2016

Mathematical Modelling of Intra and Inter Dynamics and Control of Yellow Fever in Primate and Humna Populations

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The Nelson Mandela African Institution of Science and Technology

https://doi.org/10.58694/20.500.12479/57

MATHEMATICAL MODELLING OF INTRA AND INTER DYNAMICS AND CONTROL OF YELLOW FEVER IN PRIMATE AND HUMAN POPULATIONS

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A Dissertation Submitted in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy in Mathematical and Computer Science and Engineering of the Nelson Mandela African Institution of Science and Technology

Arusha, Tanzania

April, 2016

ABSTRACT

A deterministic mathematical model was formulated using non-linear ordinary differential equations to gain an insight of dynamics of yellow fever (YF) between primates, human beings and *Aedes* mosquito for the purpose of controlling the disease. Basic reproduction number, R_0, was computed and its sensitivity analysis with respect to epidemiological parameters was performed to study the effect of model parameters to R_0.

Results showed that R_0 is most sensitive to daily biting rate of mosquitoes, recruitment rate of vectors, probability of transmission of infection, recruitment of unvaccinated immigrants and the incubation period for both vector and humans. Thus, for the minimization of YF transmission, these parameters should closely be monitored. Stability analysis of disease-free equilibrium (DFE) and endemic equilibrium (EE) points were performed to study perseverance and condition necessary for disease interruption and control. Results showed that the DFE is locally asymptotically stable if the rate of new infection from infected monkey to vector is less than unity, and is globally asymptotically stable if the rate of new infection from infected vector to human is less than unity. Lyapunov stability theory and LaSalles Invariant Principle were used to investigate stability of EE. Results show that EE is globally asymptotically stable whenever $R_0 > 1$. To assess the impact of control measures on YF dynamics, we derived and analysed the necessary conditions for optimal control using optimal control theory. Results show that multiple optimal control strategy is the most effective to bring a stable disease-free equilibrium compared to single and two controls. However, spray of insecticides alone was not effective without personal protection, and optimal use of personal protection alone is beneficial to minimize transmission of the infection to the community. Furthermore, cost-effectiveness analysis of the optimal control measures was considered. We used incremental cost-effectiveness ratio to investigate and compare the costs required against the health benefits achieved between two or more alternative intervention strategies that compete for the same resource. Results showed that combination of all strategies is the most cost-effective compared to others.

DECLARATION

I, **MONICA KUNG'ARO** do hereby declare to the Senate of Nelson Mandela African Institution of Science and Technology that this dissertation is my own original work and that it has neither been submitted nor being concurrently submitted for degree award in any other institution.

Monica Kung'aro

Name and signature of candidate **Date**

The above declaration is confirmed

Prof. Livingstone S. Luboobi 9 April 2016

Name and signature of supervisor 1 **Date**

Dr. Emmanuel Mpolya 14 April 2016

Name and signature of supervisor 2 **Date**

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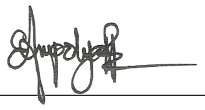
CERTIFICATION

The undersigned certify that have read and found the dissertation acceptable by the Nelson Mandela African Institution of Science and Technology.

Prof. Livingstone S. Luboobi  9 April 2016

Name and signature of supervisor 1 **Date**

Dr Emmanuel Mpolya  14 April 2016

Name and signature of supervisor 2 **Date**

ACKNOWLEDGEMENT

First and foremost, I give honour to the Almighty GOD for giving me ability, health and insight to complete this dissertation and taking me through my coursework successfully. I owe a lot to Him.

My sincere gratitude and strong appreciations goes to my principal supervisor Prof. Livingstone S. Luboobi for his patient guidance, support, advice, encouragement and contributions throughout the period of research writing. He encouraged me to become an independent thinker and researcher which is invaluable not only for my research but also for my career. Honestly, I have not been able to find the right words of appreciation for the wonderful job he has done to make this study possible. May Almighty GOD bless him abundantly as he continues helping other students.

Special thanks are also directed to my internal supervisor Dr. Emmanuel Mpolya and the Late Dr. Francis Shahada for being there when needed, generous and tireless efforts, support, unconditional love and encouragement at all stages of this work. May GOD the Almighty rest the soul of late Dr. Shahada in eternal peace.

I acknowledge with many thanks the financial support from the Nelson Mandela African Institution of Science and Technology (NM-AIST) for sponsoring my studies. I am also highly indebted to the University of Dodoma (UDOM) for offering a three years study leave.

My heartfelt thanks to all my classmates for their cooperation and challenges during course work and when preparing this dissertation. It was a pleasure and experience to have acquainted with you all. However, many people from various corners have contributed to the production of this dissertation, although it is not possible to mention all the names here, I would like to appreciate their contributions.

Lastly, my special gratitude goes to all my family members, my beloved husband Terence Julius and my beloved daughter Angeline. Thank you for your unwavering love, patience, tolerance and unyielding moral and spiritual support, and also for taking me on adventures from skipping

rocks and crossing streams to climbing mountains.

THANK YOU ALL !.

DEDICATION

I dedicate this work to my family members

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LIST OF ABBREVIATIONS

Symbols	Description
ACER	Average Cost-Effectiveness Ratio
AMCS	Applied Mathematics and Computational Science
CDC	Centre for Disease Control
DALYs	Disability Adjusted Life Years
DFE	Disease Free Equilibrium
EE	Endemic Equilibrium
GAS	Globally Asymptotically Stable
ICER	Incremental Cost-Effectiveness Ratio
MCER	Marginal Cost-Effectiveness Ratio
NM-AIST	Nelson Mandela African Institution of Science and Technology
ODE	Ordinary Differential Equation
PEI	Personal protection, Educational campaign & spray of Insecticides
QALYs	Quality Adjusted Life Years
RHS	Right Hand Side
SVEIRS	Susceptible Vaccinated Exposed Infected Recovered Susceptible
US$	United States dollar
WHO	World Health Organisation
YF	Yellow Fever
YFV	Yellow Fever Virus
YLDs	Years of Life lived with Disability
YLLs	Years of Life Lost

CHAPTER ONE

General Introduction and Background

Introduction

This chapter describes the general introduction of the study. It mainly focuses on the background of the study, where yellow fever has been explained in detail, its transmission cycle in Africa and South America is explained, epidemiology and symptoms of yellow fever is explained, justification of the research, statement of the problem, research objectives, research questions, methodology used to achieve each specific objective and significance of the study are explained.

1.1 Background Information

Yellow fever has been one of the vector borne viral infection of humans and constitute a major public health problem in Africa (Monath, 1991; Barrett and Higgs, 2007). After several decades of relative calm, its outbreak has re-emerged in Africa posing an immediate risk to the affected populations across the continent (Briand et al., 2009). The disease has brought undefinable hardship and great misery among different populations in Africa when it affects a sufficient number and density of susceptible hosts and where the environment facilitates transmission by the principal *Aedes* (Stegomyia) *aegypti* mosquito vector (Tomori, 2002; Barrett and Higgs, 2007).

A country is considered endemic for YF or its potential, due to the presence of both competent vectors (transmitters of the infection) and the yellow fever virus in monkeys. According to Robertson et al. (1996), a dramatic resurgence of yellow fever has been occurred in both sub-Saharan Africa and South America since the 1980s and it was one of the stumbling blocks to economic and social development. While complete eradication is not feasible currently due to the wildlife reservoir, large vaccination activities done in Africa during the 1940s to 1960s

reduced yellow fever incidence for several decades (Garske et al., 2014). However, after a period of low vaccination coverage, YF has been resumed in the late 1980s and early 1990s.

Every health official undertaking YF surveillance at the ports of entry, should understand the basic information regarding the disease and work under the agreed standard operating procedures. As per Bae et al. (2005) increasing migration, accelerating urbanization, and improved travel infrastructures are global trends that increase the risk of YF spreading to parts of the world where the disease had disappeared.

The under reporting of YF cases in the respective regions and lack of international interest leads to an underestimation of the constant danger in these areas. Non-vaccinated travelers without the effective protection of the Yellow Fever Virus (YFV) vaccine take a high risk as demonstrated by several imported cases of the recent years (Bae et al., 2005). Disease outbreak in towns and in mixed populations with foreigners may be more serious because of high densities of mosquito vectors and high population densities.

YF is endemic in tropical and subtropical areas of Africa and South America (Figure 1.1), even though the main transmitting vector, *Aedes aegypti* occurs also in Asia, in the Pacific and in the Middle East. According to Tomori (2002), the resurgence of YF in Africa and failure to control the disease has resulted from a combination of several factors, including:

- collapse of health care delivery systems
- lack of appreciation of the full impact of YF disease on the social and economic development of the affected communities
- insufficient political commitment to YF control by governments of endemic countries
- poor or inadequate disease surveillance
- inappropriate disease control measures and

- preventable poverty coupled with misplaced priorities in resource allocation

Figure 1.1: Global geographic distribution of yellow fever. Source: Barnett (2007); CDC (2011a)

The first recorded epidemic of YF in Africa occurred among British troops in St. Louis de Senegal in 1778 (Haddow, 1969), although major outbreaks of YF were subsequently documented in West Africa. In East Africa, YF epidemics have been historically rare, but in 1959, small outbreaks occurred on the Sudan-Ethiopian border, which subsequently spread along the Omo River valley causing a major epidemic between 1960 and 1962 (Monath et al., 1989; Haddow, 1969).

1.2 Epidemiology and Symptoms of YF

YFV is the prototype member of the genus *Flavivirus*, the virus of the family *Flaviviridae* (from the Latin *flavus*, meaning yellow) which is transmitted through the bite of an infected female yellow fever mosquito called *Aedes aegypti* (Ellis and Barrett, 2008; Robertson et al., 1996;

Cliff et al., 2004). In Africa, the disease is maintained endemically in *monkey-Ae. Africanus* jungle transmission cycles and may periodically emerge in intermediate/ savanna cycles. In America, *Haemogogus* species acts as the main vector (Ellis and Barrett, 2008; Cliff et al., 2004). Following the bite of an infected mosquito, YFV replicates and spreads to other areas of the body.

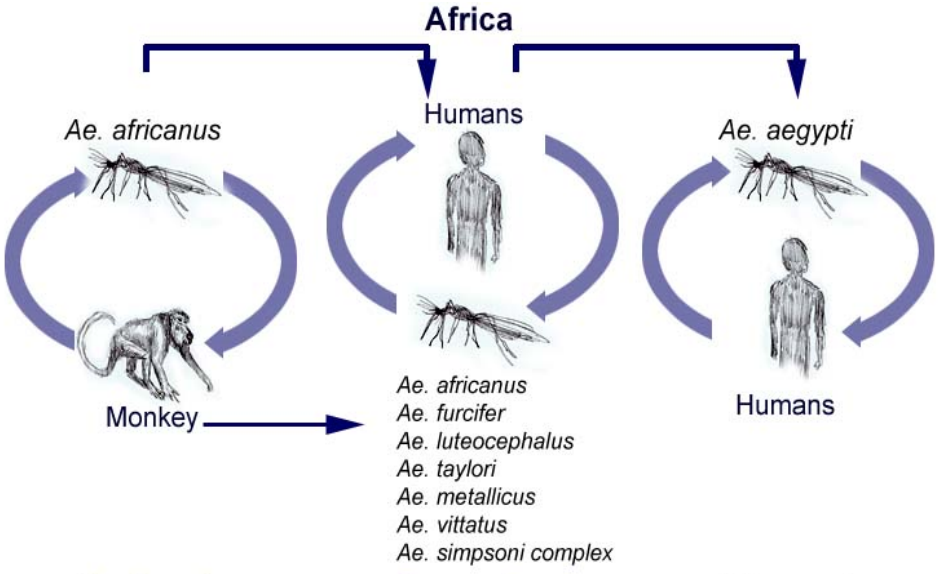


Figure 1.2: YF transmission cycle in Africa. Source: Reproduced from CDC (2011b); Barrett and Higgs (2007)

In America, two types of epidemiological cycles are in operation: the jungle and the urban, while in Africa YFV has three transmission cycles: jungle (sylvatic), intermediate (savannah), and urban (Figure 1.2) (Barrett and Higgs, 2007; WHO, 1986). Studies showed that monkeys are the primary hosts and the sources of YFV in Africa, that there were *monkey-Ae.*, *africanus-monkey* cycles in the forests, and a monkey and human cycle involving another mosquito species, *Ae. simpsoni*, in villages (Ellis and Barrett, 2008; Rogers et al., 2006; Gubler, 2004; Tomori, 2002). *Aedes africanus* is the most dangerous vector of YF in forested areas of Africa and has made many countries of Africa to be remoteness. These vectors are predominantly involved in monkey-to-human transmission of YFV in forested areas.

The jungle (sylvatic) cycle involves transmission of the virus monkeys and mosquito species found in the forest canopy. The virus is then transmitted by mosquitoes from monkeys to humans when humans are visiting or working in the jungle. An intermediate (savannah) cycle involves transmission of virus from mosquitoes to humans living or working in jungle border areas. In this cycle, the virus can be transmitted from monkey to human or from human to human via mosquitoes. The urban cycle involves transmission of the virus from human to human by mosquitoes, primarily *Aedes aegypti* (Tomori, 2002; WHO, 1986). The virus is usually brought to the urban setting by a vermin human who was infected in the jungle or savannah.

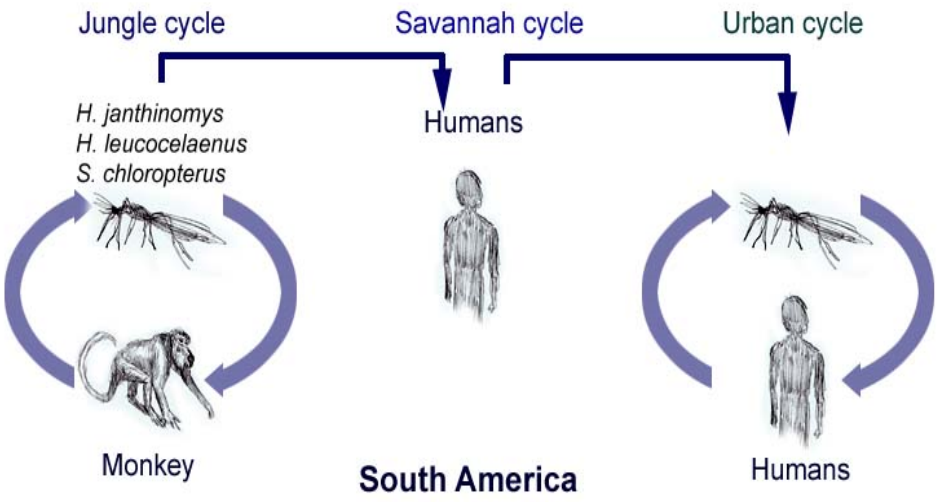


Figure 1.3: YF transmission cycle in South America. Source: Reproduced from CDC (2011b); Barrett and Higgs (2007)

In human body YF begins after an incubation period of 3 to 5 or 6 days, during which there are generally no symptoms identifiable to the host. After that time, a person infected begins with an abrupt onset of symptoms, including fever and chills, intense headache and lower backache, muscle aches, nausea, joint pain, renal failure, jaundice and haemorrhaging (Monath, 2001). In about 15% of the cases, the disease progresses to a more severe form with haemorrhagic manifestations.

Africa contributes more than 90% of the global YF morbidity and mortality, regardless of a safe and effective vaccines that are available like 17D (Ellis and Barrett, 2008; Robertson et al., 1996). Thus, it remains a significant public health concern in a region where majority of the population remains unvaccinated. Again, there are approximately 130,000 - 200,000 cases with fever and jaundice, including 30,000 - 78,000 deaths, due to YF yearly reported in the literature (Garske et al., 2014; Tolle, 2009; Ellis and Barrett, 2008), whereby many cases of these are from Africa.

Also, WHO (2013) estimates the burden of YF in Africa as 84,000 - 170,000 severe cases and 29,000 - 60,000 deaths for the year 2013. This is in accordance with a recent analysis study of African data sources. Thus, without vaccination, the effect would be much higher in the coming years.

1.3 Rationale/Justification of the Research

Since the mid-20th century, the global yellow fever risk map has depicted the best estimate of the distribution of the virus and has been used to guide vaccination recommendations for travellers (Jentes et al., 2011). Despite the availability of a safe and effective vaccine and detailed knowledge of the fundamental disease ecology and epidemiology, YF has remained a significant public health threat in many tropical areas of sub-Saharan Africa (Ellis and Barrett, 2008). The reasons why there has been such a dramatic global resurgence of YF epidemic and the emergence of YFV are not fully understood (Gubler, 2004). However, some reasons were explained by Tomori (2002) although the epidemic still exist.

As from Tomori (2002), YF disease can be understood and controlled in Sub-Saharan Africa and Africa at large within the coming ten to fifteen years, if African government seize the initiative for YF control by declaring an inflexible resolution to control the disease. However this is not the case, until now. As noted by WHO (1986) strong satiating measures are required

for the prevention and control of YF, particularly during the period of intoxication (period that cause someone to lose control of his/her faculties) when obvious clinical manifestations appear. A serious problem in the prevention and control of YF is the lack of serious and quick recognition of the disease.

However, most local hospitals are not well equipped with the intensive care facilities that might be necessary for YF patients. Thus, preventive measures need to be in place to rescue the situation. Again clinical diagnosis is often delayed even in the presence of typical illness because most physicians and many medical students are not familiar with the disease (Tomori, 2002). Hence, proper information campaign concerning the disease is required.

Epidemiological mathematical models can be used in predicting and analyzing the emergence, spread and control of infectious diseases. As per Liu et al. (2013), these models are very critical to the studying of virus spreading dynamics which can state clearly the origination, evolution and effects of viruses. Also, they can help in figuring out decisions (policy-making) that are of significant importance in a way that human reasoning cannot before time when an outbreak is forecasted (Tumwiine et al., 2007), which results to implementation of mitigation strategies for early outbreak control.

1.4 Statement of the Problem

Some diseases like measles, influenza, cholera, YF, and tuberculosis have approved medical treatments options and/or vaccine. Surprisingly, it remains a puzzle why diseases for which treatment and/or vaccine are available, are still endemic in some of our societies particularly in Tanzania. Many mathematical models have been developed to describe and analyse dynamics and control of vector borne diseases like malaria and dengue but YF is not well described and analysed by mathematical models. The few mathematical models developed, did not account for monkeys as one of the host for YF epidemic. This dissertation research uses a mathematical

model in addressing and analysing transmission dynamics of YF between and within two hosts and finding affordable optimal control strategies for mitigation.

1.5 Research Objectives

1.5.1 General Objective

The main research objective is to formulate and analyse mathematical models that can be used to study transmission dynamics and find control strategies of YF disease.

1.5.2 Specific Objectives

The research study is based on the following specific objectives:

1. To formulate mathematical models for transmission dynamics and control strategies of YF disease.
2. To analyse and assess transmission dynamics and the impact of YF infection through mathematical modelling so as to find necessary conditions for disease interruption and control.
3. To determine control strategies for minimizing the infection from the population such as personal protection, health educational campaign, insecticides or combinations.
4. To analyse the cost-effectiveness of the optimal control measures of YF.

1.6 Research Questions

The following fundamental questions guide our study:

1. Can mathematical models be formulated and used to explain transmission dynamics and optimal control strategies of YF?

2. **(a)** Why is YF still a significant public health problem in Tanzania?

   (b) What is the impact and necessary conditions for YF infection transmission dynamics to the population?

3. Are there any control strategies that can minimize transmission of the infection from the population? Or what are the options available and affordable to control yellow fever in developing countries particularly Tanzania?

4. What is the most cost-effective optimal control strategy?

1.7 Methodology

- Objective 1:

  Objective 1 is achieved by formulating a system of non-linear ordinary differential equation with two hosts and a vector to explain transmission dynamics of YF. Later the system is extended to include control mechanisms whereby personal protection and educational campaign to human host and spray of insecticides to vector were the control mechanisms considered.

- Objective 2:

  To achieve objective 2, the formulated system of non-linear ordinary differential equation is solved to determine equilibrium points (DFE and EE) of the system and the basic reproduction number. Stability of the equilibrium points is established whereby local stability of DFE is determined by trace-determinant approach of Jacobian Matrix and global stability by the approach of Kamgang and Sallet (2008) and Dumont et al. (2008) and the idea of stable Metzler matrix. Lyapunov function and LaSalle's Invariance Principle is used to explore the global stability of the EE.

- Objective 3:

  This is achieved using optimal control theory, Pontryagins maximum principal, with the inclusion of Hamiltonian and Lagrangian equation. The adjoint condition, transversality condition and the optimality condition were used to state the conditions necessary of the optimal controls.

- Objective 4:

  To achieve objective 4, cost-effectiveness analysis is done. Incremental cost-effectiveness ratio is used for comparing cost of the control mechanisms against the health benefit achieved. Cost-effectiveness ratio per infections avoided and the disability adjusted life years averted over time are done aiming to show conditions of the infection in some years later.

1.8 Significance of the Study

The following are the significance of this study;

1. The study will improve awareness and understanding of YF epidemic to the society, its transmission dynamics and how to protect themselves from being infected by taking affordable control measures.

2. It will help the government and policy makers to establish and put in place policies, programmes and optimal plans for disease prevention and control.

3. The study will help educators in general to make a comprehensive information campaign, educational seminars, workshops, media and training programmes aiming to educate and improve awareness to people in endemic areas and particulary those with high risk, about the disease effects and the importance of early vaccination for prevention and control.

4. The study will add up the knowledge to the existing literature and provide a platform for further research of infectious diseases particularly vector-borne using models.

1.9 Dissertation Structure

The dissertation is organised in chapters as follows:

Chapter 1: This chapter presents the general information of the research study which are; introduction and background of the study, rationale/justification of the study, problem statement, objectives of the research, research questions, methods used to achieve objectives and significance of the study.

Chapter 2: In this chapter, we formulate and analyse a deterministic mathematical model for YF transmission dynamics using non-linear ordinary differential equations. The model considers three populations: two hosts (humans and primates) and one vector. We calculate and analyse the basic reproduction number of the model using next generation matrix approach and perform its sensitivity analysis in order to study the effects of model parameters to disease transmission. Effects of sensitive model parameters are shown in numerical simulation.

Chapter 3: This chapter, considers the model developed in Chapter 2 to compute the disease endemic equilibrium point and analyse the stabilities of DFE and EE. Local stability of disease-free equilibrium (DFE) is established using trace-determinant approach of the Jacobian matrix of the model, which was computed and evaluated at DFE. Global stability of DFE is established using stable Metzler matrix theory and that of endemic equilibrium (EE) is established using Lyapunov method together with LaSalle's Invariance Principle.

Chapter 4: In this chapter, we extended the model of YF whereby control mechanisms were introduced aiming to derive optimal control strategies for YF intervention and prevention. We

considered personal protection and educational campaigns to human host population and insecticides which include larvicides and adulticides to mosquito (vector) population as control variables. Basing on our assumptions, we did not consider any control variable for monkeys populations.

Chapter 5: This chapter presents the cost-effectiveness analysis of different optimal control measures considered in Chapter 4. The aim is to compare costs incurred with health outcome achieved between two or more alternative interventions strategies that compete for the same resources. We use the incremental cost-effectiveness ratio (ICER) to compare the cost-effectiveness of our interventions basing on the model simulation results of Chapter 4. We then went further to investigate the cost-effectiveness ratio of the best strategy obtained per infections avoided and disability adjusted life years (DALYs) gained over time.

Chapter 6: This chapter presents summary of qualitative and numerical results of the study as well as making conclusions and recommendations that go along with the results of the study. It also points out several ways in which this study can be extended for future work.

1.10 Publications and Manuscript

Based on this study, the following articles have been published and/or presented at conference:

Monica Kung'aro, Livingstone S. Luboobi, and Francis Shahada (2014). "Reproduction Number for Yellow Fever Dynamics Between Primates and Human Beings." *Communications in Mathematical Biology and Neuroscience*, 2014: Article-ID No: 5.

Monica Kung'aro, Livingstone S. Luboobi, and Francis Shahada (2015). "Modelling and Stability Analysis of SVEIRS Yellow Fever Two Host Model." *Gulf Journal of Mathematics*, 3(3): 106-129.

Monica Kung'aro, Livingstone S. Luboobi, and Francis Shahada (2015). "Application of Optimal Control Strategies for the Dynamics of Yellow Fever." *Journal of Mathematical and Computational Science*, 5(3): 430- 453.

This article has also been presented at the International Clinic on Meaningful Modelling of Epidemiological Data at African Institute for Mathematical Sciences (AIMS), Cape Town, South Africa.

Submitted manuscript:Monica Kung'aro, Livingstone S. Luboobi, and Emmanuel Mpolya (2015). "Cost-Effectiveness Analysis of Personal Protection, Educational Campaign and Spray of Insecticides for the Dynamics of Yellow Fever." submitted to *International Journal of Advances in Applied Mathematics and Mechanics*.

CHAPTER TWO

Basic Reproduction Number for Yellow Fever Dynamics Between Primates and Human Beings [1]

Abstract: Vector borne diseases are spreading very rapidly in the populations all over the World. Thus, there is need to remind people about transmission of these diseases in order to eradicate them. In this chapter we propose a deterministic mathematical model using non-linear ordinary differential equations to gain an insight into dynamics of yellow fever between monkeys, human beings and *Aedes* mosquito for the purpose of controlling the disease. In the analysis of the model we investigate the basic reproduction number, R_0, between monkeys, vectors and human host. The disease threshold parameter is obtained using next generation matrix approach and is of the form $R_0^2 = R_h + R_m$, where R_h and R_m are the reproduction number for human-vector and vector-monkey compartments respectively.

It is proved that the global transmission dynamics of the disease are completely determined by the basic reproduction number. In order to study the effect of model parameters to R_0, the sensitivity analysis of basic reproductive number, R_0, with respect to epidemiological parameters is performed. Results call attention to parameters regarding to daily biting rate of mosquitoes, birth rate of vectors, probability of transmission from infectious vector to susceptible human and vice versa, recruitment of human host which includes unvaccinated immigrants as well as the incubation period for both vector and humans. Thus, quick and focused interventions, like personal protection and destruction of breeding sites, may be effective for controlling disease transmission.

[1] This chapter is based on the published paper:
Kung'aro, M., Luboobi, L. S., and Shahada, S. (2014). Reproduction number for yellow fever dynamics between primates and human beings. *Communications in Mathematical Biology and Neuroscience 2014*, article ID No:5

Keywords: Vector borne infectious disease, Yellow fever, Primates, Humans, Sensitivity analysis.

2010 **AMS Subject Classification:** $92B05$.

2.1 Introduction

Yellow Fever (YF) is among the vector-borne infectious diseases caused by viruses which is primarily transmitted by disease transmitting biological agents, called vectors. It is a viral hemorrhagic fever caused by yellow fever virus (YFV) and is transmitted through the bite of an infected female yellow fever mosquito (Robertson et al., 1996). It only infects humans, monkeys and several species of mosquito (WHO, 2013). The disease is endemic in tropical and subtropical areas of Africa and South America.

A dramatic resurgence of YF has occurred since 1980s in both sub-Saharan Africa and South America (Robertson et al., 1996). Increasing migration, accelerating urbanization, and improved travel infrastructure are global trends that increase the risk of YF spreading to parts of the world where the disease had disappeared. There are three epidemiologically different infectious cycles, in which the YFV is transmitted from mosquitoes to humans and/or other primates (Barrett and Higgs, 2007), which are; jungle (sylvatic), intermediate (savannah), and urban. In the 'urban cycle', only the yellow fever mosquito *Aedes aegypti* is involved.

Besides the urban cycle there is, both in Africa and South America, a sylvatic cycle (forest cycle or jungle cycle), where *Aedes africanus* (in Africa) or mosquitoes of the genus *Haemagogus* and *Sabethes* (in South America) serve as vectors. In the jungle, mosquitoes infect mainly monkeys; and the disease is mostly asymptomatic in African primates. In South America, the sylvatic cycle is currently the only way humans can infect each other (Barrett and Higgs, 2007). People who are bitten by *Aedes africanus* or *Haemogogus* in the jungle become infected and can carry the virus to urban centres, where *Aedes aegypti* acts as a vector. It is because of this sylvatic cycle that yellow fever cannot be eradicated (Barrett and Higgs, 2007).

In Africa the third infectious cycle, 'savannah cycle' or intermediate cycle, occurs between the jungle and urban cycle. Different mosquitoes of the *genus Aedes* are involved. In recent years, this has been the most common form of transmission of YF in Africa (WHO, 2006). In

humans, yellow fever's incubation period is three to five or six days. During this time, there are generally no symptoms identifiable to the host (Tolle, 2009). After that time, a person infected begins with an abrupt onset of symptoms, including fever and chills, intense headache and lower backache, muscle aches, nausea and extreme exhaustion.

The World Health Organization (WHO) estimated that YF causes 200,000 illnesses and 30,000 deaths every year in unvaccinated populations and today 90% of the infections occur in African continent (Tolle, 2009; Mutebi and Barrett, 2002).

Mathematical models have become an important tool in analysing the spread and control of infectious diseases. Thomé et al. (2010) conducted a study on optimal control of *Aedes aegypti* mosquitoes by the sterile insect technique (SIT) and insecticide. They presented a mathematical model to describe the dynamics and control of mosquito population only, where sterile male mosquitoes are introduced as a biological control, besides the application of insecticide. Their results showed that application of insecticide is needed at the beginning of the control to reduce *Aedes aegypti* populations. For us, we are going to study the dynamics and control of vector and human, and how the infection is transmitted from one population to another. However, the study of Thome and his friends, will help our study where *Aedes aegypti* is taken as a vector for YF transmission.

Monath and Cetron (2002) conducted a study to address transmission and prevention of YF in persons traveling to the tropics. They argued that because YF is maintained in nature by transmission between monkeys and mosquitoes and because it cannot be eradicated, prevention and control of the disease requires continuous immunization of human populations at risk. This study is theoretical, we are going to use mathematical models to check the relevance of their comments.

Another theoretical study was done by Amaku et al. (2011) to address the question as to why

dengue and yellow fever coexist in some areas of the world and not in others? They developed a theoretical model which includes humans and two mosquito species, *Aedes aegypti* (which transmits both infections: yellow fever and dengue) and *Aedes albopictus*(which transmits dengue only). Their results shows that in Asia, vaccination of the local community is virtually absent but travelers from endemic areas are demanded to produce a vaccination certificate at entrance of the countries of this region to reduce the probability of importing the disease. They recommended on the role of vaccination of population in the endemic regions aiming to control yellow fever epidemic. The study consider one host only, two hosts (human and monkeys) will be considered for our case.

Garba et al. (2008) use a deterministic mathematical model to study the dynamics of dengue (a YF like disease). The model assumes a homogenous mixing of human and vector populations with seven mutually-exclusive compartments representing the human and vector dynamics, whereby Susceptible, Exposed, Infectious, Recovered (SEIR) and Susceptible, Exposed, Infectious (SEI) compartments were considered for human and vector respectively. Analysis shows that the model exhibits the phenomenon of backward bifurcation, where the stable disease-free equilibrium (DFE) coexists with a stable endemic equilibrium (EE), meaning that epidemiological requirement of making the threshold parameter less than unity is no longer sufficient, although necessary for effectively controlling the spread of dengue in a community. The model is extended to incorporate an imperfect vaccine against the strain of dengue. Using the theory of centre manifold, the extended model is also shown to undergo backward bifurcation. For us we are going to consider vaccination at initial stage, whereby two hosts and a vector will be considered and the model will be extended using personal protection, educational campaign and insecticides as control mechanisms.

Another mathematical model to study dengue fever in a virgin environment by Bowman (2012) was formulated. The model includes four human classes: Susceptible, Exposed, Infected, and Recovered (SEIR) and it recognizes four groups of mosquitoes: Aquatic, Susceptible, Exposed,

and Infected (ASEI). An environment with no immunities or increased susceptibilities to the various dengue serotypes, and the existence of a single serotype throughout the epidemic was considered. Due to novelty incidence of dengue in Cape Verde and to minimal reporting, the data set for the epidemic is sparse. Thus, Bowman extended logistic model fitting technique using few data to ascertain some key parameter values of the formulated model. Threshold parameter was calculated and analysed numerically whereby result shows the reality of the disease occurrence in Cape Verde. Thus, we are going to use some of parameter values obtained by Bowman (2012) in our simulation.

In this chapter, we propose a mathematical model of YF that assesses the dynamics of YF between two hosts (monkey and human beings) with one vector. The developed model is of type SVEIRS for human host and SEI for the vector and monkey. The model is based on the basic model of Dengue transmission (the YF like disease) by Yang and Ferreira (2008). Modifications have been made to incorporate monkeys as another host, vaccination, immigration and control mechanisms.

2.2 Materials and Methods

2.2.1 Model Formulation

We formulate a model for the spread of YF in the human, vector and monkey populations with the total population sizes at time t given by $N_H(t)$, $N_V(t)$ and $N_M(t)$ respectively. The populations are further compartmentalized into epidemiological classes as shown in the model flow diagram in Figure 2.1. The vector and monkey compartments of the model do not include the immune class as they never recover from the infection, that is their infective period ends with their death due to their relatively short life cycle.

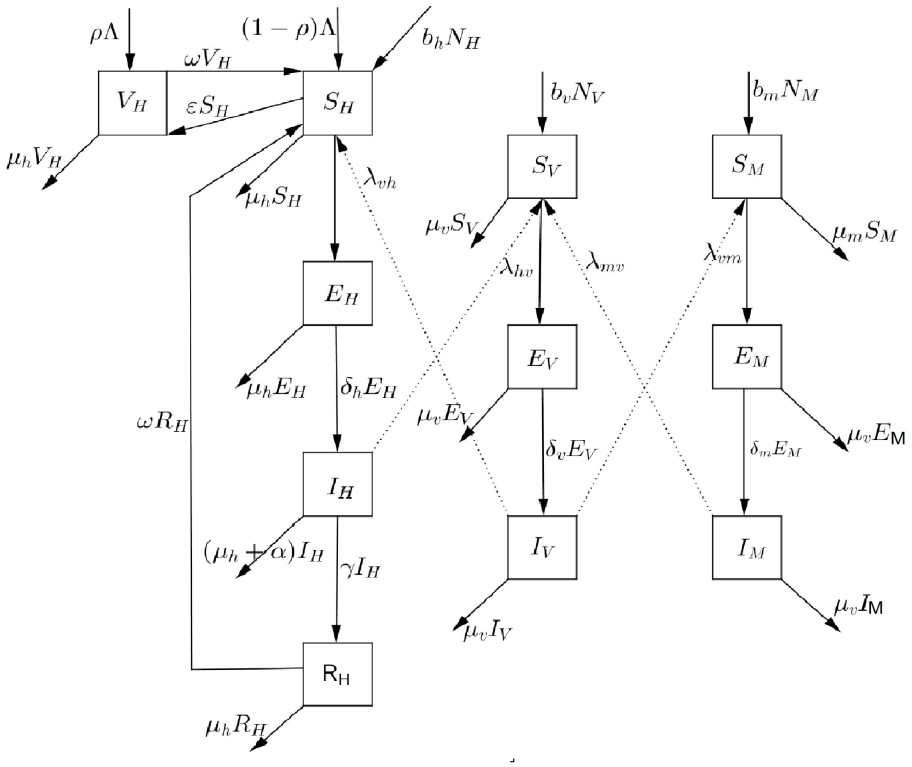


Figure 2.1: Model flow diagram for transmission dynamics of YF.

As indicated in the compartmental diagram (Figure 2.1), the model divides the human population into 5 classes: susceptible, S_H , vaccinated, V_H, exposed, E_H, infectious, I_H and recovered, R_H. People enter susceptible class either through per capita birth at a constant rate b_H or through immigration (Λ) whereby a proportion ρ of the immigrants enter in the vaccinated class. Susceptible individuals may choose to be vaccinated at the rate ε.

We divide the vector (mosquito) population into 3 classes: susceptible, S_V, exposed, E_V, and infectious, I_V. Female YF mosquitoes enter the susceptible class through birth then moves from the susceptible to the exposed class and later to the infectious class. The mosquito remains infectious for life (Dumont et al., 2008) and leave the population through a per capita density-dependent natural death rate.

We also divide the monkey population which is the source of infection (Ellis and Barrett, 2008; Rogers et al., 2006; Gubler, 2004; Gould et al., 2003) into 3 classes: susceptible, S_M, exposed,

E_M, and infectious, I_M. When an infected monkey is bitten by a tree-hole breeding mosquito, the mosquito acquires the virus and then the mosquito can pass the virus on to any number of other monkey and humans it may bite when it comes across them. When human is bitten by an infected mosquito, the human may acquire the virus. The infected human returns to the city, where an urban mosquito *(Aedes aegypt)* serves as a viral vector spreading infection rapidly by biting other humans. Parameters of the model are as shown in Table 2.1:

Table 2.1: Description of parameters of the model system (2.6)

Symbol	Description
β_1	Transmission probability of vector to human
β_2	Transmission probability of human to vector
β_3	Transmission probability of primate to vector
β_4	Transmission probability of vector to primate
δ_h	Progression rate from e_h to i_h
δ_v	Progression rate from e_v to i_v
δ_m	Progression rate from e_m to i_m
b_h	Birth rate of human
b_v	Birth rate of vector
b_m	Birth rate of primates
a	Daily biting rate
γ	Natural recovery rate
α	Death rate due to disease for human
ω	rate of relapse of vaccinated and recovered human
ε	vaccination rate of susceptible human
ρ	proportion of immigrant who are vaccinated
σ	arrival rate of immigrant per individual per time
μ_h	natural death rate of human
μ_v	natural death rate of vector
μ_m	natural death rate of primates
λ_{vh}	force of infection from vector to human
λ_{hv}	force of infection from human to vector
λ_{mv}	infection force from monkey to vector
λ_{vm}	infection force from vector to monkey

The developed model depend on the following assumptions, the new born babies do not have the disease, the efficacy of the vaccine is 100% effective for not more than ten years, the disease

has no epidemiological effect on the demographic dynamics of the vector (mosquito), we ignore bites of an infected female mosquito onto an infected human host.

However, we also assume that the rate of relapse of vaccinated individual back to susceptibility is the same as that of recovered individuals and no vertical transmission of the infection in the vector population. Migration of monkeys was ignored, that is to say; mosquitoes that go to the monkeys habitats are the ones infected by the bites of infected monkeys and can infect susceptible monkeys (primates).

2.2.2 Description of Model Flow Diagram

When an infectious female *Aedes aegypt* mosquito bites a susceptible human, there is some finite probability that the parasite will be passed on to the human and the person will move to the exposed class. After a certain period of time, people from the exposed class enter the infectious class at a rate δ that is the reciprocal of the duration of the latent period.

After some time, the infectious humans recover naturally at the rate γ, hence move to the recovered class. The recovered humans have some immunity to the disease and do not get clinically ill, after some years, they lose their immunity and return to the susceptible class at the rate ω. Humans leave the population through natural death rate μ_H, and through a per capita disease-induced death rate α, which is small in this case. However, like any other vector born diseases the YF disease induced death rate is very small in comparison with the recovery rate (Tumwiine et al., 2010).

2.2.3 Model Equations

Applying the assumptions, definition of variables and parameters as well as description of terms above, the ordinary differential equations which describe the dynamics of YF in the human,

vector and monkeys population are formulated as shown below:

Human:

$$\begin{aligned}
\frac{dS_H(t)}{dt} &= b_h N_H + (1-\rho)\Lambda + \omega(V_H + R_H) - \lambda_{vh} - \varepsilon S_H - \mu_h S_H, \\
\frac{dV_H(t)}{dt} &= \rho\Lambda + \varepsilon S_H - \omega V_H - \mu_h V_H, \\
\frac{dE_H(t)}{dt} &= \lambda_{vh} - \delta_h E_H - \mu_h E_H, \\
\frac{dI_H(t)}{dt} &= \delta_h E_H - (\mu_h + \alpha) I_H - \gamma I_H, \\
\frac{dR_H(t)}{dt} &= \gamma I_H - \mu_h R_H - \omega R_H,
\end{aligned} \tag{2.1}$$

Vector:

$$\begin{aligned}
\frac{dS_V(t)}{dt} &= b_v N_V - (\lambda_{hv} + \lambda_{mv}) - \mu_v S_V, \\
\frac{dE_V(t)}{dt} &= (\lambda_{hv} + \lambda_{mv}) - \delta_v E_V - \mu_v E_V, \\
\frac{dI_V(t)}{dt} &= \delta_v E_V - \mu_v I_V,
\end{aligned} \tag{2.2}$$

Monkeys:

$$\begin{aligned}
\frac{dS_M(t)}{dt} &= b_m N_M - \lambda_{vm} - \mu_m S_M, \\
\frac{dE_M(t)}{dt} &= \lambda_{vm} - \delta_m E_M - \mu_m E_M, \\
\frac{dI_M(t)}{dt} &= \delta_m E_M - \mu_m I_M,
\end{aligned} \tag{2.3}$$

where; $\lambda_{vh} = \dfrac{a\beta_1 S_H I_V}{N_V}$, $\lambda_{hv} = \dfrac{a\beta_2 S_V I_H}{N_H}$, $\lambda_{mv} = \dfrac{a\beta_3 S_V I_M}{N_M}$ and $\lambda_{vm} = \dfrac{a\beta_4 S_M I_V}{N_V}$.

In the model the term $\lambda_{vh} = \dfrac{a\beta_1 S_H I_V}{N_V}$ denotes the rate at which susceptible human hosts S_H get infected from the infected vector I_V (force of infection from vector to human), $\lambda_{hv} = \dfrac{a\beta_2 S_V I_H}{N_H}$ denotes the rate at which susceptible vector S_V get infected from the infected human host I_H (infection force from human host to vector), $\lambda_{mv} = \dfrac{a\beta_3 S_V I_M}{N_M}$ denotes the rate at which the susceptible vector S_V get infected from the infected monkey I_M (force of infection from monkey to vector) and the term $\lambda_{vm} = \dfrac{a\beta_4 S_M I_V}{N_V}$ denotes the rate at which the susceptible monkey S_M get infected from the infected vector I_V. However, it is observed that the infected vector I_V can transmit the infection to both the human hosts and the monkeys.

The total population sizes $N_H(t)$, $N_V(t)$ and $N_M(t)$ can be determined by:

$$\begin{aligned} N_H(t) &= S_H(t) + V_H(t) + E_H(t) + I_H(t) + R_H(t), \\ N_V(t) &= S_V(t) + E_V(t) + I_V(t), \\ N_M(t) &= S_M(t) + E_M(t) + I_M(t). \end{aligned} \tag{2.4}$$

Thus, adding from the differential equations, of the model system (2.1), (2.2), and (2.3) for the human host population, vector population and monkeys population, we have;

$$\begin{aligned} \frac{dN_H(t)}{dt} &= \Lambda + (b_h - \mu_h)N_H - \alpha I_H, \\ \frac{dN_V(t)}{dt} &= (b_v - \mu_v)N_V, \\ \frac{dN_M(t)}{dt} &= (b_m - \mu_m)N_M. \end{aligned} \tag{2.5}$$

The total population sizes of female mosquitos and monkeys, N_V and N_M are stationary for $b_v = \mu_v$ and $b_m = \mu_m$, declines for $b_v < \mu_v$ and $b_m < \mu_m$ and grows exponentially for $b_v > \mu_v$ and $b_m > \mu_m$ respectively.

2.2.4 Dimensionless Transformation

We transform our model equations into normalized quantities such that the total population for the normalized model is equal to 1. This can be done by scaling the population of each class by the total species population. We make the following transformation:

$$s_h = \frac{S_H}{N_H},\ v_h = \frac{V_H}{N_H},\ e_h = \frac{E_H}{N_H},\ i_h = \frac{I_H}{N_H},\ r_h = \frac{R_H}{N_H},\ s_v = \frac{S_V}{N_V},\ e_v = \frac{E_V}{N_V},$$

$$i_v = \frac{I_V}{N_V},\ s_m = \frac{S_M}{N_M},\ e_m = \frac{E_M}{N_M} \text{ and } i_m = \frac{I_M}{N_M}.$$

in the classes $S_H,\ V_H,\ E_H,\ I_H,\ R_H,\ S_V,\ E_V,\ I_V,\ S_M,\ E_M$ and I_M of the populations respectively. Also, we define $\sigma = \dfrac{\Lambda}{N_H}$ as the arrival rate of immigrants per individual per unit time.

Differentiating the dimensionalized equations and solving for the derivatives of the scaled variables, system (2.1), (2.2), (2.3) becomes the normalised model as:

$$\begin{aligned}
\frac{ds_h}{dt} &= b_h + \sigma(1-\rho) + \omega v_h + \omega r_h - a\beta_1 s_h i_v - s_h(\varepsilon + b_h + \sigma) + \alpha s_h i_h,\\
\frac{dv_h}{dt} &= \rho\sigma + \varepsilon s_h - v_h(\omega + b_h + \sigma) + \alpha v_h i_h,\\
\frac{de_h}{dt} &= a\beta_1 s_h i_v - e_h(\delta_h + b_h + \sigma) + \alpha e_h i_h,\\
\frac{di_h}{dt} &= \delta_h e_h - i_h(\gamma + \alpha + b_h + \sigma) + \alpha i_h^2,\\
\frac{dr_h}{dt} &= \gamma i_h - r_h(\omega + b_h + \sigma) + \alpha r_h i_h\\
\frac{ds_v}{dt} &= b_v - (a\beta_2 s_v i_h + a\beta_3 s_v i_m) - s_v b_v,\\
\frac{de_v}{dt} &= a\beta_2 s_v i_h + a\beta_3 s_v i_m - e_v(\delta_v + b_v),\\
\frac{di_v}{dt} &= \delta_v e_v - i_v b_v,\\
\frac{ds_m}{dt} &= b_m - a\beta_4 s_m i_v - s_m b_m,\\
\frac{de_m}{dt} &= a\beta_4 s_m i_v - e_m(\delta_m + b_m),\\
\frac{di_m}{dt} &= \delta_m e_m - i_m b_m.
\end{aligned} \tag{2.6}$$

However, it is easy to show that $\frac{dn_h}{dt} = 0$, $\frac{dn_v}{dt} = 0$ and $\frac{dn_m}{dt} = 0$ for the humans, vector and monkeys respectively. Where solutions are restricted to the hyperplanes, $s_h+v_h+e_h+i_h+r_h = 1$, $s_v + e_v + i_v = 1$ and $s_m + e_m + i_m = 1$.

The YF model system (2.6) monitors human, mosquito (vector) and monkeys (primates) populations, we assume that all state variables and parameters of the model are non-negative $\forall t \geq 0$. Thus, the model will be analysed in a suitable feasible region where it makes biological sense. This region will be obtained as follows:

Lemma 2.1. *Solutions of the normalised model system* (2.6) *are contained in the region* $\Phi = \Phi_H \cup \Phi_V \cup \Phi_M \subset \Gamma_+^5 \times \Gamma_+^3 \times \Gamma_+^3$.

Proof. We categorize the model system into three parts; namely the human component (n_h), vector (mosquito) component, (n_v) and the monkeys component (n_m), given respectively by,

$n_h = s_h + v_h + e_h + i_h + r_h, \quad n_v = s_v + e_v + i_v \quad \text{and} \quad n_m = s_m + e_m + i_m.$

such that

$$\Phi_H = \{(s_h, v_h, e_h, i_h, r_h) \in \Gamma_+^5 : 0 < s_h + v_h + e_h + i_h + r_h \leq 1\},$$
$$\Phi_V = \{(s_v, e_v, i_v) \in \Gamma_+^3 : 0 < s_v + e_v + i_v \leq 1\},$$
$$\Phi_M = \{(s_m, e_m, i_m) \in \Gamma_+^3 : 0 < s_m + e_m + i_m \leq 1\}.$$

Thus,

$$\Phi = \Phi_H \cup \Phi_V \cup \Phi_M \subset \Gamma_+^5 \times \Gamma_+^3 \times \Gamma_+^3$$

which can be shown to be positively invariant with respect to the model system (2.6). From this lemma, we conclude that it is sufficient to consider the dynamics of model system (2.6) in Φ. In this region, the model can be considered as being epidemiologically and mathematically well-posed (Hethcote, 2000). □

2.3 Model Analysis

We now investigate the existence of disease-free equilibrium (E_0) and basic reproduction number. E_0 is obtained by setting the derivatives with respect to time of the model system (2.6), equal to zero. On calculations, the following E_0 was obtained:

$$E_0 = \left(\frac{b_h + (1-\rho)\sigma + \omega}{\omega + \varepsilon + b_h + \sigma}, \ \frac{\rho\sigma + \varepsilon}{\omega + \varepsilon + b_h + \sigma}, \ 0, \ 0, \ 0, \ 1, \ 0, \ 0, \ 1, \ 0, \ 0 \right). \tag{2.7}$$

2.3.1 The Basic Reproduction Number, R_0

One of the most important concerns in the analysis of mathematical epidemiological models is the determination of the asymptotic behaviour of their solutions which is usually based on the stability of the associated equilibria (Moghadas, 2004). These models typically consist of a

disease-free equilibrium and at least one endemic equilibrium. The local stability of the disease-free equilibrium is determined based on a threshold parameter, known as the basic reproductive number, R_0.

An easy way to theoretically compute R_0 is to follow the approach described by Van den Driessche and Watmough (2002). In model system (2.6), we consider only the terms in which the infection is in progression, i.e e_h, i_h, e_v, i_v, e_m and i_m.

The corresponding equations can be re-written in the following way

$$x_i' = f_i(x) = \mathcal{F}_i(x) - (\mathcal{V}_i^-(x) - \mathcal{V}_i^+(x)), i = 1, ..., 6, \tag{2.8}$$

where $\mathcal{F}_i(x)$ represents the rate of appearance of new infections in compartment *i*, $\mathcal{V}_i^+(x)$ represents the rate of transfer of individuals into compartment *i* by all other means, other than the epidemic and $\mathcal{V}_i^-(x)$ represents the transfer of individuals out of the compartment *i*.

Hence, the following system is obtained:

$$\begin{aligned}
\frac{de_h}{dt} &= a\beta_1 s_h i_v - e_h(\delta_h + b_h + \sigma) + \alpha e_h i_h, \\
\frac{di_h}{dt} &= \delta_h e_h - i_h(\gamma + \alpha + b_h + \sigma) + \alpha i_h^2, \\
\frac{de_v}{dt} &= a\beta_2 s_v i_h + a\beta_3 s_v i_m - e_v(\delta_v + b_v), \\
\frac{di_v}{dt} &= \delta_v e_v - i_v b_v, \\
\frac{de_m}{dt} &= a\beta_4 s_m i_v - e_m(\delta_m + b_m), \\
\frac{di_m}{dt} &= \delta_m e_m - i_m b_m.
\end{aligned} \tag{2.9}$$

From (2.9), we derive $\mathcal{F}_i$ and $\mathcal{V}_i$ as

$$\mathcal{F}_i = \begin{bmatrix} a\beta_1 s_h i_v \\ 0 \\ a\beta_2 s_v i_h + a\beta_3 s_v i_m \\ 0 \\ a\beta_4 s_m i_v \\ 0 \end{bmatrix}, \tag{2.10}$$

and

$$\mathcal{V}_i = \begin{bmatrix} e_h(\delta_h + b_h + \sigma) - \alpha e_h i_h \\ i_h(\gamma + \alpha + b_h + \sigma) - \delta_h e_h - \alpha i_h^2 \\ e_v(\delta_v + b_v) \\ i_v b_v - \delta_v e_v \\ e_m(\delta_m + b_m) \\ i_m b_m - \delta_m e_m \end{bmatrix}. \tag{2.11}$$

Thus, to obtain R_0, we compute matrices F and V which are $m \times m$ matrices, where m represents the infected classes, defined by

$$F = \left[\frac{\partial \mathcal{F}_i}{\partial x_j}(E_0)\right],$$

and

$$V = \left[\frac{\partial \mathcal{V}_i}{\partial x_j}(E_0)\right] \quad with \quad 1 \leq i, j \leq m.$$

We then compute matrix FV^{-1}, defined as the next generation matrix (Diekmann et al., 1990). The R_0 is then defined as

$$R_0 = \rho(FV^{-1}), \tag{2.12}$$

where $\rho(FV^{-1})$ is the spectral radius of matrix FV^{-1}. Thus,

$$R_0 = \sqrt{\frac{a^2\beta_1\beta_2\delta_h\delta_v s_h^\circ}{(\delta_h + b_h + \sigma)(\gamma + \alpha + b_h + \sigma)b_v(\delta_v + b_v)} + \frac{a^2\beta_3\beta_4\delta_v\delta_m}{b_m(\delta_m + b_m)b_v(\delta_v + b_v)}}, \tag{2.13}$$

where $s_h^\circ = \dfrac{b_h + (1-\rho)\sigma + \omega}{\omega + \varepsilon + b_h + \sigma}$ from the first component of E_0 in (2.7).

In our model we have two hosts and one vector, and it is indicated in the model that the vector can transmit the infection to both the human host and the monkeys. Thus, for easy understanding, we can represent the reproduction number as,
$R_0 = \sqrt{R_h + R_m}$, such that,

$$R_h = \frac{(b_h + \sigma(1-\rho) + \omega)a^2\beta_1\beta_2\delta_h\delta_v}{(\omega + \varepsilon + b_h + \sigma)(\delta_h + b_h + \sigma)(\gamma + \alpha + b_h + \sigma)b_v(\delta_v + b_v)}, \tag{2.14}$$

which is the reproduction number of human host and vector compartments. It represents the infection from vector to human and human to vector. Again, we can represent it as $R_h = R_{vh} \times R_{hv}$. Thus,

$$R_{vh} = \frac{a\beta_1 s_h^o \delta_h}{(\gamma + \alpha + b_h + \sigma)(\delta_h + b_h + \sigma)},$$

for

$$s_h^o = \frac{(b_h + \sigma(1-\rho) + \omega)}{(\omega + \varepsilon + b_h + \sigma)}.$$

It represents the product between transmission probability of the infection from vector to human and the number of susceptible human host per vector. Also

$$R_{hv} = \frac{a\beta_2\delta_v}{(\delta_v + b_v)}.$$

This represents the product between transmission probability of the infection from human host to vector and the proportion of vectors that survive the incubation period. We also have,

$$R_m = \frac{a^2\beta_3\beta_4\delta_v\delta_m}{b_m(\delta_m + b_m)b_v(\delta_v + b_v)}, \tag{2.15}$$

as the reproduction number of monkeys to vector and vector to monkeys compartments. Again, it can be represented as $R_m = R_{mv} \times R_{vm}$ into which

$$R_{mv} = \frac{a\beta_3\delta_v}{b_v(\delta_v + b_v)},$$

represents the product between transmission probability of the infection from monkey to vector and the proportion of the vector that survive the incubation period.

$$R_{vm} = \frac{a\beta_4\delta_m}{b_m(\delta_m + b_m)},$$

represents the product between transmission probability of the infection from vector to monkey and the proportion of monkey that survive the incubation period.

2.3.2 Sensitivity Analysis of R_0

In order to determine how best to reduce mortality and morbidity due to YF infection, it is necessary to study the relative importance of different factors responsible for its transmission and prevalence (Chitnis et al., 2008). Thus, we perform sensitivity analysis of the basic reproduction number with respect to model parameters.

The sensitivity analysis will assist in curtailing the transmission of the disease by using appropriate control strategies. According to Hamby (1994) there are more ways of conducting sensitivity analysis, all resulting in a slightly different sensitivity ranking. Following the approaches of Okosun et al. (2011), Chitnis et al. (2008) and Pannell (1997), we use the normalized forward sensitivity index which is the backbone of nearly all other sensitivity analysis techniques and is computationally efficient.

Definition 2.2. The normalized forward sensitivity index of a variable, h, that depends differentiable on a parameter, l, is defined as:

$$\Upsilon_l^h = \frac{\partial h}{\partial l} \times \frac{l}{h} \tag{2.16}$$

The definition, tells us that the sensitivity index measures the relative change in variable h for a small relative change in the parameter l. A negative sensitivity index means that an increase in the value of the parameter l would lead to a decrease in the value of the variable h, and on the other hand, a positive sensitivity index means that an increase in the parameter value l would lead to an increase in the value of the variable h.

We therefore evaluate the sensitivity indices of R_0 at the baseline parameter values given in Table 2.2 to each of the seventeen parameters described in Table 2.1 using Maple software. The sensitivity index of R_0 with respect to a, for example is,

$$\Upsilon_a^{R_0} = \frac{\partial R_0}{\partial a} \times \frac{a}{R_0} = 1 \tag{2.17}$$

The detailed sensitivity indices of R_0, resulting from the evaluation to the seventeen different parameters of the model are shown in Table 2.2.

By analyzing the sensitivity indices we observe that, the most sensitive parameter is the mosquito biting rate, a. Other important parameters include the probability of disease transmission from infectious mosquitoes to susceptible humans, β_1, progression rate of exposed vector, δ_v, progression rate of exposed human, δ_h, human to mosquito disease transmission probability, β_2, mosquitoes birth rate, b_v and human host birth rate, b_h.

From the most sensitive parameters, the reproductive number, R_0 is directly related to the biting rate of mosquito, transmission probabilities of vector to human as well as the progression rate of exposed vector and exposed human and inversely related to birth rate of vector and human.

Table 2.2: Sensitivity indices of model parameters to R_0

Parameter	Description	Sensitivity index
a	Mosquito daily bitting rate	1
δ_v	Progression rate of exposed vector	0.49992
β_1	Transmission probability of vector to human	0.49947
β_2	Transmission probability of human to vector	0.49946
δ_h	Progression rate of exposed human	0.49128
β_3	Transmission probability of primate to vector	0.00054
β_4	Transmission probability of vector to primate	0.00053
δ_m	Progression rate of exposed primate	0.00053
ω	rate of relapse of vaccinated and recovered human	0.00014
b_v	Birth rate of vector	-0.99992
b_h	Birth rate of human	-0.75118
b_m	Birth rate of primates	-0.00107
α	Death rate due to disease for human	-0.13028
σ	arrival rate of immigrant per individual per time	-0.00024
γ	Recovery rate	-0.00183
ε	vaccination rate of susceptible human	-0.00065
ρ	proportion of immigrant who are vaccinated	-0.0000023

Since $\Upsilon_a^{R_0} = 1$ increasing (or decreasing) a by 10% increases (or decreases) R_0 by 10%. In the same way, increasing (or decreasing) δ_v, β_1 and β_2 by 10% increases (or decreases) R_0 by 5%. Similarly, increasing (or decreasing) b_v by 10% decreases (or increases) R_0 by 20%.

Reducing the number of contacts between humans and mosquitoes, through a reduction in either or both, the probability (frequency) of transmitting the infection, and the daily mosquitoes biting rate, would have the largest effect on disease transmission. Also, as the latent period of vector is about the same as the lifespan of mosquitoes, controlling the birth rate of vectors and decreasing the lifespan of the mosquitoes reduces the basic reproductive number because more infected mosquitoes will die before they become infectious (Okosun et al., 2011; Chitnis et al., 2008).

This suggests that strategies that can be applied in controlling the disease transmission are to target the mosquito biting rate and death rate such as the use of mosquito treated bed-nets, insect repellents, indoor residual spraying, insecticides and larvacides.

2.4 Numerical Results and Discussions

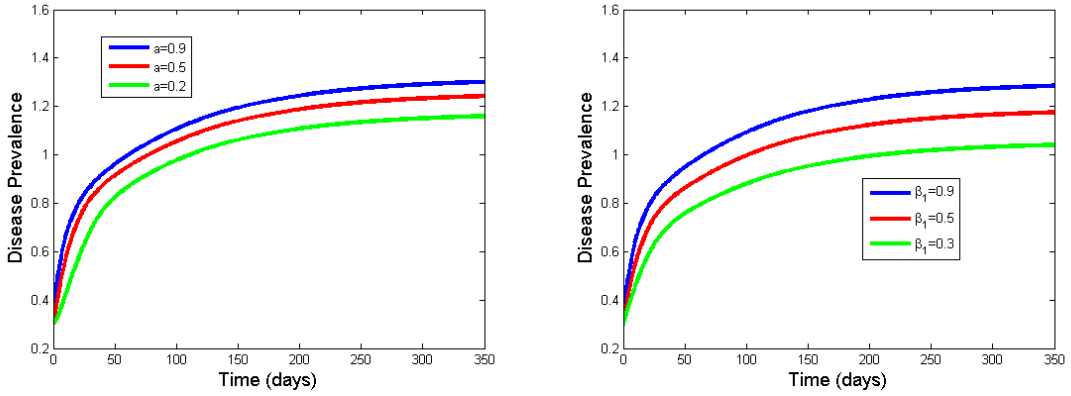
In this section we presented some numerical results for the model. The values of parameters are given in Table 2.3. Most of these values are according to the *A. aegypti* mosquitoes in vector borne diseases reported in the literature.

Table 2.3: Description of parameter values of model system (2.6)

Parameter	Range of values	Source
β_1	[0.5-0.9]	Bowman (2012); Amaku et al. (2011), Dumont et al. (2008)
β_2	[0.37-0.9]	Rodrigues et al. (2013); Bowman (2012), Nishiura (2006)
β_3	[0.5]	assumed
β_4	[0.9]	assumed
δ_h	[0.05-1] day^{-1}	Bowman (2012); Garba et al. (2008), Esteva and Vargas (1998)
δ_v	[0.02-1] day^{-1}	Bowman (2012); Amaku et al. (2011), Garba et al. (2008)
δ_m	[0.85-1] day^{-1}	assumed
b_h	[0.003] day^{-1}	Esteva and Vargas (1998)
b_v	[0.01] day^{-1}	Esteva and Vargas (1998), Coutinhoa et al. (2006)
b_m	[0.04] day^{-1}	assumed
a	[0.5-1]	Bowman (2012); Amaku et al. (2011), Dumont et al. (2008)
γ	[0.05-0.1] day^{-1}	Pinho et al. (2010); Codeço et al. (2007),
α	[10^{-3}]	Garba et al. (2008)
ω	[0.05] day^{-1}	Garba et al. (2008)
ε	[0.005]	assumed
ρ	[0.02]	Rodrigues et al. (2013)
σ	[0.009]	assumed

At first we investigate the effects of the threshold parameter, that is the basic reproductive number, R_0, governing the dynamics of populations and the proportion of individuals in each class. We have seen earlier, that R_0 obtained was expressed in the form of $R_0^2 = R_h + R_m$, this is because in our model, we have three different populations: human host, monkeys and vector. So the expected basic reproduction number reflects the infection between vector-human

and human-vector as well as monkey-vector and vector-monkey respectively since the vector is capable of transmitting the infection to both, human hosts and monkeys. This result is similar with Barrett and Higgs (2007) who argue that a key feature of YFV is the high viremia in primates (monkeys) that is critical to the transmission of the virus by mosquito vectors.

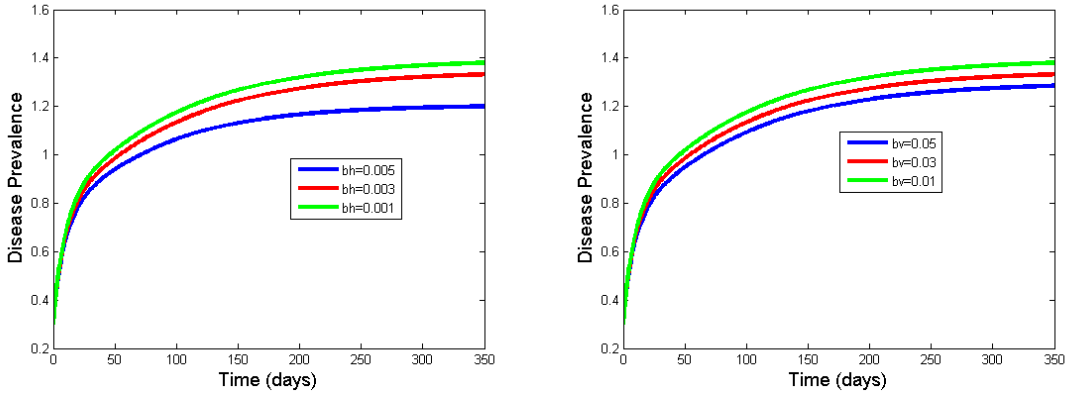


(a) (b)

Figure 2.2: Disease Prevalence with respect to variations of contact rate and transmission probability of vector to human.

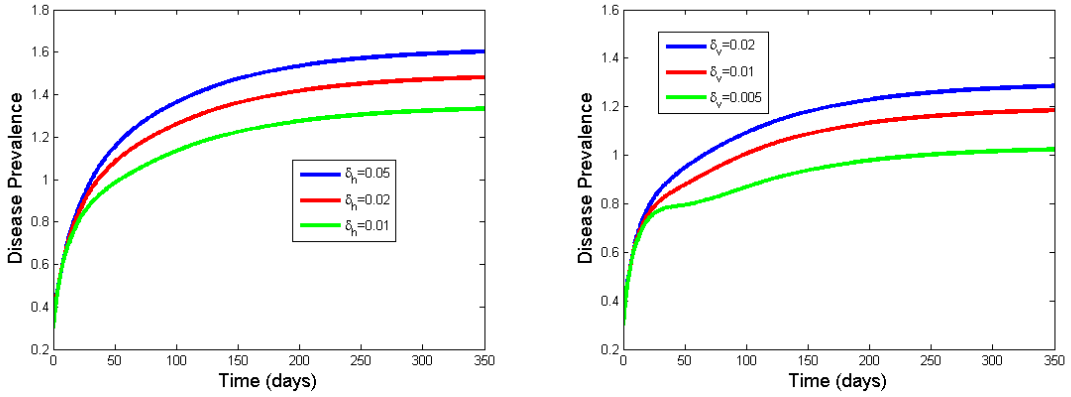
We now present numerical results with respect to the sensitive parameters to R_0, which are $a, \beta_1, b_v, b_h, \delta_v, \delta_h$ that affect disease prevalence (positively and negatively) based on sensitivity analysis and numerical results of the general YF model. Figure 2.2 shows that the disease prevalence increases with time as biting rate and transmission probability of vector to human increases.

From Figure 2.3, we see that the disease prevalence reduces as we increase the birth rates of vector and human populations respectively, as from sensitivity analysis these parameters have negative sensitivity index. Also, Figure 2.4 shows the increase in disease prevalence as progression rates from latent to infectious human and latent to infectious vector increases respectively.



(a) (b)

Figure 2.3: Disease Prevalence with respect to variations of birth rates of human b_h and vector b_v.

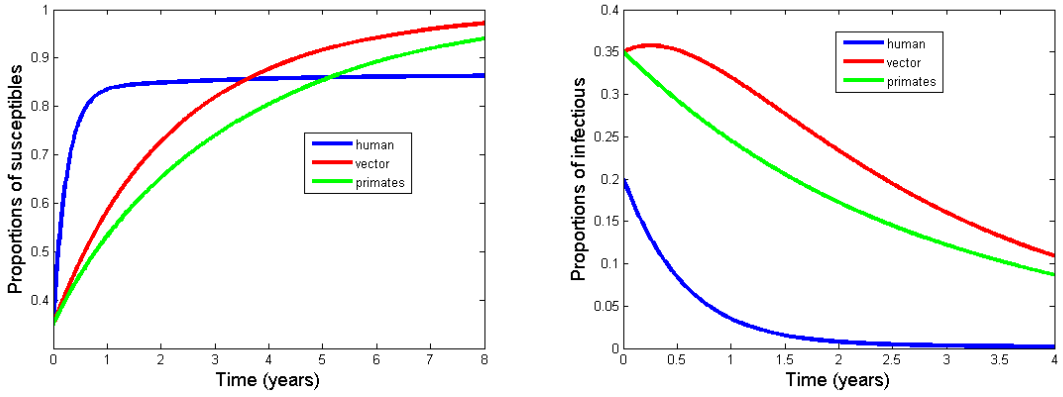


(a) (b)

Figure 2.4: Disease Prevalence with respect to variations of progression rates of human δ_h and vector δ_v.

Figure 2.5 indicates proportion of susceptible and infectious populations as they vary with time. In (a) the proportion of susceptible human increases up to value 0.86 and becomes constant. The value does not reach 1, because some of susceptible human populations are affected and might die due to disease as time goes. Proportion of susceptible vector and primates (monkeys) go on increasing to 1 as time goes, which shows that they are not affected as much as humans. Also in (b), we see that proportion of infectious human population, vectors and primates (monkeys)

decreasing with time indicating that the disease prevalence (after exposure) to human reduces to about zero in a years time, implying that it is possible to mitigate the infection in human population if we can have controls such as continuous vaccination to susceptible human population. These results are in conjecture with Ellis and Barrett (2008) who noted that without a vaccine-protected population, the disease will continue to emerge unpredictably and remain an imminent public health threat.

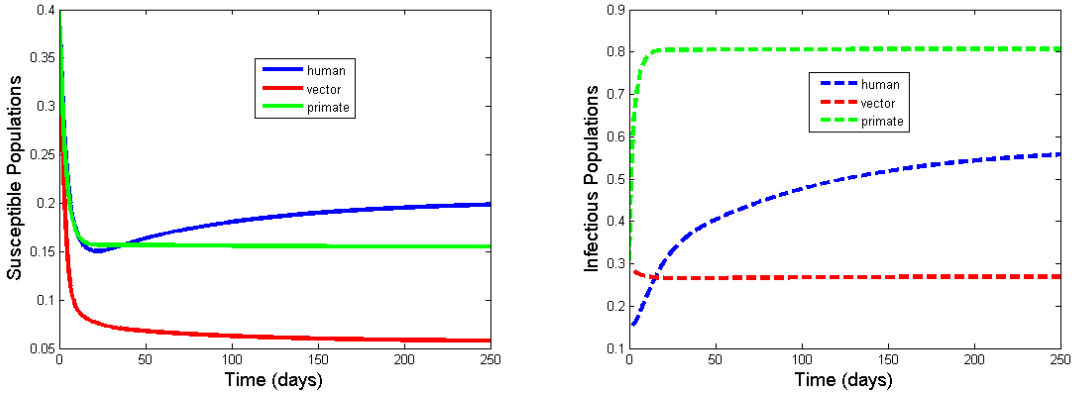


(a) (b)

Figure 2.5: Proportion of susceptible and infectious populations at DFE zone

Figure 2.6 (a) shows the proportion of susceptible human, vector and primates decreasing with time at initial stage as some are being exposed to the disease at endemic zone. However, proportion of susceptible vector seems to maintain the level of 0.02 after 150 days while proportion of susceptible primate (monkeys) decreases to 0.16 before maintaining this value for the whole time period. Proportion of susceptible human seems to decrease to 0.15 for the first 20 days then started to increase slowly up to 0.19 the time when this value becomes constant.

Figure 2.6 (b) shows proportion of infectious human, vector and primates (monkeys) increasing with time at endemic zone. Proportion of infectious human increases slowly to a value of 0.55 while proportion of infectious primates (monkeys) goes up to a value of 0.82. We see high increase in infectious monkeys as compared to infectious human. This is due to the vaccination



(a) (b)

Figure 2.6: Proportion of susceptible and infectious populations at EE zone.

taken to some human individuals as compared to monkeys, monkeys do not take vaccines for prevention and control.

2.5 Conclusion

A deterministic mathematical model for YF has been formulated using ordinary differential equations. The model considers two hosts (humans and monkeys) and one vector. The reproduction number, R_0, as a threshold of the epidemic is discussed through sensitivity analysis and simulation with different parameter values giving an illustration of the dynamics of the epidemic.

Results call for current options for prevention and control of parameters regarding to daily biting rate of mosquitoes, recruitment rate of vectors, incubation period for vectors and human hosts, probability of contact between susceptible humans and infectious vectors as well as the recruitment of human host which includes unvaccinated immigrants. Also, numerical results (Figure 2.5 b) revealed that in a year's time prevention of the disease is possible to human host but not possible to the monkeys (primates), this is because the YFV originates from the

monkey (primate) population as pointed out by Ellis and Barrett (2008), Rogers et al. (2006) among others. Also, Barrett and Higgs (2007) found that YFV is enzootic and as such cannot be eradicated, but a combination of mosquito control and vaccination is efficient in disease prevention. Again, an increase in the proportion of infected vector and biting rate of vector to human will contribute greatly to an increase in YF transmission dynamics.

However, human migration plays an important role in the transmission and spread of YF. They contribute to the sustainability of the YF epidemic either directly (infected immigrants) or indirectly (health immigrants susceptible to infection by locals). Thus, transmission factors must closely be monitored to ensure health and well being of everyone in the community. The result has been supported by other researchers in the literature like Gubler (2004), in his study titled the changing epidemiology of yellow fever and dengue, 1900 to 2003: full circle? He observed that increasing the movement of people and unprecedented population growth primarily in the urban centers of developing countries, has been a major driving force of YFV transmissions. Also Rogers et al. (2006) in his study titled the global distribution of YF and Dengue concluded that vector and disease spread to new regions seems almost inevitable, as are the consequences of co-circulation of different serotypes including unvaccinated people.

To provide further insights in planning and assessing the impact of current and future control strategies, numerous additions in the model will be required to help suggest the best mitigation strategy, for example thinking of vector control to minimize breeding of mosquito, personal protection which includes the use of mosquito repellents and treated bed-nets that can reduce the probability of contact between vectors and humans. Therefore, to ensure minimization of the outbreak human population should be educated regarding YF, its transmissions factors and control for early management of the epidemic.

CHAPTER THREE

Modelling and Stability Analysis of SVEIRS Yellow Fever Two Host Model [2]

Abstract: We describe transmission dynamics of yellow fever (YF) within two host populations, and build up a deterministic SVEIRS model with vaccination to the entire new born. The model aims at clarifying contributions of mathematical ideas in studying the impact of YF disease dynamics. We examine existence of equilibrium solutions and give out conditions that are sufficient for existence of realistic equilibria. Stability analysis of the equilibria is presented; trace-determinant approach is used in determining local stability of disease-free equilibrium (DFE) and Metzler matrix for global stability. Lyapunov function is used in establishing conditions for global stability of endemic equilibrium (EE). Our results suggests that eradication of the infection to human population is possible only if $R_{vm} < 1$ and $R_{hv} < 1$. Due to new births and immunity loss to YF after ten years, susceptible class will always be refilled and hence continuous vaccination is essential.

Keywords: Lyapunov function, Metzler matrix, stability analysis.

2010 **Mathematics Subject Classification: Primary** $46L55$**; Secondary** $44B20$.

3.1 Introduction

Yellow fever (YF) is a zoonotic arboviral disease with a long history of outbreaks in human populations (Staples and Monath, 2008). It is a viral hemorrhagic fever caused by yellow fever virus (YFV) and is transmitted through the bite of an infected female yellow fever mosquito, *Aedes aegypti* (Robertson et al., 1996).

YFV is endemic to tropical areas of Africa and South America where it is maintained in sylvatic or jungle cycles between non-human primates and tree-dwelling mosquitoes (Vainio and Cutts, 1998). Humans and primates are the principle reservoirs for the virus. Increasing migration, accelerating urbanization, and improved travel infrastructure are global trends that increase the risk of YF spreading to parts of the world where the disease had disappeared.

Liu et al. (2013) argued that, mathematical analysis and modelling operation of infectious diseases are critical to the studying of virus spreading dynamics which can state clearly the origination and evolution of viruses. Also, according to Tumwiine et al. (2007), mathematical modelling can help in figuring out decisions that are of significant importance and increase influence the theory and practice of disease management and control. They might provide comprehensive examinations that enter into decisions in a way that human reasoning and debate cannot.

Mathematical and epidemiological models have been developed in the literature to address vector-borne diseases transmission dynamics and control (Garske et al., 2014; Liu et al., 2013; Lashari et al., 2012; Johansson et al., 2010). Many of these models have a disease-free equilibrium (DFE) at which the population remains unaffected by the disease (absence of disease) Van den Driessche and Watmough (2002), and also most reasonable epidemic models, possess a positive endemic equilibria (EE).

These models usually have a threshold parameter known as the basic reproduction number, R_0, into which Heesterbeek (2000) defined it as the average number of secondary cases produced

by a 'typical' infected (assumed infectious) individual during his/her entire life as infectious (infectious period) when introduced in a population of susceptibles. This non-dimensional quantity cannot be computed explicitly in some cases because the mathematical description of what is a 'typical' infectious individual is difficult to quantify in populations with high degree of heterogeneity (Castillo-Chávez et al., 2002). Although R_0 can not be computed explicitly, its role on the study of stability of equilibria can still be determined.

Stability analysis of equilibria is one of the classical problems in mathematical epidemiology and different approaches have been proposed to the stability of the equilibria Mpeshe et al. (2014b), Kamgang and Sallet (2008). Some of the methods proposed in the literature for analysing the stability of equilibria includes trace-determinant approach of the Jacobian matrix of the model system evaluated at the DFE, Routh-Hurwitz criteria, Lyapunov techniques to obtain threshold conditions, stable Metzler matrices (Kamgang and Sallet, 2008), LaSalle's Invariance Principle, center manifold, Poincare' index and many more others.

Although there are many types of Lyapunov functions depending on the nature of the model, it is often difficult to construct such Lyapunov functions. A general form of Lyapunov functions used in the literature of mathematical biology is;

$$L(x_i) = \sum_{i=1}^{n} c_i \left(x_i - x_i^* - x_i^* ln \frac{x_i}{x_i^*} \right), \tag{3.1}$$

originally from the first integral of a Lotka-Volterra system Shuai and van den Driessche (2013). When applied to disease models, suitable coefficients c_i have to be determined such that the derivative of $L(x_i)$ along solutions of the model is non-positive, although determination becomes very challenging for models with high dimension.

According to Korobeinikov (2004a), Korobeinikov (2004b), Korobeinikov (2007), for models with relapse, that is SEIR and SEIS, the explicit Lyapunov function with the form

$$L = \sum a_i \ (x_i - x_i^* \ ln \ x_i), \tag{3.2}$$

is used.

In this chapter, we explore stability of equilibria of our SVEIRS (Susceptible, Vaccinated, Exposed, Infectious, Recovered, Susceptible) mathematical model of YF by Kung'aro et al. (2014) from chapter two.

3.2 Materials and Methods

3.2.1 Model Analysis

Recalling our disease-free equilibrium, (E_0), and basic reproduction number, (R_0), from chapter two by Kung'aro et al. (2014), we now analyse the Stability of E_0, and investigate existence and stability of disease endemic equilibrium (EE). E_0 is obtained by setting the derivatives with respect to time of the model system (2.6), equal to zero (refer chapter two). Thus, the following E_0 is obtained:

$$E_0 = \left(\frac{b_h + (1-\rho)\sigma + \omega}{\omega + \varepsilon + b_h + \sigma}, \ \frac{\rho\sigma + \varepsilon}{\omega + \varepsilon + b_h + \sigma}, \ 0, \ 0, \ 0, \ 1, \ 0, \ 0, \ 1, \ 0, \ 0 \right) \tag{3.3}$$

3.2.2 The Basic Reproduction Number, R_0

One of the most important concerns in the analysis of epidemiological models is the determination of the asymptotic behaviour of their solutions which is usually based on the stability of the associated equilibria (Moghadas, 2004). Calculation from chapter two shows a threshold

parameter of the form $R_0^2 = R_{hv} + R_{vm}$ or $R_0 = \sqrt{R_{hv} + R_{vm}}$, such that;

$$R_{hv} = \frac{(b_h + \sigma(1-\rho) + \omega)a^2\beta_1\beta_2\delta_h\delta_v}{(\omega + \varepsilon + b_h + \sigma)(\delta_h + b_h + \sigma)(\gamma + \alpha + b_h + \sigma)b_v(\delta_v + b_v)} \tag{3.4}$$

which is the reproduction number of human-vector compartments and represents the infection from vector to human and human to vector. And,

$$R_{mv} = \frac{a^2\beta_3\beta_4\delta_v\delta_m}{b_m(\delta_m + b_m)b_v(\delta_v + b_v)} \tag{3.5}$$

as the reproduction number of monkey-vector compartments. It represents the infection from monkey to vector and vector to monkey. In compact form, the following R_0 was obtained.

$$R_0 = \sqrt{\frac{a^2\beta_1\beta_2\delta_h\delta_v s_h^\circ}{(\delta_h + b_h + \sigma)(\gamma + \alpha + b_h + \sigma)b_v(\delta_v + b_v)} + \frac{a^2\beta_3\beta_4\delta_v\delta_m}{b_m(\delta_m + b_m)b_v(\delta_v + b_v)}} \tag{3.6}$$

where $s_h^\circ = \dfrac{b_h + (1-\rho)\sigma + \omega}{\omega + \varepsilon + b_h + \sigma}$ from the first component of E_0 in (3.3) (Kung'aro et al., 2014).

3.2.3 Stability Analysis of E_0

We determine condition under which the equilibrium points are asymptotically stable or unstable. Asymptotic stability implies that a solution starts close to the equilibrium, remains close to the equilibrium and approaches the equilibrium over time $0 \leq t < \infty$, while instability of the equilibrium implies that there are solutions starting arbitrary close to the equilibrium, but they do not approach it over indefinite time. However, if nearby initial conditions of a fixed point remain close to that point over a positive time, then the fixed point is said to be locally stable and if it remains close over indefinite time, it is said to be globally stable.

Local Stability Analysis

The local stability of the disease-free equilibrium is determined based on a threshold parameter, known as the basic reproductive number, R_0. To establish local stability of this equilibrium, the Jacobian of the model system (2.6) is computed and evaluated at E_0. The local stability of E_0 is then determined based on the trace-determinant approach of this Jacobian. The disease-free equilibrium point, E_0, is locally stable if trace of the Jacobian matrix is less than zero and determinant of the same matrix is greater than zero.

Thus, by letting the functions $(f_1, f_2, ..., f_{11})$, to represent the right hand sides of the model equations (2.6), at steady state the Jacobian of (2.6) is given by:

$$J_i = \frac{\partial f_i}{\partial x_j}, \tag{3.7}$$

where,

f_i , $i = 1, 2, ..., 11.$ and $x_j (j = 1, 2, ..., 11)$ represent $s_h,\ v_h,\ e_h,\ i_h,\ r_h,\ s_v,$ $e_v,\ i_v,\ s_m,\ e_m,\ i_m$, respectively. The following matrix is obtained;

$$J_{E_0} = \begin{bmatrix} -b_1 & \omega & 0 & \alpha s_h^\circ & \omega & 0 & 0 & -\eta & 0 & 0 & 0 \\ \varepsilon & -b_2 & 0 & \alpha v_h^o & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -b_3 & 0 & 0 & 0 & 0 & \eta & 0 & 0 & 0 \\ 0 & 0 & \delta_h & -b_4 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \gamma & -b_5 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -b_v & 0 & 0 & 0 & 0 & -a\beta_3 \\ 0 & 0 & 0 & 0 & 0 & 0 & -b_7 & 0 & 0 & 0 & a\beta_3 \\ 0 & 0 & 0 & 0 & 0 & 0 & \delta_v & -b_v & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -a\beta_4 & -b_m & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & a\beta_4 & 0 & -b_{10} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \delta_m & -b_m \end{bmatrix}, \tag{3.8}$$

note that, $b_1 = (\varepsilon + b_h + \sigma),\ b_2 = (\omega + b_h + \sigma),\ b_3 = (\delta_h + b_h + \sigma), \eta = a\beta_1 s_h^\circ,$ $b_4 = (\alpha + \gamma + b_h + \sigma),\ b_5 = (\omega + b_h + \sigma),\ b_7 = (\delta_v + b_v),\ b_{10} = (\delta_m + b_m).$

As seen from (3.8) trace of $J_{E_0} < 0$. Also, by reducing the dimensions of matrix J_{E_0} and calculation, we obtain sub-matrix

$$M = (b_v b_m) \begin{bmatrix} -b_1 & \omega & 0 & \alpha s_h^\circ & \omega & 0 & -\eta & 0 & 0 \\ \varepsilon & -b_2 & 0 & \alpha v_h^o & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -b_3 & 0 & 0 & 0 & \eta & 0 & 0 \\ 0 & 0 & \delta_h & -b_4 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \gamma & -b_5 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -b_7 & 0 & a\beta_3 \\ 0 & 0 & 0 & 0 & 0 & \delta_v & -b_v & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & a\beta_4 & -b_{10} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \delta_m & -b_m \end{bmatrix}. \tag{3.9}$$

Determinant of M is given by

$$det\ M = B[b_v(\delta_v + b_v)b_m(\delta_m + b_m) - a^2\beta_3\beta_4\delta_v\delta_m)], \tag{3.10}$$

where $B = b_v b_m(b_1 b_2 - \varepsilon\omega)(b_5 b_4 b_3)$. Further simplification leads to

$$det\ M = B\left[1 - R_{mv}\right] b_v(\delta_v + b_v)b_m(\delta_m + b_m). \tag{3.11}$$

For $det\ M$ to be > 0 we should have $R_{mv} < 1$ which leads to the following theorem.

Theorem 3.3. *The disease-free equilibrium point E_0 of model system (2.6) is locally asymptotically stable if $R_{mv} < 1$ and unstable if $R_{mv} > 1$.*

The epidemiological implication of Theorem 3.3 is that the YF infection can be mitigated from the community (when $R_{mv} < 1$), that is, if the initial sizes of the sub-population of the model system (2.6) are in basin of attraction of the DFE, E_0. The threshold quantity, R_0, represents the average number of secondary infections that one infected individual (or infected vector) can generate if introduced into a completely-susceptible population.

Global Stability Analysis

We address the issue of global asymptotic stability of the disease-free equilibrium, and give a sufficient condition for the global asymptotic stability for the DFE of YF. For some systems we can show that the global asymptotic stability (GAS) of the DFE is equivalent to $R_0 \leq 1$. Thus we can state the following theorem;

Theorem 3.4. *The DFE, E_0 of the YF model system given by (2.6) is globally asymptotically stable (GAS) if $R_0 \leq 1$.*

Proof. To prove the theorem, we will use the equations of the normalised model system (2.6) and approach by Kamgang and Sallet (2008) and Dumont et al. (2008), it is possible to rewrite (2.6) in the following manner;

$$\begin{cases} \dfrac{dX_s}{dt} = A_1(x)(X_s - X_{DFE,s}) + A_3(x)X_i \\ \dfrac{dX_i}{dt} = A_2(x)X_i \end{cases} \tag{3.12}$$

where X_s is the vector representing the state of different compartments of non-transmitting individuals (e.g. susceptible, vaccinated, immune) and the vector X_i represents the state of compartments of different transmitting individuals (e.g. exposed, infected). Here, we have

$$X_s = (s_h, v_h, r_h, s_v, s_m)^T, X_i = (e_h, i_h, e_v, i_v, e_m, i_m)^T, \tag{3.13}$$

and

$$X_{DFE,s} = (n_h, 0, s_v, s_m). \tag{3.14}$$

with

$$A_1(x) = \begin{bmatrix} -(\varepsilon + b_h + \sigma) & \omega & \omega & 0 & 0 \\ \varepsilon & -(\omega + b_h + \sigma) & 0 & 0 & 0 \\ 0 & 0 & -(\omega + b_h + \sigma) & 0 & 0 \\ 0 & 0 & 0 & -b_v & 0 \\ 0 & 0 & 0 & 0 & -b_m \end{bmatrix}, \tag{3.15}$$

$$A_3(x) = \begin{bmatrix} 0 & \alpha s_h & 0 & -a\beta_1 s_h & 0 & 0 \\ 0 & \alpha v_h & 0 & 0 & 0 & 0 \\ 0 & \gamma & 0 & 0 & 0 & 0 \\ 0 & -a\beta_2 s_v & 0 & 0 & 0 & a\beta_3 s_v \\ 0 & 0 & 0 & -a\beta_4 s_m & 0 & 0 \end{bmatrix}, \tag{3.16}$$

and

$$A_2(x) = \begin{bmatrix} -k_1 & 0 & 0 & a\beta_1 s_h & 0 & 0 \\ \delta_h & -k_2 & 0 & 0 & 0 & 0 \\ 0 & a\beta_2 s_v & -(\delta_v + b_v) & 0 & 0 & a\beta_3 s_v \\ 0 & 0 & \delta_v & -bv & 0 & 0 \\ 0 & 0 & 0 & a\beta_4 s_m & -(\delta_m + b_m) & 0 \\ 0 & 0 & 0 & 0 & \delta_m & -b_m \end{bmatrix}, \tag{3.17}$$

where $k_1 = \delta_h + b_h + \sigma$ and $k_2 = \alpha + \gamma + b_h + \sigma$. A direct computation shows that the eigenvalues of $A_1(x)$ are real and negative. Thus, the system

$$\frac{dX_s}{dt} = A_1(x)(X_s - X_{DFE,s}) + A_3(x)X_i, \tag{3.18}$$

is globally asymptotically stable at X_{DFE}. □

To check the stability of system $A_2(x)$, we are going to employ the idea of stable Metzler matrix and use the **lemma** by Kamgang and Sallet (2008) and Dumont et al. (2008). A Metzler matrix A is a matrix such that $A(i,j) > 0$, for any indices $i \neq j$ (Jacquez and Simon, 1993; Berman and Plemmons, 1979). These matrices are also called quasi-positive matrices or matrices whose off diagonal elements are non-negative.

Lemma 3.5. *Let Z be a square Metzler matrix written in block form*

$$Z = \begin{pmatrix} P & Q \\ R & S \end{pmatrix}$$

P and S are square matrices. Z is Metzler stable if and only if the matrices P and $S - RP^{-1}Q$ are Metzler stable.

Proof. Comparing our matrix $A_2(x)$ and a square Metzler matrix Z, we have matrices P, Q, R and S defined as;

$$P = \begin{bmatrix} -(\delta_h + b_h + \sigma) & 0 & 0 \\ \delta_h & -(\alpha + \gamma + b_h + \sigma) & 0 \\ 0 & a\beta_2 & -(\delta_v + b_v) \end{bmatrix}, \tag{3.19}$$

$$Q = \begin{bmatrix} a\beta_1 s_h^\circ & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & a\beta_2 \end{bmatrix}, R = \begin{bmatrix} 0 & 0 & \delta_v \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}, S = \begin{bmatrix} -bv & 0 & 0 \\ a\beta_4 & -(\delta_m + b_m) & 0 \\ 0 & \delta_m & -b_m \end{bmatrix}.$$

Clearly, P is a stable Metzler matrix.

Then, after some computations we obtain

$$S - RP^{-1}Q = \begin{bmatrix} k_3 & 0 & \frac{\delta_v a\beta_2}{\delta_v + b_v} \\ a\beta_4 & -(\delta_m + b_m) & 0 \\ 0 & \delta_m & -b_m \end{bmatrix}, \tag{3.20}$$

where $k_3 = -b_v + \dfrac{\delta_v \delta_h a^2 \beta_1 \beta_2 s_h^\circ}{(\delta_h + b_h + \sigma)(\alpha + \gamma + b_h + \sigma)(\delta_v + b_v)}$.

Thus, $(S - RP^{-1}Q)$ is Metzler stable iff

$$-b_v + \frac{\delta_v \delta_h a^2 \beta_1 \beta_2 s_h^\circ}{(\delta_h + b_h + \sigma)(\alpha + \gamma + b_h + \sigma)(\delta_v + b_v)} < 0. \tag{3.21}$$

that is,

$$\frac{\delta_v \delta_h a^2 \beta_1 \beta_2 s_h^\circ}{(\delta_h + b_h + \sigma)(\alpha + \gamma + b_h + \sigma)(\delta_v + b_v)} < b_v,$$

and so,

$$\frac{\delta_v \delta_h a^2 \beta_1 \beta_2 s_h^\circ}{(\delta_h + b_h + \sigma)(\alpha + \gamma + b_h + \sigma) b_v (\delta_v + b_v)} < 1, \tag{3.22}$$

$$\implies R_{hv} < 1.$$

Thus, the DFE, E_0 is globally asymptotically stable if $R_{hv} < 1$ and unstable if $R_{hv} > 1$. □

Thus, if the number of human new infections is greater than one, then the disease will persist. Alternatively, if the number of human new infections is less than one, then the disease will die

out. Essentially, we need to find ways of making sure that the number of newly human infected does not exceed one.

3.2.4 Endemic Equilibrium (EE) Point

In the presence of infection in the population, the model system (2.6) has an equilibrium point called disease endemic equilibrium point denoted by P^*. P^* as the endemic equilibrium denotes the fraction of the population that is infected at an infinite time in the future and is given by;

$P^* = (s_h^*, v_h^*, e_h^*, i_h^*, r_h^*, s_v^*, e_v^*, i_v^*, s_m^*, e_m^*, i_m^*)$.

Thus using model system (2.6), we can express each variable in terms of the other in endemic equilibrium as follows;

$$s_h^* = \frac{b_h + (1-\rho)\sigma + \omega(v_h^* + r_h^*)}{a\beta_1 i_v^* + (\varepsilon + b_h + \sigma) - \alpha i_h^*}, \qquad v_h^* = \frac{\rho\sigma + \varepsilon s_h^*}{(\omega + b_h + \sigma) - \alpha i_h^*},$$

$$e_h^* = \frac{a\beta_1 s_h^* i_v^*}{(\delta_h + b_h + \sigma) - \alpha i_h^*}, \qquad i_h^* = \frac{\delta_h e_h^*}{(\alpha + \gamma + b_h + \sigma) - \alpha i_h^*},$$

$$r_h^* = \frac{\gamma i_h^*}{(\omega + b_h + \sigma) - \alpha i_h^*}, \qquad s_v^* = \frac{b_v}{(a\beta_2 i_h^* + a\beta_3 i_m^*) + b_v},$$

$$e_v^* = \frac{(a\beta_2 s_v^* i_h^* + a\beta_3 s_v^* i_m^*)}{(\delta_v + b_v)}, \qquad i_v^* = \frac{\delta_v e_v^*}{b_v},$$

$$s_m^* = \frac{b_m}{(a\beta_4 i_v^* + b_m)}, \qquad e_m^* = \frac{(a\beta_4 s_m^* i_v^*)}{(\delta_m + b_m)}, \qquad i_m^* = \frac{\delta_m e_m^*}{b_m}.$$

3.2.5 Stability Analysis of EE

Since the DFE is locally asymptotically stable in Φ, this suggests the local stability of the EE for the reverse condition (Van den Driessche and Watmough, 2002). Hence, we only need to investigate the global stability of the EE. Thus, the crucial question of whether the long-term

disease dynamics approaches an equilibrium and how this depends on the initial size of the infection, need to be answered.

As Tian and Wang (2011) pointed out that the study of global stability of EE is not only mathematically important, but also essential in predicting the evolution of the disease in the long run so that prevention and intervention strategies can be effectively designed, and public health administrative efforts can be properly scaled.

3.3 Global stability of EE

We explore the global stability of the EE through construction of a suitable Lyapunov function using the approach by McCluskey (2006), Korobeinikov (2004a), Fall et al. (2007), Mpeshe et al. (2011) and Ullah et al. (2013). In this approach we construct Lyapunov function basing on the following form:

$$L = \sum a_i \, (x_i - x_i^* \, ln \, x_i), \tag{3.23}$$

where a_i is the constant selected properly, that is $a_i > 0$, x_i is the population of the i^{th} compartment and x_i^* is the equilibrium point, and for this case, it is an endemic equilibrium. The approach has been found to be useful for SEIR compartmental epidemic models regardless number of compartments (Korobeinikov, 2004a).

Thus, consider the Lyapunov function

$$\begin{aligned} L = {} & a_1 \, (s_h - s_h^* \, ln \, s_h) + a_2 \, (v_h - v_h^* \, ln \, v_h) + a_3 \, (e_h - e_h^* \, ln \, e_h) \\ & + a_4 \, (i_h - i_h^* \, ln \, i_h) + a_5 \, (r_h - r_h^* \, ln \, r_h) + a_6 \, (s_v - e_v^* \, ln \, e_v) \\ & + a_7 \, (e_v - e_v^* \, ln \, e_v) + a_8 \, (i_h - i_h^* \, ln \, i_h) + a_9 \, (s_m - s_m^* \, ln \, s_m) \\ & + a_{10} \, (e_m - e_m^* \, ln \, e_m) + a_{11} \, (i_m - i_m^* \, ln \, i_m), \end{aligned} \tag{3.24}$$

where $a_i > 0$ for $i = 1, 2, ...11$.

Analysing in three different compartments for human, vector and primate respectively we have;

$$\begin{aligned} L_h(s_h, v_h, e_h, i_h, r_h) = a_1 \left(s_h - s_h^* \, ln \, s_h\right) + a_2 \left(v_h - v_h^* \, ln \, v_h\right) \\ + a_3 \left(e_h - e_h^* \, ln \, e_h\right) + a_4 \left(i_h - i_h^* \, ln \, i_h\right) \\ + a_5 \left(r_h - r_h^* \, ln \, r_h\right). \end{aligned} \tag{3.25}$$

Differentiating (3.25) with respect to time we get

$$\begin{aligned} \frac{dL_h}{dt} &= a_1 \left[1 - \frac{s_h^*}{s_h}\right] \frac{ds_h}{dt} + a_2 \left[1 - \frac{v_h^*}{v_h}\right] \frac{dv_h}{dt} + a_3 \left[1 - \frac{e_h^*}{e_h}\right] \frac{de_h}{dt} \\ &\quad + a_4 \left[1 - \frac{i_h^*}{i_h}\right] \frac{di_h}{dt} + a_5 \left[1 - \frac{r_h^*}{r_h}\right] \frac{dr_h}{dt}, \\ &= a_1 \left(1 - \frac{s_h^*}{s_h}\right) \left[b_h + \sigma(1-\rho) + \omega v_h + \omega r_h - a\beta_1 s_h i_v - s_h(\varepsilon + b_h + \sigma) + \alpha s_h i_h\right] \\ &\quad + a_2 \left(1 - \frac{v_h^*}{v_h}\right) \left[\rho\sigma + \varepsilon s_h - v_h(\omega + b_h + \sigma) + \alpha v_h i_h\right] \\ &\quad + a_3 \left(1 - \frac{e_h^*}{e_h}\right) \left[a\beta_1 s_h i_v - e_h(\delta_h + b_h + \sigma) + \alpha e_h i_h\right] \\ &\quad + a_4 \left(1 - \frac{i_h^*}{i_h}\right) \left[\delta_h e_h - i_h(\gamma + \alpha + b_h + \sigma) + \alpha i_h^2\right] \\ &\quad + a_5 \left(1 - \frac{r_h^*}{r_h}\right) \left[\gamma i_h - r_h(\omega + b_h + \sigma) + \alpha r_h i_h\right]. \end{aligned}$$

At endemic equilibrium point (P^*), we have

$$\begin{aligned}\frac{dL_h}{dt} = a_1\left(1-\frac{s_h^*}{s_h}\right)\Bigg[&(a\beta_1 i_v^* + \varepsilon + b_h + \sigma)s_h^* - \omega(v_h^* + r_h^*) - \alpha s_h^* i_h^* \\ &+ \omega(v_h + r_h) - a\beta_1 s_h i_v - s_h(\varepsilon + b_h + \sigma) + \alpha s_h i_h\Bigg] \\ &+ a_2\left(1-\frac{v_h^*}{v_h}\right)\Bigg[v_h^*(\omega + b_h + \sigma) - \varepsilon s_h^* - \alpha v_h^* i_h^* \\ &+ \varepsilon s_h - v_h(\omega + b_h + \sigma) + \alpha v_h i_h\Bigg] \\ &+ a_3\left(1-\frac{e_h^*}{e_h}\right)\left[a\beta_1 s_h i_v - e_h\left(\frac{a\beta_1 s_h^* i_v^* + \alpha e_h^* i_h^*}{e_h^*}\right) + \alpha e_h i_h\right] \\ &+ a_4\left(1-\frac{i_h^*}{i_h}\right)\left[\delta_h e_h - i_h\left(\frac{\delta_h e_h^* + \alpha i_h^{*2}}{i_h^*}\right) + \alpha i_h^2\right] \\ &+ a_5\left(1-\frac{r_h^*}{r_h}\right)\left[\gamma i_h - r_h\left(\frac{\gamma i_h^* + \alpha r_h^* i_h^*}{r_h^*}\right) + \alpha r_h i_h\right].\end{aligned}$$

Further simplification yields

$$\begin{aligned}\frac{dL_h}{dt} = &-a_1\Big(\varepsilon + b_h + \sigma\Big)s_h\left(1-\frac{s_h^*}{s_h}\right)^2 - a_1\left(1-\frac{s_h^*}{s_h}\right)\left[a\beta_1 s_h i_v\left(1-\frac{i_v^* s_h^*}{i_v s_h}\right)\right. \\ &\left. - \alpha s_h i_h\left(1-\frac{i_h^* s_h^*}{i_h s_h}\right) - \omega v_h\left(1-\frac{v_h^*}{v_h}\right) - \omega r_h\left(1-\frac{r_h^*}{r_h}\right)\right] \\ &- a_2\Big(\omega + b_h + \sigma\Big)v_h\left(1-\frac{v_h^*}{v_h}\right)^2 - a_2\left(1-\frac{v_h^*}{v_h}\right)\left[\varepsilon s_h^*\left(1-\frac{s_h}{s_h^*}\right)\right. \\ &\left. + \alpha v_h^* i_h^*\left(1-\frac{v_h i_h}{v_h^* i_h^*}\right)\right] \\ &\frac{-a_3}{e_h^*}\left(1-\frac{e_h^*}{e_h}\right)\left[a\beta_1 s_h^* e_h i_v^*\left(1-\frac{s_h i_v e_h^*}{s_h^* i_v^* e_h}\right) - \alpha e_h i_h e_h^*\left(1-\frac{i_h^*}{i_h}\right)\right] \\ &\frac{-a_4}{i_h^*}\left(1-\frac{i_h^*}{i_h}\right)\left[\delta_h e_h^* i_h\left(1-\frac{e_h i_h^*}{e_h^* i_h}\right) - \alpha i_h^* i_h^2\left(1-\frac{i_h^*}{i_h}\right)\right] \\ &\frac{-a_5}{r_h^*}\left(1-\frac{r_h^*}{r_h}\right)\left[r_h\gamma i_h^*\left(1-\frac{i_h r_h^*}{i_h^* r_h}\right) - \alpha r_h i_h r_h^*\left(1-\frac{i_h^*}{i_h}\right)\right],\end{aligned}$$

which can also be written as

$$\frac{dL_h}{dt} = -a_1\bigg(\varepsilon + b_h + \sigma\bigg)s_h\bigg(1 - \frac{s_h^*}{s_h}\bigg)^2 - a_2\bigg(\omega + b_h + \sigma\bigg)v_h\bigg(1 - \frac{v_h^*}{v_h}\bigg)^2 + F_h(s_h, v_h, e_h, i_h, r_h),$$

(3.26)

where

$$\begin{aligned} F_h = &-a_1\bigg(1 - \frac{s_h^*}{s_h}\bigg)\bigg[a\beta_1 s_h i_v\bigg(1 - \frac{i_v^* s_h^*}{i_v s_h}\bigg) - \alpha s_h i_h\bigg(1 - \frac{i_h^* s_h^*}{i_h s_h}\bigg) \\ &- \omega v_h\bigg(1 - \frac{v_h^*}{v_h}\bigg) - \omega r_h\bigg(1 - \frac{r_h^*}{r_h}\bigg)\bigg] \\ &- a_2\bigg(1 - \frac{v_h^*}{v_h}\bigg)\bigg[\varepsilon s_h^*\bigg(1 - \frac{s_h}{s_h^*}\bigg) + \alpha v_h^* i_h^*\bigg(1 - \frac{v_h i_h}{v_h^* i_h^*}\bigg)\bigg] \\ &\frac{-a_3}{e_h^*}\bigg(1 - \frac{e_h^*}{e_h}\bigg)\bigg[a\beta_1 s_h^* e_h i_v^*\bigg(1 - \frac{s_h i_v e_h^*}{s_h^* i_v^* e_h}\bigg) - \alpha e_h i_h e_h^*\bigg(1 - \frac{i_h^*}{i_h}\bigg)\bigg] \\ &\frac{-a_4}{i_h^*}\bigg(1 - \frac{i_h^*}{i_h}\bigg)\bigg[\delta_h e_h^* i_h\bigg(1 - \frac{e_h i_h^*}{e_h^* i_h}\bigg) - \alpha i_h^* i_h^2\bigg(1 - \frac{i_h^*}{i_h}\bigg)\bigg] \\ &\frac{-a_5}{r_h^*}\bigg(1 - \frac{r_h^*}{r_h}\bigg)\bigg[r_h\gamma i_h^*\bigg(1 - \frac{i_h r_h^*}{i_h^* r_h}\bigg) - \alpha r_h i_h r_h^*\bigg(1 - \frac{i_h^*}{i_h}\bigg)\bigg]. \end{aligned}$$

(3.27)

Again by differentiating the Lyapunov function of vector and monkey populations, we can show their analysis respectively as

$$L_v(s_v, e_v, i_v) = a_6\ (s_v - s_v^*\ ln\ s_v) + a_7\ (e_v - e_v^*\ ln\ e_v) + a_8\ (i_v - i_v^*\ ln\ i_v), \tag{3.28}$$

into which time derivative of L_v yields

$$\begin{aligned}\frac{dL_v}{dt} &= a_6\left[1-\frac{s_v^*}{s_v}\right]\frac{ds_v}{dt} + a_7\left[1-\frac{e_v^*}{e_v}\right]\frac{de_v}{dt} + a_8\left[1-\frac{i_v^*}{i_v}\right]\frac{di_v}{dt}\\ &= a_6\left(1-\frac{s_v^*}{s_v}\right)\left[b_v-(a\beta_2 s_v i_h + a\beta_3 s_v i_m) - s_v b_v\right]\\ &\quad + a_7\left(1-\frac{e_v^*}{e_v}\right)\left[a\beta_2 s_v i_h + a\beta_3 s_v i_m - e_v(\delta_v+b_v)\right]\\ &\quad + a_8\left(1-\frac{i_v^*}{i_v}\right)\left[\delta_v e_v - i_v b_v\right].\end{aligned}$$

At P^*, we have

$$\begin{aligned}\frac{dL_v}{dt} &= a_6\left(1-\frac{s_v^*}{s_v}\right)\left[a\beta_2 s_v^* i_h^* + a\beta_3 s_v^* i_m^* + s_v^* b_v - a\beta_2 s_v i_h - a\beta_3 s_v i_m - s_v b_v\right]\\ &\quad + a_7\left(1-\frac{e_v^*}{e_v}\right)\left[a\beta_2 s_v i_h + a\beta_3 s_v i_m - e_v\left(\frac{a\beta_2 s_v^* i_h^* + a\beta_3 s_v^* i_m^*}{e_v^*}\right)\right]\\ &\quad + a_8\left(1-\frac{i_v^*}{i_v}\right)\left[\delta_v e_v - i_v\left(\frac{\delta_v e_v^*}{i_v^*}\right)\right].\end{aligned}$$

Further simplification yields

$$\begin{aligned}\frac{dL_v}{dt} &= -a_6\left(1-\frac{s_v^*}{s_v}\right)^2 b_v s_v - a_6\left(1-\frac{s_v^*}{s_v}\right)\left[a\beta_2 s_v i_h\left(1-\frac{s_v^* i_h^*}{s_v i_h}\right)\right.\\ &\quad \left. + a\beta_3 s_v i_m\left(1-\frac{s_v^* i_m^*}{s_v i_m}\right)\right] - \frac{a_7}{e_v^*}\left(1-\frac{e_v^*}{e_v}\right)\left[a\beta_2 s_v^* i_h^* e_v\right.\\ &\quad \left.\left(1-\frac{s_v i_h e_v^*}{s_v^* i_h^* e_v}\right) + a\beta_3 e_v s_v^* i_m^*\left(1-\frac{e_v^* s_v i_m}{e_v s_v^* i_m^*}\right)\right]\\ &\quad - \frac{a_8}{i_v^*}\left(1-\frac{i_v^*}{i_v}\right)\left[i_v\delta_v e_v^*\left(1-\frac{e_v i_v^*}{e_v^* i_v}\right)\right],\end{aligned}$$

which can also be written as

$$\frac{dL_v}{dt} = -a_6\left(1-\frac{s_v^*}{s_v}\right)^2 b_v s_v + F_v(s_v, e_v, i_v), \tag{3.29}$$

where

$$F_v = -a_6\left(1-\frac{s_v^*}{s_v}\right)\left[a\beta_2 s_v i_h\left(1-\frac{s_v^* i_h^*}{s_v i_h}\right)+a\beta_3 s_v i_m\left(1-\frac{s_v^* i_m^*}{s_v i_m}\right)\right] - \frac{a_7}{e_v^*}\left(1-\frac{e_v^*}{e_v}\right)\left[a\beta_2 s_v^* i_h^* e_v\left(1-\frac{s_v i_h e_v^*}{s_v^* i_h^* e_v}\right)+a\beta_3 e_v s_v^* i_m^*\left(1-\frac{e_v^* s_v i_m}{e_v s_v^* i_m^*}\right)\right]-\frac{a_8}{i_v^*}\left(1-\frac{i_v^*}{i_v}\right)\left[i_v\delta_v e_v^*\left(1-\frac{e_v i_v^*}{e_v^* i_v}\right)\right]. \tag{3.30}$$

Similarly,

$$L_m(s_m, e_m, i_m) = a_9(s_m - s_m^*\ ln\ s_m) + a_{10}(e_m - e_m^*\ ln\ e_m) + a_{11}(i_m - i_m^*\ ln\ i_m), \tag{3.31}$$

which gives

$$\begin{aligned}\frac{dL_m}{dt} &= a_9\left[1-\frac{s_m^*}{s_m}\right]\frac{ds_m}{dt}+a_{10}\left[1-\frac{e_m^*}{e_m}\right]\frac{de_m}{dt}+a_{11}\left[1-\frac{i_m^*}{i_m}\right]\frac{di_m}{dt}\\ &= a_9\left(1-\frac{s_m^*}{s_m}\right)\left[b_m - a\beta_4 s_m i_v - s_m b_m\right]\\ &\quad + a_{10}\left(1-\frac{e_m^*}{e_m}\right)\left[a\beta_4 s_m i_v - e_m(\delta_m + b_m)\right]\\ &\quad + a_{11}\left(1-\frac{i_m^*}{i_m}\right)\left[\delta_m e_m - i_m b_m\right].\end{aligned}$$

At P^*, we also have

$$\begin{aligned}\frac{dL_m}{dt} &= a_9\left(1-\frac{s_m^*}{s_m}\right)\left[a\beta_4 s_m^* i_v^* + s_m^* b_m - a\beta_4 s_m i_v - s_m b_m\right]\\ &\quad + a_{10}\left(1-\frac{e_m^*}{e_m}\right)\left[a\beta_4 s_m i_v - e_m\left(\frac{a\beta_4 s_m^* i_v^*}{e_m^*}\right)\right]\\ &\quad + a_{11}\left(1-\frac{i_m^*}{i_m}\right)\left[\delta_m e_m - i_m\left(\frac{\delta_m e_m^*}{i_m^*}\right)\right].\end{aligned}$$

Again, further simplification yields

$$\begin{aligned}\frac{dL_m}{dt} = &-a_9\left(1-\frac{s_m^*}{s_m}\right)^2 b_m s_m - a_9\left(1-\frac{s_m^*}{s_m}\right)\left[a\beta_4 s_m i_v\left(1-\frac{s_m^* i_v^*}{s_m i_v}\right)\right]\\ &-\frac{a_{10}}{e_m^*}\left(1-\frac{e_m^*}{e_m}\right)\left[a\beta_4 s_m^* i_v^* e_m\left(1-\frac{s_m i_v e_m^*}{s_m^* i_v^* e_m}\right)\right]\\ &-\frac{a_{11}}{i_m^*}\left(1-\frac{i_m^*}{i_m}\right)\left[i_m\delta_m e_m^*\left(1-\frac{e_m i_m^*}{e_m^* i_m}\right)\right],\end{aligned}$$

which can also be written as

$$\frac{dL_m}{dt} = -a_9\left(1-\frac{s_m^*}{s_m}\right)^2 b_m s_m + F_m(s_m, e_m, i_m), \tag{3.32}$$

where

$$\begin{aligned}F_m = &-a_9\left(1-\frac{s_m^*}{s_m}\right)\left[a\beta_4 s_m i_v\left(1-\frac{s_m^* i_v^*}{s_m i_v}\right)\right]\\ &-\frac{a_{10}}{e_m^*}\left(1-\frac{e_m^*}{e_m}\right)\left[a\beta_4 s_m^* i_v^* e_m\left(1-\frac{s_m i_v e_m^*}{s_m^* i_v^* e_m}\right)\right]\\ &-\frac{a_{11}}{i_m^*}\left(1-\frac{i_m^*}{i_m}\right)\left[i_m\delta_m e_m^*\left(1-\frac{e_m i_m^*}{e_m^* i_m}\right)\right].\end{aligned} \tag{3.33}$$

Thus, considering equations (3.26), (3.29) and (3.32) we can have

$$
\begin{aligned}
\frac{dL}{dt} &= \frac{dL_h}{dt} + \frac{dL_v}{dt} + \frac{dL_m}{dt}, \\
&= -a_1\Big(\varepsilon + b_h + \sigma\Big)s_h\left(1 - \frac{s_h^*}{s_h}\right)^2 - a_2\Big(\omega + b_h + \sigma\Big)v_h\left(1 - \frac{v_h^*}{v_h}\right)^2 \\
&\quad + F_h\big(s_h, v_h, e_h, i_h, r_h\big) \\
&\quad - a_6\left(1 - \frac{s_v^*}{s_v}\right)^2 b_v s_v + F_v(s_v, e_v, i_v) \\
&\quad - a_9\left(1 - \frac{s_m^*}{s_m}\right)^2 b_m s_m + F_m(s_m, e_m, i_m),
\end{aligned}
\tag{3.34}
$$

which can be written as

$$
\begin{aligned}
\frac{dL}{dt} &= -a_1\Big(\varepsilon + b_h + \sigma\Big)s_h\left(1 - \frac{s_h^*}{s_h}\right)^2 - a_2\Big(\omega + b_h + \sigma\Big)v_h\left(1 - \frac{v_h^*}{v_h}\right)^2 \\
&\quad - a_6\left(1 - \frac{s_v^*}{s_v}\right)^2 b_v s_v - a_9\left(1 - \frac{s_m^*}{s_m}\right)^2 b_m s_m \\
&\quad + F(s_h, v_h, e_h, i_h, r_h, s_v, e_v, i_v, s_m, e_m, i_m),
\end{aligned}
\tag{3.35}
$$

where

$$
\begin{aligned}
F = -a_1\left(1-\frac{s_h^*}{s_h}\right)\Bigg[a\beta_1 s_h i_v\left(1-\frac{i_v^* s_h^*}{i_v s_h}\right)-\alpha s_h i_h\left(1-\frac{i_h^* s_h^*}{i_h s_h}\right)\\
-\omega v_h\left(1-\frac{v_h^*}{v_h}\right)-\omega r_h\left(1-\frac{r_h^*}{r_h}\right)\Bigg]\\
-a_2\left(1-\frac{v_h^*}{v_h}\right)\left[\varepsilon s_h^*\left(1-\frac{s_h}{s_h^*}\right)+\alpha v_h^* i_h^*\left(1-\frac{v_h i_h}{v_h^* i_h^*}\right)\right]\\
\frac{-a_3}{e_h^*}\left(1-\frac{e_h^*}{e_h}\right)\left[a\beta_1 s_h^* e_h i_v^*\left(1-\frac{s_h i_v e_h^*}{s_h^* i_v^* e_h}\right)-\alpha e_h i_h e_h^*\left(1-\frac{i_h^*}{i_h}\right)\right]\\
\frac{-a_4}{i_h^*}\left(1-\frac{i_h^*}{i_h}\right)\left[\delta_h e_h^* i_h\left(1-\frac{e_h i_h^*}{e_h^* i_h}\right)-\alpha i_h^* i_h^2\left(1-\frac{i_h^*}{i_h}\right)\right]\\
\frac{-a_5}{r_h^*}\left(1-\frac{r_h^*}{r_h}\right)\left[r_h\gamma i_h^*\left(1-\frac{i_h r_h^*}{i_h^* r_h}\right)-\alpha r_h i_h r_h^*\left(1-\frac{i_h^*}{i_h}\right)\right]\\
-a_6\left(1-\frac{s_v^*}{s_v}\right)\left[a\beta_2 s_v i_h\left(1-\frac{s_v^* i_h^*}{s_v i_h}\right)+a\beta_3 s_v i_m\left(1-\frac{s_v^* i_m^*}{s_v i_m}\right)\right]\\
-\frac{a_7}{e_v^*}\left(1-\frac{e_v^*}{e_v}\right)\left[a\beta_2 s_v^* i_h^* e_v\left(1-\frac{s_v i_h e_v^*}{s_v^* i_h^* e_v}\right)+a\beta_3 e_v s_v^* i_m^*\right.\\
\left.\left(1-\frac{e_v^* s_v i_m}{e_v s_v^* i_m^*}\right)\right]-\frac{a_8}{i_v^*}\left(1-\frac{i_v^*}{i_v}\right)\left[i_v\delta_v e_v^*\left(1-\frac{e_v i_v^*}{e_v^* i_v}\right)\right]\\
-a_9\left(1-\frac{s_m^*}{s_m}\right)\left[a\beta_4 s_m i_v\left(1-\frac{s_m^* i_v^*}{s_m i_v}\right)\right]\\
-\frac{a_{10}}{e_m^*}\left(1-\frac{e_m^*}{e_m}\right)\left[a\beta_4 s_m^* i_v^* e_m\left(1-\frac{s_m i_v e_m^*}{s_m^* i_v^* e_m}\right)\right]\\
-\frac{a_{11}}{i_m^*}\left(1-\frac{i_m^*}{i_m}\right)\left[i_m\delta_m e_m^*\left(1-\frac{e_m i_m^*}{e_m^* i_m}\right)\right].
\end{aligned}
\tag{3.36}
$$

As it is seen in equations (3.35) and (3.36), F is non-positive by following the approach of Mukandavire et al. (2009) and McCluskey (2006).

Thus, $F \leq 0$ for $s_h, v_h, e_h, i_h, r_h, s_v, e_v, i_v, s_m, e_m, i_m > 0$.

Hence $\dfrac{dL}{dt} \leq 0$ for all $s_h, v_h, e_h, i_h, r_h, s_v, e_v, i_v, s_m, e_m, i_m > 0$. and is zero when

$s_h = s_h^*,\ v_h = v_h^*,\ e_h = e_h^*,\ i_h = i_h^*,\ r_h = r_h^*,\ s_v = s_v^*,\ e_v = e_v^*,\ i_v = i_v^*$

$s_m = s_m^*,\ e_m = e_m^*,\ i_m = i_m^*.$

Therefore, the largest compact invariant set in Φ such that $\frac{dL}{dt} = 0$ is the singleton P^* which is the endemic equilibrium point.

LaSalles invariant principle (LaSalle, 1976) guarantees that P^* is globally asymptotically stable (GAS) in $\overset{\circ}{\Phi}$, the interior of Φ. Thus, we have established the following theorem;

Theorem 3.6. *If $R_0 > 1$, then, model system (2.6) has a unique EE point which is globally asymptotically stable (GAS) in $\overset{\circ}{\Phi}$.*

3.4 Discussions and Conclusion

In this chapter, the model considered in chapter two is used. The model is analysed for the existence and stabilities of disease-free and endemic equilibrium points.

Stability of DFE point E_0 was established using the threshold parameter, R_0, whereby local stability of the E_0 was established using trace-determinant approach of the Jacobian matrix of the model system (2.6), while Metzler matrix approach is used to carry out global stability analysis of E_0. It is found that the disease-free equilibrium point is locally asymptotically stable if $R_{mv} < 1$ and unstable if $R_{mv} > 1$. Also, it is established that the disease-free equilibrium point is globally stable if $R_{vh} < 1$ and unstable otherwise. Since the disease threshold parameter had the form $R_0 = \sqrt{R_{hv} + R_{vm}}$, and from the local and global stabilities of the disease-free equilibrium point, we can generally conclude that the disease-free equilibrium point is stable locally and globally if and only if $R_0 < 1$ so that the disease always dies out. For $R_0 > 1$, the disease-free equilibrium point is unstable while the endemic equilibrium emerges as a unique equilibrium point, thus re-invasion is always possible and the disease never dies out. The result is similar with other researchers from the literature like Kamgang and Sallet (2008), Moghadas (2004), Van den Driessche and Watmough (2002), Diekmann and Heesterbeek (2000).

We further analysed the stability of EE point using a suitable Lyapunov function. Results show that a unique endemic equilibrium point exists and is globally stable when $R_0 > 1$. Thus, there is need to find ways of preventing infection and re-infection from monkeys population if we are to completely curb the disease. The results of this study indicate that the Lyapunov functions of the form $L(x_1, x_2, ...x_n) = \sum a_i \ (x_i - x_i^* \ ln \ x_i)$ can be useful especially for SEIR and/or compartmental human-vector and human-vector-monkeys models with many number of compartments. Our result are similar with other researchers like Ullah et al. (2013), Mpeshe et al. (2011), Korobeinikov (2004a) among others.

This analysis enables us to gain valuable insights and it introduces an important step in theoretical analysis of the disease. The vector being at the middle part of human host and monkeys and the transmitters of the YFV to both hosts need to be controlled to make the human host free from the infection. Thus, interventional strategies are suggested important to reduce the span of the lives of parasites and vectors.

Moreover, numerous additions in the model will be required in order to provide further insights in assessing the impact, dynamics and transmissions of YFV like temperature variations and vertical transmission of the vector for preventing the epidemic. However, as pointed out by Monath (2006) vaccination could remain as the single most important measure for preventing YF. Although there are some scenarios that would require a large quantity of YF vaccine over a short period, still it will remain as the only solution for prevention. Again, as noted by Dumont et al. (2008) control of the YF mosquito (*Aedes aegypti*) is of a major importance, especially because the same mosquito can transmit dengue fever and chikungunya disease.

CHAPTER FOUR

Application of Optimal Control Strategies for the Dynamics of Yellow Fever[3]

Abstract: In this chapter, we present an application of optimal control theory to assess the effectiveness of control measures on the dynamics of YF. We formulate and analyse a deterministic mathematical model with personal protection, educational campaign and spray of insecticides as control variables using optimal control theory and Pontryagins Maximum Principle. The optimal controls are characterized in terms of optimality system, and solved numerically for several scenarios. Results show that multiple optimal control measures is the most effective strategy to bring a stable disease-free situation compared to a single control. However, spray of insecticides alone was seen as not effective without personal protection, and optimal use of personal protection alone might be beneficial to minimize transmission of the infection to the community.

Keywords: Yellow fever, optimal control, personal protection, educational campaign, spray of insecticides.

2010 **AMS Subject Classification:** $92B05$.

[3] This chapter is based on the published paper:

Kung'aro, M., Luboobi, L. S., and Shahada, F. (2015). Application of optimal control strategies for the dynamics of yellow fever. *Journal of Mathematical and Computational Science*, **5**(3): 430-453

4.1 Introduction

Outbreaks of vector borne diseases like malaria, yellow fever (YF) and dengue that are transmitted to humans by blood-sucker mosquito have devastated several countries around the world (Misra et al., 2013). Thus, modelling their dynamics and control has gained enormous attention.

Most infectious diseases could be eradicated, if adequate and timely steps (for example vaccination, treatment, educational and enlightenment campaign) are taken in the course of the epidemic. However, many of these diseases eventually become endemic in our societies due to lack of adequate policies and timely interventions to mitigate the spread of them.

YF, in particular, is a viral haemorrhagic fever caused by yellow fever virus (YFV) and is transmitted through the bite of an infected female yellow fever mosquito (Robertson et al., 1996). Humans and primates are the principle reservoirs for YF virus and the vector, female YF mosquito (*Aedes aegypti*) is the only transmitting agent of this virus to urban settings.

The study of optimal control strategies in epidemiological models have been of much interest for informed decision-making. Over years, mathematical models of the spread of infectious diseases have been used to provide important insights into disease behaviour and optimal control strategies. For some diseases, medical treatments can be given to patients to cure the infection but there may not be vaccine to immunize susceptible individuals (e.g. Malaria). For a few other diseases, there is no cure but individuals can be vaccinated against getting infection (e.g. Polio, YF).

Optimal control theory has been applied to a number of studies in mathematical models of vector-borne diseases including malaria (Okosun and Makinde, 2013; Lashari et al., 2012), chikungunya (Moulay et al., 2012), dengue (Rodrigues et al., 2012), rift valley fever (Mpeshe et al., 2014a), among others. Regarding to YF few studies have been done to address transmission dynamics like in Amaku et al. (2011), Johansson et al. (2010), Shustov and Mason (2007)

and Monath and Cetron (2002), but not addressing control strategies of the infection. In these studies theoretical and statistical models have been used.

Recently, Kung'aro et al. (2014) used a mathematical model in addressing YF transmission dynamics between primates and human being, into which model parameters and factors affecting diseases transmission were discussed. Nothing has been done to address control strategies of YF.

Thus, in this research we formulate an optimal control model for YF aiming at deriving optimal control strategies with minimum implementation cost. We extend the current model by Kung'aro et al. (2014) by introducing time-dependent control efforts on prevention or personal protection, educational campaign and spray of insecticides efforts as controls to curtail the spread of YF. We use Pontryagins Maximum Principle in deriving the optimal control and Fleming (1975) and Lukes (1982) in proving the existence of an optimal control.

4.2 Materials and Methods

4.2.1 Model Formulation

Control terms are added to the existing deterministic mathematical model for YF transmission dynamics by Kung'aro et al. (2014) as shown in Figure 4.1, where the monkeys, m, are now represented by primates, p. Three populations are considered in the model (humans, vector and primates) with the total population sizes at time t given by $N_h(t)$, $N_v(t)$ and $N_p(t)$ respectively. The populations are further compartmentalized into epidemiological classes whereby human population is divided into 5 classes: susceptible, S_h , vaccinated, V_h, exposed, E_h, infectious, I_h and recovered (immune), R_h.

Vector and primates population are divided into 3 classes each: susceptible, exposed, and infectious. They do not include the immune class as they never recover from the infection, that is

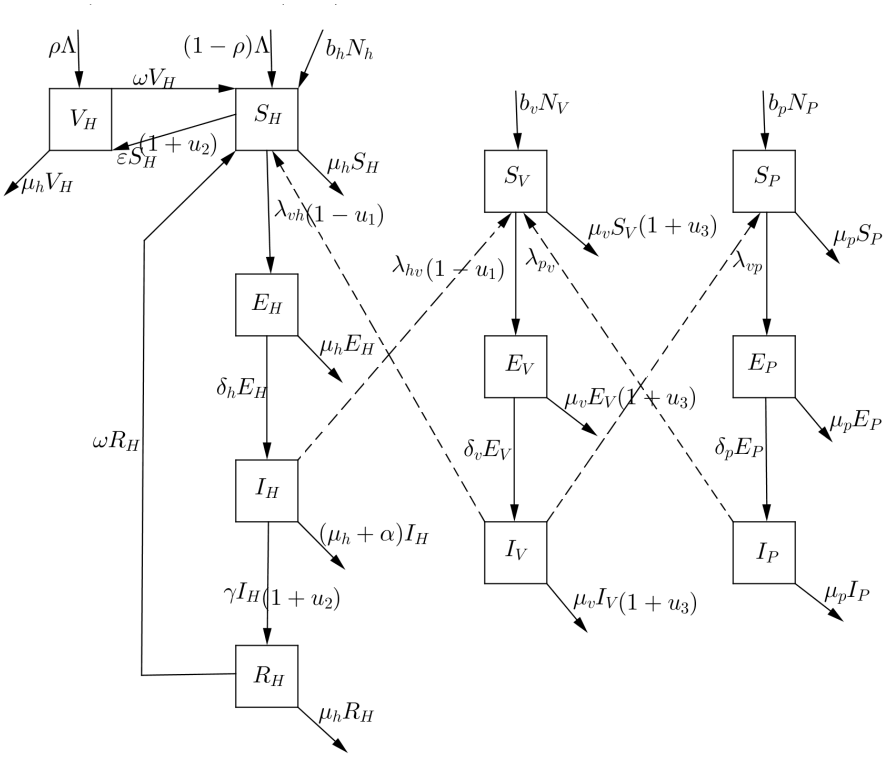


Figure 4.1: Model flow diagram for transmission dynamics of YF under control measures.

their infective period ends with their death due to their relatively short life cycle compared to humans.

We consider three control efforts, prevention or personal protection and educational campaign to human host, and spray of insecticides against the vector. We use the control mechanisms $u_i(t)$ in human host and vector populations, where $1 - u_i(t)$ is the failure probability of the control mechanism $u_i(t)$ for i = 1; 2; 3. In the model the control mechanism $u_1(t)$ and $u_2(t)$ represents prevention/personal protection and educational campaign respectively to human hosts and $u_3(t)$ represents spray of insecticides against the vector.

In the human population, prevention or personal protection includes, the use of mosquito treated bed-nets, use of mosquito coils, indoor residual spraying and use of mosquito repellents. All these things are done in order to minimize or eliminate vector-human contacts. Thus, the

associated force of infection to human from vector and vice versa is reduced by a factor of $1 - u_1$.

Educational campaign is done to the human populations in such a way that upon its successful efforts, more susceptible human individuals will be motivated to vaccination before the occurrence of the disease making the vaccination rate, ε, to be increased by a factor $1 + u_2$. Also, infectious human individuals will be encouraged and motivated to get immunity by treating any other infection in their bodies. That is to say a large number of infectious humans will be recover and hence the recovery rate, γ, will also be increased by a factor $1 + u_2$.

Spray of insecticides against the vector is done to larvacide and adultcide and applied to those places where vector bleeding occurs in order to control vector population. It is assumed that application of insecticides will increase the death rate of vector in each compartment at a rate proportional to $u_3(t)$, and hence automatically reduce the reproduction rate (Blayneh et al., 2010). We take these rates to be $\mu_v(t)u_3(t)S_v(t)$, $\mu_v(t)u_3(t)E_v(t)$ and $\mu_v(t)u_3(t)I_v(t)$ for susceptible, latent and infectious vector respectively. That is to say mortality rate of mosquito population, μ_v, is increased by a factor $1 + u_3$. Thus, we construct the optimal model equations as follows:

Human:

$$\begin{aligned}
\frac{dS_h(t)}{dt} &= b_h N_h + (1-\rho)\Lambda + \omega(V_h + R_h) - \lambda_{vh}(1-u_1) - \varepsilon(1+u_2)S_h - \mu_h S_h,\\
\frac{dV_h(t)}{dt} &= \rho\Lambda + \varepsilon(1+u_2)S_h - \omega V_h - \mu_h V_h,\\
\frac{dE_h(t)}{dt} &= \lambda_{vh}(1-u_1) - \delta_h E_h - \mu_h E_h,\\
\frac{dI_h(t)}{dt} &= \delta_h E_h - (\mu_h + \alpha)I_h - \gamma I_h(1+u_2),\\
\frac{dR_h(t)}{dt} &= \gamma I_h(1+u_2) - \omega R_h - \mu_h R_h,
\end{aligned} \tag{4.1}$$

Vector:

$$\begin{aligned}
\frac{dS_V(t)}{dt} &= b_v N_V - \lambda_{hv}(1-u_1) - \lambda_{pv} - \mu_v S_V(1+u_3),\\
\frac{dE_V(t)}{dt} &= \lambda_{hv}(1-u_1) + \lambda_{pv} - \delta_v E_V - \mu_v E_V(1+u_3),\\
\frac{dI_V(t)}{dt} &= \delta_v E_V - \mu_v I_V(1+u_3),
\end{aligned} \tag{4.2}$$

Primates:

$$\begin{aligned}
\frac{dS_p(t)}{dt} &= b_p N_p - \lambda_{vp} - \mu_p S_p,\\
\frac{dE_p(t)}{dt} &= \lambda_{vp} - \delta_p E_p - \mu_p E_p,\\
\frac{dI_p(t)}{dt} &= \delta_p E_P - \mu_p I_p,
\end{aligned} \tag{4.3}$$

where; $\lambda_{vh} = \dfrac{a\beta_1 S_h I_v}{N_v}$, $\lambda_{hv} = \dfrac{a\beta_2 S_v I_h}{N_h}$, $\lambda_{pv} = \dfrac{a\beta_3 S_v I_p}{N_p}$ and $\lambda_{vp} = \dfrac{a\beta_4 S_p I_p}{N_p}$.

In the model the term $\lambda_{vh} = \dfrac{a\beta_1 S_h I_v}{N_v}$ denotes the rate at which susceptible human hosts S_h get infected by the infected vector I_v (force of infection from vector to human), $\lambda_{hv} = \dfrac{a\beta_2 S_v I_h}{N_h}$ denotes the rate at which susceptible vector S_v get infected from the infected human host I_h (infection force from human host to vector), $\lambda_{pv} = \dfrac{a\beta_3 S_v I_p}{N_p}$ denotes the rate at which the susceptible vector S_v get infected from the infected primate I_p (force of infection from primate to vector) and the term $\lambda_{vp} = \dfrac{a\beta_4 S_p I_v}{N_v}$ denotes the rate at which the susceptible primates S_p get infected from the infected vector I_v.

Thus, we define the total population sizes $N_h(t)$, $N_v(t)$ and $N_p(t)$ for human host, vector and primates respectively as:

$$\begin{aligned}
N_h(t) &= S_h(t) + V_h(t) + E_h(t) + I_h(t) + R_h(t),\\
N_v(t) &= S_v(t) + E_v(t) + I_v(t),\\
N_p(t) &= S_p(t) + E_p(t) + I_p(t).
\end{aligned} \tag{4.4}$$

Model systems (4.1), (4.2), (4.3) can be written together to form a single system of differential equations (4.5).

$$
\begin{aligned}
\frac{dS_h}{dt} &= b_h N_h + (1-\rho)\Lambda + \omega(V_h + R_h) - \frac{a\beta_1 S_h I_v}{N_v}(1-u_1) - \varepsilon(1+u_2)S_h - \mu_h S_h,\\
\frac{dV_h}{dt} &= \rho\Lambda + \varepsilon(1+u_2)S_h - \omega V_h - \mu_h V_h,\\
\frac{dE_h}{dt} &= \frac{a\beta_1 S_h I_v}{N_v}(1-u_1) - \delta_h E_h - \mu_h E_h,\\
\frac{dI_h}{dt} &= \delta_h E_h - (\mu_h + \alpha)I_h - \gamma(1+u_2)I_h,\\
\frac{dR_h}{dt} &= \gamma(1+u_2)I_h - \omega R_h - \mu_h R_h,\\
\frac{dS_v}{dt} &= b_v N_v - \frac{a\beta_2 S_v I_h}{N_h}(1-u_1) - \frac{a\beta_3 S_v I_p}{N_p} - \mu_v S_v(1+u_3),\\
\frac{dE_v}{dt} &= \frac{a\beta_2 S_v I_h}{N_h}(1-u_1) + \frac{a\beta_3 S_v I_p}{N_p} - \delta_v E_v - \mu_v E_v(1+u_3),\\
\frac{dI_v}{dt} &= \delta_v E_v - \mu_v I_v(1+u_3),\\
\frac{dS_p}{dt} &= b_p N_p - \frac{a\beta_4 S_p I_v}{N_v} - \mu_p S_p,\\
\frac{dE_p}{dt} &= \frac{a\beta_4 S_p I_v}{N_v} - \delta_p E_p - \mu_p E_p,\\
\frac{dI_p}{dt} &= \delta_p E_p - \mu_p I_p.
\end{aligned}
\tag{4.5}
$$

Parameters as they have been used in this study are described in Table 4.1:

Table 4.1: Description of parameters of the model system (4.5)

Symbol	Description	Value	Reference
β_1	Transmission probability of vector to human	0.8	Amaku et al. (2011); Dumont et al. (2008)
β_2	Transmission probability of human to vector	0.8	Rodrigues et al. (2013); Nishiura (2006)
β_3	Transmission probability of primate to vector	0.5	Kung'aro et al. (2014)
β_4	Transmission probability of vector to primate	0.9	assumed
δ_h	Progression rate from E_h to I_h	0.95 day^{-1}	Garba et al. (2008); Esteva and Vargas (1998)
δ_v	Progression rate from E_v to I_v	0.95 day^{-1}	Amaku et al. (2011); Garba et al. (2008)
δ_p	Progression rate from E_p to I_p	0.85 day^{-1}	Kung'aro et al. (2014)
b_h	Daily birth rate of human	0.0003	assumed
b_v	Daily birth rate of vector	0.002	Bowman (2012)
b_p	Daily birth rate of primates	0.00004	assumed
a	Daily bitting rate	0.5	Amaku et al. (2011); Dumont et al. (2008)
γ	Recovery rate	0.005	Pinho et al. (2010); Codeço et al. (2007)
α	Death rate due to disease for human	0.001	Pinho et al. (2010); Codeço et al. (2007)
ω	rate of relapse of vaccinated and recovered human	0.05	Garba et al. (2008)
ε	vaccination rate of susceptible human	0.5 day^{-1}	Kung'aro et al. (2014)
ρ	proportion of immigrant who are vaccinated	0.02 day^{-1}	Garba et al. (2008)
Λ	arrival rate of immigrant per individual per time	70 day^{-1}	assumed
$\frac{1}{\mu_h}$	lifespan of human	60 years	Kung'aro et al. (2014); Mpeshe et al. (2011)
$\frac{1}{\mu_v}$	lifespan of vector	40 days	Moulay et al. (2012)
$\frac{1}{\mu_p}$	lifespan of primates	10 years	assumed

4.2.2 The Optimal Control Problem

In model system (4.5), we seek to minimize the number of exposed and infectious human with minimum implementation cost (that is the cost of applying control, personal protection, u_1, educational campaign, u_2, and spray of insecticides, u_3). Therefore for a terminal time t_f , the aim is to minimize the cost of objective functional

$$J(u_1, u_2, u_3) = \int_0^{t_f} \left(A_1 E_h + A_2 I_h + B_1 u_1^2 + B_2 u_2^2 + B_3 u_3^2\right) dt, \tag{4.6}$$

where, A_1 and A_2 are positive weight constants of the exposed and infectious humans respectively; and B_1, B_2, B_3 are the positive weight constants for the control mechanisms u_1, u_2, u_3 respectively. However, with the idea of other researchers from the literature on epidemic controls (Okosun and Makinde, 2013; Lashari et al., 2013; Hattaf and Yousfi, 2012; Lashari et al., 2012; Makinde and Okosun, 2011; Jung et al., 2002), we choose a quadratic cost function of the controls.

We also define $B_1 u_1^2$ as the cost of the control mechanism in human associated with personal protection so as to minimize the vector human contacts; $B_2 u_2^2$ is the cost of the control efforts on educational campaign to human host individuals and $B_3 u_3^2$ is the cost of control mechanism in vectors associated with spraying of insecticide against vector to adulticide and larvacide, and those places where vector breeding occurs.

Thus, we seek to obtain an optimal control (u_1^*, u_2^*, u_3^*) such that;

$$J(u_1^*, u_2^*, u_3^*) = \min J(u_1, u_2, u_3 | u_1, u_2, u_3 \in \Gamma), \tag{4.7}$$

subject to system (4.5) where the control set is defined as $\Gamma = \{u_1, u_2, u_3 | u_i(t)$ is a piece wise continuous functions on $[0, t_f]$ and that $a_i \leq u_i \leq b_i$ for $i = 1, 2, 3\}$. Here a_i and b_i, are constants in [0,1].

In order to find an optimal solution, the basic framework of the problem is to state and prove the existence of optimal control for the model system (4.5) and then characterize the optimal control by deriving the optimality system.

4.2.3 Existence of an Optimal Control Problem

In this part, we state and prove the existence of optimal control using the existence results from Fleming (1975) and Lukes (1982). We first state the following theorem;

Theorem 4.7. *Consider the optimal control problem with model system* (4.5) *as state equations. There exists an optimal control* $u^* = (u_1^*, u_2^*, u_3^*) \in \Gamma$ *such that*

$$\min_{(u_1,u_2,u_3)\in\Gamma} J(u_1, u_2, u_3) = J(u_1^*, u_2^*, u_3^*).$$

Proof. We note that the existence of an optimal control pair can be proved by using results from Fleming (1975) theorem 4.1, we first need to check the following properties:

1. The set of controls and corresponding state variables is non-empty.
2. The control set Γ is convex and closed.
3. The right hand side of the state system is bounded by a linear function in the state and control variables.
4. The integrand of the objective functional is convex.
5. There exist constants $c_1, c_2 > 0$, and $\alpha > 1$ such that the integrand of the objective functional is bounded below by $c_1 \left(|u_1|^2 + |u_2|^2 + |u_3|^2\right)^{\frac{\alpha}{2}} - c_2$.

Condition 1, is verified using results from Fleming (1975), Chapter III page 60, from them existence is assured by the state equations and control variables; in our ODE's model system

(4.5), the state equations are;

$$
\begin{aligned}
\frac{dS_h}{dt} &= b_h N_h + (1-\rho)\Lambda + \omega(V_h + R_h) - \frac{a\beta_1 S_h I_v}{N_v}(1-u_1) - \varepsilon(1+u_2)S_h - \mu_h S_h,\\
\frac{dV_h}{dt} &= \rho\Lambda + \varepsilon(1+u_2)S_h - \omega V_h - \mu_h V_h,\\
\frac{dE_h}{dt} &= \frac{a\beta_1 S_h I_v}{N_v}(1-u_1) - \delta_h E_h - \mu_h E_h,\\
\frac{dI_h}{dt} &= \delta_h E_h - (\mu_h + \alpha)I_h - \gamma(1+u_2)I_h,\\
\frac{dR_h}{dt} &= \gamma(1+u_2)I_h - \omega R_h - \mu_h R_h,\\
\frac{dS_v}{dt} &= b_v N_v - \frac{a\beta_2 S_v I_h}{N_h}(1-u_1) - \frac{a\beta_3 S_v I_p}{N_p} - \mu_v S_v(1+u_3),\\
\frac{dE_v}{dt} &= \frac{a\beta_2 S_v I_h}{N_h}(1-u_1) + \frac{a\beta_3 S_v I_p}{N_p} - \delta_v E_v - \mu_v E_v(1+u_3),\\
\frac{dI_v}{dt} &= \delta_v E_v - \mu_v I_v(1+u_3),\\
\frac{dS_p}{dt} &= b_p N_p - \frac{a\beta_4 S_p I_v}{N_v} - \mu_p S_p,\\
\frac{dE_p}{dt} &= \frac{a\beta_4 S_p I_v}{N_v} - \delta_p E_p - \mu_p E_p,\\
\frac{dI_p}{dt} &= \delta_p E_p - \mu_p I_p.
\end{aligned}
\tag{4.8}
$$

and the control variables are $(u_1, u_2, u_3) \in \Gamma$. The control set Γ is bounded by definition; hence condition 2 is also satisfied. The RHS of the state system (4.5) satisfies condition 3 since the state solutions are bounded.

The integrand of our objective functional is

$$A_1 E_h + A_2 I_h + B_1 u_1^2 + B_2 u_2^2 + B_3 u_3^2.$$

It is clearly convex on control set Γ, which gives condition 4.

Finally, there are constants $c_1, c_2 > 0$ and $\alpha > 1$ satisfying

$$c_1 \left(|u_1|^2 + |u_2|^2 + |u_3|^2\right)^{\frac{\alpha}{2}} - c_2,$$

because the state variables are bounded, which shows the existence of an optimal control solution.

Hence, we conclude that there exists an optimal control (u_1^*, u_2^*, u_3^*) that minimizes the objective functional $J(u_1, u_2, u_3)$ which follows from the existence results by Fleming (1975). □

4.2.4 Characterization of Optimal Control

With the existence of optimal control pair established, we now present the optimality system and derive the necessary conditions using Pontryagin Maximum Principle (Pontryagin et al., 1962). The aim of this principle is to minimize the objective function. To accomplish this, we begin by defining a Lagrangian of our optimal control problem which is the Hamiltonian augmented with penalty multipliers for the control constraints. Thus, we define the Hamiltonian, H, for the control problem (4.5)-(4.6) as:

$$H = \mathcal{L}(E_h, I_h, u_1, u_2, u_3) + \sum_K \lambda_K f_K, \tag{4.9}$$

where K is the set of state variables, that is $S_h, V_h, ..., I_p$; $\lambda_K, (K = 1, 2, ..., 11)$ is the adjoint functions of the K^{th} state variable, and f_K is the right hand side of the differential equation of the K^{th} state variable. This can be written as:

$$\begin{aligned} H \quad &= A_1 E_h + A_2 I_h + B_1 u_1^2 + B_2 u_2^2 + B_3 u_3^2 + \lambda_1 \frac{dS_h}{dt} + \lambda_2 \frac{dV_h}{dt} + \lambda_3 \frac{dE_h}{dt} \\ &+ \lambda_4 \frac{dI_h}{dt} + \lambda_5 \frac{dR_h}{dt} + \lambda_6 \frac{dS_v}{dt} + \lambda_7 \frac{dE_v}{dt} + \lambda_8 \frac{dI_v}{dt} + \lambda_9 \frac{dS_p}{dt} + \lambda_{10} \frac{dE_p}{dt} + \lambda_{11} \frac{dI_p}{dt}. \end{aligned} \tag{4.10}$$

Let Γ be set of controls, and Π be the set of adjoint variables, we define in more compact form the Lagrangian (augmented Hamiltonian) for our optimal problem as:

$$\mathcal{L}(K, \Gamma, \Pi) = H - \sum_{i=1}^{3} w_{ij}(u_i(t) - a_i) - \sum_{i=1}^{3} w_{ij}(b_i - u_i(t)) \text{ for } j = 1, 2, \tag{4.11}$$

where $w_{ij}(t) \geq 0$ are the penalty multipliers satisfying the following conditions

$$w_{11}(t)(u_1(t) - a_1) = w_{12}(t)(b_1 - u_1(t)) = 0 \quad \text{at optimal control} \quad u_1^*,$$

$$w_{21}(t)(u_2(t) - a_2) = w_{22}(t)(b_2 - u_2(t)) = 0 \quad \text{at optimal control} \quad u_2^*,$$

$$w_{31}(t)(u_3(t) - a_3) = w_{32}(t)(b_3 - u_3(t)) = 0 \quad \text{at optimal control} \quad u_3^*.$$

The Lagrangian can be extended as;

$$\begin{aligned}
L(K, \Gamma, \Pi) \quad &= A_1 E_h + A_2 I_h + B_1 u_1^2 + B_2 u_2^2 + B_3 u_3^2 \\
&+ \lambda_1[b_h N_h + (1-\rho)\Lambda + \omega(V_h + R_h) - \frac{a\beta_1 S_h I_v}{N_v}(1-u_1) - \varepsilon(1+u_2)S_h - \mu_h S_h] \\
&+ \lambda_2[\rho\Lambda + \varepsilon(1+u_2)S_h - \omega V_h - \mu_h V_h] \\
&+ \lambda_3[\frac{a\beta_1 S_h I_v}{N_v}(1-u_1) - \delta_h E_h - \mu_h E_h] \\
&+ \lambda_4[\delta_h E_h - (\mu_h + \alpha)I_h - \gamma(1+u_2)I_h] \\
&+ \lambda_5[\gamma(1+u_2)I_h - \omega R_h - \mu_h R_h] \\
&+ \lambda_6[b_v N_v - \frac{a\beta_2 S_v I_h}{N_h}(1-u_1) - \frac{a\beta_3 S_v I_p}{N_p} - \mu_v S_v(1+u_3)] \\
&+ \lambda_7[\frac{a\beta_2 S_v I_h}{N_h}(1-u_1) + \frac{a\beta_3 S_v I_p}{N_p} - \delta_v E_v - \mu_v E_v(1+u_3)] \\
&+ \lambda_8[\delta_v E_v - \mu_v I_v(1+u_3)] \\
&+ \lambda_9[b_p N_p - \frac{a\beta_4 S_p I_v}{N_v} - \mu_p S_p] \\
&+ \lambda_{10}[\frac{a\beta_4 S_p I_v}{N_v} - \delta_p E_p - \mu_p E_p)] \\
&+ \lambda_{11}[\delta_p E_p - \mu_p I_p] \\
&- w_{11}(t)(u_1(t) - a_1) - w_{12}(t)(b_1 - u_1(t)) - w_{21}(t)(u_2(t) - a_2) \\
&- w_{22}(t)(b_2 - u_2(t)) - w_{31}(t)(u_3(t) - a_3) - w_{32}(t)(b_3 - u_3(t)),
\end{aligned}$$

where $\lambda_1, \lambda_2, ..., \lambda_{11} = \lambda_K$ (for $K = s_h, v_h, ..., i_p$) are the adjoint variables or co-state variables. We seek the minimal value of Lagrangian.

Theorem 4.8. *Given u_i^*, $(i = 1, 2, 3)$ be the set of optimal control, and K^* be the corresponding set of solutions of the state system that minimizes J over Γ then there exists adjoint variables λ_K such that*

$$\frac{d\lambda_K}{dt} = -\frac{\partial L}{\partial K} \quad \textit{(adjoint condition)}, \tag{4.12}$$

and

$$\lambda_K(t_f) = 0 \quad \textit{(transversality/final time condition)}. \tag{4.13}$$

Furthermore

$$\frac{\partial L}{\partial u} = 0 \quad \textit{at} \quad (u_1, u_2, u_3 = 0) \quad \textit{(optimality condition)}. \tag{4.14}$$

Proof. We differentiate partially the Lagrangian (Hamiltonian augmented with penalty multiplier) with respect to states variables to obtain the adjoint system. Thus, we have;

$$\begin{aligned}
\frac{d\lambda_1}{dt} &= -\frac{\partial L}{\partial S_h} = \lambda_1\left[\frac{a\beta_1 I_v}{N_v}(1-u_1) + \varepsilon(1+u_2) + \mu_h\right] - \lambda_2\varepsilon(1+u_2) - \lambda_3\frac{a\beta_1 I_v}{Nv}(1-u_1),\\
\frac{d\lambda_2}{dt} &= -\frac{\partial L}{\partial V_h} = \lambda_2(\omega+\mu_h) - \lambda_1\omega,\\
\frac{d\lambda_3}{dt} &= -\frac{\partial L}{\partial E_h} = -A_1 + \lambda_3(\delta_h+\mu_h) - \lambda_4\delta_h,\\
\frac{d\lambda_4}{dt} &= -\frac{\partial L}{\partial I_h} = -A_2 + (\lambda_6-\lambda_7)\frac{a\beta_2 S_v}{N_h}(1-u_1) - \lambda_5\gamma(1+u_2) + \lambda_4[\mu_h+\alpha+\gamma(1+u_2)],\\
\frac{d\lambda_5}{dt} &= -\frac{\partial L}{\partial R_h} = \lambda_5(\mu_h+\omega) - \lambda_1\omega,\\
\frac{d\lambda_6}{dt} &= -\frac{\partial L}{\partial S_v} = (\lambda_6-\lambda_7)\left[\frac{a\beta_2 I_h}{N_h}(1-u_1) + \frac{a\beta_3 I_p}{N_p}\right] + \lambda_6\mu_v(1+u_3),\\
\frac{d\lambda_7}{dt} &= -\frac{\partial L}{\partial E_v} = \lambda_7(\delta_v+\mu_v) - \lambda_8\delta_v,\\
\frac{d\lambda_8}{dt} &= -\frac{\partial L}{\partial I_v} = (\lambda_1-\lambda_3)\frac{a\beta_1 S_h}{N_v}(1-u_1) + \lambda_8\mu_v(1+u_3) + (\lambda_9-\lambda_{10})\frac{a\beta_4 S_p}{Nv},\\
\frac{d\lambda_9}{dt} &= -\frac{\partial L}{\partial S_p} = (\lambda_9-\lambda_{10})\frac{a\beta_4 I_v}{Nv} + \lambda_9\mu_p,\\
\frac{d\lambda_{10}}{dt} &= -\frac{\partial L}{\partial E_p} = \lambda_{10}(\delta_p+\mu_p) + \lambda_{11}\delta_p,\\
\frac{d\lambda_{11}}{dt} &= -\frac{\partial L}{\partial i_p} = (\lambda_6-\lambda_7)\frac{a\beta_3 S_v}{N_p} + \lambda_{11}\mu_p.
\end{aligned} \tag{4.15}$$

Now, to obtain the optimal control solution ($u_i, i = 1, 2, 3$), of our Lagrangian we differentiate partially the Lagrangian L, with respect to u_1, u_2, u_3 and set it to zero as follows:

$$\begin{aligned}
\frac{\partial L}{\partial u_1} &= 2B_1u_1 + (\lambda_1-\lambda_3)\frac{a\beta_1 S_h I_v}{N_v} + (\lambda_6-\lambda_7)\frac{a\beta_2 S_v I_h}{Nh} - w_{11} + w_{12},\\
\frac{\partial L}{\partial u_2} &= 2B_2u_2 + (\lambda_2-\lambda_1)\varepsilon S_h + (\lambda_5-\lambda_4)\gamma I_h - w_{21} + w_{22},\\
\frac{\partial L}{\partial u_3} &= 2B_3u_3 - \lambda_6\mu_v S_v - \lambda_7\mu_v E_v - \lambda_8\mu_v I_v - w_{31} + w_{32}.
\end{aligned} \tag{4.16}$$

Setting $\dfrac{\partial L}{\partial u_i} = 0$ for $i = 1, 2, 3$ and solving for the optimal control, we obtain

$$\begin{aligned} u_1^*(t) &= \frac{1}{2B_1}\left[(\lambda_3 - \lambda_1)\frac{a\beta_1 S_h I_v}{N_v} + (\lambda_7 - \lambda_6)\frac{a\beta_2 S_v I_h}{N_h} + w_{11} - w_{12}\right], \\ u_2^*(t) &= \frac{1}{2B_2}\left[(\lambda_1 - \lambda_2)\varepsilon S_h + (\lambda_4 - \lambda_5)\gamma I_h + w_{21} - w_{22}\right], \\ u_3^*(t) &= \frac{1}{2B_3}\left[\lambda_6\mu_v S_v + \lambda_7\mu_v E_v + \lambda_8\mu_v I_v + w_{31} - w_{32}\right]. \end{aligned} \tag{4.17}$$

To determine an explicit expression for an optimal control without w_{11}, w_{12}, w_{21}, w_{22}, w_{31}, w_{32} we use a standard optimality technique involving the bounds of control. The following are three cases to be considered in each part

Solving for $u_1^*(t)$

- On the set $\{t|a_1 < u_1^* < b_1\}$, we have

$$w_{11}(u_1^* - a_1) = w_{12}(b_1 - u_1^*) = 0 \implies w_{11} = w_{12} = 0.$$

  Hence the optimal control is

$$u_1^*(t) = \frac{1}{2B_1}\left[(\lambda_3 - \lambda_1)\frac{a\beta_1 S_h I_v}{N_v} + (\lambda_7 - \lambda_6)\frac{a\beta_2 S_v I_h}{N_h}\right].$$

- On the set $\{t|u_1^* = b_1\}$, we have

$$w_{11}(u_1^* - a_1) = w_{12}(b_1 - u_1^*) = 0 \implies w_{11} = 0.$$

  Hence the optimal control is

$$b_1 = u_1^*(t) = \frac{1}{2B_1}\left[(\lambda_3 - \lambda_1)\frac{a\beta_1 S_h I_v}{N_v} + (\lambda_7 - \lambda_6)\frac{a\beta_2 S_v I_h}{N_h} - w_{12}\right].$$

  Since $w_{12}(t) > 0$, therefore

$$\frac{1}{2B_1}\left[(\lambda_3 - \lambda_1)\frac{a\beta_1 S_h I_v}{N_v} + (\lambda_7 - \lambda_6)\frac{a\beta_2 S_v I_h}{N_h}\right] \geq b_1.$$

- On the set $\{t|u_1^* = a_1\}$, we have

$$w_{11}(u_1^* - a_1) = w_{12}(b_1 - u_1^*) = 0 \implies w_{12} = 0.$$

Thus, the optimal control is

$$a_1 = u_1^*(t) = \frac{1}{2B_1}\left[(\lambda_3 - \lambda_1)\frac{a\beta_1 S_h I_v}{N_v} + (\lambda_7 - \lambda_6)\frac{a\beta_2 S_v I_h}{N_h} + w_{11}\right].$$

Again since $w_{11}(t) > 0$, it shows that

$$a_1 \geq \frac{1}{2B_1}\left[(\lambda_3 - \lambda_1)\frac{a\beta_1 S_h I_v}{N_v} + (\lambda_7 - \lambda_6)\frac{a\beta_2 S_v I_h}{N_h}\right].$$

We now represent $u_1^*(t)$ in compact form as

$$u_1^*(t) = \min\left\{b_1,\ \max\left\{a_1,\ \frac{1}{2B_1}\left[(\lambda_3 - \lambda_1)\frac{a\beta_1 S_h I_v}{N_v} + (\lambda_7 - \lambda_6)\frac{a\beta_2 S_v I_h}{N_h}\right]\right\}\right\}. \tag{4.18}$$

Solving for $u_2^*(t)$

- On the set $\{t|a_2 < u_2^* < b_2\}$, we have

$$w_{21}(u_2^* - a_2) = w_{22}(b_2 - u_2^*) = 0 \implies w_{21} = w_{22} = 0.$$

Hence the optimal control is

$$u_2^*(t) = \frac{1}{2B_2}\left[(\lambda_1 - \lambda_2)\varepsilon S_h + (\lambda_4 - \lambda_5)\gamma I_h\right].$$

- On the set $\{t|u_2^* = b_2\}$, we have

$$w_{21}(u_2^* - a_2) = w_{22}(b_2 - u_2^*) = 0 \implies w_{21} = 0.$$

Hence the optimal control is

$$b_2 = u_2^*(t) = \frac{1}{2B_2}\left[(\lambda_1 - \lambda_2)\varepsilon S_h + (\lambda_4 - \lambda_5)\gamma I_h - w_{22}\right].$$

Since $w_{22}(t) > 0$, therefore

$$\frac{1}{2B_2}\left[(\lambda_1 - \lambda_2)\varepsilon S_h + (\lambda_4 - \lambda_5)\gamma I_h\right] \geq b_2.$$

- On the set $\{t|u_2^* = a_2\}$, we have

$$w_{21}(u_2^* - a_2) = w_{22}(b_2 - u_2^*) = 0 \implies w_{22} = 0.$$

Thus, the optimal control is

$$a_2 = u_2^*(t) = \frac{1}{2B_2}\left[(\lambda_1 - \lambda_2)\varepsilon S_h + (\lambda_4 - \lambda_5)\gamma I_h + w_{21}\right].$$

Again since $w_{21}(t) > 0$, therefore

$$a_2 \geq \frac{1}{2B_2}\left[(\lambda_1 - \lambda_2)\varepsilon S_h + (\lambda_4 - \lambda_5)\gamma I_h\right].$$

In compact form, we represent $u_2(t)$ as:

$$u_2^*(t) = \min\left\{b_2,\ \max\left\{a_2,\ \frac{1}{2B_2}\left[(\lambda_1 - \lambda_2)\varepsilon S_h + (\lambda_4 - \lambda_5)\gamma I_h\right]\right\}\right\}. \tag{4.19}$$

Solving for $u_3^*(t)$

- On the set $\{t|a_3 < u_3^* < b_3\}$, we have

$$w_{31}(u_3^* - a_3) = w_{32}(b_3 - u_3^*) = 0 \implies w_{31} = w_{32} = 0.$$

Hence the optimal control is

$$u_3^*(t) = \frac{1}{2B_3}[\lambda_6\mu_v S_v + \lambda_7\mu_v E_v + \lambda_8\mu_v I_v].$$

- On the set $\{t|u_3^* = b_3\}$, we have

$$w_{31}(u_3^* - a_3) = w_{32}(b_3 - u_3^*) = 0 \implies w_{31} = 0.$$

Hence the optimal control is

$$b_3 = u_3^*(t) = \frac{1}{2B_3}[\lambda_6\mu_v S_v + \lambda_7\mu_v E_v + \lambda_8\mu_v I_v - w_{32}].$$

Since $w_{32}(t) > 0$, it shows that

$$\frac{1}{2B_3}[\lambda_6\mu_v S_v + \lambda_7\mu_v E_v + \lambda_8\mu_v I_v] \geq b_3.$$

- On the set $\{t|u_3^* = a_3\}$, we have

$$w_{31}(u_3^* - a_3) = w_{32}(b_3 - u_3^*) = 0 \implies w_{32} = 0.$$

thus, the optimal control is

$$a_3 = u_3^*(t) = \frac{1}{2B_3}[\lambda_6\mu_v S_v + \lambda_7\mu_v E_v + \lambda_8\mu_v I_v + w_{31}].$$

Again since $w_{31}(t) > 0$, we have

$$a_3 \geq \frac{1}{2B_3}[\lambda_6\mu_v S_v + \lambda_7\mu_v E_v + \lambda_8\mu_v I_v].$$

Also we represent $u_3^*(t)$ in compact form as:

$$u_3^*(t) = \min\left\{b_3,\ \max\left\{a_3,\ \frac{1}{2B_3}\left[\lambda_6\mu_v S_v + \lambda_7\mu_v E_v + \lambda_8\mu_v I_v\right]\right\}\right\}. \tag{4.20}$$

Thus, the optimality system comprise of the state system with adjoint system, the transversality (final time) and initial conditions as well as optimality conditions. □

4.3 Numerical Results and Discussion

In order to obtain the optimal control, we solve the optimality system, consisting of model equations, adjoint equations and control mechanisms variables by using iterative scheme of fourth order Runge-Kutta technique.

By using the initial conditions $S_h(0) = 3500,\ V_h(0) = 2500,\ E_h(0) = 1500,\ I_h(0) = 1500,\ R_h(0) = 1000,\ S_v(0) = 2500,\ E_v(0) = 1500,\ I_v(0) = 1500,\ S_p(0) = 2500,\ E_p(0) = 1500,\ I_p(0) = 1500$; we begin to solve the state system (model equations) using forward in time Runge-Kutta method.

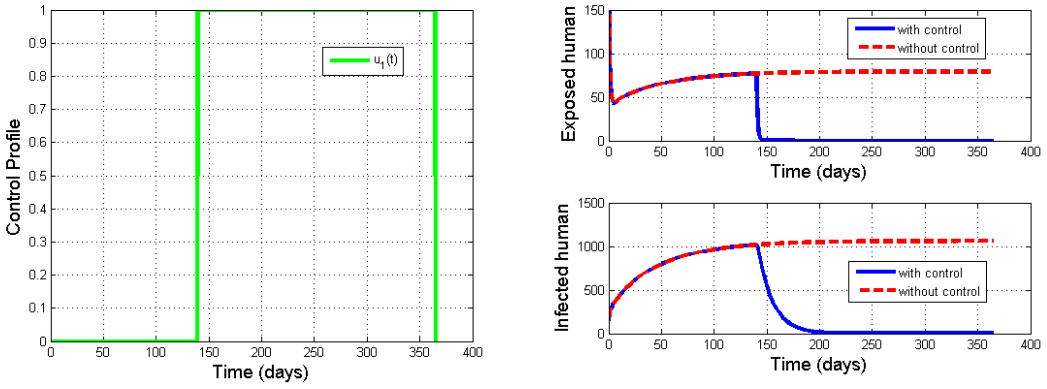
The adjoint equations are solved by a backward in time fourth order Runge-Kutta scheme using the current iterations solutions of the state equation by using terminal conditions $\lambda_K(t_f) = 0$ where $t_f = 365$ days. By referring to Lenhart and Workman (2007), the process is repeated and iterations stopped if the values of the unknowns at the previous iterations are very very close to the ones at the present iterations.

As pointed out by other researchers of optimal control in the literature, Mpeshe et al. (2014a), Okosun and Makinde (2012), Lashari et al. (2012), Makinde and Okosun (2011), computation of real weights is very involving and needs a lot of information. Thus, we start by initial guess values of the weights in the objective function as $A_1 = A_2 = 1000;\ B_1 = 0.0001,\ B_2 = 1000$ and $B_3 = 0.01$. These weights are theoretically chosen to reveal the control strategies proposed in this study. We also consider the controls to be bounded in the interval of [0,1]. In simulation we use values of parameters described in Table 4.1 and various combinations of the three controls at a time to investigate and compare their numerical results. To illustrate

the effect of different optimal control strategies on the spread of YF in a population, we have considered the spread of YF in an endemic population and the entire time period T = 365 days.

4.3.1 Using Personal Protection Only

Personal protection u_1 is used to optimize the objective function J while we set educational campaign, u_2, and spray of insecticides against vector, u_3, to zero. As it is seen in Figure 4.2 (a) & (b), due to personal protection the number of exposed and infectious humans hosts decreases to zero at time $t = 139$ days, while population of exposed and infectious human hosts increases for uncontrolled case.



(a) (b)

Figure 4.2: Using personal protection strategy.

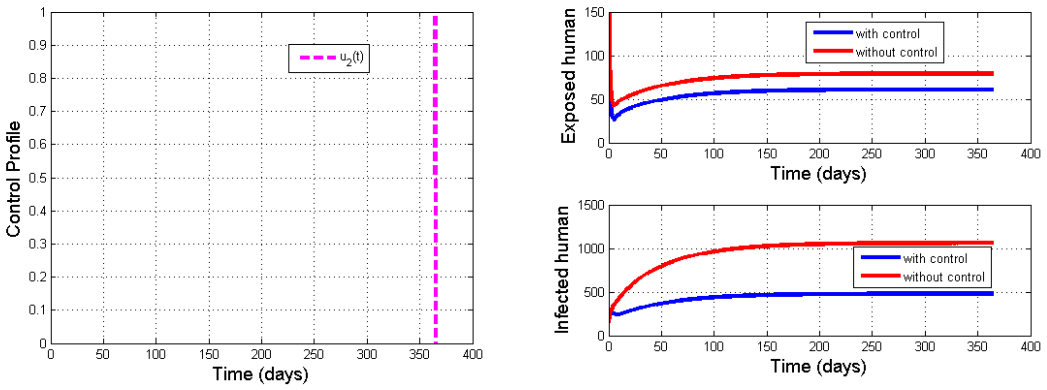
The control profile shows that from $t = 0$ to $t = 139$ days there was no change observed with respect to control strategy may be individuals were thinking on how they can start implementing the strategy, but after using preventive measures (with some cost implemented) like indoor residual spraying, use of mosquito treated bed nets, mosquito coils and mosquito repellents; the exposed and infectious individuals reduces rapidly to zero. This means that an effective use of personal protection can be beneficial to disease control even without the use of educational

campaign and insecticides. The result is similar with other researchers in the literature. Okosun and Makinde (2013), in their study of optimal control analysis of malaria in the presence of non-linear incidence rate, compared the effectiveness of two controls; prevention and treatment. Their result showed that prevention is effective to ensure the community is disease free compared to treatment. Again Okosun et al. (2011) in the study of optimal control analysis of a malaria disease transmission model that includes treatment and vaccination with waning immunity, observed that control measures are necessary for disease prevention and control, although for their case using vaccination with waning immunity is not effective than treatment this is because there is no any vaccine for malaria, for our case we have a vaccine for YF but not treatment. Moreover, Moulay et al. (2012) in the study of optimal control of chikungunya disease: larvae reduction, treatment and prevention, concluded that effort on prevention is more important than the effort for treatment, since with this control, epidemics tends to extinction. Therefore, controls have to focus on prevention that will help populations to prevent the appearance of another epidemic peak.

4.3.2 Using Educational Campaign Only

With this strategy, we optimize the objective function J using educational campaign, u_2, only while personal protection, u_1, and spray of insecticides, u_3, is set to zero. Figure 4.3 (a) shows that educational campaign is implemented with very minimal cost to some individuals that's why in (b) although control mechanism is used there is a slight difference in the number of exposed and infectious human host with and without control, and the exposed and infectious individuals with controls are not reduced exactly to zero. Thus, this strategy alone is not as good as the previous one, since we will have the exposed and infected in a years time.

The same result was also obtained by Misra et al. (2013) in their study titled a mathematical model for control of vector borne diseases through media campaigns. According to them, creating awareness through media campaigns can serve as a possibility for control of a diseases



(a) (b)

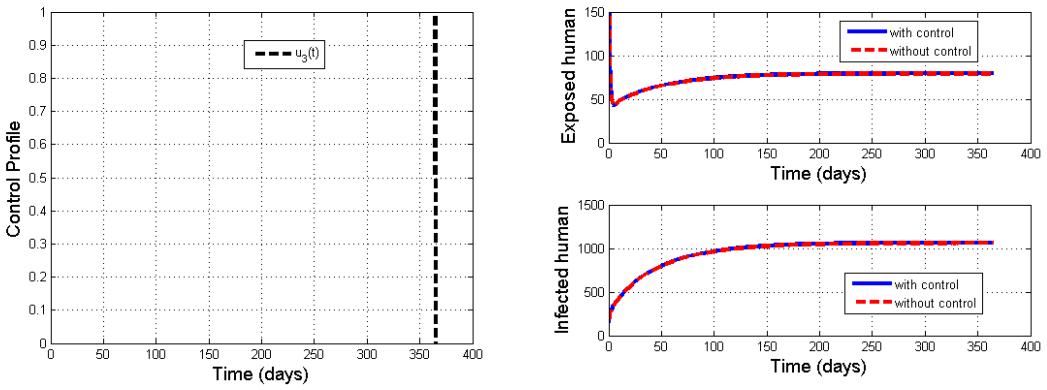
Figure 4.3: Using educational campaign strategy.

and that due to media campaigns, some people will become acquainted with the tools and techniques that are essential for prevention of a disease, but if they will not take care against those possibilities, it will not be beneficial.

4.3.3 Using Spray of Insecticides Only

The use of spray of insecticides against the vector, u_3, is used to optimize the objective function J while we set personal protection, u_1, and educational campaign, u_2, to zero, we observe in Figure 4.4 that there is no difference in the number of exposed and infectious individuals with and without control.

This numerical results indicate that this strategy leaves more infected than it is in the first two strategies, hence, suggesting that optimal use of spray of insecticides alone is not effective for disease reduction as some of vectors will remain unaffected and cause the infection to both hosts.



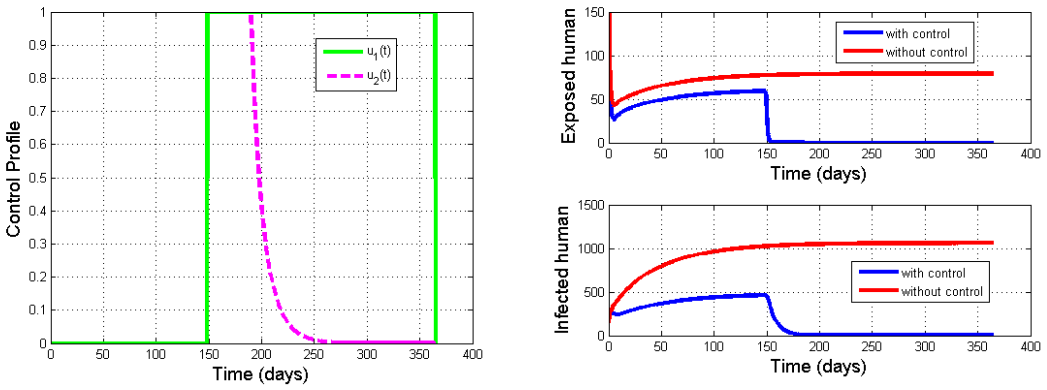
(a) (b)

Figure 4.4: Using spray of insecticides strategy.

4.3.4 Using Personal Protection and Educational Campaign

In this strategy, we use two controls personal protection, u_1, and educational campaign, u_2, to optimize the objective function J; while we set spray of insecticides, u_3, to zero. We observe in Figure 4.5 (a) & (b) that due to combination of these two control strategies, there is a significant difference in the number of exposed and infected with and without control. However, the control u_1 is zero from $t = 0$ to $t = 149$ days, while the control u_2 is at its upper bound from $t = 0$ to $t = 190$ days before it drops to zero until its final time. The numerical results indicates that combination of these two strategies is good compared to using single strategy since the infected reduces to zero from time $t = 149$ to final time.

With this strategy, the control profiles suggests that control on personal protection, u_1, should be at its upper bound from $t = 149$ days till the end of the intervention, while educational campaign, u_2, drops gradually from the upper bound to zero after $t = 190$ days. Hence, suggesting that optimal use of personal protection together with educational campaign is effective for reduction of disease transmission.



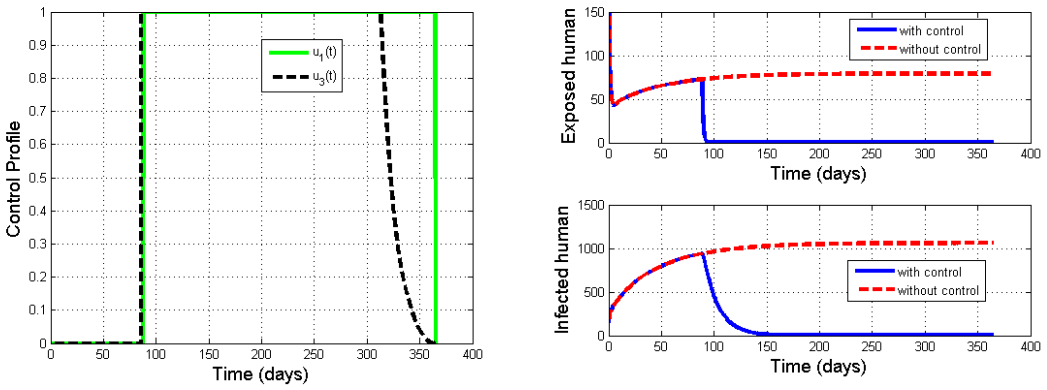
(a) (b)

Figure 4.5: Using personal protection and educational campaign strategy.

4.3.5 Using Personal Protection and Spray of Insecticides

Combination of personal protection, u_1, and spray of insecticides, u_3, is used to optimize the objective function J, while we set educational campaign, u_2 to zero. We observe in Figure 4.6 (a) & (b) that no change has been effected from $t = 0$ to $t = 85$ days, meaning that the number of exposed and infected human were increasing to both cases with and without control. However, from $t = 88$ days to $t = 312$ days the control u_3 is implemented with high cost which results to the decrease of the exposed and infected to zero, while the control u_1 is at its upper bound from $t = 88$ until the final time before it drops rapidly to zero. The numerical results indicates that combination of u_1 and u_3 is most effective compared to combination of u_1 and u_2.

This means that an effective and optimal use of personal protection and spray of insecticides against the vector may be beneficial even without the use of educational campaign, since the exposed and infected drops rapidly to zero earlier from $t = 88$ days till the final time.

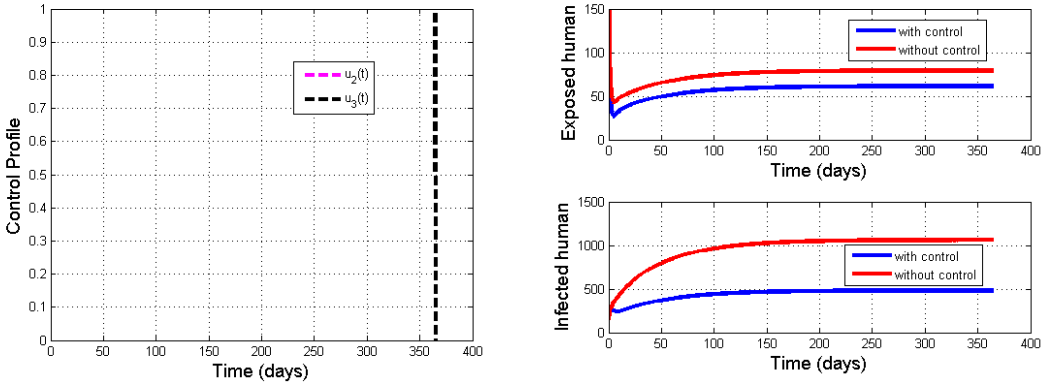


(a) (b)

Figure 4.6: Using personal protection and spray of insecticide strategy.

4.3.6 Using Educational Campaign and Spray of Insecticides

With this strategy, the control mechanism educational campaign, u_2 and spray of insecticides on vector, u_3, are together used to optimize the objective function J; while personal protection, u_1, is set to zero. Figure 4.7 (a) shows that the control u_3 is at its upper bound throughout the time before it rapidly fall down to zero at final time, while, the control u_2 is zero throughout the time. This seem spray of insecticides overrides the educational campaign. In (b), the numerical



(a) (b)

Figure 4.7: Using educational campaign and spray of insecticide strategy.

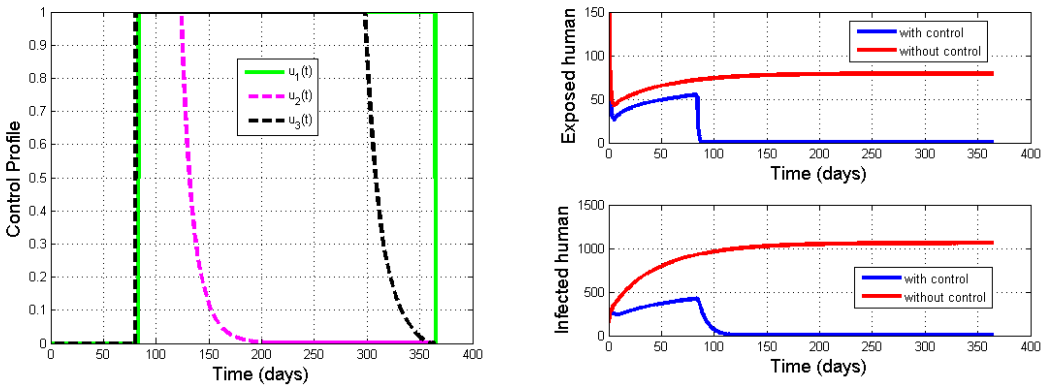
results indicates that using this strategy the infected and exposed individuals are not reduced directly to zero although there is a significant difference on using the control and without using the control. This result suggests that effective and optimal use of educational campaign and spray of insecticides could not be beneficial to disease transmission reduction without personal protection.

However, in some cases, when comparing single control versus double control strategies, result showed that using double control strategy is more beneficial and is effective. The same result was also shown by other researchers from the literature like Moulay et al. (2012), Lashari et al. (2012), Okosun et al. (2011) among others. Most of their results showed that two controls yields better result compared to a single control.

4.3.7 Using Combination of all 3 strategies

Combination of all controls personal protection, u_1, educational campaign u_2 and spray of insecticides, u_3, is used to optimize the objective function J. We observe in Figure 4.8 (a) & (b) that the control u_1 is at its upper bound from $t = 82$ days to final time before it fall rapidly to zero, the control u_2 is at its upper bound from $t = 0$ to $t = 124$ days before dropping gradually until the final time, while the control u_3 is at its upper bound from $t = 80$ days to $t = 298$ days before dropping gradually to zero until the final time. This numerical results indicates that combination of all strategies u_1, u_2 and u_3 is the most beneficial and effective compared to combination of two controls or single control, since the infected and exposed reduced to zero very early at $t = 80$ until the final time. Also there is a strong significant difference on the number of infected and exposed with and without control.

This result was also observed by other researchers of optimal control from the literature; like Mpeshe et al. (2014a) in the study of optimal control strategies for the dynamics of rift valley



(a) (b)

Figure 4.8: Using combination of strategies.

fever, Ozair et al. (2012) in the study of stability analysis and optimal control of a vector-borne disease with nonlinear incidence, Moulay et al. (2012) in the study of optimal control of chikungunya disease; larvae reduction, treatment and prevention, Lashari et al. (2012) in the study of presentation of malaria epidemics using multiple optimal controls, Makinde and Okosun (2011) in the study of impact of chemo-therapy on optimal control of malaria disease with infected immigrants. Their conclusion showed that optimal controls have a very desirable effect for reducing the number of infected individuals and that multiple optimal controls is the most effective compared to others.

4.4 Conclusion

In this chapter, we aimed at determining the optimal control measures for preventing and minimizing the YF infection from the population. We derived and analyzed the necessary conditions for the optimal control model of YF disease in the presence of personal protection and educational campaign to human hosts as well as spray of insecticides against the vector.

We have identified optimal control strategies for several scenarios. The results show that using multiple optimal control measures is the most effective strategy to bring a stable disease-free

situation compared to a single control. However, spray of insecticides alone was seen as not effective without personal protection, and optimal use of personal protection alone might be beneficial to minimize transmission of the infection to the community.

Thus control programs that follow three control strategies; personal protection, educational campaign and spray of insecticides can effectively reduce the number of latent and infectious individuals and hence disease reduction. However, single control strategy may be considered depending on objective required.

CHAPTER FIVE

Cost-Effectiveness Analysis of Personal Protection, Educational Campaign and Spray of Insecticides for the Dynamics of Yellow Fever[4]

Abstract: This chapter presents the cost-effectiveness analysis of yellow fever control programmes for the aim of comparing the costs required against the health benefits gained among the control programmes. Three strategies (strategy A - personal protection only, strategy B - personal protection and spray of insecticides and strategy C - personal protection, educational campaign combined with spray of insecticides) were compared using the incremental cost-effectiveness ratio technique. The results show that strategy C that combines all the interventions is the most cost-effective compared to others. We later went further to investigate the cost-effectiveness ratio of the strategy C per infections avoided and disability adjusted life years (DALYs) gained over time. Our result show the discounted cost of running strategy C control programme over time, where the total cost increases with an increase in the proportion of population who will take personal protection daily and those who will receive health education for their betterment. Also, we observed that the cost-effectiveness ratio (CER) per infection avoided and DALYs averted vary for each specific day and decreases with time since the start of the control programme.

Keywords: Cost-effectiveness analysis; Incremental cost effectiveness ratio; Disability-adjusted life years (DALYs).

[4] This chapter is based on a manuscript submitted to *International Journal of Advances in Applied Mathematics and Mechanics (IJAAMM)*

5.1 Introduction

The study of optimal control theories in epidemiological models have been of much interest for informed decision-making, because resources devoted to health care are very limited. These theories, can determine the optimal distribution of limited resources during epidemics (Zhou et al., 2013). Since the resources in health care are limited, to compare costs required and benefits gained among programmes (e.g. educational campaign, treatment) cost benefit analysis and/or cost effectiveness analysis need to be done.

Cost-effectiveness analysis in particular is more useful in comparing broader sets of health policies or intervention programmes to inform health sector about budget allocation decision. In health care it involves identification of all relevant use of resources (cost) and evaluation of expected health benefit (gains) derived by putting those resources to use (Edmunds et al., 1999). The purpose of cost-effectiveness analysis is to ascertain which programme or combination of programmes can achieve particular objectives at the lowest cost. By choosing those with the least cost for a given outcome, society can use its resources more effectively. Cost-effectiveness analysis measures the effects on mortality (quantity of life) and morbidity (quality of life) (Rushby and Hanson, 2001). The aim is to maximize the health benefits per dollar spent (or minimize the cost per unit of health benefit gained) (Edmunds et al., 1999).

In cost-effectiveness analysis, the effects on mortality and morbidity can be carried out using two methods; the quality-adjusted life years (QALYs) and the disability-adjusted life years (DALYs). QALYs was the first method to be developed in the 1970's (Torrance, 1970; Fanshel and Bush, 1970). In this method, the incremental effect of the control programme is based on the number of years of life that would be added and reduction of time spent in disability. QALY weights are assigned the value of one for perfect health and zero for death (Sassi, 2006). We can refer to (Sassi, 2006) for details on the formulation and calculation of QALYs.

DALYs is another method of cost-effectiveness analysis which was introduced in the World Development Report in the 1990's (WHO, 1996). DALYs are the sum of present value of future years of lifetime lost through premature mortality, and the present value of years of future time adjusted to the average severity (frequency and intensity) of any mental or physical disability caused by a disease or injury (Rushby and Hanson, 2001).

DALYs are a measure of something 'lost' rather than 'gained'. DALYs weight are coded on a scale of zero for perfect health and one for death which is the opposite of the QALYs. In this chapter, the cost-effectiveness analysis is done using the ICER and DALYs method, which is described in Section 5.3.

5.2 Epidemiological Measures

5.2.1 Measuring of Economic Impact of YF

The economic impact of a certain disease is assessed in terms of cost and cost-effectiveness of different control strategies (Hove-Musekwa et al., 2014). This involves cost measures for each strategy and the different economic evaluation methods. In our yellow fever model, personal protection was seen as the best strategy for single control, personal protection and spray of insecticide was the best for two controls and combination of all three strategies that is personal protection, educational campaign and spray of insecticides (PEI) was also seen as the best control strategy to bring a stable disease free situation for a set of three controls. Thus in our cost effectiveness analysis, we need to investigate and compare differences between the costs of these interventions per health outcome achieved.

5.2.2 Cost Measurement

In measuring costs, we identify the resources to be used, quantify them and place a monetary value on them (Hove-Musekwa et al., 2014). We calculate and compare the costs of control strategy per health outcome achieved to meet social demand. We aim at maximization of total population health. These costs include direct, indirect and intangible (pain of suffering). Indirect costs includes costs of resource inputs and existing infrastructure, while direct costs are like staff salaries and per-diem, supplies (consumable used for insecticide spraying and vector surveillance) and mobility (fuel and minor vehicle fixes during fieldwork). Morbidity and mortality costs are included in the calculation of cost-effectiveness ratio.

5.2.3 Cost-effectiveness ratio (CER)

There are three types of cost-effectiveness ratio: average cost-effectiveness ratio (ACER), marginal cost-effectiveness ratio (MCER) and the incremental cost-effectiveness ratio (ICER). The most commonly used are the average cost effectiveness ratio (ACER) and the incremental cost-effectiveness ratio (ICER). We use CER to analyse the effectiveness of control measures, and we define it mathematically as:

$$\text{CER} = \frac{\text{Total cost of an intervention}}{\text{Effectiveness of the intervention}}, \tag{5.1}$$

5.3 Cost-effectiveness analysis

To quantify the cost-effectiveness of the control measures, we examine the cost-effectiveness ratio of the strategies, so that we can draw our conclusions. The cost-effectiveness ratio is the ratio of the net costs to the net benefits (Edmunds et al., 1999). The three types mentioned in Sub-section 5.2.3 are discussed shortly as follows: The ACER deals with a single intervention

and evaluates that intervention against its baseline option (e.g., no intervention or current practice). It is calculated by dividing the net cost of the intervention by the total number of health outcomes prevented by the intervention.

The marginal cost-effectiveness ratio (MCER) is used for assessment of specific changes in cost and effect when a program is expanded or contracted, and the incremental cost-effectiveness ratio (ICER), is used to compare the differences between the costs and the health outcomes of two or more alternative intervention strategies that compete for the same resources. It is generally described as the additional cost per additional health outcome.

5.3.1 Incremental Cost-Effectiveness Ratio

In this study our interest lies foremost in the incremental cost-effectiveness ratio (ICER) which is the ratio of the incremental cost to the incremental benefit of two or more competing interventions. The ICER allows us to compare the cost-effectiveness of our interventions, that is, personal protection, personal protection and spray of insecticides, and combination of all strategies: personal protection, educational campaigns combined with spray of insecticides. The ICER represents the gradient of the line connecting the program outcome to the existing strategy on the cost-effectiveness graph. The program which has the lowest gradient or with flatter slope is the most cost-effective (Hove-Musekwa et al., 2014). That is to say a high value of ICER corresponds to a small increase in health benefit over the strategy above it, but with a relatively large additional cost (Adams et al., 2007).

In ICER, when comparing two competing intervention strategies incrementally, one intervention should be compared with the next-less-effective alternative. The ICER numerator includes the differences in intervention costs, averted disease costs, costs of prevented cases, and averted productivity losses if applicable, while ICERs denominator is the difference in health outcomes

(e.g., total number of infections averted, number of susceptibility cases prevented) (Okosun and Makinde, 2012; Okosun et al., 2011).

We therefore take our strategies to be strategy A (personal protection only), strategy B (personal protection and spray of insecticides) and strategy C (personal protection, educational campaign combined with spray of insecticides) and the baseline option of no strategy (no control). Thus, based on the model simulation results of the paper titled Application of optimal control strategies for the dynamics of YF by Kung'aro et al. (2015) [Chapter 4] we rank the strategies in order of increasing effectiveness as in Table 5.1.

Table 5.1: Strategies with costs from Chapter 4 simulation

Strategies	Total infection averted	Total costs ($)	ICER
No Strategy	0	0	-
Strategy A	0.0202	$ 4928	243960.396
Strategy B	2.9965	$ 9014	1372.845
Strategy C	1.2953×10^5	$ 2589400	19.922

The ICER, is then calculated as:

$$\text{ICER (A)} = \frac{4928}{0.0202} = 243960.396,$$

$$\text{ICER (B)} = \frac{9014 - 4928}{2.9965 - 0.0202} = \frac{4086}{2.9763} = 1372.845,$$

Comparing between strategy A and B, it shows a cost saving of $ 1372.85 for strategy B over strategy A. The higher ICER in strategy A indicates that strategy A is strongly dominated, that is, strategy A is more costly and less effective than strategy B. Therefore, strategy A is excluded from the set of alternatives since it does not consume limited resources.

Thus, we now need to compare strategy B and C; we calculate the ICER for strategy C as follows:

$$\text{ICER (C)} = \frac{2589400 - 9014}{129530 - 2.9965} = \frac{2580386}{129527.0035} = 19.922,$$

Based on this result, we conclude that strategy C (combination of all strategies) has the least ICER and therefore is more cost-effective than strategy B. Thus, it is clear that the efforts on personal protection, educational campaign and spray of insecticides is more desirable for effective control of YF.

The results are similar with Okosun and Makinde (2012) on their study titled on a drug-resistant malaria model with susceptible individuals without access to basic amenities. In this study they used ICER to compare the cost-effectiveness of the combination of at least two of the control strategies, use of treated bednets, treatment of infective individuals, and spray of insecticides. Strategy A was combination of provision of basic amenities and use of treated bednets; strategy B was combination of provision of basic amenities and treatment of infective individuals; strategy C was combination of use of treated bednets and treatment of infective individuals and strategy D was combination of provision of basic amenities, use of treated bednets and treatment of infective individuals. Their results showed that strategy D (combination of use of treated bednets, provision of basic amenities to susceptibles, and treatment of infectives) has the least ICER and therefore is more cost-effective than others.

Similarly, Hove-Musekwa et al. (2014) got the same results in the study of cost-effectiveness analysis of hospitalization and home-based care strategies for people living with HIV/AIDS: the case of Zimbabwe. Their control strategies compared were voluntary counselling and testing (VCT), VCT combined with hospitalisation, VCT combined with community home based care (CHBC), and a combination of the three strategies. The results showed that a combination of all the intervention strategies gives the best result.

We then analyse the cost and the cost-effectiveness of implementing PEI control programme (our optimal strategy). We investigate the cost-effectiveness of personal protection, educational campaign and spray of insecticides on human population by looking at human infections avoided or DALYs (disability adjusted life years) averted over time.

We assume that costs of personal protection and educational campaign are directed to all human population groups (i.e susceptible, vaccinated, exposed, infected and recovered), while spray of insecticide (which include larvicide and adulticide) costs will be directed to buying of the spraying medicine and paying the workers who engage on spraying activities for the aim of reducing vector population. Since costs fluctuate with time, in economic analysis there is discounting of the costs for the particular period and this discount rate is usually between 3% and 5% (Hove-Musekwa et al., 2014).

Let $C(t)$ be the total cost rate function (in US \$ per unit time), a proportion η from total human population are assumed to take personal protection daily making the cost of personal protection, C_P, to be associated with buying and using mosquito coils and repellents, mosquito treated bed-nets and indoor residual spraying. We also assume that educational campaign is done once a month and the cost of educational campaign, C_E, is proportional to the total number of human population at any given time and is associated to training peer educators and health workers, printing booklets and other related materials, cost of information from the radio, newspapers and televisions as well as paying salaries and per-diem during implementation of the programme.

Finally, we assume C_I to be the cost of buying medicine for spraying and paying workers who engage in spraying activities (which include larvicide and adulticide) for reducing vector population. Spraying activities is assumed to be done twice in every month because the mosquitoes that are not affected by the initial spray (i.e do not die) may reproduce and increase their population within two weeks period. Therefore the total cost function at any time t, is given by:

$$C(t) = \eta C_P N_h + \nu C_E N_h + C_I, \tag{5.2}$$

where η is the proportion of human population taking personal protection daily, and ν is the rate of human population receiving health education either from the radio, televisions, news

papers or from the trained health workers daily. The total discounted economic costs C_{TC}, direct cost of personal protection, education campaign and spraying as per control programme over T years period is given by:

$$C_{TC} = \int_0^T C(t)e^{-rt}dt, \tag{5.3}$$

where r is the discount rate, $N_h = S_h + V_h + E_h + I_h + R_h$.

We then use the CER (5.1) to analyse the effectiveness of our PEI control programme. We investigate the effectiveness, and then the cost-effectiveness of personal protection, educational campaign and the spray of insecticides on human population by looking at human infections avoided or DALYs (disability adjusted life years) averted over time. PEI programmes are typically implemented over a long period of time, hence the costs and the benefits have to be summed over time and discounted to their present value (as costs and benefits which occur in the future are valued lower than costs and benefits that occur now).

5.3.2 CER per infections avoided

Let χ^* (assumed to be constant) be the initial incidence at the start of the control programme, which is assumed to start at endemic equilibrium point in absence of any control programme. The cost-effectiveness ratio per infection avoided in human is given by:

$$\text{CER} = \frac{\int_0^T C(t)e^{-rt}dt}{\int_0^T [\chi^* - \chi(t)]e^{-rt}dt}, \tag{5.4}$$

where $C(t)$ is the net cost of the PEI programme, $\chi(t)$ is the incidence of human infection at time T and r is the discount rate (Edmunds et al., 1999).

5.3.3 DALYs averted over time

DALYs combines the measure of time lived with disability and the time lost due to premature death. That is the sum of years of life lost(YLLs) due to premature death and years of life lived with disability (YLDs). Thus;

$$\text{DALYs} = \text{YLLs} + \text{YLDs}. \tag{5.5}$$

We use the idea of other researchers from the literature Rushby and Hanson (2001) and Murray (1994) to calculate the values of YLLs and YLDs for a single death by using the following formulae

$$\begin{aligned}\text{YLLs} = \frac{KCe^{ra_1}}{(r+b)^2}\left(e^{-(r+b)(L_1+a_1)}[-(r+b)(L_1+a_1)-1] - e^{-(r+b)a_1}[-(r+b)a_1-1]\right) \\ + \frac{1-K}{r}(1-e^{-rL_1}),\end{aligned} \tag{5.6}$$

and

$$\begin{aligned}\text{YLDs} = DW\frac{KCe^{ra_2}}{(r+b)^2}\left(e^{-(r+b)(L_2+a_2)}[-(r+b)(L_2+a_2)-1] - e^{-(r+b)a_2}[-(r+b)a_2\right) \\ -1] + DW\frac{1-K}{r}(1-e^{-rL_2}),\end{aligned} \tag{5.7}$$

where K is the age-weighting modulation constant, r is the discount rate, b is the age weighting constant, C is the adjustment constant for age-weights, a_1 is the age at the onset of the disease, L_1 is the duration of disability, a_2 is the age at death, L_2 is the standard life expectancy at age of death (years) and DW is the disability weight (DW=1 for premature death, DW=0 for perfect heath) (Rushby and Hanson, 2001). We also assume that all human individuals will live up to their life expectancy, we therefore calculate DALYs averted through our optimal control

measure (PEI) from the following equation,

$$\text{DALYs}_{\text{Averted}} = YLLs\int_0^T [\phi^* - \phi(t)]e^{-rt}dt + YLDs\int_0^T [\chi^* - \chi(t)]e^{-rt}dt, \tag{5.8}$$

where ϕ^* and $\phi(t)$ are the estimated number of humans dying due to the disease per day at the beginning of the intervention and at time T respectively. The LHS of eqn (5.8) gives the DALYs averted due to death and infections avoided, respectively. Since there is no treatment of infectious cases, DALYs are taken to be averted through human infection and death avoided. Thus, the cost effectiveness ratio per DALYs averted is given by;

$$\text{CER} = \frac{\int_0^T C(t)e^{-rt}dt}{\text{DALYs}_{\text{averted}}}. \tag{5.9}$$

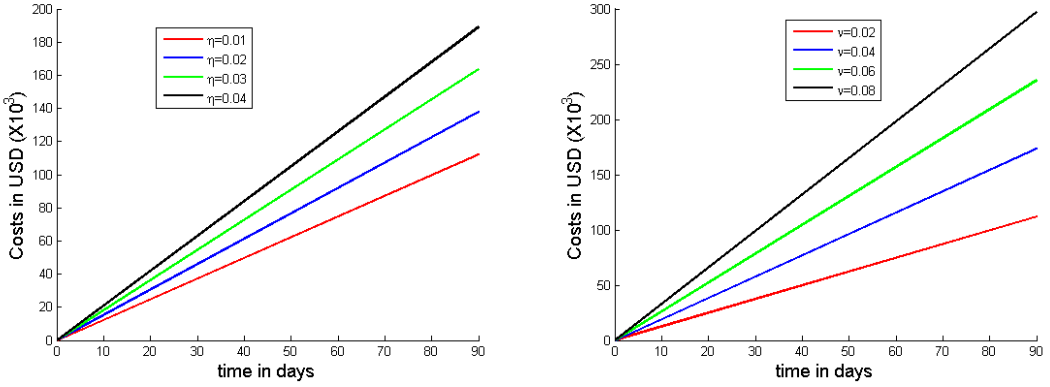
5.4 Numerical results and discussion

In this section we illustrate the numerical results of the cost-effectiveness analysis of personal protection, educational campaign and spray of insecticides (PEI) control program by carrying out numerical simulations of the model equations (5.3), (5.4) and (5.9). We assume that there is no other optimal strategy apart from the PEI programme.

We also assumed that application of insecticide spray will increase mortality rate of vectors, which automatically results in reduction of its birth rate, and that application of PEI control effort is started at the endemic situation where we have the disease in the model and in the absence of any other intervention. Most of the parameter values that we use in simulation of the model are from literature search, Tanzania Health Profile (2012), Tanzania Population Census (2012), WHO (2014) and few are assumed. Parameters as they have been used in this study are described in Chapter 4 Table 4.1.

United Republic of Tanzania with a population size of about 44.9 million people (Tanzania Population Census, 2012), and taking the initial cost of implementing the control programme per

day to be $\$0.5 \times 10^3$ for personal protection, $\$0.6 \times 10^3$ for educational campaign and $\$0.7 \times 10^3$ for spraying of insecticides, requires the estimated daily costs for running the PEI programme given in Figure 5.1.



(a) (b)

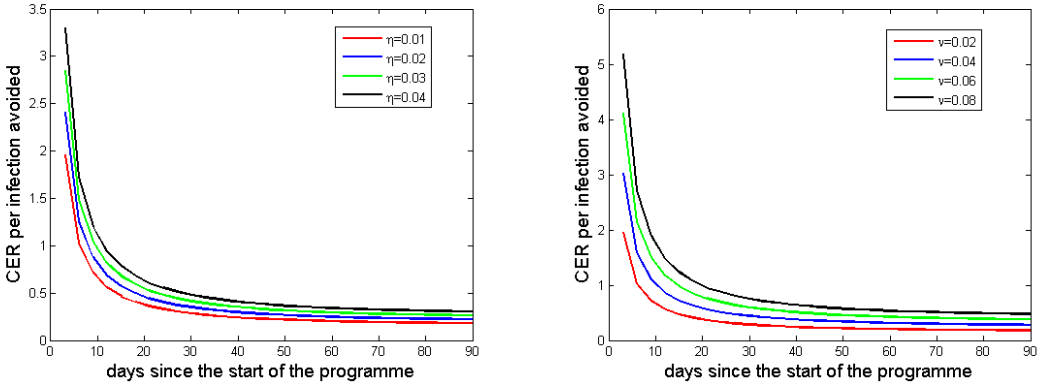
Figure 5.1: Cost of implementing PEI programme for different values of η and ν.

Results show the cost with discount of running the PEI control programme over time, where the total cost increases with an increase in the proportion of population who take personal protection daily and those who will receive health education respectively. Cost-effectiveness analysis parameters are as shown in Table 5.2.

Table 5.2: Description of cost-effectiveness analysis parameters of the model equation (5.8)

Symbol	Description	Value	Reference
DW	Disability weight	0.45	assume
r	Discount rate	0.03	Hove-Musekwa et al. (2014)
K	Age-weighting modulation constant	1	Murray (1994),
C	Adjustment constant for age-weights	0.16243	Murray (1994),
b	Age weighting constant	0.04	Murray (1994),
L_1	Duration of disability	100 days	assume
a_1	Age at the onset of the disease (mid-value of life expectancy)	30.42 years	Tanzania Health Profile (2012), WHO (2014)
a_2	Age at death	34 years	assume
L_2	Standard life expectancy at age of death	32 years	assume

Figures 5.2 (a) and (b) show the cost-effectiveness ratio per infection avoided of the personal protection, educational campaign and the spray of insecticides (PEI) control programme over time by varying η (a proportion of total human population taking care for themselves daily) and



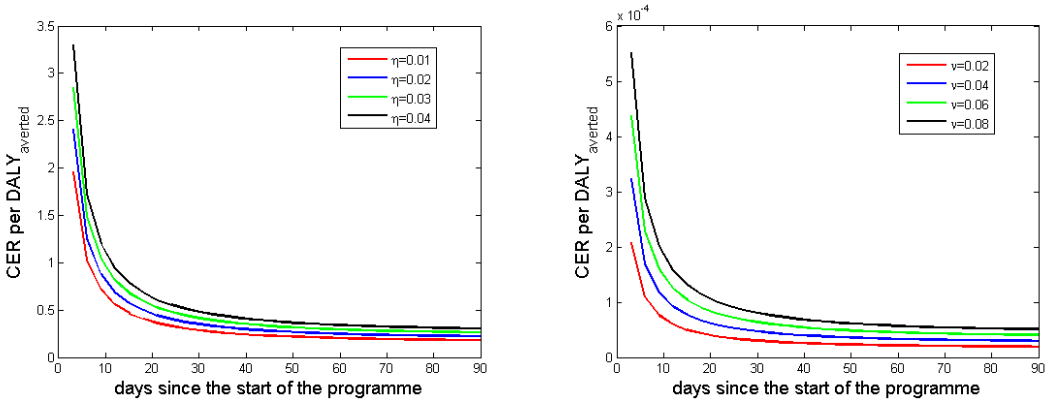
(a) (b)

Figure 5.2: Cost-effectiveness ratio per infection avoided by varying η, and ν for (a) and (b) respectively.

ν (a proportion of total human population receiving health education daily) respectively. The result show that the CER per infection avoided vary for each specific day and decreases with time since the start of the control programme and drops to a value of $\$0.3048$ and $\$0.4785$ by varying η and ν respectively.

We also see in Figures 5.3 (a) and (b) that the CER per $DALY_{averted}$ over time decreases daily to a value of about $\$5.094 \times 10^{-2}$ by varying η and $\$0.3048$ by varying ν, since the start of the control programme. Again, it should be noted that all the cost-effectiveness ratios seems to decrease as you increase the proportion of individuals who take personal protection daily, and those who acquire health education and use the knowledge to account for their life if the control programme is run for many years.

However, our results do not include the benefits that would be arising from avoided infections (cost benefit analysis is not done). If these benefits are included, then we would expect the cost-effectiveness ratio to be far less than the ones estimated in all Figures 5.1, 5.2 and 5.3 above.



(a) (b)

Figure 5.3: Cost-effectiveness ratio per $DALY_{averted}$ by varying η, and ν for (a) and (b) respectively.

5.5 Conclusion

This chapter aimed at finding out the cost-effectiveness of the control measures introduced in our yellow fever model. We first examined the cost-effectiveness ratio of the strategies by using the incremental cost-effectiveness ratio (ICER), which is used to compare the costs against the health benefits of two or more competing interventions.

Our interventions were categorized into four groups where we had baseline option; no intervention strategy (no control), strategy A (personal protection only), strategy B (personal protection and spray of insecticides) and strategy C (personal protection, educational campaign combined with spray of insecticides).

Our results indicate that strategy C, that combines all the interventions is the most cost-effective compared to others and hence, if implemented disease infection will be minimized. However, as pointed out by Hove-Musekwa et al. (2014) decisions to implement a particular strategy are not only dependent on cost-effectiveness criteria but also dependent on other factors such as, what the policy maker is willing to pay and considers to be for money.

We later used the CER per infections avoided and DALYs averted over time technique to investigate the cost-effectiveness of the PEI intervention obtained above. Result show the discounted cost of running PEI control programme over time, where the total cost increases with an increase in the proportion of population that take personal protection daily, and those who receive health education for their betterment. Again, the results show that the CER per infection avoided and DALYs averted vary for each specific day and decreases with time since the start of the control programme.

Cost-effectiveness analysis presented in this study can help to inform decision makers which control strategies they can implement. As pointed out by Klein et al. (2007) in the study of mathematical models of disease environment, that interdisciplinary collaborations can help in improving the accuracy of predictions of the course and cost of the epidemic and help policy makers in implementing the correct strategies.

CHAPTER SIX

General Discussion, Conclusion and Recommendations

6.1 Summary

In this study, a non-linear mathematical model (system of ODEs) with two hosts and one vector has been formulated, presented and analysed to study transmission dynamics of YF. The model was later extended to include control variables which were personal protection, educational campaign and spray of insecticides aiming to assess the optimal and affordable control measures for prevention and control of YF infection in Tanzania. The main objective of the study was to formulate and analyse mathematical models that are used to study transmission dynamics and find affordable control strategies of YF disease. For the model to be biologically relevant, several assumptions were made concerning behaviour of the populations, and several parameters and variables were identified for model development.

Both qualitative and numerical analyses of the model were done. Qualitative analysis of the model, involved computation of the threshold parameter R_0, which was done using the next generation operator approach as well as determining the existence and stability of the model equilibria. Sensitivity analysis of the threshold parameter R_0, with respect to epidemiological parameters was carried out in order to assess some key parameters for disease transmission.

Finally, different control strategies were evaluated to assess their effectiveness to control YF transmission dynamics using optimal control theory and Pontryagins Maximum Principle. Furthermore, cost-effectiveness analysis of optimal control measures was carried out aiming at comparing the costs required against the health benefits gained among the optimal control programmes, given that the economy of most developing countries including Tanzania is low.

6.2 Conclusion

From the study, it is noted that the transmission dynamics of YF infection is caused mostly with daily biting rate of infected mosquitoes, probability of disease transmission from infected vector to susceptible human and vice versa, birth rate of vectors, and the recruitment of unvaccinated immigrants to susceptible human populations. Most of these sensitive parameters to R_0 are preventable through control mechanisms. Thus, one effective way that can possibly reduce transmission and prevalence of the disease is quick and focused interventions, destruction of breeding sites and YF surveillance at the ports of entry.

Also from the analysis, threshold parameter of the form $R_0 = \sqrt{R_{hv} + R_{vm}}$ was obtained where R_{hv} represents the reproduction number of human-vector compartment and R_{vm} represents the reproduction number of primate-vector compartment. Disease-free equilibrium point was seen to be locally asymptotically stable if $R_{vm} < 1$ and globally asymptotically stable if $R_{hv} < 1$, meaning that YF epidemic can be prevented and controlled from human individuals if new infection from monkeys to vector is less than unity and also new infection from vector to human is less than unity. Thus, prevention of new infection from monkeys is essential since they are primary hosts and the sources of YFV as also noted from other researchers in the literature. Generally, disease-free equilibrium point is stable locally and globally if and only if $R_0 < 1$. This result calls for much attention to vectors since they are intermediary between human host and primate in the transmission of the disease.

Furthermore, we derived and analysed the conditions for optimal control of YF with personal protection, educational campaign and spray of insecticides using optimal control theory for different scenarios. Results show that using multiple optimal control measures (for this case combination of the strategies) is most effective strategy to bring a stable disease-free situation compared to a single control. However, spray of insecticides alone was seen as not effective

without personal protection, and optimal use of personal protection alone might be beneficial to minimize transmission of the infection to the community.

In addition to that, cost-effectiveness analysis of the optimal control measures was carried out to compare costs incurred with health outcome achieved between two or more alternative intervention strategies that compete for the same resources, using incremental cost-effectiveness ratio. Results showed that combination of all strategies is the most cost-effective compared to others and hence efforts on personal protection, educational campaign and spray of insecticides is more desirable for effective control of YF.

Finally, we investigated the cost-effectiveness ratio of PEI (the best strategy obtained) per infections avoided and disability adjusted life years (DALYs) gained over time. From numerical results, we see that the total cost increases with an increase in the proportion of population that take personal protection daily and those who receive health education. Also, results show that the CER per infection avoided and DALYs averted vary for each specific day and decreases with time since the start of the control programme.

6.3 Recommendations

Based on the findings of the study, we make the following recommendations:

1. Emphasize on vaccination to prevent YF transmission by introducing a government health vaccination policy to be compulsory not only to travelers but also to all citizens with the affordable cost. Since no cure is available currently, and complete eradication is not possible therefore vaccination remain as a single most important measure for preventing YF.

2. Increase and conduct massive awareness programmes to people through information campaign, educational seminars, and use of mass media programme about YF epidemic,

its transmission factors and how to protect oneself from being exposed to infection and other possible transmission factors from environment.

3. Vectors being the most risk factors for YFV transmissions, Government should plan, establish and implement fumigation policy specifically those places where most vector breeding occurs (tropical regions), so as to destroy the sites and reduce vector population. Advice on emptying stagnant water areas where vectors are most likely to live.

4. Increase collaborations with private sectors and non-governmental international organisations (NGOs) and involve them in identifying and supporting appropriate and sustainable disease control measures and surveillance system for early detection of YF cases.

6.4 Limitations and Future Work

The research results and conclusions obtained in this study are not final findings, the work can be extended in various ways to provide further insights and assess the impact of current and future control strategies to YF by:

1. Considering climate change like temperature variations effect on disease transmission. The impact of climate change on birth rate and development rates of vectors have not been considered. However, biting rate, carrying capacity, birth rate, death rate, incubation rate and other physiognomies of mosquitoes depend on climate factors, thus these factors might make the model more realistic.

2. Introducing time delay in population dynamics: when the rate of change of population is not only a function of the present population but also depends on the past population, also delay can arise from latent period of the disease. Thus employing delay differential equations in YF modelling would lead to some interesting behaviour.

3. Future direction may also consider modelling YF and other vector-borne infectious diseases without homogeneous mixing assumption. As it is really known that risks from an infection may be age related, vaccination programmes may focus on specific ages and age groups mix heterogeneously. Considering epidemiological models with age structure would lead to system of partial differential equations, the area that is in its infancy stage.

4. Including vertical transmission of the infection to the vector population, isolation as a control strategy specifically when resources are not sufficient and carrying out cost-benefit analysis of optimal control measures.

5. Re-examining the assumptions set and trying to relax some as well as validating the model using parameter values estimated from the real data of a specific endemic country of YF. For our case, inadequate real data from the country forced us to resort to literature and assume for the unavailable one.

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Appendix A

Matlab codes for Figures of Chapter Two

```
% Defining the functions for the normalised model to be
saved as 'monie.m'(first time), 'monie1.m'(second time)
and 'monie2.m'(last time). Their corresponding equations
are as follows:

function dy = monie(t,y)
function dy = monie1(t,y)
function dy = monie2(t,y)

%defining the variables
s_h = y(1);  s_v = y(6);  s_m = y(9);
v_h = y(2);  e_v = y(7);  e_m = y(10);
e_h = y(3);  i_v = y(8);  i_m = y(11);
i_h = y(4);
r_h = y(5);

% Defining parameter values
bh = 0.003; bv = 0.05; bm = 0.04; sigma = 0.009;
rho = 0.02; omega = 0.05; a =0.9; beta1 = 0.9;
beta2 = 0.9; beta3 = 0.5; beta4 = 0.9;
varepsilon = 0.005; alpha = 0.001; deltah = 0.05;
deltav = 0.02; deltam = 0.85; gamma = 0.05;

% writing the model equations
dy(1) = bh+rho*(1-sigma)+omega*(v_h+r_h)-...
        a*beta1*s_h*i_v-s_h*(varepsilon+bh+sigma)+...
        alpha*s_h*i_h;
```

```
dy(2) = rho*sigma+varepsilon*s_h-v_h*(omega+bh+sigma)
        ...+alpha*e_h*i_h;
dy(3) = a*beta1*s_h*i_v-e_h*(deltah+bh+sigma)+...
        alpha*e_h*i_h;
dy(4) = deltah*e_h-i_h*(gamma+alpha+bh+sigma)+...
        alpha*i_h*i_h;
dy(5) = gamma*i_h-r_h*(omega+bh+sigma)+alpha*r_h*i_h;
dy(6) = bv-(a*beta2*s_v*i_h+a*beta3*s_v*i_m)-s_v*bv;
dy(7) = a*beta2*s_v*i_h+a*beta3*s_v*i_m-e_v*(deltav+bv);
dy(8) = deltav*e_v-i_v*bv;
dy(9) = bm-a*beta4*s_m*i_v-s_m*bm;
dy(10) = a*beta4*s_m*i_v-e_m*(deltam+bm);
dy(11) = deltam*e_m-i_m*bm;
dy = [dy(1);dy(2);dy(3);dy(4);dy(5);dy(6);dy(7);
      dy(8);dy(9);dy(10);dy(11)];

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
% RUNNING FILE;
 clear all
 close all
 clc
 tspan=[0 350];

% Defining initial values for variables
 y0 = [0.25 0.25 0.15 0.15 0.2 0.4 0.2
       0.4 0.4 0.2 0.4];

% Define equations to be integrated
 opt=odeset('RelTol',1e-00006); % creates an integrator
```

```
 [t1 y1] = ode45(@monie,tspan,y0,opt);
 [t2 y2] = ode45(@monie1,tspan,y0,opt);
 [t3 y3] = ode45(@Monie2,tspan,y0,opt);

% Defining total human population equation
     Nh=y1(1,1)+y1(1,2)+y1(1,3)+
        y1(1,4)+y1(1,5);

% Defining prevalence of the disease function
  from human equation
     Prevalence = (y1(:,3)+y1(:,4))./Nh
     Prevalence = (y2(:,3)+y2(:,4))./Nh
     Prevalence = (y3(:,3)+y3(:,4))./Nh

% plotting
  plot(t1,(y1(:,3)+y1(:,4))/Nh,'b-',t2,(y2(:,3)+...
  y2(:,4))/Nh,'r-',t3,(y3(:,3)+y3(:,4))/Nh,
  'g-','Linewidth',3);
  xlabel('Time (days)','Fontsize',14)
  ylabel('Disease Prevalence','Fontsize',14)
  legend('a=0.9','a=0.5','a=0.2')
  hold on

% Note1: The parameter value for 'a' should be
         different in each function that is; in monie
         'a=0.9', monie1 'a=0.5', and monie2 'a=0.3'

% Note2: The same codes and procedure is used for
         variation of values of beta1, bv, bh,
```

deltav and deltah parameters.

MATLAB Codes for Figure 2.5

```
%Defining the functions for the normalized
 model to be saved as 'infree.m'
function dy =infree(t,y,bh,bm,bv,sigma,rho,
omega,a,beta1,beta2,beta3,beta4,varepsilon,
alpha,delta_h,delta_v,gamma,delta_m)

%defining the variables of the model
s_h = y(1);     s_v = y(6);    s_m = y(9);
v_h = y(2);     e_v = y(7);    e_m = y(10);
e_h = y(3);     i_v = y(8);    i_m = y(11);
i_h = y(4);
r_h = y(5);

%writing the model equations
dy(1) = bh+rho*(1-sigma)+omega*(v_h+r_h)-...
        a*beta1*s_h*i_v-s_h*(varepsilon+bh+sigma)+...
        alpha*s_h*i_h;
dy(2) = rho*sigma+varepsilon*s_h-v_h*(omega+bh+sigma)+
        ...alpha*e_h*i_h;
dy(3) = a*beta1*s_h*i_v-e_h*(delta_h+bh+sigma)+...
        alpha*e_h*i_h;
dy(4) = delta_h*e_h-i_h*(gamma+alpha+bh+sigma)+...
        alpha*i_h*i_h;
dy(5) = gamma*i_h-r_h*(omega+bh+sigma)+...
        alpha*r_h*i_h;
```

```
dy(6) = bv-(a*beta2*s_v*i_h+a*beta3*s_v*i_m)-...
        s_v*bv;
dy(7) = a*beta2*s_v*i_h+a*beta3*s_v*i_m-...
        e_v*(delta_v+bv);
dy(8) = delta_v*e_v-i_v*bv;
dy(9) = bm-a*beta4*s_m*i_v-s_m*bm;
dy(10) = a*beta4*s_m*i_v-e_m*(delta_m+bm);
dy(11) = delta_m*e_m-i_m*bm;
dy = [dy(1);dy(2);dy(3);dy(4);dy(5);dy(6);dy(7);
      dy(8);dy(9);dy(10);dy(11)];

%Displaying the reproduction number value
R0 = sqrt((a^2*beta1*beta2*delta_h*delta_v*...
     (bh+sigma(1-rho)+omega))./((delta_h+bh+sigma)*...
     (gamma+alfa+bh+sigma)*bv*(delta_v+bv)*...
     (gamma+alfa+bh+sigma)*(delta_h+bh+sigma)))+...
     ((a^2*beta3*beta4*delta_v*delta_m)./bm*...
     (delta_m+bm)*bv*(delta_v+bv))

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%RUNNING FILE
clear all
close all
clc
tspan=0:0.01:8;

%Defining initial values of the variables
 and parameters
y0 = [0.35 0.15 0.2 0.2 0.1 0.35 0.3 0.35
```

```
      0.35 0.3 0.35];
bh = 0.53;    rho = 0.02;     alpha = 1.5;
bv =0.5;      a = 0.5;        beta4 = 0.5;
bm = 0.4;    beta1 = 0.5;    delta_h = 0.05;
omega = 0.05;  beta2 = 0.3;    delta_v = 0.8;
sigma = 0.0009; beta3 = 0.37; delta_m = 0.05;
varepsilon = 0.5; gamma = 0.007;

opt=odeset('RelTol',1e-00006); %creates an integrator
[t y] = ode45(@infree,tspan,y0,opt,bh,bm,bv,sigma,rho,
omega,a,beta1,beta2,beta3,beta4,varepsilon,alpha,
delta_h,delta_v,gamma,delta_m);

%Plotting
figure,plot(t,y(:,1),'b','linewidth',3);
hold on
plot (t,y(:,6),'r','linewidth',3);
plot (t,y(:,9),'g','linewidth',3);
xlabel('Time (years)','Fontsize',14)
ylabel('Proportions of susceptibles','Fontsize',14)
legend('human','vector','primates')
hold on

figure,plot(t,y(:,4),'b','linewidth',3);
hold on
plot(t,y(:,8),'r','linewidth',3);
plot(t,y(:,11),'g','linewidth',3);
xlabel('Time (years)','Fontsize',14)
ylabel('Proportions of infectious','Fontsize',14)
```

```
legend('human','vector','primates')
hold on
```

MATLAB Codes for Figure 2.6

```
%Defining the functions for normalized model to be
saved as 'ende.m'
function dy = ende(t,y,bh,bm,bv,sigma,rho,omega,a,
beta1,beta2,beta3,beta4,varepsilon,alpha,muh,muv,
mup,deltah,deltav,gamma,deltam)

%Defining the variables
s_h = y(1);   s_v = y(6);   s_m = y(9);
v_h = y(2);   e_v = y(7);   e_m = y(10);
e_h = y(3);   i_v = y(8);   i_m = y(11);
i_h = y(4);
r_h = y(5);

%Writing the model equations
dy(1) = bh+rho*(1-sigma)+omega*(v_h+r_h)-...
        a*beta1*s_h*i_v-s_h*(varepsilon+bh+sigma)
        ...+alpha*s_h*i_h;
dy(2) = rho*sigma+varepsilon*s_h-v_h*(omega+bh+sigma)
        ...+alpha*e_h*i_h;
dy(3) = a*beta1*s_h*i_v-e_h*(deltah+bh+sigma)+...
        alpha*e_h*i_h;
dy(4) = deltah*e_h-i_h*(gamma+alpha+bh+sigma)+...
        alpha*i_h*i_h;
dy(5) = gamma*i_h-r_h*(omega+bh+sigma)+alpha*r_h*i_h;
dy(6) = bv-(a*beta2*s_v*i_h+a*beta3*s_v*i_m)-s_v*bv;
```

```
dy(7) = a*beta2*s_v*i_h+a*beta3*s_v*i_m-e_v*(deltav+bv);
dy(8) = deltav*e_v-i_v*bv;
dy(9) = bm-a*beta4*s_m*i_v-s_m*bm;
dy(10) = a*beta4*s_m*i_v-e_m*(deltam+bm);
dy(11) = deltam*e_m-i_m*bm;
dy = [dy(1);dy(2);dy(3);dy(4);dy(5);dy(6);dy(7);
      dy(8);dy(9);dy(10);dy(11)];

%Displaying the reproduction number value
R0 = sqrt((a^2*beta1*beta2*delta_h*delta_v*...
(bh+sigma(1-rho)+omega))./((delta_h+bh+sigma)*...
(gamma+alfa+bh+sigma)*bv*(delta_v+bv)*...
(gamma+alfa+bh+sigma)*(delta_h+bh+sigma)))+...
((a^2*beta3*beta4*delta_v*delta_m)./bm*...
(delta_m+bm)*bv*(delta_v+bv))

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%RUNNING FILE
clear all
close all
clc
tspan=[0 250];

%Defining initial values for variables
y0 = [0.4 0.2 0.15 0.15 0.1 0.4 0.3
      0.3 0.4 0.3 0.3];

%Defining parameter values at endemic zone
bh = 0.003;     bv = 0.05;     bm = 0.04;
```

```
sigma = 0.009;  rho = 0.02;    omega = 0.05;
a = 0.9;        beta1 = 0.9;   beta2 = 0.9;
beta3 = 0.5;    beta4 = 0.9;   varepsilon = 0.005;
alpha = 0.001;  deltah = 0.05; deltav = 0.02;
deltam = 0.85;  gamma = 0.05;

opt=odeset('RelTol',1e-00006); %creates an integrator
[t y] = ode45(@ende,tspan,y0,opt,bh,bp,bv,
        Lambda,rho,omega,a,beta1,beta2,beta3,beta4,
        varepsilon,alpha,deltah,deltav,gamma,deltam);

%Plotting
figure,
plot(t,y(:,1),'-b',t,y(:,6),'-r',t,y(:,9),
    '-g', 'LineWidth',3);
legend('human','vector','primate',2)
xlabel('Time (days)','Fontsize',14)
ylabel('Susceptible Populations','Fontsize',14)
hold on
figure,
plot(t,y(:,4),'--b',t,y(:,8),'--r', t,y(:,11),
     'g--','LineWidth',3);
legend('human','vector','primate',2)
xlabel('Time (days)','Fontsize',14)
ylabel('Infectious Populations','Fontsize',14)
```

Appendix B

Matlab codes for Figures of Chapter Four

```
% Defining function that solves the state system with
  eleven differential equations by Monie, 2014

function ydot = jims(t,yy,U,Constant)

% Definitions of Variables
%Human population %Vector population %Primate population
Sh = yy(1);          Sv = yy(6);      Sp = yy(9);
Vh = yy(2);          Ev = yy(7);      Ep = yy(10);
Eh = yy(3);          Iv = yy(8);      Ip = yy(11);
Ih = yy(4);
Rh = yy(5);

% Defining parameters used
bh = Constant(1);        beta4 = Constant(11);
bv = Constant(2);        epsilon = Constant(12);
bp = Constant(3);        alpha = Constant(13);
Lambda = Constant(4);    deltah = Constant(14);
rho = Constant(5);       deltav = Constant(15);
omega = Constant(6);     deltap = Constant(16);
a = Constant(7);         gamma = Constant(17);
beta1 = Constant(8);     muh = Constant(18);
beta2 = Constant(9);     muv = Constant(19);
beta3 = Constant(10);    mup = Constant(20);

% Defining State Equations and total population
u1=U(1); u2=U(2);u3=U(3);
```

```
% Total population
Nh = Sh+Vh+Eh+Ih+Rh;
Nv = Sv+Ev+Iv;
Np = Sp+Ep+Ip;

% State Equations (ODE)
ydot1 = bh*Nh+Lambda*(1-rho)+omega*(Vh+Rh)-...
        (a*beta1*Sh*Iv*(1-u1))./Nv-...
        epsilon*(1+u2)*Sh-muh*Sh;
ydot2 = rho*Lambda+epsilon*(1+u2)*Sh-Vh*omega-muh*Vh;
ydot3 = (a*beta1*Sh*Iv*(1-u1))./Nv-Eh*deltah-Eh*muh;
ydot4 = deltah*Eh-(muh+alpha)*Ih-gamma*(1+u2)*Ih;
ydot5 = gamma*Ih*(1+u2)-Rh*muh-omega*Rh;
ydot6 = bv*Nv*(1-u3)-(a*beta2*Sv*Ih*(1-u1))./Nh-
        ...(a*beta3*Sv*Ip)./Np-muv*Sv*(1+u3);
ydot7 = (a*beta2*Sv*Ih*(1-u1))./Nh+(a*beta3*Sv*Ip)./Np-
        ...deltav*Ev-muv*Ev*(1+u3);
ydot8 = deltav*Ev-muv*Iv*(1+u3);
ydot9 = bp*Np-(a*beta4*Sp*Iv)./Nv-mup*Sp;
ydot10 = (a*beta4*Sp*Iv)./Nv-deltap*Ep-mup*Ep;
ydot11 = deltap*Ep-mup*Ip;
ydot=[ydot1; ydot2; ydot3; ydot4; ydot5; ydot6;
      ydot7; ydot8; ydot9; ydot10; ydot11];

% Defining function which solves co-state (adjoint)
  system with eleven equations by Monie, 2014

function ydot = jims_costate(t,y,U,X,Constant);
```

```
% Setting of adjoint variables
L1 = y(1);   L6 = y(6);   L9 = y(9);
L2 = y(2);   L7 = y(7);   L10 = y(10);
L3 = y(3);   L8 = y(8);   L11 = y(11);
L4 = y(4);
L5 = y(5);

% Defining constants
bh = Constant(1);     beta3 = Constant(10);
bv = Constant(2);     beta4 = Constant(11);
bp = Constant(3);   epsilon = Constant(12);
Lambda = Constant(4); alpha = Constant(13);
rho = Constant(5);   deltah = Constant(14);
omega = Constant(6); deltav = Constant(15);
a = Constant(7);     deltap = Constant(16);
beta1 = Constant(8);  gamma = Constant(17);
beta2 = Constant(9);    muh = Constant(18);
muv = Constant(19);     B1 = Constant(23);
mup = Constant(20);     B2 = Constant(24);
A1 = Constant(21);      B3 = Constant(25);
A2 = Constant(22);

u1 = U(1); u2=U(2); u3=U(3);
Sh=X(1,:); Vh = X(2,:); Eh = X(3,:); Ih=X(4,:);
Rh=X(5,:); Sv=X(6,:); Ev=X(7,:); Iv=X(8,:);
Sp=X(9,:); Ep=X(10,:); Ip=X(11,:);

% Defining total population
```

```
Nh = Sh+Vh+Eh+Ih+Rh;
Nv = Sv+Ev+Iv;
Np = Sp+Ep+Ip;

% Defining co-state (adjoint) equations
ydot1 = L1*((a*beta1*Iv*(1-u1))./Nv+(epsilon*(1+u2))+...
        muh)-L2*epsilon*(1+u2)-L3*a*beta1.*Iv*(1-u1);
ydot2 = L2*(omega+muh)-L1*omega;
ydot3 = -A1+L3*(deltah+muh)-(L4*deltah);
ydot4 = -A2+(L6-L7)*(a*beta2.*Sv.*(1-u1))./Nh-...
         L5*(gamma*(1+u2))+L4*(muh+alpha+gamma*(1+u2));
ydot5 = L5*(omega+muh)-L1*omega;
ydot6 = (L6-L7)*((a*beta2*Ih*(1-u1))./Nh+...
        (a*beta3*Ip)./Np)+(L6*muv*(1+u3));
ydot7 = L7*(deltav+muv)-L8*deltav;
ydot8 = (L1-L3)*(a*beta1*Sh*(1-u1))./Nv+...
        ((L9-L10)*a*beta4*Sp)./Nv+(L8*muv*(1-u3));
ydot9 = (L9-L10)*(a*beta4*Iv)./Nv+L9*mup;
ydot10 = L10*(deltap+mup)+L11*deltap;
ydot11 = (L6-L7)*(a*beta3*Sv)./Np+L11*mup;
ydot=[ydot1; ydot2; ydot3; ydot4; ydot5; ydot6;
      ydot7; ydot8; ydot9; ydot10; ydot11];

% RUNNING FILE
clear all
close all
clc
t0 = 0; tf=365; N=7300;
time =linspace(t0,tf,N);
```

```
% Estimated initial condition for state system
y0 = [350 250 150 150 100 250 150 100 250 150 100];

% Defining constants
bh= Constant(1);      omega= Constant(6);
bv= Constant(2);      a= Constant(7);
bp= Constant(3);      beta1= Constant(8);
Lambda= Constant(4);  beta2= Constant(9);
rho= Constant(5);     beta3= Constant(10);
beta4= Constant(11);  epsilon= Constant(12);
alpha= Constant(13); deltah= Constant(14);
deltav= Constant(15);

deltap= Constant(16);   A1= Constant(21);
gamma= Constant(17);    A2= Constant(22);
muh= Constant(18);      B1= Constant(23);
muv= Constant(19);      B2= Constant(24);
mup= Constant(20);      B3= Constant(25);

% Defining constant values
bh bv bp Lambda rho omega a beta1 beta2 beta3
beta4 epsilon alpha deltah deltav deltap gamma
muh muv mup A1 A2 B1 B2 B3

Constant = [0.0003 0.002 0.00004 70 0.02 0.05
0.5 0.8 0.8 0.5 0.9 0.5 0.001 0.95 0.95 0.85
0.05 0.02 0.03 0.1 1000 1000 0.0001 1000 0.01];
```

```
lf = [0 0 0 0 0 0 0 0 0 0 0];

init = y0;
init2 = lf;
h = (tf-t0)/N;
u = linspace(0,0,N+1);
u1=u'; u2=u'; u3=u';
U = [u1 u2 u3];

% Implementation of the algorithm
% Test 1 stopping condition 1
delta = 0.001;
X=init;

% Initialize iteration counter
i = 0;
mm = size(X);
NumXX = 10e10;
Xnew = rand(N+1,mm(2)).*(repmat(X,N+1,1));
DenXnew = norm(Xnew);

while NumXX/DenXnew>delta
Xold = Xnew;
oldu = U;

% Forward Runge-Kutta for States System
[Tx, X] = rk4foward(@jims,t0,tf,N,init,U,Constant);

% Backward Runge-Kutta for Costates System
```

```
[Tp, P]=rk4back(@jims_costate,t0,tf,N,init2,U,X,Constant);

% Update the controls
Sh=X(1,:);Vh = X(2,:);Eh = X(3,:);Ih=X(4,:); Rh=X(5,:);
Sv=X(6,:);Ev=X(7,:);Iv=X(8,:); Sp=X(9,:);Ep=X(10,:);
Ip=X(11,:);

% Defining total population
Nh = Sh+Vh+Eh+Ih+Rh;
Nv = Sv+Ev+Iv;
Np = Sp+Ep+Ip;

L1 = P(1,:); L2 = P(2,:); L3 = P(3,:); L4 = P(4,:);
L5 = P(5,:); L6 = P(6,:); L7 = P(7,:); L8 = P(8,:);
L9 = P(9,:); L10 = P(10,:); L11 = P(11,:);

% Implementation of the cases; Do one after the other
  in each time.
% Case0: No control,
 u1 = zeros(1,N+1);
 u2 = zeros(1,N+1);
 u3 = zeros(1,N+1);

% Case1: u1/=0, u2=0, u3=0
 u1 = max(0,min(1,1/(2*B1).*(L3-L1).*(a.*beta1.*Sh.*Iv)./
      ...Nv+(L7-L6).*(a.*beta2.*Sv.*Ih)./Nh));
 u2 = zeros(1,N+1);
 u3 = zeros(1,N+1);
```

```
% Case2: u1=0, u2/=0, u3=0
 u1 = zeros(1,N+1);
 u2 = max(0,min(1,1/(2*B2).*(epsilon.*(L1-L2).*Sh+...
      gamma.*(L4-L5).*Ih)));
 u3 = zeros(1,N+1);

% Case3: u1=0, u2=0, u3/=0
 u1 = zeros(1,N+1);
 u2 = zeros(1,N+1);
 u3 = max(0,min(1,1/(2*B3).*L6.*(bv.*Nv+muv.*Sv)+...
       (L7.*muv.*Ev)+(L8.*muv.*Iv)));

% Case4: u1/=0, u2/=0, u3=0
 u1 = max(0,min(1,1/(2*B1).*(L3-L1).*(a.*beta1.*Sh.*Iv)./
      ...Nv+(L7-L6).*(a.*beta2.*Sv.*Ih)./Nh));
 u2 = max(0,min(1,1/(2*B2).*(epsilon.*(L1-L2).*Sh+...
      gamma.*(L4-L5).*Ih)));
 u3 = zeros(1,N+1);

% Case5: u1/=0, u2=0, u3/=0
 u1 = max(0,min(1,1/(2*B1).*(L3-L1).*(a.*beta1.*Sh.*Iv)./
      ...Nv+(L7-L6).*(a.*beta2.*Sv.*Ih)./Nh));
 u2 = zeros(1,N+1);
 u3 = max(0,min(1,1/(2*B3).*L6.*(bv.*Nv+muv.*Sv)+...
       (L7.*muv.*Ev)+(L8.*muv.*Iv)));

% Case6: u1=0, u2/=0, u3/=0
 u1 = zeros(1,N+1);
 u2 = max(0,min(1,1/(2*B2).*(epsilon.*(L1-L2).*Sh+...
```

```
      gamma.*(L4-L5).*Ih)));
 u3 = max(0,min(1,1/(2*B3).*L6.*(bv.*Nv+muv.*Sv)+...
       (L7.*muv.*Ev)+(L8.*muv.*Iv)));

%Case7: u1/=0, u2/=0, u3/=0
u1 = max(0,min(1,1/(2*B1).*(L3-L1).*(a.*beta1.*Sh.*Iv)./
     ...Nv+(L7-L6).*(a.*beta2.*Sv.*Ih)./Nh));
u2 = max(0,min(1,1/(2*B2).*(epsilon.*(L1-L2).*Sh+...
     gamma.*(L4-L5).*Ih)));
u3 = max(0,min(1,1/(2*B3).*L6.*(bv.*Nv+muv.*Sv)+...
     (L7.*muv.*Ev)+  (L8.*muv.*Iv)));

Uu = [u1' u2' u3'];
U = 0.5*Uu + 0.5*oldu;

Xnew = X';
NumXX = abs(norm(Xnew-Xold));
DenXnew = norm(Xnew);

% Update iteration counter
i=i+1
end

% Plotting
X=X';
Tx =Tx';
XX=X(:,3); YY=X(:,4);

Up = [0 0 0];
```

```
[T,Y] = ode45(@jims,time,y0,[],Up,Constant);
J=sum(A1*XX(end)+A2*YY(end)+B1*Uu(:,1).*Uu(:,1)+...
   B2*Uu(:,2).*Uu(:,2)+B3*Uu(:,3).*Uu(:,3));

Z = [Tx,X];
cd('C:\Users\Monicapc\Desktop\Monica_Optimalcontrolcode')
save('case1State', 'Z');
save('case1Control', 'Uu');
save('Cost', 'J');

figure(1)
 subplot(2,1,1)
 plot(Tx,X(:,3),'-b', T, Y(:,3),'--r','LineWidth',3);
 legend('with control', 'without control',3)
 xlabel('Time (days)', 'Fontsize',14)
 ylabel('Exposed human', 'Fontsize',14)
 grid on
 hold on

 subplot(2,1,2)
 plot(Tx,X(:,4),'-b',T, Y(:,4),'--r','LineWidth',3);
 legend('with control','without control',3)
 xlabel('Time (days)','Fontsize',14)
 ylabel('Infected human','Fontsize',14)
 grid on
 hold on

 figure(2)
 plot(Tx,Uu(:,1),'-g','LineWidth',3); hold on
```

```
plot(Tx,Uu(:,2),'--m','LineWidth',3);hold on
plot(Tx,Uu(:,3),'--k','LineWidth',3)
xlabel('Time (days)','Fontsize',14)
ylabel('Control Profile','Fontsize',14)
legend('u_1(t)','u_2(t)','u_3(t)','Fontsize',14)
grid on
hold off
```

Appendix C

Matlab codes for Figures of Chapter Five

```
% Defining function that highlights about the cost
  of implementing PEI control programme over time
  by Monie 2015.

function I = odes(t,y,Nv,Np,bh,rho,omega,a,beta1,
             epsilon,muh, Lambda,deltah,alpha,gamma,
             bv,beta2,beta3,deltav,muv,bp,beta4,mup,
             deltap,eta,Cp,Ce,Ci,nu,r,DW,K,C,b,L1,a1,a2,L2)

% Definition of variables
Sh = y(1); Sv=y(6); Sp=y(9);
Vh = y(2); Ev=y(7); Ep=y(10);
Eh = y(3); Iv=y(8); Ip=y(11);
Ih = y(4);
Rh = y(5);

% Defining total function for human
Nh=sum(y(1:5));

% Defining system of equations (ODE)
ydot1 = bh.*Nh+Lambda*(1-rho)+omega.*(Vh+Rh)-...
       ((a*beta1).*Sh.*Iv)./Nv-epsilon.*Sh-muh.*Sh;
ydot2 = rho*Lambda+epsilon.*Sh-omega.*Vh-muh.*Vh;
ydot3 = ((a*beta1).*Sh.*Iv)./Nv-deltah.*Eh-muh.*Eh;
ydot4 = deltah.*Eh-(muh+alpha).*Ih-gamma.*Ih;
ydot5 = gamma.*Ih-muh.*Rh-omega.*Rh;
ydot6 = bv.*Nv-((a*beta2).*Sv.*Ih)./Nh-...
```

```
        ((a*beta3).*Sv*Ip)./Np-muv.*Sv;
ydot7 = ((a*beta2).*Sv.*Ih)./Nh+((a*beta3).*Sv.*Ip)./Np-
        ...deltav.*Ev-muv.*Ev;
ydot8 = deltav.*Ev-muv.*Iv;
ydot9 = bp.*Np-((a*beta4).*Sp.*Iv)./Nv-mup.*Sp;
ydot10 = ((a*beta4).*Sp.*Iv)./Nv-deltap.*Ep-mup.*Ep;
ydot11 = deltap.*Ep-mup.*Ip;
I = [ydot1; ydot2; ydot3; ydot4; ydot5; ydot6;
   ydot7; ydot8; ydot9; ydot10; ydot11];


function I=integration(t,y,Nv,Np,bh,rho,omega,a,beta1,
           epsilon,muh,Lambda,deltah,alpha,gamma,bv,
           beta2,beta3,deltav,muv,bp,beta4,mup,deltap,
           eta,Cp,Ce,Ci,nu,r,DW,K,C,b,L1,a1,a2,L2)

Nh=sum(y(1:5));
Nv=sum(y(6:8));

Eh=y(3);
Sh=y(1);
Iv=y(8);
Ih=y(4);

global ii, global jj;

gg=(20-(((a*beta1).*Sh.*Iv)./Nv)./Nh).*exp(-r*t);
GG=(0.5-alpha*Ih).*exp(-r*t);
```

```
% Defining cost function
f=(Cp.*eta(ii).*Nh+Ce.*nu(jj).*Nh+Ci).*exp(-r.*t);

%Integrating total cost and other functions using
trapezoidal rule for i=2:length(t)
    Ctc_trapz(i)=trapz(t(1:i),f(1:i));
    g1(i)=trapz(t(1:i),gg(1:i));
    G1(i)=trapz(t(1:i),GG(1:i));
End

%Defining YLLs and YLDs functions
YLLs = (K*C.*exp(r*a1))/((r+b).^2)*(exp-(r+b)*(L1+a1))*
       ...(-(r+b)*(L1+a1)-1)-exp-(r+b)*a1*(-(r+b)*a1-1)+
       ...(1-K)./r*(1-exp(-r*L1));

YLDs = DW*(K*C.*exp(r*a2))/((r+b).^2)*(exp-(r+b)*(L2+a2)*
       ...(-(r+b)*(L2+a2)-1)-exp-(r+b)*a2*(-(r+b)*a2-1)+
       ...DW*(1-K)./r*(1-exp(-r*L2)));

% Defining DALYs averted function
DALYs_averted=YLLs*G1+YLDs*g1;

% Defining CER per DALYs averted function
CER_averted = Ctc_trapz(end)./DALYs_averted

CER = Ctc_trapz(end)./g1;

% Obtaining transpose of the functions
I = [Ctc_trapz' CER' CER_averted'];
```

```
% RUNNING FILE;
clear all
close all
clc
tspan = 0:3:90;

% The estimated initial values
y0=[350 250 150 150 100 250 150 100 250 150 100];

Nv=sum(y0(5:7));
Np=sum(y0(8:10));

% Defining parameter values
DW=0.45; K=1; C=0.16243; b=0.04; L1=100; a1=30.42;
a2=34; L2=32; bh=0.003; bv=0.01; bp=0.04; Lambda=70;
rho=0.02; omega=0.05; a=1; beta1=0.9; beta2=0.9;
beta3=0.5; beta4=0.9; alpha=0.001; deltah=0.05;
deltav=0.02; deltap=0.85; gamma = 0.05; muh=0.05;
muv=0.02; mup=0.03;
eta=[0.001 0.002 0.003 0.004];
nu=[0.002 0.004 0.006 0.008];
r=0.03; epsilon=0.005; Cp=0.5; Ce=0.6; Ci=0.8;

c = ['r','b','g','k'];
opt = odeset('RelTol',1e-00006);
global ii, global jj;
ii=1;
jj=1;
```

```
[t,y] = ode45(@odes,tspan,y0,opt,Nv,Np,bh,rho,
omega,a,beta1,epsilon,muh,Lambda,deltah,alpha,
gamma,bv,beta2,beta3,deltav,muv,bp,beta4,mup,
deltap,eta,Cp,Ce,Ci,nu,r,DW,K,C,b,L1,a1,a2,L2);

for ii=1:4
  I=integration(t,y,Nv,Np,bh,rho,omega,a,beta1,
  epsilon,muh,Lambda,deltah,alpha,gamma,bv,beta2,
  beta3,deltav,muv,bp,beta4,mup,deltap,
  eta,Cp,Ce,Ci,nu,r,DW,K,C,b,L1,a1,a2,L2);

% Plotting
  figure(1)
  subplot(1,2,1)
  hold on
  plot([t(1) t(end)],[I(1,1) I(end,1)],c(ii),'linewidth',2)
  xlabel('time in days','Fontsize',14)
  ylabel('Costs in USD (X10^3)','Fontsize',14)
  xlim([0 t(end)])
  legend('\eta=0.01','\eta=0.02','\eta=0.03','\eta=0.04')
end

ii=1;
 for jj=1:4
  I=integration(t,y,Nv,Np,bh,rho,omega,a,beta1,epsilon,
  muh,Lambda,deltah,alpha,gamma,bv,beta2,beta3,deltav,
  muv,bp,beta4,mup,deltap,eta,Cp,Ce,Ci,nu,r,DW,K,C,b,
  L1,a1,a2,L2);
```

```
  figure(2)
  subplot(1,2,2)
  hold on
  plot([t(1) t(end)],[I(1,1) I(end,1)],c(jj),'linewidth',2)
  xlabel('time in days','Fontsize',14)
  ylabel('Costs in USD (X10^3)','Fontsize',14)
  xlim([0 t(end)])
  legend('\nu=0.02','\nu=0.04','\nu=0.06','\nu=0.08')
 end

jj=1;
for ii=1:4
  I=integration(t,y,Nv,Np,bh,rho,omega,a,beta1,
  epsilon,muh,Lambda,deltah,alpha,gamma,bv,beta2,
  beta3,deltav,muv,bp,beta4,mup,deltap,
  eta,Cp,Ce,Ci,nu,r,DW,K,C,b,L1,a1,a2,L2);

  figure(3)
  plot(t, I(:,2),c(ii), 'linewidth', 2)
  xlabel('days since the start of the programme','Fontsize',14)
  ylabel('CER per infection avoided','Fontsize',14)
  xlim([0 t(end)])
  legend('\eta=0.01','\eta=0.02','\eta=0.03','\eta=0.04')
  hold on
end

ii=1;
for jj=1:4
  I=integration(t,y,Nv,Np,bh,rho,omega,a,beta1,epsilon,
```

```
  muh,Lambda,deltah,alpha,gamma,bv,beta2,beta3,deltav,
  muv,bp,beta4,mup,deltap,eta,Cp,Ce,Ci,nu,r,DW,K,C,b,
  L1,a1,a2,L2);

  figure (4)
  plot(t, I(:,2), c(jj),'linewidth', 2)
  xlabel('days since the start of the programme','Fontsize',14)
  ylabel('CER per infection avoided','Fontsize',14)
  xlim([0 t(end)])
  legend('\nu=0.02','\nu=0.04','\nu=0.06','\nu=0.08')
  hold on
end

jj=1;
for ii=1:4
  I=integration(t,y,Nv,Np,bh,rho,omega,a,beta1,epsilon,
  muh,Lambda,deltah,alpha,gamma,bv,beta2,beta3,deltav,
  muv,bp,beta4,mup,deltap,eta,Cp,Ce,Ci,nu,r,DW,K,C,b,
  L1,a1,a2,L2);

  figure(5)
  plot(t, I(:,2),c(ii),'linewidth', 2)
  xlabel('days since the start of the programme','Fontsize',14)
  ylabel('CER per DALY_{averted}','Fontsize',14)
  xlim([0 t(end)])
  legend('\eta=0.01','\eta=0.02','\eta=0.03','\eta=0.04')
  grid on
  hold on
end
```

```
ii=1;
for jj=1:4
  I=integration(t,y,Nv,Np,bh,rho,omega,a,beta1,epsilon,
  muh,Lambda,deltah,alpha,gamma,bv,beta2,beta3,deltav,
  muv,bp,beta4,mup,deltap,eta,Cp,Ce,Ci,nu,r,DW,K,C,b,
  L1,a1,a2,L2);

  figure (6)
  plot(t, I(:,3), c(jj),'linewidth', 2)
  xlabel('days since the start of the programme','Fontsize',14)
  ylabel('CER per DALY_{averted}','Fontsize',14)
  xlim([0 t(end)])
  legend('\nu=0.02','\nu=0.04','\nu=0.06','\nu=0.08')
  grid on
  hold on
end
```

Appendix D

Local Stability Analysis of E_0

Trace-determinant approach of Jacobian Matrix

To establish local stability of disease-free equilibrium, the Jacobian of the model system 3.4 is computed and evaluated at E_0. The local stability of E_0 is then determined based on the trace-determinant approach of this Jacobian. The equilibrium E_0 is locally stable if trace of the Jacobian matrix is less than zero and determinant of the same matrix is greater than zero.

If we let the right hand sides of the model equations 3.4 to be represented by the functions $(f_1, f_2, ..., f_{11})$, at steady state the Jacobian of 3.4 is given by;

$$J_i = \frac{\partial f_i}{\partial x_j}, \tag{A.1}$$

where,

f_i , $i = 1, 2, ..., 11.$ and $x_j (j = 1, 2, ..., 11)$ represent $s_h,\ v_h,\ e_h,\ i_h,\ r_h,\ s_v,$ $e_v,\ i_v,\ s_m,\ e_m,\ i_m$, respectively.

Thus, the following matrix is obtained;

$$J_{E_0} = \begin{bmatrix} -b_1 & \omega & 0 & \alpha s_h^\circ & \omega & 0 & 0 & -\eta & 0 & 0 & 0 \\ \varepsilon & -b_2 & 0 & \alpha v_h^\circ & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -b_3 & 0 & 0 & 0 & 0 & \eta & 0 & 0 & 0 \\ 0 & 0 & \delta_h & -b_4 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \gamma & -b_5 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -b_v & 0 & 0 & 0 & 0 & -a\beta_3 \\ 0 & 0 & 0 & 0 & 0 & 0 & -b_7 & 0 & 0 & 0 & a\beta_3 \\ 0 & 0 & 0 & 0 & 0 & 0 & \delta_v & -b_v & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -a\beta_4 & -b_m & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & a\beta_4 & 0 & -b_{10} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \delta_m & -b_m \end{bmatrix}. \tag{A.2}$$

where, $b_1 = (\varepsilon + b_h + \sigma),\ b_2 = (\omega + b_h + \sigma),\ b_3 = (\delta_h + b_h + \sigma), \eta = a\beta_1 s_h^\circ$
$b_4 = (\alpha + \gamma + b_h + \sigma),\ b_5 = (\omega + b_h + \sigma),\ b_7 = (\delta_v + b_v),\ b_{10} = (\delta_m + b_m).$

As seen from the matrix trace of $J_{E_0} < 0$, we can now find the determinant of the same matrix by reducing the dimensions of the matrix as follows;

The sixth and ninth columns have diagonal entries, thus excluding these columns and their corresponding rows we remain with 9×9 matrix given by

$$M = (b_v b_m) \begin{bmatrix} -b_1 & \omega & 0 & \alpha s_h^\circ & \omega & 0 & -\eta & 0 & 0 \\ \varepsilon & -b_2 & 0 & \alpha v_h^o & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -b_3 & 0 & 0 & 0 & \eta & 0 & 0 \\ 0 & 0 & \delta_h & -b_4 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \gamma & -b_5 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -b_7 & 0 & a\beta_3 \\ 0 & 0 & 0 & 0 & 0 & \delta_v & -b_v & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & a\beta_4 & -b_{10} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \delta_m & -b_m \end{bmatrix}, \tag{A.3}$$

whereby the determinant of M is now given by

$$-b_1 \begin{bmatrix} -b_2 & 0 & \alpha v_h^\circ & 0 & 0 & 0 & 0 & 0 \\ 0 & -b_3 & 0 & 0 & 0 & \eta & 0 & 0 \\ 0 & \delta_h & -b_4 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \gamma & -b_5 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -b_7 & 0 & 0 & a\beta_3 \\ 0 & 0 & 0 & 0 & \delta_v & -b_v & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & a\beta_4 & -b_{10} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \delta_m & -b_m \end{bmatrix} - \varepsilon \begin{bmatrix} \omega & 0 & \alpha s_h^\circ & \omega & 0 & -\eta & 0 & 0 \\ 0 & -b_3 & 0 & 0 & 0 & \eta & 0 & 0 \\ 0 & \delta_h & -b_4 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \gamma & -b_5 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -b_7 & 0 & 0 & a\beta_3 \\ 0 & 0 & 0 & 0 & \delta_v & -b_v & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & a\beta_4 & -b_{10} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \delta_m & -b_m \end{bmatrix},$$

further calculation gives

$$b_1b_2\begin{bmatrix} -b_3 & 0 & 0 & 0 & \eta & 0 & 0 \\ \delta_h & -b_4 & 0 & 0 & 0 & 0 & 0 \\ 0 & \gamma & -b_5 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -b_7 & 0 & 0 & a\beta_3 \\ 0 & 0 & 0 & \delta_v & -b_v & 0 & 0 \\ 0 & 0 & 0 & 0 & a\beta_4 & -b_{10} & 0 \\ 0 & 0 & 0 & 0 & 0 & \delta_m & -b_m \end{bmatrix} - \varepsilon\omega \begin{bmatrix} -b_3 & 0 & 0 & 0 & \eta & 0 & 0 \\ \delta_h & -b_4 & 0 & 0 & 0 & 0 & 0 \\ 0 & \gamma & -b_5 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -b_7 & 0 & 0 & a\beta_3 \\ 0 & 0 & 0 & \delta_v & -b_v & 0 & 0 \\ 0 & 0 & 0 & 0 & a\beta_4 & -b_{10} & 0 \\ 0 & 0 & 0 & 0 & 0 & \delta_m & -b_m \end{bmatrix}.$$

Since we have a common matrix we can factor it out

$$b_vb_m(b_1b_2 - \varepsilon\omega)\begin{bmatrix} -b_3 & 0 & 0 & 0 & \eta & 0 & 0 \\ \delta_h & -b_4 & 0 & 0 & 0 & 0 & 0 \\ 0 & \gamma & -b_5 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -b_7 & 0 & 0 & a\beta_3 \\ 0 & 0 & 0 & \delta_v & -b_v & 0 & 0 \\ 0 & 0 & 0 & 0 & a\beta_4 & -b_{10} & 0 \\ 0 & 0 & 0 & 0 & 0 & \delta_m & -b_m \end{bmatrix}.$$

Let $A = b_vb_m(b_1b_2 - \varepsilon\omega)$, we can further reduce the dimension of the matrix to remain with 4×4 matrix given by

$$M = \left\{ A(b_5b_4b_3)\begin{bmatrix} -b_7 & 0 & 0 & a\beta_3 \\ \delta_v & -b_v & 0 & 0 \\ 0 & a\beta_4 & -b_{10} & 0 \\ 0 & 0 & \delta_m & -b_m \end{bmatrix} \right\}. \tag{A.4}$$

Again we may let $B = A(b_5b_4b_3)$ in (A.4) and substitute b_7 and b_{10} to have

$$M = \left\{ B\begin{bmatrix} -(\delta_v + b_v) & 0 & 0 & a\beta_3 \\ \delta_v & -b_v & 0 & 0 \\ 0 & a\beta_4 & -(\delta_m + b_m) & 0 \\ 0 & 0 & \delta_m & -b_m \end{bmatrix} \right\}. \tag{A.5}$$

The determinant of matrix M in (A.5) will then be given by

$$-B(\delta_v + b_v)\begin{bmatrix} -b_v & 0 & 0 \\ a\beta_4 & -(\delta_m + b_m) & 0 \\ 0 & \delta_m & -b_m \end{bmatrix} - B\delta_v \begin{bmatrix} 0 & 0 & a\beta_3 \\ a\beta_4 & -(\delta_m + b_m) & 0 \\ 0 & \delta_m & -b_m \end{bmatrix},$$

whereby computation gives

$$det\ M = Bb_v(\delta_v + b_v)b_m(\delta_m + b_m) - Ba\delta_v\beta_3(a\beta_4\delta_m).$$

Further simplification gives

$$det\ M = B[b_v(\delta_v + b_v)b_m(\delta_m + b_m) - (a^2\beta_3\beta_4\delta_v\delta_m)]. \tag{A.6}$$

$$det\ M = B\left[1 - \frac{a^2\beta_3\beta_4\delta_v\delta_m}{b_v(\delta_v + b_v)b_m(\delta_m + b_m)}\right] b_v(\delta_v + b_v)b_m(\delta_m + b_m),$$

$$det\ M = B\left[1 - R_{mv}\right] b_v(\delta_v + b_v)b_m(\delta_m + b_m). \tag{A.7}$$

For $det\ M$ to be > 0 we should have $R_{mv} < 1$ which leads to the following theorem.

Theorem A.9. *The disease-free equilibrium point E_0 of model system 3.4 is locally asymptotically stable if $R_{mv} < 1$ and unstable if $R_{mv} > 1$.*