerical simulations. We found the threshold parametric value of infection i.e the basic reproduction number R_0 for each model to determine the persistence of infection in the endemic zone. Analytical study of models discussed in Chapters 2, 3 and 4 suggests that the limitation of the availability of treatment resources should be minimized for the effective treatment. It is also inferred from analysis of these models that the awareness and adequate amount of treatment among sub-populations about the infection are helpful in eradication of infection in totality. But disease can not be eradicated if either of treatment or awareness is lacking.

Secondly in Chapters 5, 6 and 7, we analyzed virus dynamics models at a cellular level. The effect of therapeutic drugs on infected cells and virus has been explored on a virus dynamics model in the presence of immune response. We incorporated the biological features step by step in pathogen-immune interaction models to understand the dynamics of infection. The biological features involved in modeling process are absorption of pathogens into uninfected cells (leading to infection) and non-cytolytic cure of infected cells. Further, the effect of combination of therapies (Reverse Transcriptase Inhibitor and Protease Inhibitor) has been investigated in an HIV infection model with acquired immune response. We found that the infection will further increase if basic reproduction number is greater than one and infection will be drastically reduced if basic reproduction number is less than one. Thus it can be inferred that the number of secondary infections decreases with the increase of immune response and drug efficacy. Increase in treatment is effective in controlling the number of infected cells and free viruses. In addition, action of immune response also reduces the virus load. The consider-

ation of both biological features (absorption and immune response) together with non-cytolytic cure is most suitable for effective control of infection. The antibody mediated immune response helps in reducing the viral load and further clearing the HIV infection. The combination of therapies (RTI and PI) reduces viral load and enhances the lifespan of HIV infected patients.

The study elucidates the mechanism of disease transmission at a population level and at a cellular level. Its outcomes can be applied for better management and control of diseases at an epidemiological level.

8.2 Future Work

It is observed that the mathematical models examined in this thesis are deterministic models. We have studied the stability behavior of these models and performed numerical simulations. In future course of research work, we would like to explore the following aspects:

- We would like to explore the chaos theory for the epidemic models.
- Time delay in spread of infection is an important factor. The models can be further explored as delay differential equation model.
- The optimal level of treatment given to infected individuals can be studied by formulating optimal control model and using the Pontryagin's maximum principle.
- Stochasticity can be involved to the epidemic models which gives more realistic dynamics of the transmission of infection.
- To include heterogeneity in the system dynamics, the development of the agent-based models (ABM) framework is required. This is particularly designed to simulate the spread of contact centric infections. Agent-Based Modeling allows to construct a comprehensive representation and simulations of the real world problems.

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Prof. Balram Dubey is Professor and Former Head in the Department of Mathematics, Birla Institute of Technology & Science, Pilani, Pilani Campus, Rajasthan. He earned his Bachelor's Degree (B.Sc. Hons) with first rank of merit from Bhagalpur University, Bhagalpur, India in 1988. He received his Master's degree in 1990 and Ph.D. degree in 1994 from Department of Mathematics, Indian Institute of Technology Kanpur, Kanpur, India. He was Research Associate in IIT, Kanpur from 1994-1995 and later he joined IIT kanpur, as visiting faculty during 2000-2002. He was awarded with "Best Teaching Award" for tutorship in MATH102 in 2001 at IIT Kanpur. During 1996-1999, Prof. Dubey served as Lecturer in Department of Mathematics, Tezpur University, India. There he guided two Ph.D. students. In 2002, he joined the Department of Mathematics, Birla Institute of Technology & Science, Pilani, Pilani campus an Assistant Professor. He got promoted to Associate Professor in August 2010 and to Professor in February 2013. His research interests are Mathematical Biology, Mathematical Ecology, Ecotoxicology, Soil Erosion and Conservation, Epidemiology, Mathematical Immunology, and Applications of ODEs & PDEs in Real-World Problems. As a result of his research accomplishment, he has published more than 70 research articles in national and international journals of repute. He is also the author of the book "Introductory Linear Algebra", Asian Books Pvt. Ltd. 2007. He has successfully guided 3 Ph.D. students.

Brief Biography of the Co-Supervisor

Dr. Uma S. Dubey is presently working as an Associate Professor in the Department of Biological Sciences at BITS Pilani, Pilani Campus. She has served this department for last 14 years at various teaching and research related posts. She earned her Master's Degree in Life Sciences from the Institute of Life Sciences, Kanpur, India in 1988. She was visiting graduate student in the Department of Plant Sciences, University of Alberta, Edmonton, Canada from 1988-89. She received her Ph.D. degree in Immunology from Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India in 1997. She has taught more than 15 different courses in the department of Biological Sciences, BITS Pilani, Pilani Campus. She has been involved in the course planning and development of many of these. Besides this, she has initiated new courses in Immunology and Cancer Biology. She has coordinated the course restructuring of M.Sc. and ME programs of the Biological Science Department as DCA Convenor from 2012 -2014. Her research interest is in both, theoretical and practical aspects of Immunology and Cancer Biology. Her interdisciplinary research involves working on the formulation and biological interpretation related aspects of mathematical modeling of cancer-immune system interaction, epidemiology and virus dynamics. In the wet lab presently, she is interested in studying the anticancer properties attributed to Camels milk and its associated mechanisms of action. She is also interested in protien sequence analysis comparison across species. She has numerous journal publications, Book chapters, conference proceedings and a Lab manual to her credit.

Brief Biography of the Candidate

Preeti Dubey earned her Bachelor's and Master's degree in Mathematics from CSJM University, Kanpur in 2004 and 2006, respectively. After completing graduation, she joined the Department of Civil Engineering, IIT Kanpur, India as Project Associate under the guidance of Prof. P. K. Mohapatra. She worked on the project to prepare Mathematical Model of two-dimensional flow on mobile bed during Aug 2006-Aug 2007. She joined the Department of Mathematics, Maharana Pratap Engineering College Kanpur, India, as Lecturer and served during Sep 2007-Apr 2008. In May 2008, She joined the Department of Electrical Engineering, IIT Kanpur, India as Senior Project Associate. She worked on a project for more than three years and earned an U.S. Patent entitled "Convergent Matrix Factorization Based Entire Frame Image Processing" with Prof. K.S. Venkatesh. She got admission to Ph.D. program in Department of Mathematics, Birla Institute of Technology & Science, Pilani, Pilani Campus, India in Aug 2011 under the guidance of Prof. Balram Dubey and Dr. Uma S. Dubey. Till date, she has published 3 papers in peer-reviewed international journals and 3 book chapters as a part of the peer-reviewed proceedings of the international conferences. At present, she is a Senior Research Fellow under UGC-BSR, New Delhi, India.

List of Publications

Papers Published/Communicated in Journals

B. Dubey, **P. Dubey** and U.S. Dubey, Modeling the intracellular pathogen-immune interaction with cure rate, *Commun Nonlinear Sci Numer Simulat*, Vol. 38, 72-90, (2016). DOI: 10.1016/j.cnsns2016.02.007.

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Analysis of a virus dynamics model with saturated infection rate and immune response in presence of therapeutic drug. (*to be communicated soon*)

Modeling the role of acquired immune response and antiretroviral therapy in the dynamics of HIV infection. (*to be communicated soon*)

Book Chapters Published in Peer Reviewed International Conference Proceedings

M. Laskowski, **P. Dubey**, M. E. Alexander, S. Collinson and S. M. Moghadas, What is the optimal level of information dissemination during an epidemic?, *BIOMAT 2014*, 206-220, 2015.

P. Dubey, B. Dubey and U.S. Dubey, Optimal control for therapeutic drug treatment on delayed model incorporating immune response, *BIOMAT 2015*. (*in press*)

P. Dubey, B. Dubey and U.S. Dubey, An SIR model with nonlinear incidence rate and Holling type III treatment rate, *ICMBAA-2015*, Springer. (*in press*)

Patents

Convergent matrix factorization based entire frame image processing, Inventors: Venkatesh K. Subramanian, **Preeti Dubey**, Publication number: CN103380414 A, Oct 30, 2013.

Convergent matrix factorization based entire frame image processing, Inventors: Venkatesh K. Subramanian, **Preeti Dubey**, Publication number: US20130127886 A1, May 23, 2013.

Convergent matrix factorization based entire frame image processing, Inventors: **Preeti Dubey**, K.S. Venkatesh, Publication number: WO2012090076 A1, Jul 5, 2012.

Conferences/Workshops Attended

3rd IMSc Workshop and Conference on **Modeling Infectious Diseases**, IMSc, Chennai, India, Nov 23-Dec 1, 2015.

International Symposium on **Mathematical and Computational Biology**, Dept of Mathematics, IIT Roorkee, Roorkee, Uttarakhand, India, November 01-06, 2015.

International Conference on **Recent Advances in Mathematical Biology, Analysis and Applications**, Dept of Mathematics, AMU, Aligarh, June 4-6, 2015.

National Workshop on **Latex and MatLab for Beginners**, Dept of Mathematics, BITS Pilani-Pilani Campus, Dec 24-28, 2014.

National Conference on **Recent Trends and Developments in Operations Research**, Dept of Mathematics, BITS Pilani-Pilani Campus, Feb 22-23, 2014.

Indo-Canadian Workshop on **Mathematical Modeling of Infectious Diseases**, Dept of Mathematics, IIT Roorkee, Jan 20-22, 2014.

International Conference on **Mathematical Modeling and Computer Simulation with Applications**, Dept of Mathematics, IIT Kanpur, Dec 31, 2013-Jan 02, 2014.

Symposium on **Computational Techniques and Mathematical Modeling**, Dept of Mathematics, South Asian University, New Delhi, April 5-6, 2013.

National Workshop on Modeling & Computation, Dept of Mathematics, BITS PilaniPilani Campus, Feb 23-24, 2013.

Advanced Instructional School on Numerical Analysis, Dept of Mathematics, Panjab University Chandigarh, June 18-July 7, 2012.

National Conference on **Modeling, Computational Fluid Dynamics & Operations Research**, Dept of Mathematics, BITS Pilani-Pilani Campus, Feb 4-5, 2012.