The Transmission Dynamics and Optimal Control of Hepatitis B in Ethiopia Using SVEIRS Model

by

Hindia Nurhasen

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Figure 1: Infectious Disease and Hepatitis B

Abstract

An epidemic model is a simplified means of describing the transmission of communicable disease through individuals. In this paper the mathematics behind the model and the various tools for judging effectiveness of policies and control methods on the spread of infectious diseases in populations has been analyzed mathematically. And it has been applied to specific diseases to study the propagation of diseases using the mathematical epidemic model.
Epidemic models are many types form that select SVEIRS model and discussed the dynamics and control of infectious diseases, but quantifying the underlying epidemic structure can be challenging especially for new and understudied diseases. SVEIRS model is that generalizes several classical deterministic epidemic models then apply it for Hepatitis B. Consider compartments of susceptible, vaccination, exposed, infected, and recovered humans without immunity and modeled the natural growth, natural death and death due to disease and the interactions between these populations.
The model has two equilibrium states namely, the disease - free and the endemic equilibrium points. The stability of each equilibrium point discussed has been found to be stable or unstable. The basic reproduction number(R_0) estimate the stability, with $(R_0 > 1)$ whenever the transmission rate was increased or the recovery rate reduced but turned to the disease die out with $(R_0 < 1)$ whenever the transmission rate was reduced or the recovery rate increased.
The results of our sensitivity analysis showed that the most sensitive parameter that controls the spread of Hepatitis B is the initial infection rate of the susceptible, β and d or death rate. Decreasing the value of β at the same rate as the other parameter values completely decreases the proportions of both the infective and the exposed more effectively than any parameter value.
Consider an optimal control problem subject to an SVEIRS Hepatitis B epidemic model with vaccination controls. Our aim is to find the best optimal control strategies to make the number of infectious individuals as small as possible and to keep the vaccination ratio of Hepatitis B as low as possible during a certain vaccination period that will minimize the cost of control. Pontryagin's maximum principle to characterize the optimal levels of the controls. The resulting optimality system is solved numerically by forward-backward sweep method. The results show that the optimal vaccination, drug and education using media differs according to the controlled and uncontrolled individuals and has a very desirable effect upon the population for reducing the number of infected individuals. The effect of vaccination on transmission dynamics of Hepatitis B is studied. The resulting optimality system also showed that, the use of vaccinating at the highest possible rate to the population as early as possible is essential for controlling an epidemic of the Hepatitis B disease. Finally model to simulate the data of Hepatitis B cases in the Ethiopia from 2015 and design a control strategy of the country to eliminate the epidemic for the future course with optimal control theory.

Keywords: SVEIRS-Model; mathematical models; vital dynamics; vaccinations; HB, HBV, Herd Immunity; epidemiology number, optimal control.

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Chapter One

1 General Introduction

Mathematical models used for the spread of infectious disease are called dynamic epidemiological models because they describe change over time [1]. Epidemiology is essentially a population biology discipline concerned with public health. As such, epidemiology is thus heavily influenced by mathematical theory. Infectious disease influences the dynamics of host populations and the structure of species communities via impacts on host demography.

One of the primary aims of epidemic modeling is helping to understand the spread of diseases in host populations, both in time and space. Indeed, the processes of systematically clarifying inherent model assumptions, interpreting its variables, and estimating parameters are invaluable in uncovering precisely the mechanisms giving rise to the observed patterns.

Many types of infectious agents exist, all of which have their own unique set of behaviors. Categorize infectious agents as one of the following: viral pathogens, bacterial pathogens, or parasitoids. Examples of such are HPV,E. Coli, Malaria, AIDS, Typhus Scabies, SARS, Cholera, Mumps, Hepatitis , Tetanus, Measles, Syphilis, Common Cold Salmonellosis, Yellow fever, Lyme Disease, Small Pox, Meningitis, Rubella Typhoid and Ebola.

The hepatitis viruses comprise a group of five unrelated, often unusual pathogens, designated hepatitis A through E, grouped according to the disease they cause rather than their virological properties [2].

Hepatitis B (HB) is an infectious disease caused by hepatitis B virus (HBV) which infects the liver of hominoids, including humans and causes an inflammation called hepatitis. Originally known as ”serum hepatitis”, the disease has caused epidemics in parts of Asia and Africa, and it is endemic in China. About a third of the world’s population, more than 2 billion people have been infected with the hepatitis B virus. This includes about 350 million chronic carriers of the virus .

The disease lasts for a few weeks and then gradually improves in most affected

people. A few patients may have more severe liver disease (fulminant hepatic failure), and may die as a result of it. Chronic infection with hepatitis B may be either asymptotic or may be associated with a chronic inflammation of the liver (Chronic hepatitis), leading to cirrhosis over a period of several years. This type of infection dramatically increases the incidence of hepatocellular carcinoma (liver cancer). Chronic carriers are encouraged to avoid consuming alcohol as it increases their risk for cirrhosis and liver cancer. The number of new infections per year has declined from an average of 260,000 in the 1980s to about 60,000 in 2004, with the highest rate of disease occurring in 20-49 year olds. The greatest decline has happened among children and adolescents due to routine hepatitis B vaccination [3].

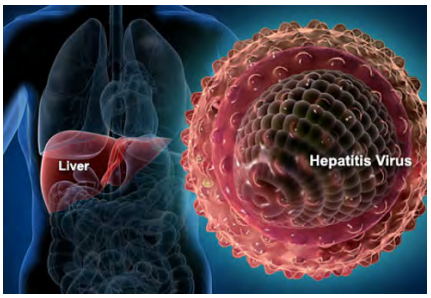


Figure 2: Liver with hepatitis virus(Source:hepatitis-s1-liver-hepatitis-virus)

1.1 Introduction To Epidomology of HBV

Disease modeling has been a tool that has led governments, public health organizations and societies out of spiritual mysticism with regards to causes and transmission of infectious diseases [4].

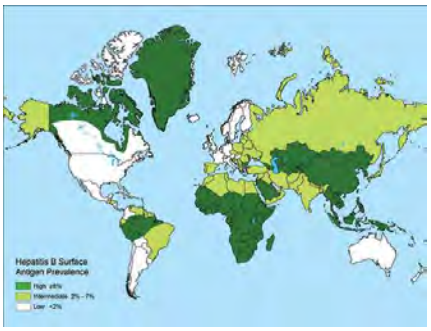


Figure 3: Prevalence of HBV. Source: http://www.library.northwestern.edu/govinfo/news/090519.jpg (accessed 9 December 2009)

Concerning hepatitis B disease, several contributions from mathematical models with deep revelations on transmission dynamics and control intervention decision making have been made.

Optimal control models have been used extensively in identifying the therapeutic strategies that could be used to eradicate or minimize the disease at a minimal cost, investigated an optimal control problem for a delay differential equation model of immune responses to hepatitis virus B infection. The model used direct approach and Pontryagin's maximum principle to solve a hepatitis B virus dynamics optimal control problem, developed a mathematical model of a chronic treatable infectious disease and used it to assess the cost and effectiveness of different levels of screening and contact tracing [5].

1.2 Background of the study

Modern mathematical biology begins with Hamer. He in 1906 first applied the Simple Mass Action Principle 1 for a deterministic epidemic model in discrete time The Law of Mass Action has applicability in many areas of science. Ross's Simple Epidemic Model was published in 1911 and Generalised Epidemic Model produced by Kermack and McKendrick in 1927 [6].

Infectious diseases are also known as transmissible diseases or communicable diseases. The illness of infectious diseases is caused by the infection, presence, and growth of pathogenic biological agents (known as pathogens) in an individual host organism. Pathogen is the microorganism (or microbe) that causes illness. Infectious pathogens include viruses, bacteria, fungi, protozoa, multicellular parasites, and aberrant proteins known as prions.

An infectious disease is termed contagious if it is easily transmitted from one person to another. The transmission mechanisms of infectious diseases can be categorized as contact transmission, vehicle transmission, and vector transmission. Contact transmission can occur by direct contact (person-to-person) between the source of the disease and a susceptible host, indirect contact through inanimate objects (such as contaminated soils), or droplet contact via mucus droplets in coughing, sneezing, laughing or talking. Vehicle transmission involves a media. Based on the

media type in transmission, the infectious diseases can be categorized as airborne (diseases transmitted through the air such as influenza, anthrax, measles), foodborne (diseases transmitted through the foods such as Hepatitis A and E), and waterborne (diseases transmitted through the water such as Cholera) [7].

Hepatitis B is contracted through the blood, semen, vaginal fluids, and other body fluids of an infected individual having hepatitis B infection. Individuals at risk are intravenous drug users, children of mothers with HBV, men who have sex with men, patients on hemodialysis and those exposed to blood or blood products. Unfortunately, once inflicted, these infections show poor response to the available treatment modalities. It is the most important precautionary measure of HBV as a vaccinated individual may never contract the infection [8].

Mathematical models have become invaluable management tools for epidemiologists, both shedding light on the mechanisms underlying observed dynamics as well as making quantitative predictions on the effectiveness of different control measures. Safe and effective vaccines have been available to prevent hepatitis B virus (HBV) infection since 1981, and the cost effectiveness of hepatitis B vaccination has been well documented.

Hepatitis B mathematical models have been developed, most focus on models of disease burden in a single country or economic evaluations of hepatitis B vaccination. To define the disease burden associated with HBV infection, we developed a mathematical model to estimate HBV related morbidity and mortality. This model can be used to estimate country hepatitis B disease burden and potential reduction in disease burden with different hepatitis B vaccination strategies [9] .

1.3 Hepatitis B

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

HBV is one of the five types of hepatitis and can cause both acute and chronic diseases.HBV is spread by direct contact with blood or other body fluids of infected

people. Since the disease is not easily spread. Persons with HBV do not pass the virus to others through casual contact, such as shaking hands or work space or bathroom facility. HBV is most commonly transmitted by sharing drug needles, by engaging in high risk sexual behavior (espesially anal sex) from a mother to her baby during childbirth and in the healthy care setting [11].

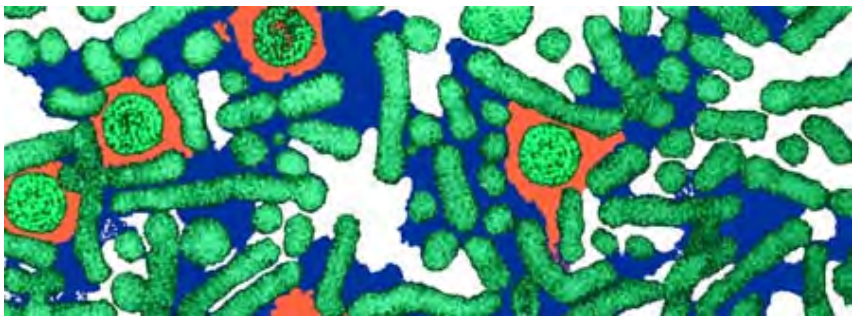


Figure 4: Hepatitis B virus: Source(SPL/Photo Researchers Inc.)

Causes and Symptoms of Hepatitis B

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

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

About 15% to 20% of patients develop short-term arthritis-like problems. Another one-third of those with hepatitis B develop only mild flu-like symptoms without jaundice. Very severe hepatitis B is rare, but it is life-threatening. Signs and symptoms, which require immediate medical attention, include prolonged blood clotting time, personality changes and agitated behavior [11].

Testing for Hepatitis B Infection

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

Acute infections

Acute HBV infections have an average incubation period of 90 days (range: 60-150 days) and can be defined as an abrupt clinical, biochemical, and/or histopathological manifestation of hepatic injury that occurs within six months of HBV exposure and that resolves spontaneously, in more than 90% of cases, within six months of the onset of symptoms. Clinical symptoms include nausea, vomiting, abdominal pain, fever, jaundice, dark urine, changes in stool colour, and hepatomegaly .

Acute hepatitis B refers to the first six months of exposure of the patients's body to HBV. In this stage the immune system is usually able to clear the virus fromthe body and the individual may completely recover withina few months.

Chronic infections

Chronic hepatitis B refers to the illness that occurs when HBV remains in the body for a long time and develops serious health problem. Individuals with chronic hepatitis often do have no history of acute illness, but it can cause liver scarring that causes liver failure and may also develop liver cancer [1].

How to Cure of Hepatitis B

There are no specific treatments for the acute symptoms of viral hepatitis B. Doctors recommend bed rest, preventing dehydration, a healthy diet and avoidance of alcoholic beverages.

There are treatment options available for those chronically infected with the hepatitis B virus. Many chronic carriers remain symptom free or develop only a mild condition, chronic persistent hepatitis. However, approximately 25 percent go on to develop the most serious complications of viral hepatitis: cirrhosis of the liver, liver cancer and immune system disorders [12].

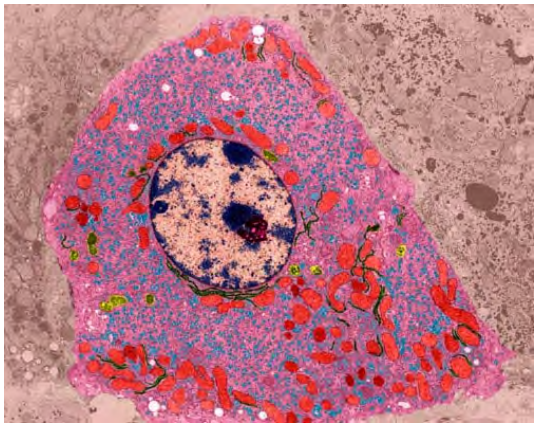


Figure 5: Liver Cell:Source(Dennis Kunkel Microscopy Inc./dennisKunkel.com)

1.3.1 The Comprehensive on HIV and Hepatitis B Infection

Between 5 and 10% of people with HIV are also infected with hepatitis B virus (often called co-infection). People with HIV are less likely to naturally clear hepatitis B without treatment. People with HIV and hepatitis co-infection can have faster liver disease progression and may not respond as well to hepatitis B treatment. But having hepatitis B does not seem to make HIV disease worse.Hepatitis B virus (HBV) and HIV can be transmitted in similar ways, but hepatitis B is more infectious. Both are spread by contact with infected body fluids such as blood, semen and vaginal fluid, or from a mother to her baby during pregnancy or delivery [12]. Markers of HBV exposure are present in a high proportion of HIV-infected individuals. HIV affects HBV viral replication and clearance, accelerates the development of liver disease, and contributes significantly to hepatic morbidity and mortality in HIV infection. HBV coinfection does not appear to influence the rate of HIV progression but may be a surrogate for factors associated with HIV seroconversion. Patients receiving HIV treatment should receive fully active HBV treatment as well, avoiding 3TC or FTC monotherapy. Conversely, it is preferred to give fully active ART in conjunction with HBV therapy, as there are limited options for effective HBV treatment that lack anti-HIV activity [12].

How is the hepatitis B vaccine made

People are protected against hepatitis B virus infection by making an immune response to a protein that sits on the surface of the virus. When hepatitis B virus grows in the liver, an excess amount of this surface protein is made. The hepatitis B vaccine is made by taking the part of the virus that makes surface protein (”surface protein gene”) and putting it into yeast cells. The yeast cells then produce many copies of the protein that are subsequently used to make the vaccine. When the surface protein is given to children in the vaccine, their immune systems make an immune response that provides protection against infection with the hepatitis B virus.

The first hepatitis B vaccine was made in the 1980s by taking blood from people infected with hepatitis B virus and separating or purifying the surface protein from the infectious virus. Because blood was used, there was a risk of contaminating the vaccine with other viruses that might be found in blood, such as HIV. Although contamination with HIV was a theoretical risk of the early, blood-derived, hepatitis B vaccine, no one ever got HIV from the hepatitis B vaccine. That is because the blood used to make vaccine was submitted to a series of chemical and treatments that inactivated any possible contaminating virus. Today, there is no risk of contaminating the vaccine with other viruses because the surface protein is manufactured in the laboratory [12].

Figure 6: hepatitis B pills and vaccination: Source (getty_rf_photo_pills and vaccination)

Who should not get hepatitis B vaccine

- Anyone with a life-threatening allergy to baker's yeast, or to any other component of the vaccine, should not get hepatitis B vaccine. Tell your provider if you have any severe allergies.
- Anyone who has had a life-threatening allergic reaction to a previous dose of hepatitis B vaccine should not get another dose.
- Anyone who is moderately or severely ill when a dose of vaccine is scheduled should probably wait until they recover before getting the vaccine.

Your provider can give you more information about these precautions. Pregnant women who need protection from HBV infection may be vaccinated [12].

1.3.2 Hepatitis B epidemiology globally

Hepatitis B disease is one of the most health problems worldwide. Now, nearly 350-400 million are carriers of hepatitis B virus (HBV) in the world. The threat posed by the global HBV epidemic continues to assume alarming proportions in areas of public health and national development. Globally, two billion people have been infected with HBV at some point in time in their life time and 360 to 400 million people which represents more than 5% of the world's population are chronic carriers with an estimated 600,000 deaths each year due to consequences of HBV. It is estimated to be the tenth cause of deaths worldwide (WHO, 2008). Hepatitis B virus mostly affects the liver and can cause liver cancer [12].

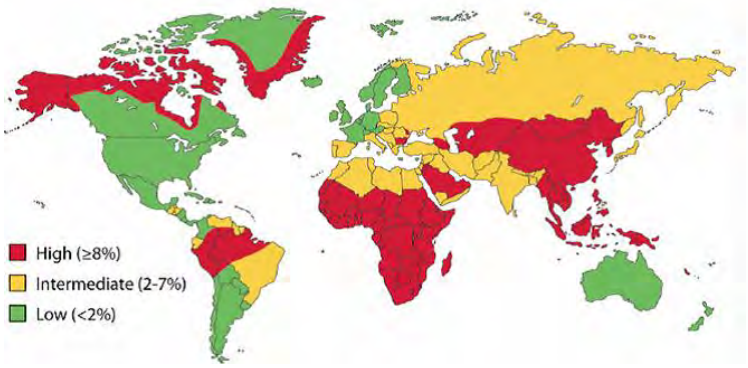


Figure 7: Worldwide prevalence of HBV (adopted from CDC, 2014)

Hepatitis B epidemiology in Africa

Africa has the second largest number of chronic HBV carriers after Asia and is considered as a region of high endemicity. From estimated that out of the 360 million chronic global carriers of HBV, about 65 million of these chronic carriers live in Africa (WHO, 2008). In addition, of the estimated 1.3 million deaths recorded annually due to HBV related causes, about 250,000 come from Africa .The world's highest prevalence is in Egypt (17.5 %), followed by Cameroon (13.8 %) and Burundi (11.3 %). Africa also has the highest hepatocellular carcinoma incidence rate in the world, partly due to a 5-25 % co-infection rate with HIV, which accelerates the progression to cirrhosis and hepatocellular carcinoma [13].

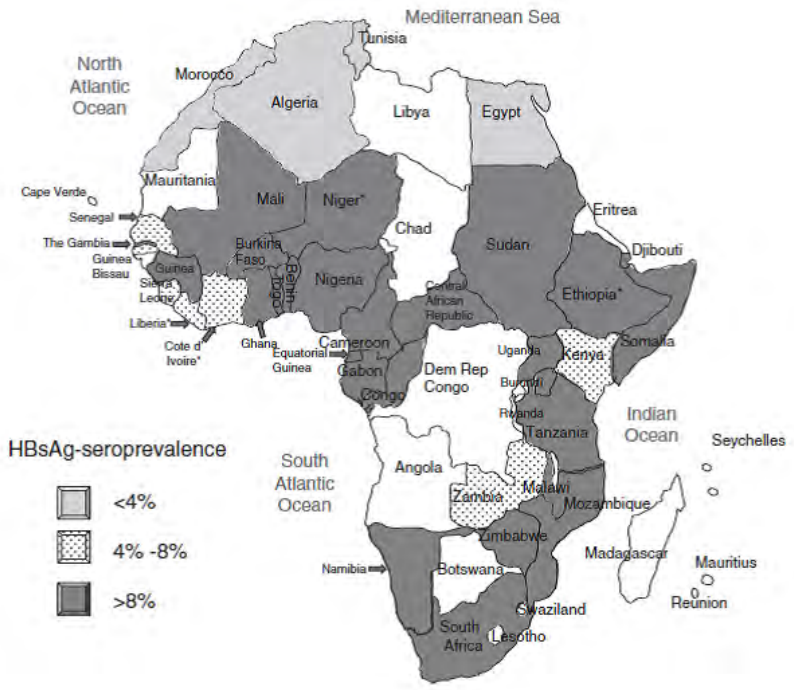


Figure 8: Prevalence of HBV across the African (Source: Kramvis and Kew (2007) Reproduced with permission)

Hepatitis B epidemiology in Ethiopia

In Ethiopia, there is a lack of nationwide representative data on hepatitis B. It is difficult to present the incidence, prevalence, and mortality rates accurately. A national survey conducted several years ago, and regional estimates have shown

wide geographic and socioeconomic variation in hepatitis B prevalence, ranging between 5.7 and 10.8 % .

It was estimated that over 5 million people are living with chronic HBV infection among the general population of Ethiopia. However, data on the epidemiology of HBV infection in Ethiopia are limited, though few studies were conducted in the northern regions of the country. Using survey based questioners of Ethiopian blood donors, one study indicated that 8% and second 14.4% are infected by HBV in northern part of Ethiopia [14].

1.3.3 Herd Immunity

Herd immunity is defined as the level of immunity in a population which can prevent epidemics of a disease, even if some transmission of that particular disease may still occur in a population. There can be certain number of immunes in the population and therefore the number of susceptibles can be too low. Although, this situation will not remain because the there is constant inflow of susceptible newborns who replace the immunes.

We may increase the level of immunes e.g. by vaccination. But this has to be done in a sufficiently high level in order to guarantee herd immunity. If we consider vaccination in the last model, we have to put in the system of equations another term depending on the vaccination, which transfers susceptibles into the recovered class [15].

1.3.4 The Threshold Effect

Another important discovery in the study of the SVEIRS model is the existence of the threshold effect. The basis of this effect is that, unless the population is initially large enough, with considerable amount of contact between individuals and a high enough rate of infection, the virus will die out before becoming established in the population. To explain this mathematically requires re-examining the equilibrium equations [16].

1.4 Optimal control

The optimal control definition and its possible formulations are introduced, followed by some examples related to epidemiological models. The Pontryagin Maxi-

mum Principle is presented with the aim of finding the best control policy. Optimal Control (OC) is the process of determining control and state trajectories for a dynamic system over a period of time in order to minimize a performance index [17].

1.4.1 Pontryagin's Maximum Principle

The necessary first order conditions to find the optimal control were developed by Pontryagin and his co-workers. This result is considered as one of the most important results of Mathematics in the 20^{th} century. Pontryagin introduced the idea of adjoint functions to append the deferential equation to the objective functional. Adjoint functions have a similar purpose as Lagrange multipliers in multivariate calculus, which append constraints to the function of several variables to be maximized or minimized [17].

1.4.2 Optimal control applied to epidemiological models

Optimal control theory is a mathematical optimization method for deriving control policies. The method is largely due to the work of Lev Pontryagin and Richard Bellman. Optimal control deals with the problem of finding a control law for a given system such that a certain optimality criterion is achieved. A control problem includes a cost functional which is a function of state and control variables. In the 1950's, motivated especially by aerospace problems, engineers became interested in the problem of controlling a system governed by a set of differential equations. It was natural to want to control the problem such that a given performance index would be minimized. Since some practical techniques were developed for the computation and implementation of optimal controls, the use of this theory became common in a large number of fields [17].

1.5 Problem Statement

Hepatitis B is a potentially life-threatening liver infection caused by the hepatitis B virus (HBV). It is a major global health problem hepatitis B is the most serious types of viral hepatitis in the world. Originally known as "hepatitis B", the disease has caused epidemics in parts of Asia and Africa . About one third of the world population has been infected hepatitis B, including 350 million who are chronic carriers which causes 620,000 deaths worldwide each year. So far different pre-

vention approaches and scientific methodologies have been applied to prevent and study this disease. However this was a new modified analysis also the epidemiology of Hepatitis B in Ethiopia has become imperative, needing research and effort to help control the spread and eradicate this disease.

1.6 Objective

The general objective:- assess the knowledge, attitude and practices concerning hepatitis B (HBV) among rural and urban adolescents in Ethiopia using SVEIRS model .

The specific objectives of the study are:

- To formulate a modified constant population SVEIRS model for hepatitis B in Ethiopia
- To determine the spread of the disease in Ethiopia
- To perform the stability analysis of the equilibrium states of the SVEIRS model
- To identify the behavior of the disease.
- To compare uncontrolled and controlled state strategies on the dynamics of the disease.
- Perform simulations to illustrate analytical results.
- Using pplane 8 we can analyze the phase portrait of the differential equation.
- Determine the general behavior of the disease using pplane8.

1.7 Methodology

An SVEIRS model would be formulated and it is one of the models used to describe the epidemiology of infectious diseases. This computes the amount of Susceptible, Vaccination, Exposed, Infected and recovered individuals in a locality. Also become susceptible to the disease again. The model equation would be solved

and analysed by the deterministic approach with and without optimal control. Simulation will be done using MatLab and sensitivity analysis will then be carried out on the parameter values to determine their effect on the spread of the disease.

1.8 Justification

Although there have been researches on Hepatitis B in Ethiopia, there has not been any Mathematical modeling of Hepatitis B using the SVEIRS model. A combination of this thesis and other models of Hepatitis B will pave a broader way for us to overcome the problem of Hepatitis B in this country. Hepatitis B is a retrogressing factor in the country's development. Death as a result of Hepatitis B hampers the country's productivity and hence a threat to socio-economic development. This thesis will therefore be of paramount importance by helping in the control of Hepatitis B in Ethiopia.

1.9 Organization of the Thesis

The thesis is made up of five main chapters. Chapter one being the introduction of the thesis comprises of the background of Hepatitis B, problem statement, objectives, methodology and organization. Related researches done by others would be reviewed in chapter two. Chapter two will also include some Mathematical definitions and theorems related to the model under study. Chapter three would be about Mathematical model formulation. The analysis and results are presented in chapter four. Chapter five is optimal control with Mathematical model formulation.chapter six is about conclusion and recommendations for further studies.

Chapter Two

2 Literature Riview

This chapter reviews the work of other researchers related to the objectives of this thesis. Some of the related works are as follows

Grob and Esteban (1995) stated that HBV may be transmitted horizontally and vertically. Horizontal transmission occurs during adolescence or childhood, throughout sexual exposure, needle stick (both accidental or through intravenous drug use), and blood transfusion. Therefore, any person with a bad history of sexually transmitted diseases (STDs), multiple sexual partners or an injecting drug user stands a higher chance of being infected with HBV (CDC, 2002). Exposure to blood is also means of open wounds in households and other close contacts and multiple transfusions in hemophiliacs. This view of exposure to risk was also shared who argued that most of the infections occur among adolescents and young adults due to exposure to high risk activities they engage in at this stage of life [18].

A vertical transmission occurs when an infected mother transmits the virus directly to the neonatal during child birth. Such transmissions are usually possible when the expectant mother suffers an acute infection of hepatitis B during pregnancy or if she is a chronic carrier during that period. The mode of this vertical transmission is not clear cut, but indications are that, infection might occur through a placenta cutting during childbirth. Majority of countries in Southeast Asia, the Western Pacific and Africa have high endemicity of HBV. In these settings the major mode of HBV transmission has been identified as vertical, where by mothers directly transmit virus to their infants during prenatal periods or where infected siblings, playmates,other members of different households transmit the virus to their younger ones. A cross-sectional study clarified that without prophylaxis, an estimated number of 6000 infants born to carrier mothers each year in the USA would develop chronic HBV infection as a consequence of prenatal transmission [18].

Unsafe blood transfusion has been a major force in the transmission of HBV globally (Wang & Wong, 1960). The enactment of a law for the donation and manage-

ment of blood in blood banks across the world has aggressively fought this channel of HBV transmission. This notwithstanding, current researches have showed that blood transfusion is regaining its position as one of the major risk factors for HBV transmission globally. This finding is attributed to the presence of occult HBV infection (OHBVI) among blood donors (Shang et al, 2007). It is also worth mentioning that the global acceptance of the auto-disposable syringes (ADS) has considerably reduced the incidence of HBV infections that occur due to unsafe injections. Also, as a result of the extensive use of invasive medical procedures, iatrogenic HBV infections are no longer frequent. There have also been speculations that dental care operations which are capable of causing oral mucous membrane injuries is becoming a major route to HBV transmission if steps are not taken to prevent it [19].

Gashu Afework from Addis Ababa University,(March, 2015) stated that Occupational exposure occurs frequently among health care workers (HCWs). The most serious occupational health hazard faced by HCWs worldwide is exposure to hepatitis B virus (HBV). Having enough Knowledge and proper attitudes toward this infection is crucial in prevention of occupational hepatitis infection. Therefore this study was conducted to assess knowledge, atti-tude and practice of HBV and its vaccination among health care professionals (HCPs) in selected public hospitals of Addis Ababa, Ethiopia. Both qualitative and quantitative methods were used. Qualitative study involved key informants interviews whereas quantitative method was carried out by using structured self-administered questionnaire. This study revealed that HCPs' knowledge regarding occupational exposure of HBV is found to be good as majority of our par-ticipants correctly answered most of the question pertaining to it. Relatively larger proportion, 103 (44.8%) of the respondents were found to have neutral attitude score. One hundred seventy eight (77.7%) of them had been screened for and received hepatitis B Vaccine, and one hundred sixty (94.1%) of them had received full course of the vaccine. Knowledge score was significantly associated with: education level, type of profession and area of practice; whereas profession type and history of training were the only predictors of vaccination sta-

tus. In conclusion, majority of the survey participants had moderate to high knowledge score, however, larger percentage of HCPs had negative or neutral attitudes on HBV and its vaccination. In spite of this, vaccination status was encouraging. The gaps identified in some areas of knowledge, attitude and practice of HBV call for concern among all stakeholders since HCPs have a high risk of being infected with HBV owing to their high frequency of exposure to infectious fluids coupled with the high infectivity of HBV [20].

Sacrifice Nana-Kyere, Joseph Ackora-Prah, Eric Okyere, Seth Marmah., Tuah Afram from Ghana in 2017 formulated and studied the transmission dynamics of hepatitis B disease that employs preventive and treatment controls for optimal control analysis of the SEIR model. The necessary conditions for the optimal control of the disease was derived and analyzed. Two types of control functions associated with the reduction of the exposed and the infective and treatment of infective strategies were considered. The control plots that were plotted showed that the number of exposed and infected human decreased in the optimality system. The control analysis indicates that the optimal control strategies have an incomparable effect for the reduction of the infected individuals as compared to the model without control as shown in the plot of figures for the models with control and without control. The simulation results showed that despite the vertical transmission incidence, the proposed control strategy is effective in the reduction of the number of the infective of the disease [5].

Jonathan E. Forde, Stanca M. Ciupe, Ariel Cintron-Arias and Suzanne Lenhart from USE in 3 August 2016 stated that Combination antiviral drug therapy improves the survival rates of patients chronically infected with hepatitis B virus by controlling viral replication and enhancing immune responses. Some of these drugs have side effects that make them unsuitable for long-term administration. To address the trade-off between the positive and negative effects of the combination therapy, we investigated an optimal control problem for a delay differential equation model of immune responses to hepatitis virus B infection. Our optimal control problem investigates the interplay between virological and immunomodulatory effects of therapy,

the control of viremia and the administration of the minimal dosage over a short period of time. Our numerical results show that the high drug levels that induce immune modulation rather than suppression of virological factors are essential for the clearance of hepatitis B virus [19].

A. A. Momoh, M. O. Ibrahim and A. Tahir from Nigeria in July-august 2012, we proposed an SVEIR model to understand the effect of detection and treatment of Hepatitis B at latent stage on the transmission dynamics of hepatitis B disease. Mathematical analysis was carried out that completely determines the global dynamics of the model. The impact of detection and treatment of Hepatitis B at latent stage on the transmission dynamics are discussed through the stability analysis of the disease free equilibrium [21].

Tahir Khan, Gul Zaman & M. Ikhlaq Chohan from United Kingdom in 2016 we presented the model for the transmission dynamic of acute and chronic HBV. We incorporated in the model acute-infected class and chronic-infected class and then developed the model with these new features. After formulating the model, we found the basic reproduction number R_0. As in epidemiological models, the model has two steady states, infected and uninfected steady states. Thus, we investigated both the states, disease-free state and endemic state and proved that the disease-free and endemic equilibria are both locally as well as globally stable under certain conditions. For the global stability, we developed the Lyapnovo function and showed that both the local and global dynamic are completely determined by the basic reproduction number R_0. Furthermore, three time-dependent control variables are taken and a control strategy for minimizing the number of infected individuals and maximizing the number of non-infected individuals was developed.Finally, we presented the numerical simulation and verified all the analytical results numerically. By using control variables isolation, treatment and vaccination, we are able to control the spreading of hepatitis B.We believe that this new extension, assumption and analysis are biologically much more plausible [22].

Tunde Tajudeen Yusuf, Francis Benyahwe studied optimal combination of vaccination and treatment strategies for driving infectious diseases with cure and vaccine

towards eradication within a specified period. We considered an SIR model with varying size population using vaccination and treatment as control measures. We established the conditions for the local and global stability of the model equilibria. We used Pontryagin's maximum principle to charaterize the controls and derive the optimality system. Numerical simulations of the resulting optimality system showed that, in the case where it is more expensive to vaccinate than to treat, resources should be invested in treating the disease until the disease prevalence begins to fall. This option, however, does not reduce the number of susceptibles quickly enough, thus resulting in an overall increase in the infected population. On the other hand, if it is more expensive to treat than to vaccinate, then more resource must be put into vaccination. This latter case resulted in a rapid reduction in the susceptibles as well as an appreciable reduction in the number of infectives. Nevertheless, the case where both measures are equally expensive showed that the optimal way to drive the epidemic towards eradication within the specified period is to use more of the vaccination control and less of the treatment control initially to drive the epidemic to below certain threshold afterwhich we can then apply less of vaccination control and more of the treatment control [23]. Many scholars have done research on how to eliminate hepatitis B. However, many previous models make an assumption that exposed hosts and infected hosts have the same infectivity. But this paper will be prepared by SEVIRS model with optimal control and formulate mathematical equation. To the best of our knowledge no research work related to the optimal vaccination strategies to combat the hepatitis B disease has ever been done in Ethiopia.

2.1 Types of epidemic models

An epidemic model is a simplified means of describing the transmission of communicable disease through individuals [25].An epidemic model is a simplified means of describing the transmission of communicable disease through individuals. The main interest was to study these models to understand the long-time behavior of the dynamics of disease transmission, thus, whether the disease would die out eventually or would persist. They looked at the effects of variable periods of latency on

the dynamics of HBV by considering an SVEIRS model.

2.1.1 Stochastic

"Stochastic" means being or having a random variable. A stochastic model is a tool for estimating probability distributions of potential outcomes by allowing for random variation in one or more inputs over time. Stochastic models depend on the chance variations in risk of exposure, disease and other illness dynamics. They are used when these fluctuations are important, as in small populations [25].

2.1.2 Deterministic

The transition rates from one class to another are mathematically expressed as derivatives, hence the model is formulated using differential equations. While building such models, it must be assumed that the population size in a compartment is differentiable with respect to time and that the epidemic process is deterministic. In other words, the changes in population of a compartment can be calculated using only the history used to develop the model [25].

2.1.3 Deterministic compartmental models

The SIR model

In 1927, W. O. Kermack and A. G. McKendrick created a model in which they considered a fixed population with only three compartments:

S(t)= the number of susceptible individuals in the population at time t.

I(t) = the number of infected individuals in the population at time t.

R(t)= the number of recovered individuals in the population at time t.

N(t)= the population size.

Correspondingly define the three groups as fractions of the total population N using lower case: The flow of this model may be considered as follows: $S \longrightarrow I \longrightarrow R$ [25]

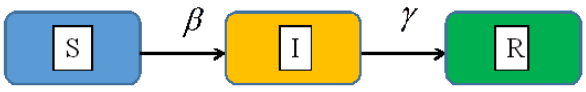


Figure 9: SIR model

Using a fixed population, N=S(t)+I(t)+R(t), Kermack and McKendrick derived the following equations:

$$\frac{dS}{dt} = \frac{-\beta SI}{N}$$
$$\frac{dI}{dt} = \frac{\beta SI}{N} - \gamma I$$
$$\frac{dR}{dt} = \gamma I$$

Table 1: Description of state variables

Variable	Description
S(t)	Susceptible humans
V(t)	Vaccinated humans
E(t)	Exposed humans
I(t)	Infected humans
R(t)	Recovered humans
M(t)	Passively immune infants
f	Average loss of immunity rate of recovered individuals
p	removed from the S category by successful vaccination
b	Birth Rate
d	Natural Death Rate
v_1	vaccinated newborns
ω	Vaccination Rate
ρ	Transmission Rate of Recovered to Susceptible
β	Rate at which the susceptibilities become exposed to HBV
δ	Transmission Rate of Exposed to Infected
ε	Rate of Infection Death
α	Transmission Rate of vaccinated to Exposed
σ	the transfer rates between the susceptible and the vaccinated
γ	Recovery rate of Infected to Recovered
γ_1	Transmission Rate of Vaccinated to Recovered

The SIR model with births and deaths

Using the case of for example, there is an arrival of new susceptible individuals into the population. For this type of situation births and deaths must be included in the model. The following differential equations represent this model, assuming a death rate μ, and birth rate equal to the death rate [25]:

$$\frac{dS}{dt} = \frac{-\beta SI}{N} + \mu(N-S)$$
$$\frac{dI}{dt} = \frac{\beta SI}{N} - \gamma I - \mu I$$
$$\frac{dR}{dt} = \gamma I - \mu I$$

The SIS model with births and deaths

The SI(S)model is a two-state deterministic model which assumes that a person can be in one of only two states, either susceptible(S) or infectious(I). These states are often called compartments and the corresponding models are called compartment model. Not all diseases are accurately described by a model with only two states, but a two-state model is useful in describing some classes of micro parasitic infections to which individuals never acquire a long lasting immunity. In a simple model for this process, individuals never enter a recovered state, but rather alternate between being susceptible and being infectious. The SIS model can be easily derived from the SIR model by simply considering that the individuals recover with no immunity to the disease, that is, individuals are immediately susceptible once they have recovered [25].

$$\frac{dS}{dt} = \frac{-\beta SI}{N} + \mu(N-S) + \gamma I$$
$$\frac{dI}{dt} = \frac{\beta SI}{N} - \gamma I - \mu I$$

The SIRS model

This model is simply an extension of the SIR model as we will see from its construction. $S \longrightarrow I \longrightarrow R \longrightarrow S$ [25]. The only difference is that it allows members of the recovered class to be free of infection and rejoin the susceptible class

$$\frac{dS}{dt} = -\beta SI/N + \mu(N-S) + fR$$
$$\frac{dI}{dt} = \beta SI/N - \gamma I - \mu I$$
$$\frac{dR}{dt} = \gamma I - \mu R - fR$$

Models with more compartments

The SEIS model

The SEIS model takes into consideration the exposed or latent period of the disease, giving an additional compartment, E(t). $S \longrightarrow E \longrightarrow I \longrightarrow S$

In this model an infection does not leave any immunity thus individuals that have recovered return to being susceptible again, moving back into the S(t) compartment. The following differential equations describe this model [25]:

$$\frac{dS}{dT} = b - \beta SI + \mu S + \gamma I$$
$$\frac{dI}{dT} = \beta SI - (\varepsilon + \mu)E$$
$$\frac{dR}{dT} = \varepsilon E - (\gamma + \mu)I$$

The SEIR model

The SIR model discussed above takes into account only those diseases which cause an individual to be able to infect others immediately upon their infection. Many diseases have what is termed a latent or exposed phase, during which the individual is said to be infected but not infectious. $S \longrightarrow \varepsilon \longrightarrow I \longrightarrow R$ that is N = S(t) + E(t) + I(t) + R(t)

$$\frac{dS}{dT} = b - \beta SI + \mu S$$
$$\frac{dE}{dT} = \beta SI - (\varepsilon + \mu)E$$
$$\frac{dI}{dT} = \varepsilon E - (\gamma + \mu)I$$
$$\frac{dR}{dT} = \gamma I - \mu R$$

The MSIR model

There are several diseases where an individual is born with a passive immunity from its mother. $M \longrightarrow S \longrightarrow I \longrightarrow R$. To indicate this mathematically, an additional compartment is added, M(t), which results in the following differential equations.

$$\frac{dM}{dT} = b - \delta M + \mu M$$
$$\frac{dS}{dT} = \delta M - \beta SI + \mu I$$
$$\frac{dI}{dT} = \beta SI - \gamma I + \mu I$$
$$\frac{dR}{dT} = \gamma I - \mu R$$

SIRV model with finite immunity

A common extension of the SIR model involves finite immunity: after some period of time, recovered individuals lose their immunity and become susceptibles again. This is modeled as a leakage $-\mu$R from the R to the S category, where μ-1 is the average time it takes to lose immunity. Vaccination is another extension: a fraction pS is removed from the S category by successful vaccination and brought to a new category V (the vaccinated). The ODE model reads [25]

$$\frac{dS}{dT} = \delta SI - PS + \mu R$$
$$\frac{dI}{dT} = \beta SI - vI$$
$$\frac{dR}{dT} = vR - \mu R$$
$$\frac{VR}{dT} = PS$$

Using tc=1/ and scaling the unknowns by S(0), we arrive at the dimensionless model

$$\frac{dS}{dT} = -R_0 SI - \delta S + \gamma R$$
$$\frac{dI}{dT} = R_0 SI - I$$
$$\frac{dR}{dT} = I - \gamma R$$
$$\frac{VR}{dT} = \delta S$$

with two new dimensionless parameters:$\gamma = \mu/v, \delta = p/v$

The quantity p-1 can be interpreted as the average time it takes to vaccinate a susceptible successfully. Writing $\gamma = \frac{v-1}{\mu-1}$ and $\delta = \frac{v-1}{p-1}$ gives the interpretation that γ

is the ratio of the average time to recover and the average time to lose immunity, while δ is the ratio of the average time to recover and the average time to successfully vaccinate a susceptible [25].

SEIR(S) Models

Many infectious diseases are also characterized by an incubation period between exposure to the pathogen and the development of clinical symptoms. If the exposed individual is not infectious during this incubation period, it is important to model the incubation time explicitly. Note that there is a difference between an incubation time and a period of latency. A virus may or may not be dormant when an individual is in an exposed state. It is important to model the Exposed (E) state explicitly when there is a delay between the time at which an individual is infected and the time at which that individual becomes infectious.

The rate parameters are the same as for an SEIR(S) model with the addition of an incubation rate e which reflects the time between exposure (infection) and becoming infectious.

The Exposed State

As shown in the SEIR model has four compartments or states, and therefore four equations are required to parameterize it. The infectious process is the same as for SI and SIR except that infected individuals first enter the exposed state where they begin an incubation time. Equation then becomes:

$$\frac{dE}{dt} = \beta(1+\alpha)SI - (\delta + d)E$$

Exposed individual transition from the E state to the I state at a rate ε, which reflects the incubation rate of the disease.

SEIR(S) Rate Equations

The rate equations for the SEIR model are shown in equations below [25]:

$$\frac{dS}{dt} = -\beta SI - dS - \varepsilon S + \rho R - \omega$$
$$\frac{dE}{dt} = \beta(1+\alpha)SI - (\delta + d)E$$

$$\frac{dI}{dt} = \delta E - (\gamma + d)I$$
$$\frac{dR}{dt} = \gamma I + \omega S - dR - \rho R$$

The four states defined by the SEIR model by no means reflect the totality of compartmental models in epidemiology. In many cases, the population itself is segmented. The reproductive rate of a disease, the incubation rate, recovery rate, and mortality can all vary based on socioeconomic factors, gender, age, and infrastructure (health care, sanitation, water quality) (Porter, 1978).

The MSEIR model

For the case of a disease, with the factors of passive immunity, and a latency period there is the MSEIR model.$M \longrightarrow S \longrightarrow \varepsilon \longrightarrow I \longrightarrow R \longrightarrow R$ [25]

The SEIRS Model For Hepatitis B

In the last two decades, mathematical models have been used frequently to study the transmission dynamics of HBV in various regions. Simple deterministic, compartmental mathematical model to illustrate the effects of carriers on the transmission of HBV.

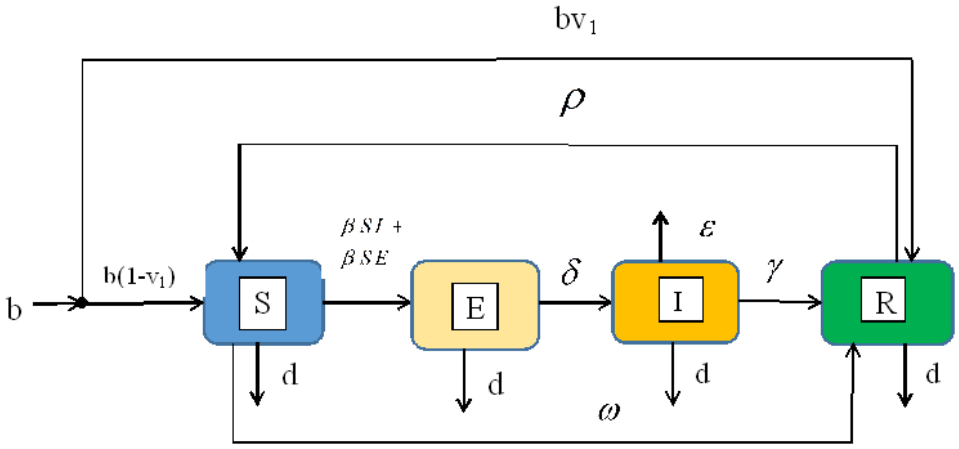


Figure 10: An SEIR(S) compartment model

$$\frac{dS}{dt} = b(1 - v_1) - \beta SI - dS + \rho R - \omega S$$
$$\frac{dE}{dt} = \beta SI - (\delta + d)E$$

$$\frac{dI}{dt} = \delta E - \gamma I - \varepsilon I - dI$$
$$\frac{dR}{dt} = bv_1 + \gamma I - \rho R + \omega S - dR$$

The SVEIRS Model

In this model the susceptible subpopulation is divided into two different subpopulations: the normal susceptible subpopulation, in which the hosts are not protected against infection, and the vaccinated subpopulation, in which the immune system of the hosts has been stimulated so that their response is more positive. Thus, the way this subpopulations is affected from the disease is different, as it may reach a complete immunity without the need to suffer the effects of the infection of the diseases itself and the model is back recovered individual to susceptible individual by ρR. The SVEIRS model takes into consideration the exposed or latent period of the disease, giving an additional compartment, E(t). $S \longrightarrow V \longrightarrow E \longrightarrow I \longrightarrow S$

S, V, E, I and R are, respectively, the susceptible, vaccinated, exposed, infected(or infective or infectious) and recovered (or removed-by-immunity) subpopulations, N is the total population being the sum of the above ones.

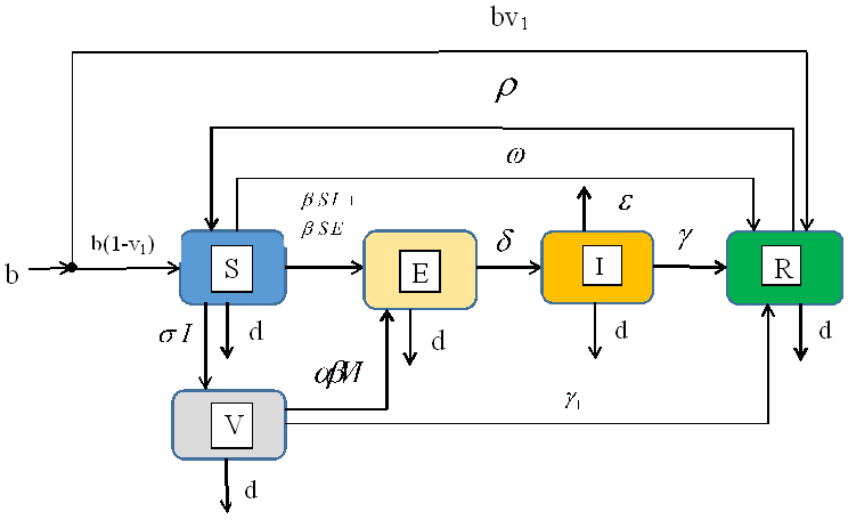


Figure 11: An SVEIR(S) compartment model

In this model an infection does not leave a long lasting immunity thus individuals that have recovered return to being susceptible again, moving back into the S(t)

compartment. The following differential equations describe this model:

$$\frac{ds}{dt} = b(1-v_1) - \beta SI - \beta SE - dS + \rho R - \omega S - \sigma S$$
$$\frac{dv}{dt} = \sigma S - \alpha\beta VI - \gamma_1 V - dV$$
$$\frac{de}{dt} = \beta SI + \beta SE - (\delta + d)E + \alpha\beta VI$$
$$\frac{di}{dt} = \delta E - \gamma I - \varepsilon I - dI$$
$$\frac{dr}{dt} = bv + \gamma I + \gamma_1 V - \rho R + \omega S - dR$$

2.2 Differential Equation

Definition: An equation containing the derivatives of one or more dependent variables, with respect to one or more independent variables, is said to be a differential equation. An example of a differential equation is shown below;

$$a\frac{d^2x}{dt^2} + b\frac{dx}{dt} + cx = d$$

where x is the dependent variable and t is independent variables, a, b, c, d are constants.

Differential equations play a prominent role in engineering, physics, economics, and other disciplines. Differential equations arise in many areas of science and technology, especially whenever a deterministic relation involving some continuously varying quantities and their rate of change in space or time is known. This is illustrated in classical mechanics, where the motion of a body is described by its position and velocity as the time value varies. Newton's laws allow one (given the position, velocity, acceleration and various forces acting on the body) to express these variables dynamically as a differential equation for the unknown position of the body as a function of time. In some cases, this differential equation may be solved explicitly.

An example of modeling a real world problem using differential equations is the determination of the velocity of a ball falling through the air, considering only gravity and air resistance. The ball's acceleration towards the ground is the acceleration due to gravity minus the deceleration due to air resistance. Gravity is considered

constant, and air resistance may be modeled as proportional to the ball's velocity. This means that the ball's acceleration, which is a derivative of its velocity, depends on the velocity (and the velocity depends on time). Finding the velocity as a function of time involves solving a differential equation [26].

Differential equations are mathematically studied from several different perspectives, mostly concerned with their solutions, the set of functions that satisfy the equation. Only the simplest differential equations admit solutions given by explicit formulas; however, some properties of solutions of a given differential equation may be determined without finding their exact form. If a self-contained formula for the solution is not available, the solution may be numerically approximated using computers. The theory of dynamical systems puts emphasis on qualitative analysis of systems described by differential equations, while many numerical methods have been developed to determine solutions with a given degree of accuracy.

2.2.1 Types of differential equations

Differential equations can be divided into several types. Apart from describing the properties of the equation itself, these classes of differential equations can help inform the choice of approach to a solution. Commonly used distinctions include whether the equation is: Ordinary/Partial, Linear/Non-linear, and Homogeneous/Inhomogeneous. [26].

Ordinary differential equation

Definition: An ordinary differential equation (ODE) is a differential equation in which the unknown function (also known as the dependent variable) is a function of a single independent variable [26]. That is,

$F(x, y, y', ..., y^n) = 0$

where y is a function of $xy' = \frac{dy}{dx}$ is the first derivative with respect to x and $y^n = \frac{d^n y}{dx^n}$is the nth derivative with respect to x.

In the simplest form, the unknown function is a real or complex valued function, but more generally, it may be vector-valued or matrix-valued. This corresponds to considering a system of ordinary differential equations for a single function.

Ordinary differential equations are further classified according to the order of the

highest derivative of the dependent variable with respect to the independent variable appearing in the equation. The most important cases for applications are first-order and second-order differential equations [4].

Partial differential equation

Definition: A partial differential equation (PDE) is a differential equation in which the unknown function is a function of multiple independent variables and the equation involves its partial derivatives. Generally, it is represented as shown below;

$F(D^k u(x), D^{k-1}u(x), ..., Du(x), u(x), x) = 0$

$x \, \varepsilon \;\; \Omega \quad where \quad u : \Omega \longrightarrow R$

The order is defined similarly to the case of ordinary differential equations, but further classification into elliptic, hyperbolic, and parabolic equations, especially for second-order linear equations, is of utmost importance. Some partial differential equations do not fall into any of these categories over the whole domain of the independent variables and they are said to be of mixed type [26].

Linear and non-linear differential equations

Both ordinary and partial differential equations are broadly classified as linear and nonlinear.

Definition: A differential equation is linear if the unknown function and its derivatives appear to the power 1. When the unknown function and its derivatives appear to the power either than 1, then the differential equation is described as nonlinear. Examples of linear and nonlinear differential equations are shown in equations.

$$\frac{dy}{dx} = t^2 y + cost$$
$$\frac{d^2y}{dx^2} = 2x(\frac{dy}{dx})^2$$

The characteristic property of linear equations is that their solutions form an affine subspace of an appropriate function space, which results in much more developed theory of linear differential equations. Homogeneous linear differential equations are also such that the sum of any set of solutions or multiples of solutions is also a solution. The coefficients of the unknown function and its derivatives in a linear

differential equation are allowed to be functions of the independent variable or variables and if these coefficients are constants then one speaks of a constant coefficient linear differential equation.

There are very few methods of solving nonlinear differential equations exactly; those that are known typically depend on the equation having particular symmetries. Nonlinear differential equations can exhibit very complicated behavior over extended time intervals, characteristic of chaos. Even the fundamental questions of existence, uniqueness, and extend ability of solutions for nonlinear differential equations, and well-posedness of initial and boundary value problems for nonlinear PDEs are hard problems and their resolution in special cases is considered to be a significant advance in the mathematical theory.

Linear differential equations frequently appear as approximations to nonlinear equations. These approximations are only valid under restricted conditions. For example, the harmonic oscillator equation is an approximation to the nonlinear pendulum equation that is valid for small amplitude oscillations.

Linear and Nonlinear Models

Another important concept in modeling is linearity. A linear model uses parameters that are constant and do not vary throughout a simulation. This means that we can enter one fixed value for the parameter at the beginning of the simulation and it will remain the same throughout.

A non-linear model introduces dependent parameters that are allowed to vary throughout the course of a simulation run, and its use becomes necessary where interdependencies between parameters cannot be considered insignificant. The choice between using a linear and a non-linear model is dependent upon how significantly the values of any of the parameters involved vary in relation to any of the other parameters.

In a linear model, all the parameters are independent of any of the others. In a real device, however, parameters are always dependent upon other parameters to some degree, but in many cases if the dependency is so small it can be ignored. For example, the density of any solid material is dependent upon its temperature, but the variation is generally so small over normal temperature ranges that it can be

ignored, and the material density is usually modeled as a linear, constant parameter. Where possible, it is always best to use a linear model, as it is simpler and faster running than a non-linear model.

To model a non-linear parameter, we must update the simulation material parameters at each iteration step of the simulation. Although modeling parameters as non-linear in a simulation gives a more accurate representation, it increases simulation run time significantly [4].

2.3 Equilibrium States

Equilibrium is a state of a system which does not change with time. If the dynamics of a system is described by a differential equation (or a system of differential equations), then equilibriums can be estimated by setting a derivative (all derivatives) to zero.

Equilibrium may be stable or unstable. Equilibrium is considered stable if the system always returns to it after small disturbances. If the system moves away from the equilibrium after small disturbances, then the equilibrium is unstable.

The notion of stability can be applied to other types of attractors (limit cycle, chaos), however, the general definition is more complex than for equilibriums. Stability is probably the most important notion in science because it refers to what we call ”reality”. Everything should be stable to be observable.

In this study, our equilibrium states will be a analyzed using the Routh-hurwitz stability criterion.

2.4 Routh-Hurwitz stability criterion

Routh-hurwitz stability criterion is a method that can be used to establish the stability of a system without solving its characteristic equation.

Consider the characteristic equation

$a_0\lambda^n + a_1\lambda^{n-1} + a_2\lambda^{n-2} + ... + a_{n-1}\lambda + a_n = 0$

describing the dynamic system. Note that the necessary condition for the stability is satisfied if all the coefficients $a_i > 0$. Therefore, we assume that the coefficient $a_0 > 0$. We write the so called Hurwitz matrix. It is composed as follows. The main

diagonal of the matrix contains elements $a_1, a_2, ..., a_n$. The first column contains numbers with odd indices $a_1, a_3, a_5, ...$ In each row, the index of each following number (counting from left to right) is 1 less than the index of its predecessor. All other coefficients a_i with indices greater than n or less than 0 are replaced by zeros. The result is a matrix shown below:

$$\begin{bmatrix} a_1 & a_0 & 0 & 0 & 0 & 0 & \vdots & 0 \\ a_3 & a_2 & a_1 & a_0 & 0 & 0 & \vdots & 0 \\ a_5 & a_4 & a_3 & a_2 & a_1 & a_0 & \vdots & 0 \\ \dots & \dots & \dots & \dots & \dots & \dots & \vdots & \dots \\ 0 & 0 & 0 & 0 & 0 & 0 & \vdots & a_n \end{bmatrix}$$

The principal diagonal minors $\triangle_i$ of the Hurwitz matrix are given by the formulas

$$\triangle_1 = a_1, \triangle_2 = \begin{vmatrix} a_1 & a_0 \\ a_3 & a_2 \end{vmatrix}, \triangle_3 = \begin{vmatrix} a_1 & a_0 & 0 \\ a_3 & a_2 & a_1 \\ a_5 & a_4 & a_3 \end{vmatrix}, \triangle_n = \begin{vmatrix} a_1 & a_0 & 0 & 0 & 0 & 0 & \vdots & 0 \\ a_3 & a_2 & a_1 & a_0 & 0 & 0 & \vdots & 0 \\ a_5 & a_4 & a_3 & a_2 & a_1 & a_0 & \vdots & 0 \\ \dots & \dots & \dots & \dots & \dots & \dots & \vdots & \dots \\ 0 & 0 & 0 & 0 & 0 & 0 & \vdots & a_n \end{vmatrix}$$

We now formulate the Routh-Hurwitz stability criterion : The roots of the characteristic equation have negative real parts if and only if all the principal diagonal minors of the Hurwitz matrix are positive provided that $a_0 > 0 : \triangle_1 > 0, \triangle_2 > 0, ..., \triangle_n > 0$. Since $\triangle_n = a_n \triangle_{n-1}$, the last inequality can be written as $a_n > 0$.

For the most common systems of the 2nd, 3rd and 4th order, we obtain the following stability criteria:

For a second order system, the condition of the stability is given by

$$a_0 = 0, \triangle_1 = a_1 > 0, \triangle_2 = \begin{vmatrix} a_1 & a_0 \\ a_3 & a_2 \end{vmatrix} = a_1 a_2 > 0 \qquad \text{Or } a_0 > 0, a_1 > 0, a_2 > 0$$

that is, all coefficients of the quadratic characteristic equation must be positive. In other words, for a system of 2nd order, the necessary condition of the stability is also the sufficient one. We emphasize that we consider here the asymptotic stability of the zero solution.

For a 3^{rd} order system, the stability criterion is defined by the inequalities

$$a_0 > 0, \triangle_1 = a_1 > 0, \triangle_2 = \begin{vmatrix} a_1 & a_0 \\ a_3 & a_2 \end{vmatrix} = a_1 a_2 - a_0 a_3 > 0$$

Or $a_0 > 0, a_1 > 0, a_2 > 0, a_1 a_2 - a_0 a_3 > 0$

Similarly, for a 4^{th} order system, we obtain the following set of inequalities:

$a_0 > 0, \triangle_1 = a_1 > 0, \triangle_2 = \begin{vmatrix} a_1 & a_0 \\ a_3 & a_2 \end{vmatrix} = a_1 a_2 - a_0 a_3 > 0$

$\triangle_3 = \begin{vmatrix} a_1 & a_0 & 0 \\ a_3 & a_2 & a_1 \\ 0 & a_4 & a_3 \end{vmatrix} = a_1 a_2 a_3 - a_1^2 a_4 - a_0 a_3^2$ or

$a_i > 0 (i = 0, ..., 4), a_1 a_2 - a_0 a_3 > 0, a_1 a_2 a_3 - a_1^2 a_4 - a_0 a_3^2 > 0$

Similarly, for a 5^{th} order system, we obtain the following set of inequalities [27]:

$$\triangle_5 = \begin{vmatrix} a_1 & a_3 & a_5 & 0 & 0 \\ 1 & a_2 & a_4 & 0 & 0 \\ 0 & a_1 & a_3 & a_5 & 0 \\ 0 & 1 & a_2 & a_4 & 0 \\ 0 & 0 & a_1 & a_3 & a_5 \end{vmatrix}$$

$a_i > 0, (i = 0, ..., 5),$

$$a_5^2 a_3 a_1 - a_5^3 - a_5^2 a_2^2 a_1 - a_5^2 a_3^2 a_2 + a_1 a_4 a_5^2 - a_1^2 a_4^2 a_5 + a_5 a_4 a_3 a_2 a_1 - a_5 a_4 a_3^2 > 0 \quad (1)$$

If all the n - 1 principal minors of the Hurwitz matrix are positive and the nth order minor is zero: $\triangle_n = 0$, the system is at the boundary of stability. Since , then there are two options: The coefficient (s,v,e,i,r) to $(s^*, v*, e^*, i^*, r^*)$ = 0. This corresponds to the case when one of the roots of the characteristic equation is zero. The system is on the boundary of a periodic stability.

The determinant $\triangle_{n-1}$=0. In this case, there are two complex conjugate imaginary roots. The system is on the boundary of the oscillatory stability. The Routh-Hurwitz stability criterion belongs to the family of algebraic criteria. It can be conveniently used to analyze the stability of low order systems. The computational complexity grows significantly with the increase of the order. In such cases, it may be preferable to use other criteria such as the Lienard-Shipart theorem or the Nyquist frequency criterion [4].

2.5 Uncertainty and Sensitivity analysis in modeling

Uncertainty in model predictions can arise from many sources including

- Conceptualization of disease, either the disease is too complex or too simple.
- Inaccuracies/ uncertainty in input data
- Use of inappropriate data/ inappropriate interpretation of data

- User error.

Impact of the uncertainty from some of these sources can be quantitatively assessed through sensitivity analysis which involves specifying a potential range over which the parameter is thought to vary. Sensitivity analysis methods can either be deterministic or stochastic [4].

Main types of sensitivity analysis used:

1. One way sensitivity analysis
2. Multi way sensitivity analysis
3. Scenario analysis
4. Threshold analysis
5. Probabilistic sensitivity analysis

One way sensitivity analysis

Estimates for each parameter are varied one at a time to investigate the impact on study results.

Multi way sensitivity analysis

This recognizes that more than one parameter is uncertain and that each could vary within its specified range. Better approach, but with many parameters there can be an infinite number of combinations to consider **Scenario analysis**

A series of scenarios are constructed representing a subset of the potential multi-way analysis.

2.5.1 Limitations of Sensitivity Analysis

- Variation of uncertain parameters one at a time ignores possible interaction between parameters.
- The analyst has discretion as to which variables and what alternative values are included in sensitivity analysis.
- Interpretation is arbitrary as there are no guidelines/standards as to what degree of variation in results is acceptable evidence that the analysis is robust.

Chapter Three

3 The Model

3.1 Introduction

Hepatitis B models are either deterministic or stochastic. Deterministic models have a finite number of states, and specify rules by which individuals move from one state to another through a series of differential equations.

In this chapter, we are going to formulate our SVEIRS model based on the deterministic approach and develop expressions for the equilibrium points. Expressions which will be used to test for the stability of these steady states will also be developed, as well as the formula that will be used to calculate for the basic reproductive number [4].

3.2 Model Formulation

Preliminaries

Differential equations have been developed as mathematical models to study the dynamics of disease transmission for many communicable diseases.

When a community identifies people infected with hepatitis B, new individuals get infected by coming in contact with members of the infected population. In epidemics, it is of high interest to know how the disease will spread. Thus, what we really want to know in many cases is how many infected individuals there will be in the next period. In this chapter, a mathematical model will be developed to study the epidemiology of hepatitis in the central region of Ethiopia. The specific model to be developed is the Susceptible-Vaccinated-Exposed-Infected-Recovered (SVEIRS) model.

3.2.1 Mathematical Models

There are different types of mathematical model in analysis of epidemic diseases. The Following are some of the models used to model different diseases. **SIR, SIS, SIRS, SIR with birth and death, SEIS, SEIR, MSIR,.. etc.**

Description of SVEIRS Model

The SVEIRS model is made up of a host population which is grouped into five classes: the susceptible, the vaccination, the exposed (latent/incubation), and infec-

tious, with sizes denoted by S, V, E, I and R respectively. The host total population, N=S+V+E+I+R. The dynamical transfer of hosts is described in the above figure.

3.2.2 Model Assumptions

- An individual can be infected only by contacting infectious individuals.
- The death rate is assumed to be the same constant d for all hosts, and the total death is balanced by total birth, hence the population is constant.
- Age, sex social status, and race do not affect the probability of being infected.
- It is assumed that after the initial infection, a host stays in a latent period for some time and either recovers and gets back into the susceptible class or become infectious.
- We assume that latently infected individuals (exposed) are not infectious, that is they are not capable of transmitting virus.
- The disease cannot be transmitted during the exposure period.
- Only the acute and chronic stages are differentiated. Patients with either acute or chronic infections are capable of transmitting the disease.
- β be the transmission rate of virus attack when susceptible individual contact with infected ones.
- The vaccinated hosts which contact infected ones before obtaining immunization have the infection probability with a transmission rate $\alpha\beta$ $(0 \leq \alpha\beta \leq 1)$ $\alpha = 0$ means that the vaccinated hosts obtain the full immunization, $\alpha = 1$ means that vaccine loses efficacy in work fully.
- σ is the transfer rates between the susceptible and the vaccinated.
- δ is the rate at which exposed hosts become infectious.
- γ is the recovered rate of infected hosts.

3.2.3 The Model Equations

The population is divided into five classes based on epidemiological status. Individuals are classified as either susceptible, vaccination, latently infected (exposed), infectious or recover. The sizes of these groups are represented by S, V, E, I and R respectively.

Susceptible

The expression that shows how susceptible individuals are infected is represented as the new born vaccinated individual is $b(1-v_1)$, ρR, βSI, ωR. Individuals who die naturally from the susceptible class is expressed as dS.

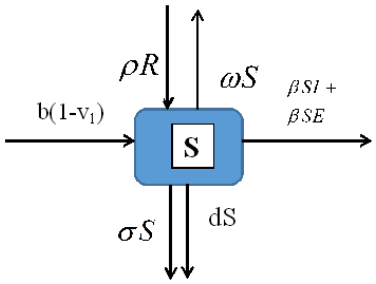


Figure 12: An S(Susceptible) - compartments model

$$\frac{dS}{dt} = b(1-v_1) - \beta SI - \beta SE - dS + \rho R - \omega S - \sigma S$$

Vaccination

From the model rate of change of vaccinated members that moved from the susceptible into the latent class and some of the vaccinated individuals die naturally while some also die due to the disease, the total death is denoted by dV., recover into the vaccinate class and also move from the susceptible class.

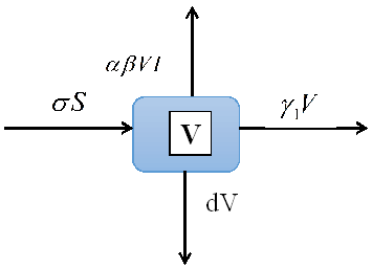


Figure 13: An V(vaccination) - compartments model

$$\frac{dV}{dt} = \sigma S - \alpha\beta VI - \gamma_1 V - dV$$

Exposed Compartment

The rate of change of the latent class is equal to the difference between exposed members that moved from the susceptible into the latent class and the rate at which exposed individuals die naturally, recover into the susceptible class and also move into the infectious class.

The population of exposed individuals reduces as a result of the following three factors;

- Death
- Recovery rate of exposed individuals into the susceptible class
- Recovery rate of exposed individuals into the vaccinated class
- Progression of exposed individuals into the infectious class

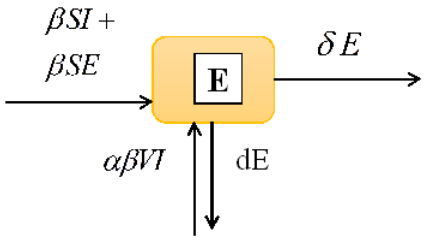


Figure 14: An E(Exposed) - compartments model

$$\frac{dE}{dt} = \beta SI + \beta SE - (\delta + d)E + \alpha\beta VI$$

Infected Component

From the model number of people leaving the exposed class for the infectious class is denoted by δE and leaving the infected class is denoted by γI. Some of the infectious individuals die naturally is denoted by dI while some also die due to the disease is εI, the total death is denoted by (d+ε)I.

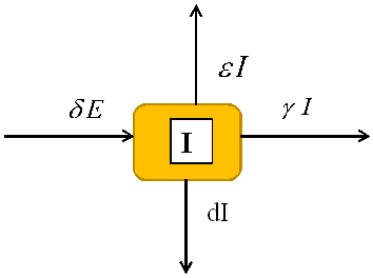


Figure 15: An I(Infected) - compartments model

From what has just been discussed above, the rate of change of the infected class can be put into an equation form as below,

$$\frac{dI}{dt} = \delta E - \gamma I - \varepsilon I - dI$$

Recovered Component

The rate of change of the recover class is equal to the number of people leaving the infected class for the recovered class is denoted by γI. Some of the infectious individuals die naturally denoted by dR.

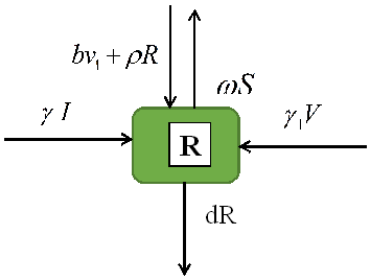


Figure 16: An R(Recovered) - compartments model

From what has just been discussed above, the rate of change of the recovered class can be put into an equation form as below,

$$\frac{dR}{dt} = bv_1 + \gamma I - \rho R + \gamma_1 V + \omega S - dR$$

3.2.4 The SVEIRS model

The SVEIRS model is made up of a host population which is grouped into five classes: the susceptible, the vaccinated, the exposed (latent/incubation), ,the infectious and recovered The host total population, N=S+V+E+I+R. The dynamical

transfer of hosts is described in the following figure.

Putting all model equations together, we obtain the following system of differential equations.

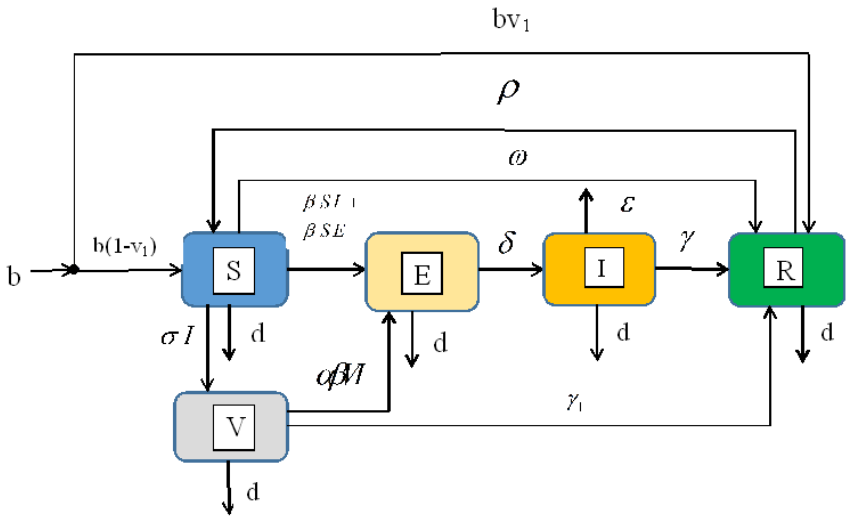


Figure 17: An SVEIR(S) compartment model

$$\frac{dS}{dt} = b(1-v_1) - \beta SI - \beta SE - ds + \rho R - \omega S - \sigma S \tag{2}$$

$$\frac{dV}{dt} = \sigma S - \alpha\beta VI - \gamma_1 V - dV \tag{3}$$

$$\frac{dE}{dt} = \beta SI + \beta SE - (\delta + d)E + \alpha\beta VI \tag{4}$$

$$\frac{dI}{dt} = \delta E - \gamma I - \varepsilon I - dI \tag{5}$$

$$\frac{dR}{dt} = bv + \gamma I + \gamma_1 V - \rho R + \omega S - dR \tag{6}$$

3.3 Reproduction Number

The reproduction number R_0 is defined as the expected number of secondary cases produced by a single infection in a completely susceptible population. The basic reproductive number is dimensionless.

If $R_0 < 1$ each individual produces, on average, less than one new infected individual and hence the disease dies out.

If $R_0 > 1$ each individual produces more than one new infected individual and hence the disease is able to invade the susceptible population.

If $R_0 = 1$, and this is defined as the disease threshold, then one individual infects one more individual [16].

Calculation of the Reproduction Number next generation matrix

The reproduction number R_0 is defined as the average number of secondary cases arising from an average primary case in an entirely susceptible population over the period of infection. The reproduction number is used to predict whether the epidemic will spread or die out. Any epidemiological model has a disease free equilibrium (DFE) at which the population remains in the absence of the disease. According to Diekmann and Heesterbeek, we call FV^{-1} the next generation matrix for the model and set the reproduction number, $R_0 = \rho(FV^{-1})$ where $F = \left[\frac{\partial F_i(x_0)}{\partial x_j}\right]$ and $V = \left[\frac{\partial V_i(x_0)}{\partial x_j}\right]$ for $i \geq 1$ for the number of compartments, and $1 \leq j \leq m$ for the infected compartments only. $\rho(FV^{-1})$ denotes the spectral radius of a matrix A. F and V are m x m matrices, where m is the number of infected classes. Consider an infected individual introduced into compartment k of a disease-free population. The (i, j) entry of F is the rate at which an infected individual in compartment j produces new infections in compartment i, and the (j, k) entry of V^{-1} is the average time an infected individual spends in compartment j during its lifetime, assuming that the population remains near the DFE and barring reinfection Hence, the (i, k) entry of the product FV^{-1} is the expected number of new infections in compartment i produced by the infected individual originally introduced into compartment k. Let us look at the following system of differential equations [28].

$$\frac{dS}{dt} = b(1-v_1) - \beta SI - \beta SE - ds + \rho R - \omega S - \sigma S \tag{7}$$

$$\frac{dV}{dt} = \sigma S - \alpha\beta VI - \gamma_1 V - dV \tag{8}$$

$$\frac{dE}{dt} = \beta SI + \beta SE - (\delta + d)E + \alpha\beta VI \tag{9}$$

$$\frac{dI}{dt} = \delta E - (\varepsilon - \gamma + d)I \tag{10}$$

Equations 7, 8, 9 and 10 are system can be represented in matrix form as shown below where F is the Jacobian of the matrix of infection rates and V is the Jacobian of the matrix of transition rates. So that

$$F = \begin{pmatrix} \beta SI + \beta SE + \alpha\beta VI \\ 0 \\ 0 \\ 0 \end{pmatrix}, \quad V = \begin{pmatrix} (\delta + d)E \\ \delta E - \gamma I - \varepsilon I - dI \\ \sigma S - \alpha\beta VI - \gamma_1 V - dV \\ b(1-v_1) - \beta SI - \beta SE - dS + \rho R - \omega S - \sigma S \end{pmatrix}$$

so that the matrix F and V differentiate(calculate the derivative) with respect to E and I

$$DF = \begin{pmatrix} \beta S & \beta S + \alpha\beta V & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}, \quad DV = \begin{pmatrix} (\delta + d) & 0 & 0 & 0 \\ -\delta & \gamma + \varepsilon + d & 0 & 0 \\ 0 & \alpha\beta V & 0 & \sigma \\ \beta S & \beta S & 0 & d + \sigma + \omega \end{pmatrix}$$

Thus, the spectral radius of the next generation matrix FV^{-1} can be found as,

$R_0 = \rho(FV^{-1}) = \frac{\beta S(\gamma+\varepsilon+d)+\delta(\beta S+\alpha\beta V)}{(\delta+d)(\gamma+\varepsilon+d)}$

The basic reproductive number, R_0 of our model equations is

$$R_0 = \frac{\beta b(1-v_1)(\gamma+\varepsilon+d) + \delta(\beta S + \alpha\beta V)}{(\delta+d)(\gamma+\varepsilon+d)} \tag{11}$$

3.4 Types Of Equilibrium

From the transformed subsystem in, the local stability is analyzed to determine the

Disease-free equilibrium (DFE): $X_{DFE} = (s, v, e, i, r) = (s^*, v^*, 0, 0, 0)$

Endemic equilibrium (EE):$X_{EE} = (s, v, e, i, r) = (s^*, v^*, e^*, i^*, r^*)$

Equilibrium is a state of a system which does not change. An equilibrium solution is a constant solution of the system, and is usually called a **Critical point**.

If the dynamics of a system is described by a system of differential equations then equilibriums can be estimated by setting a derivative (all derivatives) to zero.

Stable:the system always returns to it after small disturbances & also both eigenvalues negative

unstable the system moves away from the equilibrium after small disturbances and also both eigenvalues positive.

Saddle Point the eigenvalue one is positive the other is negative.

Complex eigenvalues with negative real value stable spiral & Positive real value

unstable spiral.

Pure imaginary The eigenvalue are pure imaginary.

Routh-Hurwitz stability criterion is a method that can be used to establish the stability of a system without solving its characteristic equation.

$a_0\lambda^n + a_1\lambda^{n-1} + a_2\lambda^{n-2} + \ldots + a_{n-i}\lambda + a_n = 0$ describing the dynamic system. Note that the necessary condition for the stability is satisfied if all the coefficients $a_i > 0$.

Null-clines:-Null-clines, which will allow us to sketch a qualitative picture of the vector field analytically.The x-nullcline is the set of points where dx/dt=0 and y-nullcline is the set of points where dy/dt=0 .The points of intersection between x-nullcline and y-nullcline are exactly the **equilibrium points**.

Under this, two equilibrium states will be considered, the disease- free equilibrium (where i = 0, e=0, r=0) and the endemic equilibrium (where s,i,v,e,r $\neq$0). We set the right hand side of equations to zero and solve for the values of s, v, e, i and r [29].

3.4.1 Disease-free Equilibrium Point

To obtain the equilibrium points for the system of differential Equations above by equating each of the equations to 0.

The SVEIRS model is differential equations describe the model instead of solving the ordinary differential equation system with known population N from , the transformations:We scale the below equations by letting $s = S/N, v = V/N, e = E/N, i = I/N$ and $r = R/N$where s, v, e, i and r are the susceptible, vaccination, exposed, infected and recover with population N .

$$\frac{ds}{dt} = b(1-v_1) - \beta si - \beta se - ds + \rho r - \omega s - \sigma s = 0$$

$$\frac{dv}{dt} = \sigma s - \alpha\beta vi - \gamma_1 v - dv = 0$$

$$\frac{de}{dt} = \beta si + \beta se - (\delta + d)e + \alpha\beta vi = 0$$

$$\frac{di}{dt} = \delta e - \gamma i - \varepsilon i - di = 0$$

$$\frac{dr}{dt} = bv_1 + \gamma i + \gamma_1 v - \rho r + \omega s - dr = 0$$

At disease-free equilibrium, it is assumed that there is no disease in the system, therefore substituting e=0,i=0 and r=0, into the above equations will yield

$$\begin{aligned} b(1-v_1) - ds - \omega s - \sigma s = 0 \\ \sigma s - \gamma_1 v - dv = 0 \\ bv_1 + \gamma_1 v + \omega s = 0 \end{aligned}$$

So from the evaluations at disease disease-free equilibrium,

$$(S,V,E,I,R) = \left(\frac{b(1-v_1)}{((\alpha + d - \sigma d))}, \frac{\alpha b v_1}{d(d+\alpha)}, 0, 0, 0 \right)$$

3.4.2 Endemic Equilibrium Point

Endemic equilibrium state indicates that the disease persists in the system. Here, we will be solving three systems of equations to obtain the values of s,v, e, i and r. However, the endemic equilibrium point will be differentiated from the disease-free equilibrium point by changing S,V,E,I,R to $(S^*, V^*, E^*, I^*, R^*)$is expressed as follows: [30]

$$\begin{aligned} \frac{ds}{dt} &= b(1-v_1) - \beta si - \beta se - ds + \rho r - \omega s - \sigma s \\ \frac{dv}{dt} &= \sigma s - \alpha\beta vi - \gamma_1 v - dv \\ \frac{de}{dt} &= \beta si + \beta se - (\delta + d)e + \alpha\beta vi \\ \frac{di}{dt} &= \delta e - (\varepsilon + \gamma + d)i \\ \frac{dr}{dt} &= bv_1 + \gamma i + \gamma_1 v - \rho r + \omega s - dr \end{aligned}$$

substituting the above expression into equations above will yield At the endemic state, the equilibrium point will be $(S^*, V^*, E^*, I^*, R^*)$

$$\frac{ds^*}{dt} = A - \beta si - \beta se + \rho r - Bs = 0 \quad (12)$$

$$\frac{dv^*}{dt} = \sigma s - \alpha\beta vi - Cv = 0 \quad (13)$$

$$\frac{de^*}{dt} = \beta si + \beta se + \alpha\beta vi - De = 0 \quad (14)$$

$$\frac{di^*}{dt} = \delta e - Fi = 0 \tag{15}$$

$$\frac{dr^*}{dt} = bv_1 + \gamma i + \gamma_1 v + \omega s - Gr = 0 \tag{16}$$

Let assume with positive constants:

A=$b(1-v_1)$ B=$\omega + d + \sigma$

C=$d+\gamma_1$ D=$\delta + d$

F=$\varepsilon + \gamma + d$ G=$d+\rho$

Based on the solutions of the subsystem , s, v,e, and i are utilized to solve for r in:
$\frac{dr}{dt} = bv + \gamma i + \gamma_1 v + \omega s - (F)r$, where: $G = d + \rho$

First step for EE:- From equation (14) and (15),

$\frac{de^*}{dt} = \beta si + \beta se - De = 0$

$\frac{di^*}{dt} = \delta e - Fi = 0 \qquad \delta e = Fi \qquad i = \frac{\delta e}{F}$

Substituting equation (14) into equation (15) will give us

$\beta si + \beta se = De \qquad \frac{(\beta s(\delta e + Fe)}{F} = D$

Reduce to

$$s^* = \frac{FD}{\beta(\delta + F)} \tag{17}$$

Second step for EE:-From equations 14, 15 and equation 17

$$\beta si + \beta se + \alpha\beta vi - De = 0 \qquad \delta e - Fi = 0$$

$$s^* = \frac{FD}{\beta(\delta + F)}$$

$$\beta s\frac{\delta e}{F} + \beta se + \alpha\beta v\frac{\delta e}{F} - De = 0$$

$$v^* = \frac{\beta s^* + \beta s^* F + DF}{\alpha\beta\delta}$$

Reduce to

$$v^* = \frac{\beta FD + \beta F^2 D + \beta DF(\delta + F)}{\alpha\beta^2\delta(\delta + F)} \tag{18}$$

Third step for EE:-From equations 13, 17 and equation 18

$$\sigma s^* - \alpha\beta vi - Cv = 0$$
$$\frac{FD}{\sigma\beta(\delta+F)} = (\alpha\beta i - C)v^*$$

where $\alpha\beta = K$ and $\delta + F = L$

$$\alpha\beta i - c = \frac{\sigma\alpha\beta\delta L}{\beta l(1+F+L)}$$

Reduce to

$$i^* = \frac{\sigma\delta KL + (c\beta L(1+F+L))}{K\beta L(1+F+L)} \tag{19}$$

Fourth step for EE:-From equations 15 and 19

$$\delta e - Fi = 0 \qquad e^* = \frac{Fi^*}{\delta}$$

Reduce to

$$e^* = \frac{F\sigma\delta KL + (c\beta L(1+F+L))}{\delta K\beta L(1+F+L)} \tag{20}$$

Fifth step for EE:-From equations 16,17 , 18 and 19 and

where $1+F+L = y$, g=βFD,$\alpha\beta = K$ and $\delta + F = L$

$$bv_1 + \gamma i + \gamma_1 v - \rho r + \omega s - dr = 0$$
$$bv_1 + \gamma i^* + \gamma_1 v^* + \omega s^* = Gr$$
$$r^* = \frac{(bv_1 + \gamma i^* + \gamma_1 v^* + \omega s^*)}{G}$$

Reduce to

$$r^* = \frac{\delta L(\sigma\gamma K\delta L + C\beta y) + \gamma_1 g y^2 + \omega FDK\delta y}{GK\beta\delta Ly} \tag{21}$$

3.5 Stability Analysis of the Equilibrium Points

Linearizion is non-linear model change to linear model. One of linearizion method is Jacobian methods.For the stability analysis of the disease-free and the endemic equilibrium points, we will find the Jacobian matrix of SVEIRS model equations.

Equilibrium points at disease-free equilibrium and endemic equilibrium will be substituted into the Jacobian matrix. After this we will solve the matrix equations to obtain an expression for the characteristic equations which will be used in the stability analysis.Finding the Jacobian matrix of the above equations becomes [10].

$$\begin{bmatrix} H \\ k \\ L \\ M \\ N \end{bmatrix} = \begin{bmatrix} \frac{ds}{dt} \\ \frac{dv}{dt} \\ \frac{de}{dt} \\ \frac{di}{dt} \\ \frac{dr}{dt} \end{bmatrix} = \begin{bmatrix} A-\beta si-\beta se+\rho r-Bs \\ \sigma s-\alpha\beta vi-Cv \\ \beta e-\beta si-De \\ \delta e-Fi \\ bv_1+\gamma i+\gamma_1 v+\omega s-Gr \end{bmatrix}$$

The using the above matrix to find Jacobian written as

$$J(S,V,E,I,R) = \begin{bmatrix} \frac{\partial(H)}{\partial(s)} & \frac{\partial(H)}{\partial(v)} & \frac{\partial(H)}{\partial(e)} & \frac{\partial(H)}{\partial(i)} & \frac{\partial(H)}{\partial(r)} \\ \frac{\partial(K)}{\partial(s)} & \frac{\partial(K)}{\partial(v)} & \frac{\partial(K)}{\partial(e)} & \frac{\partial(K)}{\partial(i)} & \frac{\partial(K)}{\partial(r)} \\ \frac{\partial(L)}{\partial(s)} & \frac{\partial(L)}{\partial(v)} & \frac{\partial(L)}{\partial(e)} & \frac{\partial(L)}{\partial(i)} & \frac{\partial(L)}{\partial(r)} \\ \frac{\partial(M)}{\partial(s)} & \frac{\partial(M)}{\partial(v)} & \frac{\partial(M)}{\partial(e)} & \frac{\partial(M)}{\partial(i)} & \frac{\partial(M)}{\partial(r)} \\ \frac{\partial(N)}{\partial(s)} & \frac{\partial(N)}{\partial(v)} & \frac{\partial(N)}{\partial(e)} & \frac{\partial(N)}{\partial(i)} & \frac{\partial(N)}{\partial(r)} \end{bmatrix} =$$

$$\begin{bmatrix} A-\beta i-\beta e-B & 0 & -\beta s & -\beta s & \rho \\ \sigma & \alpha\beta i-C & 0 & \alpha\beta s & 0 \\ \beta i+\beta e & 0 & \beta s-D & \beta s & 0 \\ 0 & 0 & \delta & -F & 0 \\ -\omega & -\gamma_1 & 0 & \gamma & G \end{bmatrix}$$

and evaluated at the equilibrium points to decide on the local stability, which is directly determined from the eigenvalues Λ of:$|J(x)-\Lambda I|=0$

Based on the eigenvalues Λ of the linearized system will either be stable (all the eigenvalues of the Jacobian evaluated at the equilibrium point contain negative real parts) or unstable (at least one of the eigenvalues of the Jacobian evaluated at the equilibrium point has positive real part) for the transformed subsystem in (14-18).

3.5.1 Stability Analysis of the Disease-free Equilibrium

Through substitution of into $\frac{ds}{dt}=0$,$\frac{dv}{dt}=0$ of the through DFE(X_{DFE}) in computed as: where I=0, E=0, R=0 $(S,V,E,I,R)=\left(\frac{b(1-v_1)}{((\alpha+d-\alpha d))},\frac{\alpha bv_1}{d(d+\alpha)},0,0,0\right)$

Substituting these values into the jacobian matrix above and solving eigenvalue $det|J-\Lambda I|=0$ the result we get

$$J(S,V,E,I,R)=\begin{bmatrix} A-\beta i-B & 0 & 0 & -\beta s & \rho \\ \sigma & -\alpha\beta vi-C & 0 & \alpha\beta v & 0 \\ \beta i+\beta e & \alpha\beta i & -D & \beta s+\alpha\beta v & 0 \\ 0 & 0 & \delta & -F & 0 \\ \omega & \gamma_1 & 0 & -\gamma & -G \end{bmatrix}$$

Where J_{DFE} represents Jacobian matrix at disease-free equilibrium From here, we begin solving the matrix equation.$|J_{DFE}-\Lambda I|=0$

$$\begin{bmatrix} A-\beta i-B-\Lambda & 0 & 0 & -\beta s & \rho \\ \sigma & \alpha\beta i+C+\Lambda & 0 & \alpha\beta v & 0 \\ \beta i+\beta e & \alpha\beta i & D+\Lambda & \beta s+\alpha\beta v & 0 \\ 0 & 0 & -\delta & F+\Lambda & 0 \\ -\omega & -\gamma_1 & 0 & \gamma & G+\Lambda \end{bmatrix} = det\,|J_{DFE}-\Lambda I|=0$$

$$\begin{vmatrix} A-\beta i-B-\Lambda & 0 & 0 & \frac{-\beta b(1-v_1)}{((\alpha+d-\sigma d))} & \rho \\ \sigma & \alpha\beta i+C+\Lambda & 0 & \frac{\alpha^2\beta bv_1}{d(d+\alpha)} & 0 \\ \beta i+\beta e & \alpha\beta i & D+\Lambda & \frac{\beta b(1-v_1)}{((\alpha+d))}+\frac{\beta\alpha^2 bv_1}{d(d+\alpha-\sigma d)} & 0 \\ 0 & 0 & \delta & F+\Lambda & 0 \\ \omega & \gamma_1 & 0 & -\gamma & G+\Lambda \end{vmatrix} = 0$$

$$det\,|J_{DFE}-\Lambda I|=0$$

$$(A-\beta i-B-\Lambda)\begin{vmatrix} \alpha\beta i+C+\Lambda & 0 & \frac{\alpha^2\beta bv_1}{d(d+\alpha)} & 0 \\ \alpha\beta i & D+\Lambda & \frac{\beta b(1-v_1)}{((\alpha+d))}+\frac{\beta\alpha^2 bv_1}{d(d+\alpha)} & 0 \\ 0 & \delta & F+\Lambda & 0 \\ \gamma_1 & 0 & -\gamma & G+\Lambda \end{vmatrix}$$

$$+\left(\frac{-\beta b(1-v_1)}{((\alpha+d))}\right)\begin{vmatrix} \sigma & \alpha\beta i+C+\Lambda & 0 & 0 \\ \beta i+\beta e & \alpha\beta i & D+\Lambda & 0 \\ 0 & 0 & \delta & 0 \\ \omega & \gamma_1 & 0 & G+\Lambda \end{vmatrix}$$

$$+\rho\begin{vmatrix} \sigma & \alpha\beta i+C+\Lambda & 0 & \frac{\alpha^2\beta bv_1}{d(d+\alpha)} \\ \beta i+\beta e & \alpha\beta i & D+\Lambda & \frac{\beta b(1-v_1)}{((\alpha+d))}+\frac{\beta\alpha^2 bv_1}{d(d+\alpha)} \\ 0 & 0 & \delta & F+\Lambda \\ \omega & \gamma_1 & 0 & -\gamma \end{vmatrix}=0$$

The above matrix equation reduce to

$$(A-\beta i-B-\Lambda)(-C-\Lambda)\Big[(-D-\Lambda)(-F-\Lambda)(-G-\Lambda) - \big(\frac{-b(\gamma_1-b\gamma_1 v_1+d(1-v_1)}{((\gamma_1\omega+d\omega))}\big)(-G-\Lambda)\delta\Big] +\rho(C+\Lambda)\Big[(D+\Lambda)(-F-\Lambda)w-\big(\frac{-b(\gamma_1-b\gamma_1 v_1+d(1-v_1)}{((\gamma_1\omega+d\omega))}(\omega+d)\big)w\delta\Big]=0$$

$$(A-\beta i-B-\Lambda)(C+\Lambda)\left[(D+\Lambda)(F+\Lambda)(G+\Lambda)+\left(\frac{b(\gamma_1+b\gamma_1 v_1+d(1-v_1)}{((\gamma_1\omega+d\omega))}\right)(G+\Lambda)\delta\right] \text{-}\rho(C+\Lambda)\left[(D+\Lambda)(-F-\Lambda)w-\left(\frac{-b(\gamma_1-b\gamma_1 v_1+d(1-v_1)}{((\gamma_1\omega+d\omega))}(\omega+d)\right)w\delta\right]=0$$

The characteristics equation becomes

$$\Lambda^5+\Lambda^4(B+C+G+D+F)+\Lambda^3(AC+AG-BC-BG-BD-BF-CG-CD-CF -GD-GF-CD+2j\delta)+\Lambda^2(ACG+DAC+FAC+AGD+AGF-BCG-BCD -BCF-BGD-BGF-BDF-CGD-CGF-GDF-Gj\delta+Bj\delta)+\Lambda(ACGB +GFAC+ACDF+AGDF+AGj\delta-BCGD-BCGF-BCDF+BCj\delta-BGDF -CGDF-BGj\delta-CGj\delta)+ACGDF-BCGDF+ACGj\delta-BCGj\delta=0$$

This is a fifth power equation and to solve it, we let the coefficients of $\Lambda^5,\Lambda^4,\Lambda^3,\Lambda^2,\Lambda$ be $C_1,C_2,C_3,C_4 and\ C_5$.That is,

$C_1=[B+C+G+D+F]$,
$C_2=[AC+AG-BC-BG-BD-BF-CG-CD-CF-GD-GF-CD+2j\delta]$ *and*
$C_3=[ACG+DAC+FAC+AGD+AGF-BCG-BCD-BCF-BGD-BGF-BDF-CGD-CGF-GDF-Gj\delta+Bj\delta]$ *and*
$C_4=ACGB+GFAC+ACDF+AGDF+AGj\delta-BCGD-BCGF-BCDF+BCj\delta-BGDF-CGDF-BGj\delta-CGj\delta$ *and*
$C_5=ACGDF-BCGDF+ACGj\delta-BCGj\delta.$

The Therefore, the corresponding characteristic equation can be denoted as

$\Lambda^5+C_1\Lambda^4+C_2\Lambda^3+C_3\Lambda^2+C_4\Lambda+C_5=0$

From equation 1 above the principal diagonal minors of Hurwitz matrix formulate Routh-Hurwitz stability criterion. The root of characterstics equation solved using Routh-Hurwitz stability criterion, if $C_1>0,C_2>0,C_3>0,C_4>0\ and\ C_5>0$.Through a simple computation, we obtain that

$C_5^2C_3C_1-C_5^3-C_5^2C_2^2C_1-C_5^2C_3^2C_2+C_1C_4C_5^2-C_1^2C_4^2C_5+C_5C_4C_3C_2C_1-C_5C_4C_3^2>0$

According to the theorem of Routh-Hurwitz, it follows that all the roots of the char-

acteristics equation have negative real parts. Therefore, the endemic equilibrium is locally asymptotically stable.

3.5.2 Stability Analysis of the Endemic Equilibrium

$$\begin{aligned}
\frac{ds}{dt} &= b(1-v_1) - \beta si - \beta se - ds + \rho r - \omega s - \sigma s = 0 \\
\frac{dv}{dt} &= \sigma s - \alpha\beta vi - \gamma_1 v - dv = 0 \\
\frac{de}{dt} &= \beta si + \beta se - (\delta + d)e + \alpha\beta vi = 0 \\
\frac{di}{dt} &= \delta e - (\varepsilon + \gamma + d)i = 0 \\
\frac{dr}{dt} &= bv_1 + \gamma i + \gamma_1 v - \rho r + \omega s - dr = 0
\end{aligned}$$

$S^*, V^*, I^*, E^* and R^*$ Substituting these values into the jacobian matrix above and solving eigenvalue $det|J - \Lambda I| = 0$

$$J(S^*, V^*, E^*, I^*, R^*) = J_{EE} = \begin{bmatrix} \beta i^* - B & 0 & 0 & -\beta s^* & \rho \\ \alpha\beta i^* & -C & 0 & \alpha\beta s^* & 0 \\ \beta i^*(1+\alpha) & 0 & -D & \beta s^*(1+\alpha) & 0 \\ 0 & 0 & \delta & -F & 0 \\ \omega & \gamma_1 & 0 & -\gamma & G \end{bmatrix}$$

$det|J_{EE} - \Lambda I| = 0$

$$\begin{vmatrix} (\beta i^* - B) - \Lambda & 0 & 0 & -\beta s^* & \rho \\ \alpha\beta i^* & -C - \Lambda & 0 & \alpha\beta s^* & 0 \\ \beta i^*(1+\alpha) & 0 & -D - \Lambda & \beta s^*(1+\alpha) & 0 \\ 0 & 0 & \delta & -F + \Lambda & 0 \\ \omega & \gamma_1 & 0 & -\gamma & G - \Lambda \end{vmatrix} = 0$$

$$(\beta i^* - B - \Lambda)[(-C-\Lambda)(-D-\Lambda)(-F+\Lambda)(G-\Lambda)] + \beta s^*[(-C-\Lambda)(\beta i^* p(\delta(G-\Lambda)))] - \rho[(-C-\Lambda)(-\alpha\beta i^* p\delta\gamma_1 - (D-\Lambda)(\omega(-F-\Lambda)))]$$

This is a fifth equation and to solve it, we let the coefficients of $\Lambda^5, \Lambda^4, \Lambda^3, \Lambda^2, \Lambda$ be C_1, C_2, C_3, C_4 *and* C_5. where BCD=m, BFG=n,CD=p, BC=p, BC=t and CDF=r. That is,

$$\Lambda^5 + \Lambda^4[-\beta i^* + p + D + F] + \Lambda^3[\beta i^*(C + D + F - G) - t - BD + n - F(B - C - D - F) + G(B + C + D + 1) - p] + \Lambda^2[\beta i^*(CF - CG + DF - DG - FG + C + p\delta) - m + qG - BDF + BDG - 2r + pG + \rho\omega C + \rho\omega D + \rho\omega F] + \Lambda[BG\delta s^* + \beta i^* pF - \beta i^* pG - \beta i^* DFG - mF - nC + Dn + rG + \beta i^* pC\delta - \beta i^* pG\delta - \rho CD\omega + \rho C\omega + \rho\alpha\beta i^* p\delta\gamma_1] + \beta B\delta G i^* s^* - B^2 s^* \delta G - Bi^* rG + \rho C\alpha\beta i^* p\delta\gamma_1 - \rho CDF\omega + B^2 s^* i^* pCG\delta.$$

$C_1 = -\beta i^* + p + D + F, C_2 = \beta i^*(C + D + F - G) - t - BD + n - F(B - C - D - F) + G(B + C + D + 1) - p,$
$C_3 = \beta i^*(CF - CG + DF - DG - FG + C + p\delta) - m + qG - BDF + BDG - 2r + pG + \rho\omega C + \rho\omega D + \rho\omega F,$
$C_4 = BG\delta s^* + \beta i^* pF - \beta i^* pG - \beta i^* DFG - mF - nC + Dn + rG + \beta i^* pC\delta - \beta i^* pG\delta - \rho CD\omega + \rho C\omega + \rho\alpha\beta i^* p\delta\gamma_1$ *and*
$C_5 = \beta B\delta G i^* s^* - B^2 s^* \delta G - Bi^* rG + \rho C\alpha\beta i^* p\delta\gamma_1 - \rho CDF\omega + B^2 s^* i^* pCG\delta$

The characteristic equation becomes

$$\Lambda^5 + C_1\Lambda^4 + C_2\Lambda^3 + C_3\Lambda^2 + C_4\Lambda + C_5 = 0$$

From equation 1 above the principal diagonal minors of Hurwitz matrix formulate Routh-Hurwitz stability criterion. The root of characterstics equation solved using Routh-Hurwitz stability criterion, if $C_1 > 0, C_2 > 0, C_3 > 0, C_4 > 0$ *and* $C_5 > 0$.Through a simple computation, we obtain that

$$C_5^2 C_3 C_1 - C_5^3 - C_5^2 C_2^2 C_1 - C_5^2 C_3^2 C_2 + C_1 C_4 C_5^2 - C_1^2 C_4^2 C_5 + C_5 C_4 C_3 C_2 C_1 - C_5 C_4 C_3^2 > 0$$

According to the theorem of Routh-Hurwitz, it follows that all the roots of the characteristics equation have negative real parts. Therefore, the endemic equilibrium is locally asymptotically stable.

3.5.3 Positivity and Well Openness of Solution

The invariant region describes the region describes the region in which the solutions of the model are biologically meaningful and positivity describes that the solutions are always positive.

Differential Equations

$$\frac{ds}{dt} = b(1 - v_1) - \beta SI - \beta SE - dS + \rho R - \omega S - \sigma S$$
$$\frac{dv}{dt} = \sigma S - \alpha\beta Vi - \gamma_1 V - dV$$
$$\frac{de}{dt} = \beta SI + \beta SE - (\delta + d)E + \alpha\beta VI$$
$$\frac{di}{dt} = \delta E - (\varepsilon + \gamma + d)I$$
$$\frac{dr}{dt} = bv_1 + \gamma I + \gamma_1 V - \rho R + \omega S - dR$$

which, together yields N=S+V+E+I+R

$S'(t)+V'(t)+E'(t)+I'(t)+R'(t)=N'(t)=\frac{dN}{dt}$

where SI is the incidence rate at which the susceptible S become infected I by a disease or vaccinated by from disease . By substitution of the five ordinary differential equations system into the relationship of the population N is governed by the ordinary differential equation:

Using the general equation $N'=S'+V'+E'+I'+R'$ the result is $N'=b+dN+I\varepsilon$

Since does not depend on any of the other variables in the system in, the population N is computed using separation of variables:

$$\frac{dN}{dt}=b+d(N+\varepsilon)$$
$$dN=(b+dN+\varepsilon I)dt$$
$$\int dN=(b+dN+I\varepsilon))\int dt$$
$$or\int\frac{dN}{(b+dN+I\varepsilon)}=\int dt$$

to yield: $ln(b+dN+I\varepsilon)$=$t+c$

As a result of solving above through exponentiation, the population N is given as:

$$N=\frac{(b+I\varepsilon)+e^{t+c}}{d}$$

with time-varying population N(t).The expression obtained above then is the condition of existence. The b is birth rate and ε death rate are fraction between 0 and 1 also $1<(b+I\varepsilon)<0$ the result $e^{t+c}>0$.

Therefore the solutions of system of SVEIRS are feasible if they enter the region.

$$\Omega=\left\{(S,V,E,I,R)\in\ \Re^5:\frac{N}{d}>0\right\}$$

Chapter Four

4 Optimal Control

Optimal control deals with the problem of finding a control law for a given system such that a certain optimality criterion is achieved. A control problem includes a cost functional that is a function of state and control variables. An optimal control is a set of differential equations describing the paths of the control variables that minimize the cost function. The optimal control can be derived using Pontryagin's maximum principle (a necessary condition also known as Pontryagin's minimum principle or simply Pontryagin's Principle) or by solving the Hamilton-Jacobi-Bellman equation (a sufficient condition) [25].

4.1 Introduction to Optimal Control

Optimization is the process in which the best feasible solution for a problem is found. This usually entails finding either a maximum or minimum, which are called extrema, of the possible solutions. This can be done in various ways, though the most common involves using some version of the derivative of the function [32] . numerical solution of optimal control was difficult using by hand computation.

Numerical mathematics is study of quantitative approximations to the solutions of mathematical problems including consideration of and bounds to the errors involved. Optimal control theory is no exception to this rule. The purpose here is to implement three different numerical algorithms in MATLAB to approximate the solution to an optimal control problem. Once the methods are developed, the concept of convergence for each method will be discussed as well as any flaws or problems with each specific method.

Mathematical epidemiology has contributed to a better understanding of the dynamical behavior of infectious diseases, its impacts, and possible future predictions about its spreading. Mathematical models are used in comparing, planning, implementing, evaluating, and optimizing various detection, prevention, therapy, and control programs. Many influential results related to the development and analysis of epidemiological models have been established and can be found in many articles

and books [32, 33].

Epidemiological models often take the form of a system of nonlinear, ordinary, and differential equations without time delay. However, for various biological reasons, the real dynamic behavior of an epidemic depends not only on its current state but also on its past history. Thus, to reflect the real behavior of some diseases, many researchers have proposed and analyzed more realistic models including delays to model different mechanisms in the dynamics of epidemics like latent period, temporary immunity and length of infection [34–37].

To the best of our knowledge, including time delay in both state and control variables in the context of an epidemic controlled model has not been studied. There have been some works like [38] which study an optimal control problem with time delay but only in the state variable. In this paper, we will investigate the effect of a vaccination program in the case of an SIR (susceptible-infected-recovered) epidemic model with time delay in the control and the state variables [39].

Consider an optimally controlled SVEIRS epidemic model with time delay, where the control means the percentage of susceptible individuals being vaccinated per time unit, and the time delay represents the required time so that a vaccinated susceptible person moves from the susceptibles class to the recovered class. Optimal control approach to minimize the number of susceptible, vaccinated, exposed and infected individuals and to maximize the number of recovered individuals during the course of an epidemic [26].

4.1.1 Computational optimal control

The solutions to many optimal control problems cannot be found by analytical means. Over the years, many numerical procedures have been developed to solve general optimal control problems. Direct methods, optimal control problems are discretized and converted into nonlinear programming problems.

Indirect methods involve iterating on the necessary optimality conditions to seek their satisfaction. This usually involves attempting to solve nonlinear two-point boundary value problems, through the forward integration of the plant equations and the backward integration of the co-state equations.

Numerical methods for optimal control

Optimal control problems are generally nonlinear and therefore, generally do not have analytic solutions. As a result, it is necessary to employ numerical methods to solve optimal control problems. The approach that has risen to prominence in numerical optimal control over the past two decades is that of so-called direct methods. In a direct method, the state and/or control are approximated using an appropriate function approximation. The disadvantage of indirect methods is that the boundary-value problem is often extremely difficult to solve (particularly for problems that span large time intervals or problems with interior point constraints) [25].

Dynamic programming

Dynamic programming is an alternative to the variational approach to optimal control. It was proposed by Bellman in the 1950s, and is an extension of Hamilton-Jacobi theory. Bellman's principle of optimality is stated as follows: "An optimal policy has the property that regardless of what the previous decisions have been, the remaining decisions must be optimal with regard to the state resulting from those previous decisions". This principle serves to limit the number of potentially optimal control strategies that must be investigated. It also shows that the optimal strategy must be determined by working backward from the final time.

Discrete-time optimal control

Most of the problems defined above have discrete-time counterparts. These formulations are useful when the dynamics are discrete, or when dealing with computer controlled systems. [25]

Optimal control solutions are now often implemented digitally, contemporary control theory is now primarily concerned with discrete time systems and solutions. A common solution strategy in many optimal control problems is to solve for the costate (sometimes called the shadow price)$\lambda(t)$. The costate summarizes in one number the marginal value of expanding or contracting the state variable next turn. The marginal value is not only the gains accruing to it next turn but associated with the duration of the program. It is nice when $\lambda(t)$ can be solved analytically, but

usually the most one can do is describe it sufficiently well that the intuition can grasp the character of the solution and an equation solver can solve numerically for the values.

Having obtained $\lambda(t)$, the turn t optimal value for the control can usually be solved as a differential equation conditional on knowledge of $\lambda(t)$. Again it is infrequent, especially in continuous-time problems, that one obtains the value of the control or the state explicitly. Usually the strategy is to solve for thresholds and regions that characterize the optimal control and use a numerical solver to isolate the actual choice values in time [40].

Finite time

Consider the problem of a mine owner who must decide at what rate to extract ore from his mine. He owns rights to the ore from date $\{0\}$ to date T. At date $\{0\}$ there is x_0 ore in the ground, and the instantaneous stock of ore x(t) declines at the rate the mine owner extracts it u(t). The mine owner extracts ore at cost $u(t)^2/x(t)$ and sells ore at a constant price p. He does not value the ore remaining in the ground at time T (there is no "scrap value"). He chooses the rate of extraction in time u(t) to maximize profits over the period of ownership with no time discounting [40].

4.2 Optimal control problem

A typical OC problem requires a performance index or cost functional (J[x(t), u(t)]), a set of state variables (x(t) εX), a set of control variables (u(t)εU) in a time t, with $t_0 \leq t \leq t_f$. The main goal consists in finding a piecewise continuous control u(t) and the associated state variable x(t) to maximize a given objective functional. The development of this chapter will be closely structured from Lenhart and Workman work [23].

Definition 1. *(Basic OC Problem in Lagrange formulation)An OC problem is in the form*

$max_u J[x(t),u(t)] = \int_{t_0}^{t_f} f(t,x(t),u(t))dt$

Subject to $x' = g(t,x(t),u(t))$

$x(t_0) = x_0, x(t_1)$

x(t_f) could be free, which means that the value of x(t_f) is unrestricted, or could be fixed, i.e, x(t_f)=x_f .

For our purposes, f and g will always be continuously differentiable functions in all three arguments. We assume that the control set U is a Lebesgue measurable function. Thus, as the control(s) will always be piecewise continuous, the associated states will always be piecewise differentiable.

We have been focused on finding the maximum of a function. We can switch back and forth between maximization and minimization by simply negating the cost functional:

$min\{J\} = -max\{J\}$An OC problem can be presented in different ways, but equivalent, depending on the purpose or the software to be used. [24]

Formulation of optimal control problems

There are various types of optimal control problems, depending on the performance index, the type of time domain (continuous, discrete), the presence of different types of constraints, and what variables are free to be chosen. The formulation of an optimal control problem requires the following:

- a mathematical model of the system to be controlled,
- a specification of the performance index,
- a specification of all boundary conditions on states, and constraints to be satisfied by states and controls,
- a statement of what variables are free.

Optimal Control Theory

Optimal control theory, an extension of the calculus of variations, is a mathematical optimization method for deriving control policies. The method is largely due to the work of Lev Pontryagin and Richard Bellman in the 1950s, after contributions to calculus of variations by Edward J. McShane. Optimal control can be seen as a control strategy in control theory [25].

From a general perspective, an optimal control problem is an optimization problem.

The difference between the two is that, in optimal control theory, the optimizer is a function, not just a single value. This function that optimizes is called the optimal control. The technical definition of an optimal control problem is the process of determining control and state trajectories for a dynamic system over a period of time to minimize a performance index. The state variable (or function) is the set of variables (functions) used to describe the mathematical state of the system. The control or control function is an operation that controls the recording, processing, or transmission of data. These two functions drive how the system works and how the desired control is found. With these definitions, a basic optimal control problem can be defined. This basic problem will be referred to as our standard problem (SP).

Standard Problem
$max_u J(x(t),u(t)) = \int_{t_0}^{t_f} f(t,x(t),u(t))$
Subject to $x' = g(t,x(t),u(t))$
$x(t_0) = x_0, x(t_1)$

The optimal control, u^*, is the function that optimizes the objective function, J(u), This control is not bounded. The other arguments in equation are t, which is the time variable, and x(t), which is the state equation. The relationship between u and x is defined by equations and is denoted by the relationship in the map $u(t) \longrightarrow x$ = x(u). Though this relationship does indeed exist, x is really just a function of the independent time variable, but in writing x(u), the dependence that x has on u is shown. Equation is the constraint equation on the state, and the initial and terminal conditions. By setting x(t) to be free, this simply means that the state can grow over time unconditionally.

To solve our basic optimal control problem, a set of what is called necessary conditions must be satisfied. In mathematics, a necessary condition is a condition that must be satisfied for a statement to be true, but that does not in and of itself make it true. In regards to (SP), there are such conditions that must be satisfied in order to solve the problem. In the 1950's, a Russian mathematician by the name of Lev Pontryagin and his co-workers [35] in Moscow derived such conditions. Pontryagin introduced the adjoint function to affix to the differential equation to the objective

functional. These functions serve a similar purpose as the Lagrange multipliers in multi variable calculus. The necessary conditions needed to solve the basic problem are derived from what is referred to as the Hamiltonian, H, which is given by equation.

$$H(t,S,V,E,I,R,u) = f(t,S,V,E,I,R,u) + \sum_{i=1}^{5} \lambda_i g_i(t,S,V,E,I,R,u)$$

Here λ denotes the adjoint and is dependent on t, x, and u. Using this, Pontryagin determined that the following conditions are satisfied by the optimal control, denoted as u^*, when the Hamiltonian is nonlinear in u.

$\frac{\partial(H)}{\partial(u)} = 0$ at $u = u^* \Rightarrow f_u(t,x,u) + \lambda g(t,x,u)$=0$\Rightarrow$optimality condition.
$\lambda' = \frac{\partial(H)}{\partial(x_i)} \Rightarrow \lambda' = -(f_x + \lambda g_x) \Rightarrow$adjoint condition
$\lambda(t_f) = 0 \Rightarrow$ transversality condition.
$x' = g(t,x,u)$
$x(t_0) = x_0$ Dynamics of the State Equation

With these conditions, there is now a process on how to solve the standard problem defined by SP [35].

Optimal control application

Optimal control is one of the useful mathematical tools through which we are able to design the control strategy for controlling various kind of infectious diseases. To develop a control strategy, we use the optimal control theory. Our purpose here is to reduce HBV infection from the population by maximizing the number of susceptible S(t) and recovered individuals R(t) and minimizing the number of infected with acute hepatitis B individuals E(t), infected with chronic hepatitis B individuals I(t) by using the time-dependent control variables isolation $u_1(t)$ treatment with media education, minimize amount dunking for each individuals $u_2(t)$ and hepatitis B drug $u_3(t)$.

In the system, we have four state variables S(t), V(t), E(t), I(t) and R(t). For the control problem, we consider the three control variables, namely isolation $u_1(t)$ treatment with media education, minimize amount dunking for each individuals $u_2(t)$ and hepatitis B drug(pills) $u_3(t)$. Thus, we have the following optimal control

problem to minimize the objective functional [4].

$$J(u_1,u_2,u_3) = \int_0^T (A_1S + A_2E + A_3I + \frac{1}{2}(B_1u_1^2 + B_2u_2^2 + B_3u_3^2))dt$$

SVEIRS model with Optimal control

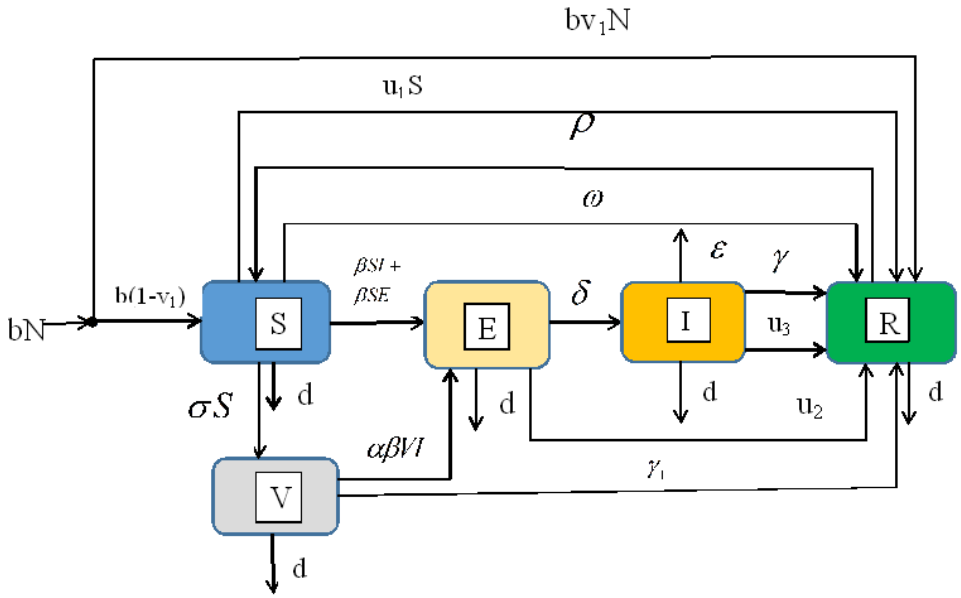


Figure 18: An SVEIR(S) with optimal control compartment model

SVEIRS model equations

$$\frac{dS}{dt} = b(1-v_1) - \beta SI - \beta SE - dS + \rho R - \omega S - \sigma S - u_1 S$$

$$\frac{dV}{dt} = \sigma S - \alpha\beta VI - \gamma_1 V - dV$$

$$\frac{dE}{dt} = \beta SI + \beta SE - (\delta + d)E + \alpha\beta VI - u_2 E$$

$$\frac{dI}{dt} = \delta E - (\varepsilon + \gamma + d)I - u_3 I$$

$$\frac{dR}{dt} = bv_1 + \gamma I + \gamma_1 V - \rho R + \omega S - dR + u_1 S + u_2 E + u_3 I$$

Table 2: Description of state variables with control variables

Parameter	value estimated
b	Birth Rate
d	Natural Death Rate

Parameter	value estimated
v_1	vaccinated newborns
ω	Vaccination Rate
ρ	Transmission Rate of Recovered to Susceptible
β	Rate at which the susceptibilities become exposed to HBV
δ	Transmission Rate of Exposed to Infected
ε	Rate of Infection Death
α	Transmission Rate of vaccinated to Exposed
σ	the transfer rates between the susceptible and the vaccinated
γ	Recovery rate of Infected to Recovered
γ_1	Transmission Rate of Vaccinated+ to Recovered
u_1	control variable treatment with media education
u_2	control variable with minimize amount dunking for each individuals
u_3	control variable with minimize using drug

Steps in formulating optimal system of an optimal control problem

1. Formulate the Hamiltonian for the problem.

   H(t,x,u_1,u_2,u_3,λ)=f(t,x,u_1,u_2,u_3)+λg(t,x,u_1,u_2,u_3)

2. Write the adjoint differential equation, transversality boundary condition and optimality condition. Now there are three unknowns, u_1^*,u_2^*,u_3^* , x^* and λ.
   $\lambda' = \frac{-\partial(H)}{\partial(x)} \Rightarrow \lambda' = -(f_x + \lambda g_x)$ ⇒adjoint condition
   $\lambda(t_f) = 0 \Rightarrow$ transversality condition.
   $\frac{-\partial(H)}{\partial(x)} = 0$ at $u_1 = u_1^*, u_2 = u_2^*, u_3 = u_3^* \Rightarrow f_u(t,x,u_1,u_2,u_3) + \lambda g(t,x,u_1,u_2,u_3)$=0⇒optimality condition.

3. Solve for u^* in terms of x^* and λ .

4. After finding the optimal states and adjoint, solve for the optimal control.

4.3 optimal control problem

If x(t) represents the group of individuals to be educated using media, minimize amount of drinking alcohol also using drug and $(u_1(t),u_2(t),u_3(t)) \in (u_1,\ u_2,\ u_3)$ represents the control where the control sets u_1, u_2 and u_3. The control function u(t), with $0 \leq u_1(t),u_2(t),u(3) \leq 1$ represents the fraction of susceptible,exposed

and infected individuals that requires education,minimize amount drinking alcohol and use drug When $u_1(t), u_2(t), u_3(t)$ is close to 1, then control methods failure is very low but with high implementation costs. The optimal control problem is to minimize the multiple objective cost functional J to be minimized considering the costs of control methods of susceptible,exposed and infected human given by:

$$J(u_1,u_2,u_3) = \int_0^T (A_1S(t)+A_2E(t)+A_3I(t)+\frac{1}{2}(B_1u_1^2(t)+B_2u_2^2(t)+B_3u_3^2(t)))dt$$

Subject to

$$\begin{aligned}
\frac{dS}{dt} &= b(1-v_1)-\beta SI-\beta SE-dS+\rho R-\omega S-\sigma S-u_1S \\
\frac{dV}{dt} &= \sigma S-\alpha\beta Vi-\gamma_1 V-dV \\
\frac{dE}{dt} &= \beta SI+\beta SE-(\delta+d)E+\alpha\beta VI-u_2E \\
\frac{dI}{dt} &= \delta E-(\varepsilon+\gamma+d)I-u_3I \\
\frac{dR}{dt} &= bv_1+\gamma I+\gamma_1 V-\rho R+\omega S-dR+u_1S+u_2E+u_3I
\end{aligned}$$

Where A_1, A_2, A_3 is balancing cost factors due to the size of susceptible, exposed and infective .

B_1, B_2, B_3 represents the "weight" attached on the cost of control methods.

4.3.1 Pontryagin's Maximum Principle (PMP)

From the definition of Hamiltonian which stated.

$$\begin{aligned}
H(t,S,V,E,I,R,u_1,u_2,u_3) &= f(t,S,V,E,I,R,u_1,u_2,u_3)+\sum_{i=1}^{5}\lambda_i g_i(t,S,V,E,I,R,u_1,u_2,u_3) \\
&\Rightarrow f(t,S,V,E,I,R,u_1,u_2,u_3)+\lambda_1\frac{dS}{dt}+\lambda_2\frac{dV}{dt}+\lambda_3\frac{dE}{dt}+\lambda_4\frac{dI}{dt}+\lambda_5\frac{dR}{dt}
\end{aligned}$$

$$\begin{aligned}
&H(t,S,V,E,I,R,u_1,u_2,u_3) = A_1S(t)+A_2E(t)+A_3I(t)+\tfrac{1}{2}(B_1u_1^2(t)+B_2u_2^2(t)+ \\
&B_3u_3^2(t)) \\
&+\begin{pmatrix}
\lambda_1(b(1-v_1)-\beta SI-\beta SE+\rho R-(\sigma+d+\omega+u_1)S)+ \\
\lambda_2(\sigma S-\alpha\beta VI-\gamma_1 V-dV) \\
+\lambda_3(\beta SI+\beta SE-(\delta+d+u_2)E+\alpha\beta VI) \\
+\lambda_4(\delta E-(\varepsilon-\gamma+d+u_3)I) \\
+\lambda_5(bv+(\gamma+u_3)I+\gamma_1 V+u_2E-(d+\rho)R+(\omega+u_1)S)
\end{pmatrix}
\end{aligned}$$

4.3.2 Find the adjoint function for each state variable(S,V,E,I,R)

- Adjoint function with respect to S

  $\lambda_1' = \frac{-\partial(H)}{\partial(S)} = -A_1 + \lambda_1(\beta I + \beta E + (\sigma + \omega + u_1 + d)) + \lambda_2(\sigma) + \lambda_3((-\beta E - \beta I) - \lambda_5(\omega + u_1)$

- Adjoint function with respect to V

  $\lambda_2' = \frac{-\partial(H)}{\partial(V)} = \lambda_2(\alpha\beta I + \gamma_1 + d) - \lambda_3(\alpha\beta I) - \lambda_5\gamma_1$

- Adjoint function with respect to E

  $\lambda_3' = \frac{-\partial(H)}{\partial(E)} = -A_2 + \lambda_1(\beta S) + \lambda_3((\beta S + \delta + d + u_2) - \lambda_4(\delta) - \lambda_5 u_2$

- Adjoint function with respect to I

  $\lambda_4' = \frac{-\partial(H)}{\partial(I)} = -A_3 - \lambda_1\beta S + \lambda_2(\beta\alpha V) + \lambda_3((\beta S + \alpha\beta V) - \lambda_4(d + \varepsilon + \gamma + u_3) - \lambda_5(\gamma + u_3)$

- Adjoint function with respect to R

  $\lambda_5' = \frac{-\partial(H)}{\partial(R)} = \lambda_1\rho + \lambda_5(\omega + d + \rho)$

4.3.3 optimality condition

In order to illustrate the characterization of the optimal control u^*, consider first the optimality condition.

$\frac{\partial(H)}{\partial(u_1)} = 0$ at $u_1 = u_1^*$
$B_1(u_1(t)) + \lambda_1 S - \lambda_5 S = 0$
$u_1^*(t) = \frac{(-\lambda_1+\lambda_5)S}{B_1}$
$u_1^*(t) = max\left\{min\left\{\frac{(-\lambda_1+\lambda_5)S}{B_1}\right\}, 0\right\}$
$\frac{\partial(H)}{\partial(u_2)} = 0$ at $u_2 = u_2^*$
$B_2(u_2(t)) + \lambda_3 E - \lambda_5 E = 0$
$u_2^*(t) = \frac{(-\lambda_3+\lambda_5)E}{B_2}$
$u_2^*(t) = max\left\{min\left\{\frac{(-\lambda_3+\lambda_5)E}{B_2}\right\}, 0\right\}$
$\frac{\partial(H)}{\partial(u_3)} = 0$ at $u_3 = u_3^*$
$B_3(u_3(t)) - \lambda_4 I + \lambda_5 I = 0$
$u_3^*(t) = \frac{(-\lambda_4+\lambda_5)I}{B_3}$
$u_3^*(t) = max\left\{min\left\{\frac{(-\lambda_4+\lambda_5)I}{B_3}\right\}, 0\right\}$

4.3.4 Analytical Process

The first method that will be discussed is the Forward Backward Sweep (FBS). This iterative method is named based on how the algorithm solves the problem's state and adjoint ODE's. Given an approximation of the control function, FBS first solves the state 'forward' in time (from t_0 to t_1) then solves the adjoint 'backward' from t_0 to t_1). Once it has found the state and adjoint functions, the control is updated based on Standard Problem and then the state, control, and adjoint are tested for convergence against a user provided tolerance and depending on that, the algorithm eithers starts the process over using the updated control or the algorithm terminates with the final approximations for the state, adjoint, and control functions considered as the solution to the optimal control problem.

1. Form the Hamiltonian for the problem.
2. Write the adjoint differential equation, transversality boundary condition, and the optimality condition in terms of three unknowns, u^*, x^*, and λ.
3. Use the optimality equation $H_u = 0$ to solve for u^* in terms of x^* and λ.
4. Solve the two differential equations for x^* and λ with two boundary conditions.
5. After finding the optimal state and adjoint, solve for the optimal control using the formula derived by step (3).

If it is possible to solve for the optimal control in terms of x^* and λ, then the formula for u^* is called the characterization of the optimal control. The state equation and adjoint equations together with the characterization and boundary conditions are called the optimality system [42].

4.3.5 Backward-forward Sweep Method

This method is described in a recent book by Suzanne Lenhart and Workman [19] and it is known as forward-backward sweep method. The process begins with an initial guess on the control variable. Then, the state equations are simultaneously solved forward in time and the adjoints equations are solved backward in time.

The control is updated by inserting the new values of states and adjoints into its characterization, and the process is repeated until convergence occurs. It can be implemented, using the following algorithm:

Algorithm Forward-Backward sweep

Step 1: Make an initial guess for $\overline{u}$ over the interval ($\overline{u}\equiv 0$ is almost always sufficient)

Step 2: Using the initial condition $x_1 = x(t_0) = a$ and the values for $\overline{u}$ solve $\overline{x}$ in time according to its differential equation in the optimality system;

Step 3: Using the transversality condition $\lambda_{(N+1)} = \lambda(t_f)$ and the values for $\overline{u}$ and $\overline{x}$, solve $\overline{x}$ backward in time according to its differential equation in the optimality system;

Step 4: Update $\overline{u}$ by entering the new $\overline{x}$ and $\overline{\lambda}$ values into the characterization of the optimal control.

Step 5: Verify convergence: if the variables are sufficiently close to the corresponding in the previous iteration, then output the current values as solutions, else return to Step 2.

Chapter Five

5 Model Application

5.1 Introduction

In this chapter, we are going to estimate parameter values that will be used for the analysis. The values will be substituted into equation obtained in chapter three to get the exact value for the basic reproductive number. Sensitivity analysis will also be carried out on the parameter values to investigate their impact on study results.

Parameter Estimate

Parameter estimation was based on the data obtained from Ethiopia from 2014 to 2015, and published standard estimates [41].

Table is below shows summary of estimated parameter values Substituting the above values into the SVEIRS model equations developed we obtain

Table 3: Description of state variables and its estimated value

Parameter	value estimated	Source
S	0.5	Assume
V	0.1	Assume
E	0.1	[31]
I	0.2	[31]
R	0.1	[31]
b	0.014	Assume
d	0.0003	[41]
v_1	0.43	Assume
ω	2.0401	Assume
ρ	0.0000118	Assume
β	0.3521	Assume
δ	2.511	Assume
ε	0.345	Assume
α	1.67	Assume
σ	1.501	Assume
γ	2.879	Assume
γ_1	1.75	Assume

$$\frac{ds}{dt} = b(1-v_1) - \beta SI - \beta SE - dS + \rho R - \omega S - \sigma S$$
$$\frac{dv}{dt} = \sigma S - \alpha\beta Vi - \gamma_1 V - dV$$
$$\frac{de}{dt} = \beta SI + \beta SE - (\delta + d)E + \alpha\beta VI$$
$$\frac{di}{dt} = \delta E - (\varepsilon + \gamma + d)I$$
$$\frac{dr}{dt} = bv_1 + \gamma I + \gamma_1 V - \rho R + \omega S - dR$$

Substituting the given values on the table into SVEIRS equations and the above equilibrium equation.

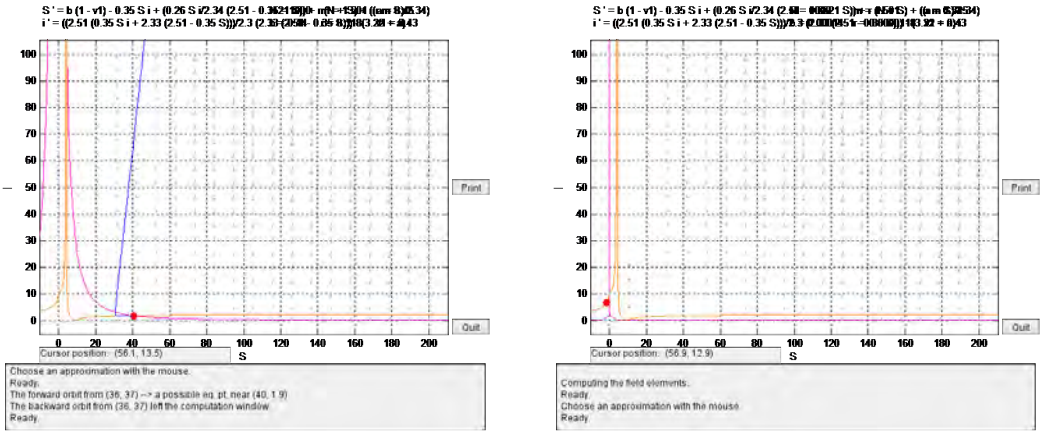
5.2 Stability Analysis

5.2.1 Qualitative Analysis SVEIRS Model

SVEIRS model can be simplified from five to two equations. Recalling that N=S+V+E+I+R a substitution of N-V-E-I-R for S in the first equation can be made and $R = \frac{N-b+dN+(\varepsilon+\gamma)I+\omega S}{1+\rho+d}$

$$\frac{dS}{dt} = b(1-v_1) + \rho R - (\beta I + d + \omega + \sigma)S - \beta S\left(\frac{N-b+dN+\varepsilon I+\alpha\beta I(N-S-I-R)}{1-\beta S+(\delta+d)\alpha\beta I}\right)$$
$$\frac{dI}{dt} = \delta\left(\frac{N-b+dN+\varepsilon I+\alpha\beta I(N-S-I-R)}{1-\beta S+(\delta+d)\alpha\beta R}\right) - (\varepsilon+\gamma+d)I$$

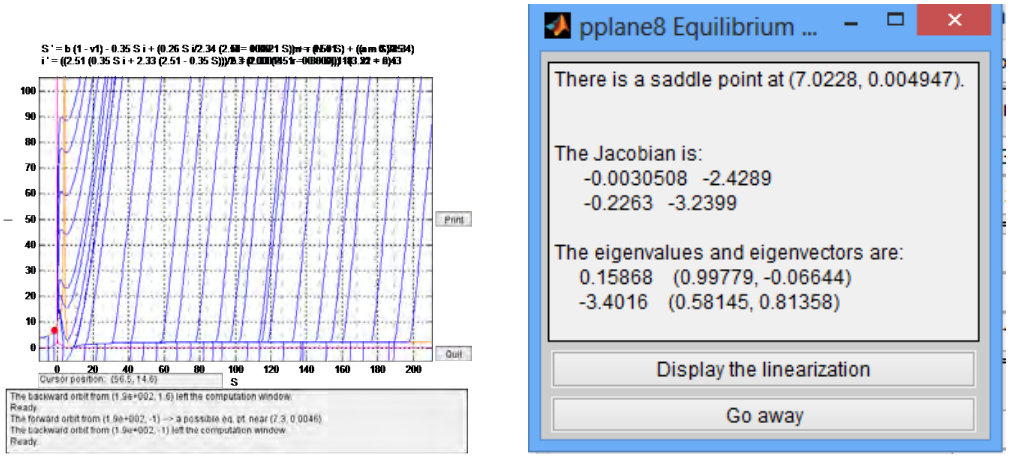
From the above equations we can plot phase plane using Matlab code and the given value of parameters.



(a) pplane plot of S and I with an nullcline & equilibrium point

(b) pplane plot of S and I with an nullcline & equilibrium point

Figure 19: A phase plane plot of S and I with an nullcline & equilibrium point



(a) pplane plot of S and I with an nullcline & equilibrium point

(b) pplane plot of S and I with an nullcline & equilibrium point

Figure 20: SVEIRS model of pplane plot of S and I & equilibrium point

Figures 19 and 20 graphs representing the SVEIRS Model for hepatitis B has been displayed in figure using pplane. The proportion of susceptible was initially the proportion of exposed population , vaccination population and recovery population were substituted and the result S and I.

The nullclines and their intersection. Also shows the equilibrium point with different value of birth rate, vaccination for new born child, σ and ρ. The equilibrium point means the infected and susceptible population is equal that show the hepatitis B disease the population number.

5.2.2 Quantitative Analysis SVEIRS Model

Sensitivity analysis enables the determination of which parameters of a model are most responsible for generating the variability in the value of the model's outputs over time. In this study, one way sensitivity analysis will be used, thus estimates for each parameter are varied one at a time to investigate the impact on study results.

Here, we are going to investigate the steady states to see which of them will be stable and this will help us confirm whether the disease will die out or persist in the region.

Disease free equilibrium(S,V,E,I,R)=(1, 1, 0, 0, 0).The eigenvalue becomes $\Lambda^5 - C_1\Lambda^4 + C_2\Lambda^3 + C_3\Lambda^2 + C_4\Lambda + C_5 = 0$. From Routh-Hurwitz criterion, the characteristic equation for the disease-free equilibrium above has unstable. This means that

hepatitis B will persist.

Endemic equilibrium point$(S^*, V^*, E^*, I^*, R^*)$ using the random estimated value $\Lambda^5 + C_1\Lambda^4 + C_2\Lambda^3 + C_3\Lambda^2 + C_4\Lambda + C_5$. From Routh-Hurwitz criterion, since the characteristic equation above corresponding to the endemic equilibrium is stable. This means that hepatitis B will persist.

Basic reproduction number:- The basic reproductive number, R_0 of our model equations is

$$R_0 = \frac{\beta b(1-v_1)(\gamma+\varepsilon+d)+\delta(\beta S+\alpha\beta V)}{(\delta+d)(\gamma+\varepsilon+d)}$$

The basic reproduction number of the SVEIRS model is substituting given values on the above R_0 formula and the result is $R_0 \cong 0.6463$; hence,we use the parameter value given above will reduce R_0 and $R_0 < 1$ that is the HBV die out.

Analysis of Hepatitis B Using Matlab

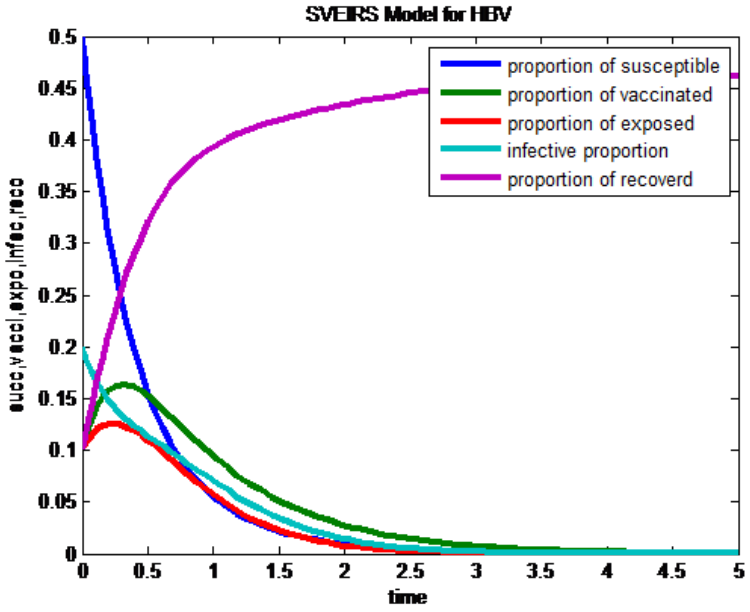


Figure 21: An SVEIR(S) compartment model using ode45

A graph representing the SVEIRS Model for hepatitis B has been displayed in figure 21. The proportion of susceptible was initially the proportion of exposed group , infected group and recovery group were 0. We increase the recovery rate of the exposed that of infected increases sharply. The exposed infective reduced.

Decreasing β increases the susceptible and increases the exposed and reduces that of the infective. when the recovery rate of the infective increases also susceptible increases sharply within the first two years and then begins to reduce gradually in the fifth year. The infective also reduces drastically and the exposed reduces. When b was reduced of susceptible reduced and a very small decrease in the exposed proportion, that is, but the proportion of infective.

Herd immunity

If the percentage or proportion of the population that is immune exceeds the herd immunity level for the disease, then the disease can no longer persist in that particular population. Thus, if this level of immunity can be exceeded by means of mass vaccination, then the disease can indeed be eliminated.

Assuming that, the herd immunity level is denoted by H. Recall that, for a stable state: $R_0 S = 1$

So that, S will be $(1-H)$, since H is the proportion of the population that are immune and H + S must equal one (since in this simplified model, everyone is either susceptible or immune). Then:

$R_0 * (1-H) = 1,\ \ 1-H = \frac{1}{R_0},\quad H = 1-\frac{1}{R_0}$

Therefore, $H = (1-0.6463)100 = 35.37\%$

Remember that this is the threshold level. If the proportion of immune individuals exceeds this level due to a mass vaccination programme, the disease will die out. For instance, when a 100 newborns benefits 90% vaccine coverage, it yields 0.43 vaccinated and 0.57 unvaccinated. Thus, it sums up immune and susceptible, and the corresponding herd immunity is 35.37%. By using the available data, we can estimate R_0. It is well known that, the higher $R_0 = 0.6463$ is for a disease, the higher the proportion of the population that need to be vaccinated to achieve herd immunity.

The Threshold Effect

To explain this mathematically requires re-examining the equilibrium equations. Disease threshold means one individual infects one more individual

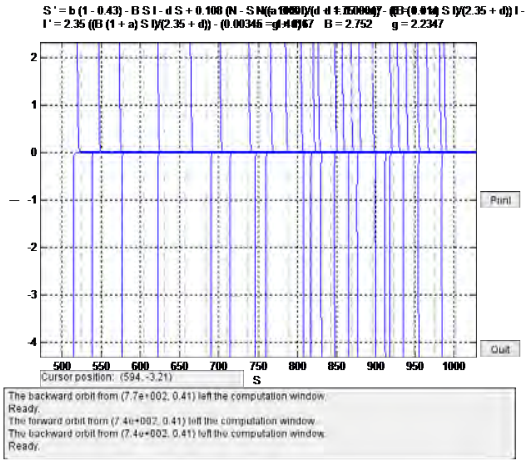


Figure 22: A phase plane plot of I and S with an threshold effect

Figure 22 shows the threshold effect is drawing by using pplane8 matlab program. The susceptible population is initially large enough, with considerable amount of contact between individuals and a high enough rate of infection.

5.3 Simulation

Mathematical modeling and simulation allows for rapid assessment. Simulation is also used when the cost of collecting data is prohibitively expensive, or there are a large number of experimental conditions to test. A mathematical model for control and elimination of the transmission dynamics of HBV is formulated and analyzed. The main objective of this study was to assess the impact of immunization strategies on the transmission dynamics of the disease. Simulations of different variables of the model have been performed and sensitivity analysis of different embedded parameters has been done. MATLAB has been used in simulations of the ordinary differential equations (ODEs) as well as the reproduction numbers. We do computer simulation using MATLAB for human population to visualize the trends in each compartment. [40]

Simulation Results

The processes begin with an initial guess on the control variable. Then, the state equations are solved simultaneously forward in time, and next the adjoint equations

are simultaneously solved backward in time. The control is updated by inserting the new values of states and adjoints into its characterization, and the process is repeated until convergence occurs. The ODE solver used for the state and adjoint systems is a Runge-Kutta fourth order procedure implemented with MATLAB.

The estimation of epidemiological parameters is based on data from Ethiopia Demographic and Health Survey 2015, Central Statistical Agency (CSA), Ethiopian health and nutrition research institute federal democratic republic of Ethiopia - Guideline on hepatitis B and Outbreak Management and from other related countries which have related characteristics.

Strategy A:-Optimal Use Control(u_1,u_2,u_3) on individuals

The control variables u_1,u_2,u_3 are used to used to optimize the objective function. In strategy A using u_1,u_2,u_3 that means number of infected individuals minimize with small time interval. All the figures(23-34) shows the control variable u_1,u_2,u_3 susceptible, vaccination and exposed individuals minimize but recovered individual increasing small time interval relative to with out control model on strategy A.

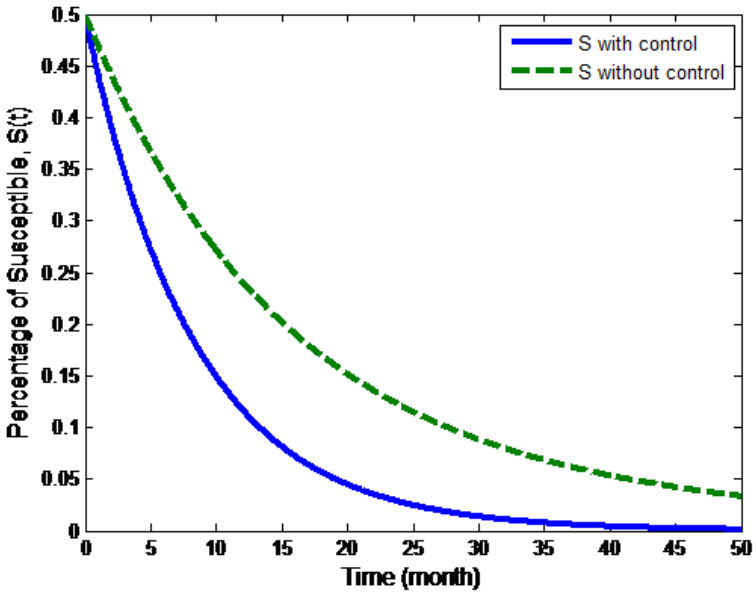
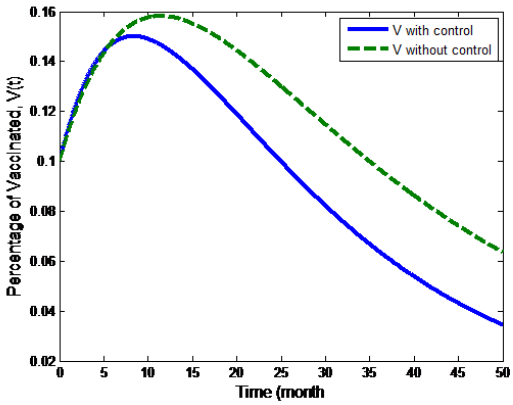


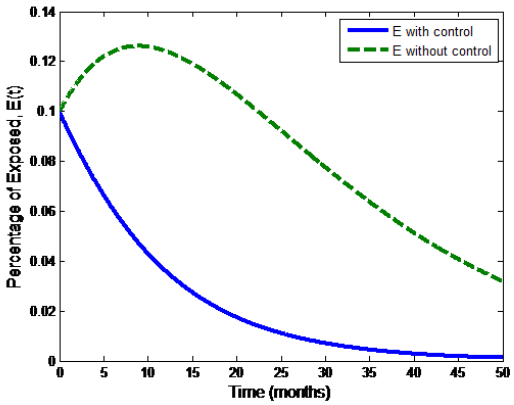
Figure 23: Comparison of susceptible individuals under with optimal control situation and without control

Figure 23 show the numerical solution of controlled and uncontrolled susceptible

individuals. From figure 23 we observe that the susceptible individuals decrease significantly when control strategies are implemented and both go to stable states at the end of control period. The results clearly show education with media given the result to minimize susceptible individual significantly of infective individuals on the dynamics of the population than minimize numbers population.

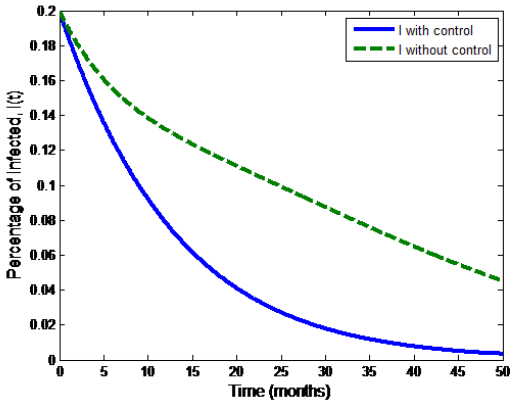


(a) Comparison vaccinated individuals

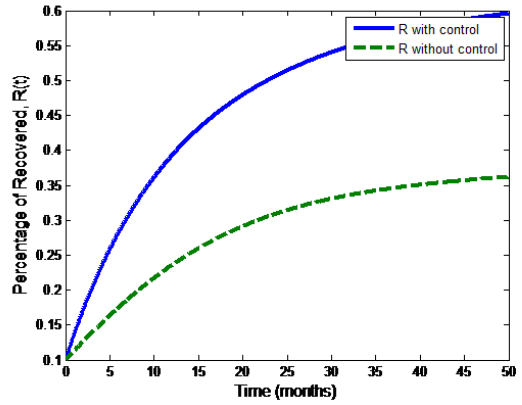


(b) Comparison of exposed individuals

Figure 24: Comparison (V,E) individuals under with optimal control situation and without control



(a) Comparison of infected individuals

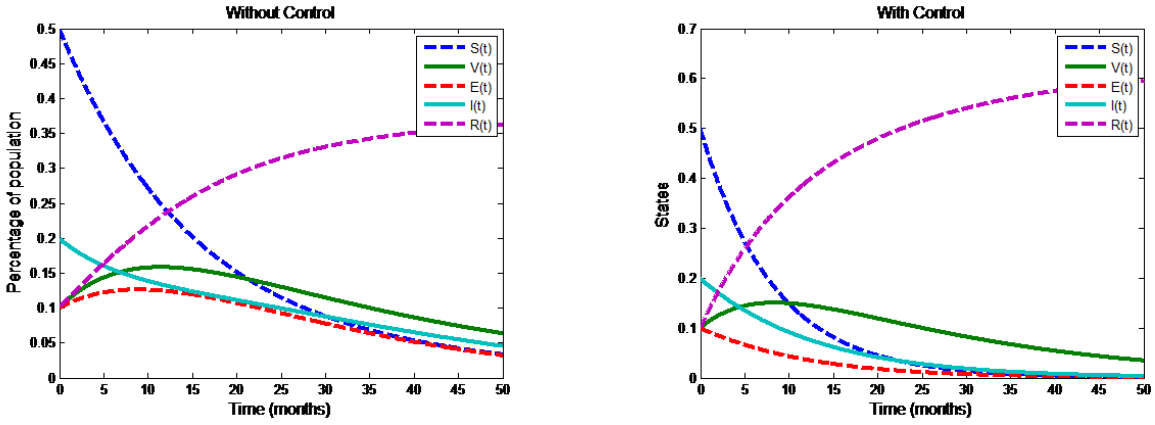


(b) Comparison of Recovered individuals

Figure 25: Comparison (I,R) individuals under with optimal control situation and without control

Figures 24, 25 show the numerical solution of controlled and uncontrolled vaccinated, exposed and infected individuals. From figure 24, 25 we observe that the vaccinated, exposed and infected individuals decrease significantly when control

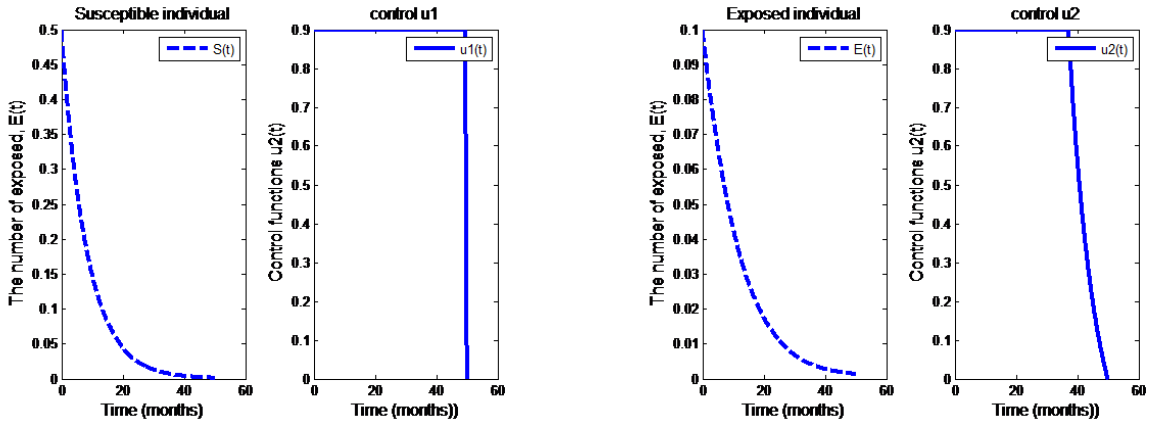
strategies are implemented and both go to stable states at the end of the control period. The results clearly show minimize numbers of drinking alcohol each persons, education with media and using drug given to the exposed, susceptible and infected individual respectively significantly reduce the number of infective individuals on the dynamics of the population than minimize numbers with direct effect or indirect ways.



(a) SVEIR Without optimal Control (b) SVEIR With optimal Control

Figure 26: SVEIR With optimal Control and Without optimal Control

Figure 26 show the numerical solution of controlled and uncontrolled SVEIRS model. From figure 26 susceptible, vaccinated,exposed and infected individuals were minimize slowly.This mean hepatitis B with out any control increasing exposed and infected individuals.But on the other figure 26 show the numerical solution of controlled SVEIRS model we observe that the infectious individuals decrease significantly when control strategies are implemented and recovered individuals increasing at the end of the control period. The results clearly show using different controlling methods given to the susceptible,exposed and infected individual. Indirectly the controlling methods also affect vaccination population to be reduced.



(a) Comparison of infected individuals (b) Comparison of infected individuals

Figure 27: susceptible,exposed individuals With optimal Control & its control variable(u_1),(u_2)

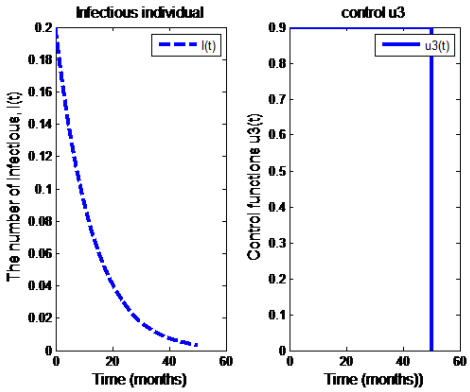


Figure 28: infected individuals With optimal Control & its control variable(u_3)

In figures 27, 28 we show the changes of the susceptible, exposed and infectious individuals and corresponding optimal strategy $u_1(t)$, $u_2(t)$ and $u_3(t)$ with time at different $A_1's$, $A_2's$ and $A_3's$ values. The first thing we observe is that to prevent the spread of hepatitis B more effectively; we should adopt a larger control ratio at the beginning of the control period followed by a reduction of control rate. Early detection of hepatitis B is therefore more substantial in reducing the infected, exposed and susceptible individuals.

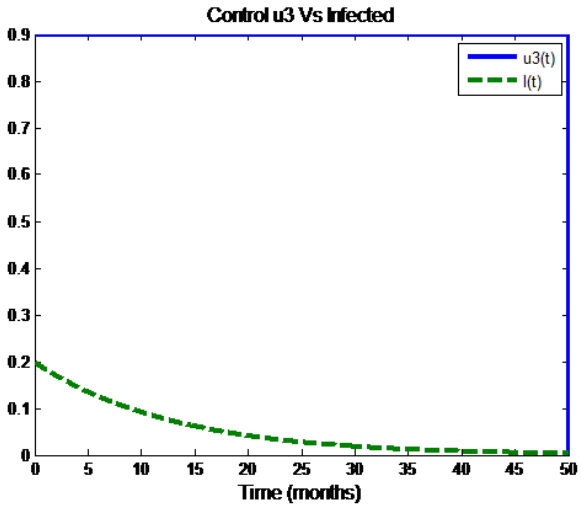
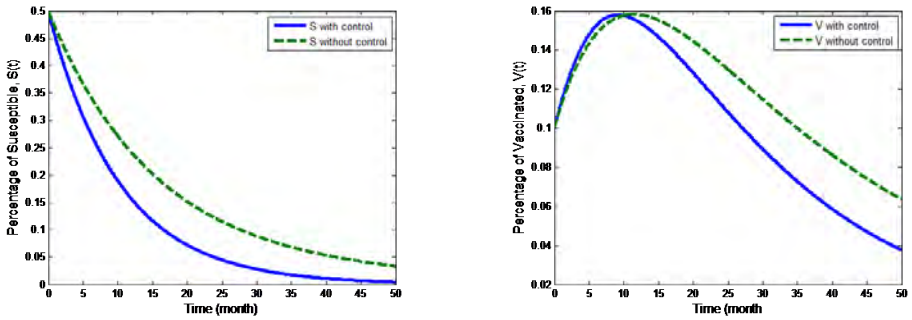


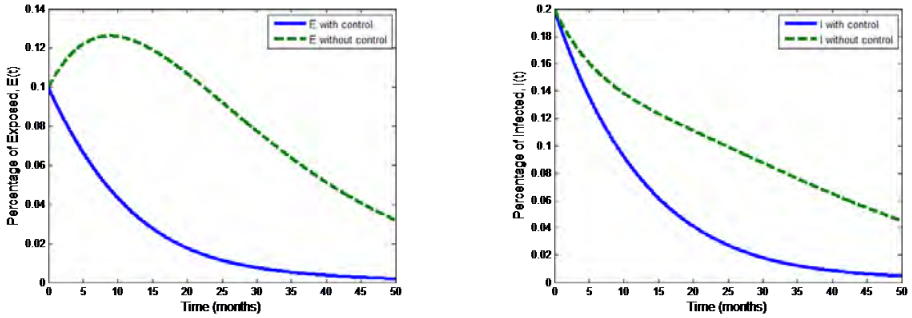
Figure 29: infected individuals With optimal Control & its control variable(u_3)

In figure 29 shows the infected individual with its optimal control variable(u_3) when the optimal control value is high and the infected individuals minimized rapidly.



(a) Comparison of susceptible individuals (b) Comparison of vaccinated individuals

Figure 30: Comparison of(S,V) individuals With optimal Control& control variable



(a) Comparison of exposed individuals (b) Comparison of infected individuals

Figure 31: Comparison of(E,I) individuals With optimal Control& control variable

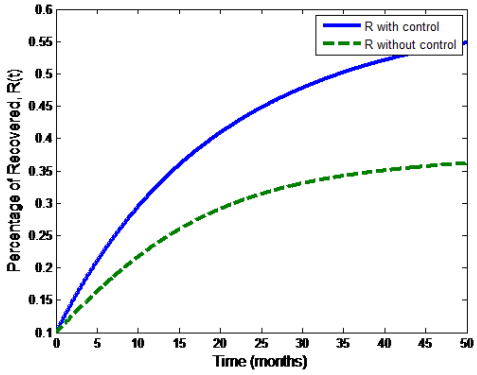
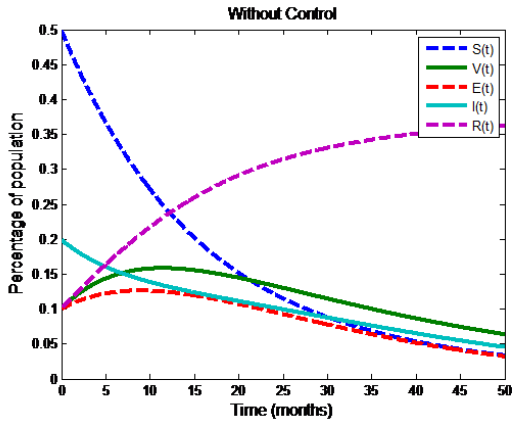
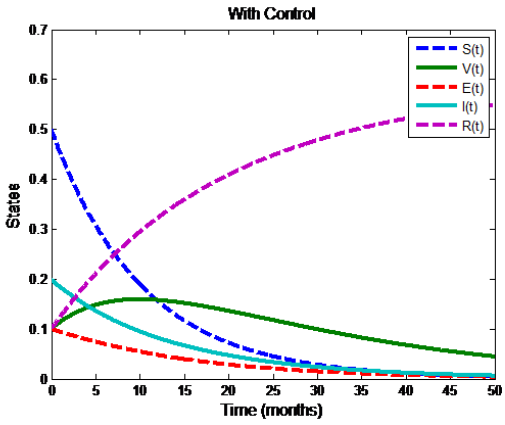


Figure 32: R individuals With optimal Control & without control

In figures 30, 31, 32 we show the numerical solutions for the adjoint variables for the case A_1=1 and A_2=10 and A_3= 100. The results indicate that as the weight parameters A_1,A_2,A_3 increases, the control function $u_1(t)$, $u_2(t)$, $u_3(t)$ increases as well. This increment leads to the increase of marginal cost of education and drug. This means that to reduce the disease burden more we have to spend more or minimize drinking amount alcohol at beginning of the control period and gradually decrease the process.



(a) SVEIR individuals Without optimal Control



(b) SVEIR individuals With optimal Control

Figure 33: SVEIR individuals With optimal Control & without control

In figure 33 we show the numerical solutions for the adjoint variables for the case A_1=1 and A_2=10 and A_3= 100. This means that to reduce the disease burden more we have to spend more or minimize drinking amount alcohol at beginning of the

control period and gradually decrease the process. On the other hand SVEIR with optimal control minimize infected and exposed as well as the susceptible individuals but increasing recovered individuals. After long time ago it may die out hepatitis B from Ethiopia with no other natural and human made factors will be induce.

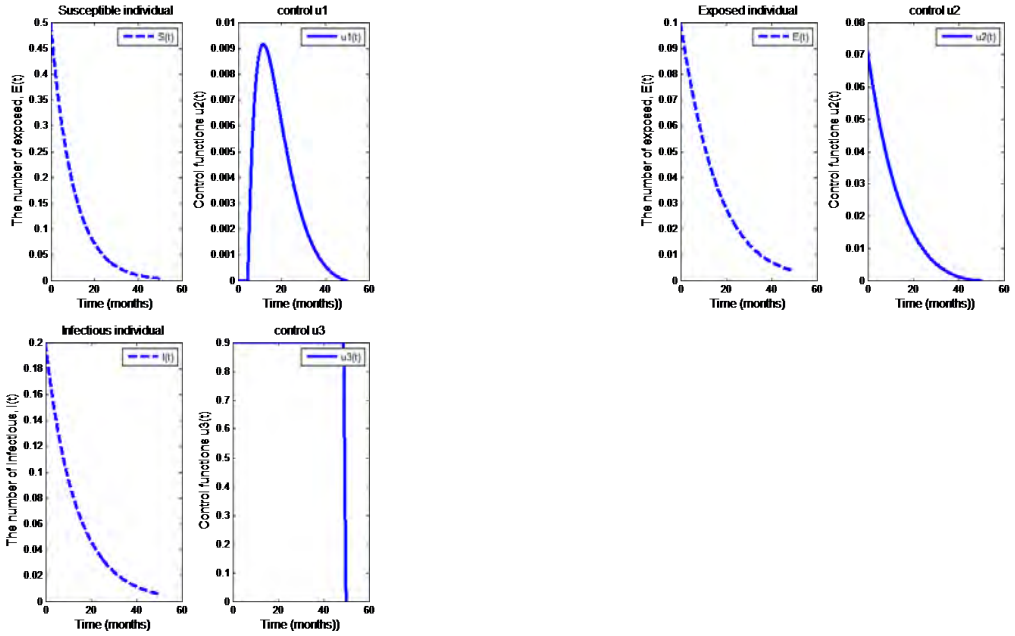


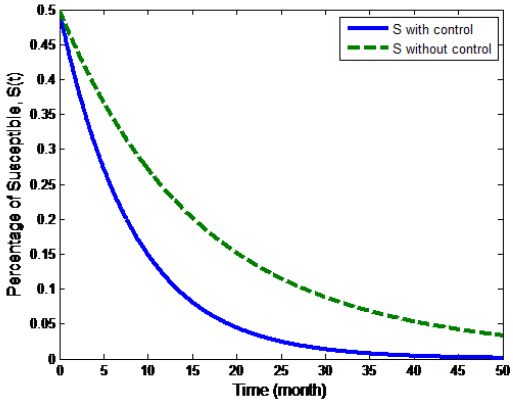
Figure 34: S, E, I individuals With control variable u_1,u_2 and u_3 respecively

Figure 34 shows the relationship between state and control variables. From the first shows when the susceptible individuals decreases continuously but u_1 at only first initial time increasing other wise decreases continuously because it is affected by the controlled state values. The second are exposed individuals as well as u_2 decreases continuously. Finally the infected individuals decreases continuously but u_3 at only initial time constant other wise decreases continuously because it is affected by the controlled state values.

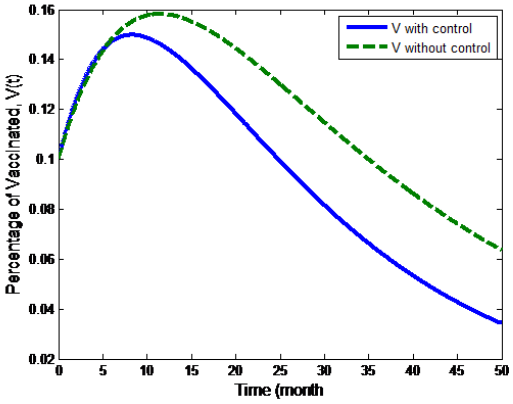
Strategy B:-Optimal Use Control(u_1,u_2) on individuals

The control variables u_1,u_2 are used to optimize the objective function. In strategy B using u_1 ,$u_2$that means number of infected individuals minimize with small time interval. All the figures below shows the control variable u_1, u_2 susceptible, vaccination and exposed individuals minimize but recovered individual increasing

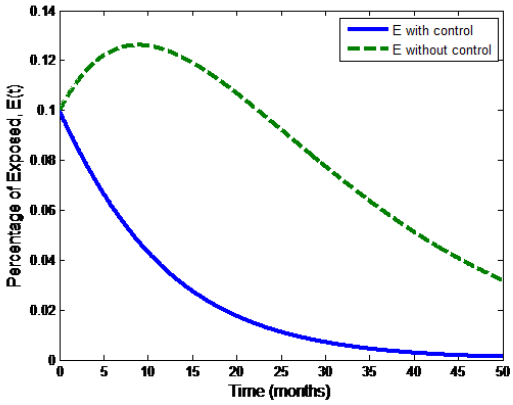
small time interval relative to with two and three control model on strategy B.



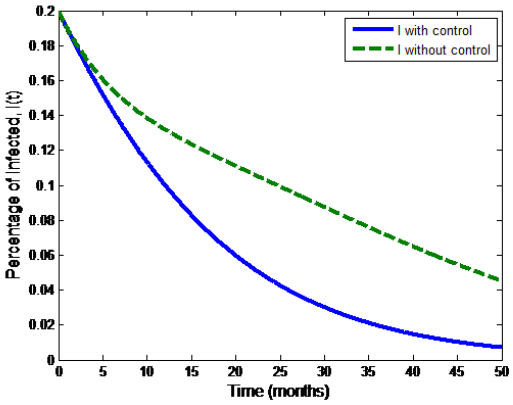
(a) Comparison of susceptible individuals



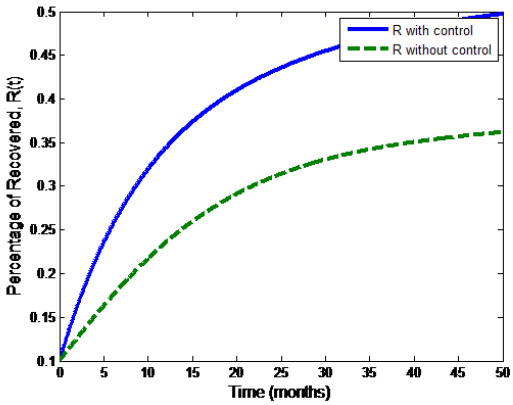
(b) Comparison of vaccination individuals



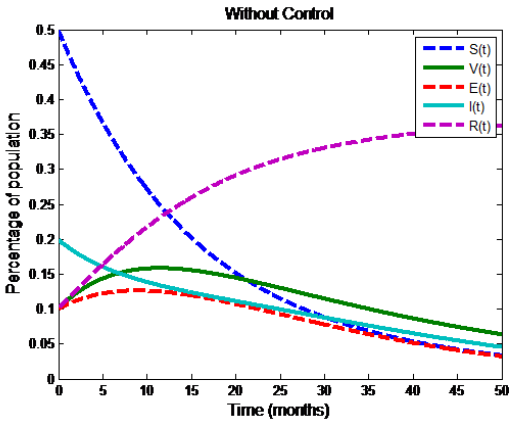
(a) Comparison of exposed individuals



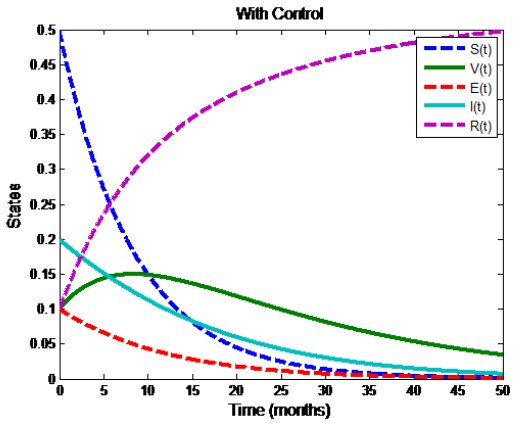
(b) Comparison of infected individuals



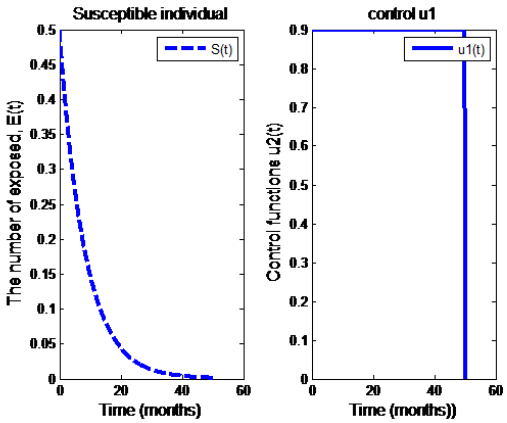
(a) Comparison of recovered individuals



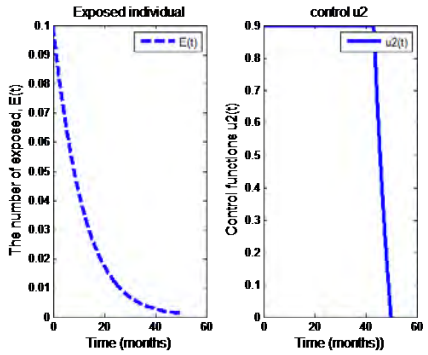
(b) Comparison of SVEIR model without control



(a) Comparison of SVEIR model with cont.



(b) Comparison of susceptible & u_1



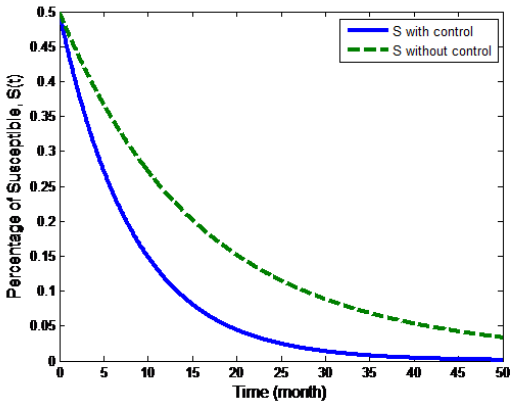
(a) Comparison of exposed individuals & u_2

Figure 39: S,V,E,I,R model on optimal controls u_3,u_2

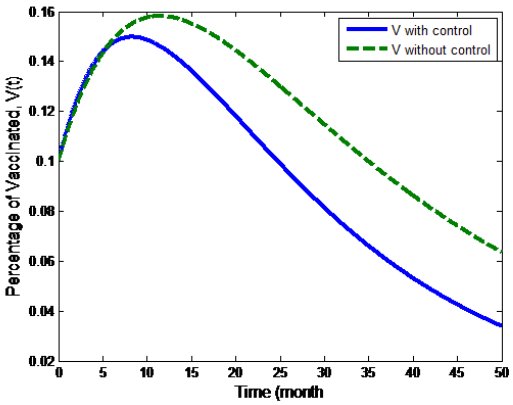
Figure 39 shows the SVEIRS model for strategy B using two optimal control u_1 and u_2 . From figures shows the susceptible and infected individuals were decrease slower than that of strategy A(with the three optimal control). The recovered individuals were increasing slower than having two optimal control variable. Finlay to get effective solution for minimize the infected individuals by hepatitis B the more perfectible method is use three optimal control variable.

Strategy C:-Optimal Use Control(u_1) on individuals

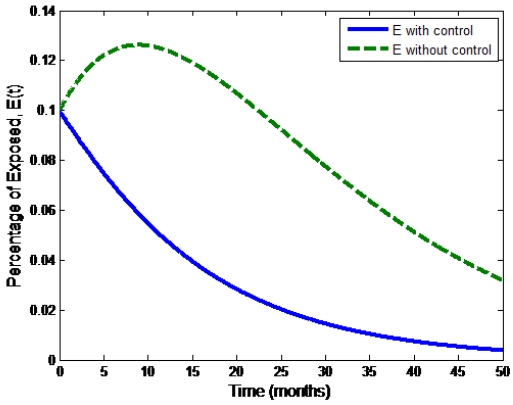
The control variables u_1 used to optimize the objective function. In strategy C using u_1 that means number of infected individuals minimize with small time interval. All the figures below shows the control variable u_1 susceptible, vaccination and exposed individuals minimize but recovered individual increasing small time interval relative to with two and three control model on strategy C.



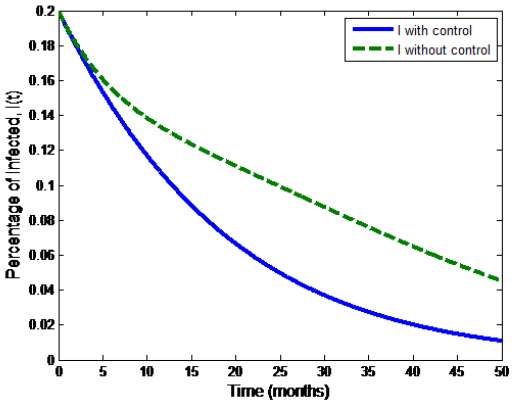
(a) Comparison of susceptible individuals



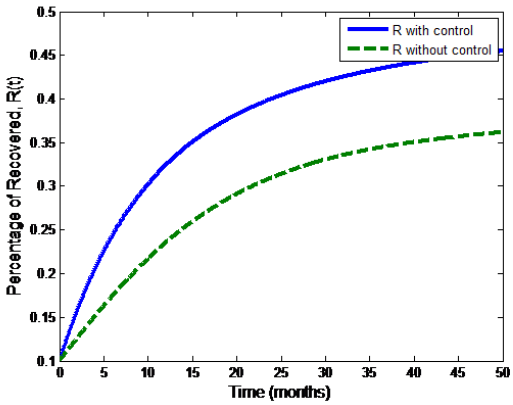
(b) Comparison of vaccinated individuals



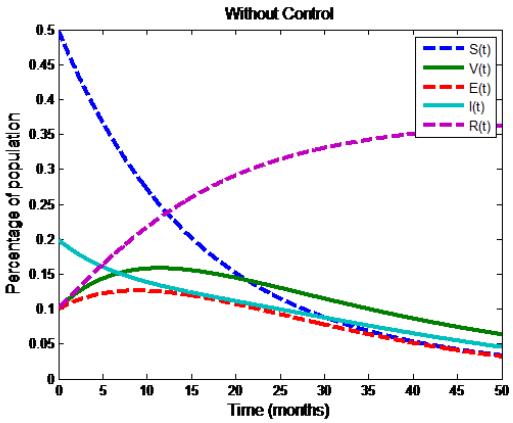
(a) Comparison of exposed individuals



(b) Comparison of infected individuals



(a) Comparison of recovered model



(b) SVEIRS model without control

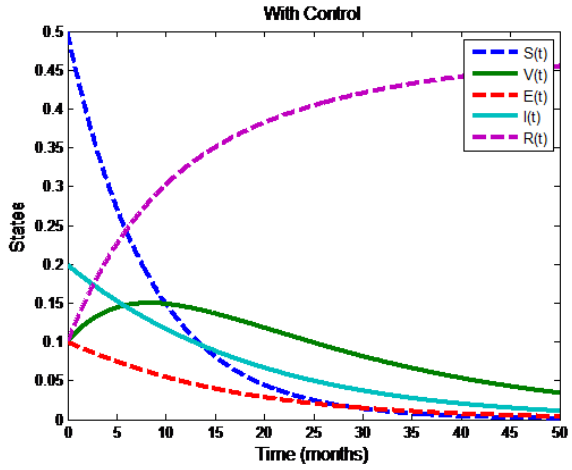
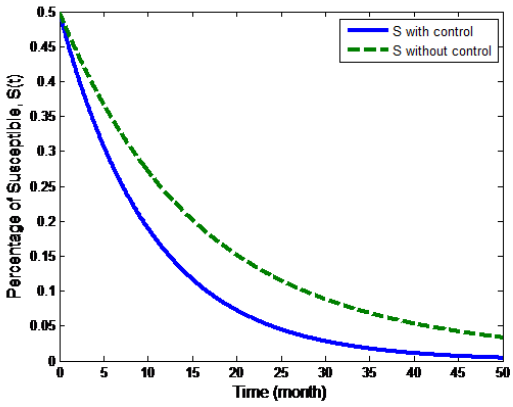


Figure 43: SVEIRS model with control

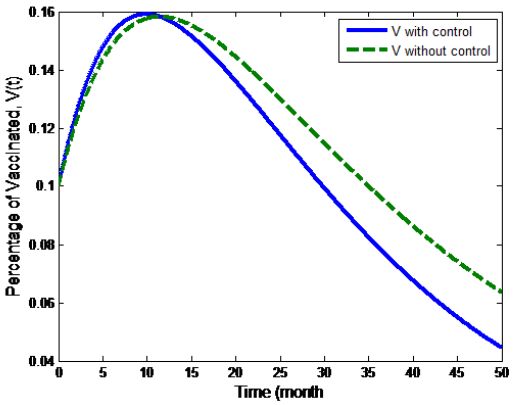
Figure 43 shows the SVEIRS model for strategy C using one optimal control u_1 . From figures shows the susceptible and infected individuals were decrease slower than that of strategy A(with the two optimal control). The recovered individuals were increasing slower than having one u_1 optimal control variable. u_1 was control variable used to minimize the susceptible individuals. Finlay to get effective solution for minimize the infected individual by hepatitis B the more perfectible method is use three optimal control than with only one control variable(u_1).

Strategy D:-Optimal Use Control(u_3) on individuals

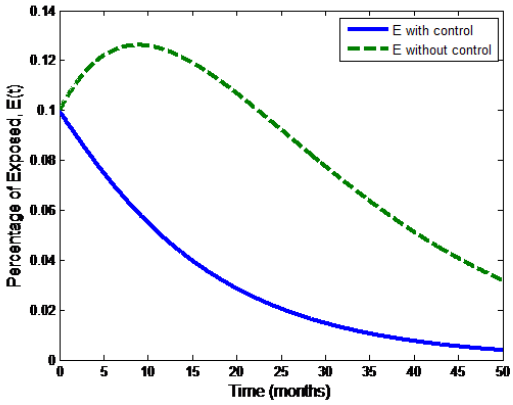
The control variables u_3 used to optimize the objective function. In strategy C using u_3 that means number of infected individuals minimize with small time interval. All the figures below shows the control variable u_3 susceptible, vaccination and exposed individuals minimize but recovered individual increasing small time interval relative to with two and three control model on strategy D.



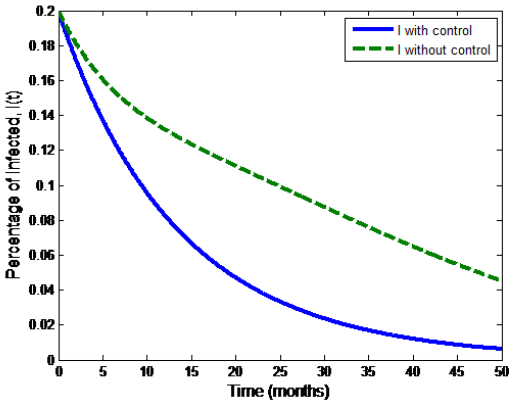
(a) Comparison of susceptible individuals



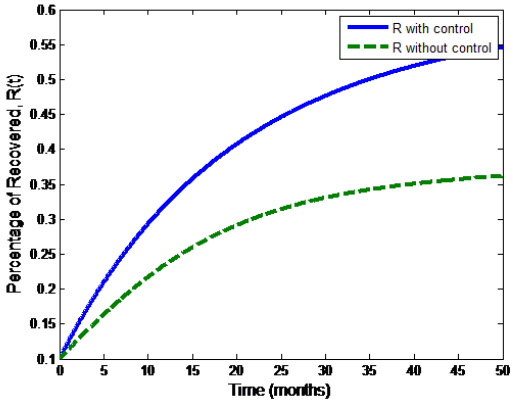
(b) Comparison of vaccinated individuals



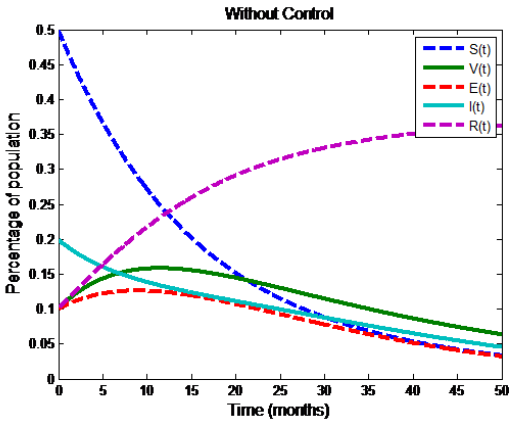
(a) Comparison of exposed individuals



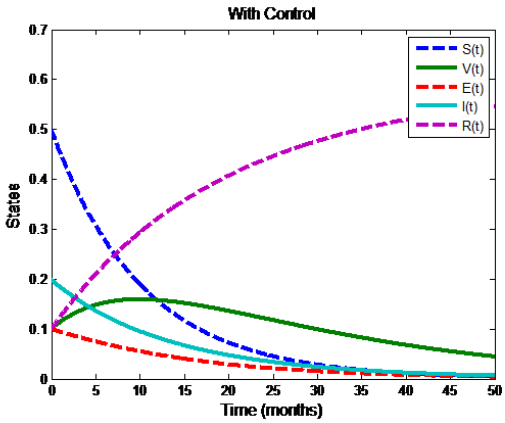
(b) Comparison of infected individuals



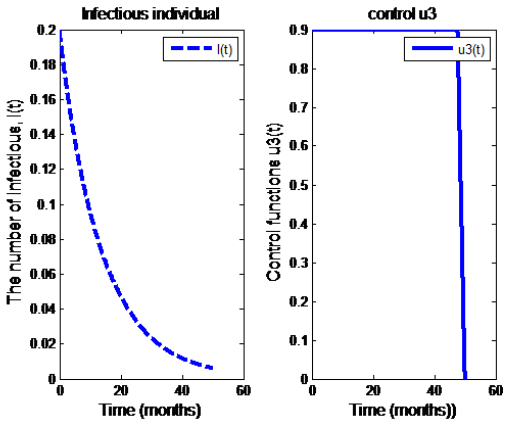
(c) Comparison of recovered individuals



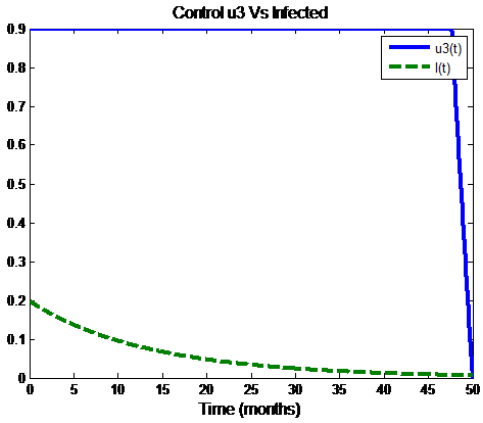
(d) SVEIRS model without optimal controls



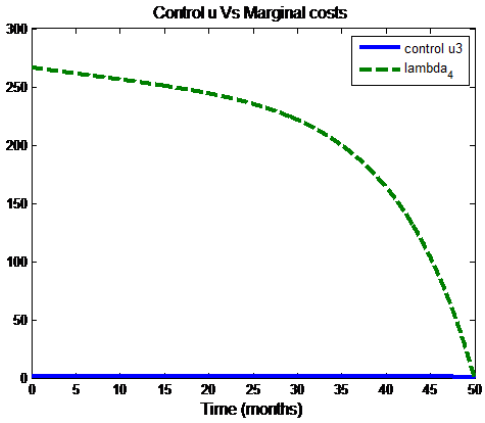
(a) SVEIRS model with optimal controls



(b) SVEIRS model on optimal controls u_1,u_2



(a) Comparison of exposed individuals



(b) SVEIRS model on optimal controls u_1,u_2

Figure 47 shows the SVEIRS model for strategy D using one optimal control u_3. From figures shows the susceptible and infected individuals were decrease slower than that of strategy A(with the two optimal control). The recovered individuals were increasing slower than having one u_3 optimal control variable. u_3 was control variable used to minimize the susceptible individuals. Finlay to get effective solution for minimize the infected individual by hepatitis B the more perfectible method is use three optimal control than with only one control variable(u_3).

Chapter Six

6 Conclusion and Recommendations

6.1 Conclusions

This model focused on HBV transmission through the deterministic approach. The basic reproductive number, R_0 of our SVEIRS model was calculated to be 0.6463, which implies that on average, each infectious individual transmits virus to 0.6463 people. The value of R_0 indicted the model is unstable or the disease die out. The stability analysis of the endemic equilibrium has been found to be stable; hence, the transmission rate of HBV is high and will persist.

Routh-hurwitz stability criterion the best way to identify the stability of higher power Λ formulating Hurwitz matrix.

The sensitivity analysis that was carried out both R_0 and simulation showed that the initial infection rate, β has a very great influence on the spread of HBV in the region than all the other parameters. We conclude that HBV transmission is primarily as a result of the effective interaction between active HBV patients and the susceptible group.

From the analysis of the model, SVEIRS epidemiological model is a good model to study the spread of hepatitis B.

I was presented the numerical simulation and verified all the analytical results numerically. By using control variables treatment using medias, minimize amount of drinking alcohol and using drug, we are able to control the spreading of hepatitis B. I believe that this new extension, assumption and analysis are biologically much more plausible.

The response to HBV infections in Ethiopia is patchy, and the country lacks tools and systems necessary for an effective response at all levels. Thus, the country needs to formulate policy and strategies in the areas of disease surveillance, risk group identification and screening, implementation of the birth dose of hepatitis B vaccine, care and treatment.

6.2 Recommendations

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

- All children should get their first dose of hepatitis B vaccine at birth and should have completed the vaccine series by 6 through 18 months of age.
- Children and adolescents through 18 years of age who did not get the vaccine when they were younger should also be vaccinated.
- Minimize the amount of drinking alcohol.
- take drug when HBV infected recommend by doctors.
- All unvaccinated adults at risk for HBV infection should be vaccinated. This includes:
  - Sex partners of people uninfected with HBV
  - People who inject street drugs
  - People with more than one sex partner
  - People with chronic liver or kidney disease
  - People with jobs that expose them to human blood
  - Household contacts of people infected with HBV
- Residents and staff in institutions for the developmentally disabled Kidney dialysis patients
- People who travel to countries where hepatitis B is common
- People with HIV infection

Some of the general management strategies for HBV recommended by medical experts include;

- Avoidance of heavy alcohol consumption, Unprotected sexual intercourse with partners who are not vaccinated, Sharing of needles or other items that potentially contain blood such as shavers or toothbrushes and donation of blood or organs.

- Screening of family members and sexual partners for HBV infection and vaccination of those who are sero-negative

- Using media for education and long-term follow-up with regular testing of liver biochemistry and surveillance of hepatocellular carcinoma in high risk groups

For further studies be done on HBV by considering how HIV influence the rate of HBV infection and the rate of HBV infection with respect to migration.The epidemic of HBV varies in migration it is possible to extent the model to modified model.

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