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APPLICATION OF OPTIMAL CONTROL TO THE EPIDEMIOLOGY OF DENGUE FEVER TRANSMISSION

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Abstract

In this paper, I build epidemiological model to investigate the dynamics of spread of dengue fever in human population. I study the demographic factors that influence equilibrium prevalence, and perform a sensitivity analysis on the basic reproduction number. Among several intervention measures, the effects of two potential control methods for dengue fever are estimated: introducing educate and treat the population. A stochastic model for transmission of dengue fever is also built to explore the effect of some demographic factors and review a number of compartmental models in epidemiology which leads to a nonlinear system of ordinary differential equations. I focus an SEIRS epidemic models with and without education and treatment.

A threshold parameter R_0 is identified which governs the spread of diseases,and this parameter is known as the basic reproductive number. The models have at least two equilibria, an endemic equilibrium and the disease-free equilibrium. We demonstrate that the disease will die out, if the basic reproductive number $R_0 < 1$. This is the case of a disease-free state, with no infection in the population. Otherwise the disease may become endemic if the basic reproductive number R_0 is bigger than unity. Furthermore, stability analysis for both endemic and disease-free steady states are investigated and we also give some numerical simulations.

The second part of this dissertation deals with optimal education and treatment by drug strategy in epidemiology. We use optimal control technique on education and treatment to minimize the impact of the disease. Hereby we mean minimizing the spread of the disease in the population, while also minimizing the effort on education and treatment roll-out. We do this optimization for the cases of SEIRS models, and show how optimal strategies can be obtained which minimize the damage caused by the dengue fever disease. Finally, we describe the numerical simulations using the fourth-order Runge-Kutta method.

Keywords

Basic reproductive number

Disease-free equilibrium

Endemic equilibrium

Epidemiology

Numerical simulation

Population model

Optimization

Stability analysis

Abbreviation

DF:- Dengue fever

DHF:- Dengue Hemorrhagic fever

SEIRS:- Susceptible-Exposed-Infective-Recovered-Susceptible

LBW:- low birth weight

PTB:- Pretern birth

WHO:- World Health organization

DEN:- Dengue

DENV:- Dengue virus

RNA:- Ribonucleic acid

OC:- Optimal control

PMP :- pontryagin's minimum principle

DFE:- Disease free equilibrium

EE:- Endemic equilibrium

Pplane:- phaseplane

DEs:- Differential equations

ODEs:- Ordinary differential equations

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Contents

List of Figures

List of Tables

CHAPTER ONE

1 INTRODUCTION

Dengue fever is a painful, debilitating mosquito-borne disease caused by one of four closely related dengue viruses. It is transmitted by the bite of an infected Aedes mosquito. The mosquito becomes infected when it bites a person with dengue virus present in their blood. Until now, more than 100 million cases of dengue fever occur worldwide in the Indian subcontinent, South-east Asia, Southern China, Taiwan, the Pacific Islands, the Caribbean Mexico, Africa, Central and South America southern United States, and southern Australia. In Indonesia, dengue cases increase yearly in almost all regions[1]. Due to high chance of serious damage impact in dengue spreading all over the world, the effective strategy for controlling dengue is vital.

The important issue in strategy to combat dengue spreading is realizing quick and effective action [1]. Quick action particularly intended for preventing another area from next spreading. Effective relate with minimize effect to environmental. Based on this issue some research was conducted. Previous study about dengue focused on strategy based on static situation. Static means connection between host (human) and vector(mosquito) occurs under assumption that people never moving across the border areas. By this point of view some strategy are established. DHF is a more severe form of dengue infection. It can be fatal if unrecognized and not properly treated in a timely manner. DHF is caused by infection with the same viruses that cause dengue fever. With good medical management, mortality due to DHF can be less than 1% [1]. The virus circulates in the blood of an infected person for 2-7 days, at approximately the same time that the person develops a fever. Patients who are already infected with the dengue virus can transmit the infection via Aedes mosquitoes after the first symptoms appear (during 4-5 days; maximum 12). It is possible to get dengue more than once. Dengue can occur because of 4 different but related strains of dengue virus. If a person has suffered from one virus, there can be a repeat occurrence of dengue if a different strain is involved subsequently. But many who suffer repeat infections have it worse. They come down with dengue hemorrhagic fever and suffer massive internal bleeding and liver damage. Oddly, the virus causing dengue fever comes in four strains, and immunity to one seems to make infection by a second strain more dangerous.

Dengue fever is found throughout the world, but mainly occurs in tropical and subtropical areas. It is widespread in regions of Africa, Central and South America, the Caribbean, the Eastern

Mediterranean, South and Southeast Asia and Oceania. When the incidence of dengue disease starts to increase in any population, people start to look for methods that are best to combat the outbreak or at least control the number of infections. Experiments for producing and testing those control measures, such as education, antiviral drugs, are costly and time consuming, so any tool that will enable us to predict the outcome is highly valuable. Mathematical models are a powerful tool for investigating dengue fever diseases, providing useful predictions about the potential transmission of a disease and the effectiveness of possible control measures. Many infectious diseases are spread by biting insects and ticks or other organisms, collectively known as vectors, which transfer pathogens between humans or other animals. The emergence or reemergence of such vector-borne diseases seems especially to have stimulated recent interest. Epidemiology has become an important issue for modern society. The relationship between mathematics and epidemiology has been increasing. For the mathematician, epidemiology provides new and exciting branches, while for the epidemiologist, mathematical modeling offers an important research tool in the study of the evolution of diseases. In 1760, a smallpox model was proposed by Daniel Bernoulli and is considered by many authors the first epidemiological mathematical model. Theoretical papers by Kermack and McKendrinck, between 1927 and 1933 about infectious disease models, have had a great influence in the development of mathematical epidemiology models [2]. Most of the basic theory had been developed during that time. Mathematical models are being increasingly used to elucidate the transmission of several diseases. These models, usually based on compartment models, may be rather simple, but studying them is crucial in gaining important knowledge of the underlying aspects of the dengue fever diseases spread out [3], and to evaluate the potential impact of control programs in reducing morbidity and mortality.

After the Second World War, the strategy of public health has been focusing on the control and elimination of the organisms that cause the diseases. The appearance of new antibiotics and vaccines brought a positive perspective of the diseases eradication. However, factors such as resistance to the medicine by the microorganisms, demographic evolution, accelerated urbanization, increased travelling and climate change, led to new diseases and the resurgence of old ones. In 1981, the human immunodeficiency virus (HIV) appears and since then, become as important sexually transmitted disease throughout the world. Futhermore, malaria, tuberculosis, dengue and yellow fever have re-emerged and, as a result of climate changes, has been spreading into new regions [4]. Recent years have seen an increasing trend in the representation of mathematical models in publications in the epidemiological literature, from specialist journals of medicine,

biology and mathematics to the highest impact generalist journals, showing the importance of interdisciplinary. Their role in comparing, planning, implementing and evaluating various control programs is of major importance for public health decision makers. The optimal control definition and its possible formulations are introduced, followed by SEIRS epidemiological models. The Pontryagin Minimum Principle is presented with the aim of finding the best control policy.

In this paper, dengue details are given, such as disease symptoms, transmission and epidemiological trends. Use an OC model for dengue, as a first approach to the disease. Due to the matlab robustness improvements and the higher computational capacity, a better solution for this problem is proposed. In order to study different discretization schemes for an OC problem, the dynamics of dengue fever transmission was analyzed through numerical simulations of the system of non-linear ordinary differential equations considering human mobility and vertical transmission as factors of interest to describe the persistence and diffusion of this disease. The system of equations consists the human population compartments. The numerical method used to solve the system was the fourth-order Runge-Kutta method.

1.1 Background of the study

Dengue is a mosquito-borne disease that is common in many tropical and subtropical areas. Dengue infections can occur at any age and time in the lifespan, including during pregnancy. Few large scale studies have been conducted to determine the risk of preterm birth (PTB) and low birth weight (LBW) for infants born to women who had symptomatic dengue infection during pregnancy.

Dengue is disease transmitted from an infected human to a female Aedes mosquito by a bite. Then, the mosquito, that needs regular meals of blood to feed their eggs, bites a potential healthy human and transmits the disease making it a cycle. There are two forms of dengue: Dengue Fever (DF) and Dengue Hemorrhagic Fever (DHF). The first one is characterized by a sudden high fever without respiratory symptoms, accompanied by intense headaches, painful joints and muscles and lasts between three to seven days. Humans may only transmit the virus during the febrile stage[5]. DHF initially exhibits a similar, if more severe pathology as DF, but deviates from the classic pattern at the end of the febrile stage [4]. The hemorrhagic form has an additionally bleeding from the nose, mouth and gums or skin bruising, nausea, vomiting and fainting due to low blood pressure by fluid leakage. It usually lasts between two to three days and can lead to death. Nowadays, Dengue is the mosquito-borne infection that has become a major international public health concern. According to the World Health Organization (WHO)[6], 50 to 100 million Dengue Fever infections occur yearly, including 500000 Dengue Hemorrhagic Fever cases and 22000 deaths, mostly among children [7]. There are four distinct, but closely related, viruses that cause Dengue. The four serotypes, named DEN- 1 to DEN-4, belong to the Flavivirus family, but they are antigenically distinct. Recovery from infection by one virus provides lifelong immunity against that virus but confers only partial and transient protection against subsequent infection by the other three viruses. There is good evidence that a sequential infection increases the risk of developing DHF [8]. Unfortunately, there is no specific effective treatment for dengue. Activities, such as triage and management, are critical in determining the clinical outcome of Dengue. A rapid and efficient front-line response not only reduces the number of unnecessary hospital admissions but also saves lives. Although up until now there is no effective and safe vaccine for dengue, a number of candidates are undergoing various phases of clinical trials[9]. With four closely related viruses that can cause the 50 disease, there is a need for a vaccine that would immunize against all four types to be effective. The main difficulty

in the vaccine production is that there is a limited understanding of how the disease typically behaves and how the virus interacts with the immune system. Another challenge is that some studies show that some secondary dengue infection can leave to DHF, and theoretically a vaccine could be a potential cause of severe disease if a solid immunity is not established against the four serotypes. Research to develop a vaccine is ongoing and the incentives to study the mechanism of protective immunity are gaining more support, now that the number of outbreaks around the world is increasing[5].

The spread of Dengue is attributed to the geographic expansion of the mosquitoes responsible for the disease: Aedes aegypti and Aedes albopictus [10]. Due to its higher interaction with humans and its urban behavior, the first mosquito is considered the major responsible for Dengue transmission and, our attention will be focused on it.

1.1.1 Dengue Virus

Dengue,in figure 1[11], is caused by Dengue virus(DENV),a mosquito borne flavivirus. DENV is single stranded RNA positive-strand virus of the family flaviviridae, genus flavivirus. This genus includes also the West Nile virus, Tick-borne Encephalitis Virus, Yellow Fever Virus, and several other viruses which may cause encephalitis.

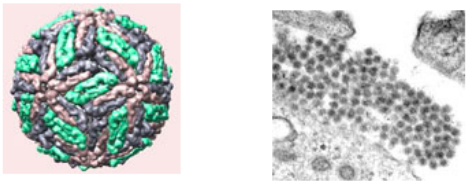

Figure 1: Dengue virus particle and microscopic picture of dengue viruses

1.1.2 Biological notes on Aedes aegypti

Aedes aegypti, in Figure 2 [11], is an insect species closely associated with humans and their dwellings, thriving in crowded cities and biting primarily during the day. Humans not only provide blood meals for mosquitoes,but also nutrients needed for them to reproduce through water-holding containers, in and around their homes. In urban areas, Aedes mosquitoes breed on water collections in artificial containers such as cans, plastic cups, used tires, broken bottles and flower pots. With increasing urbanization, crowded cities, poor sanitation and lack of hy-

giene, environmental conditions foster the spread of the disease that, even in the absence of fatal forms, breed significant economic and social costs (absenteeism, immobilization, debilitation and medication)[12].

Figure 2: Mosquito Aedes aegypti

Dengue is spread only by adult females that require a blood meal for the development of their eggs, where as male mosquitoes feed on fruit nectar and other sources of sugar. In this process the female acquire the virus while feeding on the blood of an infected person. After virus incubation from eight to ten days (extrinsic period), an infected mosquito is capable, during probing and blood feeding, of transmitting the virus for the rest of its life to susceptible humans, and the intrinsic period for humans varies from 4 to 13 days. We see figure 3.

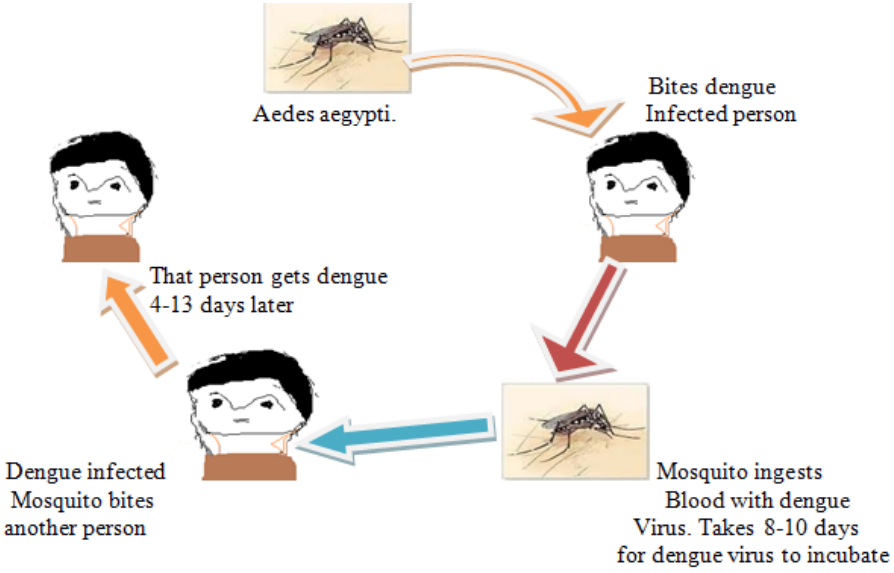

Figure 3: **Spread of Dengue Fever**

1.1.3 Dengue fever

Dengue fever is a disease caused by a family of viruses transmitted by mosquitoes (mosquito-borne disease). It is an acute illness of sudden onset that usually follows a benign course with symptoms such as fever, exhaustion, severe muscle and joint pain, swollen lymph nodes (lymphadenopathy) and rash. The presence of fever, and itchy rash,headache (the dengue triad) is characteristic of dengue. Other signs of dengue fever include bleeding gums, severe pain behind the eyes and red palms and soles.

Dengue can affect anyone but tends to be more severe in people with compromised immune systems. Because it is caused by one of five serotypes the dengue virus, it is possible to get dengue fever multiple times. However, an attack of dengue produces immunity for a lifetime to that particular viral serotype to which the patient was exposed. Dengue goes by other names,including breakbone fever or dandy fever. Victims of dengue often have contortions due to the intense pain in the joints, muscles, and bones, hence the name breakbone fever. Slaves in the West Indies who contracted dengue were said to have dandy fever because of their postures and gait.

Dengue hemorrhagic fever is a more severe form of the viral illness. Symptoms include headache, fever, rash and evidence of bleeding(hemorrhage) in the body. Petechiae(small red spots or purple splotches or blisters under the skin), bleeding in the nose or gums, black stools, or easy bruising are all possible signs of hemorrhage. This form of dengue fever can be life-threatening and can progress to the most severe form of the illness, dengue shock syndrom. It is a painful, caused by any one of four closely related dengue viruses. It is transmitted by the bite of an Aedes mosquito infected with a dengue virus. The mosquito becomes infected when it bites a person with dengue virus in their blood. It can't be spread directly from one person to another person.

1.1.4 Epidemiology of Dengue fever

Dengue fever is caused by any of four closely related viruses, or serotypes: dengue 1-4. Infection with one serotype does not protect against the others, and sequential infections put people at greater risk for dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).

A serotype is a group of viruses classified together based on their antigens on the surface of the virus. These four subtypes are different strains of dengue virus that have 60-80% homology between each other[13]. The major difference for humans lies in subtle differences in the surface proteins of the different dengue subtypes. Infection induces long-life protection against the infecting serotype, but it gives only a short time cross protective immunity against the other types. The first infection cause mostly minor disease, but secondary infections has been reported to cause severe diseases (DHF or DSS) in both children and adults. This fenomenon is called Antibody-Dependent Enhancement.

1.1.5 Treatment for dengue fever disease

There is no specific medication for treatment of a dengue fever. Persons who think they have dengue should use analgesics (pain relievers). They should rest, drink plenty of fluids to prevent dehydration, avoid mosquito bites while febrile and consult a physician.

1.1.6 Prevention of Dengue Fever

Prevention is the most important step to reduce the risk of dengue infection. There are several ways of prevention:

- **Prevention by Mosquito Control**

  The best way to reduce mosquitoes is to eliminate the places where the mosquito lays her eggs, like artificial containers that hold water in and around the home.

- **Prevention by Reducing Mosquito Bites**

  Prevention of mosquito bites is another way of preventing disease. The adult mosquitoes like to bite inside as well as around homes, during the day and at night when the lights are on. To protect yourself, use insect repellent on your skin while indoors or out, mosquito traps or mosquito nets.

1.1.7 Herd immunity

Immunity plays a crucial role in the dynamics of disease transmission. The more people are immune, the less likely it is that a pathogen will find a susceptible person. If enough people are immune, the chance of the pathogen causing an infection becomes so small that transmission stops, even though there are still susceptible people. This is called herd immunity. Herd immunity is a form of immunity that occurs when the vaccination of a significant portion of a population(or herd) provides a measure of protection for individuals who have not developed immunity. With poliomyelitis, for example, if 85 to 90 percent of the entire population is immune, the virus will disappear. A population can lose its herd immunity through births, migration of susceptible people into the population, or waning immunity in the population over time. Figure 4, presents a model of immunity in the population.

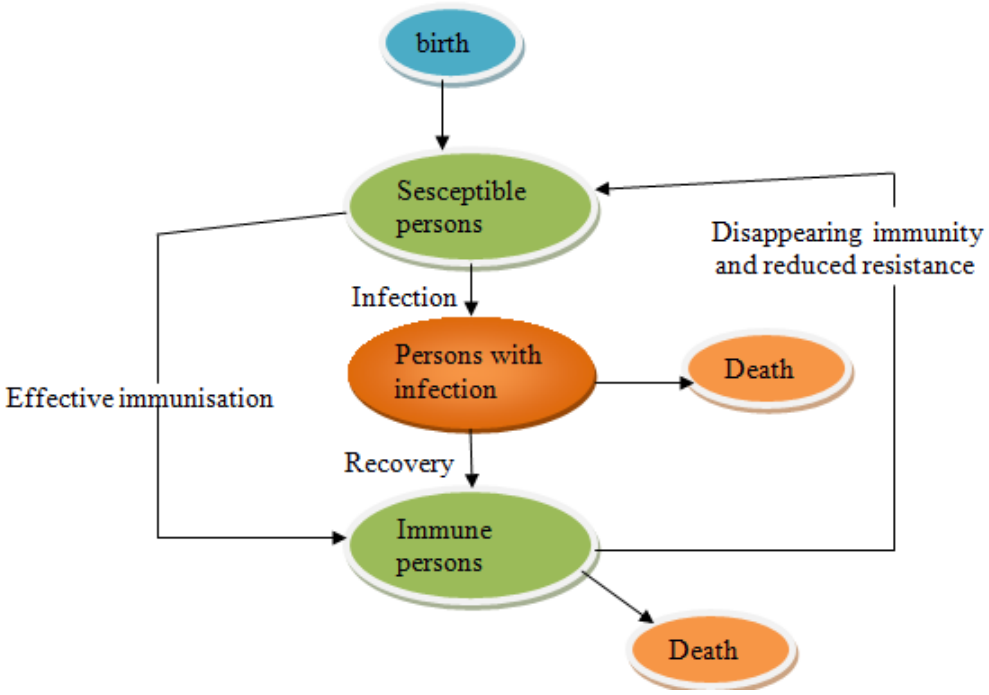

Figure 4: Model of immunity in a population

- The immunity in a population is the result of people either overcoming the infection or being immunised (vaccinated).
- The susceptibility of the population in an area increases through the influx of non-immune people, birth, and from people losing their immunity (through time or another reason).

1.2 Statement of the Problems

Dengue fever is a disease and one of the most dangerous diseases in the world. The spread of dengue fever diseases has always been a concern and poses a threat to public health, as well as the economic and social developments in a developing country. Thus, its prevention and control are very important. Limitation of resource is a main problem in minimizing the incidence rate or outbreak of dengue disease which kills millions of population every year. Most studies of epidemic control of dengue focus on increasing the drugs and education coverage in a population to control the disease, but they do not consider how this parameter affects the strategy over a period of time. Though some of these studies have considered education strategy at different level of understanding approach none of them has studied optimal education strategy by considering dengue fever disease models for countries. To control this disease a proper allocation of resource to the control parameters by way of optimization is a significant effect in controlling the diseases. This study is intended to answer the question of how an optimal education policy and control strategies can be put in place such that the cost of the implementation of the intervention is minimized the disease is controlled within specified period. Using these parameters as control variables, the study will determine the possible impact of optimal control method by using a differential mathematical model for the control of dengue the epidemic. This is attained by efficiently balancing different education strategies with varies cost scenarios.

1.3 Objective of the study

The objective of this paper involves the following,

- The general objective of this study is to model the best optimal control strategies, to make the number of infectious individuals as small as possible and to keep the education and treatment by drug therapy ratio of dengue fever as low as possible during a certain education and treatment by drug therapy period.
- Developing a mathematical model for dengue fever.
- Determine the nature of the outbreak(prevalence of dengue fever)

1.4 Specific Objective of the study

1. To formulate a non linear ordinary differential equation based on model of dengue fever disease,showing the impact of optimal control strategy and the system to produce the best outcome.
2. To verify the effect of education on spread of dengue fever disease.
3. To verify the effect of treatment by drug therapy on spread of dengue fever disease.
4. To compare uncontrolled and controlled state strategies on the dynamics of the disease.
5. To compare the best optimal treatment by drug therapy and education schedule to mitigate dengue disease.
6. To compare one(education)controlled and two(education and treatment by drug therapy) controlled state strategies on the dynamics of the disease.
7. Perform simulations to illustrate numerical results.

1.5 Scope of the study

Our work introduces SEIRS model of dengue fever by considering a closed population with (no immigration and imigration). The population is homogeneous, which means that every individual of a compartment is homogenously mixed with the other individuals.

1.6 Limitation of the study

The following are the limitation of this study,

- Assumed that all population affect by dengue virus equally.
- Assumed that, the costs of education are directly proportional to education planning.
- All drug therapy costs are assumed to be directly proportional to the treatment planning.
- Assumed that all drug therapy equally distribute for all of the world.

1.7 Thesis Organization

The thesis is organized as follows, in chapter 2, the basic building blocks of most epidemiological models are reviewed, we present the optimal control strategies of dengue fever disease model to be investigated. A precise explanation of my model can be seen in chapter 3, methodology for an SEIRS model formulation which includes reproduction number and qualitative (stability) analysis on the model equilibria. In this chapter contains the original results and is focused on dengue fever disease and we introduce optimal control problem subject to SEIRS dengue fever model. The definition of optimal control problem, its possible versions and the adapted first order necessary conditions based on the Pontryagin minimum Principle are introduced. Pontryagin's minimum principle (PMP) is used to characterize the optimal control problem. We characterize the optimal controls, and derive the optimality system. In chapter 4, a simulation of dengue fever education and treatment schedules. Finally, we draw conclusions from this thesis and assess what new insights this work gives to the body of knowledge on optimal control as a recommendations for future work. Chapter 5 is the end of the study.

CHAPTER TWO

2 LITERATURE REIVIEW

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

In Jun, 2013, Helena Sofia Rodrigues et al[4], states that Epidemiological models may give some basic guidelines for public health practitioners, allowing to analyze issues that can influence the strategies to prevent and fight a disease. To be used in decision making, however, a mathematical model must be carefully parameterized and validated with epidemiological and entomological data. Here a SIR (S for susceptible, I for infectious, R for recovered individuals) epidemiological model describing a dengue disease is presented, as well as the associated basic reproduction number. A sensitivity analysis of the epidemiological model is performed in order to determine the relative importance of the model parameters to the disease transmission.

M. S. M. Noorani[14], states that a system of differential equations that models the population dynamics of SEIR vector transmission of dengue fever. The model studied breeding value based on the number of reported cases of dengue fever in Selangor because the state had the highest case in Malaysia. The model explains hat maximum level of human infection rate of dengue fever achieved in avery short period.It is also revealed that there existed suitability result between theoretical and empirical calculation using the model. The result of SEIR model will hopefully provide an insight into the spread of dengue fever in Selangor Malaysia and basic form for modeling this area. He reported a result of the SEIR model indicates that infection to human based on real data in Selangor is not harmful yet and underline that maximum level of human infection rate of dengue fever achieved in a very short period. Dengue fever takes very long time to ensure that the number of infected people in zero values. This is due to dengue virus infection occurs when there is a continuous correlation between human and mosquito population. Mosquitoes are the carriers that can cause a virus infection to human[14]. Furthermore, the empirical SEIR model produce similar result to the theoretical model and described that the latent period variable significantly explain the transmission of dengue fever.

In March 1996, Zhilan Feng et al[15], study a system of differential equations that models the population dynamics of an SIR vector transmitted disease with two pathogen strains. This model arose from our study of the population dynamics of dengue fever. The dengue virus presents four serotypes each induces host immunity but only certain degree of cross-immunity to heterologous serotypes. Our model has been constructed to study both the epidemiological trends of the disease and conditions that permit coexistence in competing strains. Dengue is in the Americas an epidemic disease and our model reproduces this kind of dynamics. We consider two viral strains and temporary cross-immunity. Our analysis shows the existence of an unstable endemic state (saddle point)that produces a long transient behavior where both dengue serotypes cocirculate. Conditions for asymptotic stability of equilibria are discussed supported by numerical simulations. We argue that the existence of competitive exclusion in this system is product of the interplay between the host superinfection process and frequency-dependent(vector to host) contact rates.

Laurencia Ndelamo Massawe et al.[16], states that the effect of treatment of Dengue fever disease. A non linear mathematical model for the problem is proposed and analysed quantitatively using the stability theory of the differential equations. The results show that the disease-free equilibrium point is locally and globally asymptotically stable if the reproduction number(R_0) is less than unity. The additive compound matrices approach is used to show that the dengue fever model's endemic equilibrium point is locally asymptotically stable when trace, determinant and determinant of second additive compound matrix of the Jacobian matrix are all negative. However, treatment will have a control of dengue fever disease. Numerical simulation of the model is implemented to investigate the sensitivity of certain key parameters on the dengue fever disease with treatment. They reported that a compartmental model for Dengue fever disease was presented, a model based on two populations, humans and mosquitoes with treatment. Simulation shows that on the application of treatment, the number of death is reduced. It has been proved algebraically that, if a constant minimum level of a treatment is applied, it is possible to maintain the basic reproduction number below unity and the infected humans were smaller.

Rattiya Sungchasit et al.[17], they used SEIR model to describe the transmission of dengue disease in mosquito due to the different dengue transmission rate in each season. Aedes aegypti and Aedes albopictus are primary vectors for the disease. The human population is separated into three population groups such as human in rainy season, human in winter season, human in summer season and vector population. We use standard dynamical analysis method for analyzing

mathematical model. The basic reproductive number of disease is found. The stability conditions of the disease free equilibrium state for $R_0 < 1$ and the endemic state are determined for $R_0 > 1$.

Noor Badshah et al.[18], states that Dengue fever is a vector-borne viral disease which is now endemic in more than 100 countries affecting more than 2.5 billion people worldwide. In recent years, dengue fever has become a major threat to public health in Pakistan. we derived an explicit formula for reproduction number R_0 (the most important epidemiological parameter) and then used real data of dengue fever cases of different hospitals of Lahore(Pakistan) on R_0. Conditions for local stability of equilibrium points are discussed. In the end, simulations are carried out for different situations. They reported Dynamical analysis of the model showDs that the existence of two equilibrium points.One is the disease-free equilibrium point which is locally asymptotically stable when $R_0 < 1$. The second equilibrium point is endemic equilibrium point which is locally asymptotically stable if $R_0 > 1$ and obtained the basic reproduction number and then estimated its value by using data of different hospitals in Lahore (Pakistan). On the basis of these estimations they conclude that Dengue is epidemic in Lahore and serious actions must be taken to control the dengue disease.Otherwise it may spread to other parts of the country. It means that in year(2010-2011)the Dengue disease is an epidemic in Lahore (Pakistan). In the absence of dengue vaccine, public health control depends on the reduction of reproduction number, which is reduced by decreasing the contact rate of both vector to host and host to vector. This can be done by reducing the vector breeding sites, decreasing the life span of vector, reducing the mosquito biting rate by quarantine and by targeted spray on larval places.

In 992 A.D (Nobuchi 1979), the vast expansion of shipping and the development of port cities in the 18^{th} and 19^{th} centuries, the mosquito vector, Aedes aegypti and the dengue viruses spread to new geographic areas causing major epidemics. The ecological disruption occurred in the Southeast Asia and pacific theaters during and following World War II, created ideal conditions for viral transmission and an increase of mosquito borne disease and it was in the setting that a global pandemic of dengue began. Dengue virus was first isolated in Japan in 1943, by inoculation of serum of patients in suckling mice (Kimura and Hotia 1944). In 1944, the virus was isolated from the sera of US soldiers at many parts of the world including Calcutta (Sabin and Schlesinger, 1945). The severe form of dengue, called DHF epidemic occurred first time in Manila, Philippines in 1953 to 1954(Rigau-Perez et al., 1998). In Asia, epidemic dengue has expanded geographically from Southeast Asian countries west to India, Srilanka, the Maldives and Pakistan and east to China(Gubler, 1998a, 1998b). By the 1980s, the American region was

experiencing major epidemics of dengue in countries that had been free of the disease for 35 to 130 years(Gubler, 1987). Before 1980, little was known about the distribution of dengue virus in Africa. Since then, however, major epidemics caused by all four serotypes have occurred in both East and West Africa. Therefore, the further decision that has been considered in this paper are:

1. Use education and drug therapy treatment as control strategy to minimize the infective population.

2. Minimize the cost of education and drug therapy treatment. In addition to these differences we used fourth order Runge-kutta algorithm for both with and without control of the problem.

CHAPTER THREE

3 METHODOLOGY

We use the Susceptible-Exposed-Infective-Recovered (SEIRS)compartmental model which is used to describe the epidemiology of dengue fever diseases. The SEIRS model is used in epidemiology to compute the amount of susceptible, exposed, infected and recovered people in a population. For the SEIRS model to be applicable, once a person has recovered from the disease, they disappearing immunity and reduced resistance. The model equations are solved qualitatively with MatLab which use pplane8. Simulation and sensitivity analysis are then performed on the model equations to determine the effect of the parameter values on the spread of the disease. We employ an optimal control problem with extended SEIRS compartmental model as constraints and minimize an objective (cost) function.

- Education and treatment by drug therapy, which are the most effective strategies in preventing morbidity and mortality associated with dengue fever diseases is included in this model.
- We choose an optimal strategy to minimize the total number of infectious individuals and the cost associated with education and treatment as control functions.
- We derive the optimality system and solve it numerically for our optimal control problem. As stressed in the statement of the problems, dengue disease for which our optimal control model is a good approximation.
- For all numerical solutions presented we use a forward-backward sweep method and the result is executed using MATLAB.

3.1 Model Assumptions

1. The population is uniform and mixes homogeneously. The total population size, N(t)=S(t)+E(t)+I(t)+R(t) at any time t$>$0.
2. The natural birth rate b and death rates μ_n are different rate.
3. Each individual in the population is considered as having an equal probability of contacting the disease with a contact rate β.

4. An infected individual makes contact and is able to transmit the disease with βN to others per unit time, that is, the contact rate is proportional to the total population size.

5. The fraction of contacts by an infected with a susceptible is S/N. Therefore the number of new infections in unit time per infective becomes (βN)(S/N). This rate is called an infection rate. This gives the rate of new infections or those leaving the susceptible category as $(\beta N(S/N)I = \beta SI$, which is called an incidence of the disease. This type of incidence is called bilinear incidence i.e., proportional to the product of the number of infective individuals and the number of susceptible individuals.

6. The number of infected individuals move from the exposed compartment per unit time is δ E at time t.

7. The exposed E move from their compartment to I-compartment at a constant rate δ, so that 1/δ is the mean latent period.

8. The infectious I move from their compartment to R-compartment at a constant rate γ, so that 1/γ is the mean infectious period.

9. The rate of susceptible, exposed, infected and recovered individual removed from each compartments through natural death and disease induced death are μ_nS, μ_nE, μ_nI, μ_nR and μ_dI respectively.

10. The recovered individual R move from their compartment to susceptible(S)-compartment at a constant rate α.

3.2 SEIRS Model of Dengue Fever

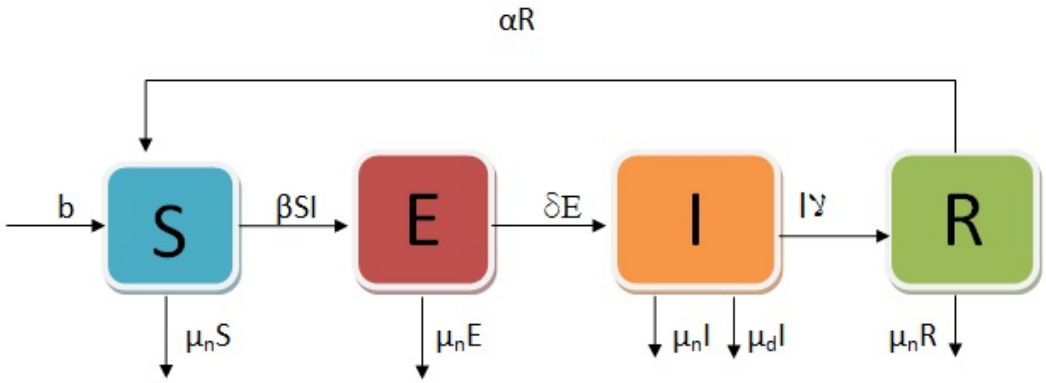

Figure 5: Epidemiological model of Dengue Fever

This is a flow chart for our model. The four boxes represent the four groups of individuals. The arrows show the movement between groups, and into and out of the compartment.

3.2.1 Model of susceptible group

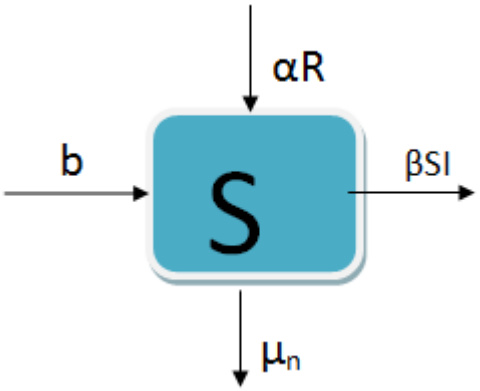

Figure 6: Compartment S

The inflow of population to the susceptible class is b, by combining assumptions 2, 5, 9 and 10 we drive the susceptible populations change per unit of time.

$$\frac{dS}{dt} = b - \beta IS - \mu_n S + \alpha R \tag{1}$$

3.2.2 Model of exposed group

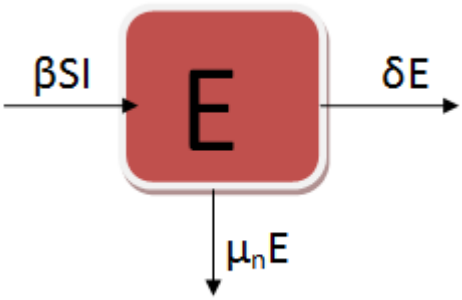

Figure 7: Model of compartment E

The number of individuals leave S and enter E, a fraction of exposed E move to infectious group I with a latent rate δ, δE an individual's move from exposed to infectious and some of the exposed group die through natural death rate μ_n, $\mu_n E$ to an individual's move from exposed to death. The exposed populations change per unit of time becomes,

$$\frac{dE}{dt} = \beta IS - \mu_n E - \delta E \tag{2}$$

3.2.3 Model of Infected group

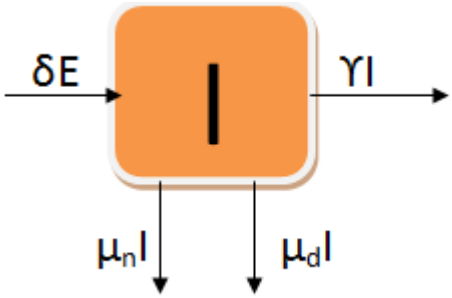

Figure 8: Model of compartment I

The number of individuals leave E and enter into the infected individuals I with latent rate δ, this gives rate of infective as follow,

$$\frac{dI}{dt} = \delta E - (\mu_n + \mu_d + \gamma)I \tag{3}$$

3.2.4 Model of Recovered group

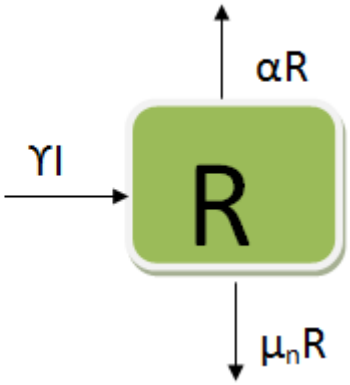

Figure 9: Model of compartment R

The number of individuals leave I enter into the recovered group with recovery rate γ, this gives rate of recovered as follow,

$$\frac{dR}{dt} = \gamma I - (\mu_n + \alpha)R \tag{4}$$

Model formulation using the assumptions as follows,

The differential equation from the assumptions and diagrams for t$\geq$ 0 is given in a system of ordinary differential equation form of eq(5)

$$\begin{cases} \frac{dS}{dt} &= b - \beta IS - \mu_n S + \alpha R \\ \frac{dE}{dt} &= \beta IS - \mu_n E - \delta E \\ \frac{dI}{dt} &= \delta E - (\mu_n + \mu_d + \gamma)I \\ \frac{dR}{dt} &= \gamma I - (\mu_n + \alpha)R \end{cases} \tag{5}$$

with initial conditions,

$S(0) = S_0 \geq 0, E(0) = E_0 \geq 0, I(0) = I_0 \geq 0$ and $R(0) = R_0 \geq 0$

Table 1: Description of variables and parameters for the model

Symbols	Description
S	Susceptibles population (proportion)
E	Exposed individual in the latent period (proportion)
I	Infectives population (proportion)
R	Recovered population (proportion)
β	Contact rate
μ_n	Natural death rate
b	Average birth rate
μ_d	Disease related death rate
δ	Exposed rate
γ	Recovery rate
α	Recovering rate of remove disease to Susceptible
$1/\delta$	Average exposed rate period
$1/\gamma$	Average Infectious Period
R_0	Basic Reproduction Number

3.3 Positivity of Solutions

The basic properties of the equation (5), are feasible solutions and positivity of solutions. The feasible solution shows the region in which the solution of the equations are biologically meaningful and describes the non-negativity of the solutions of the equation (5) by [19].

3.4 Equilibrium point

In epidemiology we have two types of equilibria points; disease free-equilibrium and endemic equilibrium.

1. If the equilibrium point has the infectious component equal to zero($I^* = 0$), this means that the disease has undergone extinction is called disease-free equilibrium (DFE).

2. If $I^* > 0$ the disease persist in the population called endemic-equilibrium(EE).

To find the equilibrium points of equation (5) the right-hand sides of each differential equation are set to zero, leading to the system.

$$\begin{cases} b - \beta I^* S^* - \mu_n S^* + \alpha R^* = 0 \\ \beta I^* S^* - (\mu_n + \delta) E^* = 0 \\ \delta E^* - (\mu_n + \mu_d + \gamma) I^* = 0 \\ \gamma I^* - (\mu_n + \alpha) R^* = 0 \end{cases} \tag{6}$$

Where $S^*,\ E^*,\ I^*\ and\ R^*$are the equilibria points of equation(5).

$$Let \quad \beta I^* S^* = \varphi \tag{7}$$

Substituting eq(7) into eq(6) gives,

1. From eq(6) we have, $\varphi - (\mu_n + \delta)E^* = 0 \Rightarrow E^* = \frac{\varphi}{\mu_n + \delta}$
2. From eq(6) we have, $\delta(\frac{\varphi}{\mu_n+\delta}) - (\mu_n + \mu_d + \gamma)I^* = 0$

   . $\Rightarrow \frac{\delta\varphi}{\mu_n+\delta} = (\mu_n + \mu_d + \gamma)I^*$

   . $\Rightarrow I^* = \frac{\delta\varphi}{(\mu_n+\delta)(\mu_n+\mu_d+\gamma)}$

   $let\ \ \theta = (\mu_n + \delta)(\mu_n + \mu_d + \gamma)$

   . $\Rightarrow I^* = \frac{\delta\varphi}{\theta}$

3. From eq(6) we have, $\gamma I^* - (\mu_n + \alpha)R^* = 0 \Rightarrow R^* = \frac{\gamma I^*}{(\mu_n+\alpha)}$

   $\Rightarrow R^* = \frac{\gamma\delta\varphi}{\theta(\mu_n+\alpha)}$

4. From eq(6) we have, $b - \beta I^* S^* - \mu_n S^* + \alpha R^* = 0$

   $$b - \varphi - \mu_n S^* + \alpha R^* = 0 \tag{8}$$

   Substitute the value of R^* into eq(8), we can find the value of S^* as follow:

   $b - \varphi - \mu_n S^* + \alpha(\frac{\gamma\delta\varphi}{\theta(\mu_n+\alpha)}) = 0$

   $\Rightarrow \mu_n S^* = b - \varphi + \frac{\alpha\gamma\delta\varphi}{\theta(\mu_n+\alpha)}$

   $\Rightarrow S^* = \frac{\theta(\mu_n+\alpha)(b-\varphi)+\alpha\gamma\delta\varphi}{\mu_n\theta(\mu_n+\alpha)}$

$$\begin{cases} S^* = & \frac{\theta(\mu_n+\alpha)(b-\varphi)+\alpha\gamma\delta\varphi}{\mu_n\theta(\mu_n+\alpha)} \\ E^* = & \frac{\varphi}{\mu_n+\delta} \\ I^* = & \frac{\delta\varphi}{\theta} \\ R^* = & \frac{\gamma\delta\varphi}{\theta(\mu_n+\alpha)} \end{cases} \tag{9}$$

Substitute eq(9) into $b - \beta I^* S^* - \mu_n S^* + \alpha R^* = 0$

$\Rightarrow b - \beta(\frac{\delta\varphi}{\theta})(\frac{\theta(\mu_n+\alpha)(b-\varphi)+\alpha\gamma\delta\varphi}{\mu_n\theta(\mu_n+\alpha)}) - \mu_n(\frac{\theta(\mu_n+\alpha)(b-\varphi)+\alpha\gamma\delta\varphi}{\mu_n\theta(\mu_n+\alpha)}) + \alpha(\frac{\gamma\delta\varphi}{\theta(\mu_n+\alpha)}) = 0$

$\Rightarrow b - (\frac{\beta\delta\varphi}{\theta})(\frac{\theta(\mu_n+\alpha)(b-\varphi)+\alpha\gamma\delta\varphi}{\mu_n\theta(\mu_n+\alpha)}) - (\frac{\theta(\mu_n+\alpha)(b-\varphi)+\alpha\gamma\delta\varphi}{\theta(\mu_n+\alpha)}) + \frac{\alpha\gamma\delta\varphi}{\theta(\mu_n+\alpha)} = 0$

$\Rightarrow b - (\frac{\beta\delta\varphi}{\theta})(\frac{\theta(\mu_n+\alpha)(b-\varphi)}{\mu_n\theta(\mu_n+\alpha)} + \frac{\alpha\gamma\delta\varphi}{\mu_n\theta(\mu_n+\alpha)}) - (b-\varphi) = 0$

$\Rightarrow b - (\frac{\beta\delta\varphi}{\theta})(\frac{(b-\varphi)}{\mu_n} + \frac{\alpha\gamma\delta\varphi}{\mu_n\theta(\mu_n+\alpha)}) - b + \varphi = 0$

$\Rightarrow -(\frac{\beta\delta\varphi}{\theta})(\frac{(b-\varphi)}{\mu_n} + \frac{\alpha\gamma\delta\varphi}{\mu_n\theta(\mu_n+\alpha)}) + \varphi = 0$

$\Rightarrow \varphi(1 - (\frac{\beta\delta}{\theta})(\frac{(b-\varphi)}{\mu_n} + \frac{\alpha\gamma\delta\varphi}{\mu_n\theta(\mu_n+\alpha)}) = 0$

$\varphi = 0$, or $1 - (\frac{\beta\delta}{\theta})(\frac{(b-\varphi)}{\mu_n} + \frac{\alpha\gamma\delta\varphi}{\mu_n\theta(\mu_n+\alpha)}) = 0$

$\Rightarrow (\frac{\beta\delta}{\theta})(\frac{(b-\varphi)}{\mu_n} + \frac{\alpha\gamma\delta\varphi}{\mu_n\theta(\mu_n+\alpha)}) = 1$

$\Rightarrow \frac{\theta}{\beta\delta} = \frac{b}{\mu_n} + \frac{\varphi}{\mu_n}(\frac{\alpha\gamma\delta}{\theta(\mu_n+\alpha)} - 1)$

$\Rightarrow \varphi = \frac{\theta(\theta\mu_n - b\beta\delta)(\mu_n+\alpha)}{\beta\delta(\alpha\gamma\delta - \theta(\mu_n+\alpha))}$

$$\varphi = 0, \quad or \quad \varphi = \frac{\theta(\theta\mu_n - b\beta\delta)(\mu_n+\alpha)}{\beta\delta(\alpha\gamma\delta - \theta(\mu_n+\alpha))} \tag{10}$$

Substituting eq(10) into eq(9) gives the following two case:

case 1: For $\varphi = 0$, equations(9) becomes

$$\begin{cases} S^* = & (\frac{b\theta(\mu_n+\alpha) - 0*\theta(\mu_n+\alpha)+\alpha\gamma\delta*0}{\mu_n\theta(\mu_n+\alpha)}) = \frac{b}{\mu_n} \\ E^* = & \frac{0}{\mu_n+\delta} = 0 \\ I^* = & \frac{\delta*0}{\theta} = 0 \\ R^* = & \frac{\gamma\delta*0}{\theta(\mu_n+\alpha)} = 0 \end{cases} \tag{11}$$

One of the equilibrium point is $(S^*, E^*, I^*, R^*) = (\frac{b}{\mu_n}, 0, 0, 0)$.

This equilibrium point is called the disease-free equilibrium point.

case 2: For $\varphi = \frac{\theta(\theta\mu_n - b\beta\delta)(\mu_n+\alpha)}{\beta\delta(\alpha\gamma\delta - \theta(\mu_n+\alpha))}$, equations(9) becomes

$$\begin{cases} S^* = \frac{\theta(b\beta\delta(1-\mu_n-\alpha)+\mu_n(\delta\alpha\gamma-\theta))}{\beta\delta(\alpha\gamma\delta-\theta(\mu_n+\alpha))} \\ E^* = \frac{\theta(\theta\mu_n-b\beta\delta)(\mu_n+\alpha)}{\beta\delta(\alpha\gamma\delta-\theta(\mu_n+\alpha))(\mu_n+\delta)} \\ I^* = \frac{(\theta\mu_n-b\beta\delta)(\mu_n+\alpha)}{\beta(\alpha\gamma\delta-\theta(\mu_n+\alpha))} \\ R^* = \frac{\gamma(\theta\mu_n-b\beta\delta)}{\beta(\alpha\gamma\delta-\theta(\mu_n+\alpha))} \end{cases}$$

Let $\omega = \theta(b\beta\delta(1-\mu_n-\alpha)+\mu_n(\delta\alpha\gamma-\theta))$

. $\omega_1 = \beta(\alpha\gamma\delta - \theta(\mu_n+\alpha))$

. $\omega_2 = (\theta\mu_n - b\beta\delta)(\mu_n+\alpha)$

The other one of the equilibrium point is,

$(S^*, E^*, I^*, R^*) = (\frac{\omega}{\delta\omega_1}, \frac{\theta\omega_2}{\delta\omega_1(\mu_n+\delta)}, \frac{\omega_2}{\omega_1}, \frac{\gamma(\theta\mu_n-b\beta\delta)}{\omega_1})$. This equilibrium point is called the endemic equilibrium point.

3.5 Reproduction number

The basic reproduction ratio of Dengue fever disease is a pivotal concept in epidemiology. It is defined as the expected number of secondary cases that would arise from the introduction of a single primary case into a fully susceptible population. Clearly, when $R_0 < 1$ each successive infection generation is smaller than its predecessor, and the infection cannot persist. Conversely, when $R_0 > 1$ successive infection generations are larger than their predecessors, and the number of cases in the population will initially increase. This increase does not continue indefinitely. The infection process reduces the pool of susceptibles, and hence reduces the probability that an infectious individual contacts a susceptible within its period of infectiousness. This non-linear effect can only be neglected at the beginning of an epidemic. It represents the average number of secondary infections infected by an individual infective. The basic reproduction number can be used to assess whether a newly dengue fever disease can invade a population and to estimate the final size of an SEIRS type epidemic. In all the models presented, the reproduction number could be obtained by inspection. This was possible because there was only one infective class. If the number of infective classes is two or more, then the technique due to [20], is

more appropriate. In the next subsection, we summarize the technique known as the next generation matrix technique.

3.5.1 The next generation matrix

We have seen how to define and calculate R_0 for simple homogeneous models. There exist methods to define R_0 for more complicated models that include heterogeneity or seasonality methods. However these methods usually provide only a threshold quantity that describes when the disease-free equilibrium loses stability and does not necessarily satisfy the original definition of the expected number of secondary infections caused by one infected individual in a fully susceptible population through the entire duration of the infectious period. A lot of these methods derive from the idea of the next generation operator introduced by Diekmann et al.[20]. This method converts a system of ordinary differential equations of a model of disease dynamics to an operator that translate from one generation of infectious individuals to the next. The basic reproductive number is defined as the spectral radius (dominant eigenvalue) of this operator. We consider a deterministic model for disease transmission with n compartments (dimensions).
We let $x(t) \in R_+^n$ where $x_i(t)$ denotes the number of individuals in compartment i at time t. For ease of notation, we order the compartments such that the first m (for m $\leq n$) compartments correspond to the states with infection.

$$\frac{x_i}{dt} = f_i(x) \tag{12}$$

with nonnegative initial conditions, $x(0) \in R_+^n$,we defineX_s to be the set of all disease free states, that is
$X_s = \{x \geq 0 \mid x_i = 0, i = 1, 2, ...m\}$.
In order to compute R_0, it is important to distinguish new infections from all other changes in the population.
Let $F_i(x)$ be the rate of appearance of new infections in compartments i, V_i^{in} be the rate of transfer of individuals into compartment i by all other means. V_i^{out} be the rate of transfer of individuals out of compartment i. It is assumed that each function ($F_i(x), V_i^{in}\ and\ V_i^{out}$) is continuously differentiable at least twice with respect to each variable. We define m by

m matrices, F and V,

$$F_{ij} = \frac{\partial F_i}{\partial x_j} \quad for \;\; 1 \leq i, j \leq m \tag{13}$$

$$V_{ij} = \frac{\partial V_i}{\partial x_j} \quad for \;\; 1 \leq i, j \leq m \tag{14}$$

Where $V_i(x) = V_i^{out} - V_i^{in}$

Following Diekmann et al., we call FV^{-1} the next generation matrix for the model and we shall set R_0 as equal to the spectral radius of FV^{-1} i.e,

$$R_0 = \rho(FV^{-1}) \tag{15}$$

where $\rho(FV^{-1})$ denotes the spectral radius(largest eigenvalue in magnitude) of the matrix FV^{-1}. In our model m = 2 (Two infected compartments). From (5), we obtain

$$\begin{cases} \frac{dE}{dt} &= \beta IS - (\mu_n + \delta)E \\ \frac{dI}{dt} &= \delta E - (\mu_n + \mu_d + \gamma)I \end{cases} \tag{16}$$

$$F = \begin{bmatrix} \beta SI \\ 0 \end{bmatrix}, V^{out} = \begin{bmatrix} (\mu_n + \delta)E \\ (\mu_n + \mu_d + \gamma)I \end{bmatrix}, V^{in} = \begin{bmatrix} 0 \\ \delta E \end{bmatrix}$$

$$F = \begin{bmatrix} \beta SI \\ 0 \end{bmatrix} \;, V = \begin{bmatrix} (\mu_n + \delta)E \\ (\mu_n + \mu_d + \gamma)I - \delta E \end{bmatrix} \tag{17}$$

We differentiate both matrices F and V with respect to E and I to get F and V respectively. Then we can find the Jacobian for each matrix F and V at no disease. The equilibrium at no disease for equation (9) is $(S^*, E^*, I^*, R^*) = (\frac{b}{\mu_n}, 0, 0, 0)$. The derivatives of F and V at $(\frac{b}{\mu_n}, 0, 0, 0)$ are given by,

$$F = \begin{bmatrix} 0 & \beta \\ 0 & 0 \end{bmatrix}, V = \begin{bmatrix} (\mu_n + \delta) & 0 \\ -\delta & (\mu_n + \mu_d + \gamma) \end{bmatrix} \tag{18}$$

respectively. The inverse of V is given by

$$V^{-1} = \frac{1}{det(V)}(\begin{bmatrix} (\mu_n + \mu_d + \gamma) & 0 \\ \delta & (\mu_n + \delta) \end{bmatrix}$$

$$\Rightarrow V^{-1} = \frac{1}{(\mu_n + \mu_d + \gamma)(\mu_n + \delta)}(\begin{bmatrix} (\mu_n + \mu_d + \gamma) & 0 \\ \delta & (\mu_n + \delta) \end{bmatrix} \tag{19}$$

$$FV^{-1} = \frac{1}{(\mu_n + \mu_d + \gamma)(\mu_n + \delta)}\left(\begin{bmatrix} 0 & \beta \\ 0 & 0 \end{bmatrix} * \begin{bmatrix} (\mu_n + \mu_d + \gamma) & 0 \\ \delta & (\mu_n + \delta) \end{bmatrix}\right)$$

$$\Rightarrow FV^{-1} = \frac{1}{(\mu_n + \mu_d + \gamma)(\mu_n + \delta)}\left(\begin{bmatrix} \beta\delta & \beta(\mu_n + \delta) \\ 0 & 0 \end{bmatrix}\right) \tag{20}$$

And we calculate spectral radius of FV^{-1}gives the reproduction number of the model as,

$$R_0 = \frac{\beta\delta}{(\mu_n + \mu_d + \gamma)(\mu_n + \delta)} \tag{21}$$

This means an exposed individual that survives $\frac{\delta}{(\mu_n+\delta)}$ becomes infectious and contacts β susceptible individuals during the period of infectivity $\frac{1}{(\mu_n+\mu_d+\gamma)}$, which result in a new exposure.

If $\beta\delta < (\mu_n + \mu_d + \gamma)(\mu_n + \delta)$, then $R_0 < 1$, the system is stable.

If $\beta\delta > (\mu_n + \mu_d + \gamma)(\mu_n + \delta)$, then $R_0 > 1$, the system is unstable.

3.5.2 Routh-Hurwitz Stability Criterion

The Routh-Hurwitz criterion is a method for determining whether a linear system is stable or not by examining the locations of the roots of the characteristic equation of the system. In fact, the method determines only if there are roots that lie outside of the left half plane; it does not actually compute the roots. Consider the characteristic equation.

$$a_n s^n + a_{(n-1)} s^{(n-1)} + ... + a_1 s + a_0 = 0 \tag{22}$$

To determine whether this system is stable or not, check the following conditions:

1. Two necessary but not sufficient conditions that all the roots have negative real parts are.

   a) All the polynomial coefficients must have the same sign.

   b) All the polynomial coefficients must be nonzero.

2. If condition (1) is satisfied,then compute the Routh-Hurwitz array[21].

3. The necessary condition that all roots have negative real parts is that all the elements of the first column of the array have the same sign. The number of changes of sign equals the number of roots with positive real parts. If any of the coefficients is zero or negative in the presence of at least one positive coefficient there are imaginary roots

or roots in the right half plane i.e., unstable roots. This process is continued until the n^{th} row is completed. The number of roots of the characteristic lying in the right half of the s-plane (unstable roots) is equal to the number of sign changes in the first column of the Routh array, assuming all coefficients are positive the condition for stable roots.

3.6 Linearization and Stability Analysis

In this section, we consider some important methods of establishing stability of equilibrium points of non-linear differential equations. Because of,stability properties depend only on the nature of the system near the equilibrium point. Therefore, to conduct an analysis of the stability, it is often theoretically legitimate and mathematically convenient to replace the full nonlinear description by a simpler description that approximates the true system near the equilibrium point[22]. We us which corresponds to the endemic state i.e., the case where the disease persists in the populations. In order to determine the stability of this point, we resort to the same approach used in determining the stability of the disease free equilibrium. We evaluate the community (or Jacobian) matrix at the endemic point. The Jacobian matrix to determine the eigenvalues and eigenvectors which in turn determines our stability of SEIRS model. Using equations(5) we can construct the following Jacobian-matrix(J).

$$J = \begin{bmatrix} \frac{df_1}{dS} & \frac{df_1}{dE} & \frac{df_1}{dI} & \frac{df_1}{dR} \\ \frac{df_2}{dS} & \frac{df_2}{dE} & \frac{df_2}{dI} & \frac{df_2}{dR} \\ \frac{df_3}{dS} & \frac{df_3}{dE} & \frac{df_3}{dI} & \frac{df_3}{dR} \\ \frac{df_4}{dS} & \frac{df_4}{dE} & \frac{df_4}{dI} & \frac{df_4}{dR} \end{bmatrix}$$

$$J = \begin{bmatrix} -(\beta I + \mu_n) & 0 & -\beta S & \alpha \\ \beta I & -(\mu_n + \delta) & \beta S & 0 \\ 0 & \delta & -(\mu_n + \mu_d + \gamma) & 0 \\ 0 & 0 & \gamma & -(\mu_n + \alpha) \end{bmatrix}$$

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

1. If all eigenvalues of J are strictly in the left half-plane, then equilibrium point is asymptotically stable for the nonlinear system.

2. If at least one eigenvalue of J has a positive real part, then equilibrium point is unstable for the nonlinear system.

3. If the eigenvalues of J are all in the left half-plane, but at least one has a zero real part then equilibrium point may be either stable, asymptotically stable or unstable for the nonlinear system.

3.6.1 Disease-free equilibrium point

At the initial state of the disease we have only the susceptible present. From earlier calculations, the disease free equilibrium is,
$(S*, E*, I*, R*) = (\frac{b}{\mu_n}, 0, 0, 0)$, (i.e., is trivial in the sense that all individuals are healthy and stay healthy all the time). In order to determine the stability of the model at this point, we evaluate the Jacobean matrix at this equilibrium point and find the eigenvalues corresponding to this point. Evaluating the Jacobean in equation at the disease free equilibrium point, we have

$$J(\frac{b}{\mu_n}, 0, 0, 0) = \begin{bmatrix} -(\beta(0) + \mu_n) & 0 & -\beta(\frac{b}{\mu_n}) & \alpha \\ \beta(0) & -(\mu_n + \delta) & \beta(\frac{b}{\mu_n}) & 0 \\ 0 & \delta & -(\mu_n + \mu_d + \gamma) & 0 \\ 0 & 0 & \gamma & -(\mu_n + \alpha) \end{bmatrix}$$

$$= \begin{bmatrix} -\mu_n & 0 & \frac{-b\beta}{\mu_n} & \alpha \\ 0 & -(\mu_n + \delta) & \frac{b\beta}{\mu_n} & 0 \\ 0 & \delta & -(\mu_n + \mu_d + \gamma) & 0 \\ 0 & 0 & \gamma & -(\mu_n + \alpha) \end{bmatrix}$$

We find the characteristic equation which is given by det(J - λI)= 0 where J is an 4 by 4 matrix and λ is the eigenvalues. Thus

$$det(J-\lambda I) = det(\begin{bmatrix} -\mu_n & 0 & \frac{-b\beta}{\mu_n} & \alpha \\ 0 & -(\mu_n+\delta) & \frac{b\beta}{\mu_n} & 0 \\ 0 & \delta & -(\mu_n+\mu_d+\gamma) & 0 \\ 0 & 0 & \gamma & -(\mu_n+\alpha) \end{bmatrix} - \lambda \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix})$$

$$\Rightarrow det(\begin{bmatrix} -\mu_n-\lambda & 0 & \frac{-b\beta}{\mu_n} & \alpha \\ 0 & -(\mu_n+\delta)-\lambda & \frac{b\beta}{\mu_n} & 0 \\ 0 & \delta & -(\mu_n+\mu_d+\gamma)-\lambda & 0 \\ 0 & 0 & \gamma & -(\mu_n+\alpha)-\lambda \end{bmatrix}) = 0$$

$$\Rightarrow (-\mu_n-\lambda) det \begin{bmatrix} -(\mu_n+\delta)-\lambda & \frac{b\beta}{\mu_n} & 0 \\ \delta & -(\mu_n+\mu_d+\gamma)-\lambda & 0 \\ 0 & \gamma & -(\mu_n+\alpha)-\lambda \end{bmatrix}) = 0$$

$$\Rightarrow (-\mu_n-\lambda)((-(\mu_n+\delta)-\lambda) det \begin{bmatrix} -(\mu_n+\mu_d+\gamma)-\lambda & 0 \\ \gamma & -(\mu_n+\alpha)-\lambda \end{bmatrix} -$$

$$\delta\ det \begin{bmatrix} \frac{b\beta}{\mu_n} & 0 \\ \gamma & -(\mu_n+\alpha)-\lambda \end{bmatrix}) = 0$$

$\Rightarrow (-\mu_n-\lambda)((-(\mu_n+\delta)-\lambda)(-(\mu_n+\mu_d+\gamma)-\lambda)(-(\mu_n+\alpha)-\lambda) - \delta(\frac{b\beta}{\mu_n})(-(\mu_n+\alpha)-\lambda)) = 0$

$\Rightarrow (-\mu_n-\lambda)(-(\mu_n+\alpha)-\lambda)((-(\mu_n+\delta)-\lambda)(-(\mu_n+\mu_d+\gamma)-\lambda) - \delta(\frac{b\beta}{\mu_n})) = 0$

$\Rightarrow \lambda^4 + \lambda^3(4\mu_n+\alpha+\delta+\mu_d+\gamma) + \lambda^2(2\mu_n(\mu_n+\alpha) + (2\mu_n+\alpha)(2\mu_n+\delta+\mu_d+\gamma)) +$

$\lambda(\mu_n(\mu_n+\alpha)(4\mu_n+\alpha+\delta+\mu_d+\gamma)) + \mu_n(\mu_n+\alpha)((\mu_n+\delta)(\mu_n+\mu_d+\gamma) - \frac{\delta b\beta}{\mu_n}) = 0$

$\Rightarrow\ a_4\lambda^4 + a_3\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0 = 0$ is the characteristic equation at disease free equilibrium point.

Where, $a_4 = 1$

$a_3 = (4\mu_n+\alpha+\delta+\mu_d+\gamma)$

$a_2 = 2\mu_n(\mu_n+\alpha) + (2\mu_n+\alpha)(2\mu_n+\delta+\mu_d+\gamma)$

$a_1 = \mu_n(\mu_n+\alpha)(4\mu_n+\alpha+\delta+\mu_d+\gamma)$

$a_0 = \mu_n(\mu_n+\alpha)((\mu_n+\delta)(\mu_n+\mu_d+\gamma) - \frac{\delta b\beta}{\mu_n})$

If $((\mu_n+\delta)(\mu_n+\mu_d+\gamma)-\frac{\delta b\beta}{\mu_n})>0$,then a_0 is positive.
If $a_3a_2-a_4a_1>0$,$a_0>0$ and $a_1-\frac{a_3^2a_0}{a_3a_2-a_4a_1}>0$, then all the elements are positive.
By Routh-Hurwitz criterion the system is stable, otherwise it is unstable.

3.6.2 Endemic equilibrium point

At the point in time where all the compartments of the population coexist is called the endemic period. The presence of an infectious person is a problem in the epidemiology of infectious diseases. we consider the situation whereby there is coexistence between the two main categories (i.e., the susceptible and the infectious). This is seen in the endemic equilibrium point in equation below.
$(S^*,E^*,I^*,R^*)=(\frac{\omega}{\delta\omega_1},\frac{\theta\omega_2}{\delta\omega_1(\mu_n+\delta)},\frac{\omega_2}{\omega_1},\frac{\gamma(\theta\mu_n-b\beta\delta)}{\omega_1})$. which corresponds to the endemic state i.e., the case where the disease persists in the populations. In order to determine the stability of this point, we resort to the same approach used in determining the stability of the disease free equilibrium. We evaluate the community (or Jacobian) matrix at the endemic point.

$$det(J-\lambda I)=det(\begin{bmatrix}\frac{-\beta\omega_2}{\omega_1}-\mu_n-\lambda & 0 & \frac{-\beta\omega}{\delta\omega_1} & \alpha\\ \frac{\beta\omega_2}{\omega_1} & -(\mu_n+\delta)-\lambda & \frac{\beta\omega}{\delta\omega_1} & 0\\ 0 & \delta & -(\mu_n+\mu_d+\gamma)-\lambda & 0\\ 0 & 0 & \gamma & -(\mu_n+\alpha)-\lambda\end{bmatrix})$$

$$det(J-\lambda I)=(\frac{-\beta\omega_2}{\omega_1}-\mu_n-\lambda)det(\begin{bmatrix}-(\mu_n+\delta)-\lambda & \frac{\beta\omega}{\delta\omega_1} & 0\\ \delta & -(\mu_n+\mu_d+\gamma)-\lambda & 0\\ 0 & \gamma & -(\mu_n+\alpha)-\lambda\end{bmatrix})$$

$$-(\frac{\beta\omega_2}{\omega_1})det(\begin{bmatrix}0 & \frac{-\beta\omega}{\delta\omega_1} & \alpha\\ \delta & -(\mu_n+\mu_d+\gamma)-\lambda & 0\\ 0 & \gamma & -(\mu_n+\alpha)-\lambda\end{bmatrix})=0$$

$\Rightarrow((\frac{\beta\omega_2}{\omega_1}+\mu_n)+\lambda)((\mu_n+\delta)+\lambda)((\mu_n+\mu_d+\gamma)+\lambda)((\mu_n+\alpha)+\lambda)-$
$\frac{\beta\omega}{\omega_1}((\frac{\beta\omega_2}{\omega_1}+\mu_n)+\lambda)((\mu_n+\alpha)+\lambda)+\frac{\beta^2\omega_2\omega}{\omega_1^2}((\mu_n+\alpha)+\lambda)-\frac{\beta\omega_2\gamma\alpha\delta}{\omega_1}=0\Rightarrow\lambda^4+\lambda^3(\frac{\beta\omega_2}{\omega_1}+$

$4\mu_n+\mu_d+\gamma+\delta+\alpha)+\lambda^2((\mu_n+\mu_d+\gamma)(\mu_n+\alpha)+(\frac{\beta\omega_2}{\omega_1}+2\mu_n+\delta)(2\mu_n+\mu_d+\gamma+$

$\alpha)+(\frac{\beta\omega_2}{\omega_1}+\mu_n)(\mu_n+\delta)-\frac{\beta\omega}{\omega_1})+\lambda((\mu_n+\mu_d+\gamma)(\mu_n+\alpha)(\frac{\beta\omega_2}{\omega_1}+2\mu_n+\delta)+(\frac{\beta\omega_2}{\omega_1}+\mu_n)+$

$(\mu_n+\delta)(2\mu_n+\mu_d+\gamma+\alpha)-\frac{\beta\omega}{\omega_1}(\frac{\beta\omega_2}{\omega_1}+2\mu_n+\alpha)+\frac{\beta^2\omega\omega_2}{\omega_1})-\frac{\beta\omega_2\gamma\alpha\delta}{\omega_1}=0$

$\Rightarrow a_4\lambda^4+a_3\lambda^3+a_2\lambda^2+a_1\lambda+a_0=0$ is the characteristic equation at endemic equilibrium point.

Where,

$$a_4=1$$

$$a_3=(\frac{\beta\omega_2}{\omega_1}+4\mu_n+\mu_d+\gamma+\delta+\alpha)$$

$$a_2=((\mu_n+\mu_d+\gamma)(\mu_n+\alpha)+(\frac{\beta\omega_2}{\omega_1}+2\mu_n+\delta)(2\mu_n+\mu_d+\gamma+\alpha)+(\frac{\beta\omega_2}{\omega_1}+\mu_n)(\mu_n+\delta)-\frac{\beta\omega}{\omega_1})$$

$$a_1=((\mu_n+\mu_d+\gamma)(\mu_n+\alpha)(\frac{\beta\omega_2}{\omega_1}+2\mu_n+\delta)+(\frac{\beta\omega_2}{\omega_1}+\mu_n)+(\mu_n+\delta)*(2\mu_n+\mu_d+\gamma+\alpha)-\frac{\beta\omega}{\omega_1}(\frac{\beta\omega_2}{\omega_1}+2\mu_n+\alpha)+\frac{\beta^2\omega\omega_2}{\omega_1})$$

$a_0=-\frac{\beta\omega_2\gamma\alpha\delta}{\omega_1}$

If $\frac{\beta\omega_2\gamma\alpha\delta}{\omega_1}<0$, then a_0 is positive.

If $(\frac{\beta\omega_2}{\omega_1}+\mu_n)(\mu_n+\delta)>\frac{\beta\omega}{\omega_1}$, then $a_2>0$

If $(\frac{\beta\omega_2}{\omega_1}+\mu_n)+(\mu_n+\delta)*(2\mu_n+\mu_d+\gamma+\alpha)>\frac{\beta\omega}{\omega_1}(\frac{\beta\omega_2}{\omega_1}+2\mu_n+\alpha)+\frac{\beta^2\omega\omega_2}{\omega_1})$, then $a_1>0$.

If $a_3a_2-a_4a_1>0$,$a_0,a_1,a_2>0$ and $a_1-\frac{a_3^2a_0}{a_3a_2-a_4a_1}>0$, then all the elements are positive.

By Routh-Hurwitz criterion the system is stable, otherwise it is unstable.

3.7 Qualitative Analysis of SEIRS Model

We use MatLab to run our simulations. For my systems of nonlinear differential equations, we use the pplane8. Sensitivity analysis is performed on the parameter values to determine the effect of these values on the rate of spread of dengue fever.

3.7.1 Nullclines and phaseplanes

1. **Definition of nullcline:** Consider the autonomous system of two DEs[23]: $\frac{dx}{dt}=f(x,y)$ and $\frac{dy}{dt}=g(x,y)$.

- The x-nullcline is a set of points in the phase plane so that $\frac{dx}{dt}=0$. Geometrically, these are the points where the vectors are either straight up or straight down. Algebraically, we find the x-nullcline by solving f(x,y)=0.

- The y-nullcline is a set of points in the phase plane so that $\frac{dy}{dt} = 0$. Geometrically, these are the points where the vectors are horizontal, going either to the left or to the right. Algebraically, we find the y-nullcline by solving g(x,y) = 0.

2. **phaseplane:** is a program designed for phase plane analysis of differential equations. Pplane is used for a system of differential equations of the form $x' = f(x, y), y' = g(x, y)$. To use pplane in our system of ODEs, first reduced the given four differential equations (5) into two.

For the fixed population(N), $N = S + E + I + R$

$R = N - (S + E + I)$ *and* $E = N - (S + R + I)$

$E = N-(S+R+I) = N-(b-\beta IS-\mu_n S+\alpha R+\delta E-(\mu_n+\mu_d+\gamma)I+\gamma I-(\mu_n+\alpha)R)$

$\Rightarrow E = \frac{N-b+\beta SI+\mu_n N}{1+\mu_n+\delta}$

$$\begin{cases} \frac{dS}{dt} = b - \beta IS - \mu_n S + \alpha(N - S - I - (\frac{N-b+\beta SI+\mu_n N}{1+\mu_n+\delta})) \\ \frac{dI}{dt} = \delta(\frac{N-b+\beta SI+\mu_n N}{1+\mu_n+\delta}) - (\mu_n + \mu_d + \gamma)I \end{cases} \tag{23}$$

2.1. phaseplane diagram:

Using pplane8 we can determine the stability.

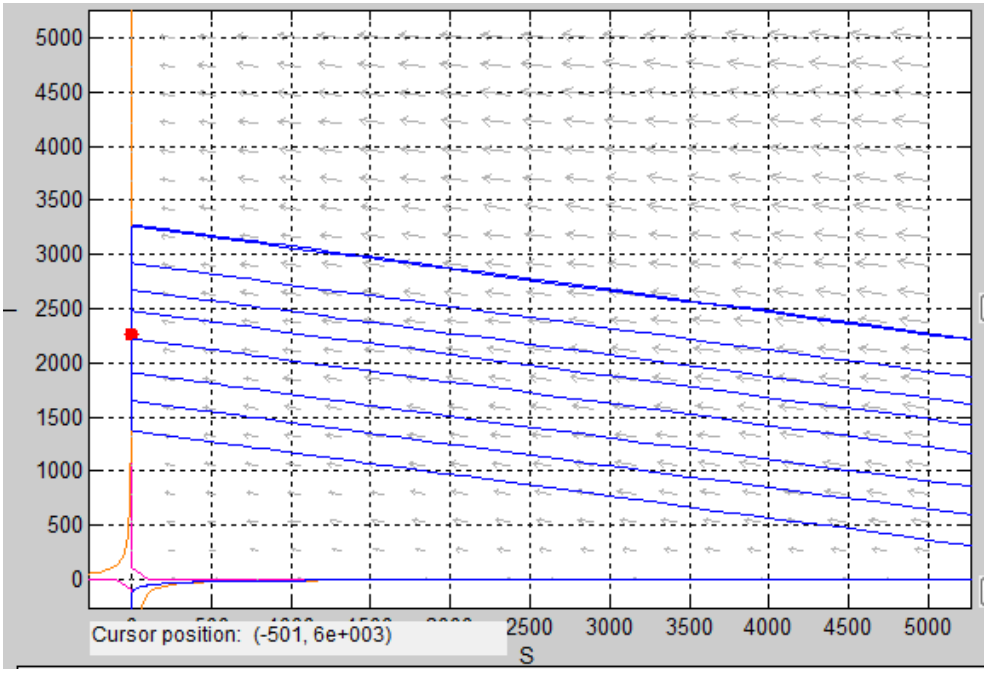

Figure 10: Graph shows equilibrium point and nullclines

Figure 10, the graph showing the stability at equilibrium point for the following parameter values: natural death rate(μ_n) $= 1/(71 * 365)$, contact rate(β) $= 0.375$, average birth rate(b) $= 1/(71 * 365)$, disease related death rate (μ_d)=1/11, exposed rate(δ) $= 1/4$, recovery rate(γ) $= 1/3$, recovering rate of remove disease to susceptible(α) $= 0.00008$. The the given system is equilibrium at point(364.6809 , 239.1216)andand the arrows goes towards the equilibrium point, it is a nodal sink. In addition the stability of the system is also determined depending on the eigenvalues result. The values of the eigenvalues $\lambda_1 = -848.5368$ and $\lambda_2 = -0.4243$ are real and negative, the SEIRS model is stable.

3.8 Optimal control

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 [24]. Some important milestones in the development of optimal control in the 20^{th}century include the formulation dynamic programming by Richard Bellman(1920-1984) in the 1950s, the development of the minimum principle by Lev Pontryagin(1908-1988) and co-workers also in the 1950s, and the formulation of the linear quadratic regulator and the Kalman filter by Rudolf Kalman (b.1930) in the 1960s. See the review papers Sussmann and Willems(1997) and Bryson (1996) for further historical details.Optimal control and its ramifications have found applications in many different fields,including aerospace, process control, robotics, bioengineering, economics, finance, and management science, and it continues to be an active research area within control theory. Before the arrival of the digital computer in the 1950s, only fairly simple optimal control problems could be solved. The arrival of the digital computer has enabled the application of optimal control theory and methods to many complex problems. 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.

The theory presented above does not deal with the existence of an optimal control that minimises the performance index J. which covers theoretical issues on the existence of optimal controls. Moreover, a key point in the mathematical theory of optimal control is the existence of the Lagrange multiplier function $\lambda(t)$[25] for details on this issue.

3.9 Optimal control problem

A typical OC problem requires a performance index or cost functional (J[(x(t), u(t))), a set of state variables ($x(t) \in X$), a set of control variables (u(t)$\in U(t)$) in a time t, with t$\in [0, T]$. The main goal consists in finding a piecewise continuous control u(t) and the associated state variable x(t) to minimize a given objective functional. The development of this chapter will be closely structured from Lenhart and Workman work[26].

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

$$\begin{cases} Min \;\; J(x(t), u(t)) = \int_0^T F(x(t), u(t), t)dt \\ \\ S.t: \;\; x'(t) = g(t, x(t), u(t)) \\ x(t_0) = x_0 \end{cases} \tag{24}$$

x(T) could be free, which means that the value of x(T) is unrestricted, or could be fixed, i.e, $x(T) = x_T$. 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[26]. Thus, as the control(s) will always be piecewise continuous, the associated states will always be piecewise differentiable.

3.10 Pontryagin's Minimum Principle

In this section, we provide a derivation of the minimum principle of Pontryagin, which is a generalization of the Euler-Lagrange equations that also includes problems with constraints on the control inputs. Only a special case of the minimum principle is stated. However, this special case covers a large class of control problems. We consider the problem of minimizing the performance index. Pontryagin introduced the idea of adjoint functions to append the differential 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 minimized.

Definition 2(Hamiltonian): Let the previous OC problem considered in (23). The function

$$H(x(t), u(t), t) = F(x(t), u(t), t) + \lambda(g(t, x(t), u(t)))$$

is called Hamiltonian function and λ is the adjoint variable.

If $u^*(t)$ and $x^*(t)$ are optimal for problem (23), then there exists a piecewise differentiable adjoint variable λ(t) such that,

H(t,$x^*(t)$, $u^*(t)$,λ(t))$\leq$ H(t, x(t), u(t), λ(t)) for all controls u at each time t, where H is the Hamiltonian previously defined and

$$\lambda'(t) = -\frac{\partial H(t, x^*(t), u^*(t), \lambda(t))}{\partial x} \Rightarrow \quad \lambda' = -(F_x + \lambda g_x)$$

$$\lambda'(T) = 0$$

The condition, $\lambda'(T) = 0$ is called transversality condition, is only used when the OC problem does not have terminal value in the state variable, i.e., x(T) is free. This principle converted the problem of finding a control which minimizes the objective functional subject to the state ODE and initial condition into the problem of optimizing the Hamiltonian pointwise. As consequence, with this adjoint equation and Hamiltonian, we have

$$\frac{\partial H}{\partial u} = 0$$

At u^* for each time t, the Hamiltonian has a critical point, this condition is called optimality condition. Thus to find the necessary conditions, we do not need to calculate the integral in the objective functional, but only use the Hamiltonian. Using this principle to calculate a differential equation of our model.

3.11 Epidemiological model SEIRS with education

A mathematical model to study the dynamic of the Dengue epidemics, in order to minimize the investments in disease control, since financial resources are always scarce. Quantitative methods are applied to the optimization of investments in the control of the epidemiologic disease, in order to obtain a maximum of benefits from a fixed amount of financial resources. The used model depends on the dynamic of the mosquito growing, but also on the efforts of public management to motivate the population to break the reproduction cycle of the mosquitoes by avoiding the accumulation of still water in open-air recipients and spraying potential zones of reproduction. Education is th most important(powerful) to mimimaze the spread of disease. We use different mechanisms to educate the people, some mechanisms are TV and Radio.

3.12 Model Formulation

3.12.1 SEIRS Model with education

In this section, an optimal control problem is formulated formulated by incorporating one intervention strategies into our basic model equation(5). The following intervention is incorporated into the basic model;

- u(t) is the control which represents the education ratio of susceptible individuals being educated per unit of time which bounds between 0 and 1.

The model is the combination of four compartment i.e., (Model of susceptible group with control(education), model of exposed group with control model of Infected group with control and model of Recovered group with control) as follow,

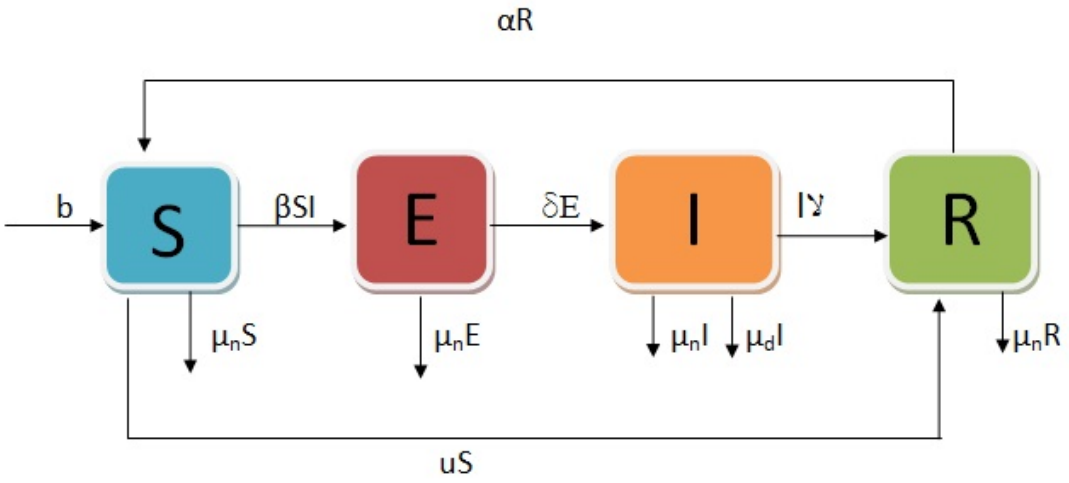

Figure 11: SEIRS model with Education

3.12.2 Model of susceptible group with education

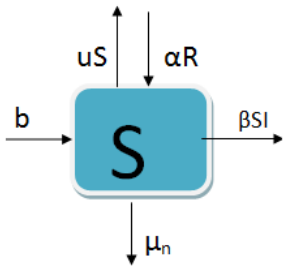

Figure 12: Compartment S

The inflow of population to the susceptible class is b, by combining assumptions 2, 5, 9, 10 and control(education) u we drive the susceptible populations change per unit of time.

$$\frac{dS}{dt} = b - \beta IS - \mu_n S + \alpha R - uS \tag{25}$$

Model of exposed group with control and model of infected group with control are the same as Model of exposed group without control and model of infected group without control, we can see figure 7 and figure 8 respectively and also there differential equations(populations change per unit of time) are the same.

3.12.3 Model of Recovered group with Education

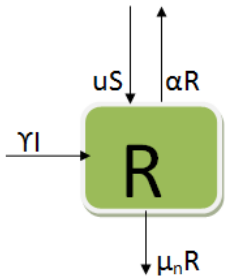

Figure 13: Compartment R

The number of individuals leave I enter into the recovered group with recovery rate γ, by combining assumptions 2, 5, 9, 10 and control u, this gives rate of recovered as follow,

$$\frac{dR}{dt} = \gamma I - (\mu_n + \alpha)R + uS \tag{26}$$

The differential equation from the assumptions and diagrams for t≥0 is given in a system of ordinary differential equation form of eq(27)

$$\begin{aligned} \tfrac{dS}{dt} &= b - \beta IS - \mu_n S - uS + \alpha R \\ \tfrac{dE}{dt} &= \beta IS - \mu_n E - \delta E \\ \tfrac{dI}{dt} &= \delta E - (\mu_n + \mu_d + \gamma)I \\ \tfrac{dR}{dt} &= \gamma I - (\mu_n + \alpha)R + uS \end{aligned} \tag{27}$$

$S(0) = S_0 \geq 0, E(0) = E_0 \geq 0, I(0) = I_0 \geq 0, R(0) = R_0 \geq 0.$

The optimal control problem is to minimize the objective (cost) functional J considering the costs of education of susceptible human given by,

J(u)=$\int_0^T (AI + \frac{1}{2}Bu^2)dt$ subject to the differential equations (27).

The Optimal Control Problem of nonlinear dynamics of SEIRS dengue fever epidemic model given by,

Min J(u)=$\int_0^T (AI + \frac{1}{2}Bu^2)dt$

Subject to:

$$\begin{aligned} \frac{dS}{dt} &= b - \beta IS - \mu_n S - uS + \alpha R \\ \frac{dE}{dt} &= \beta IS - \mu_n E - \delta E \\ \frac{dI}{dt} &= \delta E - (\mu_n + \mu_d + \gamma)I \\ \frac{dR}{dt} &= \gamma I - (\mu_n + \alpha)R + uS \end{aligned} \tag{28}$$

$S(0) = S_0 \geq 0, E(0) = E_0 \geq 0, I(0) = I_0 \geq 0, R(0) = R_0 \geq 0$

where A is balancing cost factor due to the infectives

B :the weight on the cost of education

3.13 Epidemiological model SEIRS with education and treatment by drug therapy

Antiviral drugs are an alternative to vaccinations, it is useful to people with or without a fever to decrease or prevent disease symptoms at the first sign of a dengue outbreak.

3.13.1 SEIRS Model with Education and treatment by drug therapy

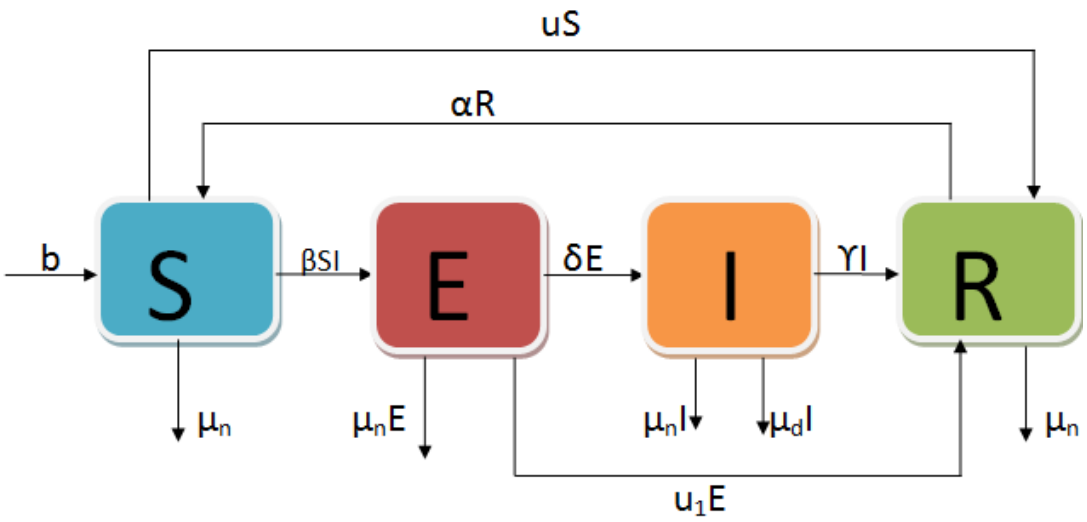

Figure 14: SEIRS model with control

3.13.2 Exposed group with Education and treatment by drug therapy

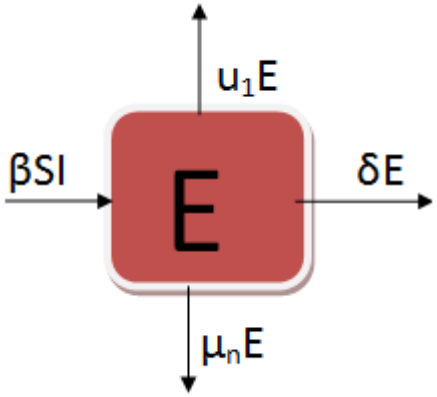

Figure 15: Compartment E

The number of individuals leave S and enter E, a fraction of exposed E move to infectious group I with a latent rate δ, δE an individual's move from exposed to infectious and some of the exposed group die through natural death rate μ_n, $\mu_n E$ to an individual's move from exposed to death; control varable u_1, u_1E to an individual's move from exposed to recovered. The exposed populations change per unit of time becomes,

$$\frac{dE}{dt} = \beta IS - \mu_n E - \delta E - u_1 E \tag{29}$$

3.13.3 Recovered group with Education and treatment by drug therapy

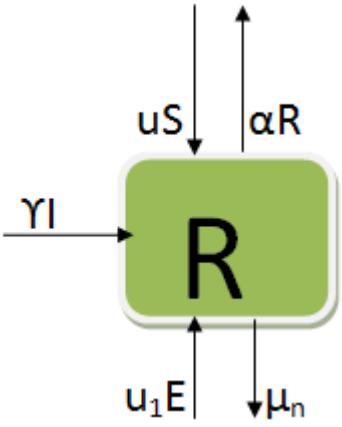

Figure 16: Compartment R

The number of individuals leave I enter into the recovered group with recovery rate γ, the

number of individuals leave S and E enter into the recovered group with controls u and u_1 respectively. This gives rate of recovered as follow,

$$\frac{dR}{dt} = \gamma I - (\mu_n + \alpha)R + uS + u_1 E \tag{30}$$

We can see figure 12 and figure 8 are model of successive group and model of Infected group respectively and also there differential equations(populations change per unit of time) are the same as the previous section.

The differential equation of the diagram for t≥ 0 is given in a system of ordinary differential equation form of eq(31)

$$\begin{aligned} \tfrac{dS}{dt} &= b - \beta IS - \mu_n S + \alpha R - uS \\ \tfrac{dE}{dt} &= \beta IS - \mu_n E - \delta E - u_1 E \\ \tfrac{dI}{dt} &= \delta E - (\mu_n + \mu_d + \gamma)I \\ \tfrac{dR}{dt} &= \gamma I - (\mu_n + \alpha)R + uS + u_1 E \end{aligned} \tag{31}$$

The Optimal Control Problem of nonlinear dynamics of SEIRS Dengue fever epidemic model given by;

Min J(u)=$\int_0^T (AI + \frac{1}{2}(Bu^2 + B_1 u_1^2))dt$

Subject to:

$$\begin{aligned} \tfrac{dS}{dt} &= b - \beta IS - \mu_n S - uS + \alpha R \\ \tfrac{dE}{dt} &= \beta IS - \mu_n E - \delta E - u_1 E \\ \tfrac{dI}{dt} &= \delta E - (\mu_n + \mu_d + \gamma)I \\ \tfrac{dR}{dt} &= \gamma I - (\mu_n + \alpha)R + uS + u_1 E \end{aligned} \tag{32}$$

$S(0) = S_0 \geq 0, E(0) = E_0 \geq 0, I(0) = I_0 \geq 0, R(0) = R_0 \geq 0$

where,

A : Is balancing cost factor due to the infectives and exposed respectively.

B and B_1 : The weight on the cost of education and drug therapy respectively.

3.14 Principle of Optimality

An important result in both optimal control and dynamic programming is the Principle of Optimality. It concerns optimizing a system over a subinterval of the original time span, and in particular, how the optimal control over this smaller interval relates to the optimal control on the full time period.

3.15 Optimal control system with Hamiltonian

An important result in both optimal control and dynamic programming is the Principle of optimality. It concerns optimizing a system over a subinterval of the original time span, and in particular, how the optimal control over this smaller interval relates to the optimal control on the full time period.

3.15.1 Necessary condition

Pontryagin introduced the adjoint function to affix to the differential equation to the objective functional. The necessary conditions needed to solve the basic problem, the calculus of this OC problem can be done by steps.

Step 1: Formulate the Hamiltonian for the problem,

For equation (28),

H(t,S,E,I,R,u,$\lambda_1, \lambda_2, \lambda_3, \lambda_4$)=F(t,S,E,I,R,u)+$\sum_{i=1}^{4} \lambda_i g_i(t, S, E, I, R, u)$

$$\begin{aligned} H = (AI + \frac{1}{2}Bu^2) + [\lambda_1(b - (\beta I + \mu_n + u)S + \alpha R) \\ +\lambda_2(\beta IS - (\mu_n + \delta)E) \\ +\lambda_3(\delta E - (\mu_n + \mu_d + \gamma)I) \\ +\lambda_4(\gamma I - (\mu_n + \alpha)R + uS)] \end{aligned} \tag{33}$$

For equation (32),

H(t,S,E,I,R,u,$u_1\lambda_1, \lambda_2, \lambda_3, \lambda_4$)=F(t,S,E,I,R,u,$u_1$) + $\sum_{i=1}^{4} \lambda_i g_i(t, S, E, I, R, u, u_1)$

$$\begin{aligned} H = (AI + \frac{1}{2}(Bu^2 + B_1 u_1^2)) + [\lambda_1(b - (\beta I + \mu_n + u)S + \alpha R) \\ +\lambda_2(\beta IS - (\mu_n + \delta)E) \\ +\lambda_3(\delta E - (\mu_n + \mu_d + \gamma)I) \\ +\lambda_4(\gamma I - (\mu_n + \alpha)R + uS)] \end{aligned} \tag{34}$$

By applying Pontryagin's principle to the Hamiltonian, we obtain the following results. Find optimal control u*, u_1* and the corresponding solution S*, E*, I* and R* of eq(27).

Step 2: Write the adjoint differential equation, the optimality condition and transversality boundary condition (if necessary). Using the Hamiltonian to find the differential equation of the adjoint λ, we obtained adjoint variable $\lambda_1,\ \lambda_2,\ \lambda_3$ and λ_4 that satisfy adjoint condition.

$$\lambda_i'(t) = -\frac{\partial H}{\partial x_i}\ ,\ where\ i = 1, 2, ..., 4$$

The adjoint differential equations of equations(32)and (33) are equal.

3.15.2 Adjoint functions

$$\lambda'(t) = -\frac{\partial H}{\partial x} \Rightarrow \ \lambda' = -(F_x + \lambda g_x) \quad adjoint\ condition \tag{35}$$

- **Adjoint function with respect to S**

  $\lambda_1' = -\frac{\partial H}{\partial S} \Rightarrow \ \lambda_1' = -[\lambda_1(-\beta I - \mu_n - u) + \lambda_2 \beta I + \lambda_4 u]$

  $\Rightarrow \ \lambda_1' = \lambda_1(\beta I + \mu_n + u) - \lambda_2 \beta I - \lambda_4 u$

- **Adjoint function with respect to E**

  $\lambda_2' = -\frac{\partial H}{\partial E} \Rightarrow \ \lambda_2' = -[\lambda_2(-\mu_n - \delta) + \lambda_3 \delta]$

  $\Rightarrow \ \lambda_2' = \lambda_2(\mu_n + \delta) - \lambda_3 \delta$

- **Adjoint function with respect to I**

  $\lambda_3' = -\frac{\partial H}{\partial I}$

$$\Rightarrow \quad \lambda_3' = -[A - \lambda_1(\beta S) + \lambda_2 \beta S + \lambda_3(-(\mu_n + mu_d + \gamma)) + \lambda_4 \gamma]$$
$$\Rightarrow \ \lambda_3' = -A + \lambda_1(\beta S) - \lambda_2 \beta S + \lambda_3(\mu_n + mu_d + \gamma) - \lambda_4 \gamma$$

- **Adjoint function with respect to R**

  $\lambda_4' = -\frac{\partial H}{\partial E} \Rightarrow \quad \lambda_4' = -[\lambda_1 \alpha + \lambda_4(-(\mu_n + \alpha)]$

  $\Rightarrow \ \lambda_4' = -\lambda_1 \alpha + \lambda_4(\mu_n + \alpha)$

  With transversality conditions $\lambda_i(T) = 0$,i=1,...,4.

The optimality condition is given by

For equation (32),

$$\frac{\partial H}{\partial u} = 0 \; at \; u = u* \Rightarrow \; F_u + \lambda g_u = 0$$

For equation (33),

$$\frac{\partial H}{\partial u} = 0 \; at \; u = u* \Rightarrow \; F_u + \lambda g_u = 0$$
$$\frac{\partial H}{\partial u_1} = 0 \; at \; u_1 = u_1* \Rightarrow \; F_{u_1} + \lambda g_{u_1} = 0$$

Step 3: Solve for u* and u_1* in terms of S*, E*, I*, R* and λ

$$\frac{\partial H}{\partial u} = Bu + S(\lambda_4 - \lambda_1) = 0 \tag{36}$$

In this way we obtain an expression for the OC:

$$\Rightarrow u = \frac{S(\lambda_1 - \lambda_4)}{B}$$
$$\Rightarrow u^* = \frac{S(\lambda_1 - \lambda_4)}{B}$$
$$\frac{\partial H}{\partial u_1} = B_1 u_1 + E(\lambda_4 - \lambda_2) = 0 \tag{37}$$

In this we obtain an expression for the OC:

$$\Rightarrow u_1 = \frac{E(\lambda_2 - \lambda_4)}{B_1}$$
$$\Rightarrow u_1^* = \frac{E(\lambda_2 - \lambda_4)}{B_1}$$

Step 4: Solve the four differential equations for S*, E*, I*, R* and λ with boundary conditions, substituting u* and u_1* in the differential equations with the expression for the optimal control from the previous step.

Step 5: After finding the optimal state and adjoint, solve for the optimal control.

We solve that system of differential equations for the optimal state and adjoint and then obtain the optimal control. When we are able to solve for the optimal control in terms of S*, E*, I*, R* and λ, we will call that formula for u* the characterization of the optimal control. The state equations and the adjoint equations together with the characterization of the optimal control and the boundary conditions are called the optimality system.

Remark 1: If the Hamiltonian is linear in the control variable u, it can be difficult to calculate u^* from the optimality equation, since $\frac{\partial H}{\partial u}$ would not contain u. Specific ways of solving these kind of problems can be found in[19].

3.16 Backward-forward Sweep Method

From the model the optimal control problem becomes,

Min J(u)=$\int_0^T (AI + \frac{1}{2}Bu^2)dt$

Subject to:

$$\begin{aligned} \frac{dS}{dt} &= b - \beta IS - \mu_n S - uS + \alpha R \\ \frac{dE}{dt} &= \beta IS - \mu_n E - \delta E \\ \frac{dI}{dt} &= \delta E - (\mu_n + \mu_d + \gamma)I \\ \frac{dR}{dt} &= \gamma I - (\mu_n + \alpha)R + uS \end{aligned} \tag{38}$$

With initial value,

$S(0) = S_0 \geq 0, E(0) = E_0 \geq 0, I(0) = I_0 \geq 0, R(0) = R_0 \geq 0$ And

Min J(u)=$\int_0^T (AI + \frac{1}{2}(Bu^2 + B_1 u_1^2))dt$

Subject to:

$$\begin{aligned} \frac{dS}{dt} &= b - \beta IS - \mu_n S - uS + \alpha R \\ \frac{dE}{dt} &= \beta IS - \mu_n E - \delta E - u_1 E \\ \frac{dI}{dt} &= \delta E - (\mu_n + \mu_d + \gamma)I \\ \frac{dR}{dt} &= \gamma I - (\mu_n + \alpha)R + uS + u_1 E \end{aligned} \tag{39}$$

With initial value,

$S(0) = S_0 \geq 0, \;\; E(0) = E_0 \geq 0, \;\; I(0) = I_0 \geq 0, \;\; R(0) = R_0 \geq 0$

We want to solve such problems numerically, that is, devise an algorithm that generates an approximation to an optimal piecewise continuous control u* at time interval [0,T]. we

saw in the previous section, any solution to the above optimal control problem must also satisfy,

$$\lambda_i'(t) = -\frac{\partial H}{\partial x_i} \tag{40}$$

Where, i=1,2,...,4 ,$x_1 = S, x_2 = E, x_3 = I, x_4 = R$

$$\frac{\partial H}{\partial u} = 0 \;\; at \;\; u^* \tag{41}$$

$$\frac{\partial H}{\partial u_1} = 0 \;\; at \;\; u_1^* \tag{42}$$

The optimal controls are,

$$u^* = \begin{cases} 0 & if \;\; \frac{\partial H}{\partial u} < 0 \\ \frac{S(\lambda_1 - \lambda_4)}{B} & if \;\; \frac{\partial H}{\partial u} = 0 \\ 0.9 & if \;\; \frac{\partial H}{\partial u} > 0 \end{cases} \tag{43}$$

$$u_1^* = \begin{cases} 0 & if \;\; \frac{\partial H}{\partial u_1} < 0 \\ \frac{E(\lambda_2 - \lambda_4)}{B_1} & if \;\; \frac{\partial H}{\partial u_1} = 0 \\ 0.9 & if \;\; \frac{\partial H}{\partial u_1} > 0 \end{cases} \tag{44}$$

Equation (32), the optimality condition, can usually be manipulated to find a representation of u^* in terms of t, state varables and λ. If this representation is substituted back into the ODEs for state varables and λ then the equations(30)and(31)form a two-point boundary value problem. Using Runge-Kutta numerical method to solve initial value problems, to solve the optimality system and the optimal control problem. It is generally referred to as the Forward-Backward Sweep method. Information about convergence and stability of this method can be found in[19]. The process begins with an initial guess on the control variable. Then, the state equations are simultaneously solved forward in time and adjoint equations are solved backward in time. The control is updated by inserting the new values of states and adjoints into its characterization, and the process is repeated until convergence occurs. A rough outline of the algorithm is given below. Here, state varables and λ_i are the vector approximations for the state and adjoint.

3.16.1 Algorithm

Step 1. Make an initial guess for u and u_1 over the interval(u=0 and u_1=0).

Step 2. Using the initial condition $x(t_0)$a and the values for u and u_1, solve state varables forward in time according to its differential equation in the optimality system;

Step 3. Solve λ backward in time according to its differential equation in the optimality system.

Step 4. Update u and u_1 by entering the new state varables and λ 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.

This is done in the provided codes, for steps 2 and 3 any standard ODE solver can be used. For the purposes of this thesis,a Runge-Kutta 4 routine is used. Specifically, given a step size h and an ODE $x_i'(t) = f_i(t, x_i(t))$, the approximation of $x_i(t+h)\ \ given\ \ x_i(t)$ is

$$x_i(t+h) = x_i(t) + \frac{h}{6}(k_1 + 2k_2 + 2k_3 + k_4) \tag{45}$$

Where,

$$\begin{aligned} k_{1i} &= f_i(t, x_i(t)) \\ k_{2i} &= f_i(t + \tfrac{h}{2}, x_i(t) + \tfrac{h}{2}k_1) \\ k_{3i} &= f_i(t + \tfrac{h}{2}, x_i(t) + \tfrac{h}{2}k_2) \\ k_{4i} &= f_i(t + h, x_i(t) + hk_3). \end{aligned} \tag{46}$$

CHAPTER fOUR

4 RESULTS AND DISCUSSION

4.1 Introduction

In this section, we solve numerically the optimality system (37)and (38) using the forward-backward sweep method developed by Suzanne lenhart and J. T. Workman [19]. In this formulation, there exist initial conditions for the state variables and terminal conditions for the adjoint variables. That is, the optimality system is a two-point boundary value problem, with separated boundary conditions at times t_0 and t_f [28]. The sixteen ordinary differential equations in eq(37) and eq(38) comprising the optimality system are numerically solved together with the control characterization which is used to simulate the dengue education and treatment strategies. The processes begin with an initial guess on the control variables. 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 [29, 30, 31]. The estimation of epidemiological parameters is based on data from [12].

The simulations were carried out using the following values:

Table 2: Initial value of variables

Symbols	Description	value	reference
S_0	Initial Susceptibles population	86.46%	[12]
E_0	Initial Exposed individual in the latent period	4.5%	
I_0	Initial Infectives population	9.04%	
R_0	Initial Recovered population	0%	
N	Total population	100%	

Table 3: Value of parameters

Symbols	Description	value	reference
μ_n	Natural death rate	1/(71*365)	[12]
β	Contact rate	0.375	
b	Average birth rate	1/(71*365)	
μ_d	Disease related death rate	1/11	Assumption
δ	Exposed rate	1/4	[12]
γ	Recovery rate	1/3	
α	Recovering rate of remove disease to Susceptible	0.00008	Assumption
A	Balancing cost factor due to the infectives	100	[28]
B	The weight on the cost of education	0.04	
B_1	The weight on the cost of treatment	0.06	Assumption

4.2 Each compartment of the model with education only

Using the above parameter value and initial value, I get the following graph, with and without control.

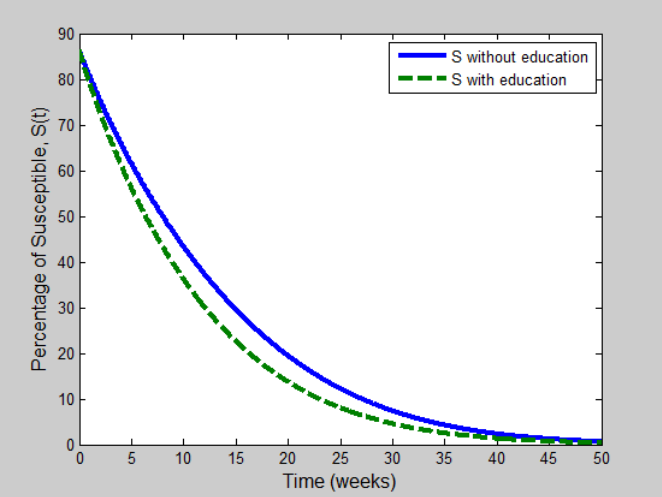

Figure 17: Susceptibles with education Vs without education

Figure 17, with the initial susceptible population of 86.46%, the graph starts there and falls down up to 50^{th}week, but with control, the susceptibleg groups start diseasing at higher

rate to 50^{th} weeks than that of without education. which implies the effect of education in control of susceptible is working.

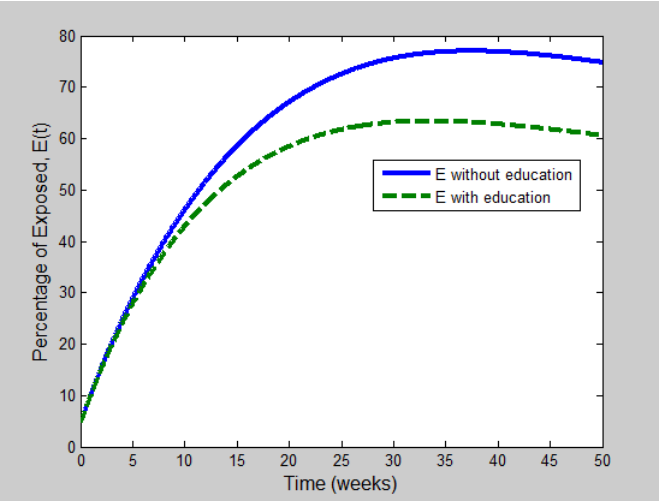

Figure 18: Exposed with education Vs without education

Figure 18, with the initial exposed population of 4.5%, as we can see from the graph, the rate of population getting exposed to the disease when there no education is higher than when population get education.

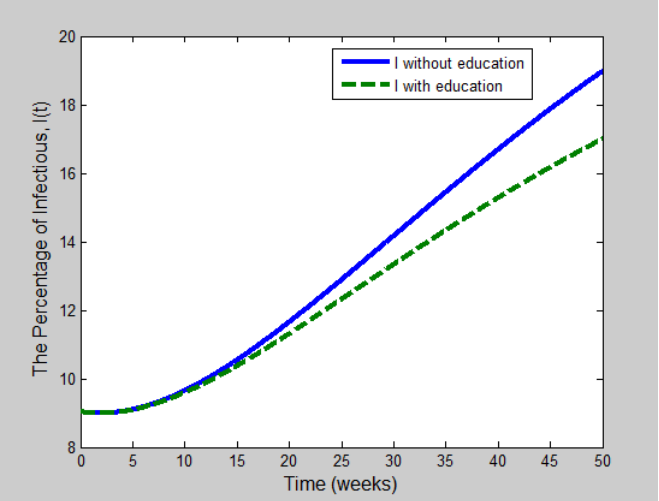

Figure 19: Infectives with education Vs without education

Figure 19, with the initial infected population of 9.04%, when we see, from the first 15 weeks eventhough the population are educated, the effect of being infected is the same. This is because it takes some time for the population to fully have aware on the disease not to infected each other. After 15 weeks the effect of educating populations are very

remarkable in decreasing the infection.

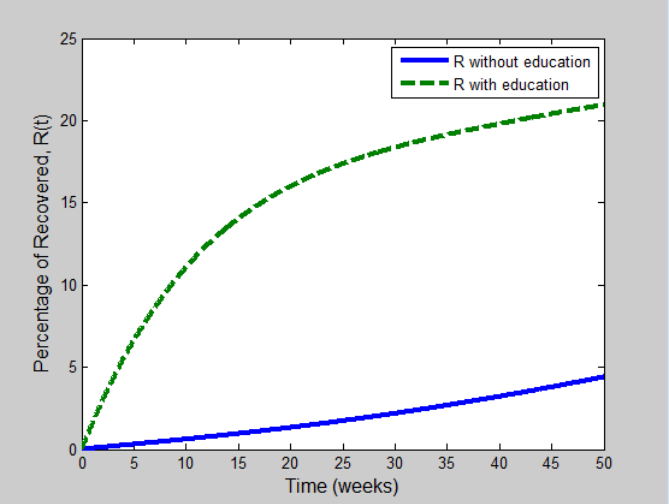

Figure 20: Recovered with education Vs without education

Figure 20, with the initial recovered population of 0%, when we see the graph at the effect of education is very rapid, i.e., after educating population the percentage of recovered individual increase.

4.3 Each compartment of the model with drug therapy treatment only

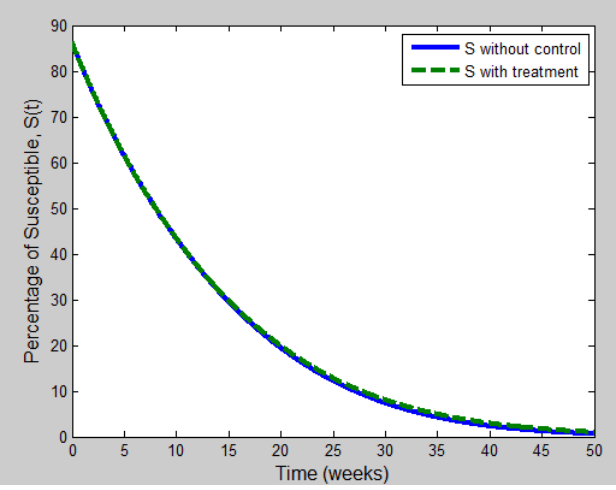

Figure 21: Susceptibles without control Vs with drug therapy treatment

Figure 21, with the initial susceptible population of 86.46%, in this graph we can see that control with drug therapy treatment none effect until 25 weeks after that it is a little effect.

This is because the recovered individual go back to susceptible group and this increases the susceptible group at higher rate.

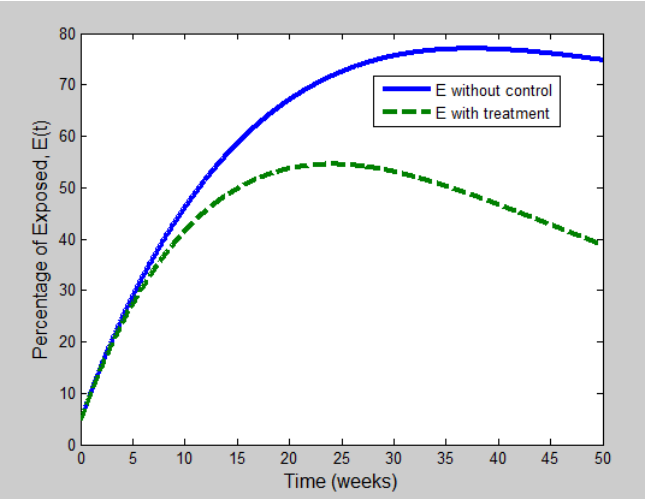

Figure 22: Exposed without control Vs with drug therapy treatment

Figure 22, with the initial exposed population of 4.5%, as we can see from the graph,during the first 5 weeks, the effect of treatment on exposed individual is not visible. But after 5 weeks the effect of treatment for exposed group is visible.

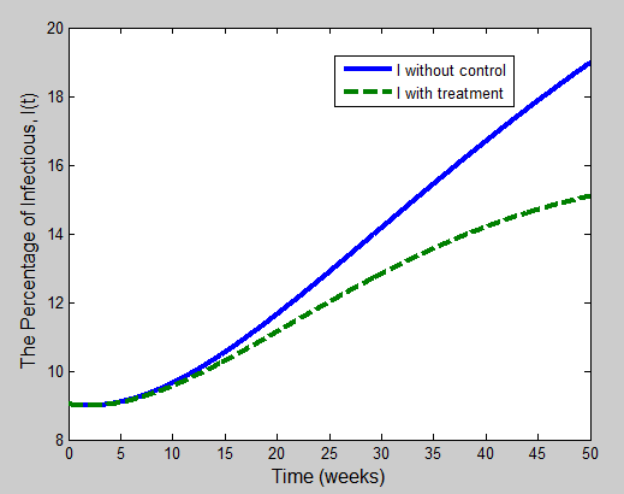

Figure 23: Infectives without control Vs with drug therapy treatment

Figure 23, with the initial infected population of 9.04%,when we see, the effect of drug therapy treatment intervention mechanism is not visible for the first 10 weeks, the graph also depicts this. But it is effective then after.

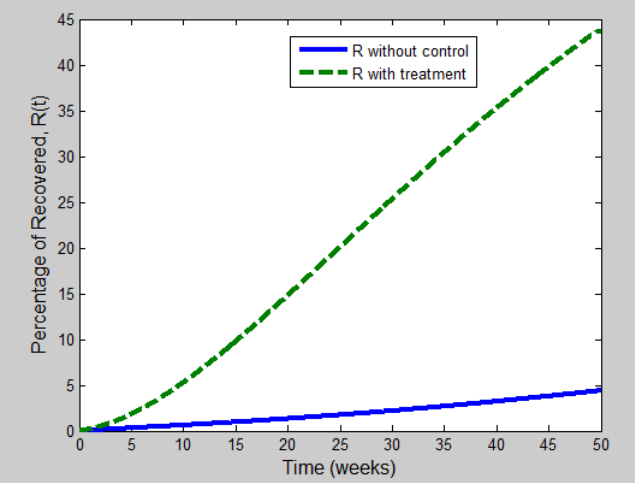

Figure 24: Recovered without control Vs with drug therapy treatment

Figure 24, with the initial recovered population of 0%, when we see the graph for the first 2 weeks the effect of drug therapy treatment control mechanism is the same as that of uncontrol. This is because for the effect to take place it takes some times, but it is effective then after.

4.4 Each compartment of the model with education and with drug therapy treatment

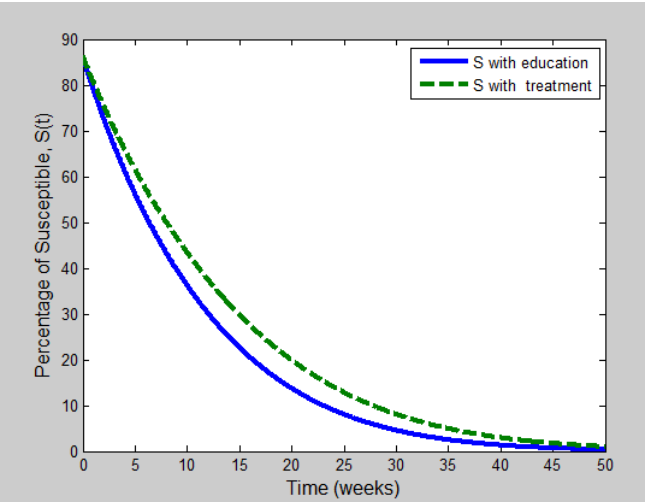

Figure 25: Susceptibles with education Vs with drug therapy treatment

Figure 25, with the initial susceptible population of 86.46%, in this graph we can see that for the first 3 weeks and after 45 weeks, the difference of education and drug therapy treat-

ment is not visible. This is because the recovered individual go back to susceptible group and this increases the susceptible group at higher rate. But between 3 and 45 weeksed, education control mechanism is more effective than drug therapy treatment control mechanism.

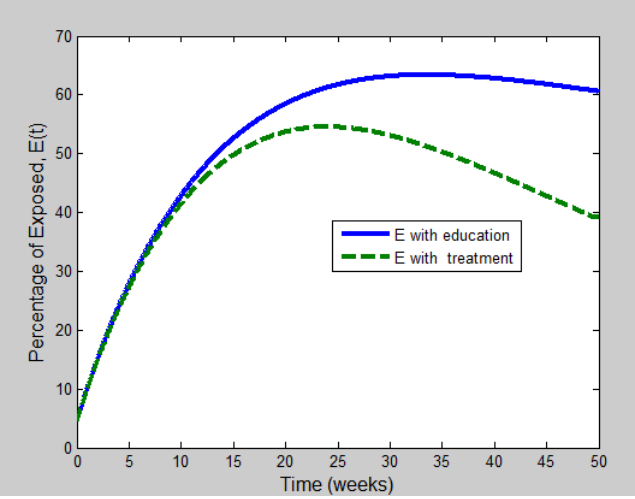

Figure 26: Exposed with education Vs with drug therapy treatment

Figure 26,with the initial exposed population of 4.5%, as we can see from the graph, during the first 10 weeks, the effect of treatment and education on exposed individual is not visible. After that the effect of drug therapy treatment more better than education,for the exposed group the effect of treatment control is more successful.

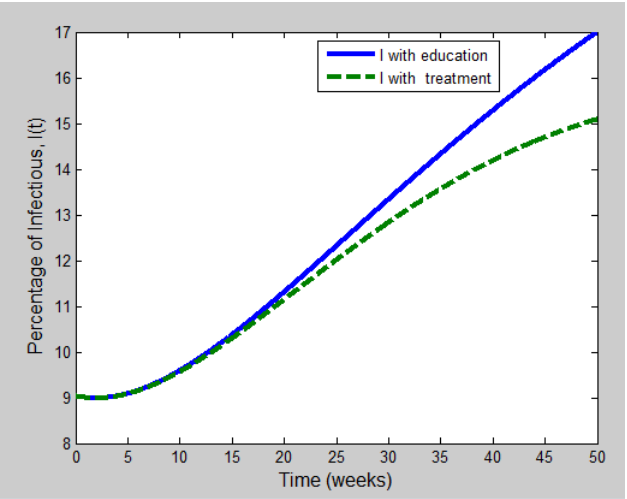

Figure 27: Infectives with education Vs with drug therapy treatment

Figure 27, with the initial exposed population of 9.04%, as we can see from the graph,

during the first 20 weeks, the effect of treatment and education on Infectives individual is not visible. After that the effect of drug therapy treatment more better than education, for the Infectives group the effect of drug therapy treatment control mechanism is more successful.

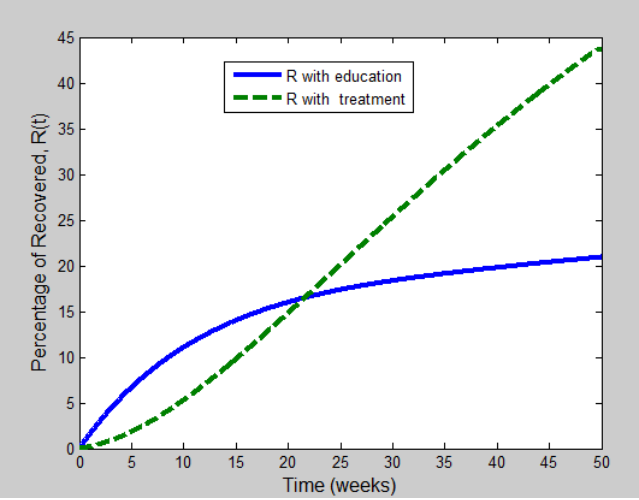

Figure 28: Recovered with education Vs with drug therapy treatment

Figure 28, with the initial recovered population of 0%, when we see the graph for the first 20 weeks the effect of use education control mechanism is better than drug therapy treatment control mechanism. After 20 weeks it is much better to use drug therapy treatment control mechanism to succeed in control. This is because for the effect to take place it takes some times.

4.5 Each compartment of the model without control and with education and drug therapy treatment

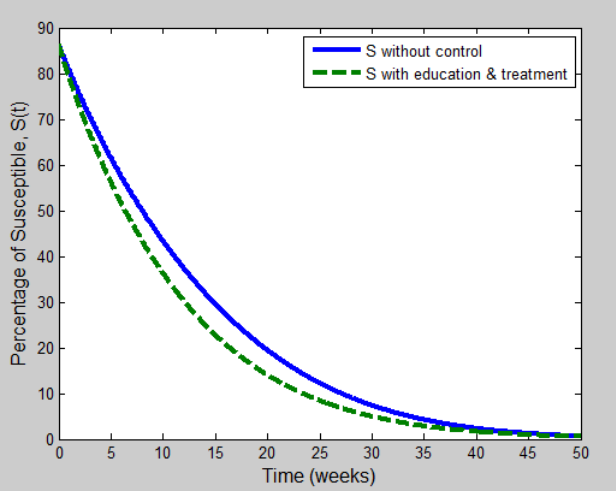

Figure 29: Susceptibles without control Vs with education and drug therapy treatment

Figure 29, with the initial susceptible population of 86.46%, in this graph we can see that control with both education and drug therapy treatment are not effect for the first three and after 38 weeks. This is because the recovered individual go back to susceptible group and this increases the susceptible group at higher rate.

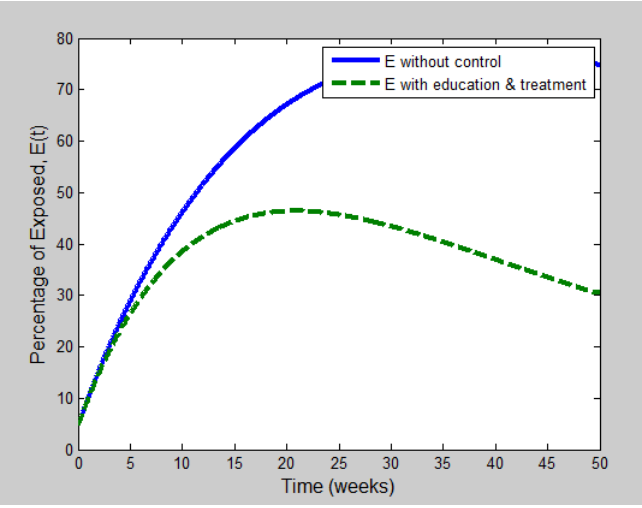

Figure 30: Exposed without control Vs with education and drug therapy treatment

Figure 30, with the initial exposed population of 4.5%, as we can see from the graph, during the first 5 weeks, the effect of the both control mechanisms on exposed individual

is not visible. After 5 weeks, when we educate and at the time give treatment for the exposed group the effect of control is more successful.

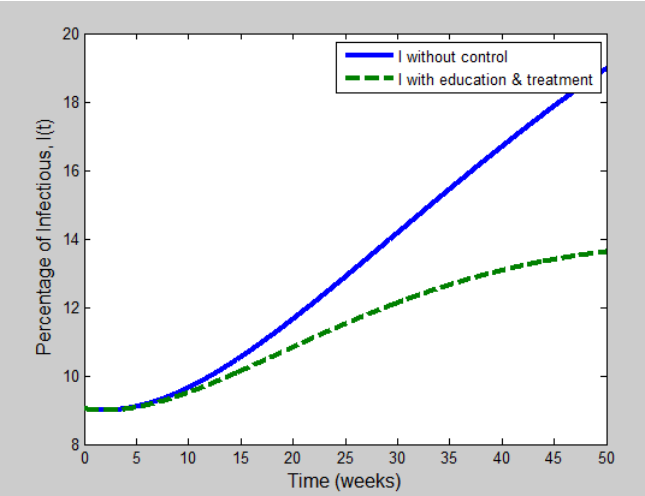

Figure 31: Infectives without control Vs with education and drug therapy treatment

Figure 31, with the initial infected population of 9.04%, when we see, using both intervention mechanism is better control mechanism. The graph also depicts this. It is shows the same effect for the first 8 weeks but it is different then after.

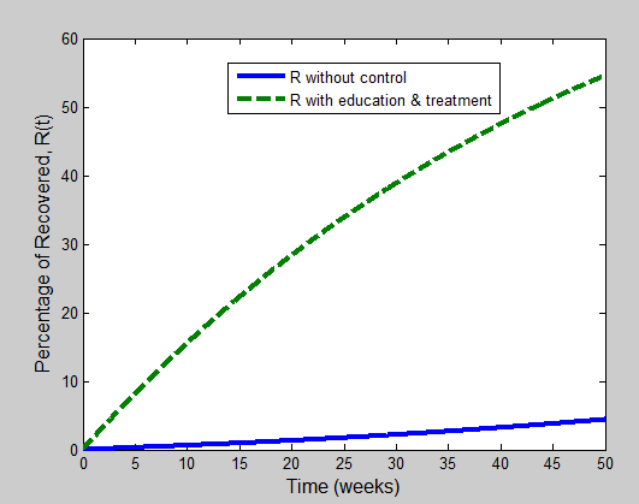

Figure 32: Recovered without control Vs with education and drug therapy treatment

Figure 32, with the initial recovered population of 0%, when we see the graph, the effect of using both education and treatment control mechanism is visible rapidly. This is because it is much better to use both control mechanism together to succeed in control.

CHAPTER FIVE

5 Sammary and Conclusions

In this thesis, I focused on minimizing the cost of education and drug treatment to control the spread of dengue fever disease. Dengue disease is an international concern disease affecting human around the world especially tropical and subtropical area. Dengue disease is caused by mosquito which is more dangerous. Global incidence of dengue disease has increased dramatically in the current decade and around half of world population is living at risk area which has reported of dengue disease. It is not only the numbers of reported cases are increasing but also the dengue disease spreads to new area that the dengue disease is endemic in more than 100 countries. The reproductive number is used to control the outbreak. It is lower than one will decrease the outbreak. At the present, the method to control the transmission of dengue disease is educate the population to controlled the spreading of mosquitoes such as environmental management of egg laying, waste disposing, and water storage. The community participation and mobilization will improve the sustained mosquito control, the resulting model can indicate the presence in an endemic area for certain parameter values by using standard dynamical modeling method. We obtained two equilibrium states, namely the disease free equilibrium state and the endemic disease equilibrium state to each model.

The basic reproductive ratio before the treatment is obtained implicitly as the positive root of the fourth order characteristic polynomial of the next generation matrix. An optimal control problem has been formulated for the above Dengue transmission model. We have derived a gradient algorithm to solve the optimization problem. For two typical scenarios, the prevention of an outbreak and the reduction of an existing epi demic, we have carried out numerical simulations to compute the optimal treatment and education rates.

This work could be considered as a first approach to finding a simple treat ment for a complicated Dengue transmission problem. An epidemic model encompasses three most important stages i.e., to understand dynamic properly, to formulate the study accurately and to predict the future circumstances. In this paper, the dengue virus epidemic has been understood appropriately and then has been formulated with accuracy. For all of the world population dengue epidemic is discussed in this paper to show the accuracy of this math-

ematical model. From this model and parameters according to the environment, one can easily predict the upcoming epidemic and can take necessary precautions.

CHAPTER SIX

6 Recommendation and Future Research

6.1 Future Research

In this thesis, there are some aspects of dengue dynamics which were not considered when formulating the mathematical models. Because to reduce the complexities which would otherwise arise in the mathematical analysis and in estimation of parameters for the numerical simulations. Modification and extension of the models can address the following points:

Seasonally varying contact rate: Dengue disease tend to have periodic outbreaks, occasioned by climatic factors and human contact rate patterns, among other factors.

Mosquito population: It has three compartment(Aquatic phase,susceptible and Infected), it is possible extend the model.

Age structure: as the epidemic of dengue varies in age structure it is possible to extent the model to the age-structured model and the relationship between epidemiology, mathematical modeling and computational tools. The spreading of dengue can be attenuated through measures to control the transmission vector, such as the use of specific insecticides and educational campaigns. Since the development of a potential vaccine has been a recent global bet, models based on the simulation of a hypothetical vaccination process in a population are proposed.

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