TRANSMISSION DYNAMICS AND OPTIMAL CONTROL OF HEPATITIS B VIRUS USING PREVENTIVE STRATEGIES

OLUDOUN, OLAJUMOKE YETUNDE

(18PGCD000025)

A Thesis submitted to the Department of Physical Sciences, Mathematics Programme, College of Pure and Applied Sciences, Landmark University, Omu-Aran. Nigeria.

In Partial Fulfilment of the Requirements for the Award of the Degree of Doctor of Philosophy (PhD) in Mathematics.

NOVEMBER, 2021

DECLARATION

I, **OLAJUMOKE, YETUNDE OLUDOUN,** a PhD student in the Department of Physical Sciences, (Mathematics Programme), Landmark University, Omu-Aran, hereby declare that this thesis entitled "**Transmission Dynamics and Optimal Control of Hepatitis B Virus using Preventive Strategies**", submitted by me is based on my original work. Any material(s) obtained from other sources or work done by any other persons or institutions have been duly acknowledged.

OLUDOUN, OLAJUMOKE YETUNDE (18PGCD000025)

Signature & Date

CERTIFICATION

This is to certify that this thesis has been read and approved as meeting the requirements of the Department of Physical Sciences, Landmark University, Omu-Aran, Nigeria, for the Award of PhD Degree.

Dr. O. Adebimpe Supervisor	Date
Dr. J. Ndako (Co- Supervisor)	Date
Dr. Mrs. A.A Inyinbor (Head of Department)	Date
Prof. M.O. Ibrahim (External Examiner)	Date

ABSTRACT

Hepatitis B Virus (HBV) is a potentially life-threatening infection of global concern that puts people at high risk of liver cancer from fibrosis and cirrhosis. The intervention of World Health Organization to minimize the spread of HBV by vaccination failed to abate the prevalence of HBV in some regions. In this research, three (3) distinct mathematical models of the Hepatitis B Virus (HBV) were developed, investigated, and analyzed. The models considered children born of carrier mothers with failed vaccination, the proportion of HBV acutely infected individuals who spontaneously recovered from the virus, infected individuals under treatment who became prone to re-infection when they fall out of treatment, and chronic carriers who were unaware of their status and, thus, transmit the virus unknowingly to others, which were not considered by previous models.

Positivity and boundedness of the models were proved using established theorems. The equilibria were shown by equating the differential equations to zero. Basic reproduction numbers were constructed for each of the models using the next generation matrix method. Local and global stabilities of the models were validated via linearization and Lyapunov function methods respectively. The center manifold theorem was used for the bifurcation analyses while the sensitivity analyses were performed on each of the models to ascertain the parameters that may positively affect the models. Numerical simulations were carried out on the models to show the effect of the parameters on each of the models. Optimal control analyses were also done to show the importance of control on the activities of the models.

The behaviour of the various compartments in relation to the basic reproduction number showed that only the susceptible and the vaccinated individuals exist when the

threshold parameter is less than unity and the other compartments tend to zero. Also, the reduced rate of acutely and chronically infected offspring in each compartment exhibited an increase in susceptible, hospitalized and vaccinated compartments, whereas other compartments displayed a reduction in their respective populations. The results showed the possibility of a reduction in the number of acute and chronic individuals by increasing the treatment rate. It was shown that at a time range $0 < t < 6$, the acute population decreases, also at a range $6 < t < 40$, the chronic population decreases. The effects of control measures on the chronic, recovered, and vaccinated compartments were also examined. These results confirm that the effects of control measures on the compartments reduce the effects of liver cancer in individuals on treatment.

The models validated the various dynamics where acutely infected individuals spontaneously recovered from the virus, treatment of all infectious classes which helps in mitigating the risk of HBV, and individuals who fall out of treatment thereby aggravate the HBV transmission process. It is recommended that testing at the acute and chronic unaware states assist in the better management of the virus.

DEDICATION

This thesis is dedicated to the great God, the Lord Almighty, the author and the finisher of my faith.

ACKNOWLEDGEMENTS

First, I would like to express my sincere gratitude to my supervisor and mentor Dr. Olukayode Adebimpe, for his encouraging words, patience, and motivation towards the completion of my PhD programme. This has indeed been a long journey and I would not have gone this far without his insightful ideas, countless useful discussions, suggestions and especially the confidence he has in my ability. He is not just a Supervisor but a father to me. I would like to thank my co-supervisor Dr. James Ndako, for his useful and valuable ideas from the medical point of view that brought out the best in this work. I am eternal grateful to you sir.

My sincere gratitude goes to the Head of Department, Dr. (Mrs.) A. A. Inyinbor for her sincere efforts in making the completion of this programme a reality. I appreciate you Ma. The good Lord shall continue to be with you in Jesus' name. I would like to appreciate the entire professorate of the Department, Professor J.O. Adeniyi, Professor B.O. Adebesin and Professor O.S. Bello for their fatherly assistance in the course of the programme. Many thanks to the Departmental Postgraduate Coordinator, Dr. S. O. Ikubanni for his valuable contributions at every stage of this programme. I would also like to appreciate every Faculty and Staff of the Department of Physical Sciences for their unwavering support towards the completion of the programme. I would like to appreciate every Faculty in Mathematics Programme, Dr. Nathaniel Oladejo, Dr. Abimbola Abolarinwa, Dr. Adewale Lukman, Dr. Olakunle Salawu, Dr. (Mrs) Esther Davids, Mr. Oluwayemi Mathew, Mr. Joshua Okoro and Mrs Benedicta Aladeitan for standing by me through the thick and thin of the programme.

Special thanks to Dr. Michael Adeniyi and Dr. Babatunde Gbadamosi for their insightful comments, encouragement and enlightenment towards this research and for always listening to my complaints. Thank you, sirs, for helping out.

Profound gratitude to my priceless parents, Pastor and Deaconess Dele Fashomi for their sacrifices, unconditional love, prayer and support. I want to appreciate my husband, Banji Oludoun for his unwavering support, for his belief in my ability and for standing by me through days and nights of prayers. My Princesses, Erioluwa Samantha and Inioluwa Emmanuella, thank you for rocking my world. My Siblings: Oyindamola, Moyosoreoluwa, Emmanuel, Dimeji and my wonderful in-laws, I appreciate you all.

Special thanks to my good friends, Dr Jummy David and Mrs Oluwakemi Abiodun. We went through the rigor of this work together and I would not fail to appreciate you for standing by me all through this programme. I will also say thank you to Mrs Temitope Osenwegie for helping out with my daughter, you are wonderful ma, God bless ma.

I will end by saying; all my life God has been faithful. I am a living testimony and a product of grace. I thank my God and my good Father. Thank you, JESUS.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF NOMENCLATURE FOR HBV MODEL CASE 1

μ: Newborn rate

ω: The percentage of children born without receiving an effective vaccination

υ: Parentally infected population ratio

φ: Induced immunity rate with declining vaccination.

β: Coefficient of transmission

γ: Reduced coefficient of transmission

δ_1: The rate of migration

$\mu_i, i = 0,1,2$: Death rates from natural causes and diseases related.

σ: The rate at which latent persons progress from latent to acute class.

γ_2: The rate at which chronic carriers progress from chronic to recovered status.

q: Failure rate of recovered individuals at the acute class

ϑ_1: Acute individuals' hospitalization rate

ϑ_2: Chronic individuals' hospitalization rate

ϑ_3: Hospitalized individuals' recovery rates.

r: Rate of children born of infected mother without active vaccine that goes to the acute compartment

b: Rate of children born of infected mother without active vaccine that becomes chronically infected

S(t): Susceptible Compartment

L(t): Latent Compartment

A(t): Acute Compartment

C(t): Chronic Compartment

H(t): Hospitalized Compartment

R(t): Recovered Compartment

V(t): Vaccinated Compartment

LIST OF NOMENCLATURE FOR HBV MODEL CASE 2

ζ: Newborn / birth rate

α: Percentage of the population that has been effectively immunized

γ: Probability that children born to carriers may develop a chronic illness

λ_s: Coefficient of horizontal transmission

ξ: Reduced coefficient of transmission

η: Proportion of spontaneous clearance

$1/\omega$: Acute phase duration

k: Recovery rate of treated individuals with full immunity

μ: Mortality rate

σ: Chronic individuals' treatment rate

ν: The percentage of the population that is recovering

ρ: HBV treatment duration

ε: The proportion of recovered population that fall out due to risk factors

S(t): Susceptible Compartment

A(t): Acute Compartment

C(t): Chronic Compartment

T(t): Treatment Compartment

R(t): Recovered Compartment

LIST OF NOMENCLATURE FOR HBV MODEL CASE 3

Π: Recruitment rate

λ: Force of infection

γ: Acute to chronic unawareness progression rate

ν_1: Acute individuals' testing rate

ν_2: Chronic unaware individuals' testing rate

δ: Treatment rate for chronic aware individuals

μ: Natural death rate

σ: Spontaneous clearance

ω: Removed/recovery rate

d_c: Disease induced death

S(t): Susceptible Compartment

A(t): Acute Compartment

$C_u(t)$: Chronic unaware Compartment

$C_a(t)$: Chronic aware Compartment

$T_c(t)$: Treatment Compartment for chronic aware carriers.

R(t): Recovered/Removed Compartment

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background to the Study

Hepatitis is an inflammation/scarring of the liver that contributes to various health complications, including deaths. It occurs due to an immune system attack by the virus in the liver and damages this vital organ of the body in the process (Ciupe *et al.*, 2014). To date, the World Health Organization (WHO) identifies six main types of Hepatitis viruses, which are referred to for purpose of proper classification as Types A, B, C, D, E and G. However, although these viruses are responsible for liver disease, their methods of transmission, disease intensity, preventive mechanisms and geographical distribution around the world vary in many important ways. Nevertheless, in particular, global health focus has been on three of these viruses: Types B, C and D. This is most probably because of their high prevalence and high mortality rate associated with them. Types B and C are, in fact, the most common causes of liver cirrhosis, cancer, and viral Hepatitis mortality. These two types of Hepatitis resulted in chronic diseases in multi-million individuals world-wide (WHO, 2019).

WHO estimates that globally 325 million people have Hepatitis B and C and most of the people affected were due to lack of means of testing and treatment. Research has, however, shown that vaccination can prevent people from suffering from some of the Hepatitis. Also, in particular, studies have shown that eradicating the Hepatitis C virus appears feasible due

to recent advances in new drugs. Nonetheless, Hepatitis B and D viruses (HBV and HDV) continue to pose a significant global health and economic challenge. According to a recent WHO study, 4.5 million premature deaths in low- and middle-income countries could be avoided through vaccination, diagnostic tests, medicine applications, enlightenment, and education by 2030. Through these measures, member-states envisaged that new infections would be reduced by 90%, while death from Hepatitis would come down by 65% by 2030 (WHO, 2020).

Hepatitis B Virus (HBV) infection is a highly fatal viral infection. It is a massive world-wide health issue that can lead to severe disease and expose individuals to the risk of developing liver cancer caused fibrosis and cirrhosis. The Hepatitis B virus can thrive outside the human body for not less than seven days. Individuals who are not protected by the vaccine can still be infected if the virus gets in contact with them. The Hepatitis virus incubates in 75days but varies between 30 to 180 days. Within 30 to 60 days of infection, the virus may be detected, persist, and grow into chronic Hepatitis B (CDC, 2019). The World Health Organization reported that approximately 360 million humans have a chronic (lifelong) infection with the Hepatitis B virus (HBV), and 887,000 of these people die from liver cirrhosis or primary hepatocellular carcinoma. In 2016, 27 million (10.5%) of those estimated to have Hepatitis B were aware of their status and 4.5 million (16.7%) of those diagnosed were treated (WHO, 2019).

Hepatitis B is most common in the Western Pacific region with prevalence rate 6.2% and Africa with prevalence rate of 6.1%, with the Americas region (0.7%) having the lowest

prevalence (WHO, 2019). Nigeria, a tropical country, has been proven as having a high prevalence of HBV infection. An estimated 75% of the population have been in contact with the virus at some point in their lives. According to Eustace *et al.,* (2019) ,18 million Nigerians are infected. The prevalence rate was 4.3% in Port Harcourt, 5.7% in Ilorin, 11.6% in Maiduguri, and 8.3% in Zaria. A sero-prevalence rate of 23.3% was found among patients presenting at all clinics at the Aminu Kano Teaching Hospital (AKTH) (Eustace *et al.*,2019).

In areas of high endemicity, Hepatitis B is commonly transmitted at birth from mother to child (vertical transmission) or through horizontal route (contact with infected blood). Transmission can also be from infected children to uninfected children at the first five years of life. Infants infected by their mothers develop chronic infection or before they are five years of age. It is often transmitted through transdermal or mucosal contact of infected persons through the blood and different body fluids such as spittle, catamenial, vaginal fluid and semen and, to a lesser degree, perspiration, breast milk, tears, and urine. In particular, Hepatitis B can be transmitted through sexual contact in unvaccinated bi-sexual men and individuals with multiple sexual partners. However, about 5% of cases of infection from adult contributes to chronic Hepatitis. This transmission may similarly ensue when needles and syringes are reused, whether in health care settings or among drug users. Infections can also happen during medical, surgical, or dental procedures, such as tattooing or the use of razors or other sharp objects infected with infected blood. (Mpeshe and Nyerere, 2019).

Hepatitis B is a highly infectious virus and is 100 times more infectious than HIV and therefore became a major global health issue. Concerned experts have noted that the effects of HBV infection include chronic liver disease; it has not been given the utmost attention and has therefore become a public health concern in the region. To educate the public about the risk, mode of transmission, and risk factors associated with the infection, this research was carried out to assess the transmission and acquisition of HBV infection.

1.1.1 Signs and Symptoms of HBV

Symptoms of HBV are classified according to the various phase of the infection which include the acute phase and the chronic phase. The early or acute phase symptoms include flu-like symptoms which are not limited to fatigue, fever, pains and aches; weight and appetite loss, continuous stooling and vomiting, naval pain, jaundice, dark urine, pale faeces (Λvert, 2021). Moreover, the symptoms at the chronic phase can be similar to that of the acute phase and also nausea, anorexia, mild upper pain, swelling in the leg and ankle, itchy skin and so on (Mayoclinic, 2021).

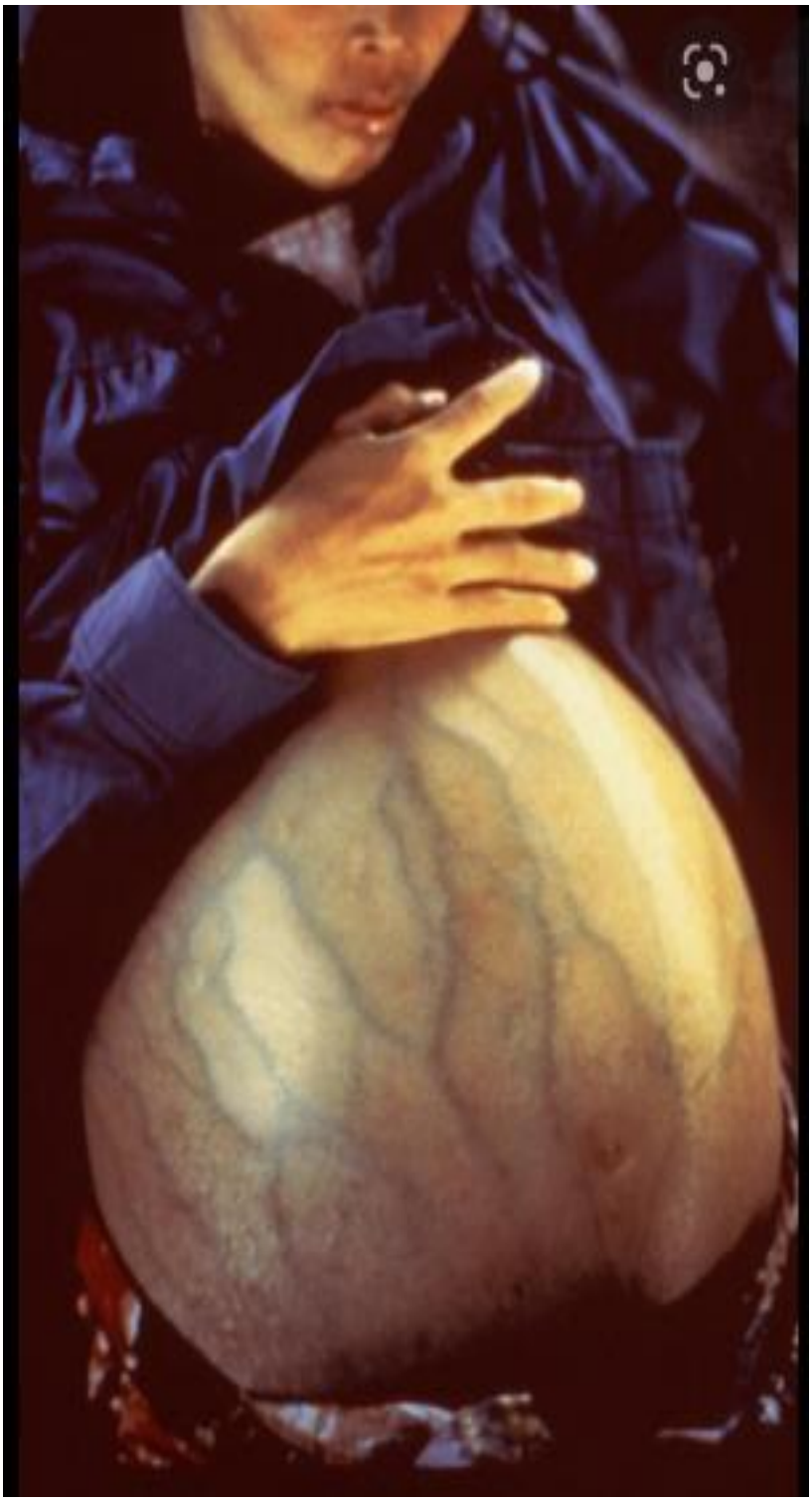

Figure 1: Picture of a person suffering from chronic HBV. (CDC, 2019)

1.1.2 Prevention and Treatment of HBV

Vaccination: Highly effective recombinant vaccines are available for HBV prevention. They are administered from time to time to neonates as a part of universal vaccination in many countries. The efficacy of newborn vaccination is also quite high (Lin *et al.*, 2003, Demirjian and Levy, 2009). Due to the implementation of newborn vaccination, several countries have observed a lower incidence and prevalence of chronic Hepatitis B infections (Peto *et al.*, 2014) and liver cancer (Qu *et al.*, 2014). For those who missed HBV vaccination at birth, an alternative catch-up vaccination among children and adults is also available (Hutton *et al.*, 2010, Hutton and Brandeau, 2013). For more effective prevention, vaccines can also be administered to those who are more likely to be infected such as workers in the health care sector. In addition to HBV newborn and adult vaccination, Hepatitis B Immunoglobulin (HBIG) can also protect persons exposed to Hepatitis B. It is particularly productive within 48 hours of the incident and therefore highly recommended post-liver transplantation to avoid reinfection (Singer *et al.*, 2015). Neonates who are at high risk of infection can also be vaccinated. Vaccines may also be given to neonates at increased risk of contracting Hepatitis B, i.e., whose mothers are both Hepatitis B surface antibody (HBsAg) and Hepatitis B e antibody (HBeAg) positive. A combination of HBIG and active HBV vaccination within 12 hours of birth has successfully eliminated vertical transmission in Germany.

Treatment: Covalently closed circular DNA **(**CccDNA) is the template of HBV infection. Therefore, the inability of antiviral treatments to clear cccDNA in the liver can lead to a

viral rebound, even after achieving complete clearance of virus in the serum (Chong *et al.,* 2011). Therefore, successful treatment requires eliminating cccDNA in the liver along with viremia clearance. Patients with an HBeAg-positive disease have a high HBV-DNA threshold of 20,000 IU/mL (or 105 copies/mL) with chronic inflammation, as shown by high ALT satisfy the care requirements (Lok and McMahon, 2004, Lok *et al.,* 2016). The ALT threshold used to decide whether a patient should be treated quite contentious, with some experts believing that care is required for those with persistently elevated ALT and others requiring ALT to be higher than twice greater than two times the upper limit of normal (ULN). It should be noted that for ALT, changed ULN levels were to 30 IU/L for males and 19 IU/L for females. The same theory applies to HBeAg-negative patients, whereby those with continuing viral replication and persistently elevated ALT meet the treatment criteria. However, the HBV DNA threshold is usually lower in these patients than in HBeAg-positive patients, with levels greater than 2000 IU/mL (or 104-105 copies/mL) (Fung and Lok, 2004, Lok and McMahon, 2007). The treatment regimens for chronic Hepatitis B infections consist of conventional interferon (IFN), Peg-IFN, and first- and second-generation nucleotide analogues (NAS) (Price, 2014). Oral NAs consist of lamivudine (LAM), adefovir (ADV), telbivudine (TBV), entecavir (ETV) and tenofovir (TDF). Peg-IFN and second-generation NAs (ETV and TDF) are commonly used as initial antiretroviral agents. NAS are effective and less susceptible to the development of resistance mutations (Wu *et al.,* 2010). They can also reverse liver fibrosis, cirrhosis and liver cancer (Liang *et al.,* 2015). Whereas oral NAs have somewhat indefinite treatment courses, Peg-IFN has a fixed-duration course and higher HBeAg and HBsAg loss rates.

Different therapies affect different compartments of HBV replication and the immune system (Thimme and Dandri, 2013). While NAs only target HBV replication at the reverse transcription phase (pgRNA to cDNA) and have no effect on cccDNA at all, IFN is expected to have both antiviral as well as immunomodulatory effects on different steps in the HBV replication cycle, including cccDNA degradation (Haller *et al.,* 1998). The antiviral effects are attributed to MxA, a 76-kDa GTPase protein from the large GTPase superfamily that accumulates in the cytoplasm in response to IFN-a/b (Haller *et al.,* 1998). MxA genes work at the post-transcriptional phase of HBV replication (i.e., encapsulation of RNA). It has also been found that MxA genes have no impact on the HBV nucleocapsid and its formation. They only affect the nucleocytoplasmic transportation export of viral mRNA's (Rosmorduc *et al.,* 1999). A decrease in the secretion of viral proteins (HBsAg) was also found in MxA expressing clones along with a momentous lessening in the synthesis of viral proteins (HBsAg), cytoplasmic RNAs, and DNA replicative intermediates (encapsulated viral DNA), showing an antiviral effect of MxA protein (Gordien *et al.,* 2001). The underlying mechanisms of interferon-stimulated genes (ISGs) are still not fully understood. HBsAg levels are used as an indicator to track the performance of these antiviral treatments (Chen *et al.,* 2014). HBV DNA and HBsAg levels may serve as a better predictor than HBeAg seroconversion in calculating the future risk of HCC (Wu and Dunn, 2015, Lin and Kao, 2013, Tseng *et al.,* 2013, Tseng *et al.,*2012). In treatment-naive patients, the recorded 5-year resistance rates are 70% for LMV, 29% for ADV and 17% for TVB (2-year rate), compared to 1.2% for ETV and 0% for TDF. (Price, 2014). ETV and TDF are more powerful and less likely to develop resistance.

Mutations, and yet they remain more expensive than other generic treatment choices (Wu *et al.,* 2010). Second generation NAs such as ETV and TDF can also reduce HBV viremia level by 6 logs within a year but have no effect on cccDNA, which has a lengthy half-life and results in the persistence of infection if patients do not adhere to treatment. Under second-generation NAs, the rates of HBeAg seroconversion (20% after one year and 40-50% after five years) and HBsAg loss (5-10% after five years) are higher than for first-generation NAs but are still lower compared to IFN. Peg-IFN has better performance than IFN and induces a stronger cccDNA and HBsAg decline in chronic patients (Wursthorn *et al.,* 2016). With Peg-IFN, weekly administration for 48 weeks resulted in 29-32% HBeAg seroconversion and 3-7% HBsAg loss in HBeAg-positive patients. In addition, HBeAg change from seropositive to seronegative is durable in up to 81% of cases, and HBsAg loss durability reaches as high as 30% in a follow-up of 3.5 years (Cooksley *et al.,* 2003, Locarnini *et al.,* 2018). Similarly, in HBeAg-non-positive patients, 3-year post completion of Peg-IFN treatment with or without LMV lead to a sustained virological response (SVR regarded as HBV DNA<10,000 IU/mL and normal ALT) in 25% of patients and HBsAg loss in 9% (Locarnini *et al.*, 2018). In contrast to SVR, the aim is to achieve a functional cure that implies HBeAg-negative, HBV DNA <2000 IU/ml and normal ALT (Locarnini *et al.,* 2018). The older studies used detection limits of around 104 to 105 copies/ml, however recent developments in detecting lower levels of HBV viremia redefined SVR and functional cure as HBV DNA <72 IU/ml and HBV DNA< 69 IU/mL, respectively (Kau *et al.,* 2018).

1.2 Statement of the Problem

Despite the intervention by WHO on vaccination for minimizing the spread of HBV, the highest prevalence of HBV is still encountered in the Western Pacific Region and the African region with 6.2% and 6.1% respectively (WHO, 2019). It has, therefore, become pertinent to carry out further research on the acquisition and the rate of spread of HBV with the view of identifying the possible way of reducing the menace and mitigating the risk of the virus.

A considerable amount of research efforts has gone into the transmission process of HBV (Hattaf and Yousffi, 2015, Liang *et al.*, 2015, Khan *et al.,* 2018, Emerenini and Inyama, 2018, Mpeshe and Nyerere, 2019, Khan *et al.,* 2019*).* Acquisition of Hepatitis B infection is by horizontal and vertical transmission process which have been identified as the main spread of the infection. This transmission process has been investigated by other researchers but neglect has been on the part that acute individuals are allowed to be full blown carrier by not considering treatment at the acute state until they are at the chronic state (Khan *et al.,* 2018; Okamoto, 2013). According to Cuipe *et al.,* (2007), offspring's born of an infected mother can be categorized as acutely or chronically born but Khan *et al.,* (2019) neglected the recruitment process where a carrier mother can give birth to an acute offspring.

However, in this research, treatment at all the infectious classes will be considered in the models to mitigate the risk of HBV; chronic carriers will be classified as chronic aware and chronic unaware. Also, children born of carrier mothers shall be regarded as whether acute

or chronic to help in better management of those children to reduce the spread of the disease in line with Lavanchy, (2004) who opined that the route of transmission has important clinical implication on the children because they have a high probability of becoming chronic spreaders. Chronic infection is developed in about 80-90% of children below the age of one and about 30-50% of children infected before the age of 6years (Kamyad *et al.,* 2014).

1.3 Justification of the Study

Disease transmission dynamics and extrapolation from epidemiological data in predicting risk have been studied through the extensive use of mathematical models. Of the 2 billion people who have been infected with the Hepatitis B virus (HBV), WHO reported that about 360 million have chronic (lifelong) infection and 887,000 of these people die from liver cirrhosis or primary hepatocellular carcinoma. Prevalence of hepatitis B is highest in Western Pacific Region with 6.2 percent, Africa region with prevalence range of 6.1 percent and lowest in the America region with range of 0.7 percent of the adult population (WHO, 2019).

1.4 Aim and Objectives

The study aims at developing a new model for transmission of HBV with treatment dynamics and optimal control.

The specific objectives are to:

1. obtain the disease-free equilibrium and endemic equilibrium of the models

2. construct the models' basic reproduction number using the next generation matrix in order to determine the nature of the outbreak.

3. investigate using the Lyapunov function the global and local stabilities of the resulting equilibria i.e., the disease free and the endemic equilibrium of the model.

4. perform numerical simulations on the model to assess the positive effect of some important parameters (testing rate, treatment rate of the models).

5. perform bifurcation analysis on the equilibrium points (either forward or backward) using the center manifold theory

6. develop and analyze an optimal control model for HBV to minimize cost and maximize treatment and recovery rate of infected individuals.

1.5 Research Questions

This research is expected to answer the following questions:

1. how is the nature of the outbreak of the disease determined?

2. how can the spread be predicted?

3. what are the mechanisms behind the spread of the disease?

4. how can the blow up be prevented through the stability analysis?

5. how effectively can parameter sensitivity determine the nature of spread of the disease?

6. how does optimal control determine the cost effectiveness of treatment?

1.6 Scope of the Study

The research seeks to examine the transmission process of Hepatitis B virus and the optimal control strategies to minimize cost and maximize treatment with the recovery rate of individuals infected. The study is restricted to the deterministic model where estimated data on already published articles and assumed values were used for the numerical simulations.

1.7 Significance of the Study

This research is expected to extend the frontiers of knowledge by improving control methods on the occurrence of HBV outbreak in a population.

Results obtained in this study are good indices that can aid some crucial decisions of health experts in policy formulation, planning, budgeting, resource allocation and making appropriate decisions on controls of the Hepatitis B virus by critically considering the testing and treatment of individuals and also contribute to WHO 90-90-90 HBV elimination and coverage target for 2030.

1.8 Description of Some Basic Terms

1.8.1 Transmission Dynamics

An infectious disease agent can be transmitted in two ways: horizontally from one individual to another by either direct contact (licking, touching, biting), or indirectly through air – cough or sneeze (vectors or fomites that allow the transmission of the agent causing the disease without physical contact), or vertically from one individual to another.

1.8.2 Epidemic Model:

An epidemic model is used to explain the transmission process of contagious (infectious) disease by individuals in a simple manner. The ability to make disease predictions would enable scientists to determine inoculation plans that could have a major impact on the mortality rate of a specific epidemic. Infectious disease modeling is a tool for studying disease transmission mechanisms, forecasting the future course of an outbreak, and evaluating epidemic control strategies (Daley and Gani, 1999). Mathematical analysis and application of infectious disease have been epidemiologically modelled. Specific models for measles, Rubella, Chicken Pox, Whooping Cough, Diphtheria, smallpox, Malaria, Syphilis, HIV/AIDS, and Hepatitis have been developed (Daley and Gani, 1999). Epidemic models can be grouped into two which are the stochastic epidemic model and the deterministic epidemic model.

1.8.2.1 Stochastic Epidemic Model

Stochastic models are based on chance variation in the risk of disease exposure and other variables. They provide much more insight into individual-level modelling, considering the small size of the population where each person plays a significant role in the model. Therefore, when heterogeneities in isolated populations are important, they are used. The stochastic model is an instrument that allows random variations in one or more inputs over time to estimate probability distributions of potential outcomes as in the case of a small population; they are used when these fluctuations are significant and are also adopted for estimating the probabilistic quantities for event outcome such as the probability distribution of extinction time, the associated mean, the probability distribution of final epidemic size etc. There are several benefits to stochastic models. More specifically, however, they enable close monitoring on a change-based basis of each individual in the population. However, they can be laborious to set up and require many simulations to produce useful forecasts. Such models can become very complex mathematically and do not explain the dynamics (Daley and Gani, 1999).

1.8.2.2 Deterministic Epidemic Model

When considering large populations, deterministic disease models are used, so they are called Compartmental models. Here, separate compartments are allocated to individuals in the populace, reflecting a particular epidemic stage. The transit rate from one compartment/state to another is mathematically represented as derivatives, so differential

equations formulate the model. The population size in a compartment is distinguishable from time, and the disease phase is deterministic. Particularly, the population changes in a case can only be measured using the history used to create the model (Braner and Castillo-chavez, 2001). Most of the models that explain the actions of infectious diseases that have been used so far are deterministic because they need fewer data; they are relatively easy to set up and are readily available and user-friendly in computer software. The dynamics of the models are now well understood to generally use deterministic models to test whether a specific control strategy would be successful. In addition, several other more complex models can combine stochastic components.

Deterministic disease models of various population sizes were formulated and mathematically analyzed (Anderson and May, 1981, 1998, Hochberg, 1991).

1.8.3 Basic Reproduction Number (R_0)

One of the basic issues in mathematical epidemiology is to establish threshold conditions that decide when a disease is introduced into the population i.e., the conditions whereby contagious diseases can be transmitted to a susceptible group (Reluga 2009). These threshold conditions are defined by the basic reproduction number, R_0.

In epidemiology, an infection's basic reproduction number (R_0) is the average number of secondary cases that a typical single infected case will cause in a population with no

immunity to the disease in the absence of infection-control interventions. It is of great importance due to its ability to detect the spread of an infection through a population. In particular, through the work of (Ross, 1911) and others, the origin of the basic reproduction principle can be traced. It was first applied by George MacDonald in 1952, who developed a mathematical model for the spread of malaria.

In infectious disease epidemiology, the basic reproduction number is arguably the most significant quantity. It is one of the urgently predicted epidemic situations for emerging infectious diseases, and its importance offers insight into the design of control interventions for existing infections. Theoretically, the number of basic reproduction numbers plays a critical role in studying infectious disease models and consequent insight.

When $R_0 < 1$, the infection fizzles out eventually (given that the rate of infection remains unchanged). However, there can be an infection blowout in a population if $R_0 > 1$. Large values may indicate the likelihood of a major outbreak (Hyman and Li, 2000). In general, the larger the values, the harder the epidemic can be managed. In particular, $(1-1/R_0)$ provides the percentage of the vaccinated population needed to stop the prolonged spread of infection (Driessche and Watmough, 2002).

Several factors affect the basic reproductive number R_0, which includes the length of the infectivity of the infected individuals, the infectivity of the organism and the number of susceptible individuals in the population who are in contact with the affected patients.

In the calculation of the basic reproduction number, several methods are used which rearrange the largest Jacobian matrix value, the next-generation process (Diekmann and Hesrterbeck, 2000), the survival function, intrinsic growth rate calculations (Chowell *et al.*, 2003), the presence of endemic equilibrium (Ajelli, 2008), among others. The choice of which approach to use depends on the model's features in question (Heffernan *et al.*, 2005).

1.9 Arrangement of the Thesis

The organization of this thesis is in five chapters. Chapter one highlights the introduction to the study carried out, statement of the problem, justification for the study, aim and objectives, research questions, scope of the study, significance of the study and description of some basic terms used. Chapter two includes a detailed review of fundamental concepts and existing related studies on Hepatitis B Virus and its transmission process. The concluding part of chapter two contains a detailed review of related literature that situate the works done on HBV and the various methods used. Chapter three covers the description of the conceptual design, materials and method. Chapter four focuses on results, discussion of the results obtained, and evaluation of the techniques. The thesis is finally concluded in chapter five with summarized discussion of results, contributions to knowledge, recommendations, and suggestions for further work.

CHAPTER TWO

2.0 LITERATURE REVIEW

Whilst there are enormous and abundant literature on the mathematical models for contagious diseases, there has been renewed interest in the dynamics of the Hepatitis B virus and how best to control the transmission dynamics of the virus. This section reviews literatures on various methods and mathematical approaches used to control the transmission dynamics of the virus.

2.1 Conceptual Issues

2.1.1 Hepatitis B Virus

Hepatitis B Virus, commonly called HBV, is a deoxyribonucleic acid (DNA) virus with a strikingly compact genomic composition. It has a relaxed circular (but not covalently closed), partially double-stranded DNA genome. The complete genome is approximately 3200 nucleotides (3.2 kilobases or kb) long. The genome economy of HBV is achieved through a competitive strategic approach to encoding four genes' proteins overlapping: the envelope (S); core (C); polymerase (P); and X regions (Rosenberg, 2001).

The virus is a part of the family of hepadnaviridae, which is divided into two genera: mammal-infecting ortho-hepadnaviruses and bird-infecting avi-hepadnaviruses. They have similar morphological shapes and are counter-parts to HBV, the antigens of the envelope and nucleocapsid virus. They reproduce in the liver but are present in extrahepatic sites and

have their own endogenous DNA polymerase and partly double-strand and partly single-strand genomes (Cossart and Field, 1970). HBV consists of an outer 42nm diameter spherical lipoprotein envelope and an inner 27nm diameter icosahedral nucleocapsid core enclosing the DNA genome, polymerase and a protein Kinase (Cossart and Field, 1970).

The virus is one of the smallest enveloped animal viruses that exist with a diameter of 42 nm. The external envelope includes embedded proteins that participate in and lead to viral binding of vulnerable cells. Although pleomorphism occurs, which consists of filamentlike and sphere-shaped bodies which lack a core, these particles are non-infective and consist of lipid and protein, which forms part of the surface of a virion known as a surface antigen (HBsAg) (Ciupe *et al.*, 2014).

2.1.2 Epidemiology of Hepatitis B Virus

The Hepatitis B virus (HBV) must first be bound, as a parasite, to a cell capable of sustaining its replication to replicate. Although, the liver is the most successful type of cell to replicate HBV, it has been found that other extrahepatic sites can support image to a lesser degree. Patients infected with acute Hepatitis B have been reported in mononuclear cells, bile duct epithelial, endothelial, pancreatic acinar cells and smooth muscle tissue, as well as in adrenal glands, gonads, cultured bone marrow, kidneys, lymph nodes, spleen and thyroid glands, HBV replicative intermediates and viral transcripts (Chang, 2011). Although, the virus does not appear to be associated with tissue damage in each of these extrahepatic sites, it invoked its existence in such remote reservoirs to explain the recurrence of HBV infection following orthotopic liver transplantation.

Hepadnaviruses rely on a special technique for replications of retroviruses in DNA viruses. They use reversal transcriptions of minus-strand DNA of the 'pregenomic' ribonucleic acid (RNA) rather than DNA replication directly from the DNA template (DNA polymerase). DNA from the minus strand DNA template is transcribed by the hepatocyte nucleus and transformed by host proteins called chaperones, which act as a template of messenger and pregenomic RNA, into covalently closed circular DNA (cccDNA). DNA is the host protein known as DNA polymerase. The messenger RNA translates viral proteins secreted from the hepatocyte and are packaged into the virion. Even though, it is tough trying to nurture HBV from clinical material in vitro in the traditional sense, there are transfected cells in vitro replication of the intact virus and its protein portion with many cell lines which have been transfected with HBV DNA (Cossart and Field, 1970)**.**

2.1.3 HBV Life Cycle

The HBV life cycle starts when the outermost envelope protein (pre S1 region of the large envelope polypeptide) of HBV binds to a cellular receptor of the host cell (Ezzikouri *et al.*, 2014). A process known as receptor-mediated endocytosis enables the entry of the nucleocapsid into the cytoplasm of the host cell. After uncoating and synthesis of viral plus-strand DNA, genomic DNA enters the nucleus of the host cell where the single-stranded gap is repaired and double-stranded DNA (dsDNA) matures to a 3.2-kb covalently closed circular DNA (cccDNA) (Chisari, 2000). The cccDNA then undergoes transcription by host cell RNA polymerase and is responsible for producing all viral mRNAs. Three smaller sub genomic mRNAs of 2.4 kb, 2.1 kb and 0.7 kb are necessary to translate

envelope proteins (S, pre S1 and pre S2) and the X protein. The translation of the larger genomic RNA (pgRNA of 3.5 kb) transcripts produces pre-core and core proteins along with hepatitis B e antigen (HBeAg) (Enders *et al.*, 1997, Nassal *et al.*, 2000, Kock and Schlicht, 2013). The core protein (HBcAg) produced earlier has an important job to rapidly form homodimers that self-assemble into capsid particles in the nucleus and cytoplasm (Chisari, 2000). Intra-nuclear capsid particles are empty and have an unknown role, while cytoplasmic capsid particles are true nucleocapsids (Chisari, 2000). Similarly, pgRNAs are translated in the cytoplasm of the host cell to produce a polymerase protein P which contains a viral packaging signal resulting in the encapsulation of the pgRNA-P protein complex within the capsids produced by the core (Miyanohara *et al*., 1986, Gallina *et al.*, 1989, Birnbaum and Nassal, 1990, Hirsch *et al.*, 2000, Bartenschlager and Schaller, 2002, Pollack and Ganem, 2014). Once encapsulation is complete, reverse transcription and DNA replication begin, which extends the negative strand. Afterwards, the positive-strand synthesis takes place, and then the endoplasmic reticulum (ER) or the Golgi apparatus are the sites where the envelope proteins are gotten. After which the assembling of progeny virions, vesicle fusion starts at the plasma membrane, followed by the release of the assembled progeny virions (Lien *et al.*, 1986, Staprans *et al.*, 1991, Loeb *et al.*, 1991, Summers and Mason, 1992, Wang and Seeger, 1992, Wang and Seeger, 1993, Miller *et al.*, 1994, Standring *et al.*, 2006, Persing *et al.*, 2006, Cheng *et al.*, 2006, Tavis and Ganem, 2013, Tavis *et al.*, 2014, Chisari *et al.*, 2016).

2.1.4 Pathogenicity of HBV

Young children (who acquire infection from their mothers at birth) typically do not show symptoms i.e., asymptomatic and do not necessarily have to go through the acute phase of HBV infection. However, 80 to 90% of these asymptomatic children develop chronic Hepatitis B, of which 25% die of cirrhosis or liver cancer in adulthood (Elgouhari *et al.,* 2008). On the other hand, adults (who acquire infection through horizontal transmission) usually go through the acute phase and mostly recover. Only 3-5% of them develop the next severe chronic state of HBV infection (Alter, 2003, Chu *et al.,* 2003). Once HBV disease has progressed to the chronic phase, it leads to more critical versions of the disease, including cirrhosis, decompensate cirrhosis, hepatocellular carcinoma (HCC, liver cancer) and liver failure. Approximately 8% to 20% of chronic infections develop cirrhosis, while 20% subsequently develop HCC within five years. Those who develop liver cancer have a 5-year survival rate of only 10% (Hui *et al.,* 2002, Fattovich *et al.,* 2002, Fattovich, 2003a, Fattovich, 2003b). A lot of factors determine the progression rates of cirrhosis and HCC which include age at infection, gender, extent of HBV replication, certain HBV genotypes and variants, coinfection with HCV, HDV, or HIV, alcohol consumption, exposure to aflatoxin B1, genetic factors of the host, and probable comorbidities including metabolic syndrome, diabetes, obesity and tobacco smoking (Locarnini *et al.,* 2018). Of all these factors, HBeAg positivity and HBV DNA levels are the main markers of HBV progression rate to HCC (Locarnini *et al.,* 2018). For example, the progression risk of cirrhosis and

HCC starts increasing at viral loads >104 copies/mL (2 x 103 IU/mL), and goes very high at viral loads >107 copies/mL (2 x 106 IU/mL).

2.1.5 Phases of HBV Infection

There are two major phases in HBV infection, the acute phase and the chronic phase.

Acute phase: The acute phase may last up to six months (with or without symptoms) and is identified by the presence of HBsAg, HBc-IgM antibodies (the first antibody to appear, which usually disappears in six months), and possibly HBeAg. There are four sub-phases in the natural history of acute HBV infection:

- The incubation phase
- The symptomatic hepatitis phase
- The recovery phase
- The HBsAg clearance phase

In the incubation phase, the infection spreads and replicates and is in an early development phase. This phase can last up to 12 weeks. Symptoms start to appear in the symptomatic phase, demonstrating increased levels of ALT. This symptomatic phase lasts for 4-12 weeks, followed by normalization of ALT levels in the recovery phase. In the last stage, clearance of HBsAg in the serum along with the development of Hepatitis B surface antibodies (anti-HBs) is observed (Lok and McMahon, 2004).

Most patients with acute hepatitis B are HBeAg-positive and highly infectious because of the high number of virions. However, HBeAg-negative and HBsAg positive patients are also very contagious (Fung and Lok, 2004). Acute fulminant hepatitis B also occurs in 1% of acutely infected patients and causes about 10% of cases of acute liver failure.

Chronic Phase: By definition, an HBV infection is chronic if HBsAg persists longer than six months (Lok and McMahon, 2004). It is also possible to classify the natural history of chronic hepatitis B into four sub-phases (but not all patients go through all four phases): immune tolerance, immune clearance, immune control, and immune escape. As the name suggests, in the immune tolerant phase, the body does not act against the HBV virus, and liver damage does not occur (usually measured by the amount of ALT produced by the liver). High levels of HBV DNA in the serum are also detected, and HBeAg positivity and anti-HBe negativity (Lok and McMahon, 2004). This phase is prevalent in those who acquire HBV infection at birth, which can last for 20-30 years (Elgouhari *et al.*, 2008). The immune clearance phase follows the immune tolerant phase and, in this phase, the body starts reacting to the virus and tries to clear the infection. This phase is also characterized by an increase in ALT levels, inducing variable inflammation of the liver (fibrosis) and fluctuating high HBV DNA levels in the serum. The seroconversion of HBeAg to anti-HBe is an important outcome of this phase. Initiation of antiviral therapy is essential (and more beneficial) in this phase; otherwise, the immune system will try to clear the infection on its own, which may lead to permanent liver damage. During the immune control phase, the immune system controls the virus and brings ALT levels down to normal, resulting in minimal liver damage. A small percentage of HBsAg and a low level of HBV DNA in the

serum were observed after the clearance of HBeAg, which is also an indicator of this phase. In some people, the virus escapes, and some inactive HBsAg re-activate, leading to liver damage. This phase is identified by negative HBeAg, positive anti-HBe and high viral load (Fung and Lok, 2004). HBeAg negativity is caused by a mutation in the precore or core promoter region of the HBV genome, preventing HBeAg production. Each of the phases, as mentioned above, can last for several years but the duration can suddenly change depending upon the complex interactions between the host, virus and the environment. The infection is usually noticed in the fourth phase, after which antiviral treatment is often provided (Yuen *et al.,* 2005).

2.2 Review of Methodological Approaches

The review of the various methods used in this research are shown in this section.

2.2.1 Next Generation Matrix

One of the ways to derive the basic reproduction number of any model with more than one infected class is the method of next-generation matrix formulation by (Diekmann *et al.,* 1990 and Dreissche and Watmough 2002). Diekmann and Hesterbeck (2002) and Hefferman *et al.* (2005) studied the next generation matrix method as a natural approach in the derivation of basic reproduction number in models that includes multiple classes of infected individuals. Hence, the basic reproduction number has been defined as the spectral radius (i.e., the domain eigenvalue) of the next generation matrix. Define x_s to be the set of all disease-free state, that is

$$x_s = \{x \geq 0 | x_i = 0, i = 1,2,\ldots.. m\} \quad (2.1)$$

In order to compute R_0, it is important to distinguish new infectious from all other changes in the population.

Let $F_i(x)$ be the rate of appearance of new infections in compartment;

V_i^+ be the rate of transfer of individuals into compartment *i* by all other means

V_i^- be the rate of transfer of individuals out of compartment *i*.

It is assumed that each function $(F_i(x), V_i^+$and $V_i^-)$is continuously differentiable at least twice with respect to each variable.

The transmission model consists of the non-negative initial conditions together with the following system of equations:

$$x_i = f_i(x) = F_i(x) - V_i(x), i = 1,2,\ldots\ldots, n \quad (2.2)$$

Where $V_i = V_i^- - V_i^+$ and the functions satisfying condition:

A1: if $x \geq 0$ then $F_{i,} V_i^-, V_i^+ \geq 0$ for $i = 1,2,n$

Note: if the compartment is empty, then through death, infection or any other means, there can be no transfer of individuals from the compartment.

A2: if $x_i = 0$, then $V_i^- = 0$ (No one leaves the compartment). In particular if $x \in X_s$, then

$V_i^- = 0$ For $i = 1,2,\ldots.. m$

A3: $F_i = 0, i > m$ (m is the number of infective classes)

A4: if $x \in X_s$, then $F_i = 0$, and $V_i = 0$ for all $i = 1,2,\ldots..m$

A5: if $F(x)$is then set to zero, then all the eigenvalues of $Df(x_0)$ having negative real parts.

Lemma 2.1: If x_0 is a disease-free equilibrium (DFE) of (2.1) and $f_i(x)$ satisfies A1-A5 then the derivatives $Df(x_0)$ and $Dv(x_0)$ are partitioned as

$$DF(x_0) = \begin{pmatrix} F & 0 \\ 0 & 0 \end{pmatrix}, V(x_0) = \begin{pmatrix} V & 0 \\ J_3 & J_4 \end{pmatrix} \quad (2.3)$$

Where F and V are the m x n matrices defined by

$$F = \left[\frac{\partial F(x_0)}{\partial x_i}\right] \text{ and } \quad V = \left[\frac{\partial V(x_0)}{\partial x_j}\right] \quad (2.4)$$

With$1 \leq i \leq m$, F is non – negative and V is a non- singular M-matrix.

From Diekmann et *at.* (1990) $FV^{-1}$is called the model's next generation matrix and R_0 is set to be equal to the spectral radius $p(FV^{-1})$ i.e.

$$R_0 = p(FV^{-1}) \quad (2.5)$$

2.2.2 Asymptotically Stable

2.2.2.1 Locally Asymptotically Stable

The equation point P_0 is said to be locally asymptotically stable if it is stable in addition there is a ball about P_0 such that every trajectory which enters the circle at some time to approaches P_0 as $t \to \infty$.

2.2.2.2 Globally Asymptotically Stable

The equilibrium point P_0 is said to be globally asymptotically stable if all trajectory approaches the equilibrium point P_0as $t \to +\infty$ (irrespective of earlier behavior), the P_0 is said to be globally asymptotically stable.

2.2.3 Stability

The stability characteristics describe how a system behaves if its state is initiated near to a given point of equilibrium but not precisely at it. If a system is originally exactly equal to an equilibrium point with the state, then by definition, it can never move. The state may, however, stay close by when initiated nearby, or it may step on.

Suppose $\overline{X}$ is an equilibrium point of time-invariant system then $\overline{X}$ is an equilibrium point of $X(t) = f(X(t))$ (2.6)

2.2.4 Linearization and Stability

According to definitions, the stability properties depend only on the nature of the system near the equilibrium point. Therefore, replacing the complete nonlinear definition with a simplified description that approximates the true system near the point of equilibrium to perform an analysis of stability is always technically valid and mathematically convenient. To disclose the properties of stability, a close approximation is often enough. In its definition, the linearization of the nonlinear system is based on the linearization of the nonlinear function f. The procedure approximates f close b, which is defined by a single function of a single variable for the first-order method.

$$f(\bar{x} + y) = f(\bar{x} + \frac{df(\bar{x})}{dx})y \tag{2.7}$$

n functions are described by an n-order system, each of which depends on n variables. In this circumstance, each operates as approximated by the relations.

$$f_i(\overline{x_1} + y_1, \overline{x_2} + y_2, \cdots \overline{x_n} + y_n) \approx f_i(\overline{x_1}, \overline{x_2}, \cdots \overline{x_n}) + \frac{\partial f_1(\overline{x_1}, \overline{x_2}, \cdots \overline{x_n})}{\partial x_1} y_1 +$$

$$\frac{\partial f_2(\overline{x_1}, \overline{x_2}, \cdots \overline{x_n})}{\partial x_2} y_2 + \cdots + \frac{\partial f_i(\overline{x_1}, \overline{x_2}, \cdots \overline{x_n})}{\partial x_i} y_n \tag{2.8}$$

where $i = 1,2, \ldots . n$ is in matrix form. This can be written as

$$f(\bar{x}+y) \approx f(\bar{x}) + f(y) \tag{2.9}$$

$$\text{where } f = \begin{bmatrix} \frac{\partial f_1}{\partial x_1} & \frac{\partial f_1}{\partial x_2} \cdots & \frac{\partial f_1}{\partial x_n} \\ \frac{\partial f_2}{\partial x_1} & \frac{\partial f_2}{\partial x_2} \cdots & \frac{\partial f_2}{\partial x_n} \\ \vdots & \vdots & \vdots \\ \frac{\partial f_n}{\partial x_1} & \frac{\partial f_n}{\partial x_2} & \frac{\partial f_n}{\partial x_n} \end{bmatrix} \tag{2.10}$$

The matrix f is called the Jacobian matrix of F. Now, consider the matrix equation

$$x = f(x(t)) \tag{2.11}$$

Setting$x(t) = \bar{x} + y(t)$, to obtain

$$y = f(\bar{x} + y(t)) = f(\bar{x}) + F(y(t)) \tag{2.12}$$

Since $\bar{x}$ is an equilibrium point of f, $f(\bar{x}) = 0$

therefore,

$$y(t) = F(y(t)) \tag{2.13}$$

Thus, the stability properties of the original system can be inferred from the linearized system using the following results:

1. If all eigenvalues of F are strictly in the left half-plane, then $\bar{x}$ is asymptotically stable for the nonlinear system.

2. If at least one eigenvalue of F has a positive real part, then $\bar{x}$ is unstable for the nonlinear system.

3. If the eigenvalues of F are all in the left half-plane, but at least one has a zero real part then $\bar{x}$ may be either stable, asymptotically stable or unstable for the nonlinear system (Lungu *et al.*, 2007).

Theorem 1.1: Derrick and Grossman, (1976): Consider the system

$$\left.\begin{aligned} x^1 &= a_{11}x + a_{12}y \\ y^1 &= a_{21}x + a_{22}y \end{aligned}\right\} \tag{2.14}$$

where the $a_{ij}$are constants and $a_{11}a_{22} - a_{12}a_{21} \neq 0$ so that the original (0, 0) is the only initial point

Let $\lambda_1$and λ_2 be the two roots of the auxiliary equation

$$\lambda^2 - (a_{11} + a_{22})\lambda + (a_{11}a_{22} - a_{12}a_{21}) = 0 \tag{2.15}$$

then

(a) The origin is stable if $\lambda_1$and λ_2 are pure imaginary.

(b) The origin is asymptotically stable if $Re\,\lambda_1 < 0$ and

(c) The origin is unstable in all other cases.

Moreover, the behavior of the orbits near the origin is shown in the Table 2.1

Table 2.1: Behaviour of the orbits near the origin (Derrick and Grossman, 1976)

	λ_1, λ_2	Type of critical point
1	Real, distinct, negative	Stable node
2	Real, distinct, positive	Unstable node
3	Real, distinct, opposite signs	Saddle point (unstable)
4	Real, equal, negative	Stable node
5	Real, equal, positive	Unstable node
6	Complex conjugate, not pure imaginary negative real parts	Stable forms
7	Complex conjugate, not pure imaginary positive real parts	Unstable
8	Pure imaginary	Center (stable)

2.2.5 Descartes' Rule of Signs

Theorem 1.2: The number of positive zeros of a polynomial with real coefficients is either equal to or even less than the number of variations in the polynomial's sign.

Proof: the idea of the proof is this: group together the factors belonging to negative and imaginary roots, on the other hand:

$$p(x) - [(x - r_1)(x - r_2)\dots(x - r_k].x[(x - r_{k+1})(x - r_{k+2})\dots(x - r_n)] \quad (2.16)$$

(We assume that the leading coefficient of $P(x)$ is unity, since the roots are unchanged by dividing by an in case $a_n$is root unity). We will show two things:

(a) The number of variations in sign of the factors corresponding to the negative and imaginary roots is even, i.e., if the expression

$$p(x) = (x - r_{k+1})(x - r_{k+2})\dots(x - r_n) \quad (2.17)$$

(b) When a polynomial $g(x)$ is multiplied by $(x - r)$,with r positive, the number of variations is sign of $(x - r)\ g(x)$ is at least one more than the number of variations in sign of $g(x)$.

Once (a) and (b) have been proved, the proof of the theorem is complete by returning to (2.16) and rewriting (2.17) as

$$p(x) - [(k - n)\dots.(x - r_k)]p(x) \quad (2.18)$$

and reworking (a), we conclude that $p(x)$has an even number of variations in sign.

Then, by (b),

$$(x - v_k)p(x) \tag{2.19}$$

has at least two more variations in sign that does $P(x)$.by (b) against;

$$(x - r_{k-1})[(x - r_k)P(x)] \tag{2.20}$$

has at least two more variations in sign than does $P(x)$,and finally

$$P(x) = [(x - r_1)(x - r_2)\dots(x - r_k]P(x) \tag{2.21}$$

has at least k more variations in sign than does $p(x)$. Observe, however, k is the number of positive zeros of $P(x)$,and if we let $n(P), n(P)$denote the number of variations in sign of $P(x)$,

$p(x)$ respectively, then,

$$\left.\begin{array}{l} n(p) \geq k + n(p) \\ \text{or} \\ k \leq n(p) - n(p) \end{array}\right\} \tag{2.22}$$

But according to (a), $n(P)$is even and hence the theorem will be proved.

The theorem also suggests that the number of negative roots is equal to or less than an even number of variations in the symbol.

2.2.6 Lyapunov Stability Method

Lyapunov stability method is used to determine the stability of the mode. In Lyapunov process, stability of linear and nonlinear systems can be obtained without any prior knowledge of solutions.

Two methods for demonstrating stability were suggested by Lyapunov (1892). In a sequence that was then shown to be convergent within limits, the first approach established the solution. The second, which is used almost exclusively nowadays, uses a function of Lyapunov$v(k)$ that has an analogy to the potential function of classical dynamics.

Consider the autonomous system.

$$\left.\begin{aligned} x_1^1 &= f_1(x_1, x_2, x_3) \\ x_2^1 &= f_2(x_1, x_2, x_3) \\ x_3^1 &= f_3(x_1, x_2, x_3) \end{aligned}\right\} \qquad (2.23)$$

where it is assumed that the origin is the critical point.

Let $v(x_1, x_2, x_3)$ be a continuous real-valued function on the x_1, x_2, x_3 plane with continuous partial derivatives. if D is the region containing the origin, then:

Theorem 1.3 (Derrick and Grossman, 1976):

I. if $v(0,0,0) = 0$ and $v(\chi_1, \chi_2, \chi_3) > 0$ for all other point in D, then $v(\chi_1, \chi_2, \chi_3)$ is said to be positive definite in D.

II. if $v(0,0,0) = 0$ and $v(\chi_1, \chi_2, \chi_3) < 0$ for all other point in D, then $v(\chi_1, \chi_2, \chi_3)$ is said to be negative definite.

III. if $v(\chi_1, \chi_2, \chi_3) \geq 0$, then $v(\chi_1, \chi_2, \chi_3)$ is said to be positive semi definite in D.

IV. if $v(\chi_1, \chi_2, \chi_3) \leq 0$, then $v(\chi_1, \chi_2, \chi_3)$ is said to be negative semi definite in D.

V. if $v(\chi_1, \chi_2, \chi_3)$ satisfies none of the above conditions, then v is said to be indefinite in D.

2.2.6.1 Lyapunov Functions

Let $v(\chi_1, \chi_2, \chi_3)$ be a continuous differentiable, positive definite function and

$$v(\chi_1, \chi_2, \chi_3) = \frac{\partial v}{\partial x_1} x_1 + \frac{\partial v}{\partial x_2} x_2 + \frac{\partial v}{\partial x_3} x_3$$

$$= \frac{\partial v}{\partial x_1} f_1(x_1, x_2, x_3) + \frac{\partial v}{\partial x_2} f_2(x_1, x_2, x_3) + \frac{\partial v}{\partial x_3} f_3(x_1, x_2, x_3) \qquad (2.24)$$

Conditions for Lyapunov function of a system

(1) $v(\chi_1, \chi_2, \chi_3)$ must be continuously differentiable

(2) $v(\chi_1, \chi_2, \chi_3)$ must be positive definite

(3) $v(\chi_1, \chi_2, \chi_3)$ must have its derivative along the orbits define by (2.24)

Theorem 1.4: (Derrick and Grossman, 1976)

let $v(\chi_1, \chi_2, \chi_3)$ be a Lyapunov function for the system (2.23), then if

I. $v(\chi_1, \chi_2, \chi_3)$ is negative semi definite, the origin is stable

II. $v(\chi_1, \chi_2, \chi_3)$ is negative definite, the origin is asymptotically stable

2.2.7 Bifurcation

Center manifold theory was used to evaluate a non-hyperbolic equilibrium's local stability (linearization matrix has at least one own value with zero real part) Carr (1981). Guckenheimer and Homes (1983), Wiggins (1990). We will describe a theory that can determine the local equilibrium of the non-hyperbolic balance and solve the problem of another balance being present (bifurcated from the non-hyperbolic stability). This theory is based on the idea of the general centre-manifold.

Let us consider a general system of ODEs with parameter φ:

$$\frac{dx}{dt} = f(x, \varphi), f: \Re^n \times \Re \to \Re^n, f \in C^2(\Re^n \times \Re) \qquad (2.25)$$

Without loss of generality, we assume that $x = 0$ is equilibrium for system (2.25) for all values of the parameter φ that is $f(0, \varphi) = 0$ for allφ.

Theorem 1.4: Assume:

A1: $A = D_x f(0,0) = \left(\frac{\partial f_i}{\partial x_j}(0,0)\right)$ is the linearization matrix of system (2.25) around equilibrium $x = 0$ with φ evaluated at 0. Zero is a simple eigenvalue of A and all other eigenvalues of A have negative real parts;

A2: Matrix A has a (nonnegative) right eigenvector w and a left eigenvector v corresponding to the zero eigenvalue.

Let $f_k$denote the k^{th}component of f,and

$$a = \sum_{k,i,j=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0) \tag{2.26}$$

$$b = \sum_{k,j=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \varphi_j}(0,0) \tag{2.27}$$

The local dynamics of system (2.25) around $x = 0$ are totally determined by a and b.

I. $a > 0, b > 0$,when $\varphi > 0$,with $|\varphi| << 1, x = 0$ is locally asymptotically stable and there exists a positive unstable equilibrium; when $0 > \varphi << 1, x = 0,$ is unstable and there exists a negative and locally asymptotically stable equilibrium;

II. $a < 0, b < 0$,when $\varphi < 0$,with$|\varphi| << 1, x = 0$ is unstable; when $0 > \varphi << 1, x = 0,$ is locally asymptotically stable and exists a positive and unstable equilibrium.

III. $a > 0, b > 0$,when $\varphi < 0,$ with $|\varphi| << 1, x = 0$ is unstable and there exists a locally asymptotically stable negative equilibrium; when $0 > \varphi << 1, x = 0,$ is stable and a positive unstable equilibrium appears;

IV. $a < 0, b < 0,$ when φ change from negative to positive, $x = 0$ changes its stability from stable to unstable. Correspondently, a negative unstable equilibrium becomes positive and locally asymptotically stable.

Proof:

Let $\xi^c$and ξ^c be the generalized eigenspaces of A for the zero eigenvalue and all other eigenvalues, respectively, it is follows from the center manifold theory that center manifold W^c is one dimensional and $\Re^n = \xi^c \otimes \xi^s$. Parameterize the center manifold by $c(t)$and decompose it into $\xi^c$and ξ^c, that is,

$$W = \{c(t)w + h(c, \varphi): v, h(c, \varphi) = 0, |c| \leq c_0, c(0) = 0\}, \quad (2.28)$$

Where $c(t) \in \xi^c$and $h(c, \varphi) \in \xi^c$. Because the center manifold is tangent to ξ^cat the origin, $h(c, \varphi)$is higher order term ($h(c, \varphi)$ has at least order 2). It also follows by the invariance of the center manifold under the flow that;

$$\frac{d}{dt}((c(t)w + h(c, \varphi)) = f(c(t)w + h(c, \varphi), \varphi), \quad (2.29)$$

Applying Taylor expansion to the right-hand side of equation (2.29) at (0,0) and noticing that $h(c,\varphi)$ is higher order, we obtain that

$$f(c(t)w + h(c,\varphi),\varphi) = f(0,0) + D_x f(0,0)((c(t)w + h(c,\varphi) + D_\varphi f(0,0)\varphi + \frac{1}{2}(I_n \otimes (cw + h(c,\varphi))^1)(D_{xx}^2 f(0,0))(c(t)w + h(c,\varphi)) + \varphi(D_{x\varphi}^2 f(0,0))(cw + h(c,\varphi)) + \frac{1}{2}\varphi^2(D_{\varphi\varphi}^2 f(0,0)) + \textit{higher order term}, \quad (2.30)$$

where$D_{x\varphi}^2$is the Hessian matrix; I_n is the identity matrix of order n; $\otimes$is the Kronecker product. Using

$$f(0,0) = D_x f(0,0)c(t)w = D_\varphi f(0,0) = D_{\varphi\varphi}^2 f(0,0) = 0 \quad (2.31)$$

and the fact that $ch(c,\varphi)$is of higher order, we simplify the above expansion for f as (higher order terms are dropped).

$$f(0,0) = (D_x f)h(c,\varphi) + \frac{c^2}{2}(I_n \otimes w')(D_{xx}^2 f)w + c\varphi(D_{x\varphi}^2)w \quad (2.32)$$

Multiplying both sides of equation (2.29) by v and using the fact that $v,h = 0$ and $vD_x f(0,0) = 0$,

we finally obtain the following equation for $c(t)$

$$\frac{dc}{dt} = \frac{c^2}{2}v(I_n \otimes w')D_{xx}^2 fw + c\varphi v D_{x\varphi}^2 fw \quad (2.33)$$

$$= \frac{c^2}{2}\sum_{k,i,j}^n v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j} + \sum_{kj}^n v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial x_\varphi} c\varphi \quad (2.34)$$

$$= \frac{q}{2}c^2 + b\varphi c \tag{2.35}$$

Namely,

$$\frac{dc}{dt} = \frac{a}{2}c^2 + b\varphi c \tag{2.36}$$

Obviously, at $\varphi = 0$ a transcritical bifurcation takes place in equation (2.36).

2.2.8 Pontryagin's Maximum Principle

In optimal control theory, Pontryagin's maximum principle is used to identify the optimum feasible control for moving a dynamical system from one state to another, particularly when state or input controls are constrained.

Theorem 1.5: The necessary conditions that $\left(x_0{}^*, u^*(t)\right)$ be an optimal initial condition and optimal control for the optimal control problem are the existence of a non-zero k-dimensional vector λ with $\lambda_1 \leq 0$ and an n-dimensional vector function $P(t)$ such that for $t \in [t_0, t_1]$:

(i) $P(t)' = -P(t)' f_x\left(t, x^*(t), u^*(t)\right)$; for $t \in (t_0, t_1)$ and $u \in U$

(ii) $P(t)'\left[f(t, x^*(t), u) - f\left(t, x^*(t), u^*(t)\right)\right] \leq 0$;

(iii) $P(t_1)' = \lambda' \phi_{x_1}(e)$;

(iv) $P(t_0)' = -\lambda' \phi_{x_0}(e)$;

(v) $P(t_1)'f\big(t_1, x^*(t_1), u^*(t_1)\big) = -\lambda'\phi_{t_1}(e)$;

(vi) $P(t_0)'f\big(t_0, x^*(t_0), u^*(t_0)\big) = \lambda'\phi_{t_0}(e)$;

If $f(t, x, u)$ has a continuous partial derivative $f_t(t, x, u)$, then the condition

(vii) $P(t)'f\big(t, x^*(t), u^*(t)\big) = \lambda'\phi_{t_0}\big(t_0, t_1, x^*(t_0), x^*(t_1)\big) +$

$\int_{t_0}^{t} P(s)'\, f_t\big(s, x^*(s), u^*(s)\big)ds$

holds for each $t \in [t_0, t_1]$.

The proof of theorem 1.5 can be found in (Fleming and Rishel, 1975)

2.2.9 Sensitivity Indices

The sensitivity of the reproduction number R_0 to each of the parameters, which measures initial disease transmission, is calculated using the approach of (Arriola and Hyman, 2005). Sensitive indices measure the relative change in state variable when the parameter changes. When the variable is a differentiable function of the parameter, the sensitivity index may be alternatively defined using partial derivatives. The forward sensitivity index with respect to each of the parameter used in the HBV models is presented below using the following formula

$$\hbar_{\ell}^{k} = \frac{\partial k}{\partial \ell}\frac{\ell}{k} \tag{2.37}$$

2.3 Gaps Identified in Literatures

Many researchers have worked on Hepatitis B Virus (HBV) and obtained good results. Some of the papers are reviewed in this section and the gaps identified which go a long way in helping to situate and establish the results emanating from this research.

Marchuk *et al.,* (1991) considered a statistical model of antiviral immune response and described a method of fitting the model to the data characterizing acute viral hepatitis B. The effect of HBsAg specific antibodies on the challenge of HBV; vaccination and challenge resistance using live hepatitis B virus; virus dose—relationships of incubation period were shown. The model's sensitivity analysis was evaluated and shown in terms of parameter variations. In their results, they obtained an estimate value region for stimulation rate constant against the established empirical approach where they made comparisons with the parameters gotten, thus creating an independent way to validate the parameters estimates.

Edmunds *et al.* (1996) investigated a deterministic, compartmental, mathematical model for the transmission dynamics of the hepatitis B virus (HBV) in a high-endemic country was identified. The model was used to preliminary analyze the potential effects of mass infant immunization for HBV epidemiology. It was pointed out in their results that HBV eradication can be accomplished by immunizing less than 70% of children, which is relatively low compared to other viral infections in infancy.

Williams *et al.,* (1996) considered a statistical model approach of the complex epidemiology of hepatitis B (HBV). Using a mathematical model of HBV transmission dynamics that can reflect universal infant and adolescent vaccination strategies and those targeting genito-urinary (GU) clinic attendants and infants born to infected mothers, a method for doing it was presented. Model structure, epidemiological support, and parameterization was also outlined. They pointed out in their results, the effect of various vaccine methods, the simulations exhibit non-linearities. For each approach used, the average number of carriers avoided per vaccine dose offers a measure of costs and benefits, varying temporarily throughout the programme and the extent of coverage of the vaccine. Screening before vaccination greatly increases payback per dose in bisexuals but not in heterosexuals; mass infant vaccination provides the lowest efficacy ratio and best after antenatal screening vaccination of children. Generally speaking, the coverage of vaccines yields lower payback per dose. The model offers a valuable framework for the cost and benefit evaluation of immunization programmes.

Wilson *et al.,* (1998) addressed the deterministic model of the potential appearance of the hepatitis B virus vaccine escape variant (HBV). The model identifies the main unknowns that decide this process: the protection offered by the current vaccines against unique variants of HBV; the infectiousness of these variants; and the current prevalence of variant infectious individuals (each factor relative to wild-type). By making assumptions about these unknowns, their results showed that even a highly contagious variant would still take decades to emerge under a vaccine program that affords little protection against the variant. It was then concluded that the current low variant prevalence is not evidence of cross-

reactivity or the current vaccines' infectiousness in the variants. Since any vaccine failure will be inconspicuous for decades, it may be reasonable to recommend vaccine changes now rather than later.

Zhao *et al.,* (2000) examined the dynamics, evaluation and transmission of mathematical model of HBV including a long-term effect of the vaccination program. The model was compartmented as a set of partial differential equations. Sero-survey data was used to estimate all parameters expressed in the model as a non-linear function of age and time since vaccination. In their findings, they discovered that the model suits well for sero-surveys both prior to and after vaccination. Also, the age-specific prevalence rates of HBV infection and HBV carriers for the observed and estimated agree with each other. According to their model, if all newborns are vaccinated according to the schedule, the rate of HBV carriage will decline sharply overtime to 0.2% in 70 years. By then, the ratio of chronic hepatitis B will be around 5%.

Ribiero *et. al.*, (2002) reviewed the state of the art in modelling and interpreting data obtained from patients treated with antiviral agents infected with the hepatitis B virus. They hope that their results will help formulate new therapies for antiviral and immune-modulating effects with increased understanding and quantitative tools and may even ultimately predict long-term patient responses based on viral kinetic studies.

Goldstein *et al.,* (2005) developed a mathematical model to measure the age-specific risk of contracting HBV infection, acute hepatitis B (illness and death), and progression to chronic infection with HBV. Deaths associated with HBV among chronically infected

individuals were estimated from the mortality curves for HBV-related cirrhosis and hepatocellular carcinoma (HCC) and corrected for background mortality. Their results pointed out the effect of hepatitis B vaccination determined from the effectiveness of the vaccine and the coverage of the vaccination sequence, with and without the first dose of vaccine given within 24 h after birth (i.e., birth dose) to avoid perinatal HBV infection. They concluded that on estimate, 620 000 people die from HBV-related causes worldwide in the year 2000: 580 000 (94%) from chronic infection-related cirrhosis and HCC and 40 000 (6%) from acute Hepatitis B. In the year, 2000 surviving birth cohort, the model predicted that 64.8 million would become HBV-infected without vaccination, and 1.4 million would die of HBV-related disease. Infections acquired in early childhood during the perinatal period (5 years of age) and >5 years of age accounted for 21%, 48%, and 31% of deaths, respectively. With 90% coverage and the first dose given at birth, they observed that routine infant vaccination against Hepatitis B will prevent 84% of global HBV-related deaths.

Wang and Wang, (2007) examined a mathematical model to simulate hepatitis B virus (HBV) infection with spatial dependency. Through the geometric singular perturbation process, the presence of moving waves was created. Numerical simulations have shown that the model supports travel profiles that are not monotonous. The influences on the minimum wave speed of different parameters were also discussed. Their result showed that if the diffusion coefficient of virus is small, we can obtain the minimal wave speed and also the numerical simulations show that the model has non-monotonic traveling waves.

Ciupe *et al.,* (2007) presented the fundamental model for the analysis of studies of HBV therapy performed in chronically infected patients. To research acute infection, they introduced additional models where immune responses presumably play an important role in deciding if the condition will be cleared or become chronic. They incrementally added complexity and clarified each step of the modelling process. They then validated the model against experimental data to assess how well the biological system is described and how useful its predictions are. They found, in particular, that a cell-mediated immune response plays an important role in controlling the virus after viral load peaks.

Long *et al.,* (2008) developed a mathematical model to explain how, based on Nowak's population dynamics model of immune responses to persistent viruses, the relationship between the hepatitis B virus (HBV) and the cellular immune response to the infection was established. There are two potential balance states in the model: full recovery, coexisting state of uninfected and contaminated hepatocytes. The stability state of each equilibrium point was discussed, with different parameter sets satisfying the various conditions used in the simulation. Indeed, their findings showed that the model could view the broad spectrum of infection clinical manifestations, including acute hepatitis, fulminant hepatitis, acute-turn-chronic hepatitis, acute-phase chronic hepatitis, recurrent hepatitis, and so on. In the underlying processes, immunomics and infectomics may both be involved. The model suggests that for HBV infection resolution, a rapid and vigorous CTL response is needed.

Lau *et al.,* (2007) investigated the mathematical model and effect of early viral load decline on virus-specific T-cell reactivity in 30 hepatitis B e antigen (HBeAg)-positive patients

with chronic hepatitis B who were randomized to receive adefovir dipivoxil (ADV) or emtricitabine (ADV/FTC) monotherapy. Their findings showed that the rate of loss of infected hepatocytes was higher in fast than in slow responders (P = 0.0007) and associated inversely with intrahepatic covalently closed circular HBV DNA pre-treatment levels. In rapid responders, the frequency of HBV core-specific CD4+ T-cells increased significantly, peaking between week 16 and 24, while in both subsets, the HBV surface-specific CD4+ T-cells increased. However, these increases in the reactivity of CD4+ T cells were temporary, and no growth was observed in HBV-specific CD8+ T cells. By week 48, just 3/30 (10 per cent) of patients had HBeAg seroconversion.

Gourley *et al.,* (2008) formulated and analyzed the global dynamics of a simple model of hepatitis B virus in terms of delay differential equations. Compared to the well-known simple virus model in the literature, the model has two major and novel characteristics. In particular, it uses the more practical standard feature of incidence and specifically introduces a time delay in developing viruses. As a result, the number of reproductive diseases no longer depends on the size of the patient's liver (number of initial healthy liver cells). Nature and component values of the endemic steady state for the model directly depended on the delay in time. Their findings showed that a globally attractive endemic equilibrium will occur in some biologically interesting limiting scenarios regardless of the time delay period.

Thornley *et al.,* (2008) examined a mathematical model of hepatitis B virus (HBV) transmission to forecast the potential prevalence of chronic hepatitis B (CHB) in the

Tongan population of New Zealand under various control strategies. Their result pointed that in the New Zealand Tongan population, most CHB was projected to plateau at 2% if coverage remained at current levels, which is insufficient to achieve long-term elimination of HBV as against 73% projected to be the crucial proportion of immunization coverage needed for virus elimination. It was not possible to measure the impact of HBV carriage screening and early disease management. Hence, they conclude that it is likely to reduce the population burden of HBV infection and accelerate elimination.

Xu and Ma, (2009) investigated a Hepatitis B virus (HBV) model with spatial diffusion and infection rate saturation response in which a distinct delay modelled the intracellular incubation period with respect to time. The local stability of both the infected steady-state and uninfected steady state was analyzed and explored by evaluating the corresponding characteristic equations. Their results showed that the uninfected steady state is asymptotically stable globally if the basic reproductive number is less than unity. If the basic reproductive number is greater than unity, appropriate conditions have been obtained by successively changing the combined lower-upper solution pairs for the global stability of the infected steady state.

Zou *et al.,* (2010) investigated a mathematical model to study the transmission dynamics and control of HBV taking into consideration HBV infection in China. The existence and stability of the equilibria were shown. The sensitivity analysis of the basic reproduction number was carried out. They thought that the optimal control strategy is a combination of

immunization of newborns, retroactive immunization of susceptible adults and reduction of contacts.

Wang *et al.*, (2010) implemented an improved HBV model with a standard incidence mechanism and cytokine-mediated 'cure' based on empirical evidence. They showed that infection-free equilibrium is globally asymptotically stable by carrying out a global analysis of the updated model and studying the stability of balance if the basic reproductive number of the virus is less than one and, on the other hand, the infection equilibrium is globally asymptotically stable if the basic reproductive number of the virus is greater than one. The research and data obtained from the model and other similar models could have a major effect on preventing hepatitis B virus mortality in the future.

Bhattacharyya and Ghosh (2010) studied the dynamics of a disease under the administration of a vaccine and antiviral drug where the disease transmits directly from the parents to the offspring (vertical transmission) and also by interaction with infectious individuals (horizontal transmission). They developed a 3D model with Susceptible-Infected-Recovered under vaccination for the susceptible and antiviral treatment of the infected. They considered a theoretical control approach to evaluate the cost-effectiveness of the control mechanism using the maximum theory of Pontryagin. Their findings showed that although vaccination decreases horizontal transmission to those susceptible, administering an antiviral drug to infected individuals reduces the probability of vertical transmission. Therefore, in managing the disease, which has vertical and horizontal communication, the vaccine and antiviral medicine play different roles.

Pang *et al.,* (2010) developed a model to examine the effects of vaccination and other HBV infection control steps. Many countries made some proposals (such as the free HBV vaccination program for all newborns in China) to control HBV transmission. The model has simple dynamic behavior that, with the basic reproduction number R_0<1, The model has a globally asymptotically stable disease-free equilibrium and, with R_0>1, a globally asymptotically stable endemic equilibrium. Their results show that vaccination is a very efficient measure of infection control.

Qesmi *et al.,* (2010) proposed a mathematical model of ordinary differential equations explaining the dynamics of the HBV/HCV and its interaction with both liver and blood cells. A single model was used to explain the infection of either virus; a single model was used because the dynamics in the host (liver infected) are identical. The transcritical and backward bifurcation method was used for the analysis. Their results pointed out that for the backward bifurcation to occurR_0<1, which has an important implication on drug therapy protocols, since it is helpful for control mechanisms and disease eradication.

Mann and Roberts (2011) provided a SECIR compartmental mathematical model for HBV transmission using local data on infection incidence and vaccine coverage, dividing the population into age groups. Their result estimated the basic reproduction number, R_0, to be 1.53 which was dramatically reduced to below one by vaccination campaign. However, the population appears to have a significant number of carriers operating as a source of infection.

Pang *et al.,* (2012) studied the dynamical behavior of a hepatitis virus model with CTL immune responses. Analyzing the model, they showed that if the basic reproductive ratio of the virus is less than one, and the virus free equilibrium is locally asymptotically stable, if the basic reproductive ratio is greater than one, the endemic equilibrium is globally asymptotically stable. Their results showed that the mechanism is uniformly persistent when the basic reproductive ratio is greater than one, meaning that the virus is endemic. Mathematical research and computational simulations indicate that CTL immune responses play a critical role in disease eradication.

Hattaf *et al.,* (2012) investigated the dynamical behavior of a virus dynamics model, focusing on general incidence rate and cure rate. Their result pointed that if the basic reproduction number $R_0 <1$, then the virus remains in the host but the infection becomes endemic if $R_0> 1$. The disease dies out and the virus is cleared if the basic reproduction number $R_0 \leq 1$.

Zhang and Zhou (2012) formulated a mathematical model to describe the spread of hepatitis B. They analyzed equilibrium stability and disease persistence. Their findings showed that the basic reproductive number q0 completely determines the model's dynamics. The disease-free balance, if $q0 < 1$, is globally stable. The disease-free balance is unstable when it is $q0 > 1$, and the disease is uniformly persistent. In addition, under certain conditions, it was shown that the endemic equilibrium is globally attractive. The model was applied in China to HBV transmission. Based on the available HBV epidemic

data in China, the parameter values of the model was estimated. The simulation results match the HBV epidemic data in China approximately.

Muhammad *et al.,* (2013) presented a mathematical model with the characteristics of HBV virus transmission. In the model, they analyzed the impact of immigrants to investigate the effect of immigrants on the host population. First, the fundamental threshold quantity R_0 and the local asymptotic stability of disease-free balance and endemic equilibrium were identified. The global stability of disease-free and endemic equilibria was also discovered. Their results emphasized the need for short stay immigrants and students to be tested to minimize the number of immigrants with illness.

Okamoto (2013) created a formula to predict the risk of infection by needle/syringe sharing in mass vaccination. The procedure was presented in a logarithmic graph allowing users to estimate how many people would be infected if how many times under some likelihood of infection a needle/syringe is exchanged by how many individuals. They then applied the formula to the historical data from mass tuberculin skin tests (TSTs) and BCG vaccination, which calculated the best estimate of how much needle/syringe sharing was done in different birth cohorts. Their results predicted the prevalence of HBV carriers, 0.65 per cent at birth via vertical transmission, more than doubled in 1995 (1.46 per cent) through horizontal information for the oldest generation born between 1951 and 1955. Suppose the risk of contamination is assumed to be 10 per cent by needle/syringe sharing. In that case, it is theoretically possible that an average of five or more individuals shared a needle/syringe four times in 1995 to reach the prevalence of HBV carriers. Nevertheless,

needle/syringe sharing effects were marginal for the youngest generation born between 1981 and 1985 because the later majority of HBV carriers was lower than the prevalence at birth.

Adu *et al.,* (2014) used the SIR model to predict the prevalence and incidence of Hepatitis B. The analysis consisted of two parts. The distribution of HBV in the district of Bosomtwe, followed by the modelling of HB with vaccination in the community, was clarified by a SIR model without immunization. There are two equilibrium states in the model: the disease-free and endemic equilibrium states, respectively. After that, they addressed the stability condition of each point of equilibrium. Their results pointed out that whenever the transmission parameter value was increased, $R_0 > 1$, but when the value is reduced, $R_0 < 1$. The combination of increasing vaccination of newborns and immunization of susceptible adults helps to reduce HB prevalence in Bosomtwe District.

Kamyad *et al.,* (2014) investigated the dynamics of hepatitis B virus (HBV) infection regulated by vaccination and treatment. Initially, for both vaccination and treatment, they found constant tests. In continuous controls, they studied the nature and stability of the model's disease-free and endemic steady-state solutions by deciding the basic reproduction number. Next, to minimize both the number of contagious people and the associated costs, they took the controls and formulated the required optimal control problem and obtained the optimal control strategy. Their findings show that the best way to monitor hepatitis B virus infection is to incorporate vaccination and treatment optimally.

Hattaf and Yousfi (2015) developed a hepatitis B virus (HBV) model with spatial diffusion, general incidence rate and time delays subject to homogeneous Neumann boundary conditions. Using the linearization method and building sufficient Lyapunov functionals, they analyzed the stability of the disease-free equilibrium and the chronic infection equilibrium. Their results showed R0 becomes less than one when all fixed and delay parameters are large which shows that delay play a crucial role in the eradication of virus from the liver.

Liang *et al.,* (2015) evaluated the independent effect of newborn hepatitis vaccination on reducing HBV prevalence in China since its implementation in 1992-2006. According to the national serosurvey in 1992, they compared the simulated results with the model's initial conditions. Their result pointed that newborn vaccination could impact HBV transmission in the population born before 1992 indirectly by its herd immunity effect, but the contribution was very limited.

Owolabi (2016) considered a multi-components nonlinear fractional-in-space reaction-diffusion equations, consisting of an enhanced deterministic model describing the spread of hepatitis B virus disease in high-end areas. Their results showed that combination of successful treatment and vaccination is strongly recommended as a good control measure, which is critical for tracking the effectiveness of HBV disease control by carefully selecting parameters.

Olayinka *et al.,* (2016) studied to determine the prevalence, HBV spread, and infection-related factors in a stable population in Nigeria. They performed a cross-sectional analysis

using a multistage sampling technique among the general population. Data on demographic, social, and behavioral variables were gathered using HBV seromarker-tested questionnaires and blood samples. There were descriptive, bivariate, and multivariate studies performed. They found that the prevalence of infection with hepatitis B was 12.2% (confidence interval [CI]= 10.3–14.5). About half of the participants, 527 (54.6%), had evidence of prior HBV exposure, while 306 (31.7%) had no serological evidence of infection or vaccination. Just 76 (7.9 per cent) participants displayed serological evidence of vaccine immunity to HBV. Dental care outside the health facility (odds ratios [OR] = 3.4, 95 percent CI = 1.52-7.70), local circumcision (OR = 1.73, 95 percent CI = 1.17-2.57), and uvulectomy (OR = 1.65, 95 percent = 1.06-2.57) were factors associated with testing positive for HBV infection. Only dental procedures outside the health facility remained relevant with logistic regression (adjusted OR = 3.32, 95 per cent CI = 1.38-7.97). This first national hepatitis B seroprevalence survey outlines Nigeria's epidemiology and high prevalence of HBV infection and highlights the need for improved HBV vaccination.

Ikobah *et al.,* (2016) conducted a cross-sectional analytical study using the multistage sampling technique in July 2014 to select 749 children from six secondary schools in Calabar, Cross River State, Nigeria. The Cross River State Medical Ethical Committee received ethical approval. Blood samples were obtained using rapid chromatographic immunoassays with test kits from ABON (China) with sensitivity, specificity and accuracy of >99 per cent, 97 per cent and 98.5 per cent, respectively, for the qualitative detection of HBsAg. The data were analyzed using version 20.2 of SPSS. Their result showed that nine of the749 students screened were positive for HBsAg giving an overall prevalence of 1.2

per cent. For males and 1.8 per cent for females, the sex-specific majority was 0.8 per cent. Age was the predictor of hepatitis B infection after multivariate analysis (OR 3.92; 95 per cent CI 1.22-12.63; p-value 0.02). The incidence was poor for infection with HBV. The implementation of the vaccine is justifiable because of the public health value of the virus, considering the low prevalence.

Fatehi *et al.,* (2018) proposed a new comprehensive mathematical model for hepatitis B immune response dynamics that considers the contributions of innate and adaptive immune responses and cytokines. To identify parameter regions where the model exhibits clearance of infection, maintenance of a chronic condition, or periodic oscillations, stability analysis of different steady states was carried out. Their results showed the effects of treatment with nucleoside analogues and interferon and determined the critical efficacy of the treatment.

Emerenini and Inyama, (2018) studied the Hepatitis B transmission dynamics, formulating a mathematical model that considers the various classes of persons, including the immunized, prone, latent, contaminated and recovered levels. The role of newborn babies' vaccination against hepatitis B and the care of people who are both latently and actively infected in controlling the spread are factored into the model. The model was based on the model of the regular SEIR. The disease-free equilibrium state of the model was established, and its stability analyzed Using the Routh-Hurwitz theorem. Their results show that effort can be made to eradicate Hepatitis B. Also, to ensure that the amount of the rate of recovery of the latent class, the rate at which latently infected individuals become actively infected and the rate of natural death has a lower bound.

Zhang and Zhang (2018) formulated a hepatitis B virus model for newborn vaccine and treatment prevention strategies. The model was used to simulate annual new infected hepatitis B cases in China from 2004 to 2016 using the least-square. In addition, the classical optimal theory studied the optimal control problem with newborn vaccine and care appearing as time functions. Their results show that the simple reproductive number R_0 determines the disease's equilibrium and persistence stability.

Khan *et al.*,(2018) proposed an epidemic model for hepatitis B virus transmission and the classification of various stages of infection and hospitalized groups. The model was formulated, and its basic mathematical properties, such as life, positivity, and biological viability, were analyzed. They found the basic reproductive number of the model by exploiting the next generation matrix method. To demonstrate the effect of different parameters on the transmission of the disease, they carried out a sensitivity analysis. The stability of the equilibrium of the model was investigated in terms of the basic number of reproductions. They also obtained the strength of their model. Their results showed that the hospitalization and vaccination are one of the effective control mechanisms to control the hepatitis B infection.

Anmole Razzaq, (2019) showed that numerical modelling is a tool to appreciate how the syndrome pushes and in what stately way. He studied HBV dynamics numerically and then framed an entirely constant Non-Standard Finite Difference (NSFD) framework for an HBV mathematical model. He introduces a numerical array that dynamically identifies and contains the solution's positivity, which is one of the key requirements when modelling a

prevalent contagious. In their findings, the showed that the utility of the proposed Non-Standard Finite Alteration scheme is demonstrated by the contrast between the revolutionary Non-Standard Finite Alteration structure, the Euler method and the Runge-Kutta system of order four (RK-4). For any time steps used, the NSFD scheme shows convergence to the exact equilibrium facts of the model, but for large time steps, Euler and RK-4 fail.

Mpeshe and Nyerere, (2019) formulated and analyzed a simple deterministic model to determine the dynamics and control of the disease using ordinary differential equations. To evaluate the impact of initial disease transmission, the simple replication number R_0 was selected, and they performed stability analysis. Their results showed that concerning the value of R_0, both the disease-free equilibrium and the endemic equilibrium are globally stable. Also, R_0 strongly impairs chronic carriers' vertical transmission and recovery rate after screening and treatment. Effective mechanisms are therefore required to minimize vertical transmission and effective screening of individuals to treat those that may be found infected. Further findings from the numerical analysis indicate that it is persistent when the disease is introduced into the population, and thus successful control measures are required.

Khan *et al.,* (2019) developed an epidemic mathematical model for hepatitis B contagious disease. They showed the model's nature, positivity, and biological viability. They found the threshold quantity of the model. Also, they analyzed the sensitivity indices to demonstrate the influence of different parameters on the propagation of the hepatitis B virus. They considered stability conditions to conduct the stability analysis by using the

linear stability method. They used the theory of the central manifold to discuss the existence of the proposed model's backward bifurcation. Their results showed that migration, vaccination, and hospitalization are the effective measures for the controlling the spread of the virus.

Ullah *et al.,* (2019) developed a mathematical model with hospitalized population to investigate the dynamics of HBV infection. Their results demonstrated the viability of the control strategy by providing simulations for both with and without control models.

Danane *et al.,* (2020) presented and investigated a fractional differential mathematical model explaining the dynamics of hepatitis B viral infection with DNA-containing capsids, liver hepatocytes and humoral immune response. Antibodies have become the humoral immunity, and the key function of these antibodies is to attack free viruses. A memory term described by a fractional derivative was applied to each equation of their proposed model to explain the time required for the interaction between biological liver cells and viral particles and the time needed to activate the humoral immune response. All alternatives with non-negative initial conditions are positive and rounded, which is biologically compatible. The global stability of all equilibria by constructing some appropriate Lyapunov functionals was performed, depending on the baseline reproduction number and the reproduction number of the antibody immune response. The results showed that the order of the fractional derivative does not affect the stability of the three equilibria.

Gahamanyi *et al.,* (2021) used the fuzzy logic strategy to solve an optimal control problem for the hepatitis B virus (HBV). Their numerical results were compared with those obtained

using the direct method to see if this numerical method is effective. They considered a patient who has been on treatment for 12 months and two drugs are used as controls. The response of HBV to drugs, in particular, can be modeled, and a feedback can be approximated by solving a linear quadratic problem. The drugs lower the risk of HBV infection. Furthermore, the results of both numerical methods agree well with experimental data, proving the efficacy of the fuzzy logic strategy in solving optimal problems.

Zada et al., (2021) presented a dynamic of the Hepatitis B virus, which can be controlled through education (awareness), vaccination, and treatment. They implemented constant controls in terms of treatment, vaccination, and public awareness campaigns (awareness). They used time as a control and formulated an appropriate optimal control problem, acquiring an optimal control strategy in order to reduce the number of infected humans and the costs associated with infection.

CHAPTER THREE

3.0 METHODOLOGY

Mathematical models are developed and analyzed in this section. These models are in three (3) cases, with solutions for each case shown.

3.1 Mathematical Formulation, Analysis and Method of Solution for HBV Model Case 1

Keeping the HBV transmission axioms in mind, Khan *et al.,* (2019) postulated a mathematical model taking into account the horizontal transmission and the vertical transmission as the primary source of transmission of HBV, the movement of susceptible, latent, and acute populations, vaccination of susceptible populations, and hospitalization of acute and chronic populations. Individuals who were susceptible, latent, acute, chronic carriers and hospitalized as well as those who had been vaccinated were all divided into different groups for this purpose. The model is presented below:

$$\left.\begin{aligned}
S'(t) &= \mu\omega(1-\nu C(t)) + \psi V(t) - (\beta A(t) + \gamma\beta C(t) + \gamma_3 + \mu_0 + \delta_1)S(t)\\
L'(t) &= (\beta A(t) + \gamma\beta C(t))S(t) - (\sigma + \mu_0 + \delta_1)L(t)\\
A'(t) &= \sigma L(t) - (\vartheta_1 + \gamma_1 + \mu_0 + \delta_1)A(t)\\
C'(t) &= q\gamma_1 A(t) - (\vartheta_2 + \gamma_2 + \mu_0 + \mu_1 - \mu\omega\nu)C(t)\\
H'(t) &= \vartheta_2 C(t) + \vartheta_1 A(t) - (\vartheta_3 + \mu_0 + \mu_2)H(t)\\
R'(t) &= \gamma_2 C(t) + (1-q)\gamma_1 A(t) + \vartheta_3 H(t) - \mu_0 R(t)\\
V'(t) &= \mu(1-\omega) + \gamma_3 S(t) - (\psi + \mu_0)V(t).
\end{aligned}\right\} \quad (3.1)$$

According to Pan and Zhang (2005), children born of carrier mothers with failed vaccination can be classified into two categories; the children born that can be acutely infected and the children born that can be chronically infected with HBV. These two categories were neglected by Khan *et al.*, (2019).

To proceed further, we extend the work of Khan *et al.,* (2019) by implementing the following assumptions on our model;

At time t, the total population denoted by $N(t)$ is categorized into the seven subgroups corresponding to different epidemiological status.

$$N(t) = S(t) + L(t) + A(t) + C(t) + H(t) + R(t) + V(t) \quad (3.2)$$

where $S(t)$ represent the susceptible population, $L(t)$ is the Latent populace, $A(t)$ is the populace who have an acute HBV infection, $C(t)$ is the populace who are chronically infected, $H(t)$ are the hospitalized individuals while $R(t)$ are removed class and $V(t)$ are the individual that receive vaccination. The schematic diagram of the epidemiology of Hepatitis B virus is presented in Figure 3.1. The different compartments are used to represent the various virus phases and the arrows indicates the progression of various individuals from one phase to the other. At time t, it is assumed that the susceptible individual S, are recruited into the population at a constant rate $\mu\omega(1 - \nu C(t))$ where μ is the new born rate, ω is the proportion of birth without effective vaccination while ν is the ratio of parentally infected population that progress to chronic state. The constant natural mortality rate for individuals in the population is, μ_0. HBV infected individuals

($C(t)\ and\ H(t)$) have an additional death rate due to HBV, $\mu_1\ and\ \mu_2$ respectively. It is assumed that infected individuals who are hospitalized are not infectious. Susceptible Individual S, may contract the virus if he or she comes into contact with other HBV-infected people in $A(t) and\ C(t)$ population at the rate $\beta(A + \gamma C)$ (The force of infection caused by HBV), where βA and βC denotes the effective contact rates for HBV infection at the acute and chronic compartment respectively and the modification parameter $\gamma > 1$ accounts for a higher risk of HBV acquisition at the chronic phase. The parameter δ_1 in the $S(t),\ L(t),\ A(t)$ represent the migration rate of individual while ψ is the Induced immunity rate with waning vaccine.

Individuals in the latent population becomes acute carriers at a rate σ, individuals at the acute stage are moved to chronic stage at a rate γ_1 while γ_2 is the rate by which chronic carriers migrate to the recovered state. Individuals who are at the acute and chronic phase get hospitalized at a rate $\vartheta_1\ and\ \vartheta_2$ respectively while ϑ_3 is the rate of recovery of hospitalized individuals. A percentage of the new born receive effective vaccination at a rate $\mu(1 - \omega)$. q is the rate at which people who have recovered from the virus fail in the acute class. The parameters $r\ and\ b$ are the rate of children born of infected mother without active vaccine that goes to the acute and chronic compartments respectively.

With these assumptions, this schematic diagram is developed:

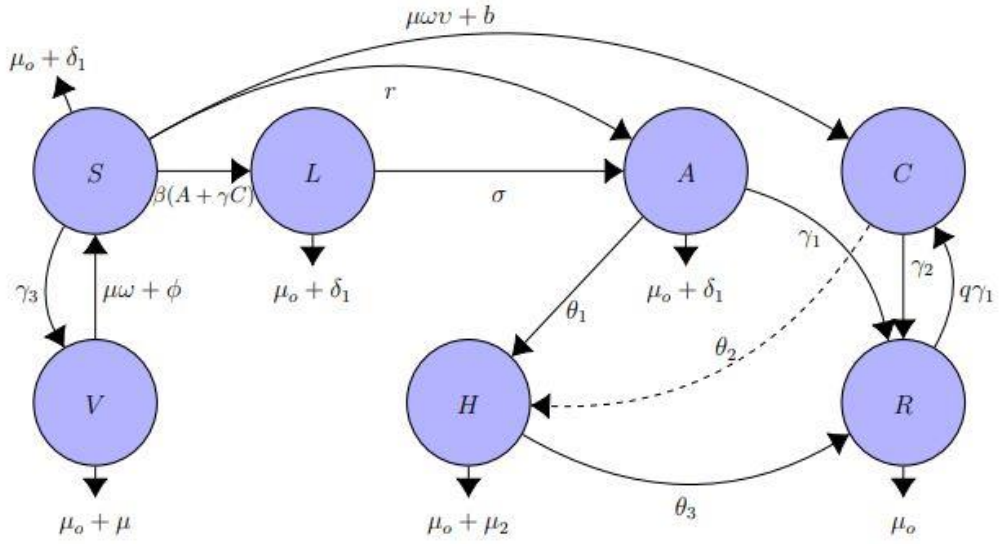

Figure 3.1: Flow diagram for HBV model case 1

$$S'(t) = \mu\omega(1 - vC(t)) + \varphi V(t) - (\beta(A(t) + \gamma C(t)) + \gamma_3 + \mu_0 + \delta_1)S(t) - rA(t) - bC(t)$$

$$\left.\begin{aligned}
L'(t) &= \beta(A(t) + \gamma C(t))S(t) - (\sigma + \mu_0 + \delta_1)L(t)\\
A'(t) &= \sigma L(t) - (\vartheta_1 + \gamma_1 + \mu_0 + \delta_1 - r)A(t)\\
C'(t) &= q\gamma_1 A(t) - (\vartheta_2 + \gamma_2 + \mu_0 + \mu_1 - \mu\omega v - b)C(t)\\
H'(t) &= \vartheta_2 C(t) + \vartheta_1 A(t) - (\vartheta_3 + \mu_0 + \mu_2)H(t)\\
R'(t) &= \gamma_2 C(t) + (1 - q)\gamma_1 A(t) + \vartheta_3 H(t) - \mu_0 R(t)\\
V'(t) &= \mu(1 - \omega) + \gamma_3 S(t) - (\varphi + \mu_0)V(t).
\end{aligned}\right\} \quad (3.3)$$

3.1.1 Positivity and Boundedness of Solution

To be epidemiologically meaningful, the system of equations (3.3) must demonstrate that all solutions with non-negative initial conditions will remain non-negative. The proof of

the positivity and boundedness of the system of equations in system (3.3) follows from the following Lemma 3.1:

Lemma 3.1: The parameters' initial values are

$\{S(0) \geq 0, L(0) \geq 0, A(0) \geq 0, C(0) \geq 0, H(0) \geq 0, T(0) \geq 0, R(0) \geq 0, N(0) \geq 0\} \in \Phi$

Then, for all $t \geq 0$, the solution of the model$\{S(t), L(t), A(t), C(t), H(t), T(t), R(t), N(t)\}$ is positive.

Proof: Taking the first equation in (3.3) to consideration,

$\frac{dS}{dt} = \mu\omega(1 - vC) + \varphi V - (\beta(A + \gamma C) + \gamma_3 + \mu_0 + \delta_1)S - rA - bC,$

then,

$\frac{dS}{dt} \geq -(\beta(A + \gamma C) + \gamma_3 + \mu_0 + \delta_1)S,$

$\int \frac{1}{S} dS \geq \int -(\beta(A + \gamma C) + \gamma_3 + \mu_0 + \delta_1)\, dt$

$S \geq S_0 e^{-(\beta(A+\gamma C)+\gamma_3+\mu_0+\delta_1)t} \geq 0.$

Hence, $S \geq 0$.

In relation to the second equation in (3.3),

$\frac{dL}{dt} = \beta(A + \gamma C)S - (\sigma + \mu_0 + \delta_1)L,$

then,

$$\frac{dL}{dt} \geq -(\sigma + \mu_0 + \delta_1)L,$$

$$\int \frac{1}{L} dL \geq \int -(\sigma + \mu_0 + \delta_1)\, dt,$$

$$L \geq L_0 e^{-(\sigma+\mu_0+\delta_1)t} \geq 0.$$

Hence, $L \geq 0$.

In relation to the third equation in (3.3),

$\frac{dA}{dt} = \sigma L - (\vartheta_1 + \gamma_1 + \mu_0 + \delta_1 - r)A,$

so that,

$\frac{dA}{dt} \geq -(\vartheta_1 + \gamma_1 + \mu_0 + \delta_1 - r)A,$

$$\int \frac{1}{A} dA \geq \int -(\vartheta_1 + \gamma_1 + \mu_0 + \delta_1 - r_1)\, dt,$$

$$A \geq A_0 e^{-(\vartheta_1+\gamma_1+\mu_0+\delta_1-r)t} \geq 0.$$

Hence, $A \geq 0$.

With respect to the fourth equation in (3.3),

$$\frac{dC}{dt} = q\gamma_1 A - (\vartheta_2 + \gamma_2 + \mu_0 + \mu_1 - \mu\omega v - b)C,$$

then,

$$\frac{dC}{dt} \geq -(\vartheta_2 + \gamma_2 + \mu_0 + \mu_1 - \mu\omega v - b)C,$$

$$\int \frac{1}{C} dC \geq \int -(\vartheta_2 + \gamma_2 + \mu_0 + \mu_1 - \mu\omega v - b)\, dt,$$

$$C \geq C_0 e^{-(\vartheta_2+\gamma_2+\mu_0+\mu_1-\mu\omega v-b)t} \geq 0.$$

Hence, $C \geq 0$.

Following from the fifth equation in (3.3),

$$\frac{\mathrm{dH}}{dt} = \vartheta_2 C(t) + \vartheta_1 A(t) - (\vartheta_3 + \mu_0 + \mu_2)H(t),$$

then,

$$\frac{dH}{dt} \geq -(\vartheta_3 + \mu_0 + \mu_2)H,$$

$$\int \frac{1}{H} dH \geq \int -(\vartheta_3 + \mu_0 + \mu_2)\, dt,$$

$$H \geq H_0 e^{-(\vartheta_3+\mu_0+\mu_2)t} \geq 0.$$

Hence, $H \geq 0$.

From the sixth equation in (3.3),

$$\frac{\mathrm{dR}}{\mathrm{dt}} = \gamma_2 C(t) + (1-q)\gamma_1 A(t) + \vartheta_3 H(t) - \mu_0 R(t),$$

then,

$$\frac{dR}{dt} \geq -\mu_0 R,$$

$$\int \frac{1}{R} dR \geq \int -\mu_0 \, dt,$$

$$R \geq R_0 e^{-(\mu_0)t} \geq 0.$$

Hence, $R \geq 0$.

with respect to the seventh equation in (3.3),

$$\frac{\mathrm{dV}}{\mathrm{dt}} = \mu(1-\omega) + \gamma_3 S(t) - (\varphi + \mu_0)V(t),$$

$$\frac{dV}{dt} \geq -(\varphi + \mu_0)V,$$

$$\int \frac{1}{V} dV \geq \int -(\varphi + \mu_0) \, dt,$$

$$V \geq V_0 e^{-(\varphi+\mu_0)t} \geq 0.$$

Hence, $V \geq 0$.

Clearly, the above state variables are positive on bounding plane $\mathbb{R}_+^7$.

For the boundedness the following calculation follows:

$$N(t) = S(t) + L(t) + A(t) + C(t) + H(t) + R(t) + V(t)$$

$$N' = S' + L' + A' + C' + H' + R' + V'$$

$$N' = \mu\omega(1 - vC) + \varphi V - (\beta(A + \gamma C) + \gamma_3 + \mu_0 + \delta_1)S - rA - bC + \beta(A + \gamma C)S - (\sigma + \mu_0 + \delta_1)L + \sigma L - (\vartheta_1 + \gamma_1 + \mu_0 + \delta_1 - r)A + q\gamma_1 A - (\vartheta_2 + \gamma_2 + \mu_0 + \mu_1 - \mu\omega v - b)C + \vartheta_2 C + \vartheta_1 A - (\vartheta_3 + \mu_0 + \mu_2)H + \gamma_2 C + (1 - q)\gamma_1 A + \vartheta_3 H - \mu_0 R + \mu(1 - \omega) + \gamma_3 S - (\varphi + \mu_0)V \quad (3.4)$$

Simplifying (3.4) gives:

$$N' = \mu - \mu_0[S + L + A + C + H + R + V] - \delta_1[S + L + A] - \mu_1 C - \mu_2 H \quad (3.5)$$

$$N' + \mu_0 N = \mu - \delta_1[S + L + A] - \mu_1 C - \mu_2 H \quad (3.6)$$

$$N' + \mu_0 N \leq \mu \quad (3.7)$$

Integrating (3.7) gives:

$$N' \leq \frac{\mu}{\mu_0} + ke^{-\mu_0 t}$$

$$\max_{\lim_{n\to\infty}} N \leq \lim_{n\to\infty}\left(\frac{\mu}{\mu_0} + ke^{-\mu_0 t}\right) \leq \frac{\mu}{\mu_0}$$

As a result, the model system's solutions (3.3) are positive and bounded in the region

$$\mathcal{T} = \{(S + L + A + C + H + R + V)\} \in \mathbb{R}_+^7 : S + L + A + C + H + R + V \leq \frac{\mu}{\mu_0}$$

It follows from Lemma 3.1 that it is sufficient to take into account the system dynamics (3.3) and the model is said to be epidemiologically well-posed.

3.1.2 Equilibrium Points and Reproduction Number

The system of equation in (3.3) has a disease-free equilibrium, which is given by:

$$E_o = \left[\frac{\mu(\mu_0\omega+\varphi)}{\varphi\delta_1+\varphi\mu_0+\delta_1\mu_0+\gamma_3\mu_0+{\mu_0}^2}, 0,0,0,0,0, \frac{\mu(\mu_0+\gamma_3+\delta_1-\omega\delta_1-\omega\mu_0)}{\varphi\delta_1+\varphi\mu_0+\delta_1\mu_0+\gamma_3\mu_0+{\mu_0}^2}\right] \tag{3.8}$$

The endemic steady states are calculated here which is done by setting system of equation in (3.3) to zero and setting $S = S^*, L = L^*, A = A^*, C = C^*, H = H^*, R = R^*$ and $V = V^*$ so that,

$$0 = \mu\omega(1 - vC(t)) + \varphi V^*(t) - (\beta(A^*(t) + \gamma C^*(t)) + \gamma_3 + \mu_0 + \delta_1)S^*(t) - rA^*(t) - bC^*(t)$$

$$\left.\begin{aligned}
0 &= \beta(A^*(t) + \gamma C^*(t))S^*(t) - (\sigma + \mu_0 + \delta_1)L^*(t)\\
0 &= \sigma L^*(t) - (\vartheta_1 + \gamma_1 + \mu_0 + \delta_1 - r)A^*(t)\\
0 &= q\gamma_1 A^*(t) - (\vartheta_2 + \gamma_2 + \mu_0 + \mu_1 - \mu\omega v - b)C^*(t)\\
0 &= \vartheta_2 C^*(t) + \vartheta_1 A^*(t) - (\vartheta_3 + \mu_0 + \mu_2)H^*(t)\\
0 &= \gamma_2 C^*(t) + (1 - q)\gamma_1 A^*(t) + \vartheta_3 H^*(t) - \mu_0 R^*(t)\\
0 &= \mu(1 - \omega) + \gamma_3 S^*(t) - (\varphi + \mu_0)V^*(t)
\end{aligned}\right\} \tag{3.9}$$

and by solving gives:

$$
\begin{aligned}
S^*(t) &= \frac{B_1 B_2 B_3}{\beta\sigma(\gamma q\gamma_1 + B_3)} \\
L^{*(}(t) &= \frac{-B_3 B_2(-((B_5-\varphi)\omega+\varphi)\mu S^* + (-\varphi\gamma_3 + B_0 B_5)}{B_5 S^*\big(rB_3 + \gamma_1 q(\mu\omega v + b)\big)\sigma} \\
A^*(t) &= -\frac{q\sigma\gamma_1\gamma\big((B_5-\varphi)\omega+\varphi\big)\beta\mu B_3 L^*}{(B_3 B_2)(\gamma q\gamma_1 + B_3)} \\
C^*(t) &= -\frac{q\gamma_1(\gamma q\gamma_1 + B_3)A^*}{q\sigma\gamma_1\gamma\big((B_5-\varphi)\omega+\varphi\big)\beta\mu B_3} \\
H^*(t) &= -\frac{(q\gamma_1\vartheta_2 + B_3\vartheta_1)A^*}{B_4} \\
R^*(t) &= -\frac{\big((B_4(_{q\text{-}1})B_3 - (B_4\gamma_2 + \vartheta_2\vartheta_3)q)\gamma_{1\text{-}B3}\vartheta_1\vartheta_3\big)H^*}{(q\gamma_1\vartheta_2 + B_3\vartheta_1)\mu_0} \\
V^*(t) &= -\frac{(\beta\mu(\omega_{\text{-}1})(\gamma q\gamma_1 + B_3)\sigma)S^*}{B_5}.
\end{aligned}
\tag{3.10}
$$

Where,

$B_1 = \sigma + \mu_0 + \delta_1, B_2 = \vartheta_1 + \gamma_1 + \mu_0 + \delta_1 - r, B_3 = \vartheta_2 + \gamma_2 + \mu_0 + \mu_1 - \mu\omega v -$

$b, B_{4=} = \vartheta_3 + \mu_0 + \mu_2, B_5 = \varphi + \mu_0$

The basic reproduction number was computed via the next generation matrix approach. To determine the next generation matrix for the model considered in case 1, the following are considered:

1. The number of ways that new infections can arise or be created

2. The number of ways that infections can be transferred between compartments

Thus, the latent L, acute A, chronic C compartments which are the infectious class of system (3.3) are considered i.e.

$$L^{'}(t) = (\beta A(t) + \gamma\beta C(t))S(t) - (\sigma + \mu_0 + \delta_1)L(t)$$

$$A^{'}(t) = \sigma L(t) - (\vartheta_1 + \gamma_1 + \mu_0 + \delta_1 - r)A(t)$$

$$C^{'}(t) = q\gamma_1 A(t) - (\vartheta_2 + \gamma_2 + \mu_0 + \mu_1 - \mu\omega v - b)C(t)$$

Then F_i and V_i are computed as follows:

$$F = \begin{pmatrix} \beta(A + \gamma C)S \\ 0 \\ 0 \end{pmatrix}$$

$$V_i^+ = \begin{pmatrix} 0 \\ \sigma L \\ q\gamma_1 A \end{pmatrix}, \qquad V_i^- = \begin{pmatrix} (\sigma + \mu_0 + \delta_1)L \\ (\vartheta_1 + \gamma_1 + \mu_0 + \delta_1 - r)A \\ (\vartheta_2 + \gamma_2 + \mu_0 + \mu_1 - \mu\omega v - b)C \end{pmatrix}$$

$$V = V_i^- + V_i^+ = \begin{pmatrix} (\sigma + \mu_0 + \delta_1)L \\ (\vartheta_1 + \gamma_1 + \mu_0 + \delta_1)A - \sigma L \\ (\vartheta_2 + \gamma_2 + \mu_0 + \mu_1 - \mu\omega v)C - q\gamma_1 A \end{pmatrix}$$

The variational matrix of F and V

$$F = \begin{pmatrix} \frac{\partial f_1}{\partial L} & \frac{\partial f_1}{\partial A} & \frac{\partial f_1}{\partial C} \\ \frac{\partial f_2}{\partial L} & \frac{\partial f_2}{\partial A} & \frac{\partial f_2}{\partial C} \\ \frac{\partial f_3}{\partial L} & \frac{\partial f_3}{\partial A} & \frac{\partial f_3}{\partial C} \end{pmatrix} = \begin{pmatrix} 0 & \beta S & \beta\gamma S \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}$$

$$V = \begin{pmatrix} \frac{\partial v_1}{\partial L} & \frac{\partial v_1}{\partial A} & \frac{\partial v_1}{\partial C} \\ \frac{\partial v_2}{\partial L} & \frac{\partial v_2}{\partial A} & \frac{\partial v_2}{\partial C} \\ \frac{\partial v_3}{\partial L} & \frac{\partial v_3}{\partial A} & \frac{\partial v_3}{\partial C} \end{pmatrix} = \begin{pmatrix} M_1 & 0 & 0 \\ -\sigma & M_2 & 0 \\ 0 & -q\gamma_1 & M_3 \end{pmatrix}$$

$$V^{-1} = \begin{pmatrix} \frac{1}{M_1} & 0 & 0 \\ \frac{-\sigma}{M_1} & \frac{1}{M_2} & 0 \\ 0 & \frac{-q\gamma_1}{(M_3)(M_2)} & \frac{1}{(M_3)} \end{pmatrix}$$

FV^{-1}

$$= \begin{pmatrix} 0 & \frac{\beta\mu(\mu_0\omega+\varphi)}{\varphi\delta_1+\varphi\mu_0+\delta_1\mu_0+\gamma_3\mu_0+{\mu_0}^2} & \frac{\beta\gamma\mu(\mu_0\omega+\varphi)}{\varphi\delta_1+\varphi\mu_0+\delta_1\mu_0+\gamma_3\mu_0+{\mu_0}^2} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} \begin{pmatrix} \frac{1}{M_1} & 0 & 0 \\ \frac{-\sigma}{M_1} & \frac{1}{M_2} & 0 \\ 0 & \frac{-q\gamma_1}{(M_3)(M_2)} & \frac{1}{(M_3)} \end{pmatrix}$$

$R_0 = \rho(FV^{-1}) = max(\lambda_1, \lambda_2, \lambda_3)$, that is the spectral radius of the given matrix which is its largest eigenvalue given by R_0

$$R_0 = \frac{\beta\sigma\mu(\mu_0\omega+\varphi)(M_3)}{(({\mu_0}^2+(\varphi+\delta_1+\gamma_3)\mu_0+\delta_1\varphi)(M_3)(M_2)(M_1))}. \quad (3.11)$$

Where, $M_1 = \sigma + \mu_0 + \delta, M_2 = \vartheta_1 + \gamma_1 + \mu_0 + \delta_1 - r, M_3 = b + \mu\omega\nu - \gamma_2 - \mu_0 - \mu_1 - \vartheta_2$

3.1.3 Local Stability Analysis of the Disease Free Equilibrium E_o

Theorem 3.1:E_o is asymptotically stable locally if R_o< 1 and it is unstable if R_o > 1.

Proof. The resulting matrix from the linearized model is $\frac{dX}{dt} = AX$

$X = (x_1, x_2, x_3, x_4, x_5, x_6, x_7)^T, (x_1, x_2, x_3, x_4, x_5, x_6, x_7) \in R_+^7$, and

$A =$

$$\begin{bmatrix} -\mu_0 - \delta_1 - \gamma_3 - \beta(A + \gamma C) & 0 & -(\beta S + r) & -(\gamma\beta S + \mu\omega\nu + b) & 0 & 0 & \varphi \\ \beta(A + \gamma C) & -M_1 & \beta S & \gamma\beta S & 0 & 0 & 0 \\ 0 & \sigma & -M_2 & 0 & 0 & 0 & 0 \\ 0 & 0 & q\gamma_1 & M_3 & 0 & 0 & 0 \\ 0 & 0 & \vartheta_1 & \vartheta_2 & \vartheta_3 - \mu_0 - \mu_2 & 0 & 0 \\ 0 & 0 & (1-q)\gamma_1 & \gamma_2 & \vartheta_3 & -\mu_0 & 0 \\ \gamma_3 & 0 & 0 & 0 & 0 & 0 & -(\varphi + \mu_0) \end{bmatrix} \quad (3.12)$$

The resulting Jacobian matrix of (3.12) at E_o is

$J(E_o)$

$$= \begin{bmatrix} -\mu_0 - \delta_1 - \gamma_3 - \lambda & 0 & -(\beta S_0 + r) & -(\gamma\beta S_0 + \mu\omega\nu + b) & 0 & 0 & \varphi \\ 0 & -M_1 & \beta S_0 & \gamma\beta S_0 & 0 & 0 & 0 \\ 0 & \sigma & -M_2 & 0 & 0 & 0 & 0 \\ 0 & 0 & q\gamma_1 & M_3 & 0 & 0 & 0 \\ 0 & 0 & \vartheta_1 & \vartheta_2 & \vartheta_3 - \mu_0 - \mu_2 - \lambda & 0 & 0 \\ 0 & 0 & (1-q)\gamma_1 & \gamma_2 & \vartheta_3 & -\mu_0 - \lambda & 0 \\ \gamma_3 & 0 & 0 & 0 & 0 & 0 & -(\varphi + \mu_0 + \lambda) \end{bmatrix} \quad (3.13)$$

from (3.13), $\lambda_1 = -(\varphi + \mu_0), \lambda_2 = -\mu_0, \lambda_3 = -\vartheta_3 - \mu_0 - \mu_2, \lambda_4 = -\mu_0 - \delta_1 - \gamma_3$ and the resulting quadratic equation is:

$$f(\lambda) = \lambda^3 + (M_1 + M_2 + M_3)\lambda^2 + (M_1M_2 + M_3M_1 + M_2M_3 - \sigma\beta S_0)\lambda - \sigma\beta S_0 M_3 + M_1M_2M_3 \quad (3.14)$$

Now, $\lambda_1, \lambda_2 \lambda_3 < 0$ since the values are assumed positive. If $R_0 < 1$, therefore, E_o is stableand unstable when $R_0 > 1$.

3.1.4 Global Stability of Disease Free Equilibrium

The global behavior of the equilibrium system (3.3) is analyzed here in this section. **Theorem 3.2:** For system (3.3), the disease-free equilibrium E_o is asymptotically stable globally if $R_0 < 1$.

Proof: Considering the Lyapunov function defined as:

$$\boldsymbol{G}(\boldsymbol{L}, \boldsymbol{A}, \boldsymbol{C}) = (M_3\sigma B)L + (M_3M_1B)A + (\beta\sigma\gamma\Lambda)C \tag{3.15}$$

$$\boldsymbol{G}' = (M_3\sigma B)L' + (M_3M_1B)A' + (\beta\sigma\gamma\Lambda)C' \tag{3.16}$$

$$\boldsymbol{G}' = (M_3\sigma B)[(\beta AS + \gamma\beta CS) - M_1L] + (M_3M_1B)[\sigma L - M_2A] + (\beta\sigma\gamma\Lambda)[q\gamma_1A - M_3C] \tag{3.17}$$

$$\boldsymbol{G}' = M_3\sigma\beta ASB + M_3\sigma\gamma\beta CSB - M_3M_1\sigma BL + M_3M_1B\sigma L - M_3M_2M_1BA + \beta\sigma\gamma q\gamma_1A\Lambda - M_3\beta\sigma\gamma\Lambda\mathrm{C} \tag{3.18}$$

$$\boldsymbol{G}' = [M_3\sigma\beta SB + \beta\sigma\gamma q\gamma_1\Lambda - M_3M_2M_1B]A + [M_3M_1B\sigma - M_2M_1\sigma B]L + [M_2\sigma\gamma\beta SB - M_3\beta\sigma\gamma\Lambda]\mathrm{C} \tag{3.19}$$

$$\boldsymbol{G}' = \frac{\mathbf{1}}{M_3M_2M_1B}\left[\frac{\beta\sigma\Lambda(M_2+\gamma q\gamma_1)}{M_3M_2M_1B} - 1\right]A + [M_3M_1B\sigma - M_3M_1\sigma B]L + [M_3\sigma\gamma\beta SB - M_3\beta\sigma\gamma\Lambda]\mathrm{C} \tag{3.20}$$

$$\boldsymbol{G'} = \frac{\mathbf{1}}{M_3 M_2 M_1 B}[\boldsymbol{R_0} - 1]A \tag{3.21}$$

From Equation (3.21), it can be deduced that the DFE is globally stable since $R_0 < 1$.

3.1.5 Bifurcation Analysis

Many traditional epidemic models contain thresholds, which are established by the basic reproductive process. If $R_0 \leq 1$, disease- free equilibrium of the equivalent model is globally stable in the feasible region. If $R_0 > 1$, the model has a unique endemic equilibrium that is globally stable in addition to the unstable disease-free equilibrium. This means that the disease is eradicated if $R_0 < 1$, and it persists in the population if $R_0 > 1$. However, there is mounting evidence that the basic reproductive number R_0 alone is insufficient to fully determine the global dynamics of disease transmission. Indeed, for some simple epidemiologic models, backward bifurcation with multiple endemic equilibria and Hopf bifurcation yielding a periodic solution can occur. (Hadler and Castillo-Chavez (1995), Alexander and Moghades (2004; 2005)).

When R_0 is greater than but close to one in a model with only forward bifurcation, the level (number of fraction) of infective individuals is low; however, when R_0 is less than but close to one in a system with backward bifurcation, the model has two endemic equilibria, one of which is a saddle and the other which is locally asymptotically stable. While the model with forward bifurcation has a unique endemic equilibrium, when R_0 is more than but near to one, the level (number or fraction) of infective individuals is higher. There are usually two thresholds for systems with backward bifurcation: $R_0 = R_c (0 <$

$R_c < 1$). There is a saddle-node bifurcation at $R_0 = R_c$, and a backward bifurcation at $R_0 = 1$.

The center manifold theory is used in this study to perform bifurcation analysis at the disease-free equilibrium as presented in (Buonomo and Lacitignola, 2011).

The focus is now on the disease-free equilibrium E_0, with the transcritical bifurcation at $R_0 = 1$ being investigated.

At the disease-free equilibrium E_0, the Jacobian matrix of equation (3.3) is given as:

$$J(E_o) = \begin{bmatrix} -\mu_0 - \delta_1 - \gamma_3 - \lambda & 0 & -(\beta S_0 + r) & -(\gamma\beta S_0 + \mu\omega\nu + b) & 0 & 0 & \varphi \\ 0 & -M_1 & \beta S_0 & \gamma\beta S_0 & 0 & 0 & 0 \\ 0 & \sigma & -M_2 & 0 & 0 & 0 & 0 \\ 0 & 0 & q\gamma_1 & M_3 & 0 & 0 & 0 \\ 0 & 0 & \vartheta_1 & \vartheta_2 & \vartheta_3 - \mu_0 - \mu_2 - \lambda & 0 & 0 \\ 0 & 0 & (1-q)\gamma_1 & \gamma_2 & \vartheta_3 & -\mu_0 - \lambda & 0 \\ \gamma_3 & 0 & 0 & 0 & 0 & 0 & -(\varphi + \mu_0 + \lambda) \end{bmatrix}$$

The Centre Manifold Theorem as stated in Theorem 1.4 is now applied to ascertain if the system (3.3) exhibits a backward or forward bifurcation at $R_0 = 1$ as follows:

Recall that

$$R_0 = \frac{\beta\sigma\mu(\mu_0\omega + \varphi)(M_3)}{((\mu_0{}^2 + (\varphi + \delta_1 + \gamma_3)\mu_0 + \delta_1\varphi)(M_3)(M_2)(M_1))}$$

Let $\beta = \beta^*$ be a bifurcation parameter and if the case $R_0 = 1$is taken into account.

By solving for $\beta = \beta^*$, then

$$\frac{\beta^*\sigma\mu(\mu_0\omega+\varphi)(M_3)}{((\mu_0{}^2+(\varphi+\delta_1+\gamma_3)\mu_0+\delta_1\varphi)(M_3)(M_2)(M_1))} = 1 \tag{3.22}$$

$$\beta = \beta^* = \frac{((\mu_0{}^2+(\varphi+\delta_1+\gamma_3)\mu_0+\delta_1\varphi)(M_3)(M_2)(M_1))}{\sigma\mu(\mu_0\omega+\varphi)(M_3))} \tag{3.23}$$

The Jacobian matrix of equation (3.3) at the disease-free equilibrium E_0, β^* is given by

$J(E_0, \beta^*) =$

$$\begin{bmatrix} -\mu_0-\delta_1-\gamma_3 & 0 & -(\beta^*S_0+r) & -(\gamma\beta^*S_0+\mu\omega\nu+b) & 0 & 0 & \varphi \\ 0 & -M_1 & \beta^*S_0 & \gamma\beta^*S_0 & 0 & 0 & 0 \\ 0 & \sigma & -M_2 & 0 & 0 & 0 & 0 \\ 0 & 0 & q\gamma_1 & -M_3 & 0 & 0 & 0 \\ 0 & 0 & \vartheta_1 & \vartheta_2 & \vartheta_3-\mu_0-\mu_2 & 0 & 0 \\ 0 & 0 & (1-q)\gamma_1 & \gamma_2 & \vartheta_3 & -\mu_0 & 0 \\ \gamma_3 & 0 & 0 & 0 & 0 & 0 & -(\varphi+\mu_0) \end{bmatrix}$$

(3.24)

The characteristic equation of (3.24) has a simple zero eigenvalue i.e.

$$|J(E_0, \beta^*) - \lambda \mathrm{I}| = 0 \tag{3.25}$$

$\lambda_1 = -(\varphi+\mu_0)$,$\lambda_2 = -\mu_0$, $\lambda_3 = -\vartheta_3-\mu_0-\mu_2$, $\lambda_4 = -\mu_0-\delta_1-\gamma_3$ and the resulting quadratic equation is:

$$f(\lambda) = \lambda^3 + (M_1+M_2+M_3)\lambda^2 + (M_1M_2+M_3M_1+M_2M_3-\sigma\beta^*S)\lambda \tag{3.26}$$

The roots of equation (3.26) are three negative eigenvalues (by Descartes rule of signs). As a result, $\lambda_5 = 0$ is a simple zero eigenvalue and the other eigenvalues are real and negative, the assumptions of theorem 1.4 (Centre Manifold theorem) are then verified.

Furthermore, the right eigenvector associated with the zero eigenvalue $\lambda_3 = 0$ given by

$w = (w_1, w_2, w_3, w_4, w_5, w_6, w_7)^T$ are obtained as follows:

$$\begin{bmatrix} -\mu_0 - \delta_1 - \gamma_3 & 0 & -(\beta^* S_0 + r) & -(\gamma\beta^* S_0 + \mu\omega\nu + b) & 0 & 0 & \varphi \\ 0 & -M_1 & \beta^* S_0 & \gamma\beta^* S_0 & 0 & 0 & 0 \\ 0 & \sigma & -M_2 & 0 & 0 & 0 & 0 \\ 0 & 0 & q\gamma_1 & -M_3 & 0 & 0 & 0 \\ 0 & 0 & \vartheta_1 & \vartheta_2 & \vartheta_3 - \mu_0 - \mu_2 & 0 & 0 \\ 0 & 0 & (1-q)\gamma_1 & \gamma_2 & \vartheta_3 & -\mu_0 & 0 \\ \gamma_3 & 0 & 0 & 0 & 0 & 0 & -(\varphi + \mu_0) \end{bmatrix} \begin{bmatrix} w_1 \\ w_2 \\ w_3 \\ w_4 \\ w_5 \\ w_6 \\ w_7 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}$$

(3.27)

$$(-\mu_0 - \delta_1 - \gamma_3)w_1 - (\beta^* S + r)w_3 - (\gamma\beta^* S + \mu\omega\nu + b)w_4 + \varphi w_7 = 0 \quad (3.28)$$

$$-M_1 w_2 + (\beta^* S)w_3 + (\gamma\beta^* S)w_4 = 0 \quad (3.29)$$

$$\sigma w_2 - M_2 w_3 = 0 \quad (3.30)$$

$$(q\gamma_1)w_3 - M_3 w_4 = 0 \quad (3.31)$$

$$\vartheta_1 w_3 + \vartheta_2 w_4 + (\vartheta_3 - \mu_0 - \mu_2)w_5 = 0 \quad (3.32)$$

$$(1-q)\gamma_1 w_3 + \gamma_2 w_4 + \vartheta_3 w_5 - \mu_0 w_6 = 0 \quad (3.33)$$

$$\gamma_3 w_1 - (\varphi + \mu_0)w_7 = 0 \quad (3.34)$$

Solving equations (3.28) to (3.34) simultaneously gives:

$$w_1 =$$

$$-\frac{1}{q\gamma_1(\mu_0+\delta_1+\gamma_3)\sigma}((\mu_0{}^3 - (b + \mu\omega\nu + r - \sigma - 2\delta_1 - \gamma_2 - \gamma_1 - \mu_1 - \vartheta_2 - \vartheta_1)\mu_0{}^2 +$$

$$(\delta_1^2 - (2b + 2\mu\omega\nu + r - \sigma - 2\gamma_2 - \gamma_1 - 2\mu_1 - 2\vartheta_2 - \vartheta_1)\delta_1 - (M_3)\sigma - (\gamma_1 + \vartheta_1 -$$

$r)(M_3))\mu_0 - (M_3)\delta_1^2 - (\gamma_1 + \vartheta_1 - r + \sigma)(M_3)\delta_1 + \sigma((\mu\omega(q-1)\nu + (q-1)b + \gamma_2 + \vartheta_2 + \mu_1)\gamma_1 - \vartheta_1(M_3))w_4$

$$w_2 = \frac{1}{q\gamma_1\sigma}(M_3M_2)w_4$$

$$w_3 = \frac{1}{q\gamma_1}(M_3)w_4$$

$$w_5 = \frac{((M_3)\vartheta_1 - q\gamma_1\vartheta_2)w_4}{q\gamma_1(\vartheta_3 + \mu_0 + \mu_2)}$$

$w_6 = \frac{1}{\mu_0 q\gamma_1(\vartheta_3+\mu_0+\mu_2)}((1-q)\mu_0 + (b + \mu\omega\nu - \mu_1)q + \gamma_2 + \mu_1 + \vartheta_2 - b - \mu\omega\nu)\vartheta_3 + (\mu_0 + \mu_2)((1-q)\mu_0 + (b + \mu\omega\nu - \mu_1 - \vartheta_2) + \gamma_2 + \mu_1 + \vartheta_2 - b - \mu\omega\nu))\gamma_1 - \vartheta_1\vartheta_3(M_3))w_4$

$w_7 =$

$-\frac{1}{q\gamma_1(\mu_0+\delta_1+\gamma_3)(\varphi+\mu_0)}((\mu_0{}^3 - (b + \mu\omega\nu + r - \sigma - 2\delta_1 - \gamma_2 - \gamma_1 - \mu_1 - \vartheta_2 - \vartheta_1)\mu_0{}^2 + (\delta_1^2 - (2b + 2\mu\omega\nu + r - \sigma - 2\gamma_2 - \gamma_1 - 2\mu_1 - 2\vartheta_2 - \vartheta_1)\delta_1 - (b + \mu\omega\nu - \gamma_2 - \gamma_1 - \mu_1 - \vartheta_2 - \vartheta_1)\sigma - (\gamma_1 + \vartheta_1 - r)(b + \mu\omega\nu - \gamma_2 - \mu_1 - \vartheta_2))\mu_0 - (b + \mu\omega\nu - \gamma_2 - \mu_1 - \vartheta_2)\delta_1^2 - (\gamma_1 + \vartheta_1 - r + \sigma)(b + \mu\omega\nu - \gamma_2 - \mu_1 - \vartheta_2)\delta_1 + \sigma((\mu\omega(q-1)\nu + (q-1)b + \gamma_2 + \vartheta_2 + \mu_1)\gamma_1 - \vartheta_1(b + \mu\omega\nu - \gamma_2 - \mu_1 - \vartheta_2))w_4$

Therefore,

$w =$

$$\begin{bmatrix} -\frac{1}{q\gamma_1(\mu_0+\delta_1+\gamma_3)\sigma}((\mu_0{}^3-(b+\mu\omega\nu+r-\sigma-2\delta_1-\gamma_2-\gamma_1-\mu_1-\vartheta_2-\vartheta_1)\mu_0{}^2+(\delta_1^2-2\gamma_2-\gamma_1-2\mu_1-2\vartheta_2-\vartheta_1)\delta_1 \\ -(b+\mu\omega\nu-\gamma_2-\gamma_1-\mu_1-\vartheta_2-\vartheta_1)\sigma-(\gamma_1+\vartheta_1-r)(b+\mu\omega\nu-\gamma_2-\mu_1-\vartheta_2))\mu_0-(b+\mu\omega\nu-\gamma_2-\mu_1-\vartheta_2)\delta_1^2-(\gamma_1+\vartheta_1-r+\sigma) \\ (b+\mu\omega\nu-\gamma_2-\mu_1-\vartheta_2)\delta_1+\sigma((\mu\omega(q-1)\nu+(q-1)b+\gamma_2+\vartheta_2+\mu_1)\gamma_1-\vartheta_1(b+\mu\omega\nu-\gamma_2-\mu_1-\vartheta_2))w_4, \\ \frac{1}{q\gamma_1\sigma}((\gamma_2+\mu_1+\vartheta_2+\mu_0-b-\mu\omega\nu)(r-\mu_0-\gamma_1-\vartheta_1-\delta_1))w_4, \frac{1}{q\gamma_1}(\gamma_2+\mu_1+\vartheta_2+\mu_0-b-\mu\omega\nu)w_4, \\ \frac{1}{\mu_0 q\gamma_1(\vartheta_3+\mu_0+\mu_2)}((1-q)\mu_0+(+\vartheta_2-b-\mu\omega\nu)\vartheta_3+(\mu_0+\mu_2)((1-q)\mu_0+(b+\mu\omega\nu-\mu_1-\vartheta_2)q \\ +\gamma_2+\mu_1+\vartheta_2-b-\mu\omega\nu))\gamma_1-\vartheta_1\vartheta_3(b+\mu\omega\nu-\gamma_2-\mu_1-\vartheta_2-\mu_0))w_4, \\ -\frac{1}{q\gamma_1(\mu_0+\delta_1+\gamma_3)(\varphi+\mu_0)}((\mu_0{}^3-(b+\mu\omega\nu+r-\sigma-2\delta_1-\gamma_2-\gamma_1-\mu_1-\vartheta_2-\vartheta_1)\mu_0{}^2+(\delta_1^2--\vartheta_1)\delta_1 \\ -(b+\mu\omega\nu-\gamma_2-\gamma_1-\mu_1-\vartheta_2-\vartheta_1)\sigma-(\gamma_1+\vartheta_1-r)(b+\mu\omega\nu-\gamma_2-\mu_1-\vartheta_2))\mu_0-(b+\mu\omega\nu-\gamma_2-\mu_1-\vartheta_2)\delta_1^2-(\gamma_1+\vartheta_1-r+\sigma) \\ (b+\mu\omega\nu-\gamma_2-\mu_1-\vartheta_2)\delta_1+\sigma((\mu\omega(q-1)\nu+(q-1)b+\gamma_2+\vartheta_2+\mu_1)\gamma_1-\vartheta_1(b+\mu\omega\nu-\gamma_2-\mu_1-\vartheta_2))w_4 \end{bmatrix}^T$$

where $w_4 > 0$ is a free right eigenvector.

Similarly, the left eigenvector associated with the zero eigenvalue is computed as follows:

Let the left eigenvector associated with the zero eigenvalue $\lambda_5 = 0$ given by

$$l = \left(l_1, l_2, l_3, l_4, l_5, l_6, l_7\right)$$

then,

$$l.\begin{bmatrix} -\mu_0-\delta_1-\gamma_3 & 0 & -(\beta^*S+r) & -(\gamma\beta^*S+\mu\omega\nu+b) & 0 & 0 & \varphi \\ 0 & -(M_1) & \beta^*S & \gamma\beta^*S & 0 & 0 & 0 \\ 0 & \sigma & -(M_2) & 0 & 0 & 0 & 0 \\ 0 & 0 & q\gamma_1 & (M_3) & 0 & 0 & 0 \\ 0 & 0 & \vartheta_1 & \vartheta_2 & \vartheta_3-\mu_0-\mu_2 & 0 & 0 \\ 0 & 0 & (1-q)\gamma_1 & \gamma_2 & \vartheta_3 & -\mu_0 & 0 \\ \gamma_3 & 0 & 0 & 0 & 0 & 0 & -(\varphi+\mu_0) \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \tag{3.35}$$

$$l_1(-\mu_0-\delta_1-\gamma_3)+l_7(\gamma_3)=0 \tag{3.36}$$

$$l_2-(M_1)+l_3\sigma=0 \tag{3.37}$$

$$l_1(-\beta^*S-r)+l_2(\beta^*S)+l_3((M_2))+l_4q\gamma_1+l_5\vartheta_1+l_6(1-q)\gamma_1=0 \tag{3.38}$$

$$l_1(-(\gamma\beta^* S + \mu\omega v + b)) + l_2(\gamma\beta^* S) + l_4(M_3)) + l_5\vartheta_2 + l_6\gamma_2 = 0 \quad (3.39)$$

$$l_5(-\vartheta_3 - \mu_0 - \mu_2) + l_6\vartheta_3 = 0 \quad (3.40)$$

$$-l_6\mu_0 = 0 \quad (3.41)$$

$$l_1\varphi + l_7(-\varphi - \mu_0) = 0 \quad (3.42)$$

The simultaneous solution of equations (3.36) - (3.42) yields:

$$l_1 = 0, l_2 = l_2, l_3 = \frac{(M_1)l_2}{\sigma}, l_4 = -\frac{\gamma(M_1)(M_2)l_2}{\sigma(\gamma q\gamma_1 + M_3)} l_5 = 0, l_6 = 0, l_7 = 0$$

therefore,

$$l = \left[0, l_2, \frac{(M_1)l_2}{\sigma}, -\frac{\gamma(M_1)(M_2)l_2}{\sigma(\gamma q\gamma_1 + M_3)}, 0,0,0\right]$$

where $l_2 > 0$ is a free left eigenvector.

3.1.5.1 The Computation of the Coefficient a and b for Model Case 1

The coefficients (as defined in theorem 1.4):

$$a = \sum_{m,i,j=1}^{7} l_m w_i w_j \frac{\partial^2 f_m(E_0, \beta^*)}{\partial x_i \partial x_j}, b = \sum_{m,i,j=1}^{7} l_m w_i \frac{\partial^2 f_m(E_0, \beta^*)}{\partial x_i \partial \varphi}$$

may now be computed explicitly using system (3.3) and only the nonzero components of the left eigenvector l, as follows:

$S = x_1, L = x_2, A = x_3, C = x_4, H = x_5, R = x_6, V = x_7$

Furthermore, introducing the vector $X = (x_1, x_2, x_3, x_4, x_5, x_6, x_7)^T$, The system (3.3) model can now be written in the form;

$\frac{dX}{dt} = f(x)$, where $f = (f_1, f_2, f_3, f_4, f_5, f_6, f_7)^T$

It implies that system of equation (3.3) can be expressed as follows in terms of the new variables:

$$\begin{aligned}
\frac{dx_1}{dt} &= \mu\omega(1 - vf_4) + \varphi f_7 - (\beta f_3 + \gamma f_4) + \gamma_3 + \mu_0 + \delta_1)f_1 - rf_3 - bf_4 \\
\frac{dx_2}{dt} &= \beta(f_3 + \gamma f_4)f_1 - (\sigma + \mu_0 + \delta_1)f_2 \\
\frac{dx_3}{dt} &= \sigma f_2 - (\vartheta_1 + \gamma_1 + \mu_0 + \delta_1 - r)f_3 \\
\frac{dx_4}{dt} &= q\gamma_1 f_3 - (\vartheta_2 + \gamma_2 + \mu_0 + \mu_1 - \mu\omega v - b)f_4 \\
\frac{dx_5}{dt} &= \vartheta_2 f_4 + \vartheta_1 f_3 - (\vartheta_3 + \mu_0 + \mu_2)f_5 \\
\frac{dx_6}{dt} &= \gamma_2 f_4 + (1 - q)\gamma_1 f_3 + \vartheta_3 f_5 - \mu_0 f_6 \\
\frac{dx_7}{dt} &= \mu(1 - \omega) + \gamma_3 f_1 - (\varphi + \mu_0)f_7
\end{aligned} \tag{3.43}$$

$$a = 2l_2 w_1 w_4 \frac{\partial^2 f_2(E_0, \beta^*)}{\partial x_1 \partial x_4} + 2l_2 w_1 w_3 \frac{\partial^2 f_2(E_0, \beta^*)}{\partial x_3 \partial x_4}$$

$$\frac{\partial^2 f_2(E_0, \beta^*)}{\partial x_1 \partial x_4} = \gamma\beta^*, \qquad \frac{\partial^2 f_2(E_0, \beta^*)}{\partial x_3 \partial x_4} = \beta^*$$

$$\therefore a = 2l_2 w_1 w_4 \gamma\beta^* + 2l_2 w_1 w_3 \beta^*$$

$$a = 2l_2w_1\beta^*(\gamma w_4 + w_3)$$

$$b = l_2w_1(\gamma x_4 + x_3) + l_2w_3x_1 + l_2w_4\gamma x_1$$

$$a = -\frac{1}{q\gamma_1(\mu_0+\delta_1+\gamma_3)\sigma}(2l_2(\mu_0{}^3 - (b + \mu\omega\nu + r - \sigma - 2\delta_1 - \gamma_2 - \gamma_1 - \mu_1 - \vartheta_2 - \vartheta_1)\mu_0{}^2 + (\delta_1^2 - (2b + 2\mu\omega\nu + r - \sigma - 2\gamma_2 - \gamma_1 - 2\mu_1 - 2\vartheta_2 - \vartheta_1)\delta_1 - (b + \mu\omega\nu - \gamma_2 - \gamma_1 - \mu_1 - \vartheta_2 - \vartheta_1)\sigma - (\gamma_1 + \vartheta_1 - r)(b + \mu\omega\nu - \gamma_2 - \mu_1 - \vartheta_2))\mu_0 - (b + \mu\omega\nu - \gamma_2 - \mu_1 - \vartheta_2)\delta_1^2 - (\gamma_1 + \vartheta_1 - r + \sigma)(b + \mu\omega\nu - \gamma_2 - \mu_1 - \vartheta_2)\delta_1 + \sigma\big((\mu\omega(q-1)\nu + (q-1)b + \gamma_2 + \vartheta_2 + \mu_1)\gamma_1 - \vartheta_1(b + \mu\omega\nu - \gamma_2 - \mu_1 - \vartheta_2)\big)w_4\beta\left(\gamma w_4 - \frac{(\mu\omega\nu - b - \gamma_2 - \mu_1 - \vartheta_2 - \mu_0)w_4}{q\gamma_1}\right)$$

$$b = \frac{l_2w_3\mu(\mu_0\omega + \varphi)}{\varphi\delta_1 + \varphi\mu_0 + \delta_1\mu_0 + \gamma_3\mu_0 + \mu_0{}^2} + \frac{l_2w_4\gamma\mu(\mu_0\omega + \varphi)}{\varphi\delta_1 + \varphi\mu_0 + \delta_1\mu_0 + \gamma_3\mu_0 + \mu_0{}^2}$$

Since the coefficient b is always positive, the sign of the coefficient a determines the local dynamics around the disease-free equilibrium for $\beta = \beta^*$., according to theorem 1.4. As a result, the following result is established.

Theorem 3.3: The unique equilibrium $E^*$is locally asymptotically stable for $R_0 > 1$. Since $a < 0$, locally stability of E^*infers its global stability.

3.1.6 Local Stability of Endemic Equilibrium

Theorem 3.4: If $R_0 > 1$, then the endemic equilibrium is locally asymptotically stable.

Proof: The endemic equilibria of system (3.3), denoted by $(S^*, L^*, A^*, C^*, H^*, R^*, V^*)$, can be rewritten as:

Let $S = x + S^*, L = y + L^*, A = z + A^*, C = c + S^*, H = h + S^*, R = p + S^*, V = j + S^*$

A

$$= \begin{bmatrix} -\mu_0 - \delta_1 - \gamma_3 - \beta A - \gamma\beta C & 0 & -(\beta S + r) & -(\gamma\beta S + \mu\omega\nu + b) & 0 & 0 & \varphi \\ \beta A + \gamma\beta C & -(\sigma + \mu_0 + \delta_1) & \beta S & \gamma\beta S & 0 & 0 & 0 \\ 0 & \sigma & -(\vartheta_1 + \gamma_1 + \mu_0 + \delta_1 - r) & 0 & 0 & 0 & 0 \\ 0 & 0 & q\gamma_1 & (b + \mu\omega\nu - \gamma_2 - \mu_0 - \mu_1 - \vartheta_2) & 0 & 0 & 0 \\ 0 & 0 & \vartheta_1 & \vartheta_2 & \vartheta_3 - \mu_0 - \mu_2 & 0 & 0 \\ 0 & 0 & (1-q)\gamma_1 & \gamma_2 & \vartheta_3 & -\mu_0 & 0 \\ \gamma_3 & 0 & 0 & 0 & 0 & 0 & -(\varphi + \mu_0) \end{bmatrix}$$

(3.44)

(3.44) can be rewritten as:

$$A = \begin{bmatrix} -m_1 & 0 & -(\beta S + r) & -m_2 & 0 & 0 & \varphi \\ m_3 & -m_4 & \beta S & \gamma\beta S & 0 & 0 & 0 \\ 0 & \sigma & -m_5 & 0 & 0 & 0 & 0 \\ 0 & 0 & q\gamma_1 & m_6 & 0 & 0 & 0 \\ 0 & 0 & \vartheta_1 & \vartheta_2 & \vartheta_3 - \mu_0 - \mu_2 & 0 & 0 \\ 0 & 0 & (1-q)\gamma_1 & \gamma_2 & \vartheta_3 & -\mu_0 & 0 \\ \gamma_3 & 0 & 0 & 0 & 0 & 0 & -(\varphi + \mu_0) \end{bmatrix} \quad (3.45)$$

J

$$= \begin{bmatrix} -m_1 - \lambda & 0 & -(\beta S* + r) & -m_2 & 0 & 0 & \varphi \\ m_3 & -m_4 - \lambda & \beta S* & \gamma\beta S* & 0 & 0 & 0 \\ 0 & \sigma & -m_5 - \lambda & 0 & 0 & 0 & 0 \\ 0 & 0 & q\gamma_1 & m_6 - \lambda & 0 & 0 & 0 \\ 0 & 0 & \vartheta_1 & \vartheta_2 & \vartheta_3 - \mu_0 - \mu_2 - \lambda & 0 & 0 \\ 0 & 0 & (1-q)\gamma_1 & \gamma_2 & \vartheta_3 & -\mu_0 - \lambda & 0 \\ \gamma_3 & 0 & 0 & 0 & 0 & 0 & -(\varphi + \mu_0 + \lambda) \end{bmatrix}$$

(3.46)

From (3.46), $\lambda_1 = -(\varphi + \mu_0)$, $\lambda_2 = -\mu_0$, $\lambda_3 = -(\vartheta_3 + \mu_0 + \mu_2)$,$\lambda_4 = -m_4$,then ;

$$J = \begin{bmatrix} -m_1 - \lambda & -(\beta S* + r) & -m_2 \\ 0 & -m_5 - \lambda & 0 \\ 0 & q\gamma_1 & -m_6 - \lambda \end{bmatrix} \quad (3.47)$$

from (3.47);

$$\lambda^3 + (m_1 + m_5 + m_6)\lambda^2 + (m_1 m_5 + m_1 m_6 + m_6 m_5)\lambda + m_1 m_5 m_6 \quad (3.48)$$

The result of the determinant of the Jacobian matrix is of the form:

$$a_0\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3$$

where

$$a_0 = 1$$

$$a_1 = m_1 + m_5 + m_6$$

$$a_2 = m_1 m_5 + m_1 m_6 + m_6 m_5$$

$$a_3 = m_1 m_5 m_6$$

By Routh-Hurwitz criterion governing the polynomials of order 3, it follows:

1. $a_2 . a_3$are positive

2. $a_1 a_2 > a_3$

From equation (3.48)1 and 2 are satisfied.

Therefore, endemic equilibrium is locally asymptotically stable.

3.1.7 Global Stability of Endemic Equilibrium

Theorem 3.5: The equations of the model have a positive distinctive endemic equilibrium whenever $R_0 > 1$, which is said to be globally asymptotically stable.

Proof: Considering the Lyapunov function defined as:

$$L(S^*, L^*, A^*, C^*, H^*, R^*, V^*) = \left(S - S^* ln\left(\frac{S}{S^*}\right)\right) + \left(L - L^* ln\left(\frac{L}{L^*}\right)\right) + \left(A - A^* ln\left(\frac{A}{A^*}\right)\right) + \left(C - C^* ln\left(\frac{C}{C^*}\right)\right) + \left(H - H^* ln\left(\frac{H}{H^*}\right)\right) + \left(R - R^* ln\left(\frac{R}{R^*}\right)\right) + \left(V - V^* ln\left(\frac{V}{V^*}\right)\right) \quad (3.49)$$

where L takes it derivative along the system of equation directly as:

$$\frac{dL}{dt} = \left(\frac{1-S^*}{S}\right)\frac{dS}{dt} + \left(\frac{1-L^*}{L}\right)\frac{dL}{dt} + \left(\frac{1-A^*}{A}\right)\frac{dA}{dt} + \left(\frac{1-C^*}{C}\right)\frac{dC}{dt} + \left(\frac{1-H^*}{H}\right)\frac{dH}{dt} + \left(\frac{1-R^*}{R}\right)\frac{dR}{dt} + \left(\frac{1-V^*}{V}\right)\frac{dV}{dt} \quad (3.50)$$

$$\frac{dL}{dt} = \left(\frac{1-S^*}{S}\right)\mu\omega(1 - vC) + \varphi V - (\beta(A + \gamma C) + \gamma_3 + \mu_0 + \delta_1)S - rA - bC + \left(\frac{1-L^*}{L}\right)\beta(A + \gamma C)S - (\sigma + \mu_0 + \delta_1)L + \left(\frac{1-A^*}{A}\right)\sigma L - (\vartheta_1 + \gamma_1 + \mu_0 + \delta_1 - r)A + \left(\frac{1-C^*}{C}\right)q\gamma_1 A - (\vartheta_2 + \gamma_2 + \mu_0 + \mu_1 - \mu\omega v - b)C + \left(\frac{1-H^*}{H}\right)\vartheta_2 C + \vartheta_1 A - (\vartheta_3 + \mu_0 + \mu_2)H + \left(\frac{1-R^*}{R}\right)\gamma_2 C + (1 - q)\gamma_1 A + \vartheta_3 H - \mu_0 R + \left(\frac{1-V^*}{V}\right)\mu(1 - \omega) + \gamma_3 S - (\varphi + \mu_0)V$$

At equilibrium,

$$\mu\omega(1-vC) = (\beta(A^* + \gamma C^*) + \gamma_3 + \mu_0 + \delta_1)S^* + rA^* + bC^* - \varphi V^*$$

$$\left.\begin{aligned}
(\sigma + \mu_0 + \delta_1) &= \frac{\beta(A^* + \gamma C^*)S^*}{L^*} \\
(\vartheta_1 + \gamma_1 + \mu_0 + \delta_1 - r) &= \frac{\sigma L^*}{A^*} \\
(\vartheta_2 + \gamma_2 + \mu_0 + \mu_1 - \mu\omega v - b) &= \frac{q\gamma_1 A^*}{C^*} \\
(\vartheta_3 + \mu_0 + \mu_2) &= \frac{\vartheta_2 C^* + \vartheta_1 A^*}{H^*} \\
\mu_0 &= \frac{\gamma_2 C^* + (1-q)\gamma_1 A^* + \vartheta_3 H^*}{R^*} \\
(\varphi + \mu_0) &= \frac{\mu(1-\omega) + \gamma_3 S^*}{V^*}
\end{aligned}\right\} \quad (3.51)$$

$$\frac{dL}{dt} = \left(\frac{1-S^*}{S}\right)(\beta(A^* + \gamma C^*) + \gamma_3 + \mu_0 + \delta_1)S^* + rA^* + bC^* - \varphi V^* + \varphi V - (\beta(A +$$

$$\gamma C) + \gamma_3 + \mu_0 + \delta_1)S - rA - bC + \left(\frac{1-L^*}{L}\right)\beta(A + \gamma C)S - \frac{\beta(A^* + \gamma C^*)S^* L}{L^*} + \left(\frac{1-A^*}{A}\right)\sigma L -$$

$$\frac{\sigma L^* A}{A^*} + \left(\frac{1-C^*}{C}\right)q\gamma_1 A - \frac{q\gamma_1 A^* C}{C^*} + \left(\frac{1-H^*}{H}\right)\vartheta_2 C + \vartheta_1 A - \frac{(\vartheta_2 C^* + \vartheta_1 A^*)H}{H^*} + \left(\frac{1-R^*}{R}\right)\gamma_2 C + (1 -$$

$$q)\gamma_1 A + \vartheta_3 H - \frac{(\gamma_2 C^* + (1-q)\gamma_1 A^* + \vartheta_3 H^{)*})R}{R^*} + \left(\frac{1-V^*}{V}\right)\mu(1-\omega) + \gamma_3 S - \frac{(\mu(1-\omega) + \gamma_3 S^*)V}{V^*} \quad (3.52)$$

$$= \left(\frac{1-S^*}{S}\right)\beta A^* S^* + \beta\gamma C^* S^* + \gamma_3 S^* + \mu_0 S^* + \delta_1 S^* + rA^* + bC^* - \varphi V^* + \varphi V - \beta AS -$$

$$\gamma CS - \gamma_3 S - \mu_0 S - \delta_1 S - rA - bC + \left(\frac{1-L^*}{L}\right)\beta AS + \gamma CS - \frac{\beta A^* S^* L}{L^*} - \frac{\gamma C^* S^* L}{L^*} +$$

$$\left(\frac{1-A^*}{A}\right)\sigma L\left(1 - \frac{L^* A}{LA^*}\right) + \left(\frac{1-C^*}{C}\right)q\gamma_1 A\left(1 - \frac{A^* C}{AC^*}\right) + \left(\frac{1-H^*}{H}\right)\vartheta_2 C + \vartheta_1 A\left(1 - \frac{(C^* + A^8)H}{(C+A)H^*}\right) +$$

$$\left(\frac{1-R^*}{R}\right)\gamma_2 C + (1-q)\gamma_1 A + \vartheta_3 H - \frac{(\gamma_2 C^* + (1-q)\gamma_1 A^* + \vartheta_3 H^{)*})R}{R^*} + \left(\frac{1-V^*}{V}\right)\mu(1-\omega) + \gamma_3 S -$$

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

let $\frac{dL}{dt} = P - Q$

where P are the positive terms and Q are the negative terms such that;

$$P = (\beta(A + \gamma C) + \gamma_3 + \mu_0 + \delta_1)S^* + \frac{rAS^*}{S} + \frac{bCS^*}{S} + (\sigma + \mu_0 + \delta_1)L^* + (\vartheta_1 + \gamma_1 + \mu_0 + \delta_1 - r)A^* + (\vartheta_2 + \gamma_2 + \mu_0 + \mu_1 - \mu\omega v - b)C^* + (\vartheta_3 + \mu_0 + \mu_2)H^* + \mu_0 R^* + (\varphi + \mu_0)V^*$$

$$Q = \frac{\mu\omega(1-vC)S^*}{S} + \frac{\varphi VS^*}{S} + \frac{\beta(A+\gamma C)SL^*}{L} + \frac{\sigma LA^*}{A} + \frac{q\gamma_1 AC^*}{C} + \frac{\vartheta_2 CH^*}{H} + \frac{\vartheta_1 AH^*}{H} + \frac{\gamma_2 CR^*}{R} + \frac{(1-q)\gamma_1 AR^*}{R} + \frac{\vartheta_3 HR^*}{R} + \frac{\mu(1-\omega)V^*}{V} + \frac{\gamma_3 SV^*}{V}$$

If P<Q, then, $\frac{dL}{dt} \leq 0$.

$\frac{dL}{dt} = 0$, on condition that$S = S^*, L = L^*, A = A^*, C = C^*, H = H^*, R = R^*, V = V^*$.

Hence, by the invariant principle postulated by LaSalle (LaSalle, 1976), the greatest invariant set in $\{S^*, L^*, A^*, C^*, H^*, R^*, V^* \in \Theta : \frac{dL}{dt} = 0\}$is a singleton of E^*, where $E^*$is the endemic equilibrium.

This implies that globally, the endemic equilibrium is asymptotically stable.

3.2 Mathematical Formulation, Analysis and Method of Solution for HBV Model Case 2

It has been clinically shown that a proportion of HBV acutely infected individuals can spontaneously clear the virus (Pan and Zhang, 2005, Zhao et al., 2000). Also, infectious individuals under treatment can become prone to re-infection if they fall out of treatment or indulge in habits like alcohol, use of drugs which can reduce the impact of the treatment. In view of this, the following model is developed where the population is divided into different states, namely: the susceptible, the acute, the chronic carriers, the treated and the recovered states.

At time t, denoted by $N(t)$, the total population is divided into the following 5 classes/subgroups corresponding to different epidemiological status.

$$N(t) = S(t) + A(t) + C(t) + T(t) + R(t) \tag{3.52}$$

where $S(t)$ are the susceptible populace, $A(t)$ is the populace thst are acutely infected with HBV, $C(t)$ are the chronically/ clinically infected individuals, while $T(t)$ are individual under treatment and $R(t)$ are the removed classes. Figure 3.2 represents schematically the epidemiology of HBV. The various disease stages are replicated by the various compartments (circle) and the arrows demonstrates the way individual progress from one state to the other). It is assumed that at time t, susceptible individual S, enter the population at a constant rate $\zeta(1-\alpha)(1-\gamma C)$where ζ is the birth rate,α is the proportion of population successfully immunized while γ is the probability that children born to carrier

mothers will develop to chronic state. At all classes, individuals die at a constant natural mortality rate, μ. It is assumed that HBV infected individuals on treatment are not infectious. Susceptible individual S, may acquire HBV infection when in contact with individuals in $A, C, and\ T$ populace at a rate λ_s (force of infection associated with HBV),

where $\lambda_s = \beta A + \xi \beta C$ (3.53)

and βA and βC are the effective contact rate for HBV infection to occur/ probability that a contact will result in an acute and chronic HBV compartment, respectively and modification $\xi > 1$ account for a higher risk of HBV acquisition for people living with chronic HBV.

A proportion of the acute HBV infected individuals η, becomes chronic carriers and then get treated at σ while the remaining proportion $(1 - \eta)$ spontaneously clear the virus, $\frac{1}{\omega}$ is the duration of acute phase. A proportion of the treated HBV individuals κ, recover with full immunity, some were in the process of recovering in the treated populace at a rate, υ and duration for the treatment is given as ρ while the remaining proportion $(1 - \kappa)$ becomes susceptible. Those individuals in the process of recovering in the treated populace at a rate, υ if engage/expose in high-risk habit and those on treatment ρ can be re-infected at the rate $\nu\rho$ if fall out of treatment at a rate, ε.

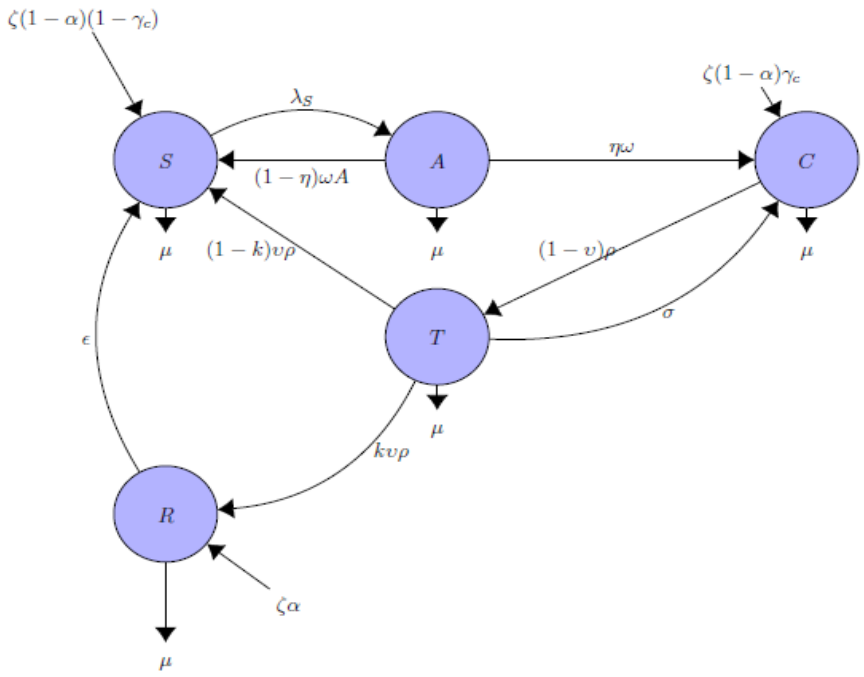

Figure 3.2: Compartmental flow diagram of HBV model Case 2.

These assumptions lead to the emergence of the systems of equation in 3.54

$$\begin{aligned}
\frac{dS}{dt} &= \zeta(1-\alpha)(1-\gamma C) - \lambda_s S + (1-\eta)\omega A - \mu S + (1-k)\nu\rho T + \varepsilon R \\
\frac{dA}{dt} &= \lambda_s S - \omega A - \mu A \\
\frac{dC}{dt} &= \eta\omega A + \zeta(1-\alpha)\gamma C + (1-\upsilon)\rho T - \sigma C - \mu C \\
\frac{dT}{dt} &= \sigma C - \rho T - \mu T \\
\frac{dR}{dt} &= \zeta\alpha + k\upsilon\rho T - \varepsilon R - \mu R
\end{aligned} \tag{3.54}$$

where $\lambda_s = \beta A + \xi\beta C$

3.2.1 Positivity and Boundedness of Solutions

For the system of equations (3.54) to be epidemiologically meaningful, it is important to prove that all solution with non-negative initial conditions will remain non-negative. The proof of the positivity and boundedness of system of equations in system (3.54) follows from Lemma 3.2.1 stated below:

Lemma 3.2.1: The initial values of the parameters are

$\{S(0) \geq 0, A(0) \geq 0, C(0) \geq 0, T(0) \geq 0, R(0) \geq ,0 and N(0) \geq 0\} \in \Phi$

Then the solution of the model $\{S(t), A(t), C(t), T(t), R(t), N(t)\}$ is positive for all

$t \geq 0$.

Proof: Considering the first equation in (3.54);

$$\frac{dS}{dt} = \zeta(1-\alpha)(1-\gamma C) - \lambda_s S + (1-\eta)\omega A - \mu S + (1-k)\nu\rho T + \varepsilon R$$

$$\frac{dS}{dt} \geq -(\lambda_s + \mu)S$$

$$\int \frac{1}{S} dS \geq \int -(\lambda_s + \mu)\, dt$$

$$S \geq S_0 e^{-(\lambda_s+\mu)t} \geq 0$$

Hence, $S \geq 0$

with respect to the second equation in (3.54);

$$\frac{dA}{dt} = \lambda_s S - \omega A - \mu A$$

$$\frac{dA}{dt} \geq -(\omega + \mu)A$$

$$\int \frac{1}{A} dA \geq \int -(\omega + \mu)\, dt$$

$$A \geq A_0 e^{-(\omega+\mu)t} \geq 0$$

Hence, $A \geq 0$

with respect to the third equation in (3.54);

$$\frac{dC}{dt} = \eta\omega A + \zeta(1-\alpha)\gamma C + (1-\upsilon)\rho T - (\sigma + \mu)C$$

$$\frac{dC}{dt} \geq \zeta(1-\alpha)\gamma C - (\sigma + \mu)C$$

$$\int \frac{1}{C} dC \geq \int (\zeta(1-\alpha)\gamma C - (\sigma + \mu)C)dt$$

$$C \geq C_0 e^{(\zeta(1-\alpha)\gamma C - (\sigma+\mu)C)t} \geq 0$$

Hence, $C \geq 0$

with respect to the fourth equation in (3.54);

$$\frac{dT}{dt} = \sigma C - \rho T - \mu T$$

$$\frac{dT}{dt} \geq -(\rho + \mu)T$$

$$\int \frac{1}{T} dT \geq \int -(\rho + \mu)\, dt$$

$$T \geq T_0 e^{-(\rho+\mu)t} \geq 0$$

Hence, $T \geq 0$

with respect to the fifth equation in (3.54);

$$\frac{dR}{dt} = \zeta\alpha + k\upsilon\rho T - \varepsilon R - \mu R$$

$$\frac{dR}{dt} \geq -(\varepsilon + \mu)R$$

$$\int \frac{1}{R} dR \geq \int -(\varepsilon + \mu)\, dt$$

$$R \geq R_0 e^{-(\varepsilon+\mu)t} \geq 0$$

Hence, $R \geq 0$

Clearly, the above state variables are positive on bounding plane $\mathbb{R}_+^5$.

For the boundedness the following calculation follows:

$$N(t) = S(t) + L(t) + A(t) + C(t) + T(t)$$

$$N' = S' + L' + A' + C' + T'$$

$$N' = \zeta(1-\alpha)(1-\gamma C) - (\beta A + \xi\beta C)S + (1-\eta)\omega A - \mu S + (1-k)\nu\rho T + \varepsilon R +$$

$$(\beta A + \xi\beta C)S - (\omega + \mu)A + \eta\omega A + \zeta(1-\alpha)\gamma C + (1-\upsilon)\rho T - \sigma C - \mu C + \sigma C - \rho T -$$

$$\mu T + \zeta\alpha + k\upsilon\rho T - \varepsilon R - \mu R \tag{3.55}$$

Simplifying (3.55) gives:

$$N' = \zeta - \mu[S + A + C + T + R] + \gamma C \tag{3.56}$$

$$N' + \mu N = \zeta + \gamma C \tag{3.57}$$

$$N' + \mu N \leq \zeta \tag{3.58}$$

Integrating (3.58) gives:

$$N' \leq \frac{\zeta}{\mu} + ke^{-\mu t}$$

$$\max_{\lim_{n\to\infty}} N \leq \lim_{n\to\infty}\left(\frac{\zeta}{\mu} + ke^{-\mu t}\right) \leq \frac{\zeta}{\mu}$$

It follows that the solutions of the model system (3.54) are positive and bounded in the region

$$\mathcal{T} = \{(S + A + C + T + R)\} \in \mathbb{R}_+^5 : S + A + C + T + R \leq \frac{\zeta}{\mu}$$

It follows from Lemma 3.2.1 that it is sufficient to consider the dynamics of system (3.54) and the model can be considered to be epidemiologically well-posed.

3.2.2 Equilibrium Points and Reproduction Number

The disease-free equilibrium of the equation (3.54) exists and is given by:

$$E_o = \left[\frac{\zeta(1-\alpha\mu)}{\mu}, 0,0,0,0\right] \tag{3.59}$$

The endemic steady states are calculated here which is done by setting system of equation in (3.54) to zero and setting $S = S^*, A = A^*, C = C^*, T = T^*, R = R^*$ so that;

$$\left.\begin{aligned} 0 &= \zeta(1-\alpha)(1-\gamma C) - \lambda_s S + (1-\eta)\omega A - \mu S + (1-k)\nu\rho T + \varepsilon R \\ 0 &= \lambda_s S - \omega A - \mu A \\ 0 &= \eta\omega A + \zeta(1-\alpha)\gamma C + (1-\upsilon)\rho T - \sigma C - \mu C \\ 0 &= \sigma C - \rho T - \mu T \\ 0 &= \zeta\alpha + k\upsilon\rho T - \varepsilon R - \mu R \end{aligned}\right\} \tag{3.60}$$

$$S^* = -\left(\frac{(\mu+\omega)(\zeta\gamma(\mu+\rho)(\alpha-1)\rho\sigma\nu+\mu^2+\mu\rho+\mu\sigma)\varepsilon(\alpha\mu-\varepsilon-\mu)}{L}\right) \tag{3.61}$$

$$A^* = \left(\frac{S^*}{\Lambda(\mu+\omega)}\right) \tag{3.62}$$

$$C^* = -\left(\frac{(\mu+\rho)\eta\omega\Lambda\xi(\alpha\mu-\varepsilon-\mu)}{L}\right) \tag{3.63}$$

$$T^* = \left(\frac{C^*}{\sigma(\mu+\rho)}\right) \tag{3.64}$$

$$R^* = \left(\frac{H}{L}\right) \tag{3.65}$$

where

$L = \mu(\Lambda\eta k\omega\rho\sigma\upsilon + \Lambda\zeta\alpha\varepsilon\gamma\mu + \Lambda\zeta\alpha\varepsilon\gamma\rho + \Lambda\zeta\alpha\gamma\mu^2 + \Lambda\zeta\alpha\gamma\mu\rho + \zeta\alpha\varepsilon\gamma\mu^2 + \zeta\alpha\varepsilon\gamma\mu\omega + \zeta\alpha\varepsilon\gamma\mu\rho + \zeta\alpha\gamma\mu^3 + \zeta\alpha\gamma\mu^2\omega + \zeta\alpha\gamma\mu^2\rho + \zeta\alpha\gamma\mu\omega\rho - \Lambda\zeta\varepsilon\gamma\mu - \Lambda\zeta\varepsilon\gamma\rho - \Lambda\zeta\gamma\mu^2 - \Lambda\zeta\gamma\mu\rho + \Lambda\varepsilon\eta\mu\omega + \Lambda\varepsilon\eta\omega\rho + \Lambda\varepsilon\eta\omega\sigma + \Lambda\varepsilon\rho\sigma\upsilon + \Lambda\eta\mu^2\omega + \Lambda\eta\mu\omega\rho + \Lambda\eta\mu\omega\sigma + \Lambda\mu\rho\sigma\upsilon - \zeta\varepsilon\gamma\mu^2 - \zeta\varepsilon\gamma\mu\omega - \zeta\varepsilon\gamma\mu\rho - \zeta\gamma\mu^3 - \zeta\gamma\mu^2\omega - \zeta\gamma\mu^2\rho - \zeta\gamma\mu\omega\rho + \varepsilon\mu\rho\sigma\upsilon + \varepsilon\omega\rho\sigma\upsilon + \mu^2\rho\sigma\upsilon + \mu\omega\rho\sigma\upsilon + \Lambda\varepsilon\mu^2 + \Lambda\varepsilon\mu\rho + \Lambda\varepsilon\mu\sigma + \Lambda\mu^3 + \Lambda\mu^2\rho + \Lambda\mu^2\sigma + \varepsilon\mu^3 + \varepsilon\mu^2\rho + \varepsilon\mu^2\sigma + \varepsilon\mu\omega\rho + \varepsilon\mu\omega\sigma + \mu^4 + \mu^3\omega + \mu^3\rho + \mu^3\sigma + \mu^2\omega\rho + \mu^2\omega\sigma$

$H = (\alpha^2 - \alpha)\gamma\mu^3 + (\Lambda + \omega + \rho)\alpha^2 + (-\Lambda - \omega - \rho)\alpha)\gamma\mu^2 + (\Lambda\rho + \omega\rho)\alpha^2 + (-\Lambda\rho - \omega\rho)\alpha)\gamma\mu)\zeta^2 + (\alpha\mu^4 + (\rho + \omega + \sigma + \Lambda)\alpha\mu^3 + ((\sigma\nu + \Lambda + \omega)\rho + (\eta\omega + \sigma)\Lambda + \omega\sigma)\alpha\mu^2 + ((\eta\omega + \sigma\nu)\Lambda + \omega\sigma\nu)\rho + \Lambda\eta\omega\sigma)\alpha\mu + \Lambda\eta k\omega\rho\sigma\nu)\zeta$

The basic reproduction number is computed using the next generation matrix approach. To determine the next generation matrix for the model considered in case 2, the following are considered:

1. The number of ways that new infections can arise or be created

2. The number of ways that infections can be transferred between compartments

Then F_i and V_i are computed as follows:

$$F = \begin{bmatrix} \frac{\zeta\beta(1-\alpha\mu)}{\mu} & \frac{\zeta\xi\beta(1-\alpha\mu)}{\mu} \\ 0 & 0 \end{bmatrix}$$

$$V = \begin{bmatrix} \omega+\mu & 0 \\ -\eta\omega & -\zeta(1\text{-}\alpha)\gamma+(\sigma+\mu) \end{bmatrix}$$

$$V^{-1} = \begin{bmatrix} \frac{1}{\omega+\mu} & 0 \\ -\frac{\eta\omega}{(\omega+\mu)(\zeta(1\text{-}\alpha)\gamma+(\sigma+\mu))} & -\frac{1}{\zeta(1\text{-}\alpha)\gamma+(\sigma+\mu)} \end{bmatrix}$$

$R_0 = \rho(FV^{-1}) = max(\lambda_1, \lambda_2)$, that is the spectral radius of the given matrix which is its largest eigenvalue given by R_0

$$R_0 = \frac{\beta\zeta(1-\alpha)}{\mu(\omega+\mu)} - \frac{\xi\beta\zeta(1-\alpha)\eta\omega}{\mu(\omega+\mu)(\zeta(1\text{-}\alpha)\gamma+(\sigma+\mu))} \quad (3.66)$$

3.2.3 Local Stability Analysis of the Disease Free Equilibrium E_o

Theorem 3.2.1:E_o is locally asymptotically stable if $R_o < 1$ and unstable if $R_o > 1$.

Proof. The resulting matrix from the linearized model is $\frac{dX}{dt} = AX$

$X = (x_1, x_2, x_3, x_4, x_5)^T, (x_1, x_2, x_3, x_4, x_5) \in R_+^5$, and

$$A=\begin{pmatrix} -\beta\ A-\xi\beta\ -\mu & (1-\eta)\omega-\beta\ S & \zeta\gamma(\alpha-1)-\xi\beta\ S & (1-k)\upsilon\rho & \epsilon \\ \beta\ A+\xi\beta\ C & -\omega-\mu+\beta\ S & \xi\beta\ S & 0 & 0 \\ 0 & \omega\eta & \zeta\gamma(1-\alpha)-\sigma-\mu & (1-\upsilon)\rho & 0 \\ 0 & 0 & \sigma & -\rho-\mu & 0 \\ 0 & 0 & 0 & k\upsilon\rho & -\epsilon-\mu \end{pmatrix} \quad (3.67)$$

The resulting Jacobian matrix of (3.67) at E_o is

$$J(E_0)=\begin{pmatrix} -\mu-\lambda & (1-\eta)\omega-\beta S_0 & \zeta\gamma(\alpha-1)-\xi\beta S_0 & (1-k)\upsilon\rho & \epsilon \\ 0 & \beta S_0-\omega-\mu-\lambda & \xi\beta S_0 & 0 & 0 \\ 0 & \omega\eta & \zeta\gamma(1-\alpha)-\sigma-\mu-\lambda & (1-\upsilon)\rho & 0 \\ 0 & 0 & \sigma & -\rho-\mu-\lambda & 0 \\ 0 & 0 & 0 & k\upsilon\rho & -\epsilon-\mu-\lambda \end{pmatrix} \quad (3.68)$$

From (3.68) $\lambda_1=-\varepsilon-\mu, \lambda_2=-\rho-\mu, \lambda_3=-\mu$ and the resulting quadratic equation is:

$$f(\lambda)=\lambda^2+(\zeta\alpha\gamma-\zeta\gamma-\beta S_0+2\mu+\omega+\sigma)\lambda-\zeta\alpha\beta\gamma S_0-\beta\eta\omega S_0\xi+\zeta\alpha\gamma\mu+\omega\sigma+\zeta\alpha\gamma\omega+\zeta\beta\gamma S_0-$$

$$\zeta\gamma\mu-\zeta\gamma\omega-\beta\mu S_0-\beta\sigma S_0+\mu^2+\mu\omega+\mu\sigma \quad (3.69)$$

Now, $\lambda_1, \lambda_2<0$ since the values are assumed positive. If $R_o<1$, therefore, E_o is stable and unstable when $R_o>1$.

3.2.4 Global Stability of the Disease Free Equilibrium

The global behavior of the equilibrium system (3.54) is analyzed here in this section.

Theorem 3.2.2: For system (3.54), the disease-free equilibrium E_o is asymptotically stable globally if $R_0<1$.

Proof: Considering the Lyapunov function defined as:

$$G(A, C, T) = \mu a_5(\sigma a_2 + a_1 a_4 - a_3 a_4)A + \xi\beta\zeta(\alpha\mu - \mu - \varepsilon)a_4 C + \xi\beta\zeta(\alpha\mu - \mu - \varepsilon)a_2 T \quad (3.70)$$

$$G' = \mu a_5(\sigma a_2 + a_1 a_4 - a_3 a_4)A' + \xi\beta\zeta(\alpha\mu - \mu - \varepsilon)a_4 C' + \xi\beta\zeta(\alpha\mu - \mu - \varepsilon)a_2 T' \quad (3.71)$$

$$G' = \mu a_5(\sigma a_2 + a_1 a_4 - a_3 a_4)\left[(\beta A + \xi\beta C)\left(\frac{-\zeta(\alpha\mu-\mu-\varepsilon)}{\mu a_5}\right) - a_0 A\right] + \xi\beta\zeta(\alpha\mu - \mu - \varepsilon)a_4[\eta\omega A + a_1 C + a_2 T - a_3 C] + \xi\beta\zeta(\alpha\mu - \mu - \varepsilon)a_2[\sigma C - a_4 T] \quad (3.72)$$

where $a_0 = (\omega + \mu),\ a_1 = \zeta(1\text{-}\alpha)\gamma,\ a_2 = (1 - \upsilon)\rho\ , a_3 = (\sigma + \mu),\quad a_4 = (\rho + \mu), a_5 = (\varepsilon + \mu), S = \frac{\zeta(1-\alpha\mu)}{\mu}$

Expanding (3.72) gives:

$$G' = \mu a_0 a_5(\sigma a_2 + a_1 a_4 - a_3 a_4)\left[\frac{-\beta\zeta(\alpha\mu-\mu-\varepsilon)}{\mu a_0 a_5} + \frac{\xi\beta\zeta a_4\eta\omega(\alpha\mu-\mu-\varepsilon)}{\mu a_0 a_5(\sigma a_2 + a_1 a_4 - a_3 a_4)} - 1\right]A + [-\xi\beta\sigma a_2\zeta(\alpha\mu - \mu - \varepsilon) - a_1 a_4\xi\beta\sigma a_2\zeta(\alpha\mu - \mu - \varepsilon) + \xi\beta\sigma a_2\zeta(\alpha\mu - \mu - \varepsilon)a_3 a_4)(-\zeta(\alpha\mu - \mu - \varepsilon)) + \xi\beta\zeta(\alpha\mu - \mu - \varepsilon)a_4 a_1 - \xi\beta\zeta(\alpha\mu - \mu - \varepsilon)a_4 a_3 + \sigma\xi\beta\zeta(\alpha\mu - \mu - \varepsilon)a_2]C + [\xi\beta\zeta(\alpha\mu - \mu - \varepsilon)a_4 a_2 - \xi\beta\zeta(\alpha\mu - \mu - \varepsilon)a_4 a_2]T \quad (3.73)$$

Simplifying (3.73) gives;

$$\boldsymbol{G'} = \mu a_0 a_5(\sigma a_2 + a_1 a_4 - a_3 a_4)\left[\frac{-\beta\zeta(\alpha\mu-\mu-\varepsilon)}{\mu a_0 a_5} + \frac{\xi\beta\zeta a_4\eta\omega(\alpha\mu-\mu-\varepsilon)}{\mu a_0 a_5(\sigma a_2 + a_1 a_4 - a_3 a_4)} - 1\right]A \quad (3.74)$$

$$\boldsymbol{G'} = \mu a_0 a_5(\sigma a_2 + a_1 a_4 - a_3 a_4)[R_0 - 1]A \quad (3.75)$$

$$\Rightarrow \boldsymbol{G'} \leq 0, if\ R_0 \leq 1. \quad (3.76)$$

Thus, the disease-free equilibrium is globally asymptotically stable.

3.2.5 Bifurcation Analysis

Here, bifurcation analysis is performed at the disease-free equilibrium by center manifold theory as presented in (Buonomo and Lacitignola, 2011).

Now, the focus is on the disease-free equilibrium E_0 and investigates the occurrence of the transcritical bifurcation at $R_0 = 1$.

The Jacobian matrix of equation (3.68) at the disease-free equilibrium E_0 is given by

$$J(E_0) = \begin{pmatrix} -\mu & (1-\eta)\omega - \beta S & \zeta\gamma(\alpha-1) - \xi\beta S & (1-k)\upsilon\rho & \epsilon \\ 0 & \beta S - \omega - \mu & \xi\beta S & 0 & 0 \\ 0 & \omega\eta & \zeta\gamma(1-\alpha) - \sigma - \mu & (1-\upsilon)\rho & 0 \\ 0 & 0 & \sigma & -\rho - \mu & 0 \\ 0 & 0 & 0 & k\upsilon\rho & -\epsilon - \mu \end{pmatrix} \tag{3.77}$$

The Centre Manifold Theorem as stated in Theorem 1.4 is now applied to determine if the model system (3.54) exhibit a backward or forward bifurcation at$R_0 = 1$ as follows:

Recall that

$$R_0 = \frac{\beta\zeta(1-\alpha)}{\mu(\omega+\mu)} - \frac{\xi\beta\zeta(1-\alpha)\eta\omega}{\mu(\omega+\mu)(\zeta(1\text{-}\alpha)\gamma + (\sigma+\mu))}$$

Let $\beta = \beta^*$ be a bifurcation parameter and if the case $R_0 = 1$ is considered.

By solving for $\beta = \beta^*$, then

$$\frac{\beta\zeta(1-\alpha)}{\mu(\omega+\mu)} - \frac{\xi\beta\zeta(1-\alpha)\eta\omega}{\mu(\omega+\mu)(\zeta(1\text{-}\alpha)\gamma+(\sigma+\mu))} = 1 \tag{3.78}$$

$$\beta = \beta^* = -\frac{\mu(\omega+\mu)(\zeta(1-\alpha)\gamma-(\sigma+\mu))}{(\zeta(1-\alpha)\gamma-\xi\eta\omega-(\sigma+\mu))(\zeta(1-\alpha))} \tag{3.79}$$

The Jacobian matrix of equation (3.54) at the disease-free equilibrium E_0, β^* is given by

$$J(E_0,\beta^*) = \begin{pmatrix} -\mu & (1-\eta)\omega - \beta^* S & \zeta\gamma(\alpha-1) - \xi\beta^* S & (1-k)\upsilon\rho & \epsilon \\ 0 & \beta^* S - \omega - \mu & \xi\beta^* S & 0 & 0 \\ 0 & \omega\eta & \zeta\gamma(1-\alpha) - \sigma - \mu & (1-\upsilon)\rho & 0 \\ 0 & 0 & \sigma & -\rho - \mu & 0 \\ 0 & 0 & 0 & k\upsilon\rho & -\epsilon - \mu \end{pmatrix} \tag{3.80}$$

The characteristic equation of (3.80) has a simple zero eigenvalue i.e.

$$|J(E_0,\beta^*) - \lambda \mathrm{I}| = 0 \tag{3.81}$$

$\lambda_1 = -\varepsilon - \mu, \lambda_2 = -\rho - \mu, \lambda_3 = -\mu$ and the resulting quadratic equation is:

$$f(\lambda) = \lambda^2 + (\zeta\alpha\gamma - \zeta\gamma - \beta^* S + 2\mu + \omega + \sigma)\lambda - \zeta\alpha\beta^*\gamma S - \beta^*\eta\omega S\xi + \zeta\alpha\gamma\mu + \omega\sigma +$$

$$\zeta\alpha\gamma\omega + \zeta\beta^*\gamma S - \zeta\gamma\mu - \zeta\gamma\omega - \beta^*\mu S - \beta^*\sigma S + \mu^2 + \mu\omega + \mu\sigma \tag{3.82}$$

Equation (3.82) gives two negative eigenvalues as its roots (by Descartes rule of signs). Thus, $\lambda_4 = 0$ is a simple zero eigenvalue and the other eigenvalues are real and negative, then the assumptions of theorem 1.9 (Centre Manifold theorem) is then verified.

Furthermore, the right eigenvector associated with the zero eigenvalue $\lambda_2 = 0$ given by $w = (w_1, w_2, w_3, w_4, w_5)^T$ are obtained as follows:

$$\begin{pmatrix} -\mu & (1-\eta)\omega - \beta^* S & \zeta\gamma(\alpha-1) - \xi\beta^* S & (1-k)\upsilon\rho & \epsilon \\ 0 & \beta^* S - \omega - \mu & \xi\beta^* S & 0 & 0 \\ 0 & \omega\eta & \zeta\gamma(1-\alpha) - \sigma - \mu & (1-\upsilon)\rho & 0 \\ 0 & 0 & \sigma & -\rho - \mu & 0 \\ 0 & 0 & 0 & k\upsilon\rho & -\epsilon - \mu \end{pmatrix} \begin{pmatrix} w_1 \\ w_2 \\ w_3 \\ w_4 \\ w_5 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} \tag{3.83}$$

$$-\mu w_1 + ((1-\eta)\omega - \beta^* S)w_2 + (\zeta\gamma(\alpha-1) - \xi\beta^* S)w_3 + ((1-k)\nu\rho)w_4 + \varepsilon w_5 = 0 \quad (3.84)$$

$$(\beta^* S - \omega - \mu)w_2 + (\xi\beta^* S)w_3 = 0 \quad (3.85)$$

$$\eta\omega w_2 + (\zeta\gamma(1-\alpha) - \sigma - \mu)w_3 + ((1-\nu)\rho)w_4 = 0 \quad (3.86)$$

$$\sigma w_3 + (-\rho - \mu)w_4 = 0 \quad (3.87)$$

$$k\nu\rho w_4 + (-\varepsilon - \mu)w_5 = 0 \quad (3.88)$$

Solving equations (3.84) - (3.88) simultaneously gives

$$w_1 = -\frac{1}{\eta\omega\sigma(\mu+\epsilon)}\begin{pmatrix} \eta\, k\omega\rho\sigma\upsilon + \zeta\alpha\,\epsilon\,\gamma\mu + \zeta\alpha\,\epsilon\,\gamma\rho + \zeta\alpha\gamma\mu^2 + \zeta\alpha\gamma\mu\rho - \zeta\,\epsilon\,\gamma\mu - \zeta\,\epsilon\,\gamma\rho \\ -\zeta\gamma\mu^2 - \zeta\gamma\mu\rho + \epsilon\,\eta\mu\omega + \epsilon\,\eta\omega\rho + \epsilon\,\eta\omega\sigma + \epsilon\,\rho\sigma\upsilon + \mu^2\eta\omega + \mu\rho\eta\omega + \\ \mu\sigma\eta\omega + \mu\rho\sigma\upsilon + \epsilon\,\mu^2 + \epsilon\,\mu\rho + \epsilon\,\mu\sigma + \mu^3 + \mu^2\rho + \mu^2\sigma \end{pmatrix} w_4$$

$$w_2 = \frac{(\zeta\alpha\gamma\mu + \zeta\alpha\gamma\rho - \zeta\gamma\mu - \zeta\gamma\rho + \rho\sigma\upsilon + \mu^2 + \mu\rho + \mu\sigma)w_4}{\eta\omega\sigma}$$

$$w_3 = \frac{(\rho+\mu)w_4}{\sigma}$$

$$w_5 = \frac{k\upsilon\rho w_4}{\mu+\epsilon}$$

Therefore;

$$w = \begin{pmatrix} -\frac{1}{\eta\omega\sigma(\mu+\epsilon)}\begin{pmatrix} \eta\, k\omega\rho\sigma\upsilon + \zeta\alpha\,\epsilon\,\gamma\mu + \zeta\alpha\,\epsilon\,\gamma\rho + \zeta\alpha\gamma\mu^2 + \zeta\alpha\gamma\mu\rho - \zeta\,\epsilon\,\gamma\mu - \zeta\,\epsilon\,\gamma\rho \\ -\zeta\gamma\mu^2 - \zeta\gamma\mu\rho + \epsilon\,\eta\mu\omega + \epsilon\,\eta\omega\rho + \epsilon\,\eta\omega\sigma + \epsilon\,\rho\sigma\upsilon + \mu^2\eta\omega + \mu\rho\eta\omega + \\ \mu\sigma\eta\omega + \mu\rho\sigma\upsilon + \epsilon\,\mu^2 + \epsilon\,\mu\rho + \epsilon\,\mu\sigma + \mu^3 + \mu^2\rho + \mu^2\sigma \end{pmatrix} w_4, \\ \frac{(\zeta\alpha\gamma\mu + \zeta\alpha\gamma\rho - \zeta\gamma\mu - \zeta\gamma\rho + \rho\sigma\upsilon + \mu^2 + \mu\rho + \mu\sigma)w_4}{\eta\omega\sigma}, \frac{(\rho+\mu)w_4}{\sigma}, w_4, \frac{k\upsilon\rho w_4}{\mu+\epsilon} \end{pmatrix}^T$$

where $w_4 > 0$ is a free right eigenvector.

Similarly, the left eigenvector associated with the zero eigenvalue is computed as follows:

Let the left eigenvector associated with the zero eigenvalue $\lambda_4 = 0$ given by

$$l = \left(l_1, l_2, l_3, l_4, l_5\right)$$

then,

$$l\begin{pmatrix} -\mu & (1-\eta)\omega - \beta^* S & \zeta\gamma(\alpha-1) - \xi\beta^* S & (1-k)\upsilon\rho & \epsilon \\ 0 & \beta^* S - \omega - \mu & \xi\beta^* S & 0 & 0 \\ 0 & \omega\eta & \zeta\gamma(1-\alpha) - \sigma - \mu & (1-\upsilon)\rho & 0 \\ 0 & 0 & \sigma & -\rho - \mu & 0 \\ 0 & 0 & 0 & k\upsilon\rho & -\epsilon - \mu \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} \tag{3.89}$$

$$l_1(-\mu) = 0 \tag{3.90}$$

$$l_1((1-\eta)\omega - \beta^* S) + l_2(\beta^* S - \omega - \mu)) + l_3\eta\omega = 0 \tag{3.91}$$

$$l_1(\zeta\gamma(\alpha-1) - \xi\beta^* S) + l_3(\zeta\gamma(1-\alpha) - \sigma - \mu) + l_4\sigma = 0 \tag{3.92}$$

$$l_1((1-k)\nu\rho) + l_3((1-\nu)\rho) + l_4(-\rho - \mu) + l_5(k\nu\rho) \tag{3.93}$$

$$l_1\varepsilon + l_5(-\varepsilon - \mu) = 0 \tag{3.94}$$

The simultaneous solution of equations (3.90) - (3.94) yields:

$$l_1 = 0, l_2$$

$$= \frac{(\zeta\alpha\gamma\mu + \zeta\alpha\gamma\rho + \eta\omega\mu\xi + \eta\omega\rho\xi + \eta\omega\sigma\xi - \zeta\gamma\mu - \xi\gamma\rho + \rho\sigma\nu + \mu^2 + \mu\rho + \mu\sigma)l_3}{\mu^2\xi + \mu\omega\xi + \mu\rho\xi + \mu\sigma\xi + \omega\rho\xi + \omega\sigma\xi}, l_3$$

$$= l_3, l_4 = \frac{(\zeta\alpha\gamma\xi - \rho\nu\xi + \mu\xi + \rho\xi + \sigma\xi)l_3}{\mu\xi + \rho\xi + \sigma\xi}, l_5 = 0$$

therefore,

l

$$= \begin{bmatrix} 0, \dfrac{(\zeta\alpha\gamma\mu + \zeta\alpha\gamma\rho + \eta\omega\mu\xi + \eta\omega\rho\xi + \eta\omega\sigma\xi - \zeta\gamma\mu - \xi\gamma\rho + \rho\sigma\nu + \mu^2 + \mu\rho + \mu\sigma)l_3}{\mu^2\xi + \mu\omega\xi + \mu\rho\xi + \mu\sigma\xi + \omega\rho\xi + \omega\sigma\xi}, \\ \dfrac{(\zeta\alpha\gamma\xi - \rho\nu\xi + \mu\xi + \rho\xi + \sigma\xi)l_3}{\mu\xi + \rho\xi + \sigma\xi}, 0 \end{bmatrix}$$

where $l_3 > 0$ is a free left eigenvector.

3.2.5.1 The Computation of the Coefficient a and b for Model Case 2

The coefficients (as defined in theorem 1.4):

$$a = \sum_{m,i,j=1}^{5} l_m w_i w_j \frac{\partial^2 f_m(E_0, \beta^*)}{\partial x_i \partial x_j}, b = \sum_{m,i,j=1}^{5} l_m w_i \frac{\partial^2 f_m(E_0, \beta^*)}{\partial x_i \partial \varphi}$$

may now be explicitly computed taking into account of system (3.54) and considering only the nonzero components of the left eigenvector l it follows that:

$S = x_1, A = x_2, C = x_3, T = x_4, R = x_5.$

Furthermore, introducing the vector $X = (x_1, x_2, x_3, x_4, x_5)^T$, then the model in system (3.54) can now be written in the form

$\frac{dX}{dt} = f(x)$, where $f = (f_1, f_2, f_3, f_4, f_5)^T$

It implies that system (3.54) can be written in term of the new variables as

$$\left.\begin{aligned}
\frac{\mathrm{dx}_1}{dt} &= f_1 = \zeta(1-\alpha)(1-\gamma x_3) - (\beta x_2 + \xi\beta x_3)x_1 + (1-\eta)\omega x_2 - \mu x_1 + (1-k)\nu\rho x_4 + \varepsilon x_5 \\
\frac{\mathrm{dx}_2}{dt} &= f_2 = (\beta x_2 + \xi\beta x_3)x_1 - (\omega+\mu)x_2 \\
\frac{\mathrm{dx}_3}{dt} &= f_3 = \eta\omega x_2 + \zeta(1-\alpha)\gamma x_3 + (1-\upsilon)\rho x_4 - (\sigma+\mu)x_3 \\
\frac{\mathrm{dx}_4}{dt} &= f_4 = \sigma x_3 - (\rho+\mu)x_4 \\
\frac{\mathrm{dx}_5}{dt} &= f_5 = \zeta\alpha + k\upsilon\rho x_4 - (\varepsilon+\mu)x_5
\end{aligned}\right\} \quad (3.95)$$

$$a = 2l_2w_1w_3\frac{\partial^2 f_2(E_0,\beta^*)}{\partial x_1\partial x_3} + 2l_2w_1w_4\frac{\partial^2 f_2(E_0,\beta^*)}{\partial x_1\partial x_4} + 2l_2w_1w_2\frac{\partial^2 f_2(E_0,\beta^*)}{\partial x_1\partial x_2}$$

$$\frac{\partial^2 f_2(E_0,\beta^*)}{\partial x_1\partial x_3} = \xi\beta^*, \qquad \frac{\partial^2 f_2(E_0,\beta^*)}{\partial x_1\partial x_4} = \xi\beta^*, \quad \frac{\partial^2 f_2(E_0,\beta^*)}{\partial x_1\partial x_2} = \beta^*$$

$$\therefore a = 2l_2w_1w_3\xi\beta^* + 2l_2w_1w_4\xi\beta^* + 2l_2w_1w_2\beta^*$$

$$a = 2l_2w_1\beta^*(w_3\xi + w_4\xi + w_2)$$

$$b = l_2w_1(x_3\xi + x_4\xi + x_2) + l_2x_1w_2 + l_2x_1w_3\xi + l_2x_1w_4\xi$$

$$\mathrm{a} = -\frac{1}{\sigma\eta\omega(\mu+\epsilon)}\big(2\beta l_2(\zeta\alpha\epsilon\gamma\mu + \zeta\alpha\epsilon\gamma\rho + \zeta\alpha\gamma\mu^2 + \zeta\alpha\gamma\mu\rho + 6\eta\omega\rho\sigma\upsilon - \zeta\epsilon\gamma\mu - \zeta\epsilon\gamma\rho -$$

$$\zeta\gamma\mu^2 - \zeta\gamma\mu\rho + \epsilon\eta\mu\omega + \epsilon\eta\omega\rho + \epsilon\eta\omega\sigma + \epsilon\eta\omega\sigma + \epsilon\rho\sigma\upsilon + \mu^2\eta\omega + \mu\rho\eta\omega + \mu\sigma\eta\omega +$$

$$\mu\rho\sigma\upsilon + \epsilon\mu^2 + \epsilon\mu\rho + \epsilon\mu\sigma + \mu^3 + \mu^2\rho + \mu^2\sigma)\big)$$

$$b = \frac{\left((\zeta\alpha\gamma\mu+\zeta\alpha\gamma\rho+\eta\omega\mu\xi+\eta\omega\rho\xi+\eta\omega\sigma\xi-\zeta\gamma\mu-\zeta\gamma\rho+\rho\sigma\upsilon+\mu^2+\mu\rho+\mu\sigma)l_3w_2\zeta(\alpha\mu-\epsilon-\mu)\right)}{\left((\mu^2\xi+\mu\omega\xi+\mu\rho\xi+\mu\sigma\xi+\omega\rho\xi+\omega\sigma\xi)\mu(\mu+\epsilon)\right)} +$$

$$\frac{\left((\zeta\alpha\gamma\mu+\zeta\alpha\gamma\rho+\eta\omega\mu\xi+\eta\omega\rho\xi+\eta\omega\sigma\xi-\zeta\gamma\mu-\zeta\gamma\rho+\rho\sigma\upsilon+\mu^2+\mu\rho+\mu\sigma)l_3w_3\xi\zeta(\alpha\mu-\epsilon-\mu)\right)}{\left((\mu^2\xi+\mu\omega\xi+\mu\rho\xi+\mu\sigma\xi+\omega\rho\xi+\omega\sigma\xi)\mu(\mu+\epsilon)\right)} +$$

$$\frac{\left((\zeta\alpha\gamma\mu+\zeta\alpha\gamma\rho+\eta\omega\mu\xi+\eta\omega\rho\xi+\eta\omega\sigma\xi-\zeta\gamma\mu-\zeta\gamma\rho+\rho\sigma\upsilon+\mu^2+\mu\rho+\mu\sigma)l_3w_4\xi\zeta(\alpha\mu-\epsilon-\mu)\right)}{\left((\mu^2\xi+\mu\omega\xi+\mu\rho\xi+\mu\sigma\xi+\omega\rho\xi+\omega\sigma\xi)\mu(\mu+\epsilon)\right)}$$

The coefficient b is always positive so that according to theorem 1.4, it is the sign of the coefficient a that decides the local dynamics around the disease-free equilibrium for $\beta = \beta^*$. Thus, the following result is established.

Theorem 3.2.3: the unique equilibrium $E^*$is locally asymptotically stable for $R_0 > 1$. Since $a < 0$, locally stability of E^*implies its global stability

3.2.6 Local Stability of Endemic Equilibrium

Theorem 3.2.4: If $R_0 > 1$, then the endemic equilibrium is locally asymptotically stable.

Proof: The endemic equilibria of system (3.54), denoted by$(S^*, A^*, C^*, T^*, R^*)$, can be rewritten as:

Let $S = x + S^*, A = y + A^*, C = z + C^*, T = p + T^*, R = j + R^*$

$$J = \begin{pmatrix} -\beta A - \xi\beta - \mu & (1-\eta)\omega - \beta S & \zeta\gamma(\alpha-1) - \xi\beta S & (1-k)\upsilon\rho & \epsilon \\ \beta A + \xi\beta C & -\omega - \mu + \beta S & \xi\beta S & 0 & 0 \\ 0 & \omega\eta & \zeta\gamma(1-\alpha) - \sigma - \mu & (1-\upsilon)\rho & 0 \\ 0 & 0 & \sigma & -\rho - \mu & 0 \\ 0 & 0 & 0 & k\upsilon\rho & -\epsilon - \mu \end{pmatrix} \quad (3.96)$$

(3.96) can be rewritten as:

$$J=\begin{pmatrix} b_1-\lambda & (1-\eta)\omega-\beta\, S & b_2 & (1-k)\upsilon\rho & \epsilon \\ b_3 & -\omega-\mu+\beta\, S-\lambda & \xi\beta\, S & 0 & 0 \\ 0 & \omega\eta & b_4-\lambda & (1-\upsilon)\rho & 0 \\ 0 & 0 & \sigma & -\rho-\mu-\lambda & 0 \\ 0 & 0 & 0 & k\upsilon\rho & -\epsilon-\mu-\lambda \end{pmatrix} \quad (3.97)$$

From (3.97), $\lambda_1=-(\epsilon+\mu), \lambda_2=-(\rho+\mu)$,then ;

$$J=\begin{bmatrix} b_1-\lambda & (1-\eta)\omega-\beta\, S & b_2 \\ b_3 & -\omega-\mu+\beta\, S-\lambda & \xi\beta\, S \\ 0 & \omega\eta & b_4-\lambda \end{bmatrix} \quad (3.98)$$

from (3.98) we have;

$$\lambda^3+(\mu+\omega-\beta S-b_1-b_4)\lambda^2+(\beta S b_1+\beta S b_3+\beta S b_4+\omega\eta b_3-\xi\beta\, S\omega\eta-\mu b_1-\mu b_4-\omega b_1-\omega b_3-\omega b_4+b_1 b_4)\lambda+\xi\beta\, S\omega\eta b_1-\beta S b_1 b_4-\beta S b_3 b_4-\omega\eta b_2 b_3-\omega\eta b_3 b_4+\mu b_1 b_4+\omega b_1 b_4+\omega b_3 b_4$$

The result of the determinant of the Jacobian matrix is of the form:

$$a_0\lambda^3+a_1\lambda^2+a_2\lambda+a_3 \quad (3.99)$$

where

$a_0=1$

$a_1=\mu+\omega-\beta S-b_1-b_4$

$a_2=\beta S b_1+\beta S b_3+\beta S b_4+\omega\eta b_3-\xi\beta\, S\omega\eta-\mu b_1-\mu b_4-\omega b_1-\omega b_3-\omega b_4+b_1 b_4$

$$a_3 = \xi\beta\ S\omega\eta b_1 - \beta S b_1 b_4 - \beta S b_3 b_4 - \omega\eta b_2 b_3 - \omega\eta b_3 b_4 + \mu b_1 b_4 + \omega b_1 b_4 + \omega b_3 b_4$$

By Routh-Hurwitz criterion governing the polynomials of order 3, we have the following:

1. $a_2 . a_3$are positive

2. $a_1 a_2 > a_3$

From equation (3.99)1 and 2 are satisfied.

Therefore, endemic equilibrium is locally asymptotically stable.

3.2.7 Global Stability of the Endemic Equilibrium

Theorem 3.2.5: The equations of the model have a positive distinctive endemic equilibrium whenever R_0> 1, which is said to be globally asymptotically stable.

Proof: Considering the Lyapunov function defined as:

$$L(S^*, A^*, C^*, T^*, R^*) = \left(S - S^* ln\left(\frac{S}{S^*}\right)\right) + \left(A - A^* ln\left(\frac{A}{A^*}\right)\right) + \left(C - C^* ln\left(\frac{C}{C^*}\right)\right) + \left(T - T^* ln\left(\frac{T}{T^*}\right)\right) + \left(R - R^* ln\left(\frac{R}{R^*}\right)\right) \quad (3.100)$$

where L takes it derivative along the system directly as:

$$\frac{dL}{dt} = \left(1 - \frac{S^*}{S}\right)\frac{dS}{dt} + \left(1 - \frac{A^*}{A}\right)\frac{dA}{dt} + \left(1 - \frac{C^*}{C}\right)\frac{dC}{dt} + \left(1 - \frac{T^*}{T}\right)\frac{dT}{dt} + \left(1 - \frac{R^*}{R}\right)\frac{dR}{dt} \quad (3.101)$$

$$\frac{dL}{dt} = \left(1 - \frac{S^*}{S}\right)[\zeta(1-\alpha)(1-\gamma C) - (\beta A + \xi\beta C)S + (1-\eta)\omega A - \mu S + (1-k)\nu\rho T + \varepsilon R] +$$

$$\left(1 - \frac{A^*}{A}\right)[(\beta A + \xi\beta C)S - (\omega + \mu)A] + \left(1 - \frac{C^*}{C}\right)[\eta\omega A + (1-\upsilon)\rho T - (\sigma + \mu - \zeta(1 -$$

$$\alpha)\gamma)C] + \left(1 - \frac{T^*}{T}\right)[\sigma C - (\rho + \mu)T] + \left(1 - \frac{R^*}{R}\right)[\zeta\alpha + k\upsilon\rho T - (\varepsilon + \mu)R] \quad (3.102)$$

At equilibrium,

$$\left.\begin{aligned} \zeta(1-\alpha)(1-\gamma C) &= (\beta A^* + \xi\beta C^*)S^* - (1-\eta)\omega A^* + \mu S^* - (1-k)\nu\rho T^* - \varepsilon R^* \\ (\omega + \mu) &= \frac{(\beta A^* + \xi\beta C^*)S^*}{A^*} \\ (\sigma + \mu - \zeta(1-\alpha)\gamma) &= \frac{\eta\omega A^* + (1-\upsilon)\rho T^*}{C^*} \\ (\rho + \mu) &= \frac{\sigma C^*}{T^*} \\ (\varepsilon + \mu) &= \frac{\zeta\alpha + k\upsilon\rho T^*}{R^*} \end{aligned}\right\} \quad (3.103)$$

$$\frac{dL}{dt} = \left(1 - \frac{S^*}{S}\right)[(\beta A^* + \xi\beta C^*)S^* - (1-\eta)\omega A^* + \mu S^* - (1-k)\nu\rho T^* - \varepsilon R^* - (\beta A +$$

$$\xi\beta C)S + (1-\eta)\omega A - \mu S + (1-k)\nu\rho T + \varepsilon R] + \left(1 - \frac{A^*}{A}\right)\left[(\beta A + \xi\beta C)S -\right.$$

$$\left.\frac{(\beta A^* + \xi\beta C^*)S^* A}{A^*}\right] + \left(1 - \frac{C^*}{C}\right)\left[\eta\omega A + (1-\upsilon)\rho T - \frac{\eta\omega A^* + (1-\upsilon)\rho T^* C}{C^*}\right] + \left(1 - \frac{T^*}{T}\right)\left[\sigma C -\right.$$

$$\left.\frac{\sigma C^* T}{T^*}\right] + \left(1 - \frac{R^*}{R}\right)\left[\zeta\alpha + k\upsilon\rho T - \frac{\zeta\alpha + k\upsilon\rho T^* R}{R^*}\right]$$

$$= \left(1 - \frac{S^*}{S}\right)\left[\begin{matrix}\beta A^* S^* + \xi\beta C^* S^* - (1-\eta)\omega A^* + \mu S^* - (1-k)\nu\rho T^* - \varepsilon R^* - \beta AS - \xi\beta CS \\ +(1-\eta)\omega A - \mu S + (1-k)\nu\rho T + \varepsilon R\end{matrix}\right] +$$

$$\left(1 - \frac{A^*}{A}\right)\left[\beta AS + \xi\beta CS + -\frac{\beta A^* S^* A}{A^*} - \frac{\xi\beta C^* S^* A}{A^*}\right] + \left(1 - \frac{C^*}{C}\right)\eta\omega A + (1-\upsilon)\rho T\left[1 - \frac{A^* T^* C}{ATC^*}\right] + \left(1 -\right.$$

$$\left.\frac{T^*}{T}\right)\sigma C\left[1 - \frac{C^* T}{CT^*}\right] + \left(1 - \frac{R^*}{R}\right)\zeta\alpha + k\upsilon\rho T\left[1 - \frac{T^* R}{TR^*}\right] \quad (3.104)$$

$$= \left(1 - \frac{S^*}{S}\right)\begin{bmatrix} -\beta AS\left(1 - \frac{A^*S^*}{AS}\right) - \xi\beta CS\left(1 - \frac{C^*S^*}{CS}\right) + (1-\eta)\omega A\left(1 - \frac{A^*}{A}\right) - \mu S\left(1 - \frac{S^*}{S}\right) \\ +(1-k)\nu\rho T\left(1 - \frac{T^*}{T}\right) + \varepsilon R\left(1 - \frac{R^*}{R}\right) \end{bmatrix} + \left(1 - \frac{A^*}{A}\right)\left[\beta AS\left(1 - \frac{A^*S^*}{SA^*}\right) + \xi\beta CS\left(1 - \frac{C^*S^*A}{SCA^*}\right)\right] + \eta\omega A + (1-\upsilon)\rho T\left(1 - \frac{C^*}{C}\right)\left[1 - \frac{A^*T^*C}{ATC^*}\right] + \sigma C\left(1 - \frac{T^*}{T}\right)\left[1 - \frac{C^*T}{CT^*}\right] + \zeta\alpha + k\upsilon\rho T\left(1 - \frac{R^*}{R}\right)\left[1 - \frac{T^*R}{TR^*}\right] \quad (3.105)$$

$$= -\mu S\left(1 - \frac{S^*}{S}\right)^2 - \beta AS\left(1 - \frac{S^*}{S}\right)\left(1 - \frac{A^*S^*}{AS}\right) - \xi\beta CS\left(1 - \frac{S^*}{S}\right)\left(1 - \frac{C^*S^*}{CS}\right) + (1-\eta)\omega A\left(1 - \frac{S^*}{S}\right)\left(1 - \frac{A^*}{A}\right) + (1-k)\nu\rho T\left(1 - \frac{S^*}{S}\right)\left(1 - \frac{T^*}{T}\right) + \varepsilon R\left(1 - \frac{S^*}{S}\right)\left(1 - \frac{R^*}{R}\right) + \beta AS\left(1 - \frac{A^*}{A}\right)\left(1 - \frac{A^*S^*}{SA^*}\right) + \xi\beta CS\left(1 - \frac{A^*}{A}\right)\left(1 - \frac{C^*S^*A}{SCA^*}\right) + \eta\omega A + (1-\upsilon)\rho T\left(1 - \frac{C^*}{C}\right)\left(1 - \frac{A^*T^*C}{ATC^*}\right) + \sigma C\left(1 - \frac{T^*}{T}\right)\left(1 - \frac{C^*T}{CT^*}\right) + \zeta\alpha + k\upsilon\rho T\left(1 - \frac{R^*}{R}\right)\left(1 - \frac{T^*R}{TR^*}\right)$$

$$= -\mu S\left(1 - \frac{S^*}{S}\right)^2 + P_1(S, A, C, T, R) + P_2(S, A, C, T, R) \quad (3.106)$$

where,

$$P_1(S, A, C, T, R) = -\beta AS\left(1 - \frac{S^*}{S}\right)\left(1 - \frac{A^*S^*}{AS}\right) - \xi\beta CS\left(1 - \frac{S^*}{S}\right)\left(1 - \frac{C^*S^*}{CS}\right)$$

$$P_2(S, A, C, T, R) = (1-\eta)\omega A\left(1 - \frac{S^*}{S}\right)\left(1 - \frac{A^*}{A}\right) + (1-k)\nu\rho T\left(1 - \frac{S^*}{S}\right)\left(1 - \frac{T^*}{T}\right) + \varepsilon R\left(1 - \frac{S^*}{S}\right)\left(1 - \frac{R^*}{R}\right) + \beta AS\left(1 - \frac{A^*}{A}\right)\left(1 - \frac{A^*S^*}{SA^*}\right) + \xi\beta CS\left(1 - \frac{A^*}{A}\right)\left(1 - \frac{C^*S^*A}{SCA^*}\right) + \eta\omega A + (1-\upsilon)\rho T\left(1 - \frac{C^*}{C}\right)\left(1 - \frac{A^*T^*C}{ATC^*}\right) + \sigma C\left(1 - \frac{T^*}{T}\right)\left(1 - \frac{C^*T}{CT^*}\right) + \zeta\alpha + k\upsilon\rho T\left(1 - \frac{R^*}{R}\right)\left(1 - \frac{T^*R}{TR^*}\right)$$

$P_1 \leq 0$ whenever $AS \geq A^*S^*, CS \geq C^*S^*, TS \geq T^*S^*$ (3.107)

and

$P_2 \leq 0$ whenever $A^*S \geq A^*S^*, A^*CS \geq AC^*S^*, TSA^* \geq T^*S^*A, ATC^* \geq A^*T^*C, CT^* \geq C^*T, TR^* \geq T^*R$ (3.108)

Thus,

$\frac{dL}{dt} \leq 0$ if the condition in (3.107) and (3.108) holds.

Therefore, by LaSalle asymptotic stability theorem (LaSalle, 1976), and Oke et al., (2020) the positive equilibrium state $\frac{dL}{dt}$ is globally asymptotically stable in the positive region R_+^5.

3.3 Mathematical Formulation, Analysis and Methods of Solutions for HBV Model Case 3

Some chronic carriers are unaware of their status and as such transmit the virus unknowingly and also at higher risk of cirrhosis and makes treatment less effective (Meffre *et al.*, 2004, Lin *et al.*, 2009, Piorkowsky, 2009, Cohen *et al.*,2011, Mcpherson *et al.*,2013, Niederau,2014).

In view of this, this model is developed to factor them in; where the population is divided into the following different groups, namely, the susceptible, the acute, the chronic unaware carriers, the chronic aware carriers, the treated chronic aware and the recovered individuals.

The total population at time t, denoted by $N(t)$ is divided into the 6 subgroups corresponding to different epidemiological status. Susceptible individuals $S(t)$, Acute $A(t)$, Unaware Chronically Infected $C_u(t)$, Aware Chronically infected $C_a(t)$, Treated

$T_c(t)$, Removed/Recovered Class $R(t)$. The model equation is subject to the initial conditions,

$$S(t) \geq 0, A(t) \geq 0, C_u(t) \geq 0, C_a(t) \geq 0, T_c(t) \geq 0, R(t) \geq 0 \quad (3.109)$$

Figure 3.3 represents schematically the epidemiology of HBV infected model. The different disease stages are reproduced by the different circle and the arrows indicate the way individual progress from one stage to the other. It is assumed that at time t, susceptible individual S, enter the population at a constant rate Π. In all classes, individuals die at a constant natural mortality rate, μ. HBV chronically infected individuals ($C_u(t)$, $C_a(t)$) have an additional death rate due to HBV, d_c Zhang and Zhang (2018**)**. It is assumed that HBV infected individuals on treatment, $T_c(t)$ do not transmit HBV infection. Susceptible individual $S(t)$, may acquire HBV infection when in contact with individuals in A, $C_u, and\ C_a$, populace at a rate λ (force of infection associated with HBV), where

$$\lambda = \frac{\beta(A+\alpha_1 C_u+\alpha_2 C_a)}{N} \quad (3.110)$$

Parameter β represent the probability that a contact will result in an HBV infection while $\alpha_1, \alpha_2 > 1$ respectively account for modification parameter of chronic HBV infected individuals

A proportion of the acute HBV infected individuals σ, spontaneously clear the virus, then return to been susceptible. The HBV acutely infected individuals develop the chronic without been aware if no testing at a rate, γ. The acutely infected and chronic unaware

individual progress to Chronic aware stage with a testing ν_1, ν_2 respectively and moved to treatment stage after testing at the rate $\delta.\omega$ is the recovery rate of treated infected individual with full immunity.

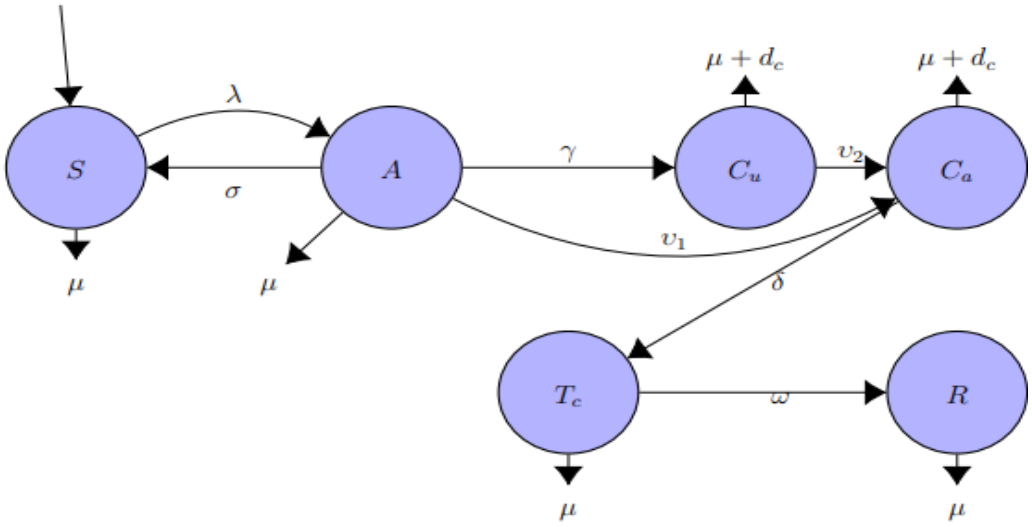

Figure 3.3:Compartmental flow diagram of HBV model case 3

These assumptions lead to the systems of equation in 3.111

$$\left.\begin{aligned}
\frac{dS}{dt} &= \Pi - \lambda S + \sigma A - \mu S \\
\frac{dA}{dt} &= \lambda S - (\sigma + \gamma + \nu_1)A \\
\frac{dC_u}{dt} &= \gamma A - (\nu_2 + \mu + d_c)C_u \\
\frac{dC_a}{dt} &= \nu_2 C_u + \nu_1 A - (\delta + \mu + d_c)C_a \\
\frac{dT_c}{dt} &= \delta C_a - (\omega + \mu)T_c \\
\frac{dR}{dt} &= \omega T_c\text{-}\mu R
\end{aligned}\right\} \qquad (3.111)$$

where $\lambda = \frac{\beta(A+\alpha_1 C_u+\alpha_2 C_a)}{N}$

3.3.1 Positivity and Boundedness of Solutions

For the system of equations (3.111) to be epidemiologically meaningful, it is important to prove that all solution with non-negative initial conditions will remain non-negative. The proof of the positivity and boundedness of system of equations in system (3.111) follows from Lemma 3.3.1 stated below:

Lemma 3.3.1: The initial values of the parameters are

$\{S(0) \geq 0, A(0) \geq 0, C_u(0) \geq 0, C_a(0) \geq 0, T_c(0) \geq 0, R(0) \geq ,0 and N(0) \geq 0\} \in \Phi$

Then the solution of the model $\{S(t), A(t), C_u(t), C_a(t), T_c(t), R(t), N(t)\}$ is positive for all $t \geq 0$.

Proof

Considering the first equation in (3.111),

$$\frac{dS}{dt} = \Pi - \lambda S + \sigma A - \mu S$$

$$\frac{dS}{dt} \geq -(\lambda + \mu)S$$

$$\int \frac{1}{S} dS \geq \int -(\lambda + \mu)\, dt$$

$$S \geq S_0 e^{-(\lambda+\mu)t} \geq 0$$

Hence, $S \geq 0$

with respect to the second equation in (3.111);

$$\frac{dA}{dt} = \lambda S - (\sigma + \gamma + \nu_1)A$$

$$\frac{dA}{dt} \geq -(\sigma + \gamma + \nu_1)A$$

$$\int \frac{1}{A} dA \geq \int -(\sigma + \gamma + \nu_1)\, dt$$

$$A \geq A_0 e^{-(\sigma+\gamma+\nu_1)t} \geq 0$$

Hence, $A \geq 0$

with respect to the third equation in (3.111);

$$\frac{dC_u}{dt} = \gamma A - (\nu_2 + \mu + d_c)C_u$$

$$\frac{dC_u}{dt} \geq -(\nu_2 + \mu + d_c)C_u$$

$$\int \frac{1}{C_u} dC_u \geq \int (\nu_2 + \mu + d_c)C_u\, dt$$

$$C_u \geq C_{u_0} e^{((\nu_2+\mu+d_c)t} \geq 0$$

Hence, $C_u \geq 0$

with respect to the fourth equation in (3.111);

$$\frac{dC_a}{dt} = \nu_2 C_u + \nu_1 A - (\delta + \mu + d_c)C_a$$

$$\frac{dC_a}{dt} \geq -(\delta + \mu + d_c)C_a$$

$$\int \frac{1}{C_a} dC_a \geq \int -(\delta + \mu + d_c)\, dt$$

$$C_a \geq C_{a_0} e^{-(\delta+\mu+d_c)t} \geq 0$$

Hence, $C_a \geq 0$

with respect to the fifth equation in (3.111);

$$\frac{dT_c}{dt} = \delta C_a - (\omega + \mu)T_c$$

$$\frac{dT_c}{dt} \geq -(\omega + \mu)T_c$$

$$\int \frac{1}{T_c} dT_c \geq \int -(\omega + \mu)\, dt$$

$$T_c \geq T_{c_0} e^{-(\omega+\mu)t} \geq 0$$

Hence, $T_c \geq 0$

with respect to the sixth equation in (3.111);

$\frac{dR}{dt} = \omega T_c$-$\mu R$

$$\frac{dR}{dt} \geq -\mu R$$

$$\int \frac{1}{R} dR \geq \int -\mu \, dt$$

$$R \geq R_0 e^{-\mu t} \geq 0$$

Hence, $R \geq 0$

Clearly, the above state variables are positive on bounding plane $\mathbb{R}_+^6$.

For the boundedness the following calculation follows:

$$N(t) = S(t) + A(t) + C_u(t) + C_a(t) + T_c(t) + R(t)$$

$$N' = S' + A' + C_u{}' + C_a{}' + T_c{}' + R'$$

$$N' = \Pi - \lambda S + \sigma A - \mu S + \lambda S - (\sigma + \gamma + \nu_1)A + \gamma A - (\nu_2 + \mu + d_c)C_u + \nu_2 C_u +$$

$$\nu_1 A - (\delta + \mu + d_c)C_a + \delta C_a - (\omega + \mu)T_c + \omega T_c\text{-}\mu R \quad (3.112)$$

Simplifying (3.112) gives:

$$N' = \Pi - \mu[S + A + C_u + C_a + T_c + R] - d_c C_u \quad (3.113)$$

$$N' + \mu N = \Pi - d_c C_u \quad (3.114)$$

$$N' + \mu N \leq \Pi \quad (3.115)$$

Integrating (3.115) gives:

$$N' \leq \frac{\Pi}{\mu} + ke^{-\mu t}$$

$$\max_{\lim_{n\to\infty}} N \leq \lim_{n\to\infty}\left(\frac{\Pi}{\mu} + ke^{-\mu t}\right) \leq \frac{\Pi}{\mu}$$

It follows that the solutions of the model system (3.111) are positive and bounded in the region

$$\mathcal{T} = \{(S + A + C_u + C_a + T_c + R)\} \in \mathbb{R}_+^6 : S + A + C_u + C_a + T_c + R \leq \frac{\Pi}{\mu}$$

It follows from Lemma 3.3.1 that it is sufficient to consider the dynamics of system (3.111) and the model can be considered to be epidemiologically well-posed.

3.3.2 Equilibrium Points and Reproduction Number

The disease-free equilibrium of the equation (3.111) exists and is given by:

$$(E_o) = \left[\frac{\Pi}{\mu}, 0,0,0,0,0\right] \tag{3.116}$$

The endemic steady states are calculated here which is done by setting system of equation in (3.111) to zero and setting $S = S^*, A = A^*, C_u = {C_u}^*, C_a = {C_a}^*, T_c = {T_c}^*, R = R^*$ so that

$$
\begin{aligned}
0 &= \Pi - \left(\frac{\beta(A + \alpha_1 C_u + \alpha_2 C_a)}{N}\right) S + \sigma A - \mu S \\
0 &= \left(\frac{\beta(A + \alpha_1 C_u + \alpha_2 C_a)}{N}\right) S - (\sigma + \gamma + \nu_1) A \\
0 &= \gamma A - (\nu_2 + \mu + d_c) C_u \\
0 &= \nu_2 C_u + \nu_1 A - (\delta + \mu + d_c) C_a \\
0 &= \delta C_a - (\omega + \mu) T_c \\
0 &= \omega T_c - \mu R
\end{aligned}
\tag{3.117}
$$

$$
S^* = \left(\frac{\Pi(\mu^3 + (\delta+\gamma+2d_c+\upsilon_1+\upsilon_2)\mu^2 + ({d_c}^2 + (\upsilon_1+\upsilon_2+\delta+\gamma)d_c + (\upsilon_2+\delta)\gamma + (\upsilon_2+\delta)\upsilon_1 + \delta\upsilon_2)\mu) + \delta(\upsilon_1 d_c + \upsilon_2(\upsilon_1+\gamma))(\upsilon_1+\sigma+\gamma)}{L} \right) \tag{3.118}
$$

$$
A^* = -\left(\frac{(\upsilon_1-\beta+\gamma+\sigma){d_c}^2 + ((2\upsilon_1-2\beta+2\gamma+2\sigma)\mu + (\upsilon_2+\delta-\beta\alpha_1)\gamma + (\upsilon_2+\delta-\beta\alpha_2)\upsilon_1 - (\beta-\sigma)(\upsilon_2+\delta))d_c + (\upsilon_1-\beta+\gamma+\sigma)\mu^2 + ((\upsilon_2+\delta-\beta\alpha_1)\gamma + (\upsilon_2+\delta-\beta\alpha_2)\upsilon_1 - (\beta-\sigma)(\upsilon_2+\delta))\mu + ((-\delta\alpha_1-\alpha_2\upsilon_2)\beta)\Pi}{L} \right) \tag{3.119}
$$

$$
{C_u}^* = A^* \gamma \tag{3.120}
$$

$$
{C_a}^* = \frac{{C_u}^*((\upsilon_1+\upsilon_1\mu+\upsilon_2((\upsilon_1+\gamma)}{\gamma} \tag{3.121}
$$

$$
{T_c}^* = -\left({C_a}^* \left(\frac{\mu^2}{{d_c}^2} + \frac{\mu}{d_c} + \frac{\upsilon_2}{\mu^2} + \frac{1}{\upsilon_1+\upsilon_2} \right) \delta \right) \tag{3.122}
$$

$$
R^* = \omega {T_c}^* \tag{3.123}
$$

where

$$L = ((\upsilon_2 + \mu + d_c)(\upsilon_1 + \gamma + \sigma)\mu^3 + ((2\upsilon_1 + 2\gamma + 2\sigma)d_c) + (\upsilon_1 + \gamma + \sigma)\upsilon_2 + (\beta + \delta)\gamma + (\beta + \delta)\upsilon_1 + \delta\sigma)\mu^2 + ((\upsilon_1 + \gamma + \sigma){d_c}^2 + ((\upsilon_1 + \gamma + \sigma)\upsilon_2 - \gamma^2 + (2\beta + \delta - \sigma - 2\upsilon_1)\gamma - \upsilon_1^2 + (2\beta + \delta - \sigma)\upsilon_1 + \delta\sigma)d_c + ((\beta + \delta)\gamma + (\beta + \delta)\upsilon_1 + \delta\sigma)\upsilon_2 + \beta(\upsilon_1 + \gamma)(\gamma\alpha_1 + \alpha_2\upsilon_1 + \delta))\mu - (\upsilon_1 + \gamma)(\upsilon_1 - \beta + \gamma + \sigma){d_c}^2 + (-(\upsilon_1 + \gamma)(\upsilon_1 - \beta + \gamma + \sigma)\upsilon_2 + (\beta\alpha_1 - \delta)\gamma^2 + ((-\delta + (\alpha_1 + \alpha_2)\beta)\upsilon_1 + \delta(\beta - \sigma))\gamma + (\delta + \alpha_2\upsilon_1)\beta\upsilon_1)d_c + \beta(\gamma\alpha_1 + \alpha_2\upsilon_1 + \delta)\upsilon_2 + \delta\gamma\alpha_1)(\upsilon_1 + \gamma)(\delta + \mu + d_c)(\mu + \omega)$$

The basic reproduction number is computed using the next generation matrix approach. To determine the next generation matrix for the model considered in case 3, the following are considered:

1. The number of ways that new infections can arise or be created

2. The number of ways that infections can be transferred between compartments

Then F_i and V_i are computed as follows:

$$F = \begin{bmatrix} \beta & \beta\alpha_1 & \beta\alpha_2 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

$$V = \begin{bmatrix} \sigma + \gamma + \upsilon_1 & 0 & 0 \\ -\gamma & d_c + \mu + \upsilon_2 & 0 \\ -\upsilon_1 & -\upsilon_2 & d_c + \mu + \delta \end{bmatrix}$$

$$V^{-1} = \begin{bmatrix} \frac{1}{\sigma+\gamma+\upsilon_1} & 0 & 0 \\ \frac{\gamma}{(\sigma+\gamma+\upsilon_1)(d_c+\mu+\upsilon_2)} & \frac{1}{d_c+\mu+\upsilon_2} & 0 \\ \frac{\gamma\upsilon_2+\upsilon_1\mu+\upsilon_1 d_c+\upsilon_1\upsilon_2}{(\sigma+\gamma+\upsilon_1)(d_c+\mu+\upsilon_2)(d_c+\mu+\delta)} & \frac{\upsilon_2}{(d_c+\mu+\upsilon_2)(d_c+\mu+\delta)} & \frac{1}{(d_c+\mu+\delta)} \end{bmatrix}$$

The reproduction number is given by (FV^{-1}), and

$$R_o = \frac{\beta}{\sigma+\gamma+\upsilon_1} + \frac{\beta\alpha_1\gamma}{(\sigma+\gamma+\upsilon_1)(d_c+\mu+\upsilon_2)} + \frac{\beta\alpha_2(\gamma\upsilon_2+\upsilon_1\mu+\upsilon_1 d_c+\upsilon_1\upsilon_2)}{(\sigma+\gamma+\upsilon_1)(d_c+\mu+\upsilon_2)(d_c+\mu+\delta)} \quad (3.124)$$

3.3.3 Local Stability Analysis of the Disease Free Equilibrium E_o

Theorem 3.3.1:E_o is locally asymptotically stable if $R_o < 1$ and unstable if $R_o > 1$.

Proof: The resulting matrix from the linearized model is $\frac{dX}{dt} = AX$

$X = (x_1, x_2, x_3, x_4, x_{5,} x_6)^T, (x_1, x_2, x_3, x_4, x_{5,} x_6) \in R_+^6$, and

The resulting Jacobian matrix at E_o is

$J(E_0) =$

$$\begin{bmatrix} -\mu-\lambda & -\beta+\sigma & -\beta\alpha_1 & -\beta\alpha_2 & 0 & 0 \\ 0 & \beta-\sigma-\gamma-\nu_1-\lambda & \beta\alpha_1 & \beta\alpha_2 & 0 & 0 \\ 0 & \gamma & -d_c-\mu-\nu_2-\lambda & 0 & 0 & 0 \\ 0 & \nu_1 & \nu_2 & -d_c-\mu-\delta-\lambda & 0 & 0 \\ 0 & 0 & 0 & \delta & -\omega-\mu-\lambda & 0 \\ 0 & 0 & 0 & 0 & \omega & -\mu-\lambda \end{bmatrix} \quad (3.125)$$

From (3.125) $\lambda_1 = -\mu,\ \lambda_2 = -\omega-\mu,\ \lambda_3 = -\mu$

and the resulting quadratic equation is:

$$(\beta-\sigma-\gamma-\nu_1-\lambda)(-d_c-\mu-\nu_2-\lambda)(-d_c-\mu-\delta-\lambda)-\beta\alpha_1(-d_c-\mu-\delta-\lambda)\gamma+\beta\alpha_2\big((-d_c-\mu-\nu_2-\lambda)\nu_1-\gamma\nu_2\big) \quad (3.126)$$

$$f(\lambda)=\lambda^3+(2\mu+\nu_1+\nu_2-\beta+\delta+\gamma+\sigma+2d_c)\lambda^2+\big(\beta\alpha_2\nu_1-\beta\delta-2\beta\mu-2\beta d_c-\beta\nu_2+\delta\gamma+\delta\mu+\delta\sigma+\delta d_c+\delta\nu_1+\delta\nu_2+2\gamma\mu+2\gamma d_c+\gamma\nu_2+\mu^2+2\mu\sigma+2\mu d_c+2\mu\nu_1+\mu\nu_2+2\sigma d_c+\sigma\nu_2+{d_c}^2+2d_c\nu_1+d_c\nu_2+\nu_1\nu_2-\gamma\beta\alpha_1\big)\lambda+\gamma\mu^2+\gamma{d_c}^2+\mu^2\sigma+\mu^2\nu_1+\sigma{d_c}^2+{d_c}^2\nu_1+\mu\sigma\nu_2+2\mu d_c\nu_1+\mu\nu_1\nu_2+\sigma d_c\nu_2+d_c\nu_1\nu_2-\beta\delta\mu-\beta\delta d_c-\beta\delta\nu_2-2\beta\mu d_c-\beta\mu\nu_2-\beta d_c\nu_2-\beta\mu^2-\beta{d_c}^2+\delta\gamma\mu+\delta\gamma d_c+\delta\gamma\nu_2+\delta\mu\sigma+\delta\mu\nu_1+\delta\sigma d_c+\delta\sigma\nu_2+\delta d_c\nu_1+\delta\nu_1\nu_2+2\gamma\mu d_c+\gamma\mu\nu_2+\gamma d_c\nu_2+2\mu\sigma d_c-\beta\delta\gamma\alpha_1-\beta\gamma\mu\alpha_1-\beta\gamma\alpha_1 d_c+\nu_2\gamma\beta\alpha_2+\nu_1\beta\alpha_2 d_c+\nu_1\beta\alpha_2\mu+\nu_1\beta\alpha_2\nu_2 \quad (3.127)$$

Now, $\lambda_1,\lambda_2,\lambda_3<0$ since the values are assumed positive. If $R_o<1$, E_o is stable and unstable when $R_o>1$.

3.3.4 Global Stability of the Disease Free Equilibrium

The global behavior of the equilibrium system (3.111) is analyzed here in this section.

Theorem 3.3.2: For system (3.111), the disease-free equilibrium E_o is asymptotically stable globally if $R_0<1$.

Proof: Considering the Lyapunov function defined as:

$$G(A, C_u, C_a) = \left(\frac{1}{B_0}\right) A + \left(\frac{\beta\alpha_1}{B_0B_1} + \frac{\beta\alpha_2\upsilon_2}{B_0B_1B_2}\right) C_u + \left(\frac{\beta\alpha_2}{B_0B_2}\right) C_a \quad (3.128)$$

$$\mathrm{G}'(A, C_u, C_a) = \left(\frac{1}{B_0}\right) A' + \left(\frac{\beta\alpha_1}{B_0B_1} + \frac{\beta\alpha_2\upsilon_2}{B_0B_1B_2}\right) C_u{}' + \left(\frac{\beta\alpha_2}{B_0B_2}\right) C_a{}' \quad (3.129)$$

$$\mathrm{G}'(A, C_u, C_a) = \left(\frac{1}{B_0}\right)\left(\left(\frac{\beta(A+\alpha_1C_u+\alpha_2C_a)}{N}\right) S - (\sigma + \gamma + \nu_1)A\right) + \left(\frac{\beta\alpha_1}{B_0B_1} + \frac{\beta\alpha_2\upsilon_2}{B_0B_1B_2}\right)(\gamma A -$$

$$(\nu_2 + \mu + d_c)C_u) + \left(\frac{\beta\alpha_2}{B_0B_2}\right)(\nu_2C_u + \nu_1A - (\delta + \mu + d_c)C_a) \quad (3.130)$$

At DFE, S=N so that (3.130) becomes:

$$\mathrm{G}'(A, C_u, C_a) = \left(\frac{1}{B_0}\right)(\beta(A + \alpha_1C_u + \alpha_2C_a) - (\sigma + \gamma + \nu_1)A) + \left(\frac{\beta\alpha_1}{B_0B_1} + \frac{\beta\alpha_2\upsilon_2}{B_0B_1B_2}\right)(\gamma A -$$

$$(\nu_2 + \mu + d_c)C_u) + \left(\frac{\beta\alpha_2}{B_0B_2}\right)(\nu_2C_u + \nu_1A - (\delta + \mu + d_c)C_a) \quad (3.131)$$

Expanding and simplifying (3.131) gives:

$$\mathrm{G}' = \left[\frac{\beta}{B_0} + \frac{\beta\alpha_1\gamma}{B_0B_1} + \frac{\beta\alpha_2\upsilon_2\gamma}{B_0B_1B_2} + \frac{\beta\alpha_2\nu_1}{B_0B_2} - 1\right]\boldsymbol{A} + \left[\frac{\beta\alpha_1}{B_0} - \frac{\beta\alpha_1B_1}{B_0B_1} - \frac{\beta\alpha_2\upsilon_2B_1}{B_0B_1B_2} + \frac{\beta\alpha_2\nu_2}{B_0B_2}\right] C_u + \left[\frac{\beta\alpha_2}{B_0} -\right.$$

$$\left.\frac{\beta\alpha_2B_2}{B_0B_2}\right] C_a \quad (3.132)$$

$$G' = [R_0 - 1]\, A \;\leq 0 \quad (3.133)$$

From Equation (3.133), it can be deduced that the DFE is globally stable since $R_0 < 1$.

3.3.5 Bifurcation Analysis

Here, bifurcation analysis is performed at the disease-free equilibrium by centre manifold theory as presented in (Buonomo and Lacitignola, 2011).

Now, the focus is on the disease-free equilibrium E_0 and investigate the occurrence of the transcritical bifurcation at $R_0 = 1$.

The Jacobian matrix of equation (3.125) at the disease- free equilibrium E_0 is given by

$$J(E_0) = \begin{bmatrix} -\mu & -\beta+\sigma & -\beta\alpha_1 & -\beta\alpha_2 & 0 & 0 \\ 0 & \beta-\sigma-\gamma-\nu_1 & \beta\alpha_1 & \beta\alpha_2 & 0 & 0 \\ 0 & \gamma & -d_c-\mu-\nu_2 & 0 & 0 & 0 \\ 0 & \nu_1 & \nu_2 & -d_c-\mu-\delta & 0 & 0 \\ 0 & 0 & 0 & \delta & -\omega-\mu & 0 \\ 0 & 0 & 0 & 0 & \omega & -\mu \end{bmatrix} \quad (3.134)$$

The Centre Manifold theorem as stated in theorem 1.4 is now applied to determine if the model system (3.111) exhibit a backward or forward bifurcation at $R_0 = 1$ as follows:

Recall that

$$R_0 = \frac{\beta}{\sigma+\gamma+\upsilon_1} + \frac{\beta\alpha_1\gamma}{(\sigma+\gamma+\upsilon_1)(d_c+\mu+\upsilon_2)} + \frac{\beta\alpha_2(\gamma\upsilon_2+\upsilon_1\mu+\upsilon_1 d_c+\upsilon_1\upsilon_2)}{(\sigma+\gamma+\upsilon_1)(d_c+\mu+\upsilon_2)(d_c+\mu+\delta)}$$

Let $\beta = \beta^*$ be a bifurcation parameter and if the case $R_0 = 1$is considered.

By solving for $\beta = \beta^*$, then

$$\frac{\beta}{\sigma+\gamma+\upsilon_1} + \frac{\beta\alpha_1\gamma}{(\sigma+\gamma+\upsilon_1)(d_c+\mu+\upsilon_2)} + \frac{\beta\alpha_2(\gamma\upsilon_2+\upsilon_1\mu+\upsilon_1 d_c+\upsilon_1\upsilon_2)}{(\sigma+\gamma+\upsilon_1)(d_c+\mu+\upsilon_2)(d_c+\mu+\delta)} = 1 \quad (3.135)$$

$$\beta = \beta^* = \frac{(\sigma+\gamma+\upsilon_1)(d_c+\mu+\upsilon_2)(d_c+\mu+\delta)}{\alpha_1\gamma(d_c+\mu+\delta)+\alpha_2\gamma\upsilon_2+\alpha_2(d_c+\mu+\upsilon_2)\upsilon_1+(d_c+\mu+\upsilon_2)(d_c+\mu+\delta)} \quad (3.136)$$

The Jacobian matrix of equation (3.111) at the disease-free equilibrium E_0, β^* is given by

$$J(E_0, \beta^*) = \begin{bmatrix} -\mu & -\beta^* + \sigma & -\beta^*\alpha_1 & -\beta^*\alpha_2 & 0 & 0 \\ 0 & \beta^* - \sigma - \gamma - \nu_1 & \beta^*\alpha_1 & \beta^*\alpha_2 & 0 & 0 \\ 0 & \gamma & -d_c - \mu - \nu_2 & 0 & 0 & 0 \\ 0 & \nu_1 & \nu_2 & -d_c - \mu - \delta & 0 & 0 \\ 0 & 0 & 0 & \delta & -\omega - \mu & 0 \\ 0 & 0 & 0 & 0 & \omega & -\mu \end{bmatrix} \quad (3.137)$$

The characteristic equation of (3.137) has a simple zero eigenvalue i.e.

$$|J(E_0, \beta^*) - \lambda \mathrm{I}| = 0 \quad (3.138)$$

$\lambda_1 = -\mu, \lambda_2 = -\omega - \mu, \lambda_3 = -\mu$ and the resulting quadratic equation is:

$$\mathrm{f}(\lambda) = \lambda^3 + (2\mu + \nu_1 + \nu_2 - \beta * + \delta + \gamma + \sigma + 2\mathrm{d_c})\lambda^2 + \big(\beta * \alpha_2\nu_1 - \beta * \delta - 2\beta * \mu - 2\beta * \mathrm{d_c} - \beta * \nu_2 + \delta\gamma + \delta\mu + \delta\sigma + \delta\mathrm{d_c} + \delta\nu_1 + \delta\nu_2 + 2\gamma\mu + 2\gamma\mathrm{d_c} + \gamma\nu_2 + \mu^2 + 2\mu\sigma + 2\mu\mathrm{d_c} + 2\mu\nu_1 + \mu\nu_2 + 2\sigma\mathrm{d_c} + \sigma\nu_2 + \mathrm{d_c}^2 + 2\mathrm{d_c}\nu_1 + \mathrm{d_c}\nu_2 + \nu_1\nu_2 - \gamma\beta * \alpha_1\big)\lambda \quad (3.139)$$

Equation (3.139) gives three negative eigenvalues as its roots (by Descartes rule of signs). Thus, $\lambda_4 = 0$ is a simple zero eigenvalue and the other eigenvalues are real and negative, then the assumptions of theorem 1.4 (Centre Manifold theorem) is then verified.

Furthermore, the right eigenvector associated with the zero eigenvalue $\lambda_3 = 0$ given by $w = (w_1, w_2, w_3, w_4, w_5, w_6)^T$ are obtained as follows:

$$\begin{bmatrix} -\mu & -\beta^* + \sigma & -\beta^*\alpha_1 & -\beta^*\alpha_2 & 0 & 0 \\ 0 & \beta^* - \sigma - \gamma - \nu_1 & \beta^*\alpha_1 & \beta^*\alpha_2 & 0 & 0 \\ 0 & \gamma & -d_c - \mu - \nu_2 & 0 & 0 & 0 \\ 0 & \nu_1 & \nu_2 & -d_c - \mu - \delta & 0 & 0 \\ 0 & 0 & 0 & \delta & -\omega - \mu & 0 \\ 0 & 0 & 0 & 0 & \omega & -\mu \end{bmatrix} \begin{bmatrix} w_1 \\ w_2 \\ w_3 \\ w_4 \\ w_5 \\ w_6 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \quad (3.140)$$

$$-\mu w_1 + (-\beta^* + \sigma)w_2 + (-\beta^*\alpha_1)w_3 + (-\beta^*\alpha_2)w_4 = 0 \quad (3.141)$$

$$(\beta^* - \sigma - \gamma - \nu_1)w_2 + (\beta^*\alpha_1)w_3 + (\beta^*\alpha_2)w_4 = 0 \quad (3.142)$$

$$\gamma w_2 + (-d_c - \mu - \nu_2)w_3 = 0 \quad (3.143)$$

$$\nu_1 w_2 + \nu_2 w_3 + (-d_c - \mu - \delta)w_4 = 0 \quad (3.144)$$

$$\delta w_4 + (-\omega - \mu)w_5 = 0 \quad (3.145)$$

$$\omega w_5 + (-\mu)w_6 = 0 \quad (3.146)$$

Solving equations (3.141) - (3.146) simultaneously gives:

$$w_1 = -\frac{1}{\gamma\mu}(\gamma\mu + \gamma d_c + \gamma\nu_2 + \mu\nu_1 + d_c\nu_1 + \nu_1\nu_2)w_3$$

$$w_2 = \frac{(d_c + \mu + \nu_2)w_3}{\gamma}$$

$$w_4 = \frac{(\gamma\nu_2 + \mu\nu_1 + d_c\nu_1 + \nu_1\nu_2)w_3}{(d_c + \mu + \delta)\gamma}$$

$$w_5 = \frac{\delta(\gamma\nu_2 + \mu\nu_1 + d_c\nu_1 + \nu_1\nu_2)w_3}{(\omega+\mu)(d_c+\mu+\delta)\gamma}$$

$$w_6 = \frac{\delta\omega(\gamma\nu_2 + \mu\nu_1 + d_c\nu_1 + \nu_1\nu_2)w_3}{(\omega+\mu)\mu(d_c+\mu+\delta)\gamma}$$

Therefore,

w

$$= \begin{pmatrix} -\frac{1}{\gamma\mu}(\gamma\mu + \gamma d_c + \gamma\nu_2 + \mu\nu_1 + d_c\nu_1 + \nu_1\nu_2)w_3, \frac{(d_c+\mu+\nu_2)w_3}{\gamma}, w_3 \\ \frac{(\gamma\nu_2 + \mu\nu_1 + d_c\nu_1 + \nu_1\nu_2)w_3}{(d_c+\mu+\delta)\gamma}, \frac{\delta(\gamma\nu_2 + \mu\nu_1 + d_c\nu_1 + \nu_1\nu_2)w_3}{(\omega+\mu)(d_c+\mu+\delta)\gamma}, \frac{\delta\omega(\gamma\nu_2 + \mu\nu_1 + d_c\nu_1 + \nu_1\nu_2)w_3}{(\omega+\mu)\mu(d_c+\mu+\delta)\gamma} \end{pmatrix}^T$$

where $w_3 > 0$ is a free right eigenvector.

Similarly, the left eigenvector associated with the zero eigenvalue is computed as follows:

Let the left eigenvector associated with the zero eigenvalue $\lambda_3 = 0$ given by

$$l = (l_1, l_2, l_3, l_{4,}, l_5, l_6)$$

then,

$$l\begin{bmatrix} -\mu & -\beta^* + \sigma & -\beta^*\alpha_1 & -\beta^*\alpha_2 & 0 & 0 \\ 0 & \beta^* - \sigma - \gamma - \nu_1 & \beta^*\alpha_1 & \beta^*\alpha_2 & 0 & 0 \\ 0 & \gamma & -d_c - \mu - \nu_2 & 0 & 0 & 0 \\ 0 & \nu_1 & \nu_2 & -d_c - \mu - \delta & 0 & 0 \\ 0 & 0 & 0 & \delta & -\omega - \mu & 0 \\ 0 & 0 & 0 & 0 & \omega & -\mu \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \qquad (3.147)$$

$$l_1(-\mu) = 0 \tag{3.148}$$

$$l_1(-\beta^* + \sigma) + l_2(\beta^* - \sigma - \gamma - \nu_1) + l_3\gamma + l_4\nu_1 = 0 \tag{3.149}$$

$$l_1(-\beta^*\alpha_1) + l_2(\beta^*\alpha_1) + l_3(-d_c - \mu - \nu_2) + l_4\nu_2 = 0 \tag{3.150}$$

$$l_1(-\beta^*\alpha_2) + l_2(\beta^*\alpha_2) + l_4(-d_c - \mu - \delta) + l_5(\delta) = 0 \tag{3.151}$$

$$l_5(-\omega - \mu) + l_6(\omega) = 0 \tag{3.152}$$

$$l_6(-\mu) = 0 \tag{3.153}$$

The simultaneous solution of equations (3.148) - (3.153) yields:

$$l_1 = 0, l_2 = \frac{\begin{pmatrix}\delta\gamma\alpha_1 + \gamma\mu\alpha_1 + \gamma\alpha_1 d_c + \gamma\alpha_2\nu_2 + \mu\alpha_2\nu_1 + \alpha_2\nu_1 d_c + \alpha_2\nu_1\nu_2 \\ +\mu\delta + \delta d_c + \delta\nu_2 + \mu^2 + 2\mu d_c + \mu\nu_2 + {d_c}^2 + d_c\nu_2\end{pmatrix} l_4}{\gamma\mu + \gamma d_c + \gamma\nu_2 + \mu\nu_1 + d_c\nu_1 + \nu_1\nu_2}, l_3$$

$$= \frac{(\delta\alpha_1 + \mu\alpha_1 + \alpha_1 d_c + \alpha_2\nu_2) l_4}{\alpha_2(d_c + \mu + \nu_2)}, l_4 = l_4, l_5 = 0, l_{6=0}$$

therefore,

$$l = \begin{bmatrix} 0, \frac{\begin{pmatrix}\delta\gamma\alpha_1 + \gamma\mu\alpha_1 + \gamma\alpha_1 d_c + \gamma\alpha_2\nu_2 + \mu\alpha_2\nu_1 + \alpha_2\nu_1 d_c + \alpha_2\nu_1\nu_2 \\ +\mu\delta + \delta d_c + \delta\nu_2 + \mu^2 + 2\mu d_c + \mu\nu_2 + {d_c}^2 + d_c\nu_2\end{pmatrix} l_4}{\gamma\mu + \gamma d_c + \gamma\nu_2 + \mu\nu_1 + d_c\nu_1 + \nu_1\nu_2}, \\ \frac{(\delta\alpha_1 + \mu\alpha_1 + \alpha_1 d_c + \alpha_2\nu_2) l_4}{\alpha_2(d_c + \mu + \nu_2)}, 0, 0 \end{bmatrix}$$

where $l_4 > 0$ is a free left eigenvector.

3.3.5.1 The Computation of the Coefficient a and b for Model Case 3

The coefficients (as defined in theorem 1.4):

$$a = \sum_{m,i,j=1}^{6} l_m w_i w_j \frac{\partial^2 f_m(E_0, \beta^*)}{\partial x_i \partial x_j}, b = \sum_{m,i,j=1}^{6} l_m w_i \frac{\partial^2 f_m(E_0, \beta^*)}{\partial x_i \partial \varphi}$$

may now be explicitly computed taking into account of system (3.111) and considering only the nonzero components of the left eigenvector l it follows that:

$S = x_1$, $A = x_2$,$C_u = x_3$, $C_a = x_4$, $T_c = x_5$, $R = x_6$

Furthermore, introducing the vector $X = (x_1, x_2, x_3, x_4, x_5, x_6)^T$, then the model in system (3.111) can now be written in the form

$\frac{dX}{dt} = f(x)$, where $f = (f_1, f_2, f_3, f_4, f_5, f_6)^T$

It implies that system (3.111) can be written in term of the new variables as:

$$\left.\begin{aligned}
\frac{\mathrm{dx}_1}{dt} &= f_1 = \Pi - \left(\frac{\beta(x_2 + \alpha_1 x_3 + \alpha_2 x_4)}{N}\right) x_1 + \sigma x_2 - \mu x_1 \\
\frac{\mathrm{dx}_2}{dt} &= f_2 = \left(\frac{\beta(x_2 + \alpha_1 x_3 + \alpha_2 x_4)}{N}\right) x_1 - (\sigma + \gamma + \nu_1) x_2 \\
\frac{\mathrm{dx}_3}{dt} &= f_3 = \gamma x_2 - (\nu_2 + \mu + d_c) x_3 \\
\frac{\mathrm{dx}_4}{dt} &= f_4 = \nu_2 x_3 + \nu_1 x_2 - (\delta + \mu + d_c) x_4 \\
\frac{\mathrm{dx}_5}{dt} &= f_5 = \delta x_4 - (\omega + \mu) x_5 \\
\frac{\mathrm{dx}_6}{dt} &= f_6 = \omega x_5 - \mu x_6
\end{aligned}\right\} \quad (3.154)$$

$$a = -\frac{1}{(x_1+x_2+x_3+x_4+x_5+x_6)^3}\big(2\beta^* l_2(\omega_1 x_2 + \omega_1 x_3 + \omega_1 x_4 + \omega_1 x_5 + \omega_1 x_6 - \omega_2 x_1 - \omega_3 x_1 - \omega_4 x_1 - \omega_5 x_1 - \omega_6 x_1)(\alpha_1\omega_1 x_3 + \alpha_1\omega_2 x_3 - \alpha_1\omega_3 x_1 - \alpha_1\omega_3 x_2 - \alpha_1\omega_3 x_4 - \alpha_1\omega_3 x_5 - \alpha_1\omega_3 x_6 + \alpha_1\omega_4 x_3 + \alpha_1\omega_5 x_3 + \alpha_1\omega_6 x_3 + \alpha_2\omega_1 x_4 + \alpha_2\omega_2 x_4 + \alpha_2\omega_3 x_4 - \alpha_2\omega_4 x_1 - \alpha_2\omega_4 x_2 - \alpha_2\omega_4 x_3 - \alpha_2\omega_4 x_5 - \alpha_2\omega_4 x_6)\big) + \alpha_2\omega_5 x_4 + \alpha_2\omega_6 x_4 + \omega_1 x_2 - \omega_2 x_1 - \omega_2 x_3 - \omega_2 x_4 - \omega_2 x_5 - \omega_6 x_2 + \omega_3 x_2 + \omega_4 x_2 + \omega_5 x_2 + \omega_6 x_2$$

$$b = \frac{\begin{pmatrix}\delta\gamma\alpha_1+\gamma\mu\alpha_1+\gamma\alpha_1 d_c+\gamma\alpha_2\nu_2+\mu\alpha_2\nu_1+\alpha_2\nu_1 d_c+\alpha_2\nu_1\nu_2\\ +\mu\delta+\delta d_c+\delta\nu_2+\mu^2+2\mu d_c+\mu\nu_2+{d_c}^2+d_c\nu_2\end{pmatrix} l_4\big((d_c+\mu+\nu_2)\omega_3\big)}{\big((\gamma\mu+\gamma d_c+\gamma\nu_2+\mu\sigma+\mu\nu_1+\sigma d_c+\sigma\nu_2+d_c\nu_1+\nu_1\nu_2)\gamma\alpha_2\big)} +$$

$$\frac{\begin{pmatrix}\delta\gamma\alpha_1+\gamma\mu\alpha_1+\gamma\alpha_1 d_c+\gamma\alpha_2\nu_2+\mu\alpha_2\nu_1+\alpha_2\nu_1 d_c+\alpha_2\nu_1\nu_2\\ +\mu\delta+\delta d_c+\delta\nu_2+\mu^2+2\mu d_c+\mu\nu_2+{d_c}^2+d_c\nu_2\end{pmatrix} l_4(\omega_3\alpha_1)}{\big((\gamma\mu+\gamma d_c+\gamma\nu_2+\mu\sigma+\mu\nu_1+\sigma d_c+\sigma\nu_2+d_c\nu_1+\nu_1\nu_2)\alpha_2\big)} +$$

$$\frac{\begin{pmatrix}\delta\gamma\alpha_1+\gamma\mu\alpha_1+\gamma\alpha_1 d_c+\gamma\alpha_2\nu_2+\mu\alpha_2\nu_1+\alpha_2\nu_1 d_c+\alpha_2\nu_1\nu_2\\ +\mu\delta+\delta d_c+\delta\nu_2+\mu^2+2\mu d_c+\mu\nu_2+{d_c}^2+d_c\nu_2\end{pmatrix} l_4\big((\gamma\nu_2+\mu\nu_1+d_c\nu_1+\nu_1\nu_2)\omega_3\big)}{\big((\gamma\mu+\gamma d_c+\gamma\nu_2+\mu\sigma+\mu\nu_1+\sigma d_c+\sigma\nu_2+d_c\nu_1+\nu_1\nu_2)(d_c+\mu+\delta)\gamma\big)}$$

The coefficient b is always positive so that according to theorem 1.4, it is the sign of the coefficient a that decides the local dynamics around the disease-free equilibrium for $\beta = \beta^*$. Thus, the following result is established.

Theorem 3.3.3: The unique equilibrium $E^*$is locally asymptotically stable for $R_0 > 1$. Since $a < 0$, locally stability of E^*implies its global stability

3.3.6 Local Stability of Endemic Equilibrium

Theorem 3.3.4: If $R_0 > 1$, then the endemic equilibrium is locally asymptotically stable.

Proof:

The endemic equilibria of system (3.111), denoted by$(S^*, A^*, {C_u}^*, {C_a}^*, {T_c}^*, R^*)$,can be rewritten as:

Let S = x + $S^*, A = y + A^*, C_u = z + {C_u}^*, C_a = h + {C_a}^*, T_c = p + {T_c}^*, R = j + R^*$

$$J = \begin{bmatrix} B_0 - \mu - \lambda & -B_1 + \sigma & -B_2 & -B_3 & B_4 & B_5 \\ -B_6 & B_7 - \sigma - \gamma - \nu_1 - \lambda & B_8 & B_9 & -B_{11} & -B_{12} \\ 0 & \gamma & -d_c - \mu - \nu_2 - \lambda & 0 & 0 & 0 \\ 0 & \nu_1 & \nu_2 & -d_c - \mu - \delta - \lambda & 0 & 0 \\ 0 & 0 & 0 & \delta & -\omega - \mu - \lambda & 0 \\ 0 & 0 & 0 & 0 & \omega & -\mu - \lambda \end{bmatrix} \quad (3.155)$$

From (3.155), $\lambda_1 = -\mu, \lambda_2 = -(\omega + \mu), \lambda_3 = -(d_c + \mu + \nu_2)$,then;

$$J = \begin{bmatrix} B_0 - \mu - \lambda & -B_1 + \sigma & -B_2 \\ -B_6 & B_7 - \sigma - \gamma - \nu_1 - \lambda & B_8 \\ 0 & \gamma & -d_c - \mu - \nu_2 - \lambda \end{bmatrix} \quad (3.156)$$

from (3.156);

$$\lambda^3 + (\gamma + 2\mu + \sigma - B_0 - B_4 + d_c + \nu_1 + \nu_2)\lambda^2 + (2\gamma\mu - B_0\gamma + \gamma d_c + \gamma\nu_2 + \mu^2 + 2\mu\sigma - \mu B_0 - 2\mu B_4 + \mu d_c + 2\mu\nu_1 + \mu\nu_2 - \sigma B_0 + \sigma B_3 + \sigma d_c + \sigma\nu_2 + B_0B_4 - B_0d_c - B_0\nu_1 - B_0\nu_2 - B_3B_1 - B_4d_c - B_4\nu_2 + d_c\nu_1 + \nu_1\nu_2)\lambda + B_5\gamma + \gamma\mu\nu_2 + \mu\sigma\nu_2 + \mu\nu_1\nu_2 + B_3B_2\gamma + \gamma\mu^2 + \mu^2\sigma + \mu^2\nu_1 + \mu d_c\nu_1 + \gamma\mu d_c + \mu\sigma d_c - \mu^2B_4 - \gamma\mu B_0 - \gamma B_0 d_c - \gamma B_0\nu_2 - \mu\sigma B_0 + \mu\sigma B_3 + \mu B_0B_4 - \mu B_0\nu_1 - \mu B_3B_1 - \mu B_4d_c - \mu B_4\nu_2 - \sigma B_0d_c - \sigma B_0\nu_2 + \sigma B_3d_c + \sigma B_3\nu_2 + B_0B_4d_c + B_0B_4\nu_2 - B_0d_c\nu_1 - B_0\nu_1\nu_2 - B_3B_1d_c - B_3B_1\nu_2$$

The result of the determinant of the Jacobian matrix is of the form:

$$a_0\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 \quad (3.157)$$

where

$$a_0 = 1$$

$$a_1 = \gamma + 2\mu + \sigma - B_0 - B_4 + d_c + \nu_1 + \nu_2$$

$$a_2 = 2\gamma\mu - B_0\gamma + \gamma d_c + \gamma\nu_2 + \mu^2 + 2\mu\sigma - \mu B_0 - 2\mu B_4 + \mu d_c + 2\mu\nu_1 + \mu\nu_2 - \sigma B_0 + \sigma B_3 + \sigma d_c + \sigma\nu_2 + B_0B_4 - B_0d_c - B_0\nu_1 - B_0\nu_2 - B_3B_1 - B_4d_c - B_4\nu_2 + d_c\nu_1 + \nu_1\nu_2$$

$$a_3 = B_5\gamma + \gamma\mu\nu_2 + \mu\sigma\nu_2 + \mu\nu_1\nu_2 + B_3B_2\gamma + \gamma\mu^2 + \mu^2\sigma + \mu^2\nu_1 + \mu d_c\nu_1 + \gamma\mu d_c + \mu\sigma d_c - \mu^2B_4 - \gamma\mu B_0 - \gamma B_0d_c - \gamma B_0\nu_2 - \mu\sigma B_0 + \mu\sigma B_3 + \mu B_0B_4 - \mu B_0\nu_1 - \mu B_3B_1 - \mu B_4d_c - \mu B_4\nu_2 - \sigma B_0d_c - \sigma B_0\nu_2 + \sigma B_3d_c + \sigma B_3\nu_2 + B_0B_4d_c + B_0B_4\nu_2 - B_0d_c\nu_1 - B_0\nu_1\nu_2 - B_3B_1d_c - B_3B_1\nu_2$$

By Routh-Hurwitz criterion governing the polynomials of order 3, we have the following:

1. $a_2.a_3$are positive

2. $a_1a_2 > a_3$

From equation (3.157)1 and 2 are satisfied.

Therefore, endemic equilibrium is locally asymptotically stable.

3.3.7 Global Stability of the Endemic Equilibrium

Theorem 3.3.5: The equations of the model have a positive distinctive endemic equilibrium whenever $R_0 > 1$, which is said to be globally asymptotically stable.

Proof: Considering the Lyapunov function defined as:

$$L(S^*, A^*, {C_u}^*, {C_a}^*, {T_c}^*, R^*) = \left(S - S^* ln\left(\frac{S}{S^*}\right)\right) + \left(A - A^* ln\left(\frac{A}{A^*}\right)\right) + \left(C_u - {C_u}^* ln\left(\frac{C_u}{{C_u}^*}\right)\right) + \left(C_a - {C_a}^* ln\left(\frac{C_a}{{C_a}^*}\right)\right) + \left(T_c - {T_c}^* ln\left(\frac{T_c}{{T_c}^*}\right)\right) + \left(R - R^* ln\left(\frac{R}{R^*}\right)\right) \quad (3.158)$$

where L takes it derivative along the system directly as:

$$\frac{dL}{dt} = \left(1 - \frac{S^*}{S}\right)\frac{dS}{dt} + \left(1 - \frac{A^*}{A}\right)\frac{dA}{dt} + \left(1 - \frac{{C_u}^*}{C_u}\right)\frac{dC_u}{dt} + \left(1 - \frac{{C_a}^*}{C_a}\right)\frac{dC_a}{dt} + \left(1 - \frac{{T_c}^*}{T_c}\right)\frac{dT_c}{dt} + \left(1 - \frac{R^*}{R}\right)\frac{dR}{dt} \quad (3.159)$$

$$\frac{dL}{dt} = \left(1 - \frac{S^*}{S}\right)\left[\Pi - \left(\frac{\beta(A+\alpha_1 C_u+\alpha_2 C_a)}{N}\right)S + \sigma A - \mu S\right] + \left(1 - \frac{A^*}{A}\right)\left[\left(\frac{\beta(A+\alpha_1 C_u+\alpha_2 C_a)}{N}\right)S - (\sigma+\gamma+\nu_1)A\right] + \left(1 - \frac{{C_u}^*}{C_u}\right)[\gamma A - (\nu_2+\mu+d_c)C_u] + \left(1 - \frac{{C_a}^*}{C_a}\right)[\nu_2 C_u + \nu_1 A - (\delta + \mu + d_c)C_a] + \left(1 - \frac{{T_c}^*}{T_c}\right)[\delta C_a - (\omega+\mu)T_c] + \left(1 - \frac{R^*}{R}\right)[\omega T_c - \mu R] \quad (3.160)$$

At equilibrium,

$$\Pi = \left(\frac{\beta(A*+\alpha_1 C_u*+\alpha_2 C_a*)}{N*}\right) S* - \sigma A* + \mu S*$$

$$(\sigma + \gamma + \nu_1) = \left(\frac{\beta(A*+\alpha_1 C_u*+\alpha_2 C_a*)}{AN*}\right) S*$$

$$(\nu_2 + \mu + d_c) = \frac{\gamma A*}{C_u*}$$

$$(\delta + \mu + d_c) = \frac{\nu_2 C_u *}{C_a *} + \frac{\nu_1 A *}{C_a *}$$

$$(\omega + \mu) = \frac{\delta C_a *}{T_c *}$$

$$\omega = \frac{\mu R *}{T_c *} \qquad (3.161)$$

$$\frac{dL}{dt} = \left(1 - \frac{S^*}{S}\right)\left[\left(\frac{\beta(A*+\alpha_1 C_u*+\alpha_2 C_a*)}{N*}\right) S* - \sigma A* + \mu S* - \left(\frac{\beta(A+\alpha_1 C_u+\alpha_2 C_a)}{N}\right) S + \sigma A - \mu S\right] + \left(1 - \frac{A^*}{A}\right)\left[\left(\frac{\beta(A+\alpha_1 C_u+\alpha_2 C_a)}{N}\right) S - \left(\frac{\beta(A*+\alpha_1 C_u*+\alpha_2 C_a*)}{AN*}\right) S * A\right] + \left(1 - \frac{C_u{}^*}{C_u}\right)\left[\gamma A - \frac{\gamma A*}{C_u*} C_u\right] + \left(1 - \frac{C_a{}^*}{C_a}\right)\left[\nu_2 C_u + \nu_1 A - \frac{\nu_2 C_u*}{C_a*} + \frac{\nu_1 A*}{C_a*} C_a\right] + \left(1 - \frac{T_c{}^*}{T_c}\right)\left[\delta C_a - \frac{\delta C_a*}{T_c*} T_c\right] + \left(1 - \frac{R^*}{R}\right)\left[\frac{\mu R*}{T_c*} T_c - \mu R\right]$$

$$= \left(1 - \frac{S^*}{S}\right)\left[\frac{\beta A*S*}{N*} + \frac{\beta \alpha_1 C_u*S*}{N*} + \frac{\beta \alpha_2 C_a*S*}{N*} - \sigma A* + \mu S* - \frac{\beta AS}{N} - \frac{\beta \alpha_1 C_u S}{N} - \frac{\beta \alpha_2 C_a S}{N} + \sigma A - \mu S\right] + \left(1 - \frac{A^*}{A}\right)\left[\frac{\beta AS}{N} - \frac{\beta AS*}{N*} + \frac{\beta \alpha_1 C_u S}{N} - \frac{\beta \alpha_1 C_u*S*A}{A*N*} + \frac{\beta \alpha_2 C_a S}{N} - \frac{\beta \alpha_2 C_a*S*A}{A*N*}\right] + \left(1 - \frac{C_u{}^*}{C_u}\right)\gamma A\left[1 - \frac{A*C_u}{AC_u*}\right] + \left(1 - \frac{C_a{}^*}{C_a}\right)\left[\nu_2 C_u\left(1 - \frac{C_u{}^* C_a}{C_u C_a*}\right) + \nu_1 A\left(1 - \frac{A^* C_a}{AC_a*}\right)\right] + \delta C_a\left(1 - \frac{T_c{}^*}{T_c}\right)\left[1 - \frac{C_a*T_c}{C_a T_c*}\right] - \mu R\left(1 - \frac{R^*}{R}\right)\left[1 - \frac{R*T_c}{RT_c*}\right] \qquad (3.162)$$

$$= \left(1 - \frac{S^*}{S}\right)\left[-\frac{\beta AS}{N}\left(1 - \frac{A*S*N}{ASN*}\right) - \frac{\beta\alpha_1 C_u S}{N}\left(1 - \frac{C_{u*}S*N}{C_u SN*}\right) + \frac{\beta\alpha_2 C_a S}{N}\left(1 - \frac{C_{a*}S*N}{C_a SN*}\right) - \sigma A\left(1 - \frac{A^*}{A}\right) - \mu S - \left(1 - \frac{S^*}{S}\right)\right] + \left(1 - \frac{A^*}{A}\right)\left[\frac{\beta AS}{N}\left(1 - \frac{A*S*N}{ASN*}\right) - \frac{\beta\alpha_1 C_u S}{N}\left(1 - \frac{C_{u*}S*AN}{C_u SA*N*}\right) + \frac{\beta\alpha_2 C_a S}{N}\left(1 - \frac{C_{a*}S*AN}{C_a SA*N*}\right)\right] + \left(1 - \frac{C_u{}^*}{C_u}\right)\gamma A\left[1 - \frac{A*C_u}{AC_{u*}}\right] + \left(1 - \frac{C_a{}^*}{C_a}\right)\left[\nu_2 C_u\left(1 - \frac{C_u{}^* C_a}{C_u C_{a*}}\right) + \nu_1 A\left(1 - \frac{A^* C_a}{AC_{a*}}\right)\right] + \delta C_a\left(1 - \frac{T_c{}^*}{T_c}\right)\left[1 - \frac{C_a * T_c}{C_a T_{c*}}\right] - \mu R\left(1 - \frac{R^*}{R}\right)\left[1 - \frac{R*T_c}{RT_{c*}}\right] \quad (3.163)$$

$$= -\mu S\left(1 - \frac{S^*}{S}\right)^2 - \frac{\beta AS}{N}\left(1 - \frac{S^*}{S}\right)\left(1 - \frac{A^*S^*N}{ASN*}\right) - \frac{\beta\alpha_1 C_u S}{N}\left(1 - \frac{S^*}{S}\right)\left(1 - \frac{C_{u*}S*N}{C_u SN*}\right) - \frac{\beta\alpha_2 C_a S}{N}\left(1 - \frac{S^*}{S}\right)\left(1 - \frac{C_{a*}S*N}{C_a SN*}\right) - \sigma A\left(1 - \frac{S^*}{S}\right)\left(1 - \frac{A^*}{A}\right) + \frac{\beta AS}{N}\left(1 - \frac{A^*}{A}\right)\left(1 - \frac{S^*N}{SN*}\right) + \frac{\beta\alpha_1 C_u S}{N}\left(1 - \frac{A^*}{A}\right)\left(1 - \frac{C_{u*}S*AN}{C_u SA*N*}\right) + \frac{\beta\alpha_2 C_a S}{N}\left(1 - \frac{A^*}{A}\right)\left(1 - \frac{C_{a*}S*AN}{C_a SA*N*}\right) + \sigma A\left(1 - \frac{C_u{}^*}{C_u}\right)\left(1 - \frac{A^* C_u}{AC_{u*}}\right) + \nu_2 C_u\left(1 - \frac{C_a{}^*}{C_a}\right)\left(1 - \frac{C_u{}^* C_a}{C_u C_{a*}}\right) + \nu_1 A\left(1 - \frac{C_a{}^*}{C_a}\right)\left(1 - \frac{A^* C_a}{AC_{a*}}\right) + \delta C_a\left(1 - \frac{T_c{}^*}{T_c}\right)\left(1 - \frac{C_a * T_c}{C_a T_{c*}}\right) - \mu R\left(1 - \frac{R^*}{R}\right)\left(1 - \frac{R*T_c}{RT_{c*}}\right)$$

$$= -\mu S\left(1 - \frac{S^*}{S}\right)^2 + P_1(S, A, C_a, C_u, T_c, R) + P_2(S, A, C_a, C_u, T_c, R) \quad (3.164)$$

where,

$$P_1(S, A, C_a, C_u, T_c, R) = -\frac{\beta AS}{N}\left(1 - \frac{S^*}{S}\right)\left(1 - \frac{A^*S^*N}{ASN*}\right) - \frac{\beta\alpha_1 C_u S}{N}\left(1 - \frac{S^*}{S}\right)\left(1 - \frac{C_{u*}S*N}{C_u SN*}\right) - \frac{\beta\alpha_2 C_a S}{N}\left(1 - \frac{S^*}{S}\right)\left(1 - \frac{C_{a*}S*N}{C_a SN*}\right) - \sigma A\left(1 - \frac{S^*}{S}\right)\left(1 - \frac{A^*}{A}\right) - \mu R\left(1 - \frac{R^*}{R}\right)\left(1 - \frac{R*T_c}{RT_{c*}}\right)$$

$$P_2(S, A, C_a, C_u, T_c, R) = \frac{\beta AS}{N}\left(1 - \frac{A^*}{A}\right)\left(1 - \frac{S^*N}{SN*}\right) + \frac{\beta\alpha_1 C_u S}{N}\left(1 - \frac{A^*}{A}\right)\left(1 - \frac{C_{u*}S*AN}{C_u SA*N*}\right) +$$

$$\frac{\beta\alpha_2 C_a S}{N}\left(1 - \frac{A^*}{A}\right)\left(1 - \frac{C_{a*}S*AN}{C_a SA*N*}\right) + \sigma A\left(1 - \frac{{C_u}^*}{C_u}\right)\left(1 - \frac{A^*C_u}{AC_{u*}}\right) + \nu_2 C_u\left(1 - \frac{{C_a}^*}{C_a}\right)\left(1 -$$

$$\frac{{C_u}^*C_a}{C_u C_{a*}}\right) + \nu_1 A\left(1 - \frac{{C_a}^*}{C_a}\right)\left(1 - \frac{A^*C_a}{AC_{a*}}\right) + \delta C_a\left(1 - \frac{{T_c}^*}{T_c}\right)\left(1 - \frac{C_{a*}T_c}{C_a T_{c*}}\right)$$

$P_1 \leq 0$ whenever $ASN* \geq A^*S^*N, C_uSN* \geq {C_u}^*S^*N, C_aSN* \geq {C_a}^*S^*N, RT_c* \geq R*T_c$ (3.165)

and $P_2 \leq 0$ whenever $S^*N \geq SN*, C_u*S*AN \geq C_uSA*N*, {C_a}^*S^*AN \geq C_aSA*N*, A*C_u \geq AC_u*, C_u*C_a \geq C_u{C_a}^*, A*C_a \geq A{C_a}^*, {C_a}^*T_c \geq C_aT_c*$ (3.166)

Thus, $\frac{dL}{dt} \leq 0$if the condition in (3.165) and (3.166) holds.

Therefore, by LaSalle asymptotic stability theorem (LaSalle, 1976), and Oke *et al.*, (2020) the positive equilibrium state $\frac{dL}{dt}$ is globally asymptotically stable in the positive region R_+^6.

3.4 Application of Optimal Control to the HBV Models

Here, the main interest of this study is to suggest possible(s) optimal method of reducing/minimizing HBV transmission. Many mathematical models already exist describing HBV but the best control for the diseases still remain a subject of debate.

Previous mathematical models have considered vaccination and treatment as controls. However, these have their limitations. Generally, vaccines are not 100% effective, and therefore only a proportion of vaccinated individuals are protected, then some proportion of the vaccinated individuals may be susceptible again to that disease. (Keeling and Rolani

,2008).

However, testing and treatment will be more effective in a vaccinated population hence, the inclusion of testing as control in the present work (Niederau, 2014).

The preventive and treatment control for Hepatitis B includes vaccination, testing at various infectious stage and appropriate treatment (Niederau, 2014). It is believed that, if appropriate preventive measures are instituted globally, liver cirrhosis will be reduced greatly as early testing will help reduce death rate through liver cirrhosis (WHO, 2019)

3.4.1 The Optimal Control Strategy for HBV Model Case 1

Here, the formulation of the optimal control problem, analysis of the optimal control problem, adjoint conditions, optimality conditions and the optimality system for the Hepatitis B model case 1 are considered.

3.4.2 The Optimal Control Formulation for HBV Model Case 1

$$\left.\begin{aligned}
S'(t) &= \mu\omega(1-vC) + \varphi V - (\beta(A+\gamma C) + \gamma_3 + \mu_0 + \delta_1)S - rA - bC \\
L'(t) &= \beta(A+\gamma C)S - (\sigma + \mu_0 + \delta_1)L \\
A'(t) &= \sigma L - (u_1 + \gamma_1 + \mu_0 + \delta_1 - r)A \\
C'(t) &= q\gamma_1 A - (u_2 + \gamma_2 + \mu_0 + \mu_1 - \mu\omega v - b)C \\
H'(t) &= u_2 C + u_1 A - (\vartheta_3 + \mu_0 + \mu_2)H \\
R'(t) &= \gamma_2 C + (1-q)\gamma_1 A + \vartheta_3 H - \mu_0 R \\
V'(t) &= \mu(1-\omega) + \gamma_3 S - (\varphi + \mu_0)V
\end{aligned}\right\} \quad (3.167)$$

The controls used in system (3.167) represent effective time dependent testing measures

(u_1) and treatment efforts (u_2) to reduce the case of liver cirrhosis. The controls u in (3.167) is defined to be $u \in [0,1]$, where u ranges from no control $(u = 0)$ to maximum control $(u = 1)$.Note that $u_1, u_2 \in u$.

The interest of this research is to find the optimal control strategy u throughout the length of $0 \leq t \leq t_f$ such that the numbers of chronic carriers C is minimized whileminimizing the cost of control u.Thus, the objective function is

$$J(u_1, u_2) = \int_0^{tf} (G_1 L + G_2 A + G_3 C + G_4 {u_1}^2 + G_5 {u_2}^2) dt \quad (3.168)$$

where coefficients $G_1, G_2, G_3, G_4 \; and \; G_5$ are positive weights to balance the factors.

As a result, an optimal control

$$u^* = \{{u_1}^*, {u_2}^*\}$$

is defined, such that,

$$J({u_1}^*, {u_2}^*) = \min_{u_1, u_2} \{J(u_1, u_2)|_{u_1, u_2} \in u\} \quad (3.169)$$

where

$$u = \{(u_1, u_2)|_{u_1, u_2} : [0, t_f] \to [0,1]\} \quad (3.170)$$

is Lebesgue measurable and convex on u, then there exists an optimal control u satisfying the conditions in section 2.2.8.

3.4.3 The Analysis of the HBV Optimal Control Problem Model Case 1

Since there exist an optimal control for minimizing the functional (3.168) subject to system of equations (3.167), the Pontryagins' maximum principle (Fleming and Rishel, 1975) is used to derive necessary conditions for this optimal control.

The Hamiltonian is defined as follows:

$$\bar{H} = G_1 L + G_2 A + G_3 C + G_4 {u_1}^2 + G_5 {u_2}^2 + \lambda_1[\mu\omega(1 - vC) + \varphi V - (\beta(A + \gamma C) + \gamma_3 + \mu_0 + \delta_1)S - rA - bC] + \lambda_2[\beta(A + \gamma C)S - (\sigma + \mu_0 + \delta_1)L] + \lambda_3[\sigma L - (u_1 + \gamma_1 + \mu_0 + \delta_1 - r)A] + \lambda_4[q\gamma_1 A - (u_2 + \gamma_2 + \mu_0 + \mu_1 - \mu\omega v - b)C] + \lambda_5[u_2 C + u_1 A - (\vartheta_3 + \mu_0 + \mu_2)H] + \lambda_6[\gamma_2 C + (1 - q)\gamma_1 A + \vartheta_3 H - \mu_0 R] + \lambda_7[\mu(1 - \omega) + \gamma_3 S - (\varphi + \mu_0)V] \quad (3.171)$$

3.4.4 The Adjoint Conditions for HBV Model Case 1

In order to attach the system of ordinary differential equation in (3.167) on to the objective function in (3.168), the adjoint functions (or co-state variables) were used. The Pontryagins' Maximum Principle gives the necessary conditions that the adjoint functions must satisfy. Thus, the differential equations satisfied by system (3.167) are:

$$\left.\begin{aligned}
\frac{d\lambda_1}{dt} &= -\frac{\partial \bar{H}}{\partial S} = -\lambda_1(-\beta A - \beta\gamma C - \gamma_3 - \mu_0 - \delta_1) - \lambda_2(\beta A + \beta\gamma C) - \lambda_7\gamma_3 \\
\frac{d\lambda_2}{dt} &= -\frac{\partial \bar{H}}{\partial L} = -\lambda_2(\sigma - \mu_0 - \delta_1) - \lambda_3\sigma - G_1 \\
\frac{d\lambda_3}{dt} &= -\frac{\partial \bar{H}}{\partial A} = -\lambda_1(-\beta S - r) - \lambda_2\beta S - \lambda_3(-u_1 - \gamma_1 - \mu_0 - \delta_1 + r) - \lambda_4 q\gamma_1 - \lambda_5 u_1 - \lambda_6(1-q)\gamma_1 - G_2 \\
\frac{d\lambda_4}{dt} &= -\frac{\partial \bar{H}}{\partial C} = -\lambda_1(-\beta\gamma S - \mu\omega v - b) - \lambda_2\beta\gamma S - \lambda_4(\mu\omega v + b - u_2 - \gamma_2 - \mu_0 - \mu_1) - \lambda_5 u_2 - \lambda_6\gamma_2 - G_3 \\
\frac{d\lambda_5}{dt} &= -\frac{\partial \bar{H}}{\partial H} = -\lambda_5(-\vartheta_3 - \mu_0 - \mu_2) - \lambda_6\vartheta_3 \\
\frac{d\lambda_6}{dt} &= -\frac{\partial \bar{H}}{\partial R} = \lambda_6\mu_0 \\
\frac{d\lambda_7}{dt} &= -\frac{\partial \bar{H}}{\partial T} = -\lambda_1\varphi - \lambda_7(-\varphi - \mu_0)
\end{aligned}\right\} \quad (3.172)$$

with the boundary conditions (or Transversality conditions) at the final time, t_f:

$$\lambda_1(t_f) = 0,\ \lambda_2(t_f) = 0,\ \lambda_3(t_f) = 0,\ \lambda_4(t_f) = 0,\ \lambda_5(t_f) = 0, \lambda_6(t_f) = 0, \lambda_7(t_f) = 0$$

3.4.5 The Optimality Conditions for HBV Model Case 1

The Hamiltonian in equation (3.171) is minimized with respect to the controls u_1 and u_2 separately in order to obtain the optimal value of u_1^*, u_2^*. At these controls' values, the maximum Hamiltonian is obtained. The derivative of the Hamiltonian with respect to u_1 and u_2 is thus zero, since at the absolute minimum or maximum the slope of a function is zero. Thus,

$$\frac{\partial \bar{H}}{\partial u_1} = 2G_4 u_1 - \lambda_3 A + \lambda_5 A = 0$$

Thus,

$$u_1 = \frac{A(\lambda_3 - \lambda_5)}{2G_4} \tag{3.173}$$

Similar reasoning gives

$$\frac{\partial \overline{H}}{\partial u_2} = 2G_5 u_2 - \lambda_4 C + \lambda_5 C = 0$$

Thus

$$u_2 = \frac{C(\lambda_4 - \lambda_5)}{2G_5} \tag{3.174}$$

At the absolute minimum $u = u^*$, therefore the optimality conditions are

$$\left.\begin{aligned} u_1{}^* &= min\{1, max(0, u_1)\} \\ u_2{}^* &= min\{1, max(0, u_2)\} \end{aligned}\right\} \tag{3.175}$$

3.4.6 The Optimality System for the HBV Model Case 1

The optimality system consists of the state system, the adjoint system, initial conditions and the transversality conditions. Thus,

$$
\left.
\begin{gathered}
S^{'}(t) = \mu\omega(1 - vC) + \varphi V - (\beta(A + \gamma C) + \gamma_3 + \mu_0 + \delta_1)S - rA - bC \\
L^{'}(t) = \beta(A + \gamma C)S - (\sigma + \mu_0 + \delta_1)L \\
A^{'}(t) = \sigma L - (u_1 + \gamma_1 + \mu_0 + \delta_1 - r)A \\
C^{'}(t) = q\gamma_1 A - (u_2 + \gamma_2 + \mu_0 + \mu_1 - \mu\omega v - b)C \\
H^{'}(t) = u_2 C + u_1 A - (\vartheta_3 + \mu_0 + \mu_2)H \\
R^{'}(t) = \gamma_2 C + (1 - q)\gamma_1 A + \vartheta_3 H - \mu_0 R \\
V^{'}(t) = \mu(1 - \omega) + \gamma_3 S - (\varphi + \mu_0)V \\
{\lambda_1}'(t) = -\lambda_1(-\beta A - \beta\gamma C - \gamma_3 - \mu_0 - \delta_1) - \lambda_2(\beta A + \beta\gamma C) - \lambda_7\gamma_3 \\
{\lambda_2}'(t) = -\lambda_2(\sigma - \mu_0 - \delta_1) - \lambda_3\sigma - G_1 \\
{\lambda_3}'(t) = -\lambda_1(-\beta S - r) - \lambda_2\beta S - \lambda_3(-u_1 - \gamma_1 - \mu_0 - \delta_1 + r) - \lambda_4 q\gamma_1 - \lambda_5 u_1 - \lambda_6(1 - q)\gamma_1 - G_2 \\
{\lambda_4}'(t) = \lambda_1(-\beta\gamma S - \mu\omega v - b) - \lambda_2\beta\gamma S - \lambda_4(\mu\omega v + b - u_2 - \gamma_2 - \mu_0 - \mu_1) - \lambda_5 u_2 - \lambda_6\gamma_2 - G_3 \\
{\lambda_5}'(t) = -\lambda_5(-\vartheta_3 - \mu_0 - \mu_2) - \lambda_6\vartheta_3 \\
{\lambda_6}'(t) = \lambda_6\mu_0 \\
{\lambda_7}'(t) = -\lambda_1\varphi - \lambda_7(-\varphi - \mu_0) \\
S(0) = 700, L(0) = 100, A(0) = 100, C(0) = 100, H(0) = 50, R(0) = 30, V(0) = 600 \\
\lambda_1(t_f) = 0, \lambda_2(t_f) = 0, \lambda_3(t_f) = 0, \lambda_4(t_f) = 0,\ \lambda_5(t_f) = 0,\ \lambda_6(t_f) = 0
\end{gathered}
\right\} \quad (3.176)
$$

The optimality system in (3.176) was solved numerically by using both the forward and backward finite difference scheme.

3.5 The Optimal Control Strategy for HBV Model Case 2

Here, the formulation of the optimal control problem, analysis of the optimal control problem, adjoint conditions, optimality conditions and the optimality system for the HBV model case 2 are considered.

3.5.1 The Optimal Control Formulation for HBV Model Case 2

$$
\left.
\begin{aligned}
S' &= \zeta(1 - \alpha)(1 - \gamma C) - (\beta A + \xi\beta C)S + (1 - \eta)\omega A - \mu S + (1 - k)v\rho T + \varepsilon R \\
A' &= (\beta A + \xi\beta C)S - (\omega + \mu + \mu_1)A \\
C' &= \eta\omega A + \zeta(1 - \alpha)\gamma C + (1 - v)\rho T - (\mu + \mu_2)C \\
T' &= \mu_1 A + (\mu_2)C - (\rho + \mu)T \\
R' &= \zeta\alpha + kv\rho T - (\varepsilon + \mu)R
\end{aligned}
\right\} \quad (3.177)
$$

The controls used in system (3.177) represent effective time dependent testing measures (u_1) and treatment efforts (u_2) to reduce the case of liver cirrhosis. The controls u in (3.177) is defined to be $u \in [0,1]$, where u ranges from no control $(u = 0)$ to maximum control $(u = 1)$.Note that $u_1, u_2 \in u$.

The interest of this research is to find the optimal control strategy u throughout the length of $0 \leq t \leq t_f$ such that the numbers of chronic carriers C is minimized while minimizing the cost of control u.Thus, the objective function is

$$J(u_1, u_2) = \int_0^{tf} (D_1 A + D_2 C + D_3 {u_1}^2 + D_4 {u_2}^2) dt \tag{3.178}$$

where coefficients $D_1, D_2, D_3 \; and D_4$ are positive weights to balance the factors.

Thus, an optimal control

$$u^* = \{{u_1}^*, {u_2}^*\}$$

is defined such that,

$$J({u_1}^*, {u_2}^*) = \min_{u_1, u_2} \{J(u_1, u_2)|_{u_1, u_2} \in u\} \tag{3.179}$$

where

$$u = \{(u_1, u_2)|_{u_1, u_2} : [0, t_f] \to [0,1]\} \tag{3.180}$$

is Lebesgue measurable and convex on u, then there exists an optimal control u satisfying the conditions in section 2.2.8.

3.5.2 The Analysis of the HBV Optimal Control Problem Model Case 2

Since there exist an optimal control for minimizing the functional (3.178) subject to system of equations (3.177), the Pontryagins' maximum principle (Fleming and Rishel, 1975) is used to derive necessary conditions for this optimal control.

The Hamiltonian is defined as follows:

$$\bar{H} = D_1A + D_2C + D_3{u_1}^2 + D_4{u_2}^2 + \lambda_1[\zeta(1-\alpha)(1-\gamma C) - (\beta A + \xi\beta C)S + (1-\eta)\omega A - \mu S + (1-k)\nu\rho T + \varepsilon R] + \lambda_2[(\beta A + \xi\beta C)S - (\omega + \mu + \mu_1)A] + \lambda_3[\sigma\eta\omega A + \zeta(1-\alpha)\gamma C + (1-\upsilon)\rho T - (\sigma + \mu + \mu_2)C] + \lambda_4[\mu_1 A + (\mu_2 + \sigma)C - (\rho + \mu)T] + \lambda_5[\zeta\alpha + k\upsilon\rho T - (\varepsilon + \mu)R] \quad (3.179)$$

3.5.3 The Adjoint Conditions for HBV Model Case 2

In order to attach the system of ordinary differential equation in (3.177) on to the objective function in (3.178), the adjoint functions (or co-state variables) were used. The Pontryagins' Maximum Principle gives the necessary conditions that the adjoint functions must satisfy. Thus, the differential equations satisfied by system (3.177) are:

$$\left.\begin{aligned}
\frac{d\lambda_1}{dt} &= -\frac{\partial\bar{H}}{\partial S} = -\lambda_1(-\beta A - \xi\beta C - \mu) - \lambda_2(\beta A + \xi\beta C)\\
\frac{d\lambda_2}{dt} &= -\frac{\partial\bar{H}}{\partial A} = -\lambda_1(-\beta S + (1-\eta)\omega) - \lambda_2(\beta S - \omega - \mu - u_1) - \lambda_3\eta\omega - \lambda_4\mu_1 - D_1\\
\frac{d\lambda_3}{dt} &= -\frac{\partial\bar{H}}{\partial C} = -\lambda_1(-\zeta(1-\alpha)\gamma - \xi\beta S) - \lambda_2\xi\beta S - \lambda_3(\zeta(1-\alpha)\gamma - u_2 - \mu) - \lambda_4 - u_2 - D_2\\
\frac{d\lambda_4}{dt} &= -\frac{\partial\bar{H}}{\partial T} = -\lambda_1((1-k)\nu\rho) - \lambda_3((1-\nu)\rho) - \lambda_4(-\rho - \mu) - \lambda_5 k\nu\rho\\
\frac{d\lambda_5}{dt} &= -\frac{\partial\bar{H}}{\partial R} = -\lambda_1\varepsilon - \lambda_5(-\varepsilon - \mu)
\end{aligned}\right\} \quad (3.180)$$

with the boundary conditions (or Transversality conditions) at the final time, t_f:

$\lambda_1(t_f) = 0,\ \lambda_2(t_f) = 0,\ \lambda_3(t_f) = 0,\ \lambda_4(t_f) = 0,\ \lambda_5(t_f) = 0$

3.5.4 The Optimality Conditions for HBV Model Case 2

The Hamiltonian in (3.179) is minimized with respect to the controls u_1 and u_2 separately in order to obtain the optimal value of ${u_1}^*, {u_2}^*$. At these controls' values, the maximum Hamiltonian is obtained. The derivative of the Hamiltonian with respect to u_1 and u_2 is thus zero, since at the absolute minimum or maximum the slope of a function is zero. Thus,

$$\frac{\partial \overline{H}}{\partial u_1} = 2D_3u_1 - \lambda_2 A + \lambda_4 A = 0$$

Thus,

$$u_1 = \frac{A(\lambda_2 - \lambda_4)}{2D_3} \tag{3.181}$$

Similar reasoning gives

$$\frac{\partial \overline{H}}{\partial u_2} = 2D_4u_2 - \lambda_3 C + \lambda_4 C = 0$$

Thus

$$u_2 = \frac{C(\lambda_3 - \lambda_4)}{2D_4} \tag{3.182}$$

At the absolute minimum $u = u^*$, therefore the optimality conditions are

$$\left.\begin{aligned} u_1{}^* &= min\{1, max(0, u_1)\} \\ u_2{}^* &= min\{1, max(0, u_2)\} \end{aligned}\right\} \tag{3.183}$$

3.5.5 The Optimality System for the HBV Model Case 2

The optimality system consists of the state system, the adjoint system, initial conditions and the transversality conditions. Thus,

$$\left.\begin{aligned}
S'(t) &= \zeta(1-\alpha)(1-\gamma C) - (\beta A + \xi\beta C)S + (1-\eta)\omega A - \mu S + (1-k)\nu\rho T + \varepsilon R \\
A'(t) &= (\beta A + \xi\beta C)S - (\omega + \mu + \mu_1)A \\
C'(t) &= \sigma\eta\omega A + \zeta(1-\alpha)\gamma C + (1-\upsilon)\rho T - (\sigma + \mu + \mu_2)C \\
T'(t) &= \mu_1 A + (\mu_2 + \sigma)C - (\rho + \mu)T \\
R'(t) &= \zeta\alpha + k\upsilon\rho T - (\varepsilon + \mu)R \\
\lambda_1{}'(t) &= -\lambda_1(-\beta A - \xi\beta C - \mu) - \lambda_2(\beta A + \xi\beta C) \\
\lambda_2{}'(t) &= \ -\lambda_1(-\beta S + (1-\eta)\omega) - \lambda_2(\beta S\ - \omega - \mu\ -\ u_1) - \lambda_3\eta\omega - \lambda_4\mu_1 - D_1 \\
\lambda_3{}'(t) &= -\lambda_1(-\zeta(1-\alpha)\gamma - \xi\beta S) - \lambda_2\xi\beta S - \lambda_3(\zeta(1-\alpha)\gamma - u_2 - \mu - \sigma) - \lambda_4 - u_2 - D_2 \\
\lambda_4{}'(t) &= -\lambda_1\big((1-k)\nu\rho\big) - \lambda_3\big((1-\nu)\rho\big) - \lambda_4(-\rho - \mu) - \lambda_5 k\nu\rho \\
\lambda_5{}'(t) &= -\lambda_1\varepsilon - \lambda_5(-\varepsilon - \mu) \\
S(0) &= 700, A(0) = 100, C(0) = 100, T(0) = 50, R(0) = 30 \\
\lambda_1(t_f) &= 0, \lambda_2(t_f) = 0, \lambda_3(t_f) = 0, \lambda_4(t_f) = 0,\ \lambda_5(t_f) = 0
\end{aligned}\right\} \tag{3.184}$$

The optimality system in (3.184) was solved numerically by using both the forward and backward finite difference scheme.

3.6 The Optimal Control Strategy for HBV Model Case 3

Here, the formulation of the optimal control problem, analysis of the optimal control problem, adjoint conditions, optimality conditions and the optimality system for the HBV model case 3 are considered.

3.6.1 The Optimal Control Formulation for HBV Model Case 3

$$\left.\begin{aligned}
\frac{dS}{dt} &= \Pi - \left(\frac{\beta(A+\alpha_1 C_u+\alpha_2 C_a)}{N}\right)S + \sigma A - \mu S \\
\frac{dA}{dt} &= \left(\frac{\beta(A+\alpha_1 C_u+\alpha_2 C_a)}{N}\right)S - (\sigma+\gamma+\mu_1)A \\
\frac{dC_u}{dt} &= \gamma A - (\mu_2+\mu+d_c)C_u \\
\frac{dC_a}{dt} &= \mu_2 C_u + \mu_1 A - (\mu_3+\mu+d_c)C_a \\
\frac{dT_c}{dt} &= \mu_3 C_a - (\omega+\mu)T_c \\
\frac{dR}{dt} &= \omega T_c\text{-}\mu R
\end{aligned}\right\} \qquad (3.185)$$

The controls used in system (3.185) represent effective time dependent testing measures (u_1, u_2) and treatment efforts (u_3) to reduce the case of liver cirrhosis. The controls u in (3.185) is defined to be $u \in [0,1]$, where u ranges from no control $(u = 0)$ to maximum control $(u = 1)$.Note that $u_1, u_2, u_3 \in u$.

It is of interest to find the optimal control strategy u throughout the length of $0 \leq t \leq$

$t_f$such that the numbers of chronic carriers C is minimized while minimizing the cost of control u.Thus, the objective function is

$$J(u_1, u_2, u_3) = \int_0^{tf} (D_1 A + D_2 C_u + D_3 C_a + D_4 {u_1}^2 + D_5 {u_2}^2 + D_6 {u_3}^2) dt \quad (3.186)$$

where coefficients $D_1, D_2, D_3, D_4, D_5 \; and D_6$ are positive weights to balance the factors.

Thus, an optimal control

$$u^* = \{{u_1}^*, {u_2}^*, {u_3}^*\}$$

is defined such that,

$$J({u_1}^*, {u_2}^*, {u_3}^*) = \min_{u_1, u_2} \{J(u_1, u_2, u_3)|_{u_1, u_2, u_3} \in u\} \quad (3.187)$$

where

$$u = \{(u_1, u_2, u_3)|_{u_1, u_{2,}, u_3} : [0, t_f] \to [0,1]\} \quad (3.188)$$

is Lebesgue measurable and convex on u, then there exists an optimal control u satisfying the conditions in section 2.2.8.

3.6.2 The Analysis of the HBV Optimal Control Problem Model Case 3

Since there exist an optimal control for minimizing the functional (3.186) subject to system of equations (3.185), the Pontryagins' maximum principle (Fleming and Rishel, 1975) is used to derive necessary conditions for this optimal control.

The Hamiltonian is defined as follows:

$$\bar{H} = D_1A + D_2C_u + D_3C_a + D_4{u_1}^2 + D_5{u_2}^2 + D_6{u_3}^2 + \lambda_1\left[\Pi - \left(\frac{\beta(A+\alpha_1C_u+\alpha_2C_a)}{N}\right)S + \sigma A - \mu S\right] + \lambda_2\left[\left(\frac{\beta(A+\alpha_1C_u+\alpha_2C_a)}{N}\right)S - (\sigma+\gamma+\mu_1)A\right] + \lambda_3[\gamma A - (\mu_2+\mu+d_c)C_u] + \lambda_4[\mu_2C_u + \mu_1A - (\mu_3+\mu+d_c)C_a] + \lambda_5[\mu_3C_a - (\omega+\mu)T_c] + \lambda_6[\omega T_c - \mu R] \quad (3.187)$$

3.6.3 The Adjoint Conditions for HBV Model Case 3

In order to attach the system of ordinary differential equation in (3.185) on to the objective function in (3.186), the adjoint functions (or co-state variables) were used. The Pontryagins' maximum principle gives the necessary conditions that the adjoint functions must satisfy. Thus, the differential equations satisfied by system (3.185) are:

$$\frac{d\lambda_1}{dt} = -\frac{\partial\bar{H}}{\partial S} = -\lambda_1\left(\frac{\beta(A+\alpha_1C_u+\alpha_2C_a)S}{(S+A+C_u+C_a+T_c+R)^2} - \frac{\beta(A+\alpha_1C_u+\alpha_2C_a)}{S+A+C_u+C_a+T_c+R} - \mu\right) - \lambda_2\left(-\frac{\beta(A+\alpha_1C_u+\alpha_2C_a)S}{(S+A+C_u+C_a+T_c+R)^2} + \frac{\beta(A+\alpha_1C_u+\alpha_2C_a)}{S+A+C_u+C_a+T_c+R}\right)$$

$$\frac{d\lambda_2}{dt} = -\frac{\partial\bar{H}}{\partial A} = -\lambda_1\left(\frac{\beta(A+\alpha_1C_u+\alpha_2C_a)S}{(S+A+C_u+C_a+T_c+R)^2} - \frac{\beta S}{S+A+C_u+C_a+T_c+R} + \sigma\right) - \lambda_2\left(-\frac{\beta(A+\alpha_1C_u+\alpha_2C_a)S}{(S+A+C_u+C_a+T_c+R)^2} - \frac{\beta S}{S+A+C_u+C_a+T_c+R} - \sigma - \gamma - \mu_1\right) - \gamma\lambda_3 - \mu_1\lambda_4 - D_1$$

$$\frac{d\lambda_3}{dt} = -\frac{\partial\bar{H}}{\partial C_u} = -\lambda_1\left(\frac{\beta(A+\alpha_1C_u+\alpha_2C_a)S}{(S+A+C_u+C_a+T_c+R)^2} - \frac{\beta\alpha_1S}{S+A+C_u+C_a+T_c+R}\right) - \lambda_2\left(-\frac{\beta(A+\alpha_1C_u+\alpha_2C_a)S}{(S+A+C_u+C_a+T_c+R)^2} + \frac{\beta\alpha_1S}{S+A+C_u+C_a+T_c+R}\right) - \lambda_3(-\mu_2-\mu-d_c) - \mu_2\lambda_4 - D_2$$

$$\frac{d\lambda_4}{dt} = -\frac{\partial \bar{H}}{\partial C_a} = -\lambda_1\left(\frac{\beta(A+\alpha_1 C_u+\alpha_2 C_a)S}{(S+A+C_u+C_a+T_c+R)^2} - \frac{\beta\alpha_2 S}{S+A+C_u+C_a+T_c+R}\right) - \lambda_2\left(-\frac{\beta(A+\alpha_1 C_u+\alpha_2 C_a)S}{(S+A+C_u+C_a+T_c+R)^2} + \frac{\beta\alpha_2 S}{S+A+C_u+C_a+T_c+R}\right) - \lambda_4(-\mu_3-\mu-d_c) - \mu_3\lambda_5 - D_3$$

$$\frac{d\lambda_5}{dt} = -\frac{\partial \bar{H}}{\partial R} = -\lambda_1\left(\frac{\beta(A+\alpha_1 C_u+\alpha_2 C_a)S}{(S+A+C_u+C_a+T_c+R)^2}\right) + \lambda_2\left(\frac{\beta(A+\alpha_1 C_u+\alpha_2 C_a)S}{(S+A+C_u+C_a+T_c+R)^2}\right) - \lambda_5(-\omega-\mu) - \omega\lambda_6$$

$$\frac{d\lambda_6}{dt} = -\frac{\partial \bar{H}}{\partial R} = -\lambda_1\left(\frac{\beta(A+\alpha_1 C_u+\alpha_2 C_a)S}{(S+A+C_u+C_a+T_c+R)^2}\right) + \lambda_2\left(\frac{\beta(A+\alpha_1 C_u+\alpha_2 C_a)S}{(S+A+C_u+C_a+T_c+R)^2}\right) + \mu\lambda_6$$

with the boundary conditions (or Transversality conditions) at the final time, t_f:

$$\lambda_1(t_f) = 0,\ \lambda_2(t_f) = 0,\ \lambda_3(t_f) = 0,\ \lambda_4(t_f) = 0,\ \lambda_5(t_f) = 0,\ \lambda_6(t_f) = 0$$

3.6.4 The Optimality Conditions for HBV Model Case 3

The Hamiltonian equation in (3.187) is minimized with respect to the controls u_1, u_2 and u_3 separately in order to obtain the optimal value of ${u_1}^*, {u_2}^*, {u_3}^*$. At these controls' values, the maximum Hamiltonian is obtained. The derivative of the Hamiltonian with respect to u_1,$u_2$and u_3 is thus zero, since at the absolute minimum or maximum the slope of a function is zero. Thus,

$$\frac{\partial \bar{H}}{\partial u_1} = 2D_4 u_1 - \lambda_2 A + \lambda_4 A = 0$$

Thus,

$$u_1 = \frac{A(\lambda_2-\lambda_4)}{2D_4} \qquad (3.188)$$

Similar reasoning gives

$$\frac{\partial \overline{H}}{\partial u_2} = 2D_5 u_2 - \lambda_3 C_u + \lambda_4 C_u = 0$$

Thus

$$u_2 = \frac{C_u(\lambda_3 - \lambda_4)}{2D_5} \tag{3.189}$$

Also,

$$\frac{\partial \overline{\mathrm{H}}}{\partial \mathrm{u}_3} = 2\mathrm{D}_6\mathrm{u}_3 - \lambda_4\mathrm{C}_\mathrm{a} + \lambda_5\mathrm{C}_\mathrm{a} = 0$$

Thus

$$u_3 = \frac{C_a(\lambda_4 - \lambda_5)}{2D_6} \tag{3.190}$$

At the absolute minimum $u = u^*$, therefore the optimality conditions are

$$\left.\begin{aligned} u_1{}^* &= min\{1, max(0, u_1)\} \\ u_2{}^* &= min\{1, max(0, u_2)\} \\ u_3{}^* &= min\{1, max(0, u_3)\} \end{aligned}\right\} \tag{3.191}$$

3.6.5 The Optimality System for the HBV Model Case 3

The optimality system consists of the state system, the adjoint system, initial conditions and the transversality conditions. Thus,

$$S'(t) = \Pi - \left(\frac{\beta(A + \alpha_1 C_u + \alpha_2 C_a)}{N}\right) S + \sigma A - \mu S$$

$$A'(t) = \left(\frac{\beta(A+\alpha_1 C_u+\alpha_2 C_a)}{N}\right) S - (\sigma + \gamma + \mu_1)A$$

$$C_u{}'(t) = \gamma A - (\mu_2 + \mu + d_c)C_u$$

$$C_a{}'(t) = \mu_2 C_u + \mu_1 A - (\mu_3 + \mu + d_c)C_a$$

$$T_c{}'(t) = \mu_3 C_a - (\omega + \mu)T_c$$

$$R'(t) = \omega T_c\text{-}\mu R$$

$$\left.\begin{aligned}
&\lambda_1{}'(t) = -\lambda_1\left(\frac{\beta(A+\alpha_1 C_u+\alpha_2 C_a)S}{(S+A+C_u+C_a+T_c+R)^2} - \frac{\beta(A+\alpha_1 C_u+\alpha_2 C_a)}{S+A+C_u+C_a+T_c+R} - \mu\right) - \lambda_2\left(-\frac{\beta(A+\alpha_1 C_u+\alpha_2 C_a)S}{(S+A+C_u+C_a+T_c+R)^2} + \right.\\
&\left.\frac{\beta(A+\alpha_1 C_u+\alpha_2 C_a)}{S+A+C_u+C_a+T_c+R}\right)\\
&\lambda_2{}'(t) = -\lambda_1\left(\frac{\beta(A+\alpha_1 C_u+\alpha_2 C_a)S}{(S+A+C_u+C_a+T_c+R)^2} - \frac{\beta S}{S+A+C_u+C_a+T_c+R} + \sigma\right) - \lambda_2\left(-\frac{\beta(A+\alpha_1 C_u+\alpha_2 C_a)S}{(S+A+C_u+C_a+T_c+R)^2} + \right.\\
&\left.\frac{\beta S}{S+A+C_u+C_a+T_c+R} - \sigma - \gamma - \mu_1\right) - \gamma\lambda_3 - \mu_1\lambda_4 - D_1\\
&\lambda_3{}'(t) = -\lambda_1\left(\frac{\beta(A+\alpha_1 C_u+\alpha_2 C_a)S}{(S+A+C_u+C_a+T_c+R)^2} - \frac{\beta\alpha_1 S}{S+A+C_u+C_a+T_c+R}\right) - \lambda_2\left(-\frac{\beta(A+\alpha_1 C_u+\alpha_2 C_a)S}{(S+A+C_u+C_a+T_c+R)^2} + \right.\\
&\left.\frac{\beta\alpha_1 S}{S+A+C_u+C_a+T_c+R}\right) - \lambda_3(-\mu_2 - \mu - d_c) - \mu_2\lambda_4 - D_2\\
&\lambda_4{}'(t) = -\lambda_1\left(\frac{\beta(A+\alpha_1 C_u+\alpha_2 C_a)S}{(S+A+C_u+C_a+T_c+R)^2} - \frac{\beta\alpha_2 S}{S+A+C_u+C_a+T_c+R}\right) - \lambda_2\left(-\frac{\beta(A+\alpha_1 C_u+\alpha_2 C_a)S}{(S+A+C_u+C_a+T_c+R)^2} + \right.\\
&\left.\frac{\beta\alpha_2 S}{S+A+C_u+C_a+T_c+R}\right) - \lambda_4(-\mu_3 - \mu - d_c) - \mu_3\lambda_5 - D_3\\
&\lambda_5{}'(t) = -\lambda_1\left(\frac{\beta(A+\alpha_1 C_u+\alpha_2 C_a)S}{(S+A+C_u+C_a+T_c+R)^2}\right) + \lambda_2\left(\frac{\beta(A+\alpha_1 C_u+\alpha_2 C_a)S}{(S+A+C_u+C_a+T_c+R)^2}\right) - \lambda_5(-\omega - \mu) - \omega\lambda_6\\
&\lambda_6{}'(t) = -\lambda_1\left(\frac{\beta(A+\alpha_1 C_u+\alpha_2 C_a)S}{(S+A+C_u+C_a+T_c+R)^2}\right) + \lambda_2\left(\frac{\beta(A+\alpha_1 C_u+\alpha_2 C_a)S}{(S+A+C_u+C_a+T_c+R)^2}\right) + \mu\lambda_6
\end{aligned}\right\} \quad (3.192)$$

$$S(0) = 700, A(0) = 100, C_u(0) = 100, C_a(0) = 100, T_c(0) = 50, R(0) = 30$$

$$\lambda_1(t_f) = 0, \lambda_2(t_f) = 0, \lambda_3(t_f) = 0, \lambda_4(t_f) = 0,\ \lambda_5(t_f) = 0, \lambda_6(t_f) = 0$$

The optimality system in (3.192) was solved numerically by using both the forward and backward finite difference scheme.

CHAPTER FOUR

4.0 RESULTS AND DISCUSSION OF FINDINGS

4.1 Results

The numerical computations are carried out using the MAPLE 18 program pseudocode with computation times of 5.0s on windows 13 operating system. The complete solutions of the study are numerically demonstrated in tables and graphs for the various population dynamics.

4.1.1 Results for HBV Model Case 1

For comprehensive understanding of the transmission process of Hepatitis B virus, a numerical computation of the mathematical analysis is carried out along with optimal control analysis. Based on various reports on the theoretical studies of related HBV model, the following default parameter values are gotten from existing literatures. Therefore, the results from this study are taken from the appropriate parameter defined except otherwise declared on each graph. Hence, the HBV mathematical formulation solutions for case 1 are presented as follows:

Table 4.1 Parameter's specifications for HBV model case 1

Parameter	Values	Source
β	0.095	Khan et al., (2019)
σ	0.016	Khan et al., (2019)
γ	0.16	Khan et al., (2019)
q	0.885	Khan et al., (2019)
γ_1	0.01095	Khan et al., (2019)
μ	0.0121	Khan et al., (2019)
ω	0.32	Khan et al., (2019)
υ	0.11	Khan et al., (2019)
γ_2	0.0000684	Khan et al., (2019)
μ_0	0.00693	Khan et al., (2019)

μ_1, μ_2	0.002	Khan et al., (2019)
ϑ_1	0.36	Khan et al., (2019)
ϑ_2	0.2	Khan et al., (2019)
ϑ_3	0.34	Khan et al., (2019)
δ_1	0.95	Khan et al., (2019)
r	0.2	Estimated
γ_3	0.5	Estimated
φ	0.1	Khan et al., (2019)
b	0.2	Estimated

Table 4.2:Sensitivity Indices on R_0 for HBV model formulation of case 1.

Parameter	Sensitivity Index	Parameter	Sensitivity Index
b	0.0069333	υ	0.0001477
β	1.0000000	γ_2	-0.0023712
γ	0.0229172	γ_3	-0.0327537
μ	1.0001477	μ_0	-0.0928449
ω	0.0218425	μ_1	-0.0069333
φ	0.0737448	ϑ_1	-0.2935349
q	0.0229172	ϑ_2	-0.0204534
r	0.1630749	γ_1	-0.0663663
σ	0.8567502	δ_1	-2.5853932

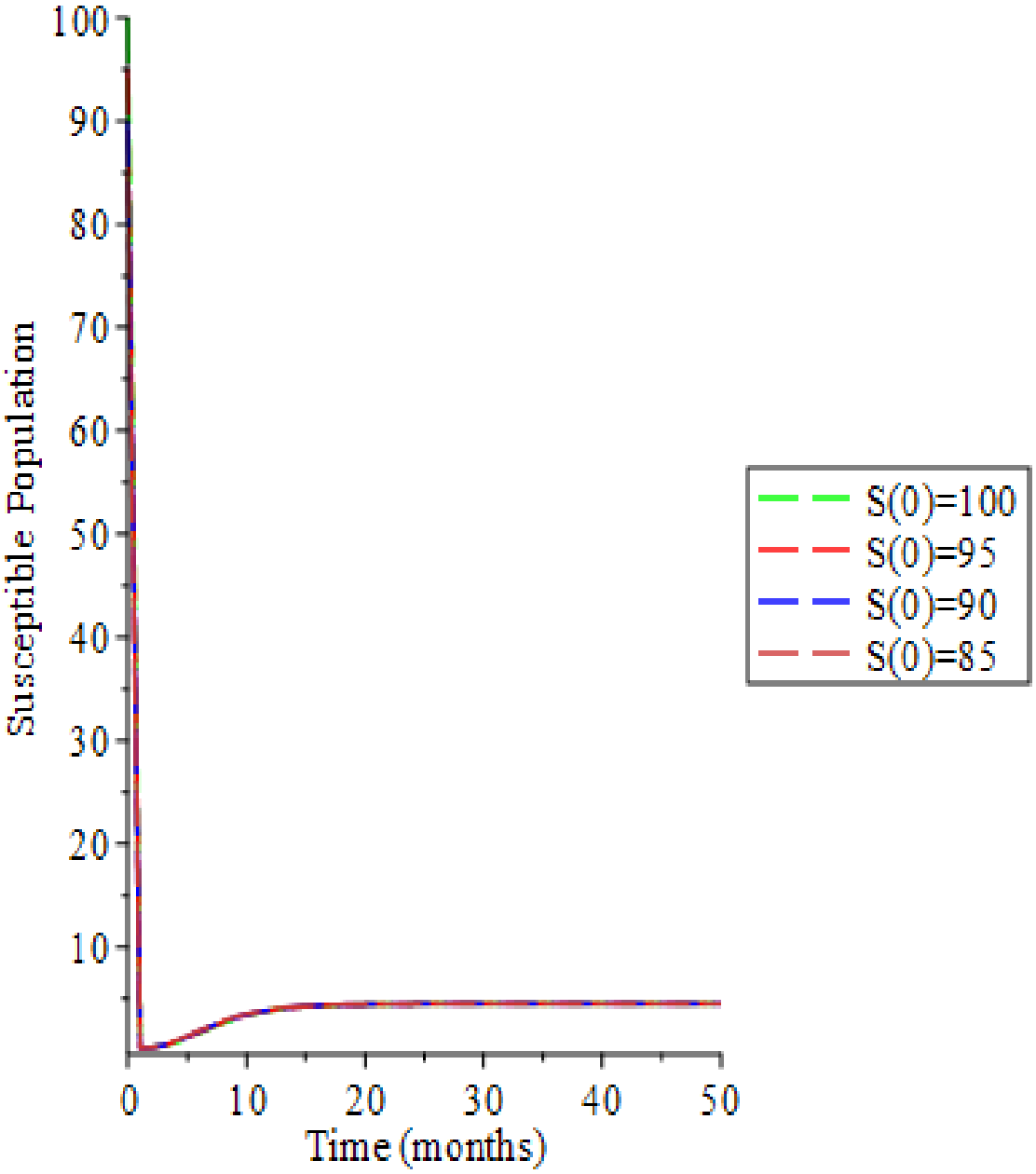

Figure 4.1: Behavioural dynamics of susceptible population when $R_0 < 1$

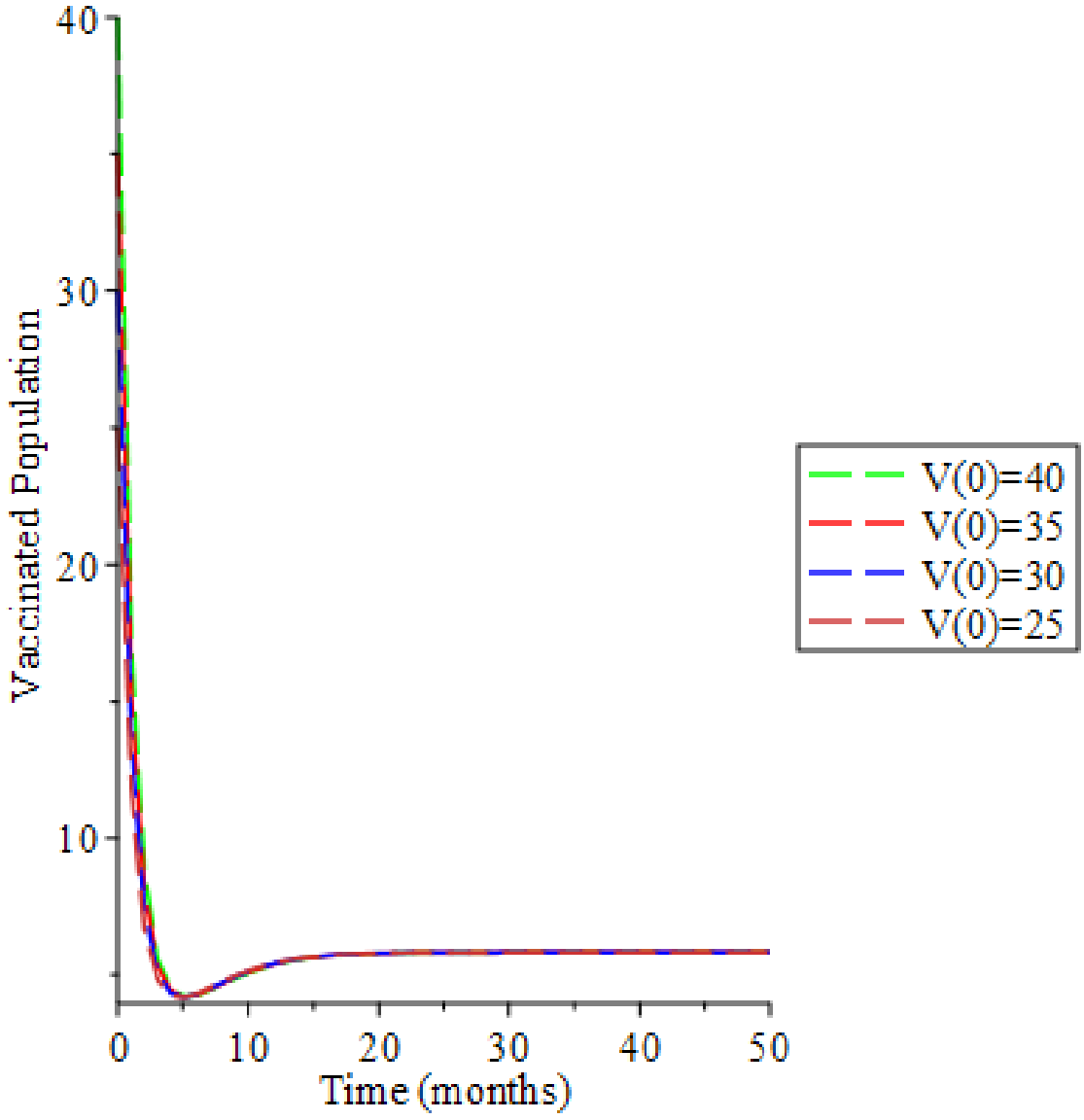

Figure 4.2: Behavioural dynamics of vaccinated population when $R_0 < 1$

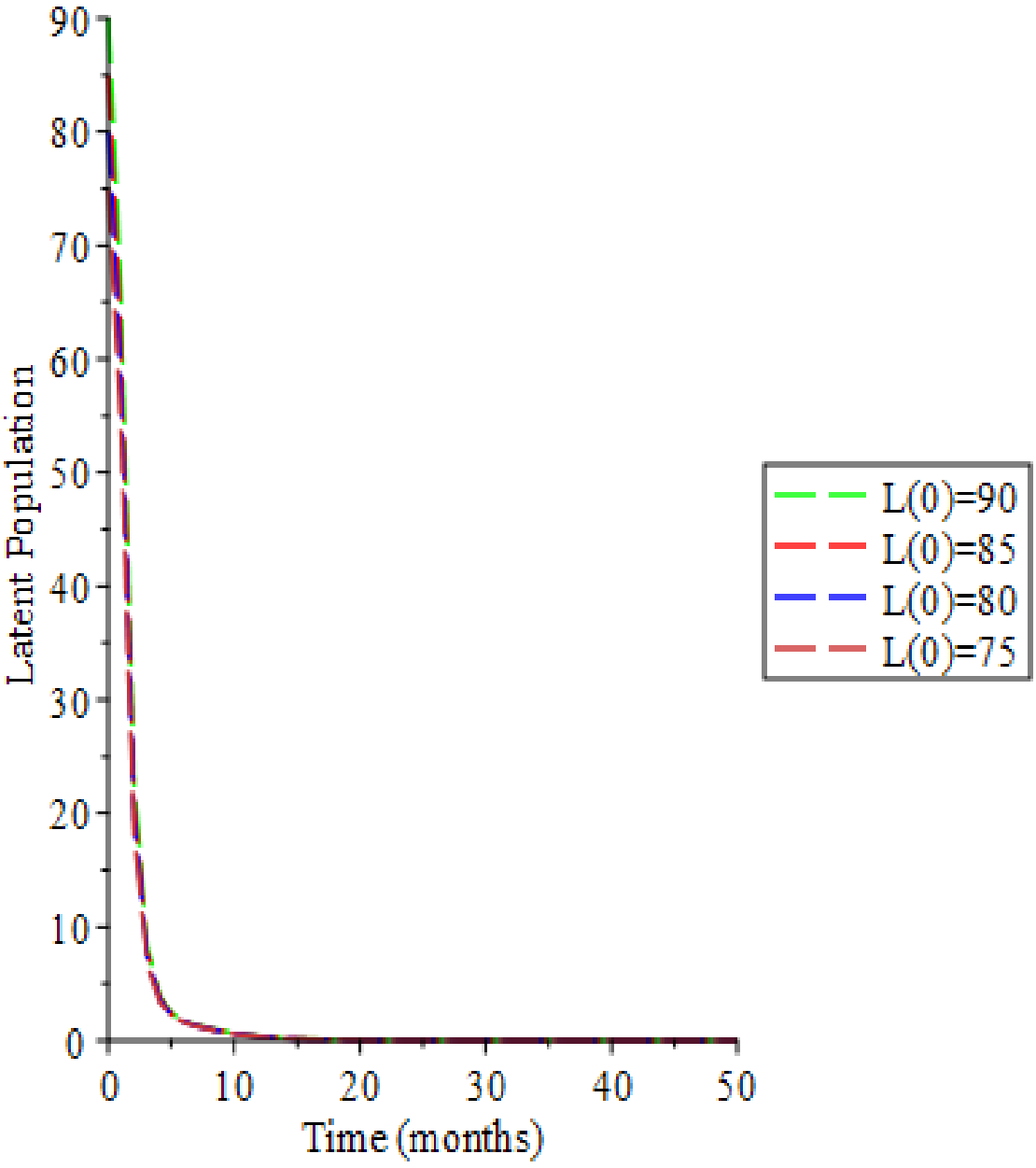

Figure 4.3: Behavioural dynamics of latent population when $R_0 < 1$

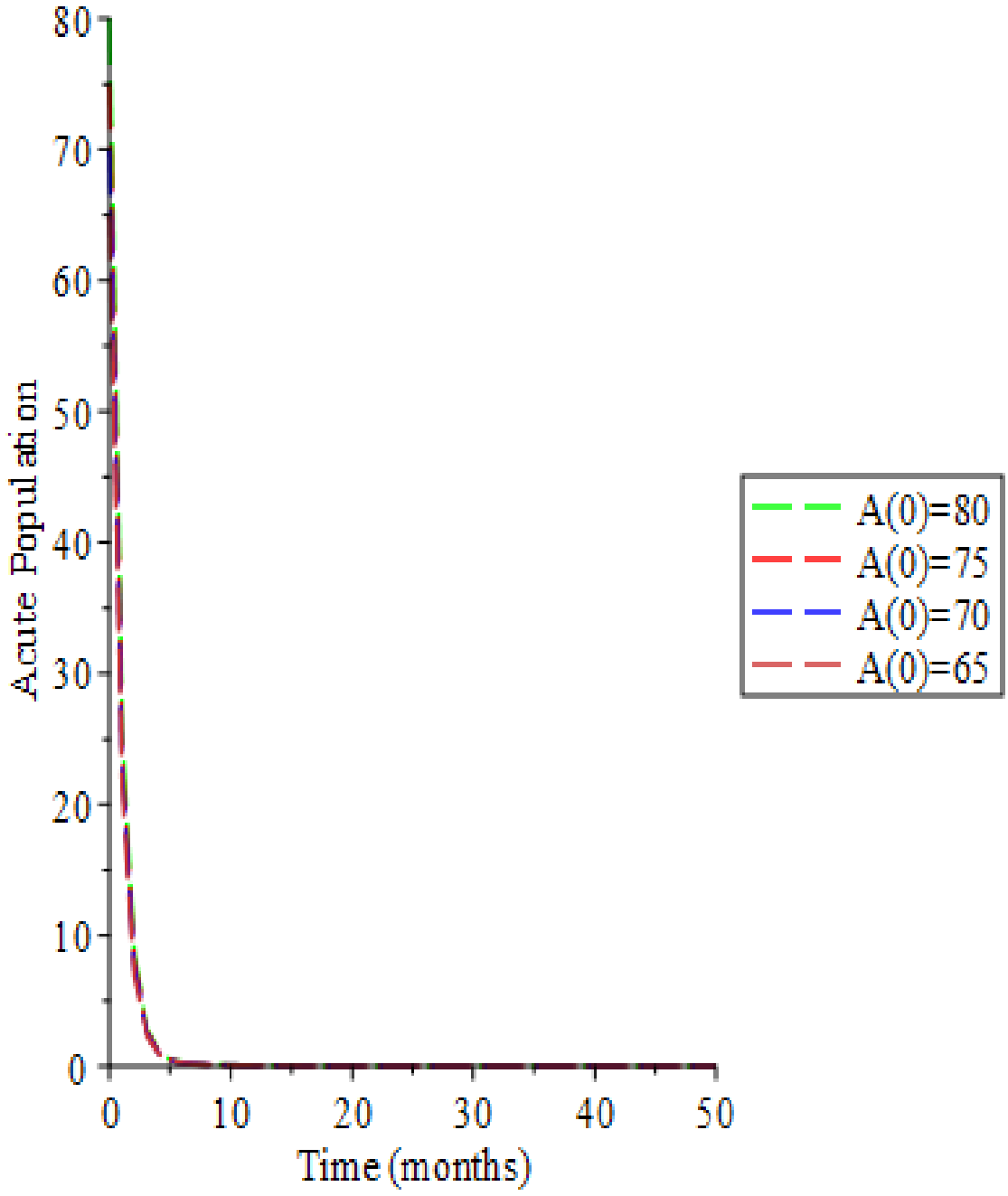

Figure 4.4: Behavioural dynamics of acute population when $R_0 < 1$

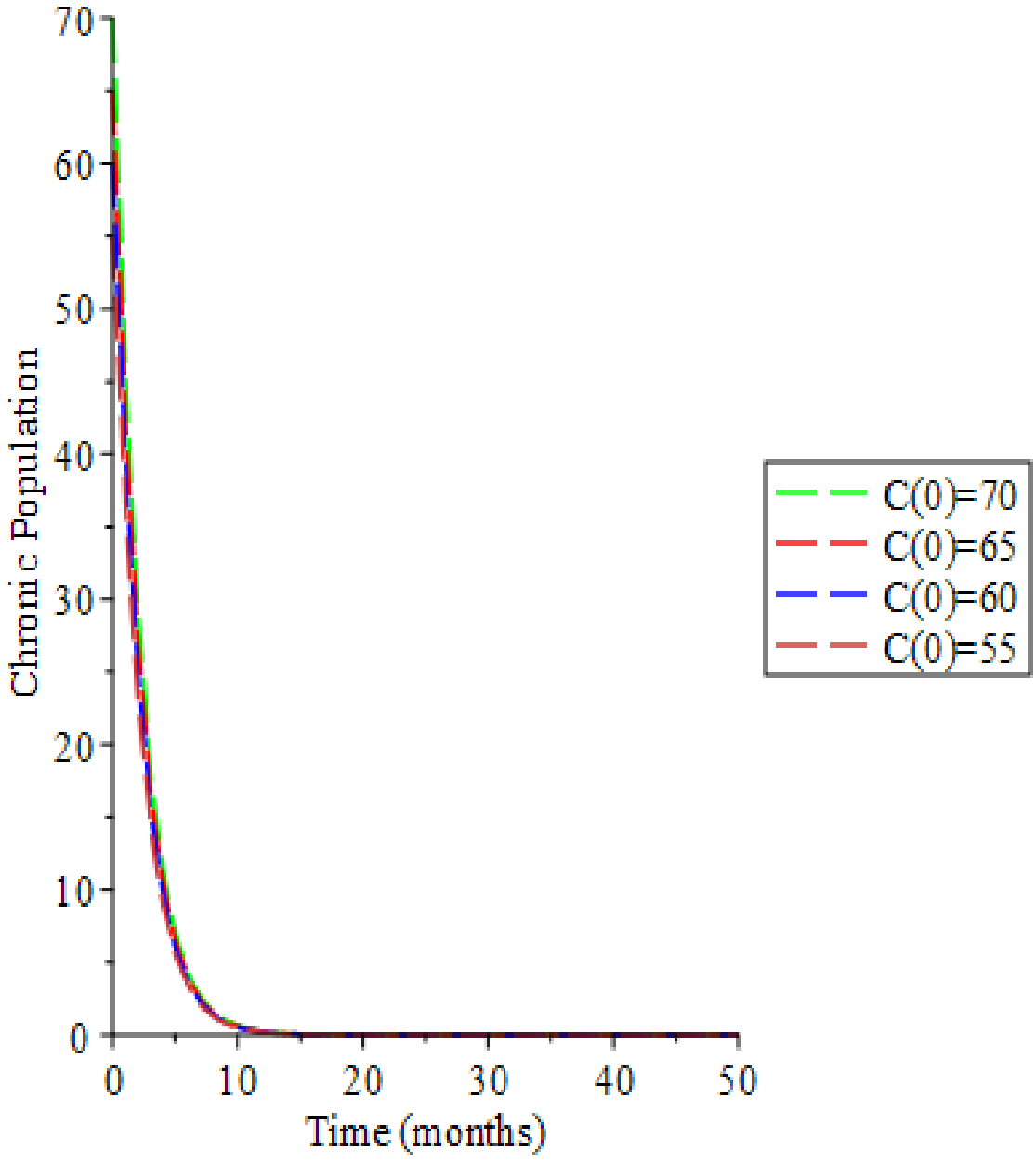

Figure 4.5: Behavioural dynamics of chronic population when $R_0 < 1$

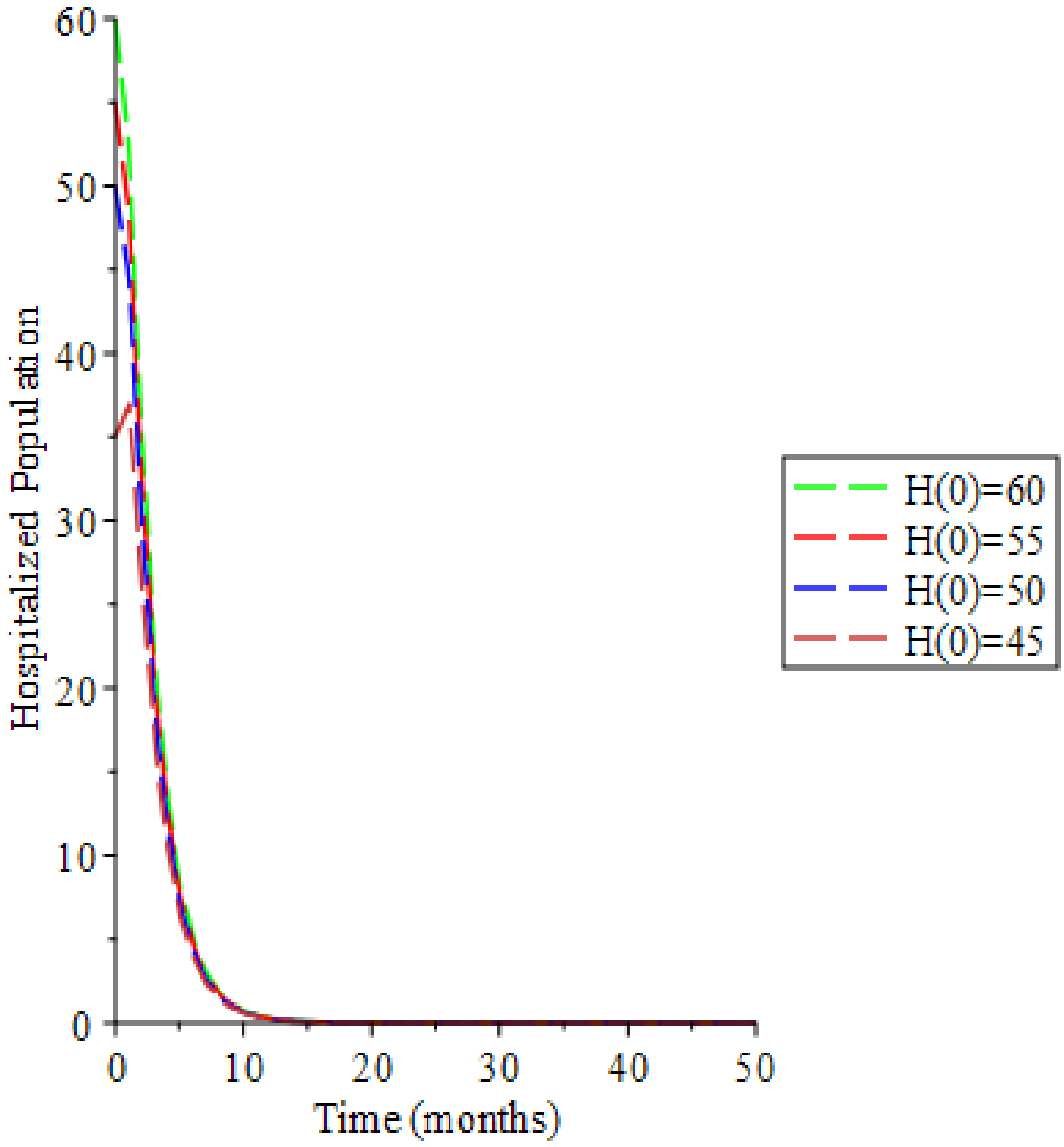

Figure 4.6: Behavioural dynamics of hospitalized population when $R_0 < 1$

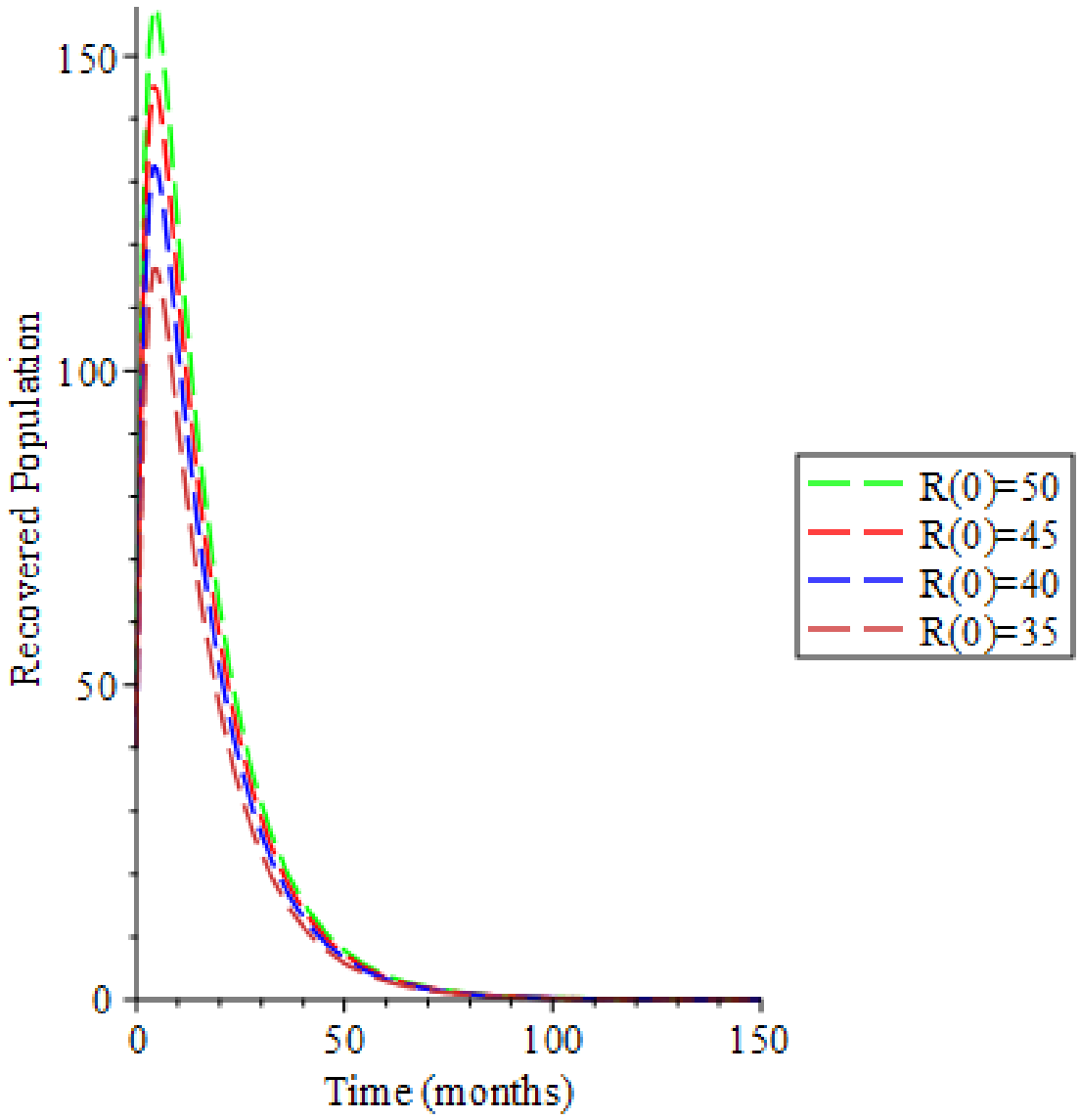

Figure 4.7: Behavioural dynamics of recovered population when $R_0 < 1$

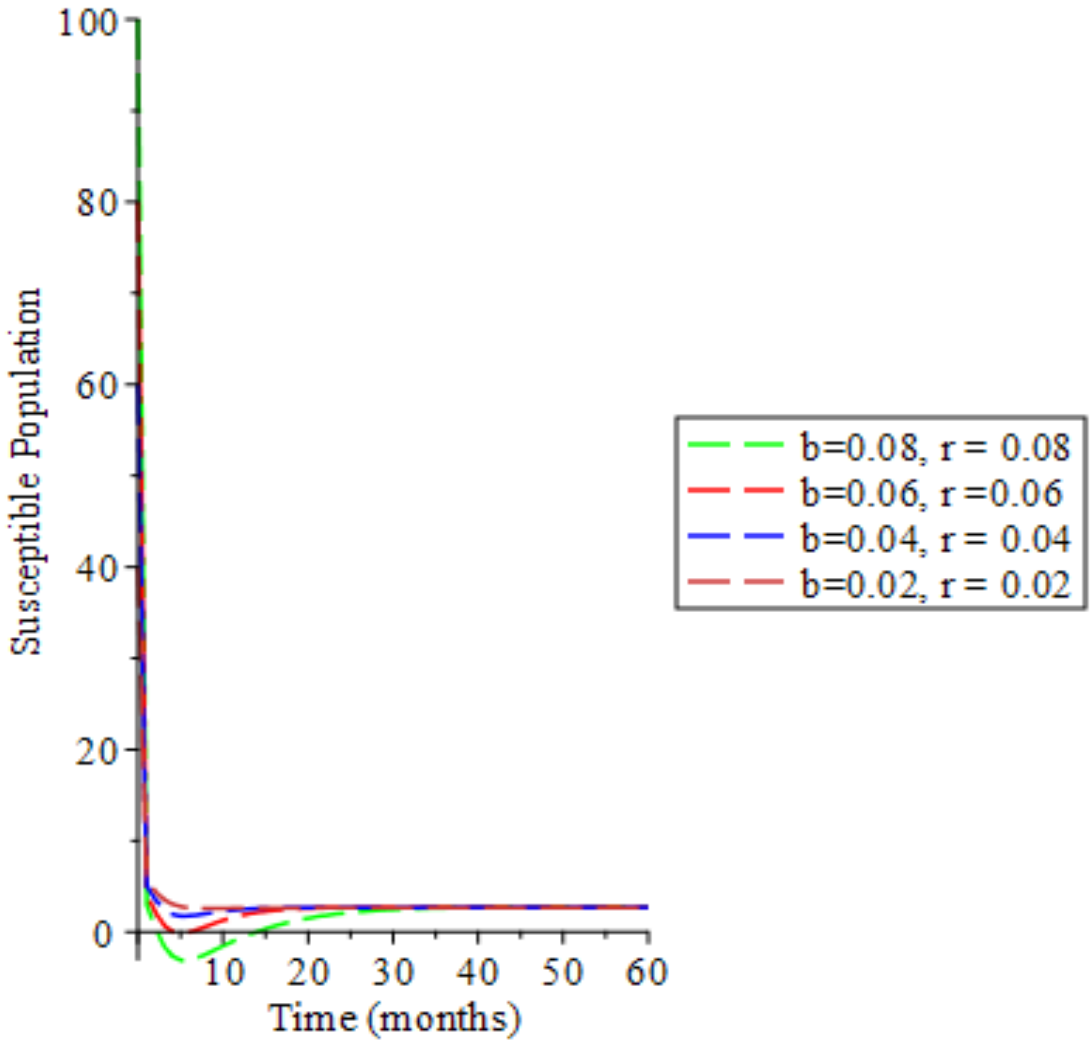

Figure 4.8: Behavioural dynamics of susceptible population when varying the acutely and chronically infected rate

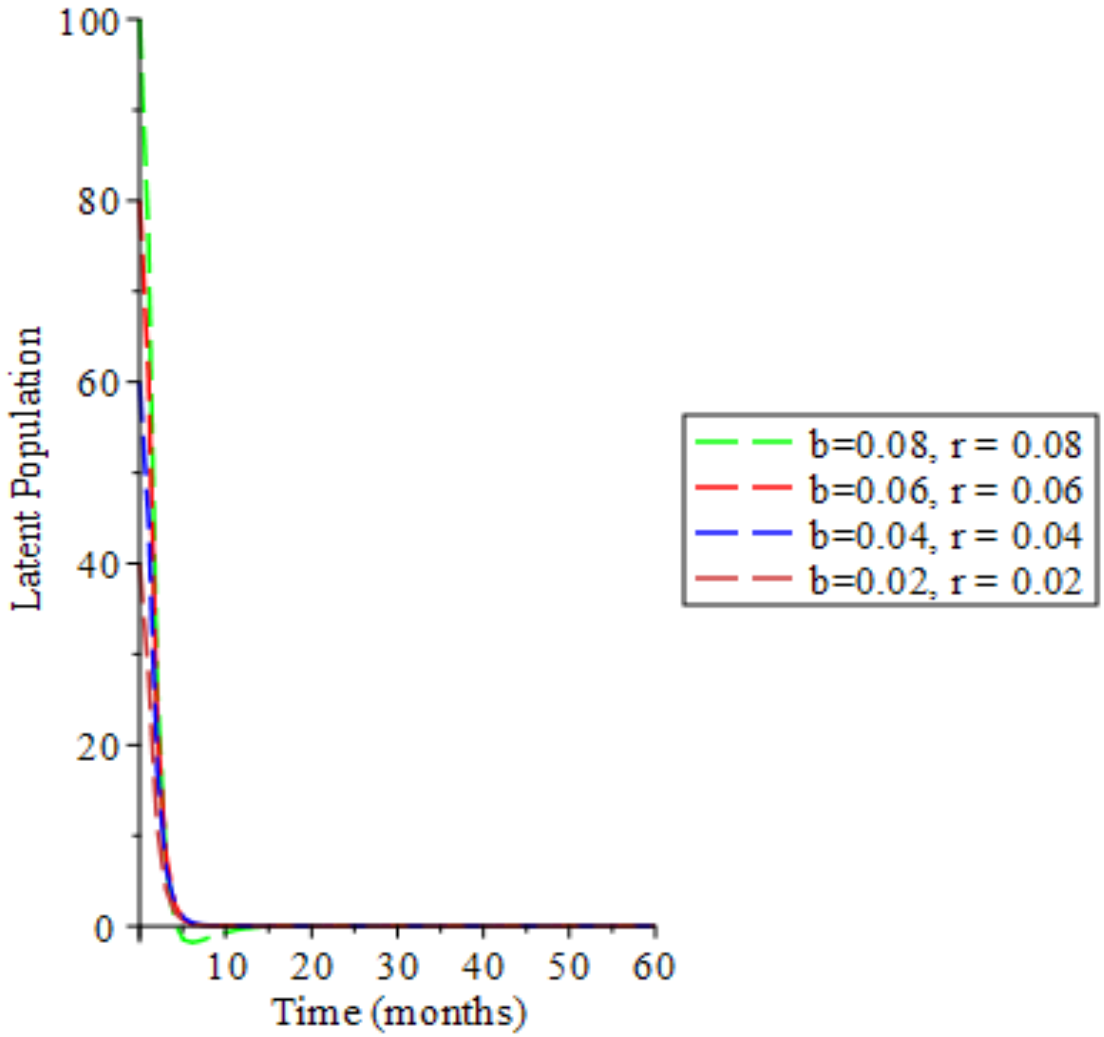

Figure 4.9: Behavioural dynamics of latent population when varying the acutely and chronically infected rate

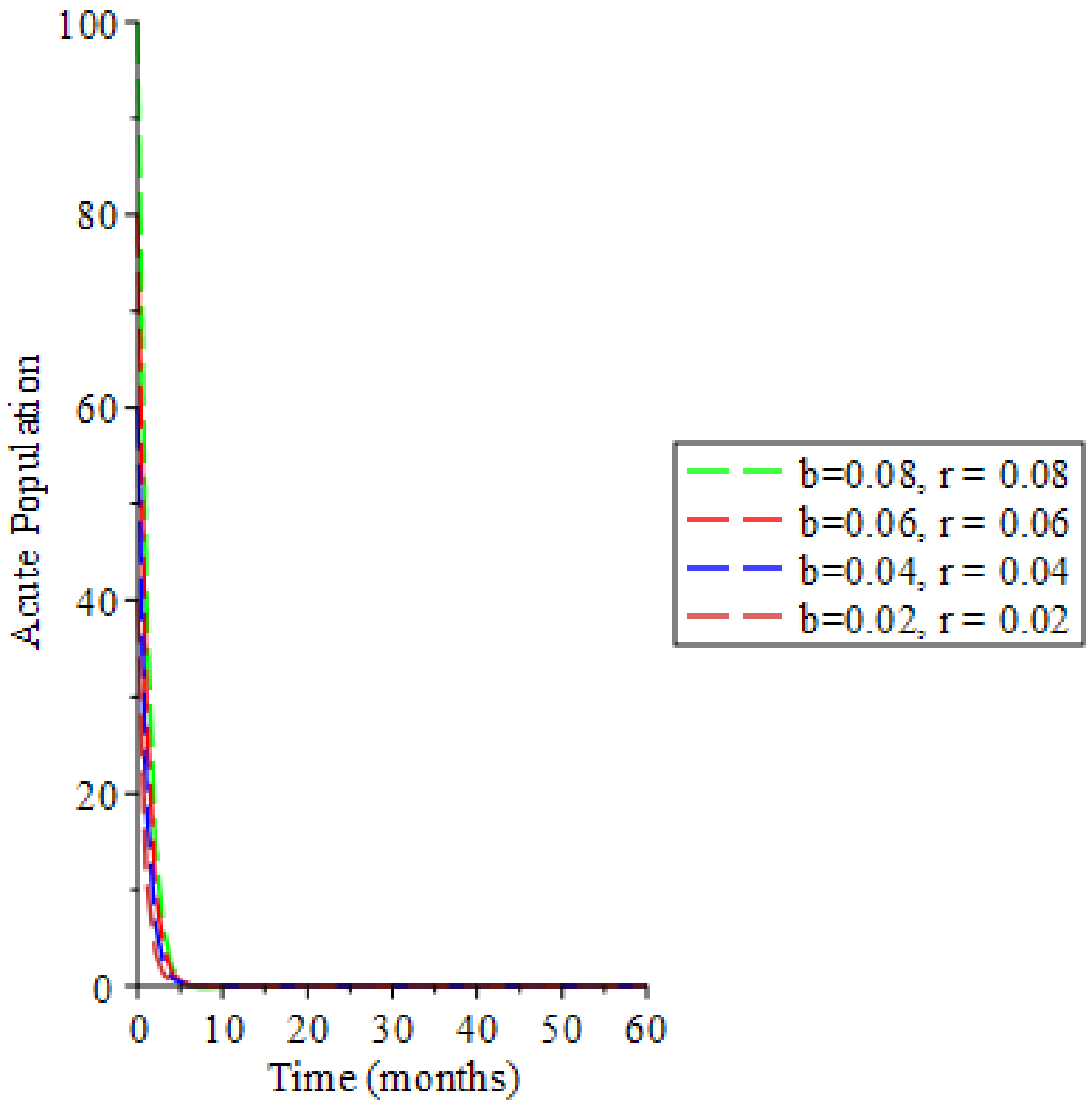

Figure 4.10: Behavioural dynamics of acute population when varying the acutely and chronically infected rate

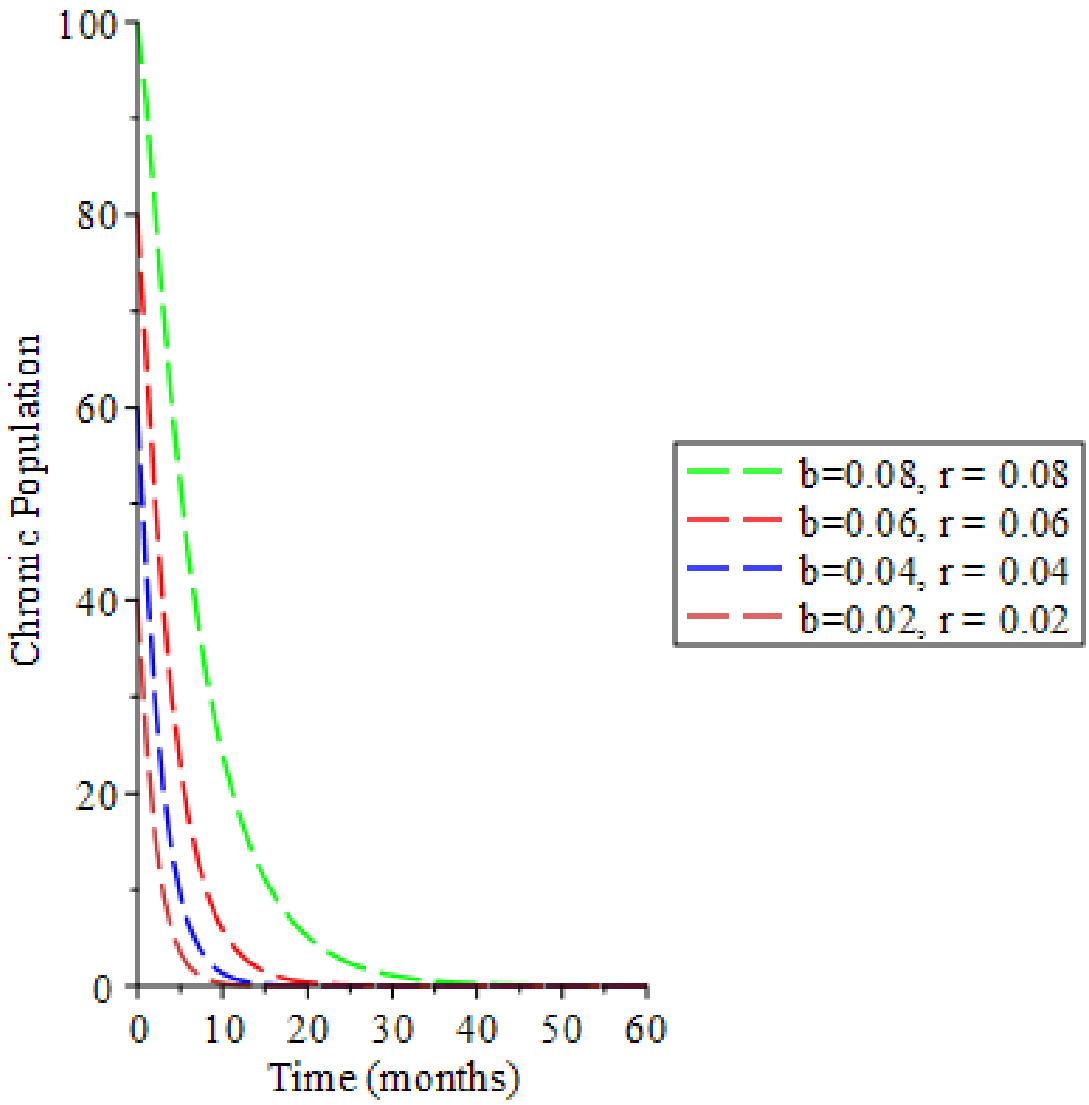

Figure 4.11: Behavioural dynamics of chronic population when varying the acutely and chronically infected rate

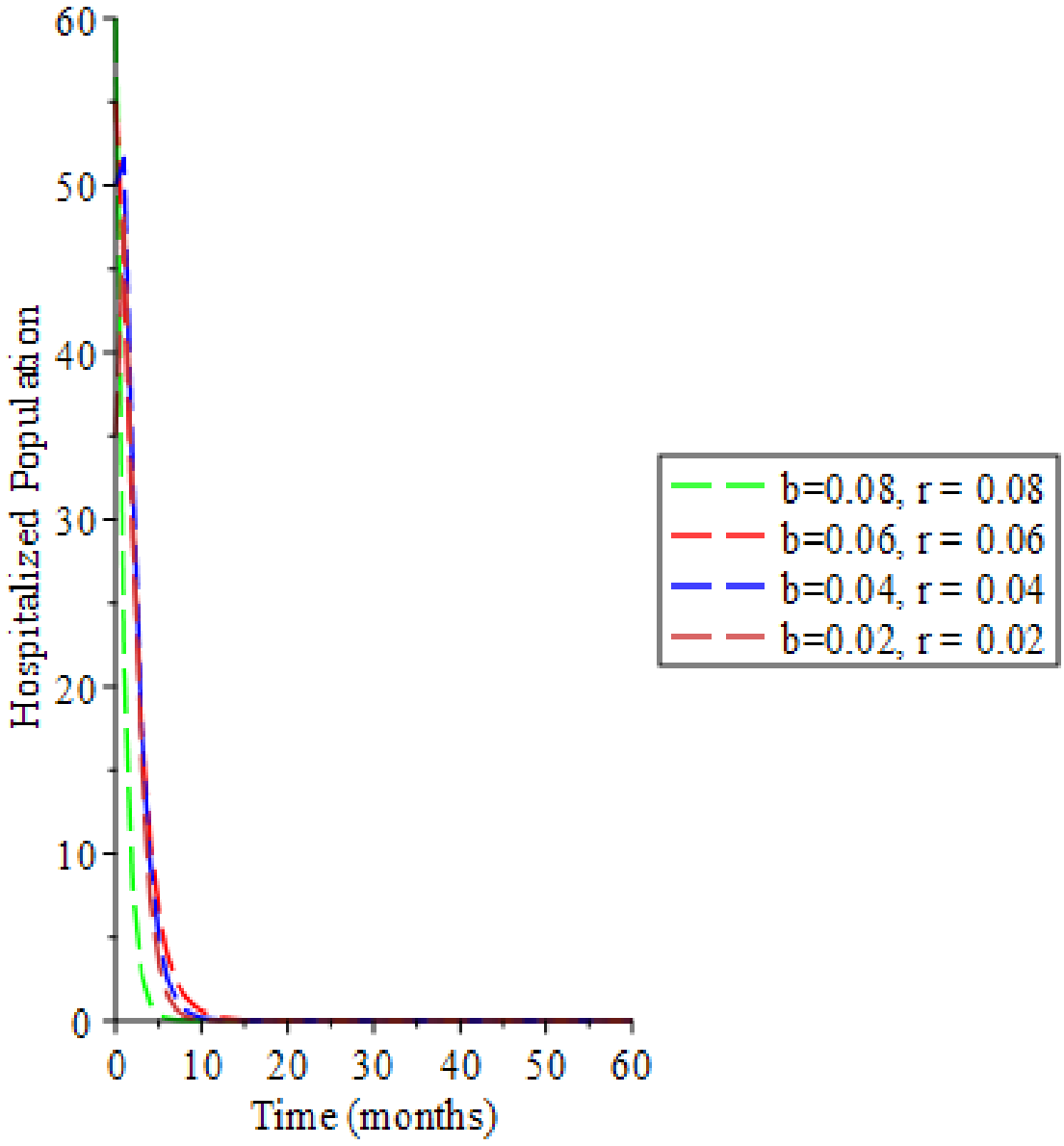

Figure 4.12: Behavioural dynamics of hospitalized population when varying the acutely and chronically infected rate

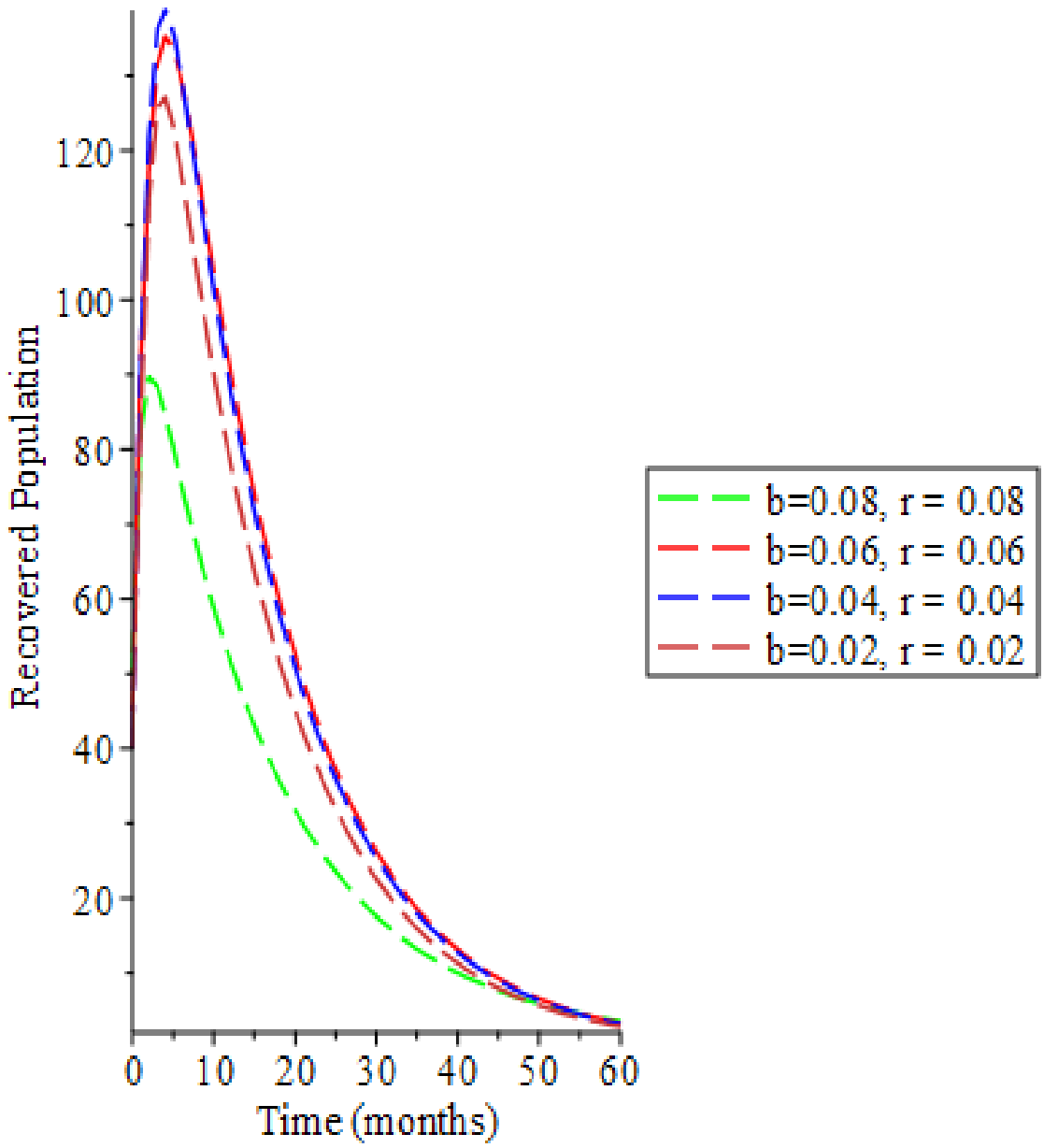

Figure 4.13: Behavioural dynamics of recovered population when varying the acutely and chronically infected rate

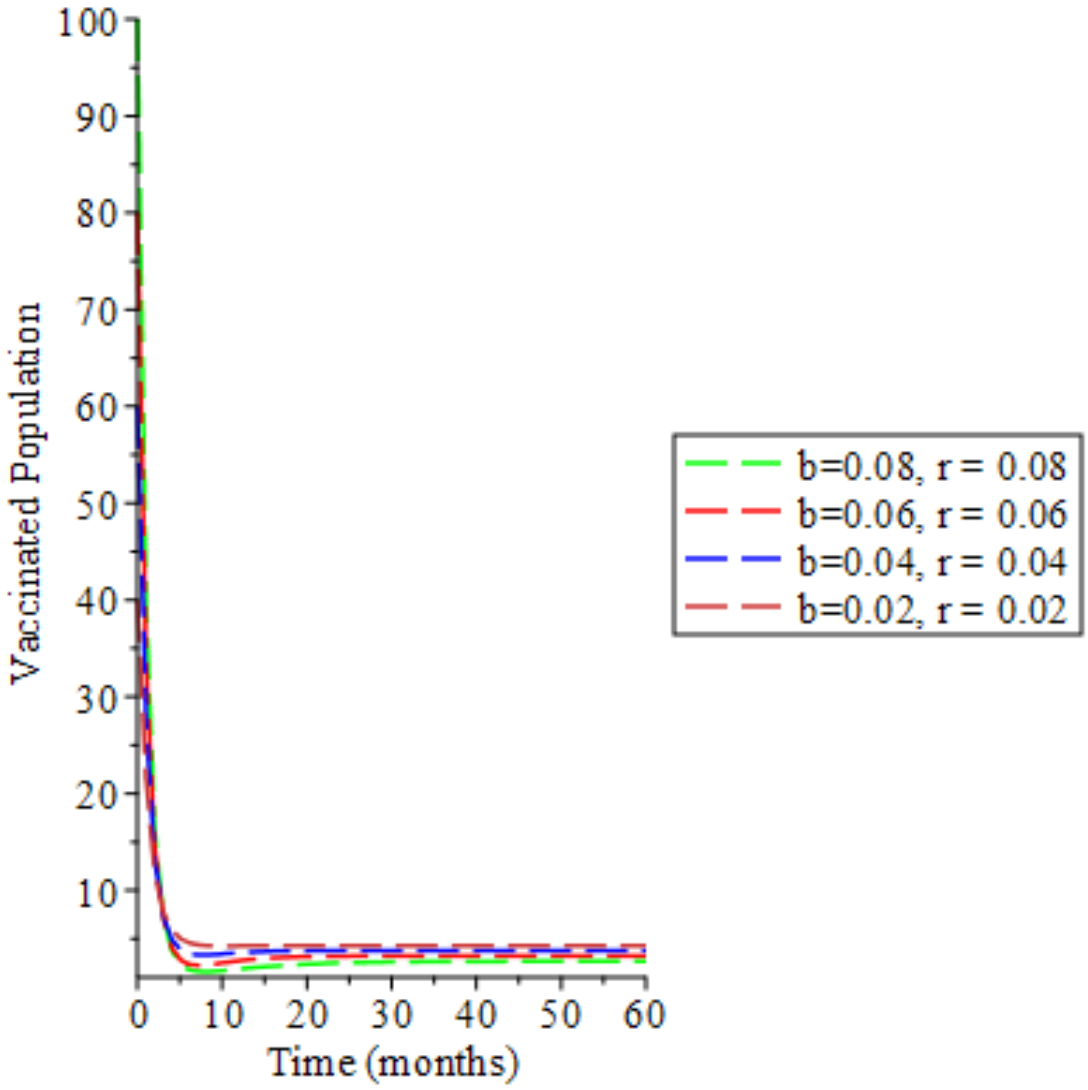

Figure 4.14: Behavioural dynamics of vaccination population when varying the acutely and chronically infected rate

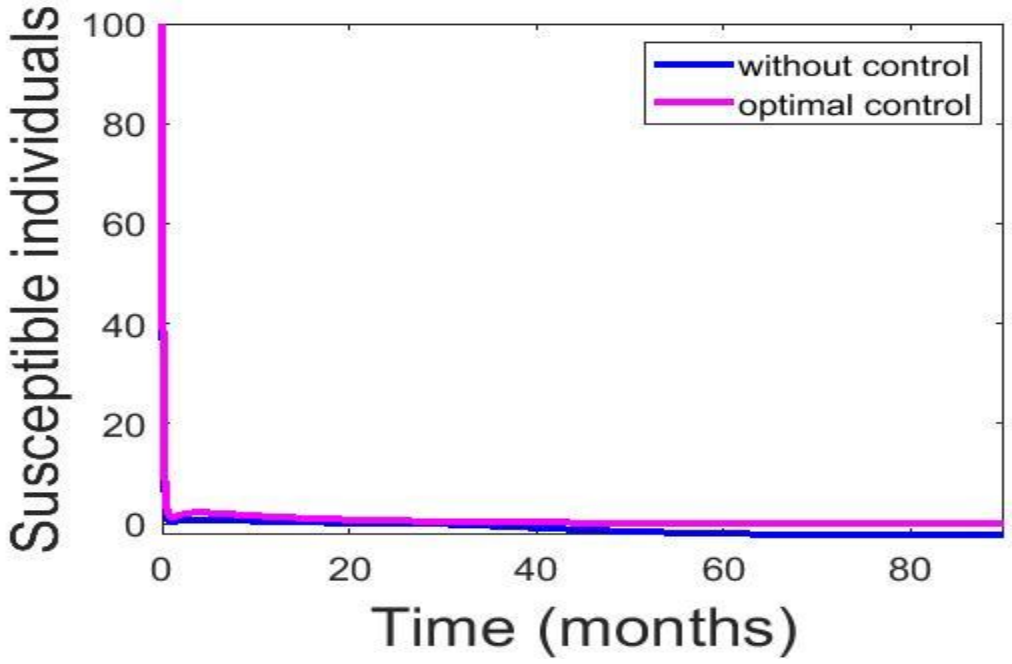

Figure 4.15: The effect of control on susceptible individuals for HBV model case1

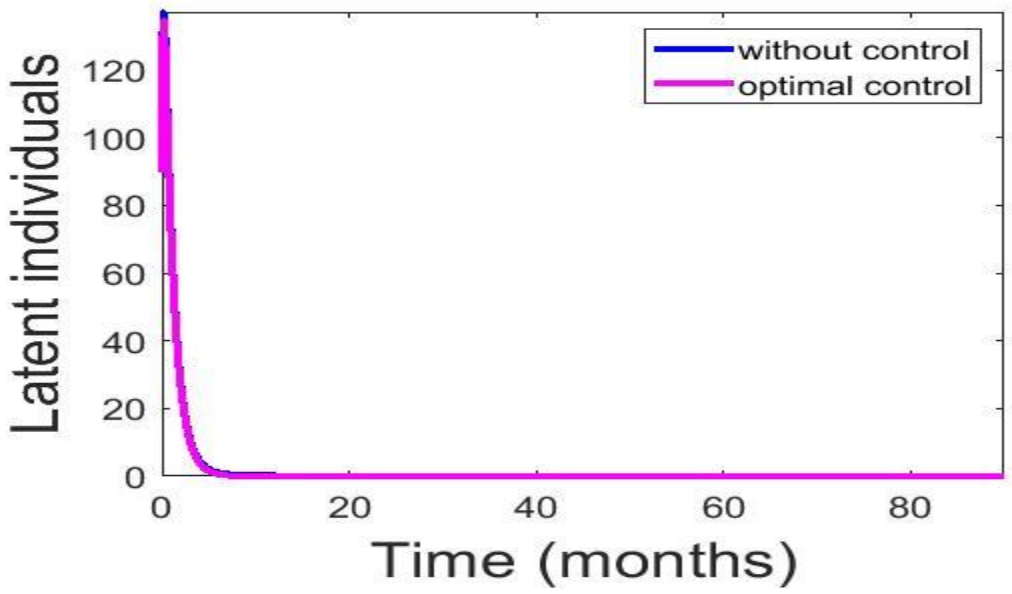

Figure 4.16: The effect of control on latent individualsfor HBV model case1

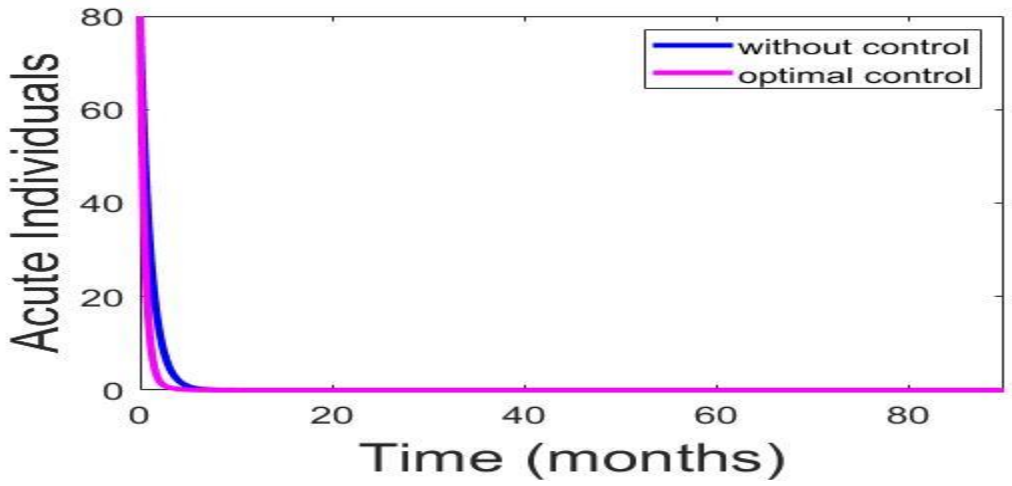

Figure 4.17: The effect of control on acute individuals for HBV model case1

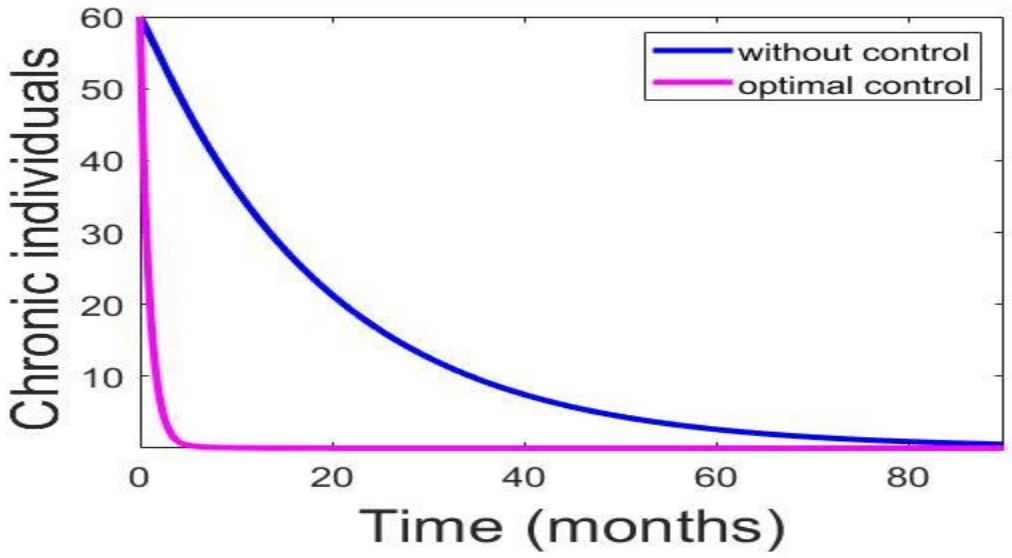

Figure 4.18: The effect of control on chronic individuals for HBV model case1

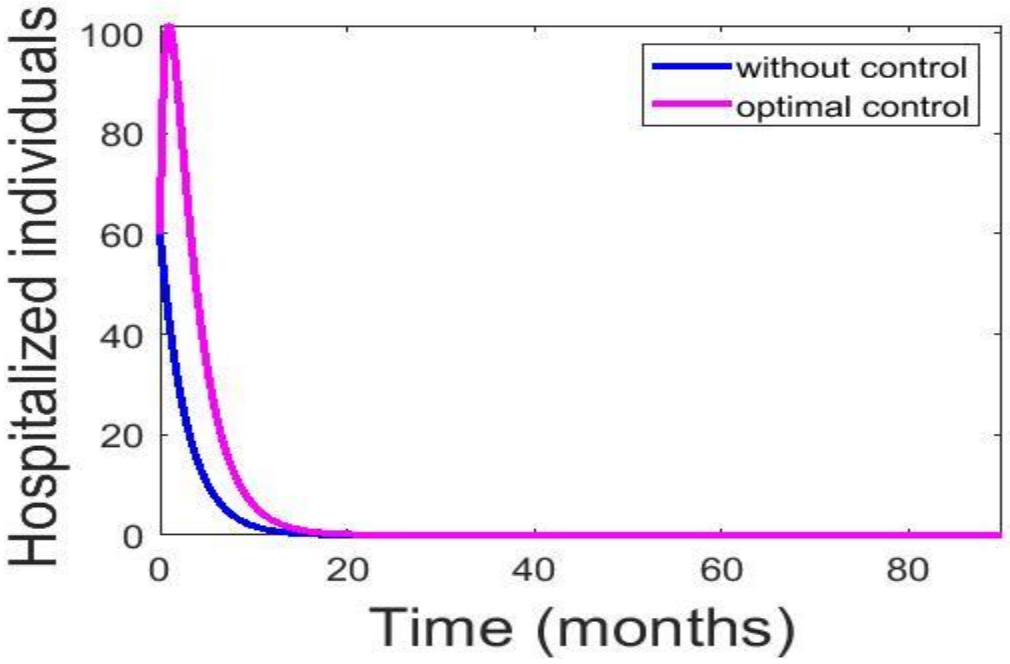

Figure 4.19: The effect of control on hospitalized individuals for HBV model 1

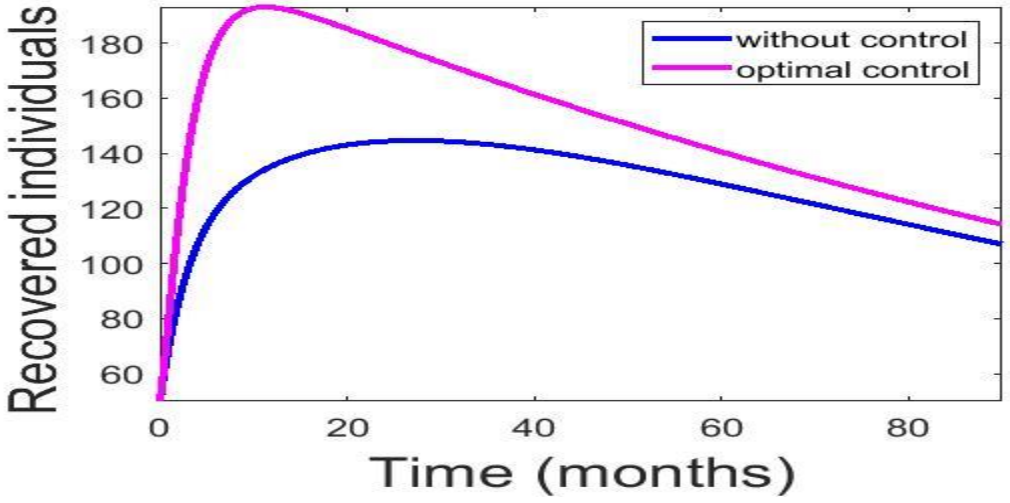

Figure 4.20: The effect of control on recovered individuals for HBV model case1

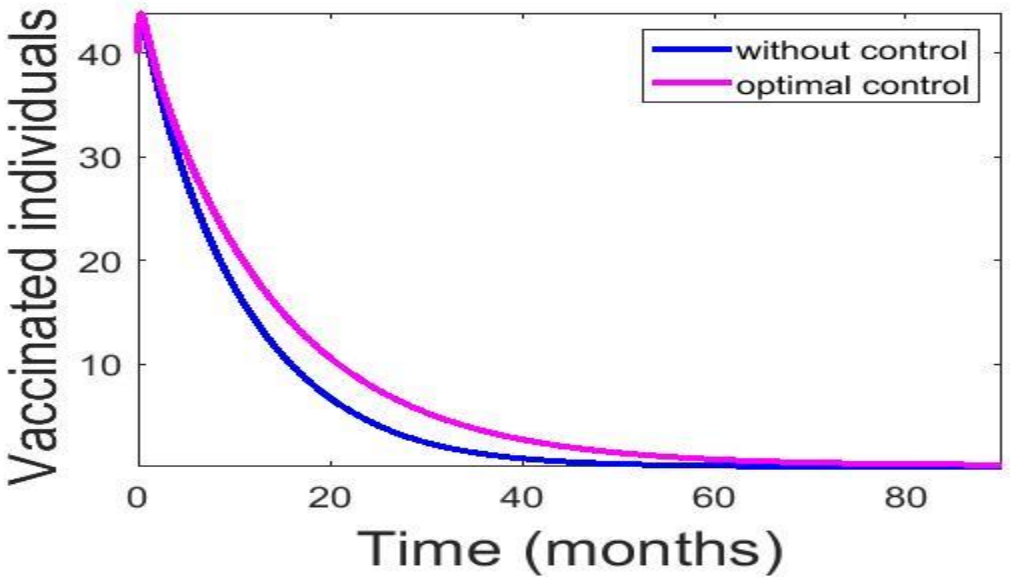

Figure 4.21: The effect of control on vaccinated individuals for HBV model case1

4.1.2 Results for HBV Model Case 2

To enhance insight to the clarity of the Hepatitis B virus spontaneous clearance of acutely infected individuals with high immune response, individuals who fall out of treatment due to risk factors and impacts of treatment at the infectious state of the virus, a computational analysis and optimal control analysis is done. The parameter values adopted are gotten from existing studies. The results are tabulated and graphically presented. However, each graph defined the variation in the values.

Table 4.3 Parameter's specification for HBV model case 2

Parameter	Values	Sources
ζ	0.0121	Zhang and Zhou, (2012)
α	0.320	Zhao et al., (2000)
γ	0.11	Liang et al., (2015)
β	0.0095	Khan et al., (2019)
ξ	0.16	Owolabi (2016)
η	0.067	Pang et al., (2011)
ω	0.16	Zhang and Zhou, (2012)
μ	0.00693	Khan et al., (2019)
κ	0.34	Estimated
υ	0.05	Pang et al., (2011)

ρ	0.05	Pang et al., (2011)
ϵ	0.02	Estimated
σ	0.59	Zhang and Zhou, (2012)

Table 4.4: Sensitivity Indices on R_0 of HBV model case 2

Parameter	Sensitivity Index	Parameter	Sensitivity Index
ζ	1.0022506	η	-0.471635
β	0.9999999	ω	-0.579735
ρ	0.5736264	υ	-0.030395
γ	0.0092650	ξ	-0.011490
σ	0.0022251	μ	-1.046896

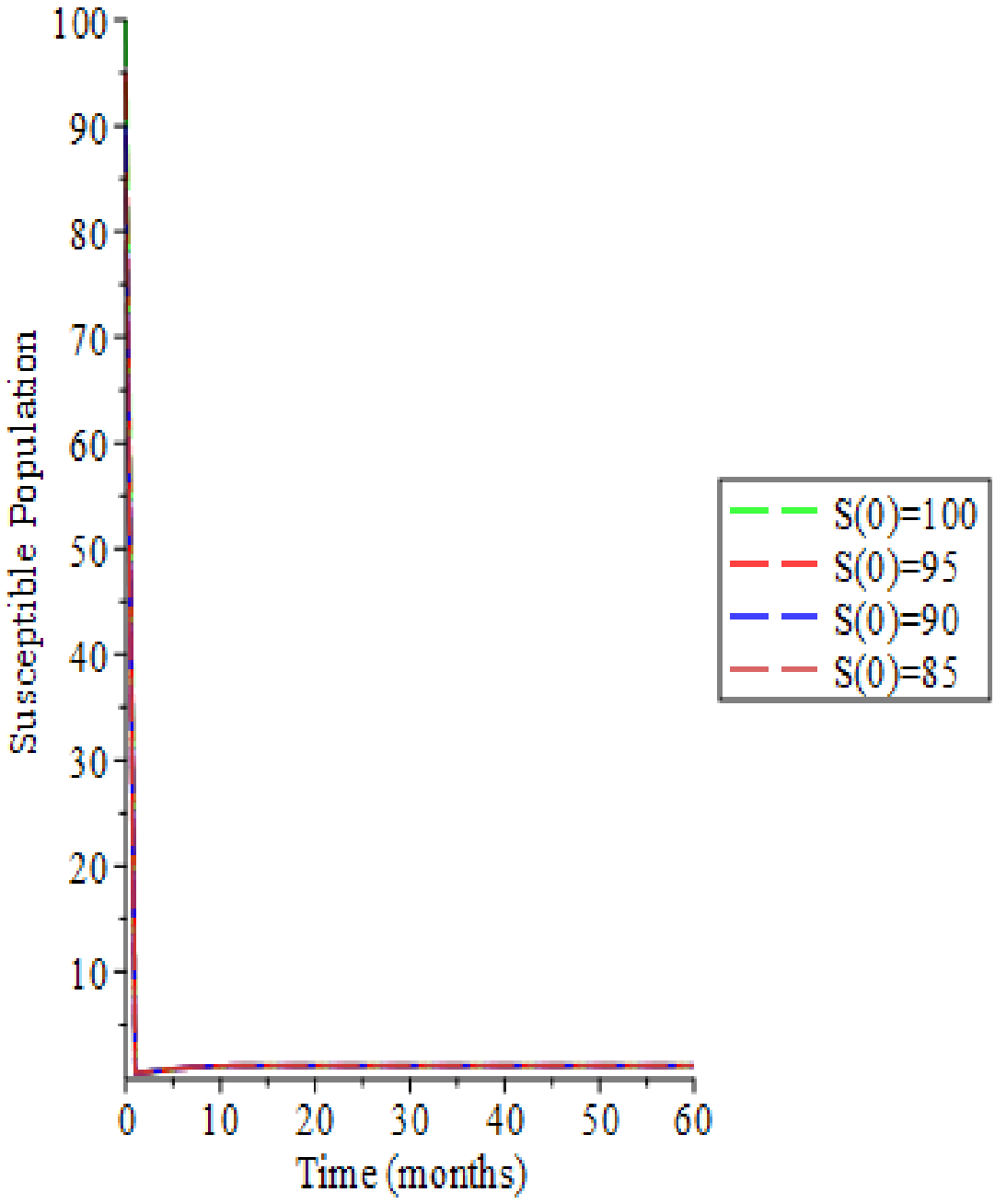

Figure 4.22: Behavioural dynamics of susceptible population when $R_0 < 1$

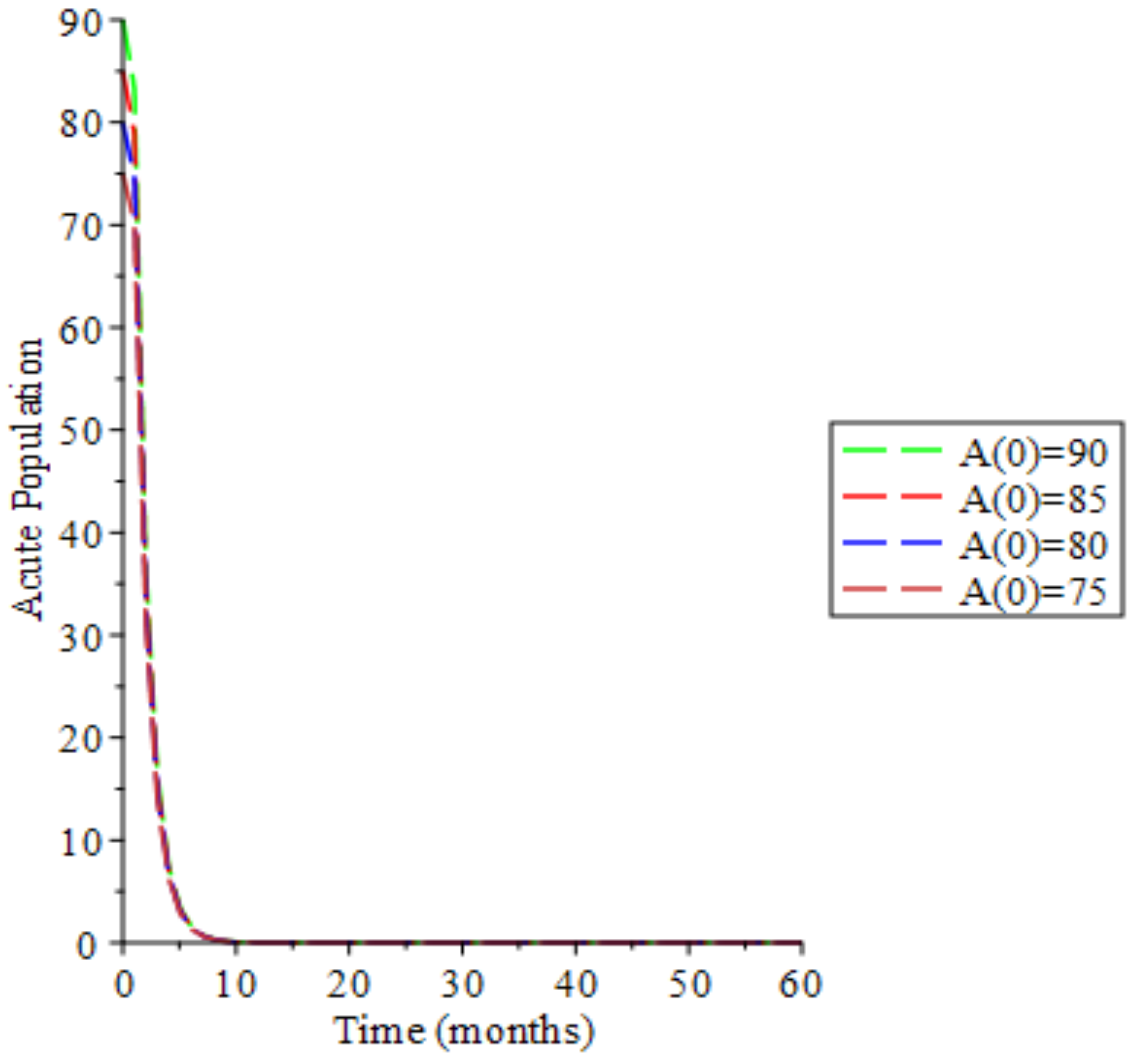

Figure 4.23: Behavioural dynamics of acute population when $R_0 < 1$

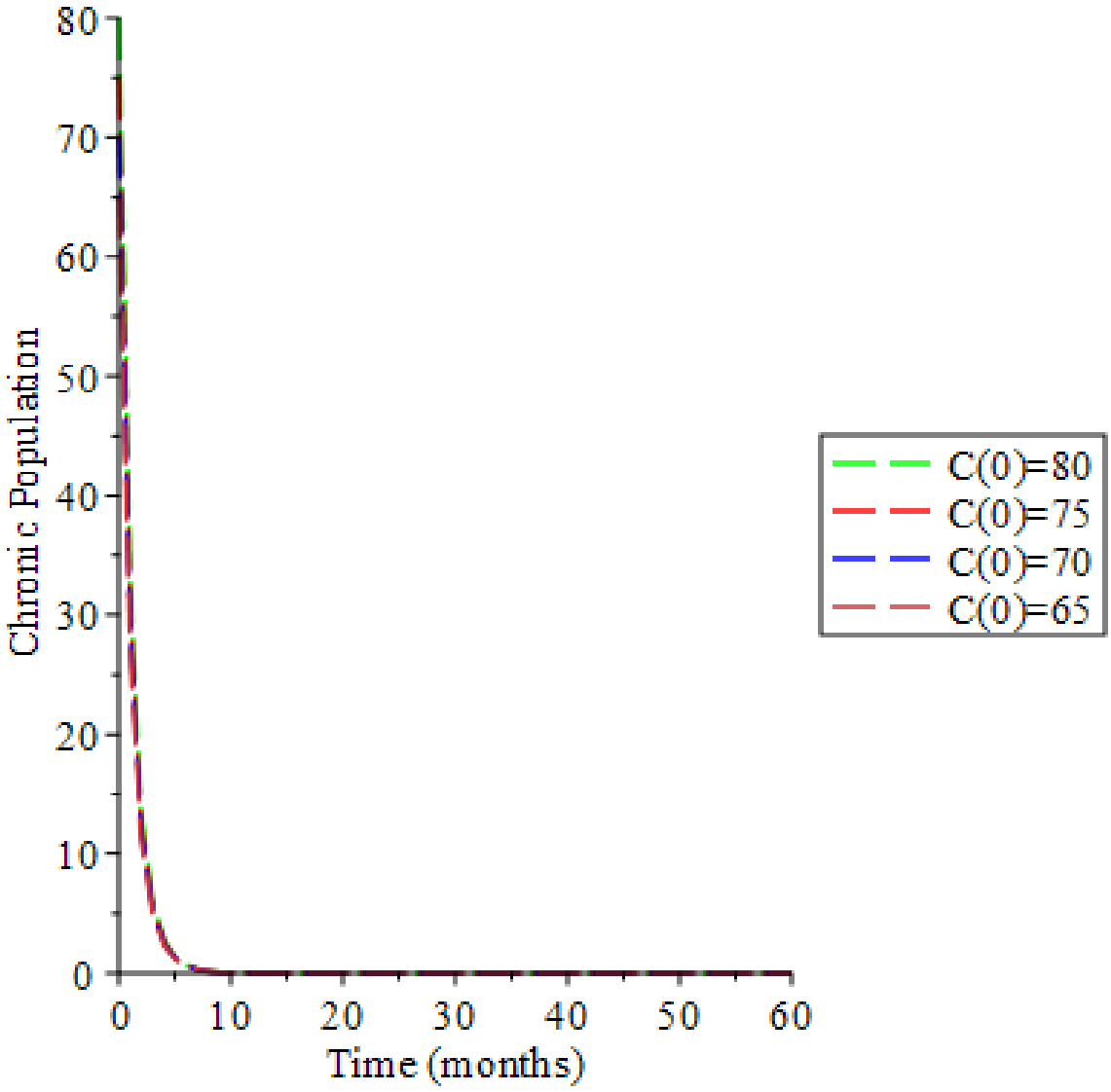

Figure 4.24: Behavioural dynamics of chronic population when $R_0 < 1$

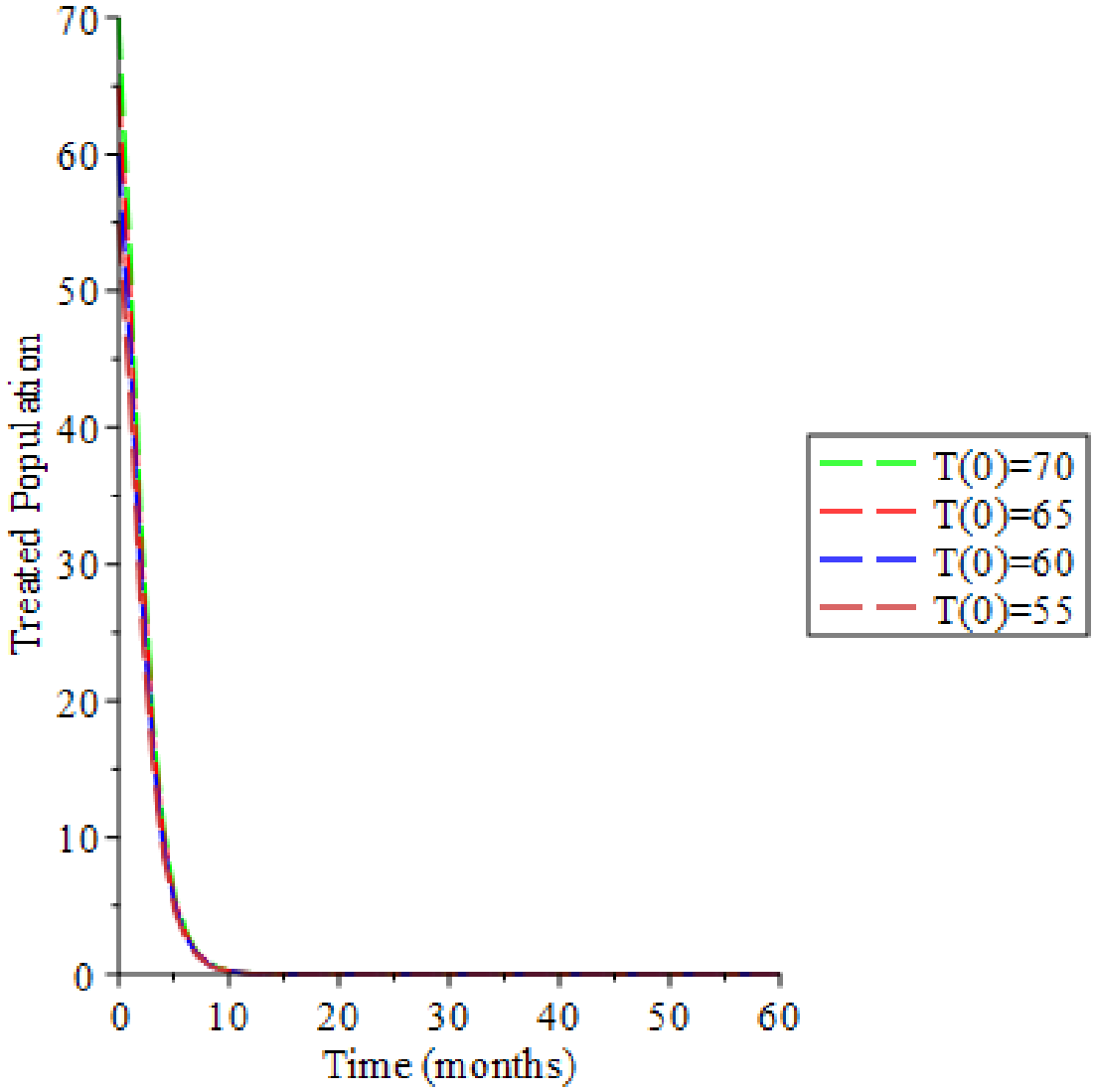

Figure 4.25: Behavioural dynamics of treated population when $R_0 < 1$

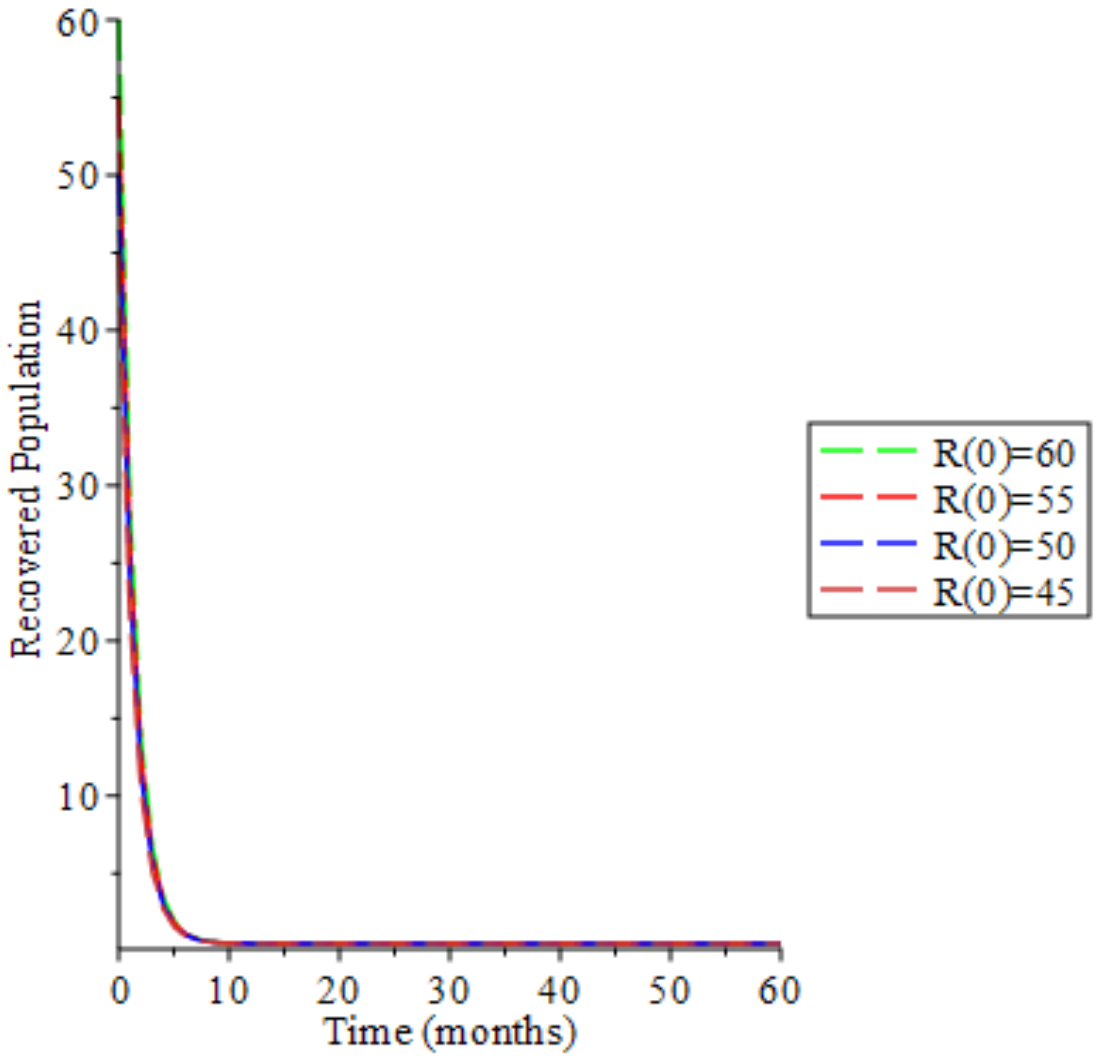

Figure 4.26: Behavioural dynamics of recovered population when $R_0 < 1$

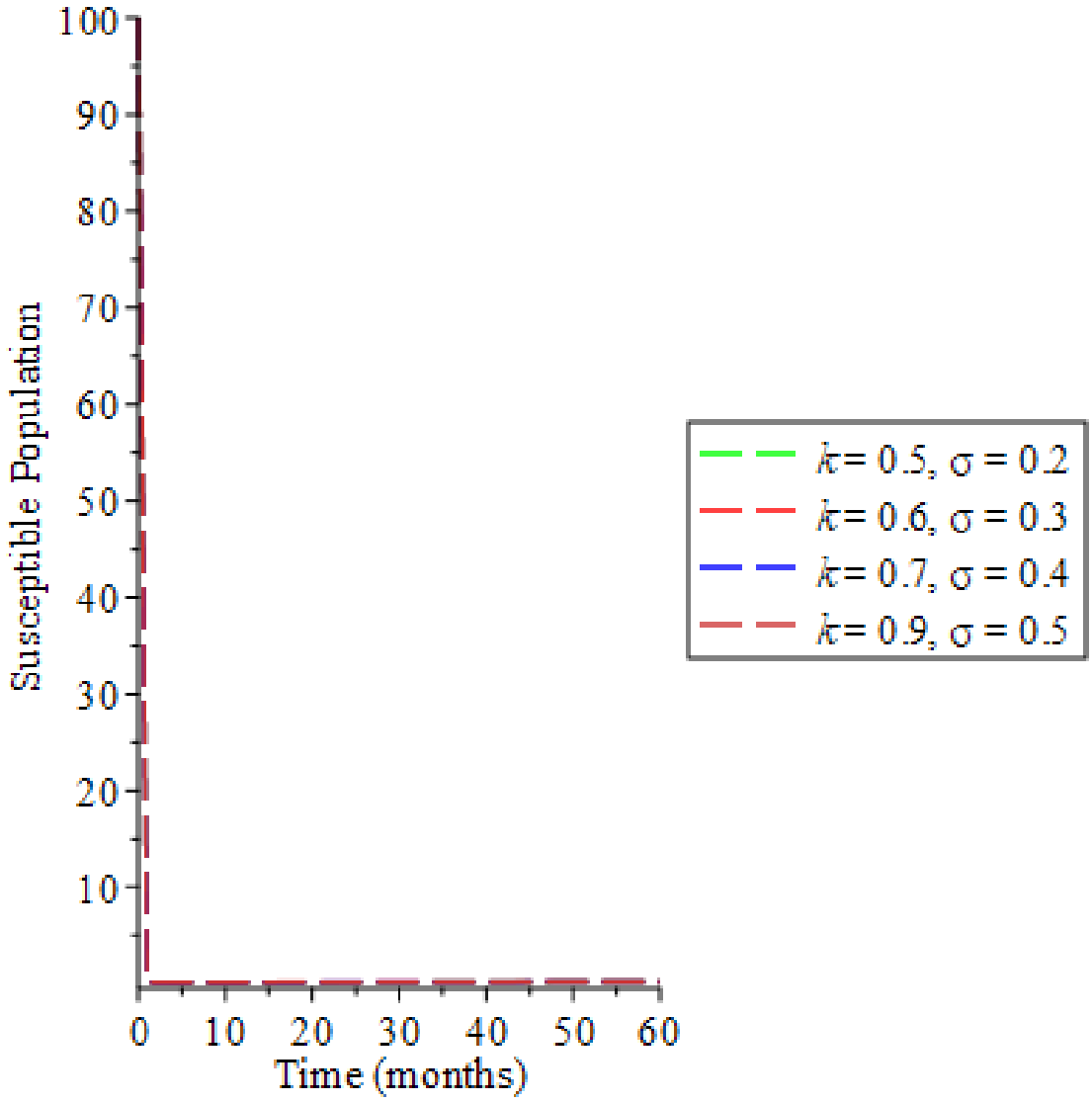

Figure 4.27: Behavioural dynamics susceptible population when varying treatment rate of chronic individuals and recovery rate

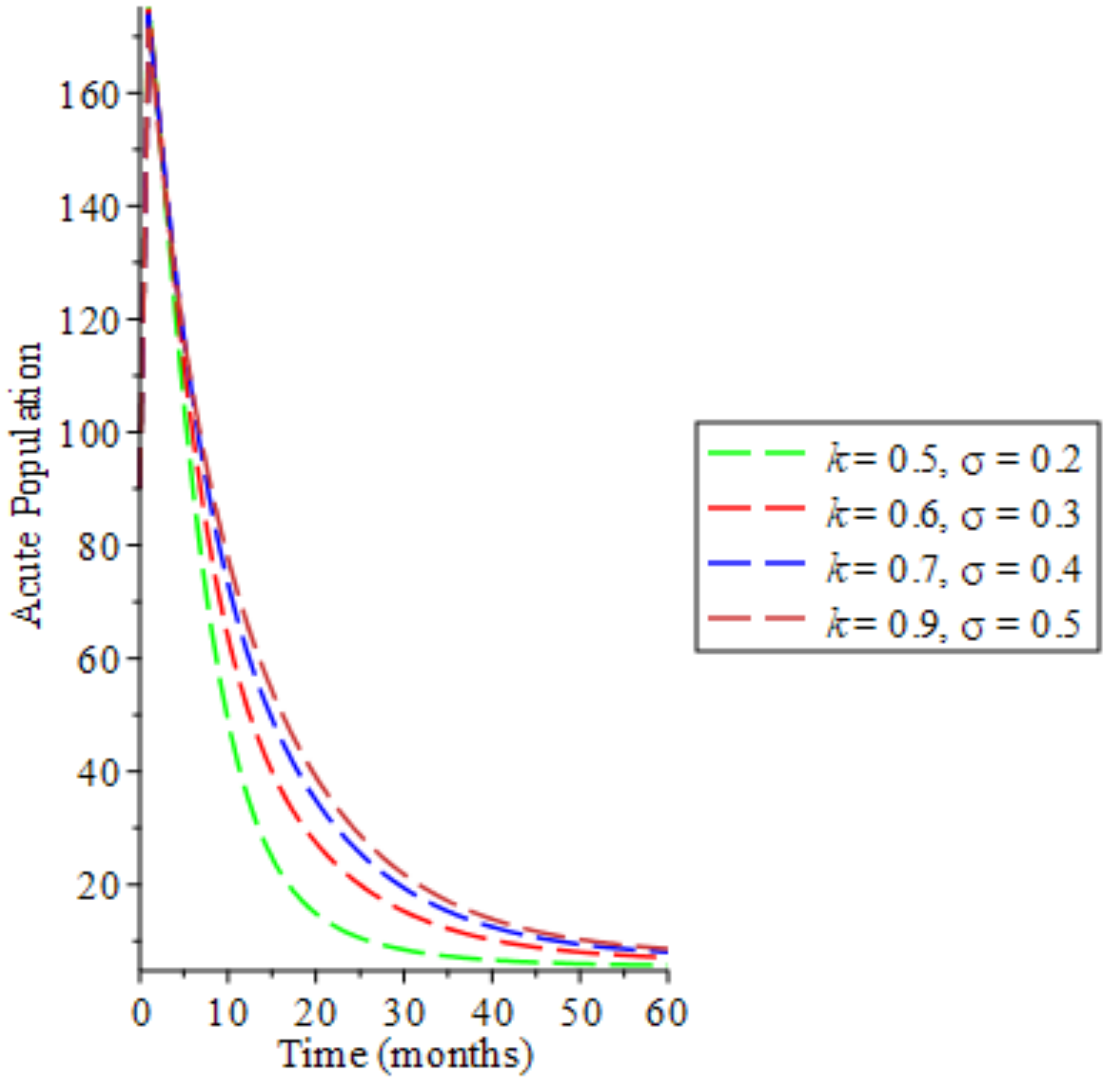

Figure 4.28: Behavioural dynamics acute population when varying treatment rate of chronic individuals and recovery rate

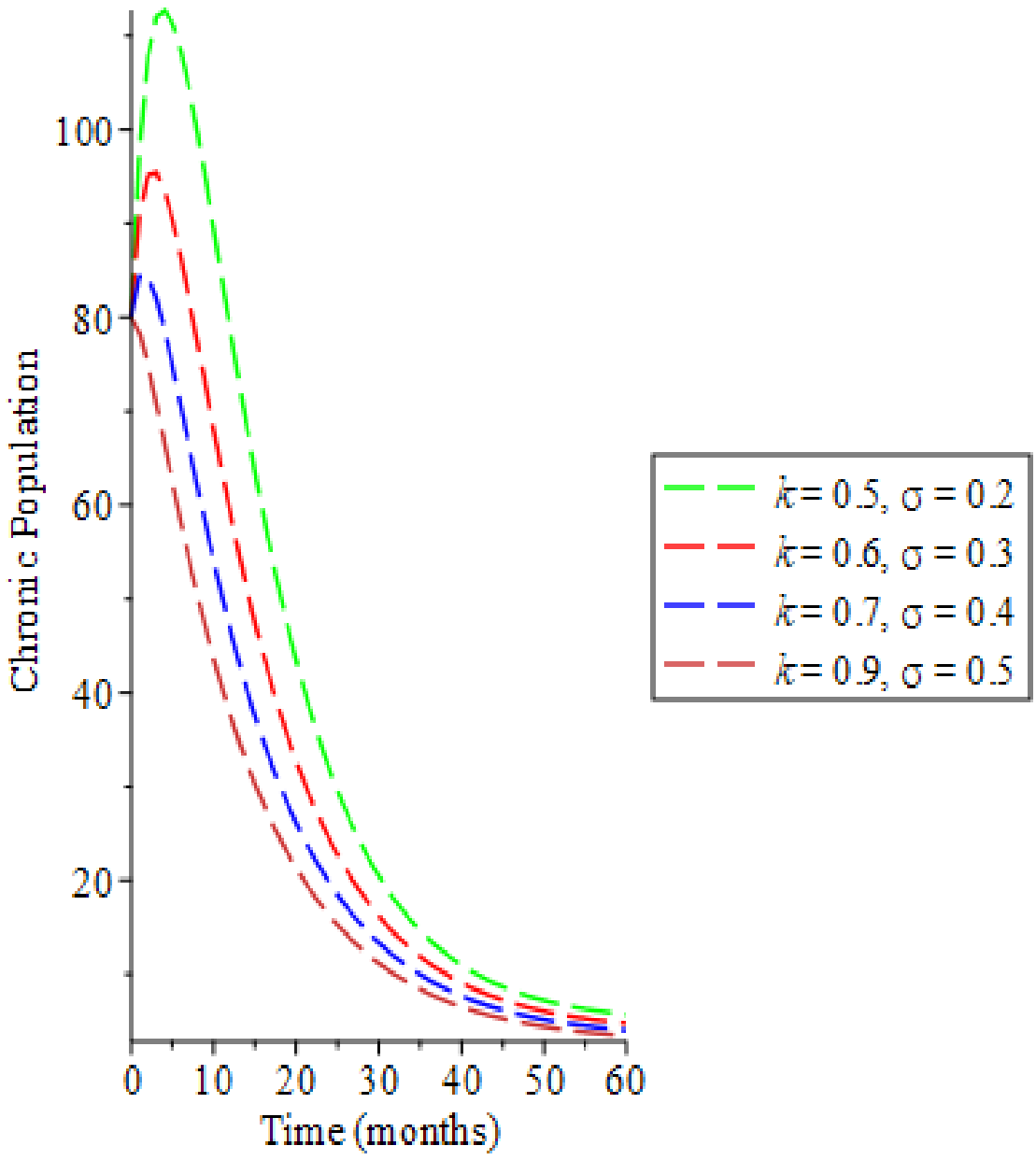

Figure 4.29: Behavioural dynamics chronic population when varying treatment rate of chronic individuals and recovery rate

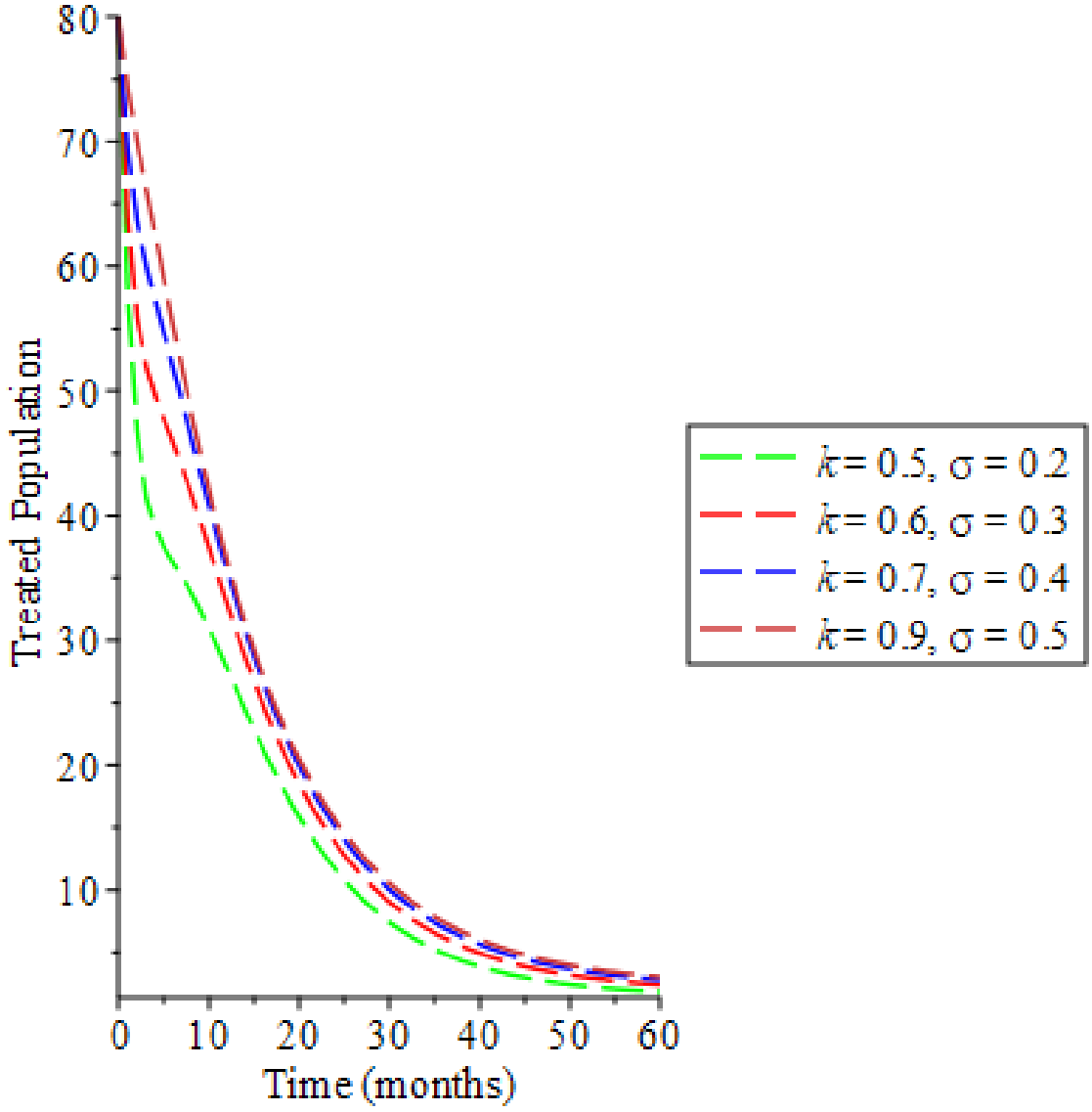

Figure 4.30: Behavioural dynamics treated population when varying treatment rate of chronic individuals and recovery rate

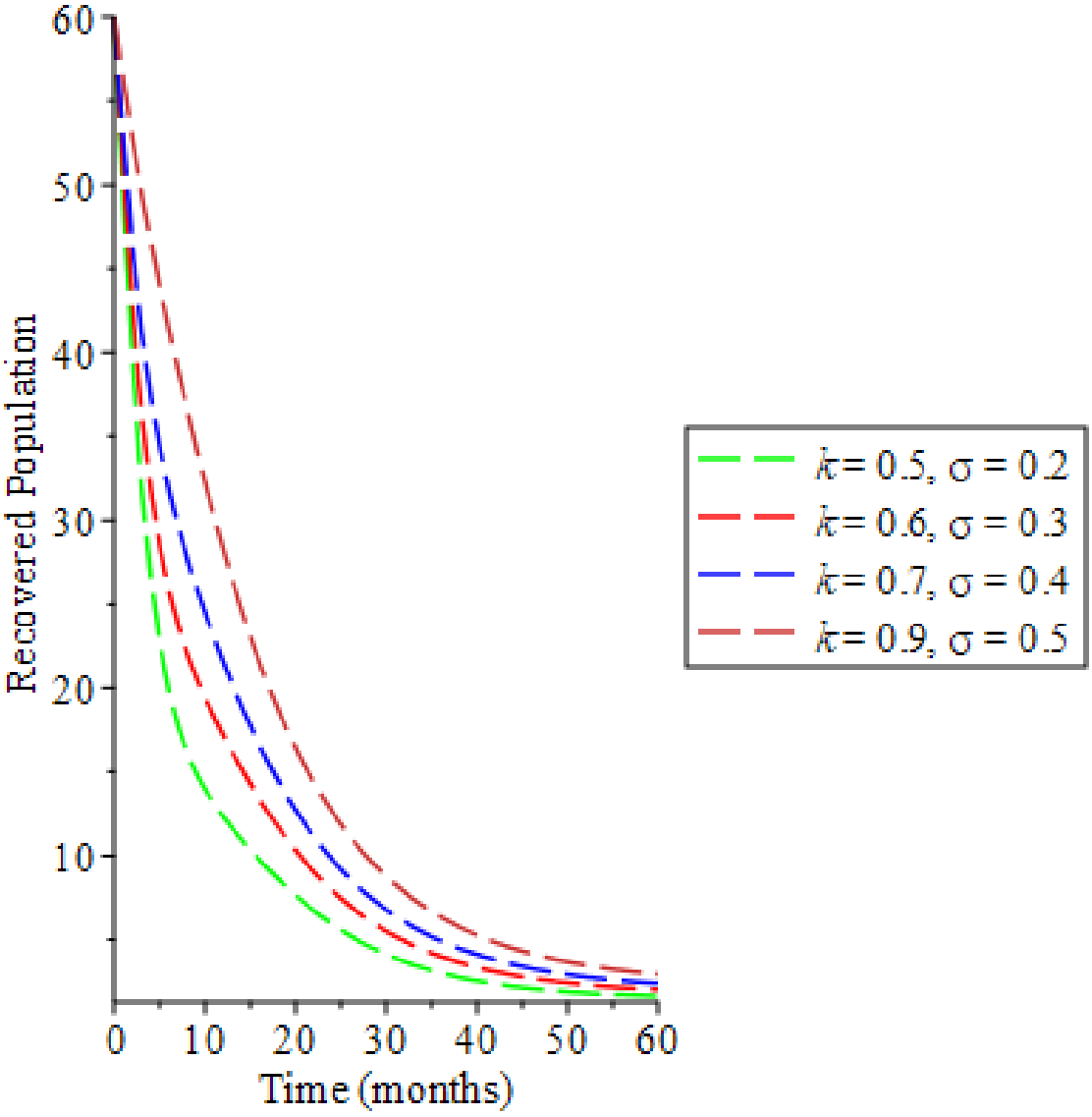

Figure 4.31: Behavioural dynamics recovered population when varying treatment rate of chronic individuals and recovery rate

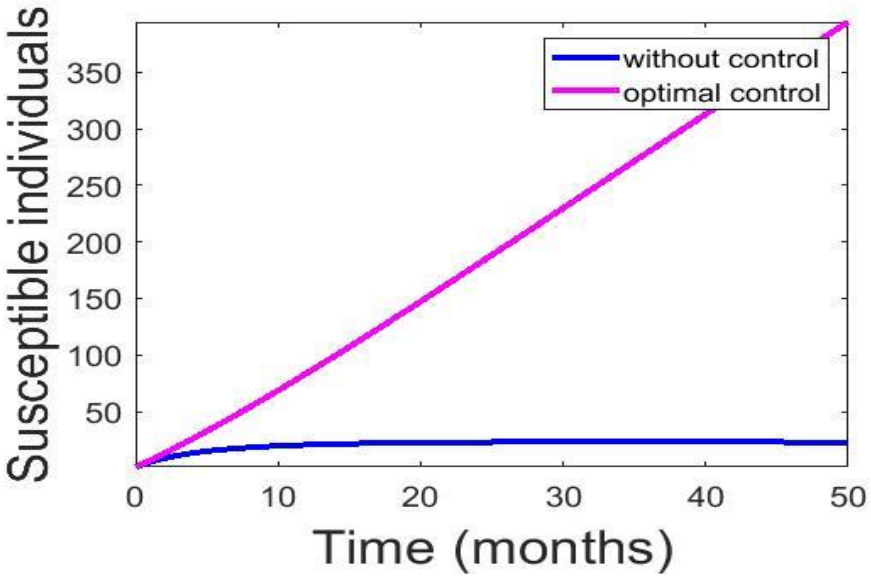

Figure 4.32: The effect of control on susceptible individuals for HBV model case2

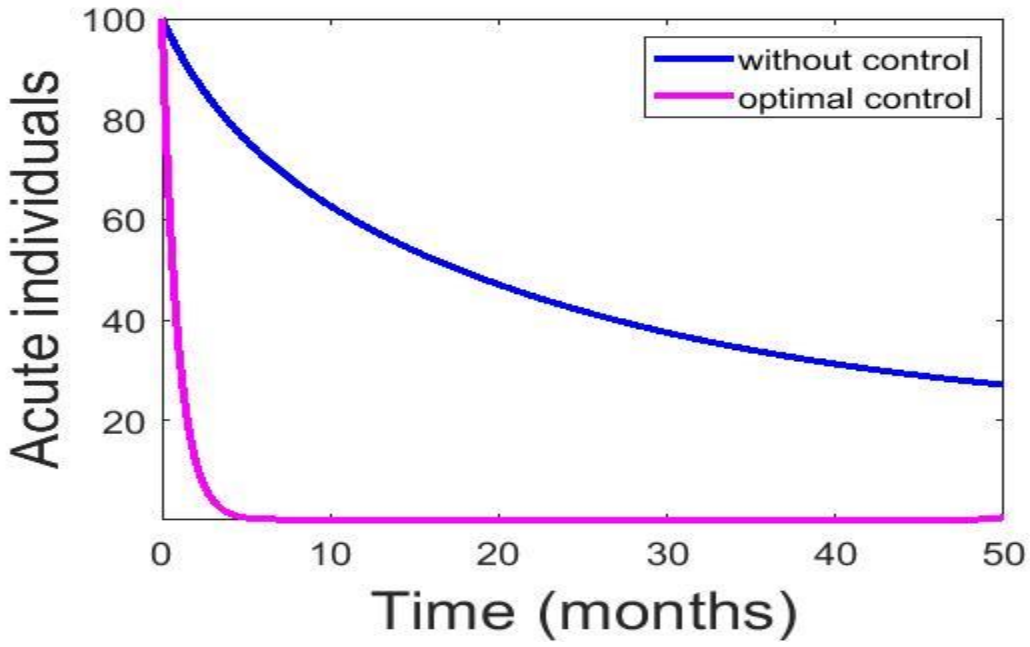

Figure 4.33: The effect of control on acute individualsfor HBV model case2

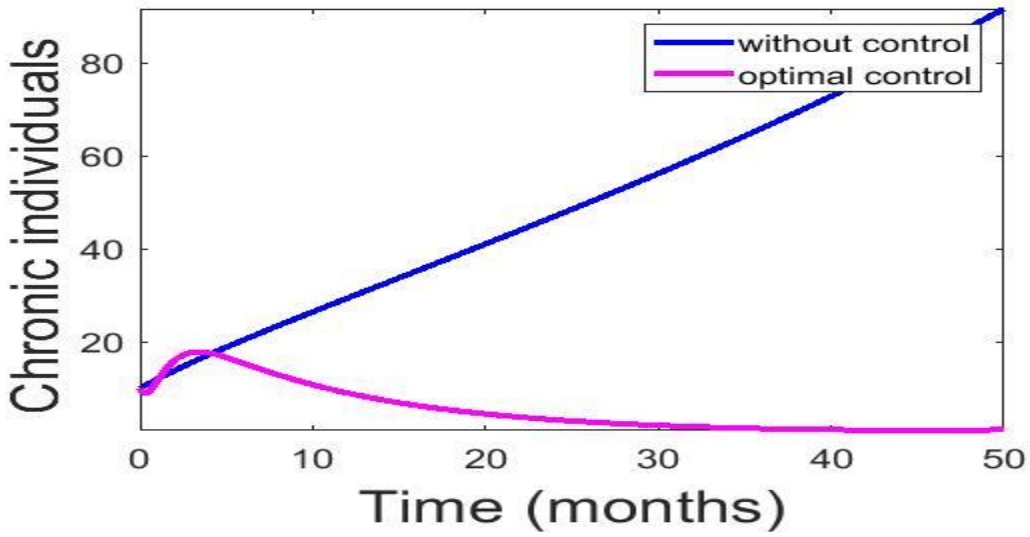

Figure 4.34: The effect of control on chronic individuals for HBV model case2

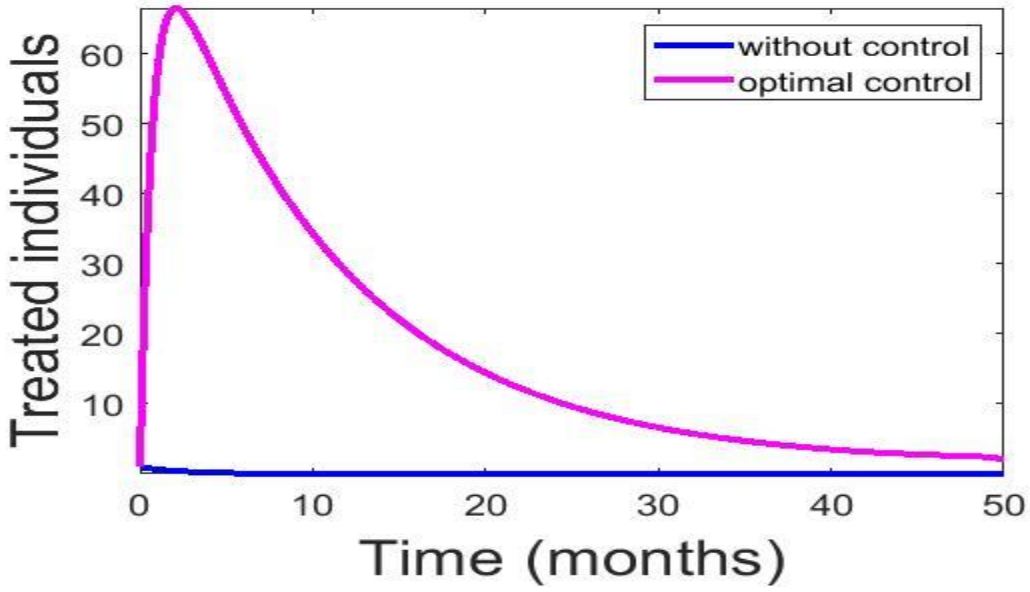

Figure 4.35: The effect of control on treated individuals for HBV model case2

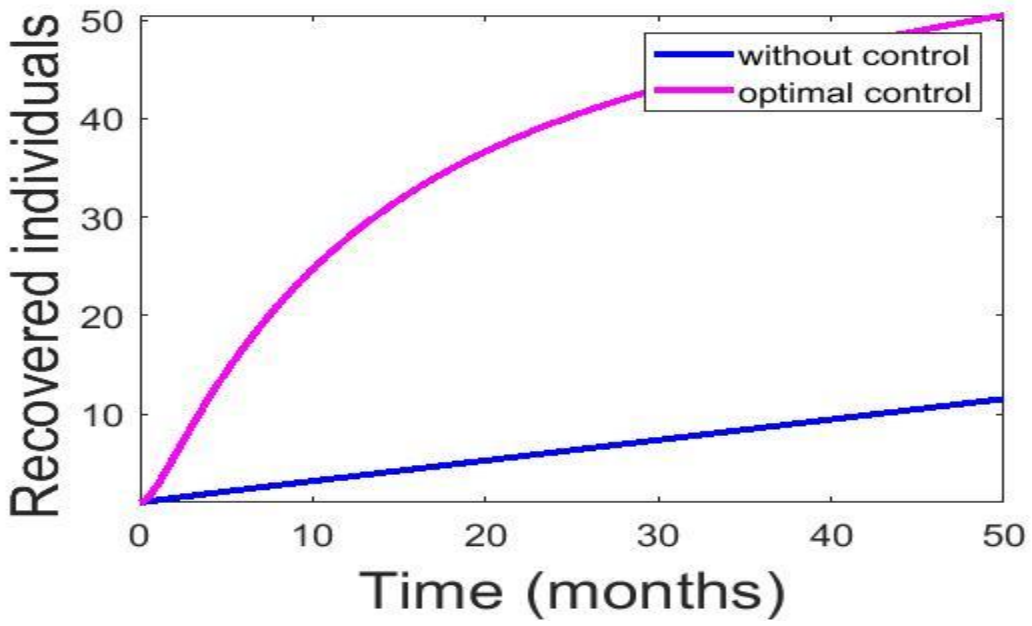

Figure 4.36: The effect of control on recovered individuals for HBV model case2

4.1.3 Results for HBV Model Case 3

The quantitative and qualitative analysis of the HBV chronic unaware and chronic aware individuals with impact on testing and treatment are comprehensively examined along with the optimal controls' analysis by numerical computational method. Here, the subsequent default values are assumed for the embedded parameters taken from theoretical studies in literatures. The values remain unchanged although the computations except otherwise indicated. The obtained results are offered in tabular form and graphical representation.

Table 4.5 Parameter's specification for HBV model case 3

Parameter	Values	Sources
Π	0.07	Zhao et al., (2000)
γ	0.9	Liang et al., (2015)
β	0.008	Zhang and Zhou, (2012)
σ	0.59	Zhang and Zhou, (2012)
$\mu, \mathrm{d(c)}$	0.00693	Khan et al., (2019)
ν_1, ν_2	0.002	Zhang and Zhou, (2012)
ω	0.1	Zhao et al., (2000)
α_1, α_2	0.0016	Zhao et al., (2000)
δ	0.0085	Khan et al., (2019)

Table 4.6:Sensitivity Indices on R_0 for HBV model case 3

Parameter	Sensitivity Index	Parameter	Sensitivity Index
β	1.000000	μ	-0.028545
δ	0.018176	α_1	-0.471635
σ	0.037853	α_2	-0.045644
υ_1	0.0022251	γ	-0.579735
υ_2	0.471635	d_c	-1.538220

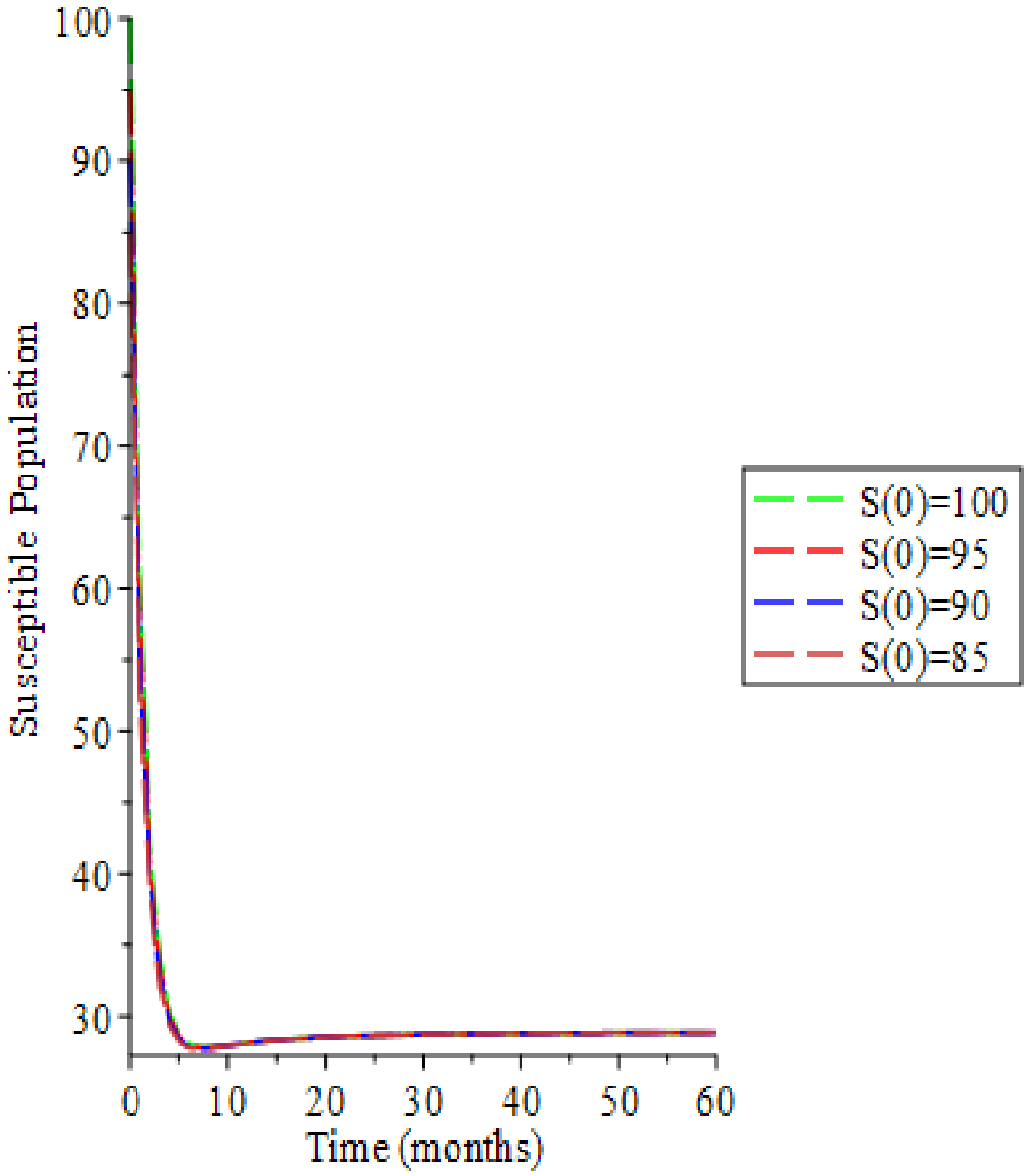

Figure 4.37: Behavioural dynamics of susceptible population when $R_0 < 1$

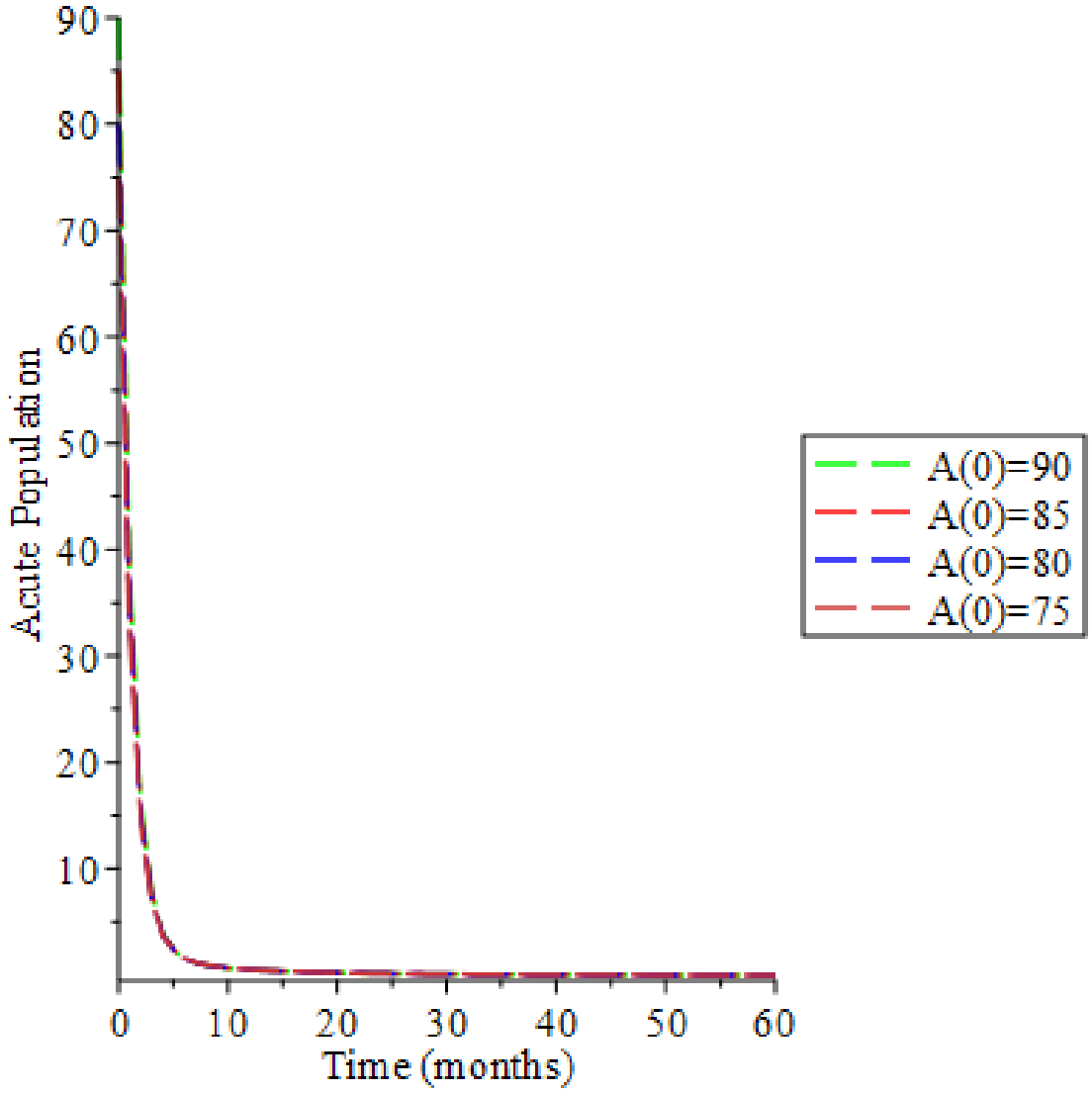

Figure 4.38:Behavioural dynamics of acute population when $R_0 < 1$

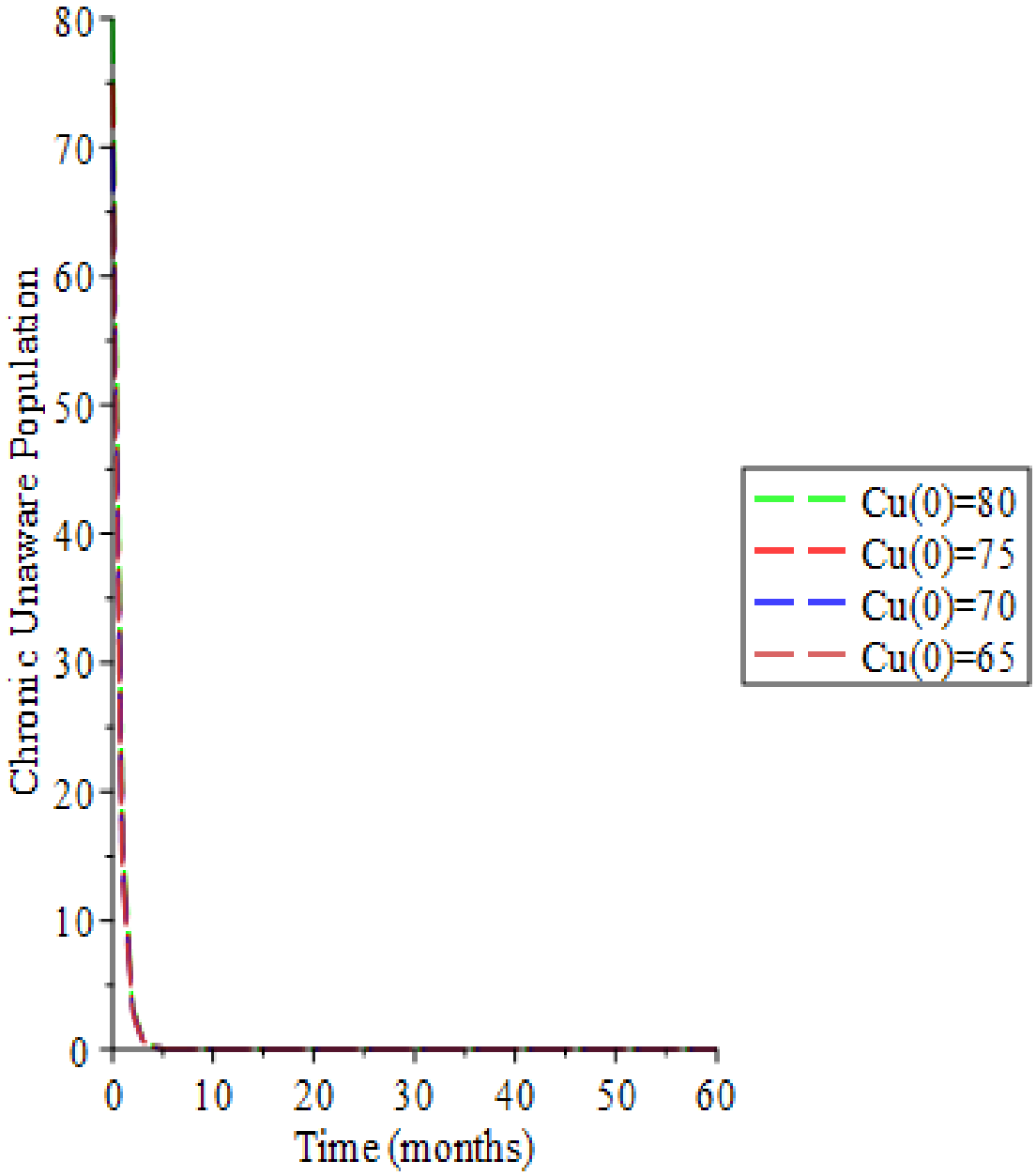

Figure 4.39: Behavioural dynamics of chronic unaware population when $R_0 < 1$

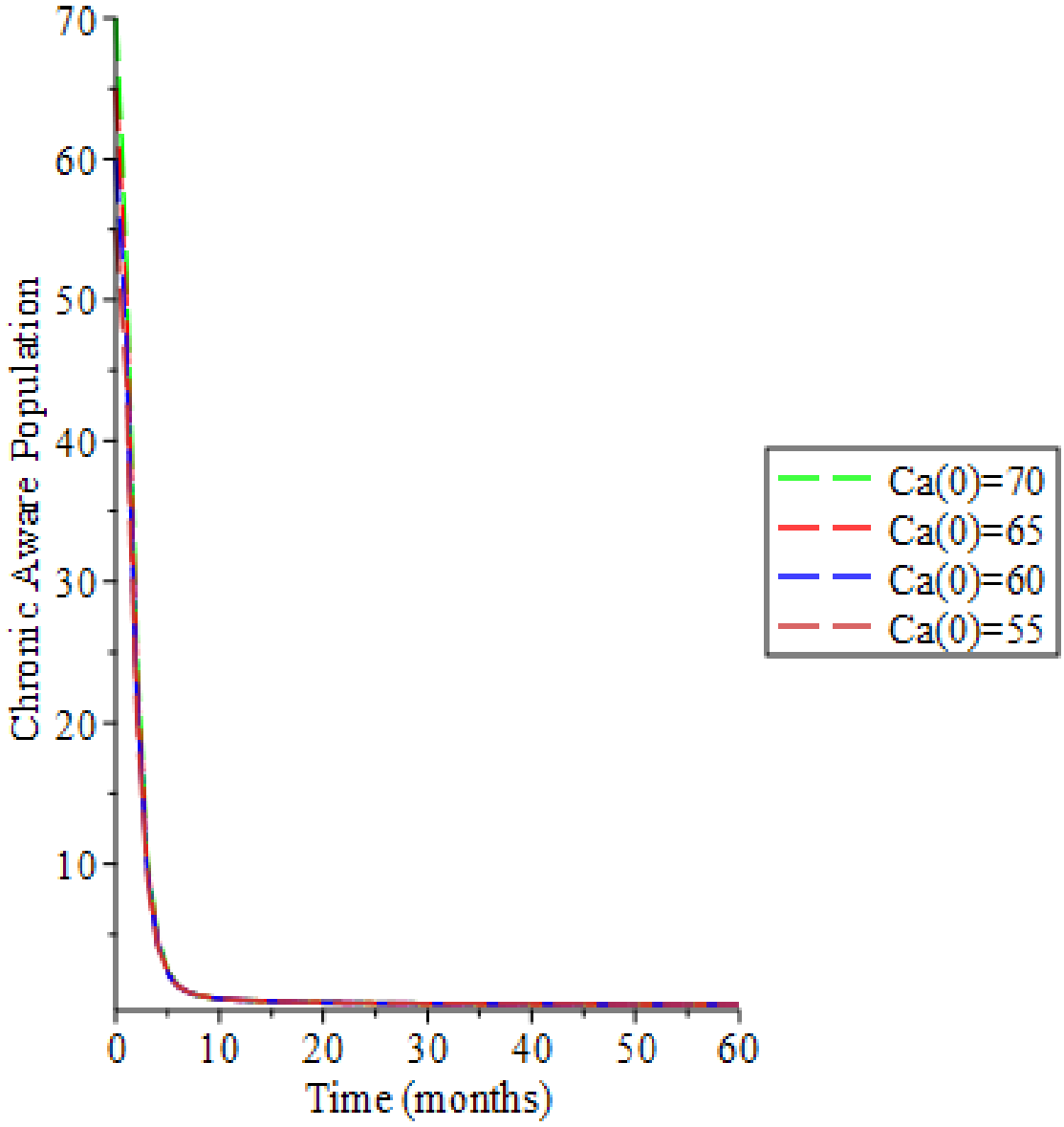

Figure 4.40: Behavioural dynamics of chronic aware population when $R_0 < 1$

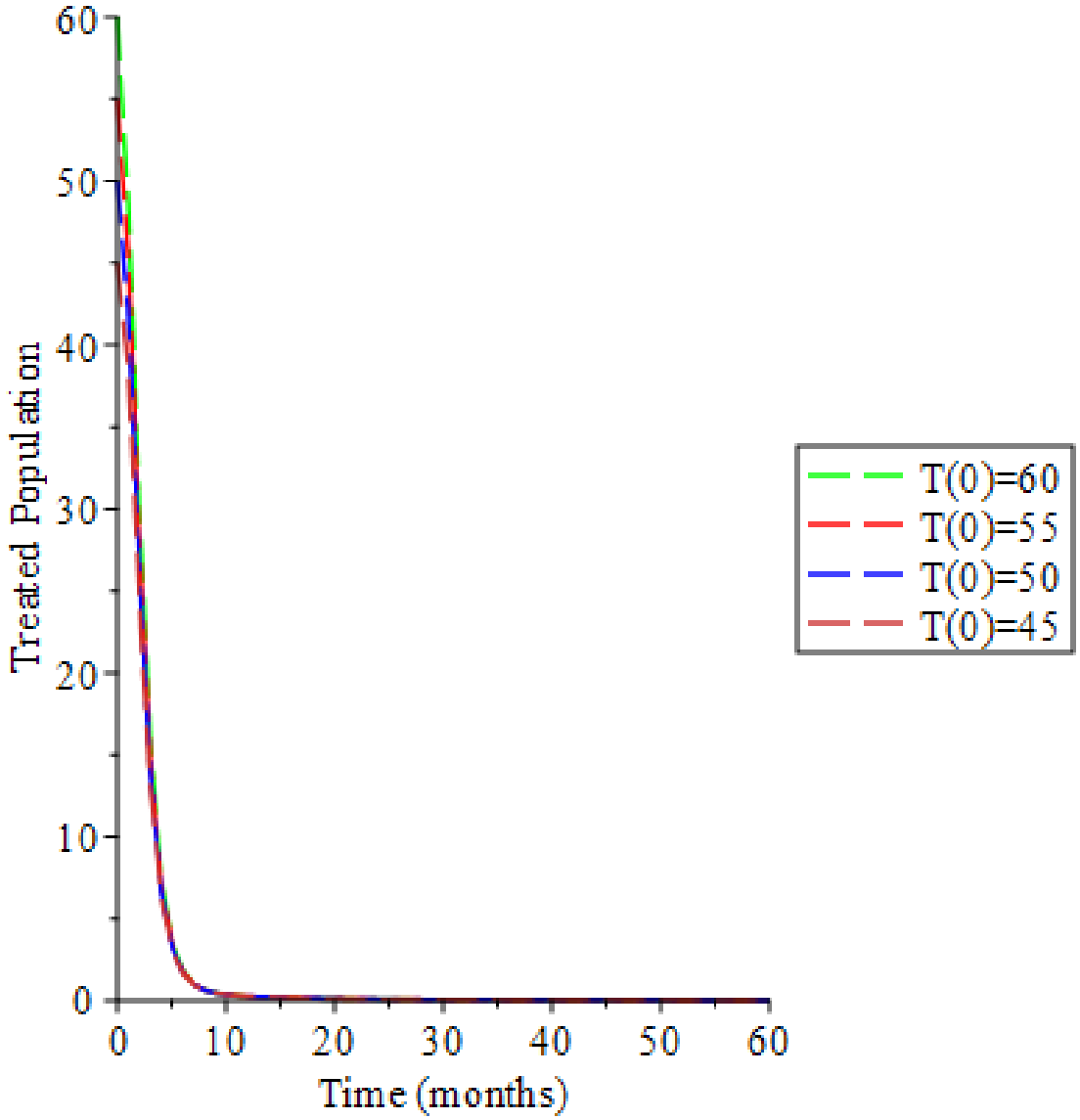

Figure 4.41: Behavioural dynamics of treated population when $R_0 < 1$

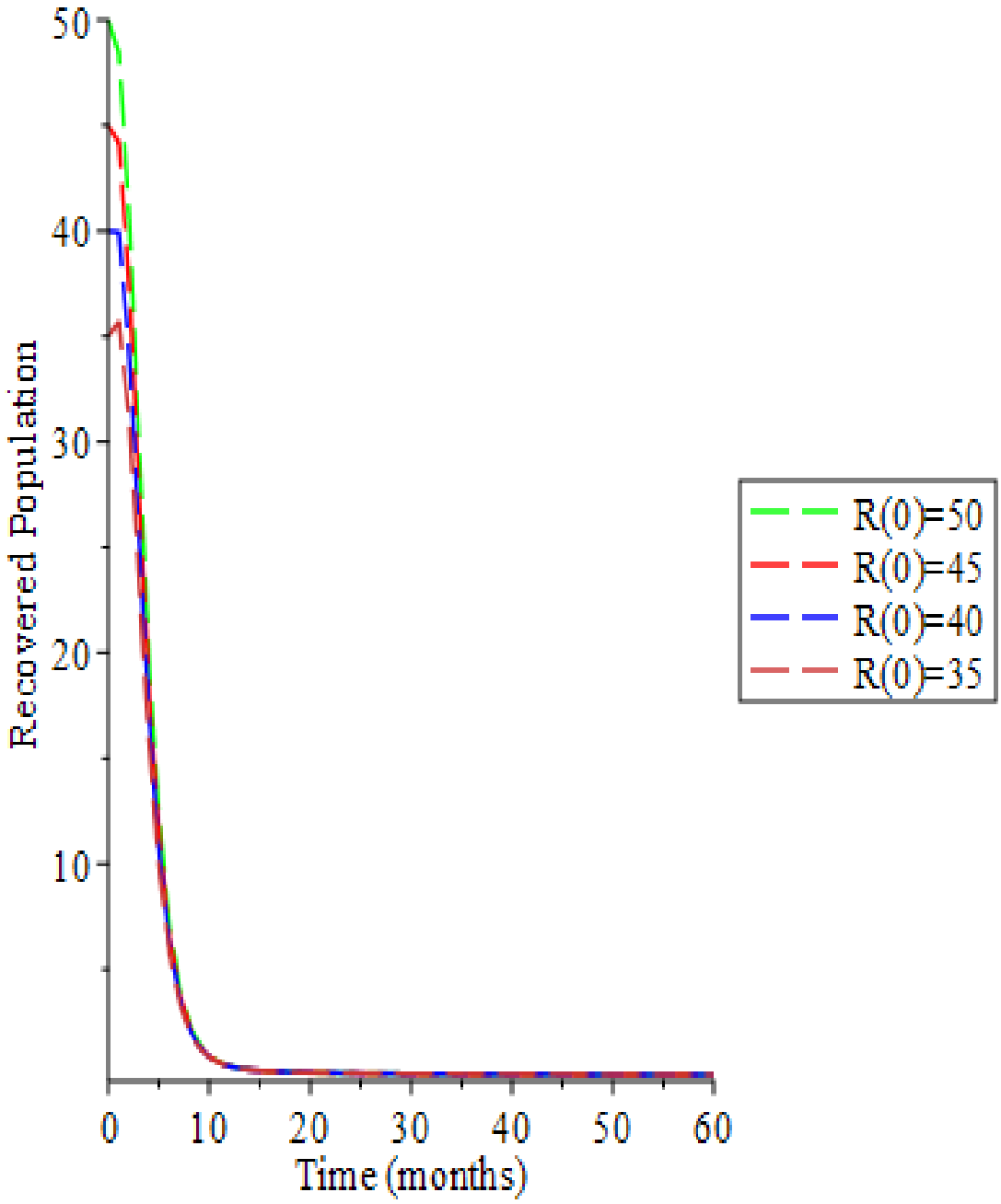

Figure 4.42: Behavioural dynamics of recovered population when $R_0 < 1$

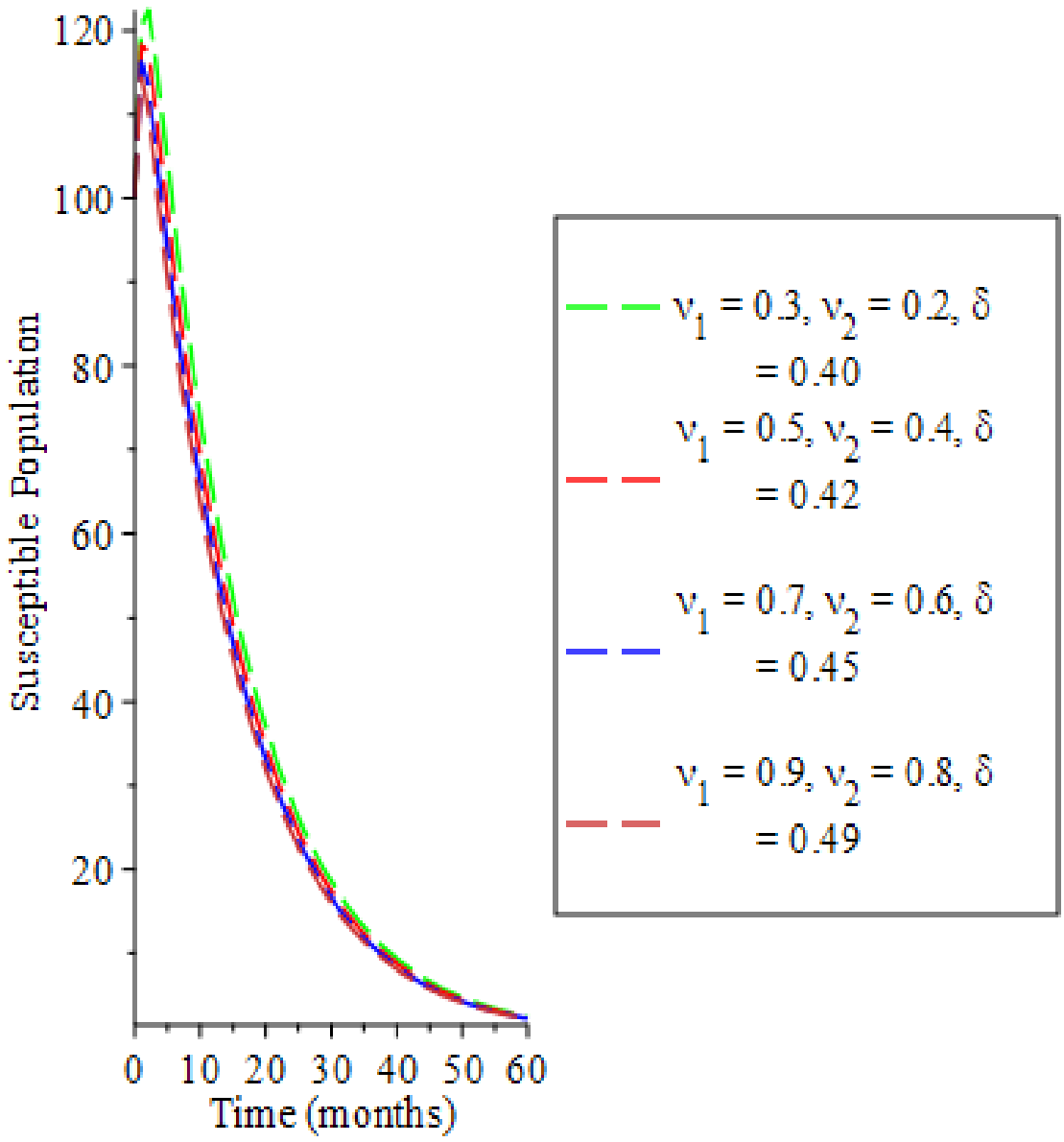

Figure 4.43: Behavioural dynamics of susceptible population when varying testing rate for acute and chronic individuals and treatment for chronic individuals

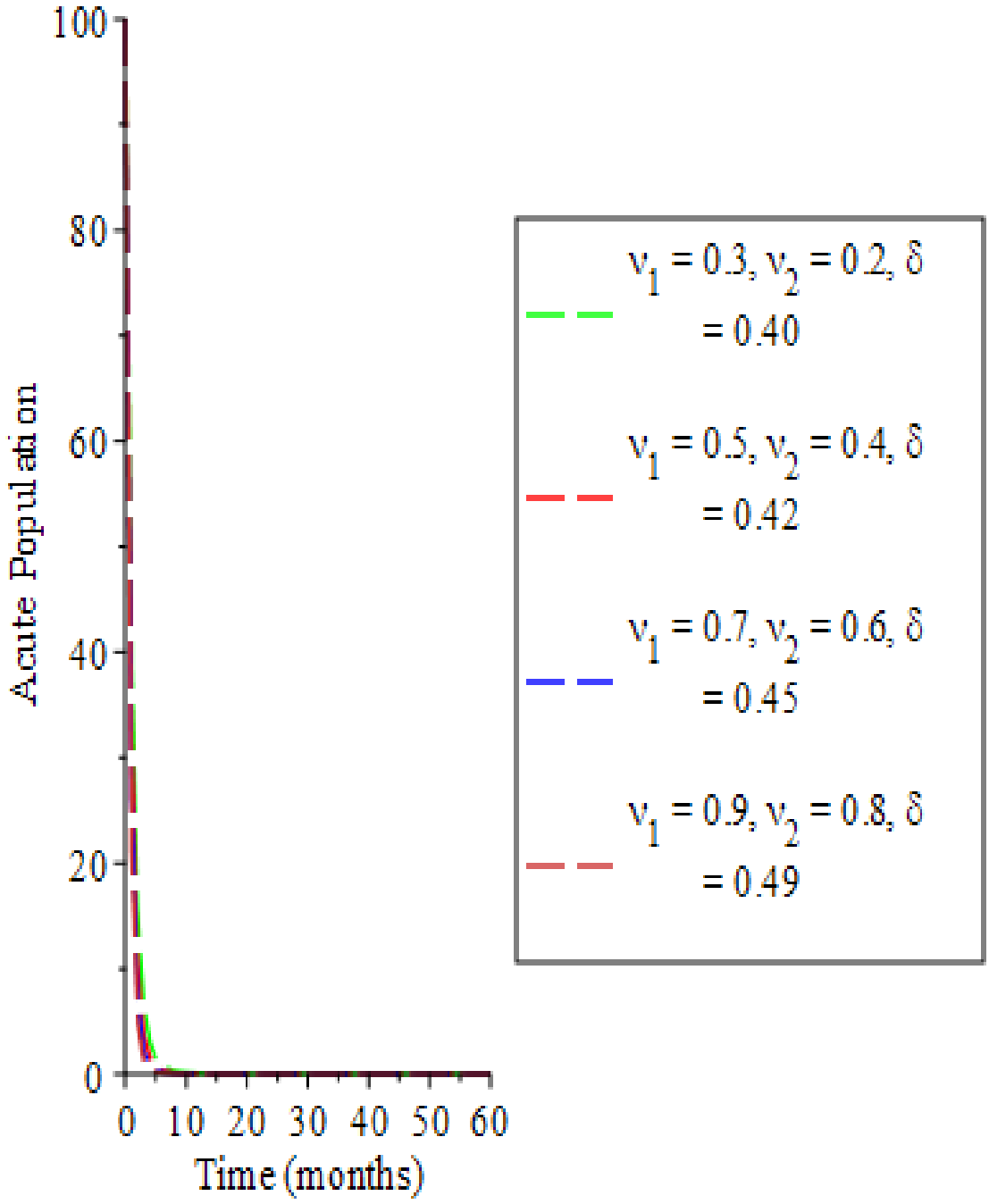

Figure 4.44: Behavioural dynamics of acute population when varying testing rate for acute and chronic individuals and treatment for chronic individuals

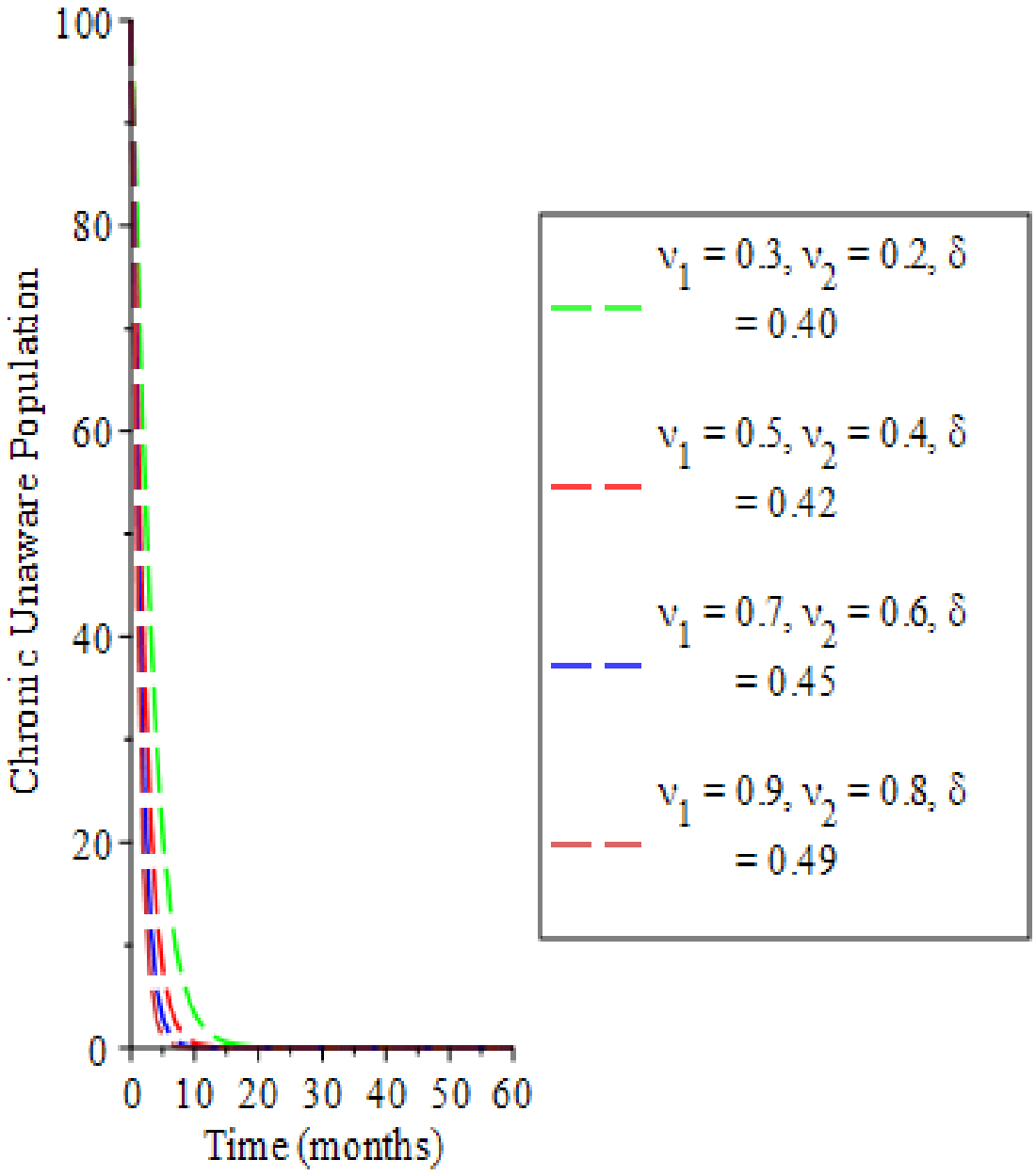

Figure 4.45: Behavioural dynamics of chronic unaware population when varying testing rate for acute and chronic individuals and treatment for chronic individuals

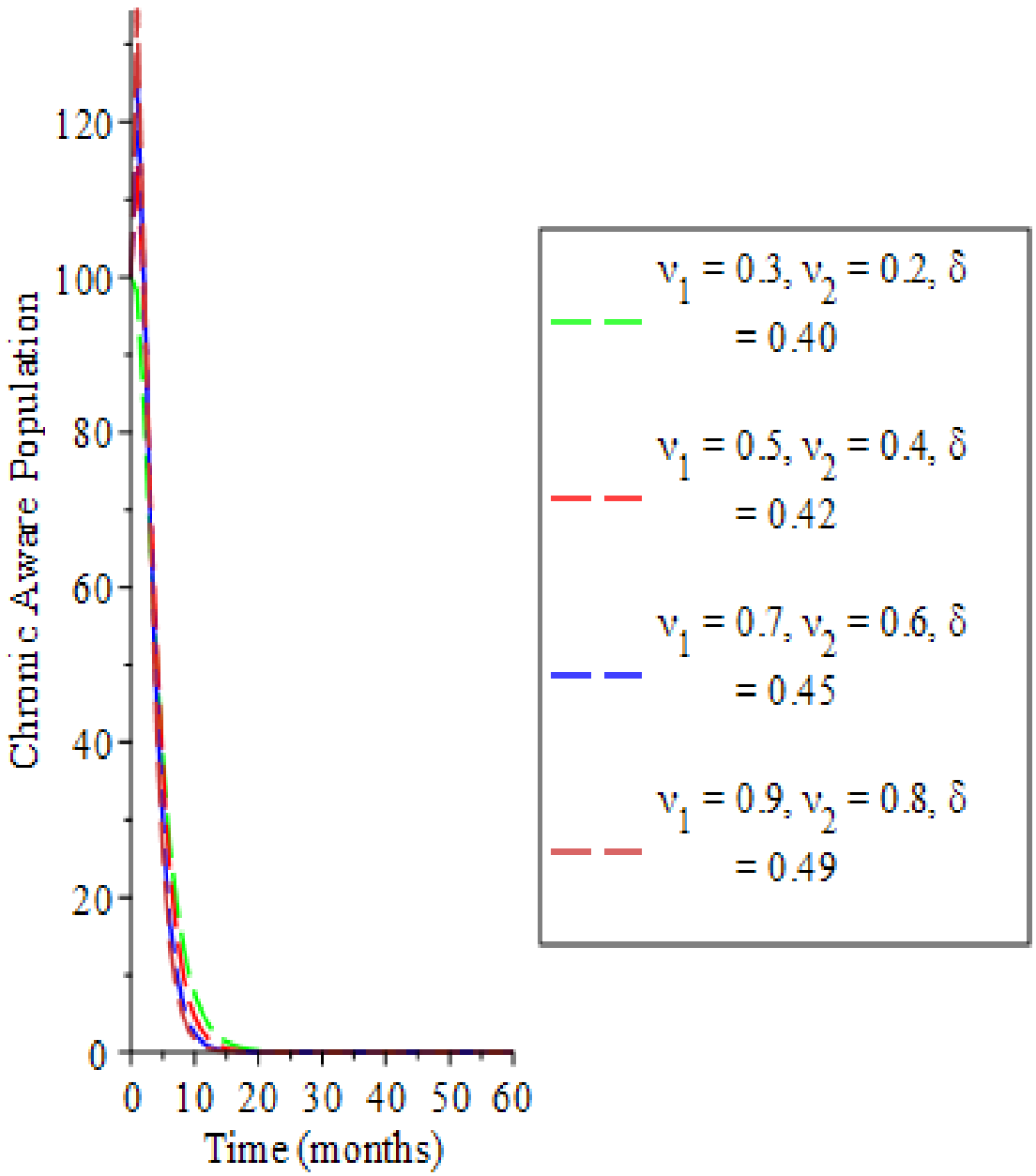

Figure 4.46: Behavioural dynamics of chronic aware population when varying testing rate for acute and chronic individuals and treatment for chronic individuals

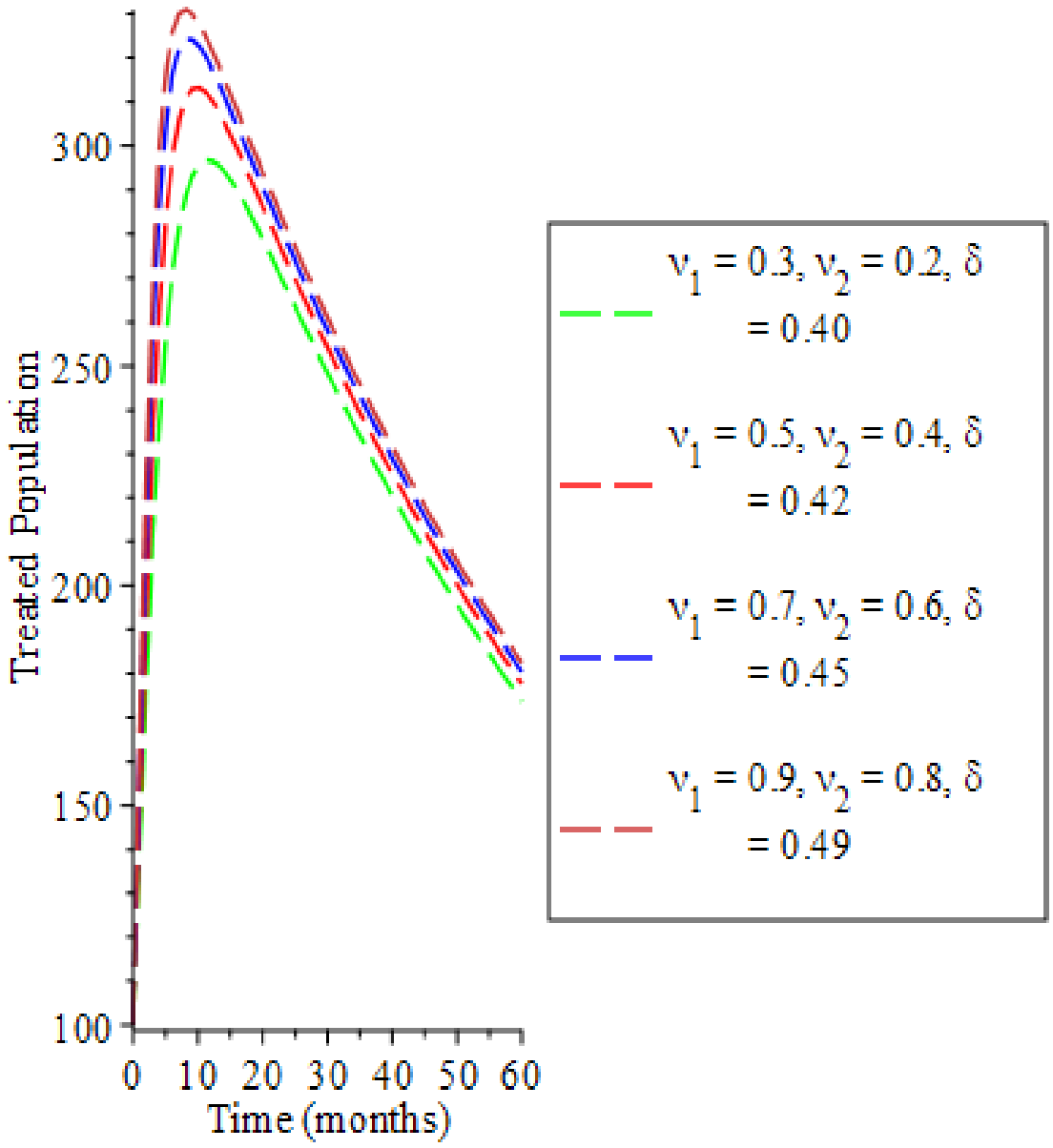

Figure 4.47: Behavioural dynamics of treated population when varying testing rate for acute and chronic individuals and treatment for chronic individuals

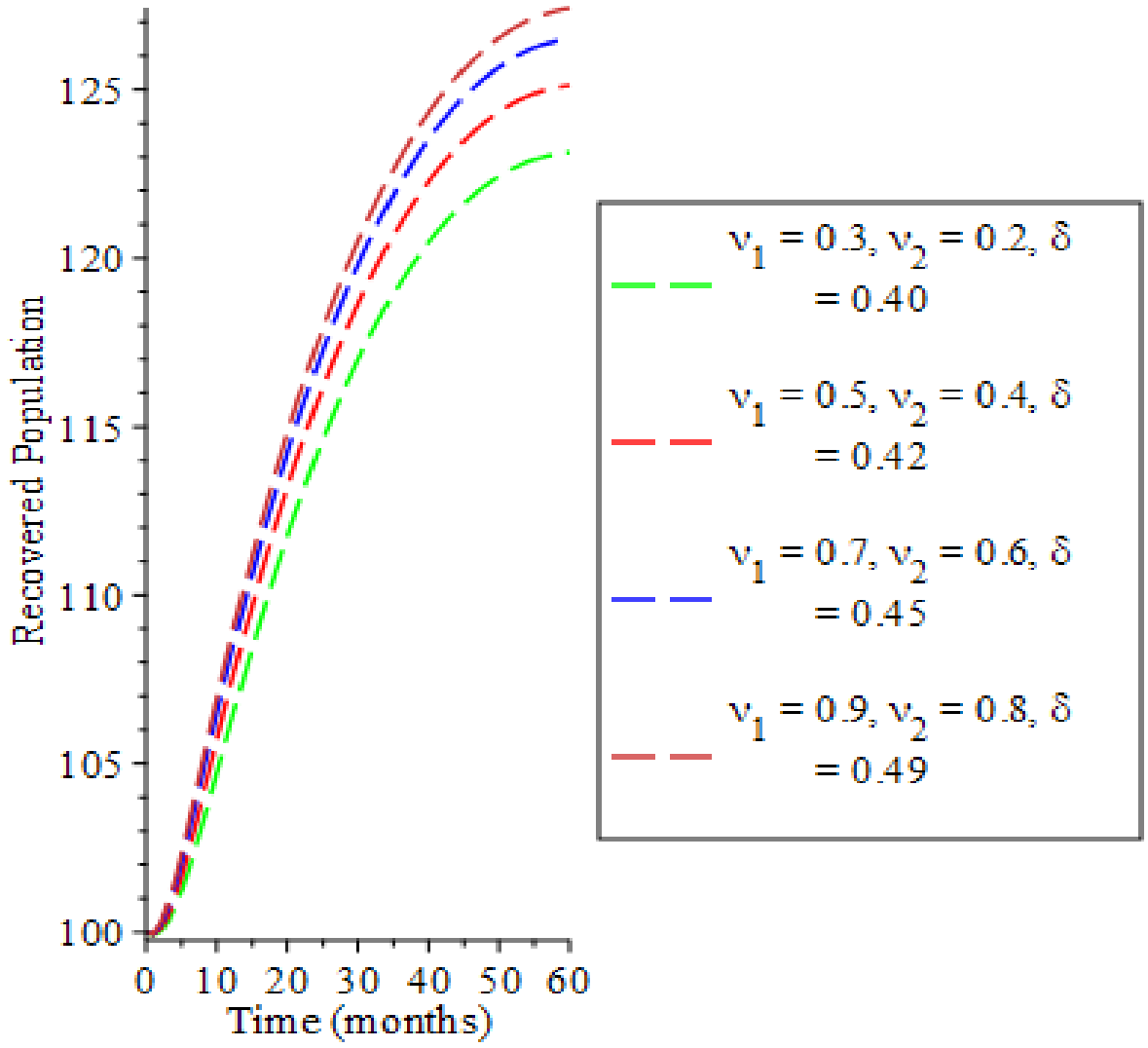

Figure 4.48: Behavioural dynamics of recovered population when varying testing rate for acute and chronic individuals and treatment for chronic individuals

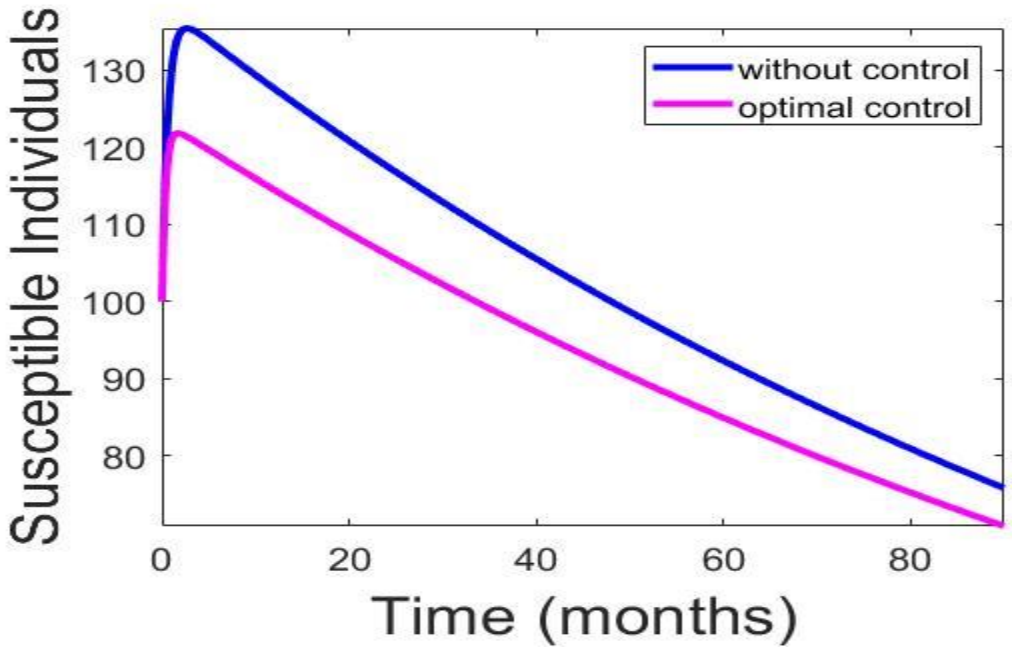

Figure 4.49: The effect of control on susceptible individuals for HBV model 3

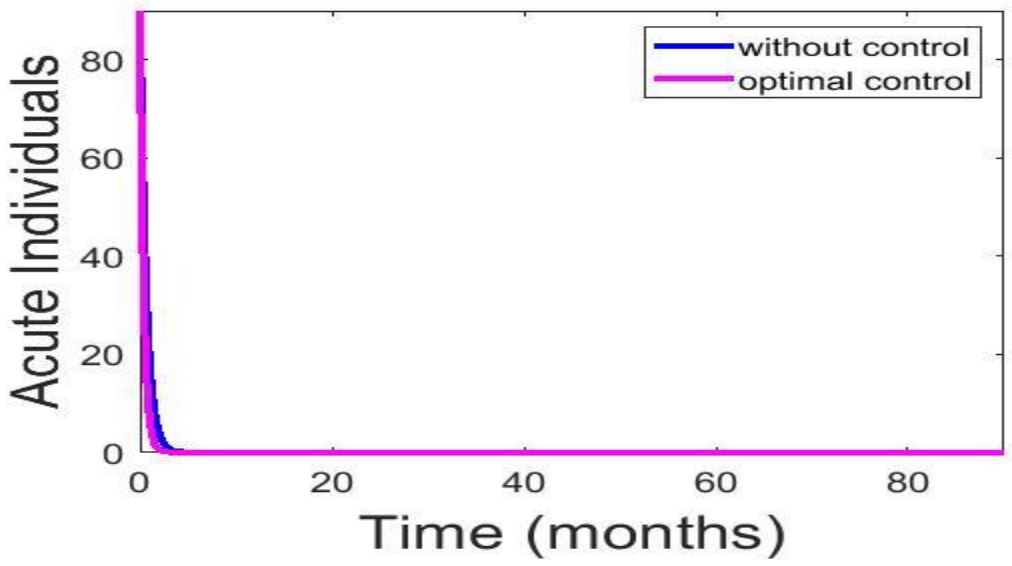

Figure 4.50: The effect of control on acute individuals for HBV model 3

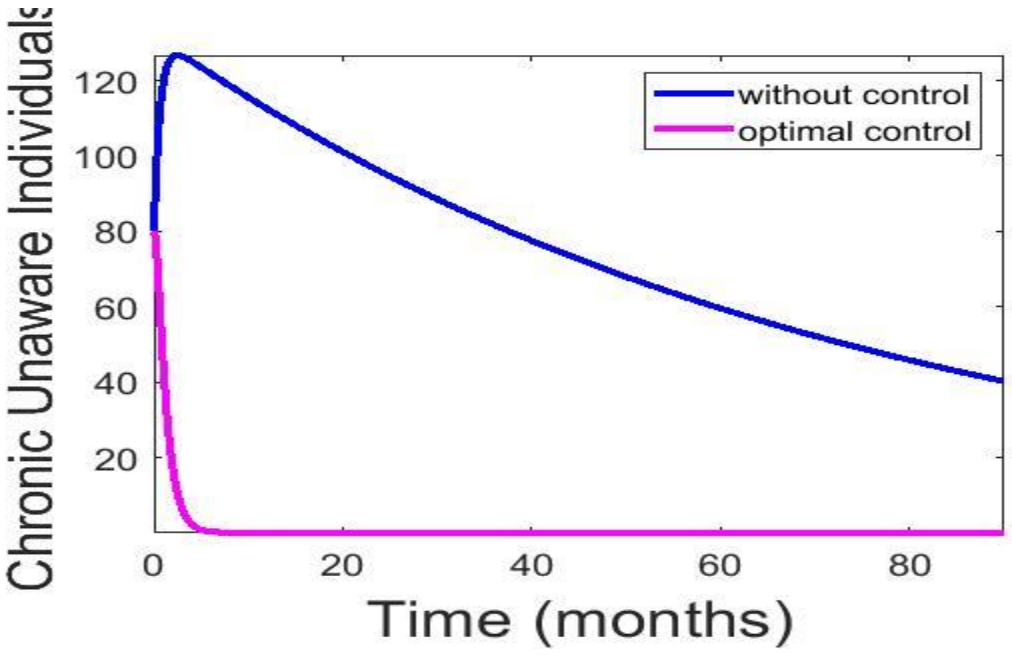

Figure 4.51: The effect of control on chronic unaware individuals for HBV model 3

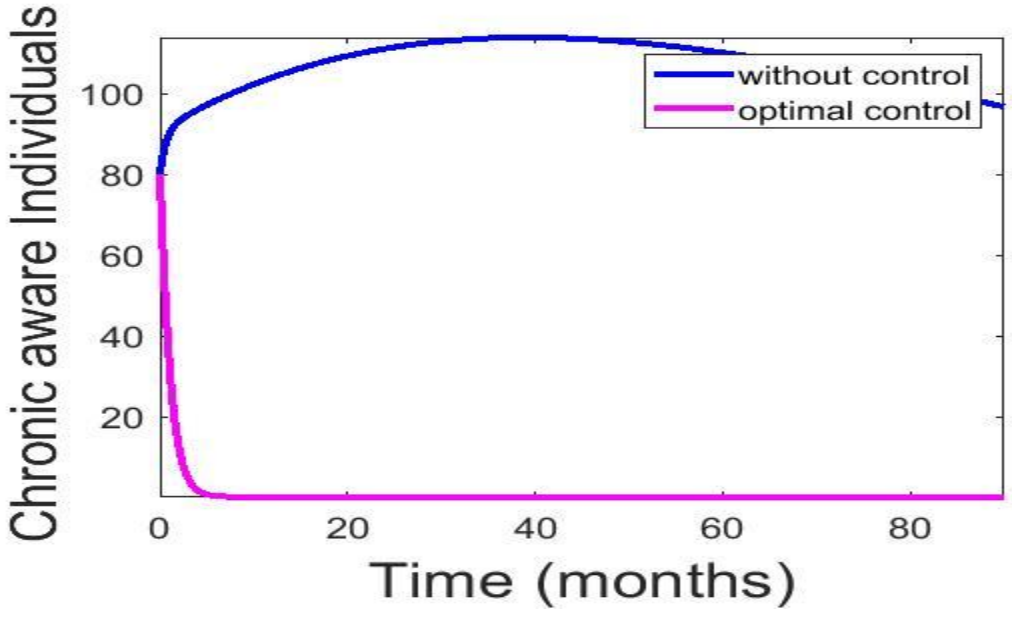

Figure 4.52: The effect of control on chronic aware individuals for HBV model 3

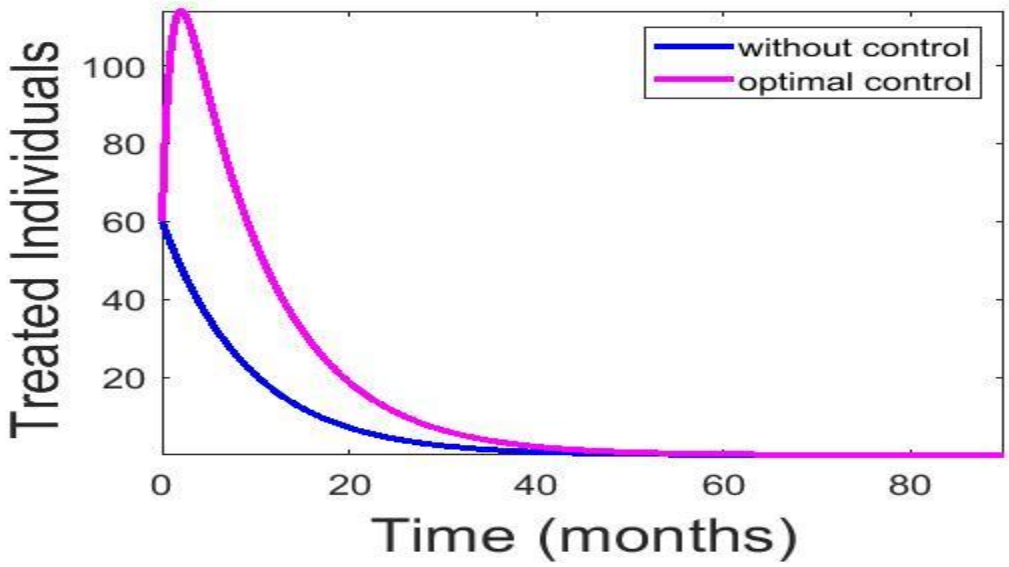

Figure 4.53: The effect of control on treated individuals for HBV model 3

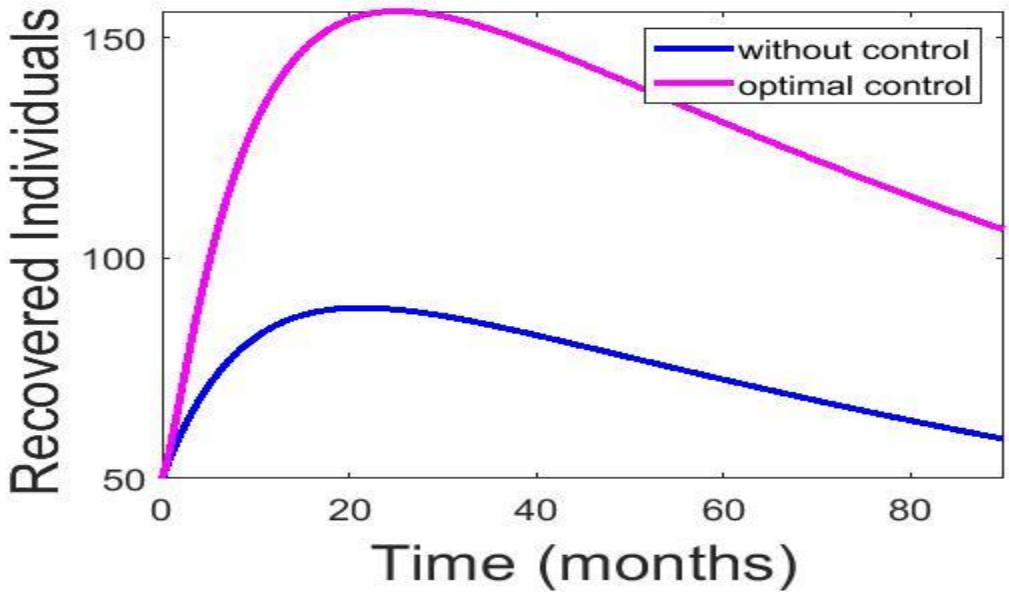

Figure 4.54: The effect of control on recovered individuals for HBV model 3

4.2 Discussion of Results

The discussion of results for the three cases of the considered HBV mathematical models are expansively presented for various population dynamics with different emerging terms. The behavioral dynamics of the various population when the basic reproduction number is less than unity ($R_0 < 1$), the parametric sensitive of various population and the control strategies of Hepatitis B virus are presented.

4.2.1 Discussion of Results for HBV Model Case 1

Table 4.1 shows the contribution of each parameter to the basic reproduction number (R_0) when it is less than 1. From the table, it was observed that $b, \beta, \gamma, \mu, \omega, \varphi, q, r, \sigma, \nu$ are all sensitive to R_0. It is also clear that R_0 is most sensitive to changes in the rate of children born without effective vaccination that goes to the chronic compartment. This change leads to a proportional increase or decrease in the reproduction number due to the efficacy of the vaccine appropriated to the children. Meanwhile, the parameters $\delta_1, \gamma_1, \gamma_2, \gamma_3, \mu_0, \mu_1, \vartheta_1,$ and ϑ_2 exhibit an inverse response on an increasing ratio of infected contact to an infected individual. Therefore, the sensitivity index of children without effective vaccination should be discouraged by ensuring proper vaccination as reported by Zhao *et al.,* (2000).

Behavioral dynamics of susceptible population when $R_0 < 1$ is demonstrated in Figure 4.1. As noticed, a strong early asymptotical decrease toward a limiting zero of susceptible population exists. However, overtime, a gradual increase in the susceptible population is obtained which later remain stable and does not tends to zero. This indicates that

susceptible population will never be zero and endemicity will not exist as such the disease will die out over time due to the basic reproduction number less than unity. In Figure 4.2, the same behavioural dynamics of the vaccinated population is seen as susceptible population. The disease vanishes over time due to non-existence of endemicity showing vaccination population will not be zero when $R_0 < 1$ which authenticates the analysis shown in section 3.1.1. The observation obtained agrees well with the findings of Khan *et al.*, (2019) for population dynamics with basic reproduction number less than 1, and as such, the average contact infected number in relation to infectious persons decline in magnitude.

Figures 4.3 - 4.7 display the dynamical performance of the latent, acute, chronic, hospitalized and the recovered population respectively. A downward momentous decrease is observed in the population at the early time of the disease as depicted in Figures 4.3 - 4.6. As the time progresses, an insignificant variation in the population dynamics is noticed indicating that the disease dies out early due to the reproduction number that is less than unity. Though, the behaviour is influenced by increasing vaccination and other intervention strategies that resist the upsurge in the spread of the disease. Meanwhile, in Figure 4.7, a sharp rise in the recovery population is obtained demonstrating the effectiveness of the control strategies employed. The recovery reached the peak thereby eliminating the virus from the population. This resulted to overall declination in the population which tends to zero overtime. The results complement existing reports on Hepatitis B Virus and basic reproduction number.

The effect of varying acutely infected offspring (r) and chronically infected offspring (b) on the susceptible and latent population are investigated in Figures 4.8 and 4.9 respectively. A decrease in the parameters (b) and (r) boosts the susceptible and latent populations but reduces the spread HBV due to low interaction between the host immune system and the virus. Therefore, the appearance of HBV and the pathogenesis reduces which thereby lessen the potential injury on the liver. Hence, the liver is shielded from hepatocellular carcinoma over time. The rate of acutely infected and chronically infected individuals is examined in Figures 4.10 and 4.11. The parameter variations show a slight decrease in the acute population between the time range of $0 < t < 6$ which implies that the individuals are indeed in the acute phase of the virus. The vertical transmission dies down as the time progresses this discourages liver inflammation as a result of lowering the infected individuals. Meanwhile, the chronic population in Figure 4.11, depicts a high significant influence of the acutely infected and chronically infected individuals over time. A chronic infection phase is found at the time range $6 < t < 40,$ as such, the individuals are exposed to liver carcinoma or cirrhosis. Hence, the chronic population diminishes as the parameters are reduced.

In Figures 4.12 to 4.14, the impact of rate of children born of infected mother without active vaccine which goes into the acute compartment (r) and chronic compartment (b) on the hospitalized, recovered and the vaccinated population are presented. The hospitalized population decreases with parameters variation along the rising time (t) as a result of short time effect of the acute and chronic population. This satisfies the earlier report on the chronic and acute populace. The recovery rate is enhanced as observed in Figure 4.13 due

to significant simulation of surface antibodies of Hepatitis B. In the plot maximum recovery rate is reached early as the parameter values are varied and a decline in the plot is noticed which portrays total recovery of the population. An asymptotically rise in the vaccinated population with variation in parameter values of (b) and (r) is seen in Figure 4.14. This is expected as the number of successful vaccination rate increases due to reduction in the rate of unsuccessful vaccination of children born of infected mothers at birth. The results are in conformity with the work of Lavenchy (2004) and Emerenini and Inyama (2018), which established the fact that the impact of the treatment reduces the effects of vertical transmission. It also showed that it is possible to reduce the number of acute and chronic individuals by increasing the treatment rate. Also, the results are in consonance with the findings by World Health Organization (WHO, 2020) which says with effective information and active vaccination at birth, there is tendency to have a reduction in the susceptible, recovered and vaccinated individuals.

Figures 4.15 - 4.21 explore an optimal control model with time preventive (hospitalization at the acute state and hospitalization at the chronic state) strategies as control measures on HBV transmission. First, the controls are used to optimize the objective function. Then, the effect of those controls on the various compartments is shown. In Figure 4.15, the impact of the controls on the susceptible individuals was considered. From the figure, there is a slight increase on the controlled plot than the uncontrolled plot as observed on the graph which is as result of controls which aid recovery with full immunity on the populace. Also, in figure 4.16, the effect of controls was checked on the latent state, the figure depicts that there is no visible difference between the control plot and the

uncontrolled plot because, at the latent state, there cannot be any control measures that can be put in place at that time.

The impact of the controls on the acute populace is considered in Figure 4.17. From the plot, it was observed that there is a reduction in the population of acute(early) individuals under control, which implies that treatment at the acute state significantly affects the disease transmission model. From Figure 4.18, there is a significant decline in the population of chronic individuals under control over time than the uncontrolled as observed on the plot. The control measures' impact on the chronic individuals reduces the effect of liver cancer or Hepatocellular carcinoma.

In Figure 4.19, the effect of control measures on the hospitalized (treated) individuals was considered. From the plot, there is a significant difference between the control plot and the uncontrolled plot as noticed. There is an early rise on the controlled plot which signifies the effect of the controls on the hospitalized this implies that with control, the number of individuals on treatment will be more than those without control thereby reducing the chances of liver cancer and possibly death. The effect of the control measure on the recovered individuals was depicted in Figure 4.20. From the figure, it was observed that the population of recovered individuals at the control levels is far greater than those without control. This is an indication that with control, a large population of infected individuals recovers on time, making it cost-effective, i.e., profit will be maximized. The impact of controls on the vaccinated individuals was shown in Figure 4.21. From the plot, there is an increase in the number of vaccinated individuals on control than those without

control, which implies that vaccination can eradicate the virus in the population with many successful vaccinated individuals and according to WHO, (2020) successful vaccination still remains the surest method of mitigating the transmission process of Hepatitis B virus.

4.2.2 Discussion of Results for HBV Model Case 2

Table 4.2 shows the contribution of each parameter to the basic reproduction number, R_0 when it is less than unity. It was observed from the table that $\zeta, \beta, \gamma, \sigma, \rho$ are all sensitive to R_0. It is also clear that R_0 is most sensitive to changes in ζ, σ, ρ . An increase in the treatment rate of chronic individual (σ)and also duration of treatment (ρ) will bring about a proportional increase in R_0 and a decrease in parameter values σ, ρ will result in a decrease in R_0 with about an equivalent magnitude.The parameters$\eta, \mu, \upsilon, \omega, \xi_1, \xi_2$ have an inverse proportional relationship with R_0 implying that any increase in $\eta, \mu, \upsilon, \omega, \xi_1, \xi_2$will reduce the number of secondary infections arising from the case of HBV. This suggest that more effort should be concentrated at first identifying carrier mothers who are prone to giving birth to chronic offspring and then increasing the treatment rate of such individuals while adhering strictly to the duration of treatment which is in consonance with the result obtained by Zhang and Zhang (2018).

Figure 4.22 demonstrates the behavioral dynamics of susceptible population when $R_0 < 1$. An early asymptotical decrease toward a limiting zero of susceptible population was noticed. Nevertheless, overtime, an increase in the susceptible population is attained which later remain stable and does not tends to zero. This shows that susceptible population will

never be zero and the disease will die out over time due to the basic reproduction number less than unity. Figures 4.23 - 4.26 show the dynamical performance of the acute, chronic, treated and the recovered population respectively. A downward significant decrease is observed in the population at the early time of the disease as shown in Figures 4.23 - 4.26. With the passage of time, an inconsequential variation in the population dynamics is observed indicating that the disease dies out early due to the reproduction number that is less than unity. Though, the behaviour is influenced by increasing vaccination and other intervention strategies that resist the upsurge in the spread of the disease. This analysis results into the overall declination in the population which tends to zero overtime and this also validates the analysis shown section 3.2.2. Existing reports on Hepatitis B Virus and basic reproduction number complement the results obtained.

The impact of varying the treatment rate at the chronic state (σ) and recovery rate with full immunity (κ) are investigated in Figures 4.27 to 4.31. In Figure 4.27, an increase in in the treatment rate of individuals at chronic compartment (σ) and also, increase in the recovery rate of individuals under treatment with full immunity (κ) brings about an indifference in the susceptible population because those who recover don't go back to been susceptible again i.e., recovery with full immunity is achieved which is in conformity with the work of Zhang and Zhou (2012). Figure 4.28 depicts the behavior of the acute population. From the plot, an increasing population was noticed then a fall over time which is as a result of those that spontaneously clear the virus due to their body immune response as stated by Cuipe *et al.,* (2011) and Scagiloni *et al.,* (2016).

Figure 4.29 depicts the chronic population when varying the treatment rate at the chronic state (σ) and recovery rate with full immunity (κ), an increase in these parameters values leads to a decline in chronic population which is expected as treatment at the chronic population lowers the incidence of chronic Hepatitis B and invariably drops the risk of Hepatocellular carcinoma. Meanwhile, an inverse relationship is observed in Figures 4.30 and 4.31, treatment rate at the chronic state (σ) and recovery rate with full immunity (κ) will definitely bring about a significant increase in treated population so also the recovery population as shown in the plots. This finding implies that treatment of chronic individuals and adherence with treatment brings about an increase in recovery rate which is also an effective measure of reducing the menace HBV which is been justified by the work of Zhao (2000) and Zhang and Zhou (2012).

Figures 4.32 – 4.36 depicts an optimal control model plot with time preventive (treatment at the acute state and treatment at the chronic state) strategies as control measures on HBV transmission process. These controls are used to optimize the objective function. The impact of these controls on the various compartments is hereby discussed. From figure 4.32, the impact of the controls on the susceptible individuals is significant and evident as there is a sharp rise in the susceptible individual population as the control measures are in place because several people that are treated and recovered move into the susceptible class again since they can be re-infected whereas when the control measures are not put in place, there is no noticeable increment in the susceptible population. Figure 4.33 shows the impact of controls on the acute individual population. From the plot, an asymptotical decline in the acute individual population under control is noticed which significantly

shows that the application of the control measures helps in the reduction of the acute class and this is expected. It shows the impact of the control measures in the acute population is momentous. Figure 4.34 displays the impact of the control measures on the chronic individual's population. It is observed from the figure that there is a reduction in the chronic individuals when control measures are applied compared to where there are no control measures. This implies that the impact of the control measures on chronic individuals is significantly felt. In figure 4.35, there is a significant increase in the treated class due to the availability of the control measure which later reduces because of the movement of the treated individuals to the recovered class. In figure 4.36, the effect of the control measure on the recovered individuals is shown. From the figure, it is discovered that there is a significant increase in the recovered class where there is control than when there is no control. This is an indication that with control, a large population of infected individuals recovers on time, making it cost-effective. This is justified in the work of Oke *et al.,* (2020) that control strategies help in maximizing profits and minimizing deaths.

4.2.3 Discussion of Results for HBV Model Case 3

Table 4.3 shows the contribution of each parameter to the basic reproduction number. R_0 when it is less than 1. From the table, it was observed that $\beta, \delta, \sigma, \upsilon_1, \upsilon_2$ are all sensitive to the basic reproduction number R_0. It is also evident that $R_0$is most sensitive to changes in $\delta, \sigma, \upsilon_1, \upsilon_2$. An increase in the testing rate of acute individuals (υ_1), testing at the chronic unaware state (υ_2), treatment of the chronic aware individuals (δ) and also spontaneous

clearance rate (σ) results in a corresponding proportionate increase or decrease in thebasic reproduction numberR_0.However, an inverse relationship is observed for the parametersμ, α_1, α_2 and γ with R_0 implying that any increase in μ, α_1, α_2 and γwill reduce the number of infected contacts to an infected individual. Therefore, the result from this sensitivity analysis of R_0 suggest that more effort should be concentrated at first testing of individuals at all levels for HBV and once found positive treatment should commence immediately in order to reduce the risk of cirrhosis or death.

Figure 4.37 shows the dynamical behavior of susceptible population when $R_0 < 1$. An early decrease toward a limiting zero of susceptible population was observed. Nonetheless, overtime, an increase in the susceptible population is attained which later remain stable and does not tends to zero. This shows that susceptible population will never be zero and the disease will die out over time due to the basic reproduction number less than unity. Figures 4.38 to 4.42 depicts the dynamical performance of the acute, chronic unaware, chronic aware, treated and the recovered population respectively. A descending momentous decrease is observed in the population at the early time of the disease as shown in Figures 4.39 - 4.43. As time progresses, an insignificant variation in the population dynamics is observed indicating that the disease dies out early due to the reproduction number that is less than unity. Though, the behaviour is influenced by increasing testing and other intervention strategies that resist the upsurge in the spread of the disease. This results to total declination in the population which tends to zero overtime which authenticate the analysis shown section 3.3.2 that says there is no HBV in the population,

only the susceptible individuals exist. Existing reports on Hepatitis B virus and basic reproduction number complement the results obtained.

The effect of varying the testing rate of the acute individuals (υ_1), testing rate of chronic individuals (υ_2) and treatment rate of chronic individuals (δ) on the population dynamics are shown in Figures 4.43 to 4.48. From Figures 4.43 and 4.44, an increase in the parameters values reduces susceptible and acute populations thereby reducing the spread of HBV due to low interaction between the host immune system and the virus. Therefore, the appearance of HBV and the pathogenesis reduces which in so doing lessen the potential injury on the liver. Hence, the liver is shielded from hepatocellular carcinoma over time. The rate of chronic unaware and chronically aware individuals is examined in Figures 4.45 and 4.46. The parameter variations show a significant decrease in the chronic unaware population which implies that testing at the stage is a great tool for reducing the disease transmission. The transmission process dies down as the time progresses this discourages liver inflammation as a result of lowering the infected individuals. Meanwhile, the chronic population in Figure 4.46, depicts a high significant influence of the acutely infected and chronically unaware infected individuals over time. A chronic infection phase is found at the time range $10 < t < 20$, as such, the individuals are exposed to liver carcinoma or cirrhosis. Hence, the chronic population diminishes as the parameters are increased.

In Figures 4.47 to 4.48, the impact of varying the testing rate of the acute individuals(υ_1), testing rate of chronic individuals (υ_2) and treatment rate of chronic individuals (δ) on the

treated and the recovered population are presented. The treated population increases with parameters variation along the rising time (t) as a result of long-time effect of parameter values. The recovery rate is enhanced as observed in Figure 4.48 due to significant simulation of surface antibodies of Hepatitis B. This is in alignment with the works of Pang (2010) and Ullah (2019). This result implies that an intensification in testing at all infectious states and rise in treatment of chronic individual will bring about a reduction in the HBV transmission process which is response to the WHO goal for 2030 that concentrating efforts on awareness program and campaign will sure bring about a decrease or eradication in the transmission process of the virus (WHO, 2020).

Figures 4.49 -4.54 show an optimal control model plots with time preventive (treatment at the acute state, testing at the chronic unaware condition, and treatment at the chronic aware state) strategies as control measures. These three controls are used to optimize the objective function on HBV transmission process. The effect of the control measures on the different compartments is discussed. Figure 4.49 shows the impact of the controls on the susceptible individuals. From the figure, it was observed that the population of susceptible individuals in the control plot is lesser than those individual not under control. Awareness is a form of testing that is an important control tool that helps reduce the number of people who will be susceptible to the virus because as they are informed, they take all precautionary measures to guard against the virus. In Figure 4.50, the effects of the controls on the acute populations are shown. From the figure, it is observed that the acute population reduces with time with control, indicating that treatment at the acute state helps the transmission process of the diseases.

In Figure 4.51, the impact of the control measures on the chronic unaware population are considered. From the figure, an asymptotical substantial difference between the control plot and the uncontrolled plot is noticed which signifies the number of chronic unaware individuals reduces as testing on the chronic unaware individual is implemented as a control measure for the transmission process. Figure 4.52 depicts the effect of the control measures on the chronic aware population. From the figure, a great fall in the controlled plot is observed which shows the impact of the controls as against the uncontrolled plot. The number of aware individuals reduces greatly as treatment at the chronic aware state is implemented as a control measure for the transmission process. Figure 4.53 shows the impact of the control measures on the treated population. From the figure, a significant difference between the control plot and the uncontrolled plot is noticed. The number of the treated individuals increases under control as against without control which shows the cumulative effect of testing at the acute and the chronic unaware state. Figure 4.54 depicts the effect of the control measures on the recovered individuals. From the figure, the number of recovered individuals on the control plot is far greater than those without control from the plot. It is a clear sign that combining testing at the acute and chronic unaware state is a smart way to keep HBV transmission under control (Niederau, 2014), which is line with the WHO 90-90 – 90 HBV elimination and coverage target for 2030 (WHO, 2020).

4.3 Findings

In solving the problem of transmission and acquisition process of HBV, three models were developed. Following a mathematical modelling approach, keeping in view the horizontal transmission process, this study demonstrated that children born of chronically infected mother can be divided into acutely infected offspring or chronically infected offspring. It has also been shown that acutely infected individuals spontaneously clear the virus and treatment at all infectious class helps in mitigating the risk of HBV. However, individuals who fall out of treatment or indulge in habits or lifestyles that reduces the potency or effects of treatment which aggravate HBV transmission process, also testing at the acute state of the virus and chronic unaware state helps in better management of the virus.

Impact of testing and treatment cannot be over-emphasized in this study as it is the bedrock of reducing the disease transmission process, strategies and control interventions are cost effective i.e., minimize cost and maximize the number of recovered individuals. Hence, early treatment could be the most fruitful way to reduce the menace of liver cirrhosis.

CHAPTER FIVE

5.0 SUMMARY, CONCLUSION AND RECOMMENDATIONS

5.1 Summary

This work studied the transmission and acquisition process of Hepatitis B virus, the impact of testing as well as treatment as control strategies using mathematical models. Specifically, vertical transmission which is the main route of the disease transmission was checked using the basic reproduction number and the stability analysis. In addition, different intervention scenarios for the Hepatitis B virus were addressed and investigated.

The background of the infectious disease; Hepatitis B Virus was discussed. Conceptual issues arising from Hepatitis B virus were raised and also reviews of methods used were analyzed. The gaps identified in literatures were vividly discussed.

Mathematical model formulation, analysis and methods of solutions for HBV model were discussed. A class of ODE system was formulated and analyzed using established theorems. The positivity and boundedness of the solutions was investigated which showed that the solution is bounded and well posed in the various regions. Also, the basic reproduction number was constructed, the disease free and endemic equilibrium points were analyzed to be locally and globally asymptotically stable under certain conditions of the basic reproduction number using the Lyapunov method. When the basic reproduction $R_o = 1$, the behavior of the disease-free equilibrium was investigated using the bifurcation

analysis. Afterwards, the formulation of the optimal control problem, analysis of the optimal control problem, adjoint conditions, optimality conditions and the optimality system for the HBV models were considered using the Portryagin's maximum principle.

The numerical computation of the model considered was carried out. It was analytically and numerically established the necessary conditions under which disease-free equilibrium is asymptotically stable using the basic reproduction number (R_o). Using parameters from published articles and some assumed values, the possibility of diseases eradication was shown. The results further showed the effects of varying some sensitive parameters on the dynamics of various populations. Thereafter, the computation on optimal control was highlighted to depict the impacts of control measures on the population.

5.2 Conclusion

A nonlinear mathematical model has been developed and analyzed to study the HBV transmission process. The numerical study was carried out using maple software embedded code for the Runge-Kutta of fourth order, and the optimal control was comprehensively analyzed on MATLAB pseucode for numerical computation. From this study, the following deductions were made:

1. The disease-free and endemic equilibria for the various HBV models were obtained by setting the various compartments to zero. For the disease-free equilibrium, the susceptible individuals and the vaccinated individuals were determined while for the endemic equilibrium, all the compartmental values were determined. It was

noted that the disease free and endemic equilibrium of the various models exist. This demonstrates that the disease is controllable under various circumstances.

2. The basic reproduction number is calculated to investigate the spread of secondary infected cases caused by primary infected individuals. The numerical solutions for $R_0 < 1$ were validated, and it was discovered that the average contact infected number in relation to infectious persons decreases in magnitude. This has an effect on the virus's transmission process.
3. The stability analysis was determined by the linearization of the various models. The Jacobian matrix of the linearized models were taken and the eigenvalues were evaluated. It was revealed from the study that the disease-free equilibrium is asymptotically stable for $R_0 < 1$. This means that solutions converge to the equilibrium and stay close to the equilibrium, as such, the solution is stable and the disease will die out as time passes. Meanwhile, the endemic equilibrium is asymptotically stable when $R_0 > 1$. Thus, this portrays that the there is an urgent need for curbing of the disease in order not to result into endemicity; a cogent measure to mitigate the spread of the virus should be encouraged.
4. The sensitivity analyses of the various models were examined and the importance of the most sensitive parameters is shown. This enables proper prediction and behavioral characteristics of some entrenched parameters in the models. The sensitivity analyses confirm that some parameters must be carefully monitored to avoid the disease blow up that may lead to uncontrollable effect of Hepatitis B virus in the society.

5. The center manifold theory was used to computationally obtain the bifurcation results of the models. The stable upper bifurcation and unstable lower bifurcation revealed that overtime, bifurcation transition will exist. The results showed that the various models' endemic equilibriums are locally asymptotically stable for the associated basic reproduction number greater than unity since $a > 0$.
6. It was computationally ascertained that models formulated and the control measures placed on them has significant effect in reducing the transmission and acquisition process of Hepatitis B virus. Thus, it is safe to argue that controls strategies help to mitigate the menace of Hepatitis B virus in a population.

The objectives of the study were achieved as the models were formulated, analyzed qualitatively and quantitatively to situate that the combination of testing and treatment increase the recovery rate of an individual thereby reducing the possibility for liver cancer or Hepatocellular carcinoma.

5.3 Recommendations

The recommendations arising from this research are:

1. Proper diagnosis i.e., testing should be carried out on an individual that shows symptoms of HBV before treatment is commenced.

2. Urgent measures should be taken by the health workers and health policy makers in order to reduce liver cirrhosis among HBV patients and treatments at various state of HBV should be carried out.

3. For HBV control, patients who are on treatment should be properly monitored and encouraged to obey the treatment processes in order not to fall out of treatment or indulge in habits that can jeopardize the effects of the treatment.

4. Awareness should be created; testing should be made compulsory and free as it is shown that chronic unaware individuals are the fast spreaders and they die faster of liver cirrhosis.

5. The combination of the three control strategies proves to be the most effective in interrupting the transmission of HBV, vaccination still remains the best control strategy for mitigating the spread of the disease. It is therefore advisable that vaccination of susceptible individuals should be carried out in order to prevent individuals from contacting the disease and thereby reducing the number of infected individuals in the population.

5.4 Contributions to Knowledge

The findings of the present work and hence the contributions to knowledge are:

1. Mathematical modeling of HBV involving vertical transmission only includes children born of infected mothers who are chronically infected, but the findings of this study have validated that children born of infected mothers can be acutely infected as well as chronically infected. Possible solutions for reducing these two modes of HBV vertical transmission were also presented.

2. Individuals who drop out of treatment due to their habits contribute to an increase in infected HBV individuals, which policymakers must address through a series of public awareness campaigns about the dangers of not adhering to treatment procedures and patterns.
3. The formulation of the mathematical model incorporating chronically unaware individuals in the population is a significant contribution to this work because, to the best of our knowledge, it has not been considered in the literature. It has been clinically demonstrated that the chronically unaware individual exists, and this has now been confirmed by some of the findings in this study. It has been established in some of our findings that chronically unaware individuals exist and can be curtailed.

REFERENCES

Adu, I. K., Aidoo, A. Y., Darko, I. O., and Osei-Frimpong, E. (2014). Mathematical model of hepatitis B in the Bosomtwe district of Ashanti region, Ghana. *Applied Mathematical Sciences*, 8 (65), 3343–3358.

Ajelli, M., Jannelli, M., Manfredi, P. and Ciofi deglinth, M.L.(2008). Basic mathematical models for the temporal dynamics of HIV in medium-endemility Italian areas. *Vaccines,* 26 (13), 1697-1707

Alexander M.E and Moghadas S.M. (2004). Periodicity in an epidemic model with a generalized nonlinear incidence. *Math Bioscience,* 189(22),75-96.

Alexander M.E and Moghadas S.M. (2005). Bifurcation analysis of a SIRS epidemic model with generalized incidence. *SIAM Journal of Applied Math Biosciences,* 65(55), 1794-1816.

Alter, M. J. (2003). Epidemiology of hepatitis B in Europe and worldwide. *Journal of Hepatology*, 39(1), 64-69.

Anderson, R. M. and May, R. M. (1998). Population biology of infectious diseases: Part I. *Nature, London.* 280(5), 361-367.

Anderson, R. M. and May, R. M. (1981). The population dynamics of microparasites and their invertebrate hosts. *Philosophical Transactions of the Royal Society,* 291(9), 451-524.

Anmolle Razzaq (2019). Numerical Modeling for Transmission Dynamics of Hepatitis B Virus Disease. *Mathematical Theory and Modeling*, *3*(3), 84–90.

Arriola L. and Hyman J. (2005). Lecture notes, Forward and adjoint sensitivity analysis: with Application in Dynamical Systems, Linear Algebra and Optimization Mathematical and Theoretical Biology Institute, summer, 2005,1-20

Bartenschlager, R. and Schaller, H. (2002). Hepadnaviral assembly is initiated by polymerase binding to the encapsidation signal in the viral RNA genome. *EMBO Journal*, 11(1), 3413-3420

Brauer, F. and Castillo-Chavez, C. (2001). Mathematical models in population biology and epidiemiology, texts in applied maths, 40, Springer-Verlag, New York, 411-468.

Bhattacharyya, S., and Ghosh, S. (2010). Optimal control of vertically transmitted disease: An integrated approach. *Computational and Mathematical Methods in Medicine, 11*(4), 369–387.

Birnbaum, F. and Nassal, M. (1990). Hepatitis B virus nucleocapsid assembly: primary structure requirements in the core protein. *Journal of Virology*, 64(2), 3319-3330.

Buonomo B. and Lacitignola D., (2011): On the backward bifurcation of a vaccination model with nonlinear incidence. *Nonlinear Analysis: Modelling and Control*, 16(1), 30-46

Carr, J. (1981) Application of centre manifold theory. *Springer* ,New York,NY,USA, 1-13

Centre for Disease Control (CDC) (2019). Hepatitis B [Online]. Available:http://www.cdc.int/csr/disease/hepatitis/cdcsrncs11/en/.

Chang, M. H. (2011). Hepatitis b virus infection. *Liver Disease in Children, Fourth Edition*, 4(1),176–294.

Chen, C.-H., Chiu, Y.-C., Lu, S.-N., Lee, C.-M., Wang, J.-H., Hu, T.-H. & Hung, C.-H. (2014).Serum hepatitis B surface antigen levels predict treatment response to nucleos(t)ideanalogues. *World Journal of Gastroenterology*: *WJG*, 20(2), 7686-7695.

Cheng, K. C., Smith, G. L. and Moss, B. (2006). Hepatitis B virus large surface protein is notsecreted but is immunogenic when selectively expressed by recombinant vacciniavirus. *Journal of Virology*, 60(1), 337-344

Chisari, F. V. (2000). Rous-Whipple Award Lecture. Viruses, immunity, and cancer: lessons from hepatitis B. *American Journal of Pathology*, 156(2), 1117-1132.

Chisari, F. V., Filippi, P., Mclachlan, A., Milich, D. R., Riggs, M., Lee, S., Palmiter, R. D.,Pinkert, C. A. and Brinster, R. L. (2016). Expression of hepatitis B virus large envelopepolypeptide inhibits hepatitis B surface antigen secretion in transgenic mice. *Journal of Virology*, 60(1), 880-887

Chong, C. L., Chen, M. L., Wu, Y. C., Tsai, K. N., Huang, C. C., Hu, C. P., Jeng, K. S., Chou, Y.C. and Chang, C. (2011). Dynamics of HBV cccDNA expression and transcription in different cell growth phase. *Journal of Biomedical Sciences*, 18(4), 96-106.

Chowell, G., Fenimore, P. W., Castillo-Garsow, M. A., and Castillo-Chavez, C. (2003). SARS outbreaks in Ontario, Hong Kong and Singapore: the role of diagnosis and isolation as a control mechanism. *Journal of Theoretical Biology*, 224(1), 1–8.

Chu, C. J., Keeffe, E. B., Han, S. H., Perrillo, R. P., Min, A. D., Soldevila-Pico, C., Carey,W., Brown, R. S., Jr., Luketic, V. A., Terrault, N. and Lok, A. S. (2003). Hepatitis B virusgenotypes in the United States: results of a nationwide study. *Gastroenterology*, 125(1), 444-451.

Ciupe, S. M., Catllá, A. J., Forde, J. and Schaeffer, D. G. (2011). Dynamics of Hepatitis B VirusInfection: What Causes Viral Clearance? *Mathematical Population Studies*, 18(2), 87-105

Ciupe, S. M., Ribeiro, R. M., Nelson, P. W., and Perelson, A. S. (2007). Modeling the mechanisms of acute hepatitis B virus infection. *Journal of Theoretical Biology*, 247(1), 23–35.

Ciupe, S. M., Ribeiro, R. M. and Perelson, A. S. (2014). Antibody Responses during Hepatitis B Viral Infection. *PLoS Computational Biology*, 10(7), e1003730.

Cohen C., Holmberg S.D., McMahon B.J., Block J.M., Brosgart C.L., Gish R.G., London W.T., and Block T.M. (2011) Is chronic hepatitis B being undertreated in the United States? *Journal of Viral Hepatology*, 18(1), 377–383

Cooksley, W. G., Piratvisuth, T., Lee, S. D., Mahachai, V., Chao, Y. C., Tanwandee, T.,Chutaputti, A., Chang, W. Y., Zahm, F. E. and Pluck, N. (2003). Peginterferon alpha-2a(40 kDa): an advance in the treatment of hepatitis B e antigen-positive chronichepatitis B. *Journal of Viral Hepatology,* 10(1), 298-305.

Cossart, Y. E., and Field, A. M. (1970). Virus-Like Particles in Serum of Patients With Australia-Antigen-Associated Hepatitis. *The Lancet*, 295(7651), 848-856.

Danane, J., Allali, K., and Hammouch, Z. (2020). Mathematical analysis of a fractional differential model of HBV infection with antibody immune response. *Chaos, Solitons and Fractals*, 136(3), 1–9.

Daley, D.J., and Gani, J.(1999). Epidemic modelling; an introduction. Cambridge University Press. Cambridge, 175-194

Demirjian, A. and Levy, O. (2009). Safety and Efficacy of Neonatal Vaccination. *European journal of immunology*, 39(1), 36-46.

Derrick, W. R and Grossman, S.I.(1976). Elementary differential equations with application. Addison Wesley Publications Company, Philippine, 20-126

Diekmann, O., Heesterbeek, J. A. P., and Metz, J.A.J. (1990). On the definition and the computation of the basic reproduction ratio models for infectious diseases in heterogeneous populations. *Journal of Mathematical Biosciences*, 28(1), 365-382

Diekmann, O., and Heesterbeek, J. A. P. (2000). Mathematical epidemiology of infectious diseases: model building, analysis and interpretation .Wiley, New York, 143-167

Driessche, P. Van den and Watmough J.(2002). Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Journal of Mathematical Biosciences.*180, 29-48

Edmunds, W. J., Medley, G. F., and Nokes, D. J. (1996). The transmission dynamics and control of hepatitis B virus in the Gambia. *Statistics in Medicine, 15*(20), 2215–2233.

Elgouhari, H. M., Abu-Rajab Tamimi, T. I. and Carey, W. D. (2008). Hepatitis B virus infection:understanding its epidemiology, course, and diagnosis. *Cleveland Clinic Journal of Medicine,* 75(1), 881-889.

Enders, G. H., Ganem, D. and Varmus, H. E. (1997). 5'-terminal sequences influence thesegregation of ground squirrel hepatitis virus RNAs into polyribosomes and viral coreparticles. *Journal of Virology,* 61(4), 35-41.

Emerenini, B. O., and Inyama, S. C. (2018). Mathematical model and analysis of hepatitis B virus transmission dynamics [version1; peer review:1 not approved]. *F1000Research*, 7(1), 1–5.

Eustace, B. B., Adenike, A. R., Bala, M. A., Shukurat, B. B., Musili, O. R., Banke, O. M., and Abdullateef, L. (2019). Prevalence of Hepatitis B Virus in Nigeria *:* Review Update. *Annals of Public Health & Epidemiology*, 5(3), 1–7.

Ezzikouri, S., Ozawa, M., Kohara, M., Elmdaghri, N., Benjelloun, S. and Tsukiyamakohara,K. (2014). Recent insights into hepatitis B virus-host interactions. *Journal of Medical Virology*, 86(1), 925-932.

Fatehi Chenar, F., Kyrychko, Y. N., and Blyuss, K. B. (2018). Mathematical model of immune response to hepatitis B. *Journal of Theoretical Biology*, 447(1), 98–110.

Fattovich, G. (2003a). Natural history and prognosis of hepatitis B. *Seminars in Liver Disease*, 23(1), 47-58.

Fattovich, G. (2003b). Natural history of hepatitis B. *Journal of Hepatology*, 39 (1), 50-58.

Fattovich, G., Pantalena, M., Zagni, I., Realdi, G., Schalm, S. W. and Christensen, E.(2002). Effect of hepatitis B and C virus infections on the natural history of compensated cirrhosis: a cohort study of 297 patients. *American Journal of Gastroenterology*, 97(2), 2886-2895.

Fleming W.H., and Rishell R.W.(1975). Deterministic and Stochastic Optimal Control. Springer Verlag, New York.51-79

Fung, S. K. and Lok, A. S. (2004). Treatment of chronic hepatitis B: who to treat, what to use, andfor how long?*Clinical Gastroenterology and Hepatology*, 2(1), 839-848.

Gallina, A., Bonelli, F., Zentilin, L., Rindi, G., Muttini, M. and Milanesi, G. (1989). A recombinant hepatitis B core antigen polypeptide with the protamine-like domain deleted self-assembles into capsid particles but fails to bind nucleic acids. *Journal of Virology*, 63(2), 4645-4652.

Ghamanyi, M., Banzi W., and Ntaganda M. (2021). Solving an optimal control problem of Hepatitis B virus dynamics; Efficacy of fuzzy logic strategy. *Rwanda Journal of Engineering, Science, Technology and Environment.*4(1), 2617-2621

Goldstein, S. T., Zhou, F., Hadler, S. C., Bell, B. P., Mast, E. E., and Margolis, H. S. (2005). A mathematical model to estimate global hepatitis B disease burden and vaccination impact. *International Journal of Epidemiology*, *34*(6), 1329–1339.

Gordien, E., Rosmorduc, O., Peltekian, C., Garreau, F., Brechot, C. and Kremsdorf, D.(2001). Inhibition of hepatitis B virus replication by the interferon-inducible MxA protein. *Journal of Virology*, 75(1), 2684-2691.

Gourley, S. A., Kuang, Y., and Nagy, J. D. (2008). Dynamics of a delay differential equation model of hepatitis B virus infection. *Journal of Biological Dynamics*, *2*(2), 140–153.

Gukerhamer, J. and Homes, P. (1983). Non linear oscillations, dynamical syatems and bifurcation of sector fields, Springer- Verlag.1-110

Hadler K.P and Castillo-Chavez. C (1995). A core group model for disease transmission . *Mathematical Biosciences,* 128(5), 41-55

Hahné S.J., De Melker H.E., Kretzschmar M., Mollema L., Van Der Klis F.R., Van Der Sande M.A., and Boot H.J.(2012) Prevalence of hepatitis B virus infection in The Netherlands in 1996 and 2007. *Epidemiology and Infection*, 140(9), 1469–1480.

Haller, O., Frese, M. and and Kochs, G. (1998). Mxs proteins: mediators of innate resistance to RNAviruses. *Revue scientifique et technique* 17(5), 220-230.

Hattaf, K., and Yousfi, N. (2015). A generalized HBV model with diffusion and two delays. *Computers and Mathematics with Applications*, *69*(1), 31–40.

Hattaf, K., Yousfi, N., and Tridane, A. (2012). Mathematical analysis of a virus dynamics model with general incidence rate and cure rate. *Nonlinear Analysis: Real World Applications*, *13*(4), 1866–1872.

Heffernan, J.M, Smith, R.J and Wahl, L.M. (2005). Perspective on the basic reproduction ratio. *Journal of the Royal Society Interface*, 2(4), 281-293

Hirsch, R. C., Lavine, J. E., Chang, L. J., Varmus, H. E. and Ganem, D. (2000). Polymerase gene products of hepatitis B viruses are required for genomic RNA packaging as well as for reverse transcription. *Nature*, 344(2), 552-555.

Hochberg, M. E. (1991). Non-linear transmission rates and the dynamics of infectious disease. *Journal of Theoretical Biology*, 153(3), 301–321.

Hui, A. Y., Chan, H. L., Leung, N. W., Hung, L. C., Chan, F. K. and Sung, J. J. (2002). Survival and prognostic indicators in patients with hepatitis B virus-related cirrhosis after onset ofhepatic decompensation. *Journal of Clinical Gastroenterology*, 34(4), 569-572.

Hutton, D. W. and Brandeau, M. L. (2013). Too much of a good thing? When to stop catch-upvaccination. *Medical Decision Making*, 33(4), 920-936.

Hutton, D. W., So, S. K. and Brandeau, M. L. (2010). Cost-effectiveness of nationwide hepatitis Bcatch-up vaccination among children and adolescents in China. *Hepatology*, 51(1), 405-514.

Hyman, J.M., Li, J. (2000).An intuitive formulation for the reproductive number for the spread of diseases in heterogeneous populations. *Mathematical Biosciences.* 167(2), 65-86.

Ikobah, J., Okpara, H., Elemi, I., Ogarepe, Y., Udoh, E., and Ekanem, E. (2016). The prevalence of hepatitis B virus infection in Nigerian children prior to vaccine introduction into the national programme on immunization schedule. *Pan African Medical Journal*, 23(1), 1–9.

Kamyad, A. V., Akbari, R., Heydari, A. A., and Heydari, A. (2014). Mathematical modeling of transmission dynamics and optimal control of vaccination and treatment for hepatitis B virus. *Computational and Mathematical Methods in Medicine*, 5(1), 80–90.

Kau, A., Vermehren, J. and Sarrazin, C. (2018). Treatment predictors of a sustained virologic response in hepatitis B and C. *Journal of Hepatology*, 49(2), 634-651

Keeling M. J. and Rohani P. (2008) Modeling Infectious Diseases in Humans and Animals, Princeton University Press, Princeton,NJ, USA, 1-50

Khan, T., Ahmad, S., and Zaman, G. (2019). Modeling and qualitative analysis of a hepatitis B epidemic model. *Chaos*, *29*(10), 31-39

Khan, T., Zaman, G., and Ikhlaq Chohan, M. (2018). The transmission dynamic of different hepatitis B-infected individuals with the effect of hospitalization. *Journal of Biological Dynamics*, *12*(1), 611–631.

Kock, J. and Schlicht, H. J. (2013). Analysis of the earliest steps of hepadnavirus replication:genome repair after infectious entry into hepatocytes does not depend on viral polymerase activity. *Journal of Virology*, 67(10), 4867-4874.

LaSalle J.P.(1976).The Stability of Dynamical Systems, Regional Conference Series in Applied Mathematics, SIAM, Philadelphia, Pa,USA.7-8

Lau, G. K. , Cooksley, H., Ribeiro, R. M., Powers, K. A., Shudo, E., Bowden, S., Hui, C. K., Anderson, J., Sorbel, J., Mondou, E., Rousseau, F., Lewin, S., Perelson, A. S., Locarnini, S., and Naoumov, N. V. (2007). Impact of early viral kinetics on T-cell reactivity during antiviral therapy in chronic hepatitis B. *Antiviral Therapy*, *12*(5), 705–718.

Lavanchy, D. (2004). Hepatitis B virus epidemiology, disease burden, treatment, arid current and emerging prevention and control measures. *Journal of Viral Hepatitis*, *11*(2), 97–107.

Liang, P., Zu, J., Yin, J., Li, H., Gao, L., Cui, F., Wang, F., Liang, X., and Zhuang, G. (2015). The independent impact of newborn hepatitis B vaccination on reducing HBV prevalence in China, 1992-2006: A mathematical model analysis. *Journal of Theoretical Biology*, 386(2*)*, 115–121.

Lien, J. M., Aldrich, C. E. and Mason, W. S. (1986). Evidence that a capped oligoribonucleotide isthe primer for duck hepatitis B virus plus-strand DNA synthesis. *Journal of Virology*, 57(4), 229-236.

Lin, C. L. and Kao, J. H. (2013). Risk stratification for hepatitis B virus related hepatocellularcarcinoma. *Journal of Gastroenterology Hepatology*, 28(2), 10-17

Lin S.Y., Chang E.T., and So S.K. (2009). Stopping a silent killer in the underserved asian and pacific islander community: a chronic hepatitis B and liver cancer prevention clinic by medical students. *Asian Pacific Journal of Cancer Prevention*, 10(9), 383–386.

Lin, Y.-C., Chang, M.-H., Ni, Y.-H., Hsu, H.-Y. and Chen, D.-S. (2003). Long TermImmunogenicity and Efficacy of Universal Hepatitis B Virus Vaccination in Taiwan. *Journal of Infectious Diseases*, 187(7), 134-138.

Liu, J., Zhang, E., Ma, Z., Wu, W., Kosinska, A., Zhang, X., Moller, I., Seiz, P., Glebe, D.,Wang, B., Yang, D., Lu, M. and Roggendorf, M. (2014). Enhancing virus-specificimmunity in vivo by combining therapeutic vaccination and PD-L1 blockade in chronichepadnaviral infection. *PLOS Pathogens*, 10, e1003856.

Liu, S., Cipriano, L. E., Holodniy, M., Owens, D. K. & Goldhaber-Fiebert, J. D. (2012). Newprotease inhibitors for the treatment of chronic hepatitis C: a cost-effectiveness analysis. *Annals of Internal Medicine*, 156(8), 279-290.

Locarnini, S., Hatzakis, A., Chen, D. S. and Lok, A. (2018). Strategies to control hepatitis B:Public policy, epidemiology, vaccine and drugs. *Journal of Hepatology*, 62(1), S76-S86.

Loeb, D. D., Hirsch, R. C. and Ganem, D. (1991). Sequence-independent RNA cleavages generatethe primers for plus strand DNA synthesis in hepatitis B viruses: implications for otherreverse transcribing elements. *EMBO Journal*, 10(2), 3533-3540.

Long, C., Qi, H., and Huang, S. H. (2008). Mathematical modeling of cytotoxic lymphocyte-mediated immune response to hepatitis B virus infection. *Journal of Biomedicine and Biotechnology*, 14(2), 1-9.

Lok, A. S. and Mcmahon, B. J. (2004). [AASLD Practice Guidelines. Chronic hepatitis B: update of therapeutic guidelines]. *Roman Journal of Gastroenterology*, 13(2), 150-154.

Lok, A. S., Mcmahon, B. J., Brown, R. S., Jr., Wong, J. B., Ahmed, A. T., Farah, W.,Almasri, J., Alahdab, F., Benkhadra, K., Mouchli, M. A., Singh, S., Mohamed, E.A.,

Abu Dabrh, A. M., Prokop, L. J., Wang, Z., Murad, M. H. and Mohammed, K.(2016). Antiviral therapy for chronic hepatitis B viral infection in adults: A systematic review and meta-analysis. *Hepatology*, 13(5), 284-306.

Lok, A. S. F. and Mcmahon, B. J. (2007). Chronic hepatitis B. *Hepatology*, 45(3), 507-539.

Lungu, E.M., Kgosimore, M. and Nyabadza, F. (2007). Lecture notes mathematic; mathematical epidemiology, 12-45

Mann, J., and Roberts, M. (2011). Modelling the epidemiology of hepatitis B in New Zealand. *Journal of Theoretical Biology*, *269*(1), 266–272.

Marchuk, G. I., Petrov, R. V., Romanyukha, A. A., and Bocharov, G. A. (1991). Mathematical model of antiviral immune response. I. Data analysis, generalized picture construction and parameters evaluation for hepatitis B. *Journal of Theoretical Biology*, *151*(1), 1–40.

Mayoclinic (2021). Liver Disease https://www.mayoclinic.org/diseases-conditions/liver-problems/symptons-causes Available online January 2021.

McPherson S., Valappil M., Moses S.E., Eltringham G., Miller C., Baxter K., Chan A., Shafiq K., Saeed A., and Qureshi R. (2013). Targeted case finding for hepatitis B using dry blood spot testing in the British-Chinese and South Asian populations of the North-East of England. *Journal of Viral Hepatology*, 20(1), 638–644

Meffre C., Le Strat Y., Delarocque-Astagneau E., Dubois F., Antona D., Lemasson J.M., Warszawski J., Steinmetz J., Coste D., and Meyer J.F., (2010). Prevalence of hepatitis B and hepatitis C virus infections in France in 2004: social factors are important predictors after adjusting for known risk factors. *Journal of Medical Viro*logy ,82(2), 546–555.

Miller, R. H., Marion, P. L. and Robinson, W. S. (1994). Hepatitis B viral DNA-RNA hybridmolecules in particles from infected liver are converted to viral DNA molecules duringan endogenous DNA polymerase reaction. *Virology*, 139(3), 64-72.

Miyanohara, A., Imamura, T., Araki, M., Sugawara, K., Ohtomo, N. and Matsubara, K.(1986). Expression of hepatitis B virus core antigen gene in Saccharomyces cerevisiae: synthesis of two polypeptides translated from different initiation codons. *Journal of Virology*, 59(3), 176-80.

Mpeshe, S. C., and Nyerere, N. (2019). Modeling approach to assess the transmission dynamics of Hepatitis B infection in Africa. *International Journal of Advances in Applied Mathematics and Mechanics*,6(3), 51 – 61.

Nassal, M., Junker-Niepmann, M. and Schaller, H. (2000). Translational inactivation of RNA function: discrimination against a subset of genomic transcripts during HBV nucleocapsid assembly. *Cell*, 63(1), 1357-1363.

Niederau C. (2014). Chronic hepatitis B in 2014: great therapeutic progress, large diagnostic deficit. *World journal of gastroenterology*, 20(33), 11595–11617.

Okamoto, E. (2013). A mathematical model to predict the risk of hepatitis B infection through needle/syringe sharing in mass vaccination. *Infectious Diseases of Poverty*, *2*(1), 1–9.

Oke I.S., Ojo M. M., Adeniyi O. M., and Maba B. M. (2020). Mathematical modeling of malaria disease with control strategy; *Communications in Mathematical Biology and Neuroscience.*,43(1), 180-188.

Olayinka, A. T., Oyemakinde, A., Balogun, M. S., Ajudua, A., Nguku, P., Aderinola, M., Egwuenu-Oladejo, A., Ajisegiri, S. W., Sha'aibu, S., Musa, B. O. P., Gidado, S., and Nasidi, A. (2016). Seroprevalence of Hepatitis B infection in Nigeria: A national survey. *American Journal of Tropical Medicine and Hygiene*, *95*(4), 902–907.

Owolabi, K. M. (2016). Numerical solution of diffusive HBV model in a fractional medium. *SpringerPlus*, *5*(1), 16-43

Pan, C. Q., and Zhang, J. X. (2005). Natural history and clinical consequences of hepatitis B virus infection. *International Journal of Medical Sciences*, *2*(1), 36–40.

Pang, J., Cui, J. A., and Zhou, X. (2010). Dynamical behavior of a hepatitis B virus transmission model with vaccination. *Journal of Theoretical Biology*, *265*(4), 572–578.

Persing, D. H., Varmus, H. E. and Ganem, D. (2006). Inhibition of secretion of hepatitis B surfaceantigen by a related presurface polypeptide. *Science*, 234(2), 1388-1391.

Peto, T. J., Mendy, M. E., Lowe, Y., Webb, E. L., Whittle, H. C. and Hall, A. J. (2014). Efficacyand effectiveness of infant vaccination against chronic hepatitis B in the Gambia Hepatitis Intervention Study (1986-90) and in the nationwide immunisation program.*BMC Infectious Disease*, 14(2), 7-16

Piorkowsky N.Y (2009). Europe's hepatitis challenge: defusing the "viral time bomb" *Journal of Hepatology*, 51(1), 1068–1073.

Pollack, J. R. and Ganem, D. (2014). Site-specific RNA binding by a hepatitis B virus reversetranscriptase initiates two distinct reactions: RNA packaging and DNA synthesis. *Journal of Hepatology*, 68(2), 5579-5587.

Price, J. (2014). An update on hepatitis B, D, and E viruses. *Top Antiviral Medicine*, 21(4), 157-163.

Qesmi, R., Wu, J., Wu, J., and Heffernan, J. M. (2010). Influence of backward bifurcation in a model of hepatitis B and C viruses. *Mathematical Biosciences*, *224*(2), 118–125.

Qu, C., Chen, T., Fan, C., Zhan, Q., Wang, Y., Lu, J., Lu, L.-L., Ni, Z., Huang, F., Yao, H., Zhu,J., Fan, J., Zhu, Y., Wu, Z., Liu, G., Gao, W., Zang, M., Wang, D., Dai, M., Hsia, C. C.,Zhang, Y. and Sun, Z. (2014). Efficacy of Neonatal HBV Vaccination on Liver

Cancer andOther Liver Diseases over 30-Year Follow-up of the Qidong Hepatitis B InterventionStudy: A Cluster Randomized Controlled Trial. *PLoS Medicine*, 11, e1001774.

Reluga, T.C., Medlock, J. and Galvani, A.(2009). The discounted reproductive number for epidiemiology. *Journal of mathematical biosciences and engineerimg.* 6(2), 379-395

Richter C., Beest G.T., Sancak I., Aydinly R., Bulbul K., Laetemia-Tomata F., De Leeuw M., Waegemaekers T., Swanink C., and Roovers E. (2012). Hepatitis B prevalence in the Turkish population of Arnhem: implications for national screening policy? *Epidemiology and Infection*, 140(2), 724–730.

Rosenberg, S. (2001). Recent advances in the molecular biology of Hepatitis C virus. *Journal of Molecular Biology*, *313*(3), 451–464.

Rosmorduc, O., Sirma, H., Soussan, P., Gordien, E., Lebon, P., Horisberger, M.,Brechot, C. and Kremsdorf, D. (1999). Inhibition of interferon-inducible MxA protein expression by hepatitis B virus capsid protein. *Journal of General Virology*, 80 (5), 1253-1262.

Ross, R. (1911) The Prevention of Malaria. *John Murray*, London.1-100

Scagiloni P.P.,Melegari M. and Wands J.R. (2016). Recent advances in the molecular biology of hepatitis B virus. *Bailliere's clinical Gastroenterology*, 10(2), 19-29

Singer, G. A., Zielsdorf, S., Fleetwood, V. A., Alvey, N., Cohen, E., Eswaran, S., Shah,N., Chan, E. Y., Hertl, M. and Fayek, S. A. (2015). Limited hepatitis B immunoglobulin with potent nucleos(t)ide analogue is a cost-effective prophylaxis against hepatitis B virus after liver transplantation. *Transplantation Proceedings*, 47(4), 478-484.

Standring, D. N., Ou, J. H. and Rutter, W. J. (2006). Assembly of viral particles in Xenopusoocytes: pre-surface-antigens regulate secretion of the hepatitis B viral surfaceenvelope particle. *Proceedings of the National Academy of Sciences of the United States of America*, 83(5), 9338-9342.

Staprans, S., Loeb, D. D. and Ganem, D. (1991). Mutations affecting hepadnavirus plus-strandDNA synthesis dissociate primer cleavage from translocation and reveal the origin oflinear viral DNA. *Journal of Virology*, 65(1), 1255-1262.

Summers, J. and Mason, W. S. (1992). Replication of the genome of a hepatitis B--like virus byreverse transcription of an RNA intermediate. *Cell*, 29(2), 403-415.

Tavis, J. E. and Ganem, D. (2013). Expression of functional hepatitis B virus polymerase in yeast reveals it to be the sole viral protein required for correct initiation of reverse transcription. *Proceedings of the National Academy of Sciences of the United States of America*, 90(6), 4107-4111.

Tavis, J. E., Perri, S. and Ganem, D. (2014). Hepadnavirus reverse transcription initiates withinthe stem-loop of the RNA packaging signal and employs a novel strand transfer. *Journal of Virology*, 68(3), 3536-3543.

Tseng, T. C., Liu, C. J., Chen, C. L., Yang, H. C., Su, T. H., Wang, C. C., Yang, W. T., Kuo, S. F.,Liu, C. H., Chen, P. J., Chen, D. S. and Kao, J. H. (2013). Risk stratification of hepatocellular carcinoma in hepatitis B virus e antigen-negative carriers by combiningviral biomarkers. *Journal of Infectious Diseases*, 208(3), 584-593.

Tseng, T. C., Liu, C. J., Yang, H. C., Su, T. H., Wang, C. C., Chen, C. L., Kuo, S. F., Liu, C. H.,Chen, P. J., Chen, D. S. and Kao, J. H. (2012). High levels of hepatitis B surface antigenincrease risk of hepatocellular carcinoma in patients with low HBV load. *Gastroenterology*, 142(2), 1140-1149.

Thornley, S., Bullen, C., and Roberts, M. (2008). Hepatitis B in a high prevalence New Zealand population: A mathematical model applied to infection control policy. *Journal of Theoretical Biology*, *254*(3), 599–603.

Thimme, R. and Dandri, M. (2013). Dissecting the divergent effects of interferon-alpha onimmune cells: time to rethink combination therapy in chronic hepatitis B? *Journal of Hepatology*, 58(4), 205-209.

Ullah, S., Khan, M. A., and Gómez-Aguilar, J. F. (2019). Mathematical formulation of hepatitis B virus with optimal control analysis. *Optimal Control Applications and Methods*, *40*(3), 529–544.

Wang, K., Fan, A., and Torres, A. (2010). Global properties of an improved hepatitis B virus model. *Nonlinear Analysis: Real World Applications*, *11*(4), 3131–3138.

Wang, G. H. and Seeger, C. (1992). The reverse transcriptase of hepatitis B virus acts as a protein primer for viral DNA synthesis. *Cell*, 71(1), 663-670.

Wang, G. H. and Seeger, C. (1993). Novel mechanism for reverse transcription in hepatitis Bviruses. *Journal of Virology*, 67(2), 6507-6512.

Wang, K., and Wang, W. (2007). Propagation of HBV with spatial dependence. *Mathematical Biosciences*, *210*(1), 78–95.

Wiggins, S. (1990). An introduction to applied nonlinear dynamical syatems and chaos. Springer- Verlag, Berlin

Williams, J. R., Nokes, D. J., Medley, G. F., and Anderson, R. M. (1996). The transmission dynamics of hepatitis B in the UK: A mathematical model for evaluating costs and effectiveness of immunization programmes. *Epidemiology and Infection*, *116*(1), 71–89.

Wilson, J. N., Nokes, D. J., and Carman, W. F. (1998). Current status of HBV vaccine escape variants - A mathematical model of their epidemiology. *Journal of Viral Hepatitis*, *5*(2), 25–30.

World Health Organization. (2019). Hepatitis B [Online]. Available:http://www.who.int/csr/disease/hepatitis/whocdscsrncs112/en/.

World Health Organization. (2020). Hepatitis B [Online]. Available:http://www.who.int/csr/disease/hepatitis/whocdscsrncs211/en/.

Wu, C. and Dunn, W. (2015). Is it worthy of switching to PegIFN alfa-2a in patients achievingvirological suppression with entecavir? *Journal of Hepatology*, 62(3), 1439-1440.

Wu, B., Li, T., Chen, H. and Shen, J. (2010). Cost-Effectiveness of Nucleoside Analog Therapy for Hepatitis B in China: A Markov Analysis. *Value in Health*, 13(1), 592-600.

Wursthorn, K., Lutgehetmann, M., Dandri, M., Volz, T., Buggisch, P., Zollner, B.,Longerich, T., Schirmacher, P., Metzler, F., Zankel, M., Fischer, C., Currie, G.,Brosgart, C. and Petersen, J. (2016). Peginterferon alpha-2b plus adefovir induce strong cccDNA decline and HBsAg reduction in patients with chronic hepatitis B.*Hepatology*, 44(5), 675-684.

Xu, R., and Ma, Z. (2009). An HBV model with diffusion and time delay. *Journal of Theoretical Biology*, *257*(3), 499–509.

Yuen, M. F., Tanaka, Y., Ng, I. O., Mizokami, M., Yuen, J. C., Wong, D. K., Yuan, H. J., Sum, S. M., Chan, A. O. and Lai, C. L. (2005). Hepatic necroinflammation and fibrosis in patients with genotypes Ba and C, core-promoter and precore mutations. *Journal of Viral Hepatology*, 12(2), 513-518.

Zhang, J., and Zhang, S. (2018). Application and Optimal Control for an HBV Model with Vaccination and Treatment. *Discrete Dynamics in Nature and Society*,20(7), 69-73.

Zhang, S., and Zhou, Y. (2012). The analysis and application of an HBV model. *Applied Mathematical Modelling*, *36*(3), 1302–1312.

Zhao, S., Xu, Z., and Lu, Y. (2000). A mathematical model of hepatitis B virus transmission and its application for vaccination strategy in China. *International Journal of Epidemiology*, *29*(4), 744–752.

Zada, I., Naeem Jan, M., Ali, N. (2021). Mathematical analysis of hepatitis B epidemic model with optimal control. *Advance Difference Equations*, 36(62), 451-480.

Zou, L., Zhang, W., and Ruan, S. (2010). Modeling the transmission dynamics and control of hepatitis B virus in China. *Journal of Theoretical Biology*, *262*(2), 330–338.

Λvert, (2021). Hepatitis B symptoms and treatment. http://www.avert.org/sex-stis-sexually-transmitted-infections/hepatitis-b, available online May, 2021.

APPENDICES

APPENDIX I: ALGORITHM FOR HBV OPTIMAL CONTROL CASE 1

```
function HBV_CONTROL


% the model parameter values %%%%%%%%%%%%%%%%%%


global beta sigma a_2  q gamma_1 a_1 omega  upsilon b gamma_2 mu_0 mu_1
mu_2 vartheta_1  vartheta_2 vartheta_3 ...

        x0 tempControl_u1 tempControl_u2 delta_1 r gamma_3 phi G4 G5
...


    format long

%%%%%%%%%%%%%%

    beta   = 0.095;

   sigma   = 0.016;

   a_2 = 0.16;

   q = 0.885;

   gamma_1 = 0.01095;

   a_1 = 0.0252;

  omega = 0.6496;

   upsilon = 0.2994;

   b = 0.02;

   gamma_2 = 0.0684;

   mu_0 = 0.00693;

   mu_1 = 0.002;
```

```
    mu_2=0.002;
    vartheta_2=0.590;
    vartheta_1=0.36;
    vartheta_3=0.34;
    delta_1=0.95;
    r=0.02;
    gamma_3=0.5;
    phi = 0.1;
    G4=1;
    G5=1;
    delta_1=0.95;
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
    dt =  0.1; tf =90; 150;  3.0;  365;   51; 2122;
    tvec = 0 : dt : tf;
    tfvec = tf : -dt : 0;
    del = 0.0001;

    M = length(tvec);

    x = zeros(M,7);
    lambda = zeros(M,7);
    u=zeros(M,2);
    maxu = [1 1];

%initial values
    S = 100;
```

```
    L= 90;
    A=80;
    C=60;
    T=60;
    R=50;
    V=40;
     x0 = [S L A C T R V];
     lambda0 = [0 0 0 0 0 0 0];

%%%% Without Control
solx = ode45(@(t,x) Xde(t,x,u,tvec),tvec,x0,[]);
xout = deval(solx,tvec)';

    test = -1;
    count = 0;

while((test < 0)&&(count<500))

   oldtx = x;
   oldLambda = lambda;
   oldtu = u;
    solx = ode45(@(t,x) Xde(t,x,u,tvec),tvec,x0);
    x = deval(solx,tvec)';%

    tx=x;
    tu=u;
```

```
    sollamb = ode45(@(t,lambda) Lde(t,lambda,tvec,x,u),tfvec,lambda0);


 lambda = deval(sollamb,tvec)';


        u1 = u(:,1);

        u2 = u(:,2);


    oldu1=u1;

        oldu2=u2;
% declaration of state variable in vector


        S = x(:,1);

        L = x(:,2);

        A = x(:,3);

        C = x(:,4);

        T = x(:,5);

        R = x(:,6);

        V = x(:,7);


        lambda1 = lambda(:,1);

        lambda2 = lambda(:,2);

        lambda3 = lambda(:,3);

        lambda4 = lambda(:,4);

        lambda5 = lambda(:,5);

        lambda6 = lambda(:,6);

        lambda7 = lambda(:,7);
```

```
% %  %   UPDATE CONTROL

          tempControl_u1 = A.*(lambda3-lambda5)/(2*G4);

          Controltemp_u1 = min(maxu(1),max(0, tempControl_u1 ));

        u1 = 0.5*(Controltemp_u1 + oldu1);


       tempControl_u2 = C.*(lambda4-lambda5)/(2*G5);

         Controltemp_u2 = min(maxu(2),max(0, tempControl_u2));

        u2 = 0.5*(Controltemp_u2 + oldu2);




global beta sigma a_2 q gamma_1 a_1 omega  upsilon b gamma_2 mu_0 mu_1
mu_2 vartheta_1  vartheta_2 vartheta_3 ...

         delta_1 r gamma_3 phi G_4 G_5 ...

% Defined parameters for easy computation

dS = a_1*omega*(1-upsilon*C)+phi*V-
(beta*A+a_2*beta*C+gamma_3+mu_0+delta_1)*S-r*A-b*C;

dL = (beta*A+a_2*beta*C)*S-(sigma+mu_0+delta_1)*L;

dA = sigma*L-(u1+gamma_1+mu_0+delta_1-r)*A;

dC = q*gamma_1*A-(-a_1*omega*upsilon-b+gamma_2+mu_0+mu_1+u2)*C;

dT = u2*C+u1*A-(vartheta_3+mu_0+mu_2)*T;

dR = gamma_2*C+(1-q)*gamma_1*A+vartheta_3*T-mu_0*R;

dV = a_1*(1-omega)+gamma_3*S-(phi+mu_0)*V;



Xprime = [dS;dL;dA;dC;dT;dR;dV];
```

```
function Lprime = Lde(t,lambda,tvec,tx,tu)


tspan = tvec;



    u1=tu(:,1);

    u2=tu(:,2);


    tx=interp1(tspan,tx,t);

    u1=pchip(tspan,u1,t);

    u2=pchip(tspan,u2,t);

    S = max(0,tx(1));

    L = max(0,tx(2));

    A = max(0,tx(3));

    C = max(0,tx(4));

    T = max(0,tx(5));

    R = max(0,tx(6));

    V = max(0,tx(7));


    lambda1=lambda(1);

    lambda2=lambda(2);

    lambda3=lambda(3);

    lambda4=lambda(4);

    lambda5=lambda(5);

    lambda6=lambda(6);

    lambda7=lambda(7);
```

```
global beta sigma a_2 q gamma_1 a_1 omega  upsilon b gamma_2 mu_0 mu_1
mu_2 vartheta_1  vartheta_2 vartheta_3 ...

         delta_1 r gamma_3 phi ...



dlambda1 = -lambda1*(-beta*A-a_2*beta*C-gamma_3-mu_0-delta_1)-
lambda2*(beta*A+a_2*beta*C)-lambda7*gamma_3;



dlambda2 = -1-lambda2*(-sigma-beta-mu_0-delta_1)-lambda3*sigma;



dlambda3 =  -1-lambda1*(-beta*S-r)-lambda2*beta*S-lambda3*(-u1-gamma_1-
mu_0-delta_1+r)-lambda4*q*gamma_1-lambda5*u1-lambda6*(1-q)*gamma_1;



dlambda4 = -1-lambda1*(-a_1*omega*upsilon-b-a_2*beta*S)-
lambda2*(a_2*beta*S)-lambda4*(a_1*omega*upsilon+b-gamma_2-mu_0-mu_1-
u2)-lambda5*u2-lambda6*gamma_2;



dlambda5 =  -lambda5*(-vartheta_3-mu_0-mu_2)-lambda6*vartheta_3;



dlambda6 = -lambda6*(-mu_0);



dlambda7 = -lambda1*phi-lambda7*(-phi-mu_0);



 Lprime =
[dlambda1;dlambda2;dlambda3;dlambda4;dlambda5;dlambda6;dlambda7];
```

APPENDIX II: ALGORITHM FOR HBV OPTIMAL CONTROL CASE 2

```
function HBV_CONTROL


% the model parameter values %%%%%%%%%%%%%%%%%%


global zeta beta alpha gamma eta omega  upsilon xi mu_0 mu_1 rho k ...

        x0 tempControl_u1 tempControl_u2 epsilon  G4 G3 ...


    format long

%%%%%%%%%%%%%
  beta   = 0.002;

  zeta = 0.693;

  alpha = 0.65;

  gamma = 0.11;

  xi = 0.1096;

  eta = 0.25;

  omega = 0.06496;

  upsilon = 0.2995;

   epsilon = 0.2323;

   mu_0 = 0.0095;

   mu_1 = 0.002;

   k = 0.36;

   rho = 0.4;
```

```
   G3=1;
   G4=1;

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%%%%%%%%%%%%%

    dt =  0.1; tf =50;
    tvec = 0 : dt : tf;
    tfvec = tf : -dt : 0;
    del = 0.0001;

    M = length(tvec);

    x = zeros(M,5);
    lambda = zeros(M,5);
    u=zeros(M,2);
    maxu = [1 1];

%initial values

    S = 1;
    A=100;
    C=10;
    T=1;
```

```
    R=1;


     x0 = [S A C T R];
     lambda0 = [0 0 0 0 0];


%%%% Without Control
solx = ode45(@(t,x) Xde(t,x,u,tvec),tvec,x0,[]);
xout = deval(solx,tvec)';


    test = -1;
    count = 0;


while((test < 0)&&(count<500))


   oldtx = x;
   oldLambda = lambda;
   oldtu = u;




    solx = ode45(@(t,x) Xde(t,x,u,tvec),tvec,x0);
    x = deval(solx,tvec)';%


    tx=x;
    tu=u;
```

```
    sollamb = ode45(@(t,lambda) Lde(t,lambda,tvec,x,u),tfvec,lambda0);


 lambda = deval(sollamb,tvec)';


        u1 = u(:,1);

        u2 = u(:,2);

        oldu1=u1;

        oldu2=u2;


% declaration of state variable in vector


        S = x(:,1);

        A = x(:,2);

        C = x(:,3);

        T = x(:,4);

        R = x(:,5);


        lambda1 = lambda(:,1);

        lambda2 = lambda(:,2);

        lambda3 = lambda(:,3);

        lambda4 = lambda(:,4);

        lambda5 = lambda(:,5);


% %  %   UPDATE CONTROL
```

```
          tempControl_u1 = A.*(lambda2-lambda4)/(2*G3);
          Controltemp_u1 = min(maxu(1),max(0, tempControl_u1 ));
         u1 = 0.5*(Controltemp_u1 + oldu1);

        tempControl_u2 = C.*(lambda3-lambda4)/(2*G4);
         Controltemp_u2 = min(maxu(2),max(0, tempControl_u2));
         u2 = 0.5*(Controltemp_u2 + oldu2);

         tu(:,1) = u1;
         tu(:,2) = u2;
% For control profile
         temp1 = del*sum(abs(tu),2) - sum(abs(oldtu - tu),2);
         temp2 = del*sum(abs(tx),2) - sum(abs(oldtx - tx),2);

          test = min(min(min(temp1),min(temp2)));


         x = tx;
         u = tu;

         count = count + 1;
end
=================================================================
S = x(:,1);
```

```
 A = x(:,2);

 C = x(:,3);

 T = x(:,4);

 R = x(:,5);


Su = xout(:,1);

Au = xout(:,2);

Cu = xout(:,3);

Tu = xout(:,4);

Ru = xout(:,5);


 u1 = u(:,1);

 u2 = u(:,2);


function Xprime = Xde(t,tx,tu,tvec)

tspan=tvec;


    u1=tu(:,1);

    u2=tu(:,2);

    u1=pchip(tspan,u1,t);

    u2=pchip(tspan,u2,t);

    S = max(0,tx(1));

    A = max(0,tx(2));

    C = max(0,tx(3));
```

```
    T = max(0,tx(4));

    R = max(0,tx(5));



global zeta beta alpha gamma eta omega  upsilon xi mu_0  rho k epsilon
...


% Defined parameters for easy computation


dS = zeta*(1-alpha)*(1-gamma*C)-(beta*A+xi*beta*C)*S+(1-eta)*omega*A-
mu_0*S+(1-k)*upsilon*rho*T+epsilon*R;

dA = (beta*A+xi*beta*C)*S-(omega+mu_0+u1)*A;

dC = eta*omega*A+zeta*(1-alpha)*gamma*C+(1-upsilon)*rho*T-(mu_0+u2)*C;

dT = u2*C+u1*A-(rho+mu_0)*T;

dR = zeta*alpha+k*upsilon*rho*T-(mu_0+epsilon);



Xprime = [dS;dA;dC;dT;dR];



function Lprime = Lde(t,lambda,tvec,tx,tu)


tspan = tvec;
```

```
    u1=tu(:,1);
    u2=tu(:,2);
%     u3=tu(:,3);



    tx=interp1(tspan,tx,t);
    u1=pchip(tspan,u1,t);
    u2=pchip(tspan,u2,t);
%     u3=pchip(tspan,u3,t);


    S = max(0,tx(1));
    A = max(0,tx(2));
    C = max(0,tx(3));
    T = max(0,tx(4));
    R = max(0,tx(5));


    lambda1=lambda(1);
    lambda2=lambda(2);
    lambda3=lambda(3);
    lambda4=lambda(4);
    lambda5=lambda(5);
% display('============================== Start Adjoint Equation
==============================================================')
```

```
global zeta beta alpha gamma eta omega  upsilon xi mu_0  rho k epsilon
...


dlambda1 = -lambda1*(beta*A+xi*beta*C-mu_0)-lambda2*(beta*A+xi*beta*C);


dlambda2 = -1-lambda1*(beta*S+(1-eta)*omega)-lambda2*(beta*S-omega-
mu_0-u1)-lambda3*(eta*omega)-lambda4*u1;


dlambda3 =  -1-lambda1*(zeta*alpha*gamma-xi*beta*S)-lambda2*xi*beta*S-
lambda3*(zeta*(1-alpha)*gamma-u2-mu_0)-lambda4*u2;


dlambda4 = -lambda1*((1-k)*upsilon*rho)-lambda3*((1-upsilon)*rho)-
lambda4*(-rho-mu_0)-lambda5*(k*upsilon*rho);


dlambda5 =  -lambda1*epsilon-lambda5*(-mu_0-epsilon);


 Lprime = [dlambda1;dlambda2;dlambda3;dlambda4;dlambda5];
```

APPENDIX III: ALGORITHM FOR HBV OPTIMAL CONTROL CASE 3

```
global pie beta alpha_1 alpha_2 sigma  gamma mu d_c upsilon_1 upsilon_2
omega  ...

        x0 tempControl_u1 tempControl_u2 tempControl_u3 G4 G5 G6 ...

    format long

%%%%%%%%%%%%%

pie = 0.07

   beta   = 0.008;

   sigma   = 0.67;

   alpha_1 = 0.0016;

   alpha_2 = 0.0016;

   gamma = 0.9;

   d_c = 0.00693;

  omega = 0.1;

   upsilon_1 = 0.2;

   upsilon_2 = 0.02;

   mu = 0.00693;

    G4=1;

    G5=1;

   G6=1;



%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
dt =  0.1; tf =90; 150;  3.0;  365;   51; 2122;

    tvec = 0 : dt : tf;

    tfvec = tf : -dt : 0;

    del = 0.0001;
```

```
    M = length(tvec);


    x = zeros(M,6);
    lambda = zeros(M,6);
    u=zeros(M,3);
    maxu = [1 1];


%initial values
    S = 100;
    A= 90;
    C=80;
    D=80;
    T=60;
    R=50;
 x0 = [S A C D T R];
 lambda0 = [0 0 0 0 0 0];


%%%% Without Control
solx = ode45(@(t,x) Xde(t,x,u,tvec),tvec,x0,[]);
xout = deval(solx,tvec)';


    test = -1;
    count = 0;


while((test < 0)&&(count<500))
```

```
   oldtx = x;
   oldLambda = lambda;
   oldtu = u;



    solx = ode45(@(t,x) Xde(t,x,u,tvec),tvec,x0);
    x = deval(solx,tvec)';%


    tx=x;
    tu=u;
    sollamb = ode45(@(t,lambda) Lde(t,lambda,tvec,x,u),tfvec,lambda0);


 lambda = deval(sollamb,tvec)';


        u1 = u(:,1);
        u2 = u(:,2);
        u3 = u(:,3);
        oldu1=u1;
        oldu2=u2;
        oldu3=u3;


% declaration of state variable in vector


        S = x(:,1);
```

```
A = x(:,2);

C = x(:,3);

D = x(:,4);

T = x(:,5);

R = x(:,6);



lambda1 = lambda(:,1);

lambda2 = lambda(:,2);

lambda3 = lambda(:,3);

lambda4 = lambda(:,4);

lambda5 = lambda(:,5);

lambda6 = lambda(:,6);



% %  %   UPDATE CONTROL

  tempControl_u1 = A.*(lambda2)/(2*G4);

  Controltemp_u1 = min(maxu(1),max(0, tempControl_u1 ));

u1 = 0.5*(Controltemp_u1 + oldu1);


tempControl_u2 = C.*(lambda3)/(2*G5);

 Controltemp_u2 = min(maxu(2),max(0, tempControl_u2));

u2 = 0.5*(Controltemp_u2 + oldu2);

tempControl_u3 =  D.*(lambda4-lambda5)/(2*G6);

Controltemp_u3 = min(maxu(3),max(0, tempControl_u3));
```

```
        u3 = 0.5*(Controltemp_u3 + oldu3);
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
        tu(:,1) = u1;
        tu(:,2) = u2;
        tu(:,3) = u3;

% For control profile
        temp1 = del*sum(abs(tu),2) - sum(abs(oldtu - tu),2);
        temp2 = del*sum(abs(tx),2) - sum(abs(oldtx - tx),2);
        temp3 = del*sum(abs(lambda),2) - sum(abs(oldLambda -
lambda),2);
         test = min(min(min(temp1),min(temp2),min(temp3)));
        x = tx;
        u = tu;

        count = count + 1;
end

t=tvec; %tspan ;

print(t,xout,x,u);

x(end,:);

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
global  beta alpha_1 alpha_2 sigma  gamma mu d_c upsilon_1 upsilon_2
omega  ...
```

```
dlambda1 = -lambda1*((beta*A+alpha_1*C+alpha_2*D)*S/(S+A+C+D+T+R)^2-
(beta*A+alpha_1*C+alpha_2*D)/(S+A+C+D+T+R)-mu)-lambda2*(-
(beta*A+alpha_1*C+alpha_2*D)*S/(S+A+C+D+T+R)^2+(beta*A+alpha_1*C+alpha_
2*D)/(S+A+C+D+T+R));



dlambda2 = -1-lambda1*(-
beta*S/(S+A+C+D+T+R)+(beta*A+alpha_1*C+alpha_2*D)*S/(S+A+C+D+T+R)^2+sig
ma)-lambda2*(beta*S/(S+A+C+D+T+R)-
(beta*A+alpha_1*C+alpha_2*D)*S/(S+A+C+D+T+R)^2-sigma-gamma-u1)-
lambda3*gamma-lambda4*upsilon_1;



dlambda3 =  -1-lambda1*(-
beta*alpha_1*S/(S+A+C+D+T+R)+(beta*A+alpha_1*C+alpha_2*D)*S/(S+A+C+D+T+
R)^2)-lambda2*(beta*alpha_1*S/(S+A+C+D+T+R)-
(beta*A+alpha_1*C+alpha_2*D)*S/(S+A+C+D+T+R)^2)-lambda3*(-d_c-mu-u2)-
lambda4*upsilon_2;



dlambda4 = -1-lambda1*(-
beta*alpha_2*S/(S+A+C+D+T+R)+(beta*A+alpha_1*C+alpha_2*D)*S/(S+A+C+D+T+
R)^2)-lambda2*(beta*alpha_2*S/(S+A+C+D+T+R)-
(beta*A+alpha_1*C+alpha_2*D)*S/(S+A+C+D+T+R)^2)-lambda4*(-d_c-mu-u3)-
lambda5*u3;



dlambda5 =  -
lambda1*(beta*A+alpha_1*C+alpha_2*D)*S/(S+A+C+D+T+R)^2+lambda2*(beta*A+
alpha_1*C+alpha_2*D)*S/(S+A+C+D+T+R)^2-lambda5*(-omega-mu)-
lambda6*omega;



dlambda6 = -
lambda1*(beta*A+alpha_1*C+alpha_2*D)*S/(S+A+C+D+T+R)^2+lambda2*(beta*A+
alpha_1*C+alpha_2*D)*S/(S+A+C+D+T+R)^2+lambda6*mu;

Lprime = [dlambda1;dlambda2;dlambda3;dlambda4;dlambda5;dlambda6];
```