Mathematical epidemiology of Malaria disease transmission and its optimal control analyses

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KEYWORDS

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Basic reproduction number

Disease-free equilibrium

Endemic equilibrium

Bifurcation analysis

Stability analysis

Optimal control

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Pontryagin's Maximum Principle

Optimality conditions

Shadow price or adjoint variable or costate variable

Cost-effectiveness analysis

Vaccination strategies

Susceptible-Exposed-Infectious (SEI) model

Susceptible-Exposed-Infectious-Recovered (SEIR) model

Susceptible-Exposed-Infectious-Recovered-Vaccinated (SEIRV) model

Abstract

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In this thesis, we present and analyse an SEIR (susceptible-exposed-infectious-recovered) model for malaria disease transmission. The model consist treatment and control strategies such as the use of bednets and spray of insecticides with the costs associated with each control measure. Firstly, we analyze the model without treatment and investigate its stability and bifurcation behaviour. Then, we incorporate treatment and investigated the effects of different control strategies on the spread of malaria. Further, we use optimal control methods to determine the necessary conditions for the optimality of the disease eradication or control. We determined the most cost-effective strategies in fighting malaria disease by carrying out a cost-effectiveness study. We found that mass action model exhibited transcritical bifurcation. The disease-free equilibrium (DFE) is globally stable whenever, basic reproductive number is less than unity, while the models with standard incidence form exhibited backward bifurcation. In examining the cost-effectiveness analysis we found that the most cost effective strategy is the combination of insecticides spray and treatment of infective individuals.

Furthermore, we modified the SEIR model to incorporate treat-

ment and vaccination with waning immunity and an appropriate cost function. We analyze the model and investigated its stability and bifurcation property. Also, we use optimal control theory to determine the necessary optimal conditions for the disease eradication, and when eradication of the disease is unachievable we derived the necessary conditions for its control. Further, we carried out a cost-effectiveness analysis of the control strategies. In our findings, the mass action model exhibits a backward bifurcation phenomenon, while the standard incidence model exhibited a phenomenon of multiple endemic equilibria. We also found that the most cost-effective strategy to eliminate malaria is the combination of treatment of infective individuals and vaccination. From the analysis, we found that eradication will be possible and optimal when the community marginal cost is less than the community marginal benefits.

2010.

Declaration

I declare that "Mathematical epidemiology of Malaria disease transmission and its optimal control analyses" is my own work, that it has not been submitted before for any degree or examination in any other university, and that all the sources I have used or quoted have been indicated and acknowledged as complete references.

Okosun Kazeem Oare August 20 2010

Signed:.....

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Contents

Chapter 1

General Introduction

The last thirty years witnessed a resurgence of deadly infectious diseases which were once thought to have been eradicated, due to the appearance of antibiotic-resistant strains and climate changes, which helped in propagating the diseases to new geographical areas, where they were initially not present. Malaria, tuberculosis, dengue, yellow fever and HIV/AIDS are just a few diseases which continue to persist despite all efforts committed to getting these diseases eradicated. In particular, malaria is endemic in 109 countries and territories in tropical and sub-tropical zones, spanning all continents of the world except Antarctica and Australia, with intensities of transmission that vary from very low to extremely high. The World Health Organization (WHO) (2007) estimated about 40% of the world's population to be at risk with malaria disease. This accounts for over a million deaths each year in areas with high malaria transmission probability. Children under the age of 5 years and pregnant woman are the most susceptible to the disease. Sub-Saharan Africa, Asia and parts of Latin America are mostly affected.

1.1 Malaria biological background

The word malaria is derived from the Italian phrase, (Mal aria) meaning bad air as it was initially thought that the disease came from fetid marshes; but later in the 1880, Laveran discovered that the real cause of malaria was *Plasmodium*, a parasite which can only be transmitted to humans when they are bitten by a *Plasmodium* carrier female Anopheles mosquito.

In humans, the parasites grow and multiply firstly in the liver cells and then move into the red blood cells. In the blood, successive broods of parasites grow inside the red

blood cells and destroy them, producing new parasites "merozoites" to continue the cycle by invading other red cells. Most bites inject a minimum of 20 sporozoites, and very few can inject more than 100 sporozoites. About half of the successful (infectious) bites will result in blood-stage infections. The first asexual multiplication (*exoerythrocytic schizogony*) occurs within liver cells. This results in the birth of more merozoites per sporozoite between 10 thousand to 40 thousand. These merozoites then flow into the bloodstream 5-9 days after inoculation and invade red blood cells. Here they continue to multiply asexually (erythrocytic schizogony) by producing new merozoites. This can either lead to the repeat cycle within red blood cells every 48 or 72 hours or develop into the sexual transmission stages called gametocytes. Mature gametocytes of will then first appear in the bloodstream about 10 days later. These gametocytes may remain infectious for about three weeks or more. The incubation period within the mosquito may last 8-22 days. Sporozoites can remain viable for 30-40 days within the salivary glands for as long as the mosquito lives.

In 1886, Golgi Camillo [18] discovered that there were more than one species of *Plasmodium* that infected humans. In fact there are over 120 species of the parasite genus *Plasmodium* [23], though only four of them cause malaria: These are

1. *P. falciparium* - It is common in tropical areas and is majorly responsible for the most life-threatening form of malaria and caused majority of the deaths worldwide. Its incubation period is 5 - 12 days. It is also resistant to most of the drugs used in the prevention and treatment of malaria.

2. *P. ovale* - It is not as common as *P. falciparium* and is mostly in Africa. It has an incubation period of 8 - 17 days in an infected person and can hide in the liver of partially treated people to reemerge later on.

3. *P. malariae* - Is also not common, and less frequent than the other forms of malaria parasite. Its incubation period is 2 - 4 weeks in an infected person.

4. *P. vivax* - It is more common in temperate areas, such as India, Central and South America. The incubation period in the human body is approximately 8 - 13 days for the symptoms of the disease to become apparent. This can lead to life-threatening rupture of spleen. The parasite hides in the liver and returns later to the blood stream.

As deadly as it is, if diagnosed early, malaria is a curable disease with very high chances of survival when the correct medication is administered. In addition to preventive measures currently put in place to combat malaria, there are available drugs for the treatment of malaria, such as *artemisinin (Qinghao plant), chloroquine, Fansider* (*sulfadoxine-pyrimethamine*), *quinine, quindine gluconate* and *primaquine phosphate.* The preventive measures can be divided into two parts:

1. Personal protection against infection:- It is important to state that the best way to prevent malaria is to avoid mosquito bites. Firstly, on personal protection against infection, the common approaches are the use of insect repellant (DEET (*N,N-diethylmethyltoicamide*)), *chemoprophylaxis* drugs, and insecticides treated bednets.

2. Mosquito control:- The aim of controlling mosquitoes is to eliminate/reduce mosquitoes population below the number required for the disease to transmit. The existing methods for mosquito control include:

    - Biological methods such as introducing genetically modified mosquitoes into the population and introduction of mosquito larvae eating fish,
    - Elimination of mosquito breeding sites by using insecticides to treat standing waters to kill larvae before they develop into adult mosquito, indoor and outdoor residual spray.

In an effort to eradicate the disease, WHO led a campaign based on findings of G. Macdonald [62] to eradicate malaria globally between 1955 - 1978. Macdonald predicted that the mortality rate of the mosquito had to be increased from 5% to 45% in order to eradicate malaria in Africa. This finding was the basis for the widespread use of *DichloroDiphenylTrichloroethane* (DDT) in endemic malaria areas at that time. Although the campaign did not achieve its objective of eradicating malaria, it did result in enormous and sustained reductions in the burden of malaria in dozens of countries around the world. However, malaria eradication failed in Africa and parts of India, Asia and Latin America [82]. The main causes of this are

- The spread of drug-resistance to first-line drug and insecticide resistant mosquitoes.
- Limitations and improper implimentation of the resources allocated to malaria control. Many of the intervention programs established to support malaria control lack sufficient funds and as a result they are rendered ineffective operationally.

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Based on these reasons, WHO reoriented and redirected its policy from disease eradication and elimination to disease control. In 1978, however, WHO while reassessing and analyzing the failures during the consolidation phase, recognized that the basic requirements for achieving and sustaining malaria control are

- integration of malaria control into a reasonably well-established health system,
- an uninterrupted, continued effort, and
- research into new and improved tools.

As a result, new initiatives took place to control the spread of the disease. These include the malaria vaccine initiative (1999), multilateral initiative on malaria (1997), medicines for malaria venture (1999) and the global fund to fight AIDS, TB and malaria (2002) and they support the implementation of prevention and treatment programs [83].

1.2 Research questions, aims and objectives

The initiatives mentioned in the previous section mainly focussed on human treatment and (possible) vaccination, which may be costly and time consuming. The question then is,

1. should the control aim at disease in humans by treating infected individuals or preventing new infections by vaccinating susceptibles and using mosquitoes bednets?
2. should it rather focus on the control/elimination of mosquitoes by using treated bednets, insecticides and destruction of mosquitoes breeding sites?
3. and what is the most cost-effective measure?

The main goal of this study is to investigate the impact of treatment and preventive measures such as vaccination, use of treated bednets and insecticides on the burden of malaria. We construct the sensitivity analysis index of the model parameters, in order

- develop two SEIR models, one with treatment and prevention (treated bednets and insecticides) and in the second model we consider treatment with vaccination, where we assume that the vaccine effect wanes with time.

- use optimal control to examine the costs and effectiveness of the control measures and determine the most cost effective control measure(s).

The thesis is organized as follows: In Chapter 1, we describe the biological background of malaria, as well as research questions, aims and objectives. Chapter 2 is devoted to a literature review on mathematical modelling of malaria and applications of optimal control methods in epidemiological models. Chapter 3 presents the preliminary background of epidemiological modelling as well as a background on ordinary differential equations and optimal control theory. In Chapter 4, we develop and analyze an SEIR model with treatment. The existence and stability of equilibria without disease (disease free equilibrium) and endemic equilibria is also presented. In Chapter 5, we incorporate into the SEIR model treatment and preventive measures such as treated bednets and insecticides. We apply optimal control methods to determine the most cost effective strategy from the combination of at least two of treated bednets, treatment and insecticides. In Chapter 6, we develop and analyze an SEIRV model with treatment and vaccination with waning immunity. We analyze the existence and stability of equilibrium points. Incorporating control functions we show the optimal control analysis of the SEIRV malaria model and find optimal conditions for eradication of the disease rather than control. Furthermore, when eradication is impossible, we find the necessary conditions for optimal control of malaria disease transmission. In Chapter 7, we give a concluding summary of the whole study.

Chapter 2

Literature Review

Mathematical modelling of the spread of infectious diseases continues to be an area of active research and has become an important tool in understanding the dynamics of diseases and in decision making processes regarding intervention programs for controlling these diseases in many countries. Greenhalgh et al. [32, 33], studied an infectious disease model with population-dependent death rate using computer simulation. Nikolaos et al. [71] proposed a detailed analysis of a dynamical model to describe pathogenesis of HIV infection. Christopher and Jorge [16] derived a simple two-dimensional SIS (susceptible-infected-susceptible) model with vaccination and multiple endemic states. Brauer and van den Driessche [9] proposed and analyzed simple models for disease transmission that include immigration of infective individuals and variable population size. van den Driessche and Watmough [88], developed a precise definition for the basic reproduction number of a general compartmental disease transmission model based on system of ordinary differential equations. Roberts and Heesterbeek [78], proposed the popularly known next generation matrix for estimating the effort required to control an infectious disease. Ghosh et al. [27, 28], studied the environmental effect on an SIS model for bacteria and the spread of carrier-dependent infectious diseases, like cholera and diarrhea. Guihua and Zhen [29], studied the global dynamics of an SEIR (susceptible-exposed-infected-recovered) epidemic model in which latent and immune states were infective. Okosun and Yusuf [72] derived and analyzed a mathematical model to study bird flu disease transmission. More studies on modelling of infectious diseases can be found in [2, 7, 10, 11, 14, 17, 20, 21, 26, 30, 38, 37, 40, 44, 51, 52, 53, 81, 89, 100].

Concerning the malaria disease, Ronald Ross [80] in 1897 discovered that mosquitoes

transmit malaria and he used a mathematical model to described the dynamics of the disease transmission. His study focused more on the mosquito control. He showed that for the disease to be eliminated the mosquito population should be brought below a certain threshold. This work has been extended by Macdonald [61, 62] to account for superinfection. These two works were further extended by Koella and Anita [55] by including a latent class for mosquitoes. They evaluated the different strategies to reduce the spread of resistance and also studied the sensitivity properties of the parameters. Anderson and May [2] derived a malaria model with the assumption that acquired immunity in malaria is independent of exposure duration. Different control measures and role of transmission rate on the disease prevalence were further examined. Hyun in [41, 42] using mass action incidence, studied a malaria transmission model for different levels of acquired immunity and temperature dependent parameters, relating it also to global warming and local socioeconomic conditions. In [49], Kawaguchi et al. examined the combined use of insecticide spray and zooprophylaxis as malaria control strategy. Dietz et al. [22] proposed a model that accounts for acquired immunity in a mass action model. Chiyaka et al. [14], formulated a deterministic model with two latent periods in the hosts and vector populations to assess the impact of personal protection, treatment and possible vaccination strategies on the transmission dynamics of malaria and in [15] they considered treatment and spread of drug resistance in an endemic population. Jia [43] formulated and examined a compartmental model for malaria transmission that includes incubation periods for both infected human hosts and mosquitoes. Mukandavire et al. [66], proposed and examined a deterministic model for the co-infection of HIV and malaria in a community. More studies on malaria modelling can be found in [4, 14, 15, 17, 67, 68, 41, 49, 43, 55, 69, 70, 85, 86, 87, 95]

However, all these works did not put into consideration the optimality, costs and cost-effectiveness of the preventive and treatment interventions, which are mainly limited by availability of resources. In view of this, application of optimal control theory to epidemiology can be an important tool to test the efficacy of various policies and control measures vis a vis the cost of implementing them. Pontryagin et al. [75] developed the theoretical foundation of optimal control for ordinary differential equations. Since then it has been successfullly used in decision making in various applications.

In particular, there have been studies of epidemiological models where optimal control methods were applied. Okosun et al. [73] formulated and analyzed an optimal control problem with an SIS epidemic model to investigate the impact of infected immigrant

in an avain influenza transmission dynamics. In [75], Okosun and Agusto used optimal control to study the optimal seasonal biocontrol for Eichhornia crassipes. Castilho [12], specifically applied optimal control methods in a simplified SIR model, to study the best strategy for educational campaigns during the outbreak of an epidemic. Zaman et.al [100] studied a general SIR epidemic model and applied stability analysis theory to find the equilibrium solutions and then used optimal control to determine the optimal vaccination strategies to reduce the susceptible and infective individuals. Suresh [84, 85] formulated and analyzed an optimal control problem with a simple epidemic model to examine effect of a quarantine program. He also considered an optimal control problem to study the effect of the level of medical program effort in minimizing the social and medical costs [85]. Gupta and Rink in [31] considered the application of optimal control to find the most economical use of active and passive immunization in controlling infectious disease. Karrakchou et al. [48] used optimal control to examine the role of chemotherapy in controlling the virus reproduction in an HIV patient. Adams et al. [1] derived HIV therapeutic strategies by formulating and analyzing an optimal control problem using two types of dynamic treatments. Xiefei et al. [97] applied optimal control methods to study the outbreak of SARS using Pontryagin's Maximum Principle and a genetic algorithm. Wickwire [94] applied optimal control to mathematical models of pests and infectious diseases control. Marco and Takashi [64] used optimal control to study dengue disease transmission. Wiemer [95] studied Schistosomiasis using optimal control methods. More studies on the applications of optimal control to infectious diseases, mainly HIV/AIDS and Tuberculosis can be found in [1, 3, 6, 19, 24, 46, 45, 47, 77, 54, 59, 93, 98, 99], these studies focuses more on cost minimization analysis of the examined control strategies.

Very few studies have been carried out on applying optimal control theory to study the dynamics of malaria. Only recently, Kbenesh et al. [50], presented an autonomous ordinary differential equation model with vector-control and treatment model and a time dependent counter part of the model involving an optimal control of vector-borne diseases with treatment and prevention as control measures. Rafikov et al. [78], formulated a continuous model for malaria vector control with the aim of studying how genetically modified mosquitoes should be introduced in the environment using optimal control problem strategies.

In this thesis, we derive and analyze a mathematical models for malaria disease transmission. Firstly, we incorporate into the model control(s) parameters, mainly, use of

treated bednets, treatment and spray of insecticides against mosquitoes with appropriate cost functions in order to study, examine the possible impacts of the combination of at least two of these optimal strategies for controlling the disease and also to determine the most cost effective optimal strategies. Secondly, we incorporate into the malaria model control(s) parameters, mainly, vaccination and treatment with appriopriate cost function in order to study and determine the possible impacts of each or the combination of these optimal strategies for controlling the disease.

This current model differs from the one proposed in [50] and [78] by the inclusion of a vaccination class, control term for the vector population and the cost effectiveness analysis carried out using optimal control techniques. Its stability properties are theoretically analyze and conditions on the parameters for the existence of equilibrium solutions are determined. Also detailed qualitative optimal control analysis of the resulting model are carried out and the necessary conditions for optimal control of the disease using Pontryagin's Maximum Principle are obtained, in order to determine optimal and cost effective strategies for controlling the spread of the disease.

Our main goal in Chapter five of this thesis is to develop mathematical models with control strategies to investigate the role of use of treated bednets, treatment and spray of insecticides in malaria transmission, and also carry out the cost minimization and cost effective analysis of the strategies. While in Chapter six, we aim to develop mathematical models with control strategies to investigate the possible role of vaccination and treatment and also carry out cost effectiveness analysis of the strategies, in order to determine optimal control strategies for controlling the spread of malaria transmission in human-vector interactions.

Some results related to this thesis have been presented in both international and local conferences/workshops. Specifically, two articles are already in press (Optimal control strategies and economic evaluation of malaria disease model [72] and Optimal seasonal biocontrol for Eichhornia crassipes: a major harbour for moquito vector of malaria [75]), one article under second review in a reputable journal (Application of optimal control to the epidemiology of malaria), one other article (Optimal control analysis of a malaria disease transmission model that includes treatment and vaccination with waning immunity) is currently under review for publication in other reputable journal.

Next chapter, we present the preliminary background of epidemiological modelling as well as a background on ordinary differential equations and optimal control theory.

Chapter 3

Preliminary Background

3.1 Existence and uniqueness of solutions

To prove that there is a unique solution to a first order ordinary differential equations (ODEs) initial value problem, consider the first order ordinary differential equation (ODE), initial value problem of the form,

$$\frac{dx}{dt} = F(x) \qquad x(0) = x_0 \tag{3.1.1}$$

where $F(x)$ is bounded in a neighborhood of the initial condition. We record some known results for application in the thesis.

Theorem 3.1.1.

If F is Lipschitz then there exists $c > 0$ such that the initial value problem (3.1.1) has a unique solution $x(t)$ for $t \in (t_0 - c,\ t_0 + c)$.

Theorem 3.1.2.

If the functions F and $\frac{\partial F}{\partial y}$ are continuous on a region R of the ty-plane and if (t_0, y_0) is a point of R, then the IVP (3.1.1) has a solution $y(t)$ on an interval l containing t_0 in its interior.

Theorem 3.1.3.

Suppose that x^* is an equilibrium solution of (3.1.1) if $F(x^*) = 0$

- *x^* is locally asymptotically stable (LAS) if all the eigenvalues of $DF(x^*)$ have negative real parts.*
- *If at least one eigenvalue has a positive real part then x^* is unstable.*

The eigenvalues are the roots of the characteristic equations of the Jacobian matrix.

3.1.1 Routh-Hurwitz criteria

Consider the characteristic equation

$$\Omega^n + a_1\Omega^{n-1} + a_2\Omega^{n-2} + ... + a_{n-1}\Omega + a_n = 0 \tag{3.1.2}$$

determining the n eigenvalues Ω of a real $n \times n$ square matrix A, where Ω is the identity matrix. Then the eigenvalues Ω all have negative real parts if

$$H_1 > 0,\ H_2 > 0,\ H_3 > 0, ... H_n > 0$$

where

$$H_n = \begin{vmatrix} a_1 & 1 & \cdots & 0 \\ a_3 & a_2 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ a_{2n-1} & a_{2n-2} & \cdots & a_n \end{vmatrix}.$$

The steady state is stable (that is, $Re(\Omega) < 0$) for all λ if and only if $detH_j \geq 0$ for all $j = 1, 2, 3, ..., n$.

3.1.2 Hartman-Grobman Theorem

Theorem 3.1.4. *Let $f : R^n \to R^n$ be a smooth map with a hyperbolic fixed point p. Let A denote the linearization of f at point p. Then there exists a neighborhood $\cup$ of p and a homeomorphism*

$$h : \cup \to R^n$$

such that

$$f_{\cup} = h^{-1} \circ A \circ h$$

that is, in the neighborhood $\cup$ of p, f is topologically conjugate to its linearization.

3.2 Compartmental Modelling

The approach for modelling the transmission of infectious disease in human populations is usually to subdivide the population under consideration into subpopulation or small number of epidemiological classes called compartments and the resulting model is called a compartmental model. The classes usually considered are primarily the following

- Susceptible class (S): A collection of individuals in a population are classified as susceptibles if they are not infected and however at risk of being infected.

- Exposed class (E): These are individuals who have been infected with the disease pathogen, but are not able to infect others. They may still be in the incubating stage, and do not possess immunity. This class is also known as latent class.

- Infected class (I): This is a collection of individuals who are infected and are infectious.

- Recovered/removed class (R): These are individuals who recover and acquire temporary or permanent immunity and may not contract or transmit the disease, either because they are no longer infectious and are immuned or because they have been vaccinated.

Compartmental models have provided valuable insights into the epidemiology of many infectious diseases including malaria. Diseases that confer immunity have a different compartmental structure from diseases without immunity. For diseases which confer immunity, the SIR terminology is used, describing the passage of individuals from susceptible class "S" to the infective "I" and then to the removed/recovered class "R". The term SIS describes a disease with no immunity, indicating the movement of individuals from susceptible class to infective and then back to susceptible class. Other possibilities include the SEIR and the SEIS models with an exposed period, a stage of being infected and becoming infective after a period of time, and SIRS models with temporary immunity on recovery from infection [8].

Some other classes may be added to increase accuracy of the model. Specifically a class V of vaccinated individuals. The sizes of each class at the time t are represented by $S(t), E(t), I(t), R(t)$ respectively, $N(t)$ denotes the total population size, that is, $S(t) + E(t) + I(t) + R(t)$

The transmission of diseases may be through horizontal incidence, from infected to susceptibles and the vertical transmission, for example from mothers to newborns. The probability per unit time at which susceptible members of the population are infected is called **force of infection** and generally seen as a function of total number of infective individuals. The term **incidence** represents the number of individuals that become infected in any given period of time. It is often referred to as incidence rate, which is the

incidence per unit time. **Prevalence** is defined as the proportion of the population that is infected.

3.2.1 The basic reproductive number and next generation method

The basic reproductive number which measures the ability of the disease to reproduce, is denoted by R_0. This is defined as the expected number of secondary cases reproduced by one infected individual in his/her entire infectious period. When $R_0 < 1$, each infected individual can produce an average of less than one new infected individual during his entire period of infectiousness. In this case the disease will not persist in the population and may be eradicated. But in a situation where $R_0 > 1$, it implies that each infected individual can produce an average of more than one new infected individuals during his entire period of infectiousness, this is a strong indication that the disease can persist and invade the population.

The next generation method introduced by van den driesche and Watmough [21], is a general method for deriving R_0 in cases where one or more classes of infective are involved. Suppose we have n disease compartments and m non-disease compartments, and let $x \in R^n$ and $y \in R^m$ be the sub-populations in each of these compartments. Also denoting the rate of secondary infection increase of the i^{th} disease compartment by $\mathbf{F}_i$ and $\mathbf{V}_i$ the rate disease of progression, death and recovery decrease the i^{th} compartment, the compartmental model can then be written in the form:

$$\frac{dx_i}{dt} = \mathbf{F}_i(x, y) - \mathbf{V}_i(x, y), \quad i = 1, ..., n,$$

$$\frac{dy_j}{dt} = g_j(x, y), \quad j = 1, ..., m,$$

The calculation of the basic reproduction number is based on the linearization of the ordinary differential equations (ODE) model about a disease-free equilibrium, while the following assumptions ensure the existence of the equilibrium and well possessedness of the model [21]:

1. Assume $\mathbf{F}_i(0, y) = 0$ and $\mathbf{V}_i(0, y) = 0$ for all $y \geq 0$ and $i = 1, ..., n$. All new infections are secondary infections arising from infected hosts; there is no immigration of individuals into the disease compartments.

2. Assume $\mathbf{F}_i(0, y) \geq 0$ for all non-negative x and y and $i = 1, ...n$. The function $\mathbf{F}$ represents new infections and can not be negative.

3. $\mathbf{V}_i(0, y) \leqslant 0$ whenever $x_i = 0$, $i = 1, ...n$. Each component, $\mathbf{V}_i$ represents a net outflow from compartment i and must be negative (inflow only) whenever the compartment is empty.

4. Assume $\sum_{i=1}^{n} V_i(x, y) \geq 0$ for all non-negative x and y. This sum represents the total outflow from all infected compartments. Terms in the model leading to increases in $\sum_{i=1}^{n} x_i$ are assumed to represent secondary infections and therefore belong in $\mathbf{F}$.

5. Assume the disease-free system $\frac{dy}{dt} = g(0, y)$ has a unique equilibrium that is asymptotically stable. That is, all solutions with initial conditions of the form $(0, y)$ approach a point $(0, y_o)$ as $t \to \infty$. This point is referred to as disease-free equilibrium.

Now assuming that $\mathbf{F}_i$ and $\mathbf{V}_i$ meet the above conditions, we can form the next generation matrix (operator) $\mathbf{FV}^{-1}$ from matrices of partial derivatives of $\mathbf{F}_i$ and $\mathbf{V}_i$. particularly

$$F = [\frac{\partial F_i(x_0)}{\partial x_j}] \quad and \quad V = [\frac{\partial V_i(x_0)}{\partial x_j}],$$

where $i, \quad j = 1, ..., m$ and where x_0 is the disease-free equilibrium. The entries of FV^{-1} give the rate at which infected individuals in x_j produce new infections in x_i, times the average length of time an individual spends in a single visit to compartment j. R_0 is given by the spectral radius (dominant eigenvalue) of the matrix FV^{-1}.

3.2.2 Mass Action (Density Dependent)

The probability of transmission in a given time period is a function of the number of infectious individuals in a given area. In this case the contact rate depends on the size of the total host population. This type of incidence has been used in modelling several infectious diseases and malaria in particular, see [22, 41, 42, 43, 49, 50, 55]. This form of infection is mostly suitable when a small population size is considered. The typical SIR model for a mass action (density dependent) transmission is given by

$$\begin{aligned} \frac{dS}{dt} &= -\beta SI, \\ \frac{dI}{dt} &= \beta SI - \gamma I, \\ \frac{dR}{dt} &= \gamma I. \end{aligned} \tag{3.2.3}$$

3.2.3 Standard Incidence (Frequency Dependent)

The probability of transmission in a given time period is a function of the prevalence of infection in the population. The contact rate is assumed to be constant, that is, it depends on the proportion of susceptibles and infecteds within the population, not the total population size that affects the level of interactions. Malaria and other infectious diseases has been studied using this form of infection approach, see [14, 15, 26, 30, 66, 67, 68, 86]. The typical SIR model for a standard (frequency dependent) transmission is given by

$$\begin{aligned} \frac{dS}{dt} &= \frac{-\beta SI}{N}, \\ \frac{dI}{dt} &= \frac{\beta SI}{N} - \gamma I, \\ \frac{dR}{dt} &= \gamma I. \end{aligned} \tag{3.2.4}$$

The basic compactmental models to describe the transmission of communicable diseases are contained in a sequence of three papers of Kermack and McKendrick [51, 52, 53], the simpliest models they proposed are of the form

$$\begin{aligned} \frac{dS}{dt} &= -\beta SI, \\ \frac{dI}{dt} &= \beta SI - \gamma I, \\ \frac{dR}{dt} &= \gamma I, \end{aligned} \tag{3.2.5}$$

with the following assumptions:

βN : average infective individual making appropriate contact sufficient to transmit infection per unit time

$\frac{S}{N}$: probability of contact between infective with a susceptible individual

γ: fraction of infectives recovered per time.

In this model, once I is known, R can then be determined, so we consider the S and

I equations only.

$$\frac{dI}{dS} = \frac{(\beta S - \gamma)I}{-\beta SI},$$
$$= -1 + \frac{\gamma}{\beta S}. \tag{3.2.6}$$

By integrating both sides, we get

$$I = -S + \frac{\gamma}{\beta}\log S + c,$$
$$V(S,I) = I + S - \frac{\gamma}{\beta}\log S\frac{\beta}{\gamma} = \frac{ln\frac{S_0}{S_\infty}}{K - S}. \tag{3.2.7}$$

It follows then that

$$I_{max} = S_0 + I_0 - \frac{\gamma}{\beta}\log S_0 - \frac{\gamma}{\beta} + \frac{\gamma}{\beta}\log\frac{\gamma}{\beta}. \tag{3.2.8}$$

Kermack and McKendrick (1932) proposed another SIR model that includes births in the susceptible class and deaths from all classes with tha rate proportional to each class

$$\frac{dS}{dt} = -\beta SI + \mu(K - S),$$
$$\frac{dI}{dt} = \beta SI - \gamma I - \mu I, \tag{3.2.9}$$
$$\frac{dR}{dt} = \gamma I - \mu R,$$

where the total population size, N is defined as the total sum of the population in the classes. $N(t) = S(t) + I(t) + R(t)$ with the assumptions that there is no disease induced death. Hethcote in 1976 [38], proposed a more general model

$$\frac{dS}{dt} = \mu K - \beta SI - \mu S,$$
$$\frac{dI}{dt} = \beta SI - (\gamma + \mu + \alpha)I, \tag{3.2.10}$$
$$\frac{dR}{dt} = \gamma I - \mu R,$$

where α is the disease induced death fraction; γ rate of recovery with acquired immunity, natural death rate μ and birth rate μK is assumed constant. By ignoring the R class of

the system (3.2.10), the system reduced to

$$\begin{aligned} \frac{dS}{dt} &= -\beta SI + \mu(K - S), \\ \frac{dI}{dt} &= \beta SI - \gamma I - \mu I. \end{aligned} \tag{3.2.11}$$

The first step is to study the steady state, the equilibrium points is obtained by setting the right hand side of the system (3.2.11) to zero.

$$\begin{aligned} -\beta SI + \mu(K - S) &= 0, \\ \beta SI - \gamma I - \mu I &= 0. \end{aligned} \tag{3.2.12}$$

The disease-free equilibrium (DFE) which describes the state where no infection is present in the population is obtained when $I^* = 0$, hence $S^* = K$. The endemic equilibrium where infection persists at a fixed level is obtained when $I^* \neq 0$, hence $S^* = \frac{\mu(\beta K - (\gamma+\mu+\alpha))}{\beta(\gamma+\mu+\alpha)}$, $I^* = \frac{\gamma+\mu+\alpha}{\beta}$. The eigenvalues of the Jacobian evaluated at these points will determine their linear stability. Therefore, linearizing the system (3.2.12) to study the local stability of the fixed point, the Jacobian matrix is obtained

$$J = \begin{bmatrix} -\mu - \beta I & -\beta S \\ \beta I & \beta S - (\gamma + \mu + \alpha) \end{bmatrix},$$

At the DFE, the Jacobian matrix is given by

$$\begin{bmatrix} -\mu & -\beta K \\ 0 & \beta K - (\gamma + \mu + \alpha) \end{bmatrix}.$$

From the trace of this matrix, disease-free equilibrium of the system will be stable if $\beta K < (\gamma + \mu + \alpha)$. The Jacobian matrix evaluated at the endemic equilibrium is

$$\begin{bmatrix} \frac{-\mu\beta K}{(\gamma+\mu+\alpha)} & -(\mu + \alpha) \\ \frac{\mu(\beta K-(\gamma+\mu+\alpha))}{\beta(\gamma+\mu+\alpha)} & 0 \end{bmatrix},$$

It is clear from this matrix that the trace is negative and the determinant will be positive if $\beta K - (\gamma + \mu + \alpha) > 0$

If $R_0 < 1$, the disease-free equilibrium is stable and the endemic equilibrium does not

exist

If $R_0 > 1$, the disease-free equilibrium is unstable and the endemic equilibrium does exist and asymtotically stable

The basic reproduction number R_0 is then given by $\frac{\beta K}{(\gamma+\mu+\alpha)}$

3.3 Optimal control method

Optimal control theory has been a powerful mathematical technique derived from the calculus of variation and is very useful in decision making regarding complex biological situations. The behavior of a dynamical system is described by the state variable(s). The assumption is that there is a way to control the state variable(s) x, by acting upon it with a suitable control. Thus the dynamics of the system (state x) depends on the control u. The ultimate goal is to adjust control u to minimize or maximize a given objective functional, $J(u(t), x(t), t)$, that attains the desired goal and the required cost to achieving it. The optimal solution is then obtained when the most desired goal is achieved with least cost. The functional depends on the control and the state variables. There are a number of different methods for calculating the optimal control for specific model. Pontryagin's Maximum Principle for example allows the calculation of the optimal control for an ordinary differential equations model system with given constraints. In [58, 65], other powerful optimal control techniques have been derived for partial differential equations and difference equations.

Reasons for optimal control

Optimal control can be use for the following reasons:

1. Controllability:- using controls to steer a system from one position to another,

2. Observability:- deducing system information from control input and observe output,

3. Stabilization:- implementing controls to force stability.

3.3.1 The general optimal control problem

We consider optimal control problems of the form

$$J(x(t), u(t), t) = \min_u \left\{ \phi(t_f, x(t_f) + \int_0^{t_f} g(t, x(t), u(t))dt \right\}.$$

Here, $t \in \mathbb{R}$ stands for the independent variable, called time, for $T = [0, \infty)$, where

$$x(t) = [x_1(t), x_2(t), ..., x_n(t)]^T \in \mathbb{R}^n$$

is a n-vector of state variables $(x_i(t))$. These describes the state of the system at any point in time, and

$$u(t) = [u_1(t), u_2(t), ..., u_m(t)]^T \in \mathbb{R}^m$$

is a m-vector of control variables at any point in time. These are the choice variables in the optimization problem.

The dynamics of the state variables are governed by the described set of first order ordinary differential equations (for $1 \leqslant i \leqslant n$):

$$\frac{dx_i}{dt} = f_i(t, x(t), u(t)); \; x_0 = x(0), 0; \leq i \leq n. \tag{3.3.13}$$

The functions:

$$f_i : T \times \mathbb{R}^n \times \mathbb{R}^m \to \mathbb{R}$$

$$g : T \times \mathbb{R}^n \times \mathbb{R}^m \to \mathbb{R}$$

and

$$\phi : T \times \mathbb{R}^n \to \mathbb{R}$$

are continuously differentiable with respect to each component of $\mathbf{x}$ and $\mathbf{u}$ (where relevant), and piecewise continuous with respect to t. In the case where f_i does not depend explicitely on t, the system is said to be *autonomous*. The functions $u(t)$ belong to a certain class of "admissible" functions.

Definition: Admissible Control. A piecewise continuous control $u(.)$, defined on some time interval $t_0 \leqslant t \leqslant t_f$, with range in the control region U,

$$u(t) \in U, \qquad \forall t \in [t_0, t_f],$$

is said to be an admissible control.

3.3.2 Pontryagin's Maximum Principle

This principle says that we can solve the optimization problem $J(u(t), x(t), t)$ using Hamiltonian function H over one period. That is, the principle converts the maximization/minimization of the objective functional, J, coupled with the state variable into maximizing/minimizing pointwise the Hamiltonian with respect to the control.

Theorem 3.3.1. *From [58], in order that $u^*(t)$ and $x^*(t)$ be optimal for problem (3.3.13), it is necessary that there exist a piecewise differential adjoint variable $\lambda(t)$, where for all $0 \leqslant t \leqslant T$ we have $\lambda(t) \neq 0$ such that for every $0 \leqslant t \leqslant T$*

$$H(t, x^*(t), u(t), \lambda(t)) \leq H(t, x^*(t), u^*(t), \lambda(t)) \tag{3.3.14}$$

for all controls u at each time t, where the Hamiltonian H is

$$H = g(t, x(t), u(t)) + \lambda(t) f(t, x(t), u(t)) \tag{3.3.15}$$

and

$$\begin{aligned} \frac{\lambda(t)}{dt} &= -\frac{\partial H(t, x^*(t), u^*(t), \lambda(t))}{\partial x}, \\ \lambda(t_f) &= 0. \end{aligned} \tag{3.3.16}$$

Necessary conditions

If $u^*(t)$ and $x^*(t)$ are optimal, then the following conditions hold:

$$\begin{aligned} \frac{\lambda(t)}{dt} &= -\frac{\partial H(t, x^*(t), u^*(t), \lambda(t))}{\partial x}, \\ \lambda(t_f) &= 0, \\ \frac{\partial H(t, x^*(t), u^*(t), \lambda(t))}{\partial u} &= 0. \end{aligned} \tag{3.3.17}$$

Sufficient conditions

If all the functions f_i and g are jointly convex with respect to x and u and if $\lambda_i(t) \geq 0$ for all i and all t then jointly with the stated necessary conditions, we have a set of sufficient conditions for optimality.

Here $\lambda(t)$ is the shadow price or co-state variable. This denotes the increase of the objective function due to marginal increase of the state variable. At any time the decision maker can use the control variable to generate direct contributions to the objective

then $u^*(t)$ and $x^*(t)$ are optimal.

Here $\lambda(t)$ is the shadow price or co-state variable. This denotes the increase of the objective function due to marginal increase of the state variable. At any time the decision maker can use the control variable to generate direct contributions to the objective function (represented by the term $f(t, x(t), u(t))$ in the Hamiltonian (3.3.15)), or it can use the control variable to change the value of the state variable in order to generate contributions to the objective function in the future. These indirect contributions are measured by the term $\lambda(t)g(t, x(t), u(t))$ in the Hamiltonian.

In the next chapter, we develop and analyze an SEIR model with treatment.

Chapter 4

Malaria model with treatment

In this chapter, we present and analyze an SEIR model for malaria disease transmission. The model incorporates treatment. We first start by the model without treatment and analyze its stability and bifurcation behavior.

4.1 Malaria model without treatment

4.1.1 Model description

The total human population, N_h, is sub-divided into sub-populations of susceptible individuals, S_h, those exposed to malaria parasite, E_h, individuals with malaria symptoms, I_h. So that

$$N_h = S_h + E_h + I_h.$$

The total vector (mosquito) population denoted by N_v, is sub-divided into susceptible mosquitoes, S_v, mosquitoes exposed to the malaria parasite, E_v and infectious mosquitoes, I_v. Thus,

$$N_v = S_v + E_v + I_v.$$

To formulate a meaningful model as close as possible to the real life phenomenon we made the following assumptions:

1. We consider two population groups, the human with variable population size and the mosquito population.

2. Only adult female mosquitoes were considered in the model, since only these need human blood for egg production.

3. All new-born are susceptible in both populations. The infection of a susceptible human occurs when the individual is bitten by an infectious mosquito, the infected individual (exposed) after a period of time becomes infectious. Susceptible mosquitoes become infected when an infectious human is bitten by a susceptible mosquito, the infected mosquito (exposed) become infectious after a period of time.

4. Exposed humans and mosquitoes can not transmit the disease.

Susceptible individuals are recruited at a rate Λ_h and acquire malaria through contact with infectious mosquitoes at a rate $\beta\epsilon\phi$, where β is the transmission probability per bite, ϵ is the per capita biting rate of mosquitoes and ϕ is the contact rate of vector per human per unit time. Infected individuals move to the exposed class at a rate β_m, where β_m is the force of infection. Exposed individuals move to the infectious class at a rate α_1. When the disease is fatal, infected individuals die at a rate ψ. The natural death rate is μ_h.

Susceptible mosquitoes are generated at a per capita rate Λ_v and acquire malaria through contacts with infected humans at a rate $\lambda\epsilon\phi$, where λ is the probability for a vector to get infected by an infectious human. Mosquitoes are assumed to suffer death due to natural causes at a rate μ_v. Newly-infected mosquitoes move into the exposed class and progress to the class of infectious mosquitoes at a rate α_2.

The resulting system of equation is shown below:

$$\begin{cases} \dfrac{dS_h}{dt} = \Lambda_h - \beta_m S_h - \mu_h S_h, \\ \dfrac{dE_h}{dt} = \beta_m S_h - (\alpha_1 + \mu_h) E_h, \\ \dfrac{dI_h}{dt} = \alpha_1 E_h - (\psi + \mu_h) I_h, \\ \dfrac{dS_v}{dt} = \Lambda_v - \lambda_v S_v - \mu_v S_v, \\ \dfrac{dE_v}{dt} = \lambda_v S_v - (\alpha_2 + \mu_v) E_v, \\ \dfrac{dI_v}{dt} = \alpha_2 E_v - \mu_v I_v. \end{cases} \tag{4.1.1}$$

Here we consider two forms of infection for mosquitoes and humans:

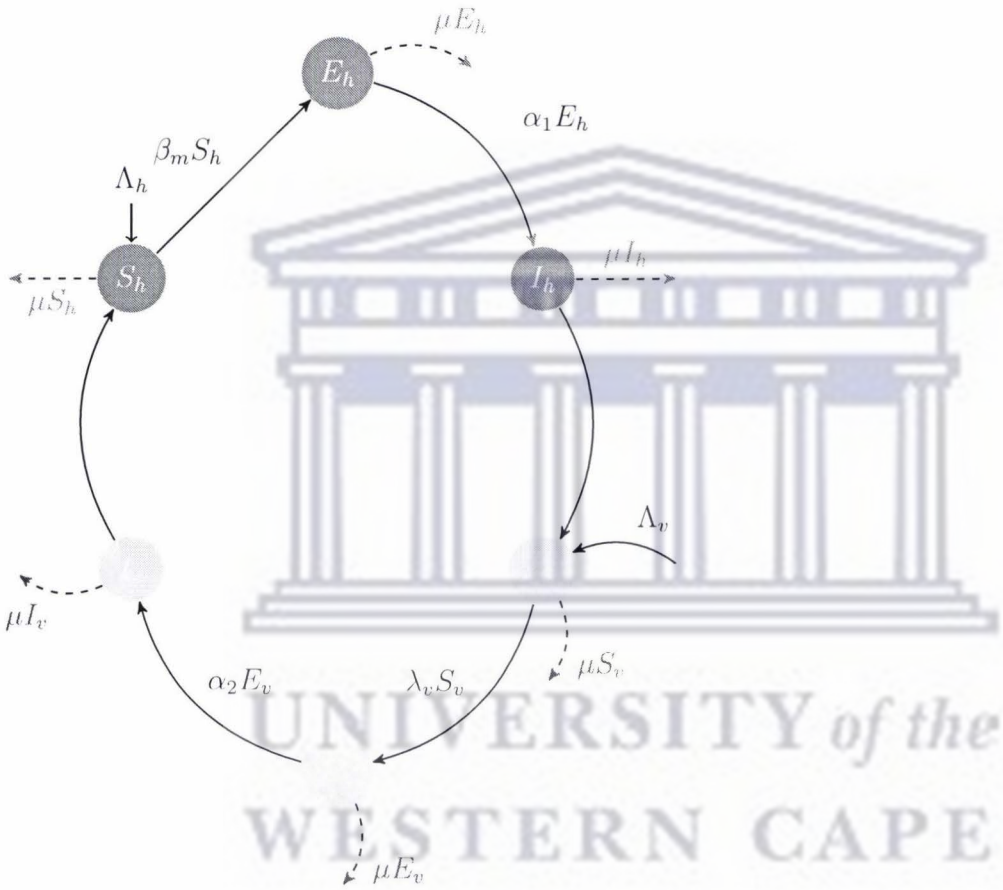


Figure 4.1: Flow diagram for Malaria disease transmission

i. The mass action force of infection

$$\begin{aligned} \beta_m &= \beta\epsilon\phi I_v, \\ \lambda_v &= \lambda\epsilon\phi I_h. \end{aligned} \tag{4.1.2}$$

ii. The standard force of infection

$$\begin{aligned} \beta_m &= \frac{\beta\epsilon\phi I_v}{S_h + E_h + I_h} \\ \lambda_v &= \frac{\lambda\epsilon\phi I_h}{S_h + E_h + I_h}. \end{aligned} \tag{4.1.3}$$

These two forms of infection have been considered in different models of infectious diseases, see for instance [22, 41, 42, 43, 49, 50, 55] for the mass action and [14, 15, 26, 30, 66, 67, 68, 86] for the standard incidence.

The SEI malaria model (4.1.1) will be analyzed in a biologically-feasible region as follows. This region should be feasible for both human and mosquito populations. More precisely, we have

Theorem 4.1.1. *If $S_h(0), E_h(0), I_h(0), S_v(0), E_v(0)$ and $I_v(0)$ are non-negative, then so are $S_h(t), E_h(t), I_h(t), S_v(t), E_v(t)$ and $I_v(t)$ for all $t > 0$. Moreover*

$$\limsup_{t\to\infty} N_h(t) \leq \frac{\Lambda_h}{\mu_h}, \quad \limsup_{t\to\infty} N_v(t) \leq \frac{\Lambda_v}{\mu_v}.$$

Furthermore, if in addition $N_h(0) \leq \frac{\Lambda_h}{\mu_h}$ $\left(N_v(0) \leq \frac{\Lambda_v}{\mu_v}\right)$ then $N_h(t) \leq \frac{\Lambda_h}{\mu_h}$ $\left(N_v(t) \leq \frac{\Lambda_v}{\mu_v}\right)$. In particular, the region

$$\mathcal{D} = \mathcal{D}_h \times \mathcal{D}_v$$

with,

$$\mathcal{D}_h = \{(S_h, E_h, I_h) \in \mathbb{R}^3_+ : S_h + E_h + I_h \leq \frac{\Lambda_h}{\mu_h}\},$$

and

$$\mathcal{D}_v = \{(S_v, E_v, I_v) \in \mathbb{R}^3_+ : S_v + E_v + I_v \leq \frac{\Lambda_v}{\mu_v}\}.$$

is positively invariant.

Proof: Let $t_1 = \sup\{t > 0 : S_h, E_h, I_h, S_v, E_v$ and I_v are positive on $[0, t]\}$. Since $S_h(0) > 0, E_h(0) > 0, I_h(0) > 0, S_v(0) > 0, E_v(0) > 0$ and $I_v(0) > 0$ then $t_1 > 0$. If $t_1 < +\infty$ then by using the variation of constants formula to the first equation of the system (4.1.1) we have

$$S_h(t_1) = \mathcal{U}(t_1, 0)S_h(0) + \int_0^{t_1} \Lambda\mathcal{U}(t_1, \tau)d\tau.$$

where $\mathcal{U}(t,\tau) = e^{-\int_\tau^t (\beta_m+\mu_h)(s)ds}$.

Clearly $S_h(t_1) > 0$ and it can be shown in the same manner that this is the case for the other variables. This contradicts the fact that t_1 is the supremum because at least one of the variables should be equal to zero at t_1. Therefore $t_1 = \infty$ which implies that S_h,E_h, I_h, S_v, E_v and I_v are positive for all $t > 0$.

For the second part of the proof, we obtain by adding the first three equations and the last three equations of the model (4.1.1)

$$\begin{aligned} \frac{dN_h}{dt}(t) &= \Lambda_h - \mu_h N_h(t) - \psi I_h(t), \\ \frac{dN_v}{dt}(t) &= \Lambda_v - \mu_v N_v(t). \end{aligned} \tag{4.1.4}$$

Since $0 < I_h(t) \leq N_h(t)$

$$\Lambda_h - (\mu_h + \psi) N_h(t) \leq \frac{dN_h}{dt}(t) \leq \Lambda_h - \mu_h N_h(t). \tag{4.1.5}$$

By using a standard comparison theorem [56], we obtain

$$N_h(0)e^{-(\mu_h+\psi)t} + \frac{\Lambda_h}{\mu_h+\psi}(1 - e^{-(\mu_h+\psi)t}) \leq N_h(t) \leq N_h(0)e^{-\mu_h t} + \frac{\Lambda_h}{\mu_h}(1 - e^{-\mu_h t})$$

$$N_v(t) = N_v(0)e^{-\mu_v t} + \frac{\Lambda_v}{\mu_v}(1 - e^{-\mu_v t}).$$

Therefore, if $N_h(0) \leq \frac{\Lambda_h}{\mu_h}$ (resp. $N_v(0) \leq \frac{\Lambda_v}{\mu_v}$) then $N_h(t) \leq \frac{\Lambda_h}{\mu_h}$ (resp. $N_v(t) \leq \frac{\Lambda_v}{\mu_v}$). Moreover

$$\frac{\Lambda_h}{\mu_h+\psi} \leq \liminf_{t\to\infty} N_h(t) \leq \limsup_{t\to\infty} N_h(t) \leq \frac{\Lambda_h}{\mu_h}$$

$$\lim_{t\to\infty} N_v(t) = \frac{\Lambda_v}{\mu_v}.$$

This establishes the invariance of $\mathcal{D}$ as required.■

From this theorem we conclude that it is sufficient to consider the dynamics of (4.1.1) in $\mathcal{D}$. In this region, the model can be considered as being epidemiologically and mathematically well-posed [40].

4.1.2 Steady states and stability analysis

The steady states of the model are obtained by equating the right hand side of (4.1.1) to zero. We obtain

$$\begin{cases} S_h^* = \dfrac{\Lambda_h}{\mu_h + \beta_m^*}, \\ E_h^* = \dfrac{\beta_m^* \Lambda_h}{(\mu_h + \alpha_1)(\mu_h + \beta_m^*)}, \\ I_h^* = \dfrac{\alpha_1 \Lambda_h \beta_m^*}{(\mu_h + \alpha_1)(\beta_m^* + \mu_h)(\mu_h + \psi)}, \\ S_v^* = \dfrac{\Lambda_v}{\mu_v + \lambda_v^*}, \\ E_v^* = \dfrac{\lambda_v^* \Lambda_v}{(\mu_v + \alpha_2)(\mu_v + \lambda_v^*)}, \\ I_v^* = \dfrac{\alpha_2 \lambda_v^* \Lambda_v}{\mu_v(\mu_v + \alpha_2)(\mu_v + \lambda_v^*)}. \end{cases} \tag{4.1.6}$$

Mass action

By using (4.1.2) and (4.1.6) we obtain

$$\beta_m^* \left(A\beta_m^* + B\right) = 0, \tag{4.1.7}$$

where

$$A = \mu_v(\alpha_2 + \mu_v)(\epsilon\phi\lambda\alpha_1\Lambda_h + (\psi + \mu_h)(\alpha_1 + \mu_h)\mu_v),$$

$$B = \mu_h\mu_v^2(\alpha_2 + \mu_v)(\alpha_1 + \mu_h)(\mu_h + \psi)(1 - R_0^2).$$

Clearly, $A > 0$ and $B \geq 0$ whenever $R_0 \leq 1$.

Notice that the solution $\beta_m^* = 0$ of (4.1.7) corresponds to the disease free equilibrium

$$\mathcal{E}_0 = (\frac{\Lambda_h}{\mu_h}, 0, 0, \frac{\Lambda_v}{\mu_v}, 0, 0,).$$

The other root of (4.1.7), when it exists, corresponds to an endemic equilibrium point.

The basic reproduction number of (4.1.1), R_0, is calculated by using the next generation matrix [88]. It is given by

$$R_0 = FV^{-1},$$

where

$$F = \begin{pmatrix} 0 & 0 & 0 & \beta\epsilon\phi S_h^* \\ 0 & 0 & 0 & 0 \\ 0 & \lambda\epsilon\phi S_v^* & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix},$$

and

$$V = \begin{pmatrix} \alpha_1 + \mu_h & 0 & 0 & 0 \\ -\alpha_1 & \psi + \mu_h & 0 & 0 \\ 0 & 0 & \alpha + \mu_v & 0 \\ 0 & 0 & -\alpha_2 & \mu_v \end{pmatrix}.$$

We obtain

$$R_{0m} = \sqrt{\frac{\alpha_1 \alpha_2 \lambda \Lambda_h \Lambda_v (\epsilon\phi)^2 \beta}{\mu_h \mu_v^2 (\mu_h + \alpha_1)(\mu_h + \psi)(\mu_v + \alpha_2)}}.$$

The square root in (4.1.2) agrees with the findings of [60] as the biological requirement in the human-vector host system for the parasite to pass through two types of individuals to complete its life cycle. Further, using Theorem 2 in [88], the following result is established.

Proposition 1. *1. If $R_{0m} < 1$, system (4.1.1) has a unique equilibrium point, the DFE and it is locally asymptotically stable.*

2. If $R_{0m} > 1$, the DFE becomes unstable and system (4.1.1) has an additional steady state.

Standard incidence

The resulting standard incidence SEI malaria model obtained by using (4.1.1) and (4.1.3) has the same DFE given as in the mass action SEI model. The basic reproduction number is given by

$$R_0 = \sqrt{\frac{\alpha_1 \alpha_2 \lambda \Lambda_v \mu_h (\epsilon\phi)^2 \beta}{\Lambda_h \mu_v^2 (\mu_h + \alpha_1)(\mu_h + \psi)(\mu_v + \alpha_2)}}. \tag{4.1.8}$$

The stability of the disease free steady state is the same as for the model with the mass action but the existence results of endemic steady states are different.

For the standard incidence form of infection we obtain the following result:

Proof: Using (4.1.6) and (4.1.3) we have β_m^* or

$$A\beta_m^{*2} + B\beta_m^* + C = 0, \tag{4.1.9}$$

where,

$$A = \mu_h^2 \Lambda_h^2 \mu_v (\alpha_2 + \mu_v)(\psi + \alpha_1 + \mu_h)(\epsilon\lambda\phi\alpha_1 + (\psi + \alpha_1 + \mu_h)\mu_v),$$

$$B = \mu_h \Lambda_h (\alpha_1 + \mu_h)(\psi + \mu_h)\Lambda_h \mu_v^2 (\mu_h + \alpha_1)(\mu_h + \psi)(\mu_v + \alpha_2)(R_\# - R_0^2),$$

$$C = \mu_h^2 \mu_v^2 \Lambda_h^2 (\alpha_2 + \mu_v)(\alpha_1 + \mu_h)^2 (\psi + \mu_h)^2 (1 - R_0^2).$$

Proposition 2. *Where* $R_{\#} := \dfrac{\mu_h(\epsilon\lambda\phi\alpha_1 + 2\mu_v(\psi + \alpha_1 + \mu_h))}{\mu_v(\mu_h + \alpha_1)(\mu_h + \psi)}$. *We have the following bifurcation behaviors:*

1. *If* $R_{\#} > 1$, *then the basic malaria model (4.1.1) with standard incidence exhibits transcritical bifurcation.*

2. *If* $R_{\#} < 1$, *then the basic malaria model (4.1.1) with standard incidence exhibits backward bifurcation. That is, there exists* R_c *in* $(0, 1)$ *such that*

   i. *When* $1 < R_0$ *(4.1.1) has one endemic equilibrium point.*

   ii. *When* $R_c < R_0 < 1$ *(4.1.1) has two endemic equilibrium points.*

   iii. *When* $R_0 < R_c$ *(4.1.1) has no endemic equilibrium points.*

1. If $R_{\#} > 1$ we have the following

   i. When $R_0 > 1$, $C < 0$. In this case (4.1.9) has a unique positive solution.

   ii. When $R_0 < 1$, $C > 0$ and $B > 0$ (because $R_0 < 1 < R_{\#}$). This together with $A > 0$ imply that (4.1.9) has no positive solution.

2. If $R_{\#} < 1$ we obtain

   i. For $R_0 > 1$, we have $C < 0$, which implies that (4.1.9) has a unique positive solution.

   ii. For $R_0 < \sqrt{R_{\#}}$, we have $B > 0$ and $C > 0$. This implies that (4.1.9) has no positive solution.

   iii. If $\sqrt{R_{\#}} < R_0$, we consider the discriminant of (4.1.9) $\Delta(R_0) := B^2 - 4AC$. One can see that $\Delta\left(\sqrt{R_{\#}}\right) := -4AC < 0$ and $\Delta(1) := B^2 > 0$. Therefore, there exists $R_c \in (\sqrt{R_{\#}}, 1)$ such that $\Delta(R_c) = 0$ and $\Delta < 0$ for $R_0 \in (\sqrt{R_{\#}}, R_c)$ and $\Delta > 0$ for $R_0 \in (R_c, 1)$. In this case we have

      a. If $\sqrt{R_{\#}} < R_0 < R_c$ then (4.1.9) has no positive solution.

      b. If $R_c < R_0 < 1$ then (4.1.9) has two real solutions which are positive since $C > 0$ and $B < 0$. ■

Proposition 2 establishes the existence of two endemic equilibria for R_0 in $(R_c, 1)$. To investigate the stability of these equilibria we use the following centre manifold theorem by Castillo-Chavez and Song [10].

Theorem 4.1.2. *(Castillo-Chavez and Song [10]) Consider the following general system of ordinary differential equations with a parameter ϕ*

$$\frac{dx}{dt} = f(x, \phi), \tag{4.1.10}$$

where $f : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R}^n$ is C^2 with $f(0, \phi) = 0$ for all ϕ and satisfying the following:

1. *The Jacobian matrix has $D_x f(0, 0)$ zero simple eigenvalue and the other eigenvalues have negative real parts;*

2. *$D_x f(0, 0)$ has a non negative right eigenvector w and a left eigenvector v corresponding to the zero eigenvalue.*

Let f_k be the k^{th} component of f and

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

$$b = \sum_{k,i=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0, 0).$$

The local dynamics of system (4.1.10) around 0, are totally determined by a and b. More precisely, we have following cases

1. *If $a > 0$, and $b > 0$, then*

   i. *When $\phi < 0$ with $|\phi| \ll 1$, 0 is locally asymptotically stable and there exists a positive unstable equilibrium*

   ii. *When $0 < \phi \ll 1$, 0 is unstable and there exists a negative and locally asymptotically stable equilibrium.*

2. *If $a < 0$, and $b < 0$, then*

   i. *When $\phi < 0$ with $|\phi| \ll 1$, 0 is unstable;*

   ii. *When $0 < \phi \ll 1$, 0 is locally asymptotically stable and there exists a positive unstable equilibrium.*

3. *If $a > 0$, and $b < 0$, then*

   i. *When $\phi < 0$ with $|\phi| \ll 1$, 0 is unstable, and there exists a locally asymptotically stable negative equilibrium.*

ii. *When $0 < \phi \ll 1$, 0 is stable, and a positive unstable equilibrium appears.*

4. *If $a < 0$, and $b > 0$, then as ϕ changes from negative to positive, 0, changes its stability from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and locally asymptotically stable.*

Particularly, if $a > 0$ and $b > 0$, then a backward bifurcation occurs at $\phi = 0$.

Using the Center Manifold theorem [10, 30], we carry out bifurcation analysis. First, we consider the transmission rate β as a bifurcation parameter so that $R_0 = 1$ if and only if

$$\beta = \beta^* = \frac{\Lambda_h \mu_v^2 (\alpha_1 + \mu_h)(\psi + \mu_h)(\alpha_2 + \mu_v)}{\alpha_1 \alpha_2 \lambda (\epsilon\phi)^2 \Lambda_v \mu_h}.$$

Then we make the following change of variables $S_h = x_1, E_h = x_2, I_h = x_3, S_v = x_4, E_v = x_5, I_v = x_6$, and $N_h = x_1 + x_2 + x_3$. In addition, using vector notation $\mathbf{x} = (x_1, x_2, x_3, x_4, x_5, x_6)^T$, the malaria model can then be written in the form $\frac{dx}{dt} = F(\mathbf{x})$, with $F = (f_1, f_2, f_3, f_4, f_5, f_6)^T$, as shown below:

$$\begin{cases} \dfrac{dx_1}{dt} = \Lambda_h - \beta_m x_1 - \mu_h x_1, \\ \dfrac{dx_2}{dt} = \beta_m x_1 - (\alpha_1 + \mu_h) x_2, \\ \dfrac{dx_3}{dt} = \alpha_1 x_2 - (\psi + \mu_h) x_3, \\ \dfrac{dx_4}{dt} = \Lambda_v - \lambda_v x_4 - \mu_v x_4, \\ \dfrac{dx_5}{dt} = \lambda_v x_4 - (\alpha_2 + \mu_v) x_5, \\ \dfrac{dx_6}{dt} = \alpha_2 x_5 - \mu_v x_6. \end{cases} \tag{4.1.11}$$

with

$$\beta_m = \frac{\beta^* \epsilon \phi x_6}{x_1 + x_2 + x_3}, \quad \lambda_v = \frac{\lambda \epsilon \phi x_3}{x_1 + x_2 + x_3}.$$

This method involves evaluation of the Jacobian of the system (4.1.11) at the disease free equilibrium (DFE) $\mathcal{E}_0$, denoted by $J(\mathcal{E}_0)$. This becomes

$$J(\mathcal{E}_0) = \begin{bmatrix} -\mu_h & 0 & 0 & 0 & 0 & -J_1 & \\ 0 & -J_2 & 0 & 0 & 0 & 0 & J_1 \\ 0 & \alpha_1 & -J_3 & 0 & 0 & 0 & 0 \\ 0 & 0 & -J_4 & 0 & -\mu_v & 0 & 0 \\ 0 & 0 & J_4 & 0 & 0 & -J_5 & 0 \\ 0 & 0 & 0 & 0 & 0 & \alpha_2 & -\mu_v \end{bmatrix},$$

where

$$J_1 = \beta^* \epsilon \phi, \;\; J_3 = \psi + \mu_h,$$

$$J_4 = \tfrac{\lambda \epsilon \phi \Lambda_v \mu_h}{\Lambda_h \mu_v}, \;\; J_2 = \alpha_1 + \mu_h,$$

$$J_5 = \alpha_2 + \mu_v.$$

$J(\mathcal{E}_0)$ has a simple zero eigenvalue, with other eigenvalues having negative real parts. Hence, the Center Manifold theorem (4.1.2) can be applied. For this we need to calculate a and b.

We first start by calculating the right and the left eigenvector of $J(\mathcal{E}_0)$ denoted respectively by $\mathbf{w} = [w_1, w_2, w_3, w_4, w_5, w_6]^T$, and $\mathbf{v} = [v_1, v_2, v_3, v_4, v_5, v_6]$. We obtain

$$w_1 = \tfrac{-1}{\mu_h}\left[\frac{\kappa\lambda\epsilon\phi\Lambda_v\mu_h\alpha_1\beta^*\epsilon\phi}{\Lambda_h\mu_v^2(r+\psi+\mu_h)(\alpha_1+\mu_h)} + \beta^*\epsilon\phi\right], \quad w_2 = \frac{\beta^*\epsilon\phi}{(\alpha_1+\mu_h)},$$

$$w_3 = \frac{\alpha_1\beta^*\epsilon\phi}{(r+\psi+\mu_h)(\alpha_1+\mu_h)}, \quad w_4 = -\frac{\lambda\epsilon\phi\Lambda_v\mu_h\alpha_1\beta^*\epsilon\phi}{\Lambda_h\mu_v^2(r+\psi+\mu_h)(\alpha_1+\mu_h)},$$

$$w_5 = \frac{\mu_v}{\alpha_2}, \quad w_6 = 1$$

and

$$v_1 = v_4 = 0, \quad v_2 = 1,$$

$$v_3 = \frac{\alpha_1+\mu_h}{\alpha_1}, \quad v_5 = \frac{\alpha_2\beta^*\epsilon\phi}{\mu_v(\alpha_2+\mu_v)}, \quad v_6 = \frac{\beta^*\epsilon\phi}{\mu_v}.$$

After rigorous computations, it can be shown that

$$a = -\frac{v_5\lambda\epsilon\phi\mu_h^2\Lambda_h(w_4 - 2w_1\frac{\Lambda_v}{\mu_v})(2w_1+w_2+w_3) + v_2w_6\beta^*\epsilon\phi\mu_h\Lambda_h(w_2+w_3)}{\Lambda_h^2}$$

$$b = v_2w_6\epsilon\phi > 0.$$

Using Mathematica we obtained that if $R_\# < 1$ then $a > 0$ implying that the SEI malaria model exhibits a backward bifurcation and that one of the endemic steady states is unstable. One can show numerically that depending on the initial values the system will stabilise on the other steady state or the disease free steady state.

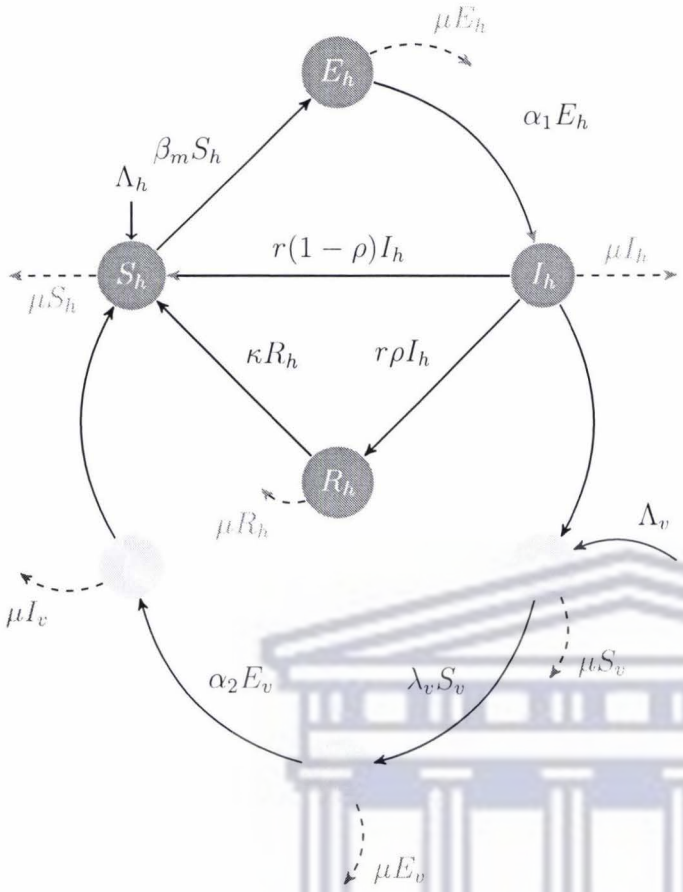


Figure 4.2: Flow diagram for Malaria disease transmission

4.2 Malaria model with treatment

The SEIR model is obtained by including a class for recovered individuals into the model. We obtain the following SEIR model:

$$\begin{cases} \dfrac{dS_h}{dt} = \Lambda_h + r(1-\rho)I_h - \beta_m S_h - \mu_h S_h + \kappa R_h, \\ \dfrac{dE_h}{dt} = \beta_m S_h - (\alpha_1 + \mu_h)E_h, \\ \dfrac{dI_h}{dt} = \alpha_1 E_h - (r + \psi + \mu_h)I_h, \\ \dfrac{dR_h}{dt} = r\rho I_h - (\mu_h + \kappa)R_h, \\ \dfrac{dS_v}{dt} = \Lambda_v - \lambda_v S_v - \mu_v S_v, \\ \dfrac{dE_v}{dt} = \lambda_v S_v - (\alpha_2 + \mu_v)E_v, \\ \dfrac{dI_v}{dt} = \alpha_2 E_v - \mu_v I_v. \end{cases} \tag{4.2.12}$$

Here we consider two forms of infection for mosquitoes and humans:

i. The mass action force of infection

$$\begin{aligned} \beta_m &= \beta\epsilon\phi I_v, \\ \lambda_v &= \lambda\epsilon\phi I_h. \end{aligned} \tag{4.2.13}$$

ii. The standard force of infection

$$\begin{aligned} \beta_m &= \frac{\beta\epsilon\phi I_v}{N_h = S_h + E_h + I_h + R_h}, \\ \lambda_v &= \frac{\lambda\epsilon\phi I_h}{N_h = S_h + E_h + I_h + R_h}. \end{aligned} \tag{4.2.14}$$

In a similar way as for the SEI model we show that the SEIR malaria model (4.2.12) is biologically-feasible in

$$\mathcal{D} = \mathcal{D}_h \times \mathcal{D}_v \subset \mathbb{R}_+^4 \times \mathbb{R}_+^3,$$

with,

$$\mathcal{D}_h = \{(S_h, E_h, I_h, R_h) \in \mathbb{R}_+^4 : S_h + E_h + I_h + R_h \leq \frac{\Lambda_h}{\mu_h}\},$$

and

$$\mathcal{D}_v = \{(S_v, E_v, I_v) \in \mathbb{R}_+^3 : S_v + E_v + I_v \leq \frac{\Lambda_v}{\mu_v}\}.$$

4.2.1 Analysis of the mass action incidence SEIR model

Stability of the disease-free equilibrium

The DFE of the malaria model (4.2.12) exists and is given by

$$\mathcal{E}_0 = \left(\frac{\Lambda_h}{\mu_h}, 0, 0, 0, \frac{\Lambda_v}{\mu_v}, 0, 0\right).$$

The basic reproduction number of the model (4.2.12), R_T, is calculated by using the next generation matrix [88]. It is given by

$$F = \begin{pmatrix} 0 & 0 & 0 & \beta c\phi S_h^* \\ 0 & 0 & 0 & 0 \\ 0 & \lambda\epsilon\phi S_v^* & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix},$$

and

$$V = \begin{pmatrix} (\alpha_1 + \mu_h) & 0 & 0 & 0 \\ -\alpha_1 & r + \psi + \mu_h & 0 & 0 \\ 0 & 0 & \alpha + \mu_v & 0 \\ 0 & 0 & -\alpha_2 & \mu_v \end{pmatrix},$$

$$\widehat{R}_T = FV^{-1} = \sqrt{\frac{\mu_h + \psi}{\mu_h + \psi + r}} R_0, \tag{4.2.15}$$

where R_0 the is basic reproduction number of the disease without treatment which is given by

$$R_0 = \sqrt{\frac{\alpha_1 \alpha_2 \lambda \Lambda_h \Lambda_v (\epsilon\phi)^2 \beta}{\mu_h \mu_v^2 (\mu_h + \alpha_1)(\mu_h + \psi)(\mu_v + \alpha_2)}}. \tag{4.2.16}$$

The DFE, is locally asymptotically stable if $\widehat{R}_T < 1$ and unstable if $\widehat{R}_T > 1$. Concerning existence and stability of the endemic equilibrium points we have the following result:

Proposition 3. *1. If $R_0 < 1$, system (4.2.12) has a unique equilibrium point, the DFE and it is locally asymptotically stable.*

2. If $R_0 > 1$, the DFE becomes unstable and system (4.2.12) has an additional steady state.

Proof: The steady states of (4.2.12) are obtained by equating its right hand side to zero. We obtain

$$\begin{cases} S_h^* = \dfrac{\Lambda_h(\mu_h + \kappa)\beta_m^*(SH1) + \mu_h((\mu_h + \kappa)(\mu_h + \psi + r)(\mu_h + \alpha_1))) + G^*}{(\mu_h + \beta_m^*)(\mu_h + \kappa)\beta_m^*(SH1) + \mu_h((\mu_h + \kappa)(\mu_h + \psi + r)(\mu_h + \alpha_1)))}, \\ E_h^* = \dfrac{\beta_m^*(\Lambda_h(\mu_h + \kappa)\beta_m^*(SH1) + \mu_h((\mu_h + \kappa)(\mu_h + \psi + r)(\mu_h + \alpha_1))) + G^*)}{(\mu_h + \alpha_1)(\mu_h + \beta_m^*)(\mu_h + \kappa)\beta_m^*(SH1) + \mu_h((\mu_h + \kappa)(\mu_h + \psi + r)(\mu_h + \alpha_1)))}, \\ I_h^* = \dfrac{\alpha_1 \Lambda_h \beta_m^*(\mu_h + \kappa)}{\beta_m^*(SH1) + \mu_h((\mu_h + \kappa)(\mu_h + \psi + r)(\mu_h + \alpha_1)))} \\ R_h^* = \dfrac{r\rho\alpha_1 \Lambda_h \beta_m^*(\mu_h + \kappa)}{(\mu_h + \kappa)\beta_m^*(SH1) + \mu_h((\mu_h + \kappa)(\mu_h + \psi + r)(\mu_h + \alpha_1)))}, \\ S_v^* = \dfrac{\Lambda_v}{\mu_v + \lambda_v^*}, \\ E_v^* = \dfrac{\lambda_v^* \Lambda_v}{(\mu_v + \alpha_2)(\mu_v + \lambda_v^*)} \\ I_v^* = \dfrac{\alpha_2 \lambda_v^* \Lambda_v}{\mu_v(\mu_v + \alpha_2)(\mu_v + \lambda_v^*)}, \end{cases} \tag{4.2.17}$$

where

$$G^* = r((1-\rho)(\mu_h+\kappa)+\kappa\rho), SH1 = (\mu_h+\psi+r)(\mu_h+\alpha_1)(\mu_h+\kappa)+r\alpha_1(\mu_h\rho-(\kappa+\mu_h)), \tag{4.2.18}$$

Using(4.2.13) and (4.2.17) we obtain $\beta_m^* = 0$ or

$$\beta_m^* A_\rho + B = 0$$

where

$$A_\rho = \mu_h^2\Lambda_h^2\mu_v(\alpha_2+\mu_v)(\psi+\alpha_1+\mu_h)(\epsilon\lambda\phi\alpha_1+(\psi+\alpha_1+\mu_h)\mu_v)+\rho\omega_q$$

$$B = \mu_h\mu_v^2(\alpha_2+\mu_v)(\kappa+\mu_h)(\alpha_1+\mu_h)(\mu_h+\psi+r)(1-\widehat{R}_T^2)$$

$$\omega_q = r\alpha_1\mu_h\mu_v^2(\alpha_2+\mu_v).$$

Clearly, $A_\rho > 0$ and $B \geq 0$ whenever $\widehat{R}_T \leqslant 1$, implying that $\beta_m^* = \frac{-B}{A_\rho} \leqslant 0$. Therefore the mass action SEIR malaria model has no endemic equilibrium whenever $\widehat{R}_T \leqslant 1$ and one unique endemic equilibrium when $\widehat{R}_T > 1$.■

Global stability of the DFE of the mass action SEIR malaria model

We investigate the global stability of the disease-free equilibrium (DFE), using the following theorem.

Theorem 4.2.1.

1. *The disease-free equilibrium* $\mathcal{E}_0 = (S_h^*, E_h^*, I_h^*, R_h^*, S_v^*, E_v^*, I_v^*) = \left(\frac{\Lambda_h}{\mu_h}, 0, 0, 0, \frac{\Lambda_v}{\mu_v}, 0, 0,\right)$, *globally asymptotically stable when* $\widehat{R}_T \leqslant 1$ *and unstable when* $\widehat{R}_T > 1$.

2. *When* $\widehat{R}_T > 1$, *system (4.2.12) has a unique endemic equilibrium.*

Proof. Consider the Lyapunuv function

$$L_F = \Big(\frac{\epsilon\phi\lambda S_v(r+\psi+\mu_h+\alpha_1)}{(\alpha_1+\mu_h)(r+\psi+\mu_h)\widehat{R}_T}\Big)E_h + \Big(\frac{\epsilon\phi\lambda S_v}{(r+\psi+\mu_h)\widehat{R}_T}\Big)I_h + E_v + I_v,$$

$$\frac{dL_F}{dt} = \Big(\frac{\epsilon\phi\lambda S_v(r+\psi+\mu_h+\alpha_1)}{(\alpha_1+\mu_h)(r+\psi+\mu_h)\widehat{R}_T}\Big)\dot{E}_h + \Big(\frac{\epsilon\phi\lambda S_v}{(r+\psi+\mu_h)\widehat{R}_T}\Big)\dot{I}_h + \dot{E}_v + \dot{I}_v$$

$$= \Big(\frac{\epsilon\phi\lambda S_v(r+\psi+\mu_h+\alpha_1)}{(\alpha_1+\mu_h)(r+\psi+\mu_h)\widehat{R}_T}\Big)\Big[\epsilon\phi\beta S_h I_v - (\alpha_1+\mu_h)E_h\Big],$$

$$+ \Big(\frac{\epsilon\phi\lambda S_v}{(r+\psi+\mu_h)\widehat{R}_T}\Big)\Big[\alpha_1 E_h - (r+\psi+\mu_h)I_h\Big] + (\epsilon\phi I_h S_v - (\alpha_2+\mu_v)E_v) + (\alpha_2 E_v - \mu_v I_v)$$

$$= \Big[-\frac{\epsilon\phi\lambda S_v(r+\psi+\mu_h+\alpha_1)}{(r+\psi+\mu_h)\widehat{R}_T} + \frac{\epsilon\phi\lambda\alpha_1 S_v}{(r+\psi+\mu_h)\widehat{R}_T}\Big]E_h + \Big[-\frac{\epsilon\phi\lambda\alpha_1 S_v}{\widehat{R}_T} + \epsilon\phi\lambda\alpha_1 S_v\Big]I_h,$$

$$- \alpha_2 E_v + \Big(\frac{(\epsilon\phi)^2\lambda\beta S_v S_h}{(\alpha_1+\mu_h)(r+\psi+\mu_h)\widehat{R}_T} - \mu_v\Big)I_v$$

$$= -\frac{\epsilon\phi\lambda S_v}{\widehat{R}_T}E_h + \epsilon\phi\lambda S_v\Big[1-\frac{1}{\widehat{R}_T}\Big]I_h - \alpha_2 E_v + \Big[\frac{\mu_v\widehat{R}_T^2}{\widehat{R}_T} - \mu_v\Big]. \tag{4.2.19}$$

Since $S_h \leqslant S_h^*$, we have,

$$-\frac{\epsilon\phi\lambda S_v}{\widehat{R}_T}E_h + \frac{\epsilon\phi\lambda S_v}{\widehat{R}_T}\Big(\widehat{R}_T - 1\Big)I_h - \mu_v E_v + \mu_v(\widehat{R}_T - 1)I_v$$

$$\leqslant 0 \quad for \quad \widehat{R}_T \leqslant 1 \tag{4.2.20}$$

Therefore the DFE of the mass action model is globally stable for $\widehat{R}_T \leqslant 1$ □

4.2.2 Analysis of the standard incidence SEIR model

For the standard incidence form we have the same disease free equilibrium. The basic reproduction number of the model (4.2.12), R_T, is calculated by using the next generation matrix [89]. It is given by

$$R_T = FV^{-1} = \sqrt{\frac{\mu_h + \psi}{\mu_h + \psi + r}} R_0, \tag{4.2.21}$$

where R_0 the is basic reproduction number of the disease without treatment given by

$$R_0 = \sqrt{\frac{\alpha_1 \alpha_2 \lambda \Lambda_v \mu_h (\epsilon\phi)^2 \beta}{\Lambda_h \mu_v^2 (\mu_h + \alpha_1)(\mu_h + \psi)(\mu_v + \alpha_2)}}. \tag{4.2.22}$$

In a similar way to the SEI model (4.1.1) with standard incidence, we obtain an equation for the endemic steady states given by

$$\beta_m^*(A_\rho \beta_m^{*2} + B_\rho \beta_m^* + C_\rho) = 0. \tag{4.2.23}$$

where

$$\begin{aligned}
A_\rho = &\ (\kappa + \mu_h)^2 A + \rho^2 r^2 \alpha_1^2 \Lambda_h^2 \mu_h^2 \mu_v^2 (\alpha_2 + \mu_v), \\
&+\rho r \alpha_1 \Lambda_h^2 \mu_h^2 \mu_v (\kappa + \mu_h)(\alpha_2 + \mu_v)(\epsilon\phi\lambda\alpha_1 + 2(r + \psi + \alpha_1 + \mu_h)\mu_v), \\
B_\rho = &\ \Lambda_h \mu_v^2 M (\alpha_2 + \mu_v)(\alpha_1 + \mu_h)(r + \psi + \mu_h)(R_{s\#} - R_T^2), \\
C_\rho = &\ \mu_h^2 \mu_v^2 \Lambda_h^2 (\alpha_2 + \mu_v)(\kappa + \mu_h)^2 (\alpha_1 + \mu_h)^2 (r + \psi + \mu_h)^2 (1 - {R_T}^2),
\end{aligned}$$

with

$$\begin{aligned}
A &= \mu_h^2 \Lambda_h^2 \mu_v (\alpha_2 + \mu_v)(\psi + \alpha_1 + \mu_h)(\epsilon\lambda\phi\alpha_1 + (\psi + \alpha_1 + \mu_h)\mu_v), \\
M &= \mu_h(\kappa + \mu_h)^2 (r\mu_h + (\psi + \mu_h)(\alpha_1 + \mu_h)) + \rho r \alpha_1 (\kappa + \mu_h), \\
R_{s\#} &= \frac{1}{M}\left[2\rho r \alpha_1 \Lambda_h \mu_h^2 (\kappa + \mu_h) + (\epsilon\phi\lambda\alpha_1 + 2(r + \psi + \alpha_1 + \mu_h)\mu_v)\frac{(\kappa + \mu_h)^2}{\mu_v}\right],
\end{aligned}$$

We obtain the same bifurcation results as in proposition (2).

Local stability analysis of the standard incidence force of infection

The stability of the disease free steady state is the same as for the model with the mass action but the existence results of endemic steady states are different.

Theorem 4.2.2. *For basic SEIR malaria model with standard incidence, the DFE, is locally asymptotically stable if* $\widehat{\mathcal{R}}_T < 1$ *and unstable if* $\widehat{\mathcal{R}}_T > 1$

Proof. We evaluate the Jacobian matrix of the SEIR model at the disease-free equilibrium, using $S_h = N_h - (E_h + I_h + R_h)$, we obtain

$$J_s = \begin{pmatrix} -(\alpha_1+\mu_h) & 0 & 0 & 0 & 0 & \beta\epsilon\phi \\ \alpha_1 & -(r+\psi+\mu_h) & 0 & 0 & 0 & 0 \\ 0 & r\rho & -(\kappa+\mu_h) & 0 & 0 & 0 \\ 0 & -\frac{\epsilon\phi\lambda\Lambda_v\mu_h}{\Lambda_h\mu_v} & 0 & -\mu_v & 0 & 0 \\ 0 & \frac{\epsilon\phi\lambda\Lambda_v\mu_h}{\Lambda_h\mu_v} & 0 & 0 & -(\alpha_2+\mu_v) & 0 \\ 0 & 0 & 0 & 0 & \alpha_2 & -\mu_v \end{pmatrix},$$

It is clear that the third and fourth columns have diagonal enteries, so, these diagonal enteries $-(\kappa+\mu_h)$, $-\mu_v$ are two eigenvalues. Hence, removing these columns and the rows corresponding to them, the Jacobian matrix (J_s) is then reduced to the following:

$$J_s = \begin{pmatrix} -(\alpha_1+\mu_h) & 0 & 0 & \beta\epsilon\phi \\ \alpha_1 & -(r+\psi+\mu_h) & 0 & 0 \\ 0 & \frac{\epsilon\phi\lambda\Lambda_v\mu_h}{\Lambda_h\mu_v} & -(\alpha_2+\mu_v) & 0 \\ 0 & 0 & \alpha_2 & -\mu_v \end{pmatrix}.$$

We therefore calculate the eigenvalues of the reduced matrix. Solving the eigenvalues of J_s, requires that

$$det(J_s - \Omega) = 0,$$

which leads to the following characteristic polynomial,

$$(B_s+\Omega)(C_s+\Omega)(D_s+\Omega)(\mu_v+\Omega) - \alpha_1\alpha_2 E_s F_s = 0,$$

which results to

$$\Omega^4 + a_1\Omega^3 + a_2\Omega^2 + a_3\Omega + a_4 = 0.$$

Here,

$$\begin{aligned} a_1 &= (B_s + C_s + D_s + \mu_v), \\ a_2 &= (B_sC_s + B_sD_s + \mu_v(B_s + C_s + D_s)), \\ a_3 &= (B_sC_sD_s + \mu_v(B_sC_s + B_sD_s + C_sD_s)), \\ a_4 &= B_sC_sD_s\mu_v - \alpha_1\alpha_2E_sF_s = B_sC_sD_s\mu_v(1-\widehat{\mathcal{R}}^2), \end{aligned} \tag{4.2.24}$$

where $B_s = \alpha_1 + \mu_h$, $C_s = r + \psi + \mu_h$, $D_s = \alpha_2 + \mu_v$, $E_s = \frac{\epsilon\phi\lambda\Lambda_v\mu_h}{\mu_v\Lambda_h}$, $F_s = \beta\epsilon\phi$.
By applying the Routh-Hurwitz stability conditions, we establish the following for the polynomial that $a_1 > 0$, $a_2 > 0$, $a_3 > 0, a_4 > 0$ and

$$H_1 = a_1 > 0,\ H_2 = \begin{vmatrix} a_1 & 1 \\ a_3 & a_2 \end{vmatrix} > 0,\ H_3 = \begin{vmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ 0 & a_4 & a_3 \end{vmatrix} > 0,$$

$$H_4 = \begin{vmatrix} a_1 & 1 & 0 & 0 \\ a_3 & a_2 & a_1 & 1 \\ 0 & a_4 & a_3 & a_2 \\ 0 & 0 & 0 & 0 \end{vmatrix} > 0.$$

The steady state is stable (that is, $Re < 0$) for all λ if and only if $detH_j \geq 0$ for all $j = 1, 2, 3, 4$. Furthermore, it is clear that $a_4 > 0$, whenever, $R_m < 1$, we only need here to prove that $H_2 > 0,\ H_3 > 0,\ H_4 > 0$.

$H_2 = a_1a_2 - a_3$, $H_3 = a_3(a_1a_2 - a_3) - a_1a_4$ and $H_4 = a_aH_3$. Using Mathematica 5.0, we found that

$$\begin{aligned} H_2 &= C_s^2(B_s + C_s + \mu_v) + C_s(B_s^2 + B_s(D_s + \alpha_2) + D_s(2\alpha_2 + \mu_v) + \mu_v(3B_s + 2\mu_v + \alpha_2)) \\ &\quad + B_s^2(D_s + \mu_v) + B_s(D_s(2\alpha_2 + \mu_v) + \mu_v(\alpha_2 + 2\mu_v)) + D_s\alpha_2(\alpha_2 + 2\mu_v), \end{aligned}$$

$$\begin{aligned} H_3 &= C_s^3(B_s + D_s)(B_s + \mu_v)(D_s + \mu_v) \\ &\quad + C_s^2(B_s^2D_s(B_s + D_s) + \alpha_2(E_sF_s\alpha_1 + (B_s + \mu_v)(D_s(B_s + 2D_s) + (B_s + D_s)\mu_v)) \\ &\quad + \mu_v(B_s(B_s + D_s)(B_s + 3D_s) + \mu_v(3B_s^2 + 3B_sD_s + D_s^2 + 2(B_s + D_s)\mu_v)) + C_s(B_s^3D_s^2 \\ &\quad + B_s\mu_v(B_sD_s(2B_s + 3D_s) + (B_s + D_s)(B_s + 2D_s)\mu_v + 2B_s\mu_v^2) \\ &\quad + \alpha_2^2(2E_sF_s\alpha_1 + D_s^2(B_s + \mu_v)) + \alpha_2(2B_s^2D_s^2 + 2B_sD_s(B_s + 3D_s)\mu_v \\ &\quad + (B_s^2 + 2D_s^2)\mu_v^2 + 2E_sF_s\alpha_1(B_s + 2\mu_v)) + E_sF_s\alpha_1\alpha_2(B_s + \alpha_2 + 2\mu_v)^2 \\ &\quad + B_sD_s\mu_v(D_s(B_s + \alpha_2)^2 + (B_s(B_s + D_s) + (B_s + 2D_s)\alpha_2)\mu_v + 2B_s\mu_v^2), \end{aligned}$$

$$H_4 = a_4H_3.$$

(4.2.25)

Consequently from the above, it is clear that $H_2 > 0,\ H_3 > 0,\ H_4 > 0$. Therefore, the eigenvalues of the Jacobian matrix, J_s, are all having negative real part whenever $\widehat{\mathcal{R}}_m < 1$. But if $\widehat{\mathcal{R}}_T > 1$, clearly we can see that $a_4 < 0$, moreover, having $a_1 > 0,\ a_2 > 0,\ a_3 > 0$, shows that not all the roots of the polynomial will have a negative real part. This means that whenever, $\widehat{\mathcal{R}}_T > 1$, the disease-free equilibrium point is unstable, that is, it is not globally stable. □

Bifurcation analysis of the standard form SEIR model

Using Center Manifold theory [30, 10], we carry out bifurcation analysis. First, we consider the transmission rate β as a bifurcation parameter so that $R_T = 1$ if and only if

$$\beta = \beta^* := \frac{\Lambda_h \mu_v^2 (\alpha_1 + \mu_h)(\psi + \mu_h + r)(\alpha_2 + \mu_v)}{\alpha_1 \alpha_2 \lambda (\epsilon\phi)^2 \Lambda_v \mu_h}.$$

Then we make the following change of variables on the model, $S_h = x_1, E_h = x_2, I_h = x_3, R_h = x_4, S_v = x_5, E_v = x_6, I_v = x_7$, and $N_h = x_1 + x_2 + x_3 + x_4$. Using vector notation $\mathbf{x} = (x_1, x_2, x_3, x_4, x_5, x_6, x_7)^T$, the malaria model can then be written in the form $\frac{dx}{dt} = F(\mathbf{x})$, with $F = (f_1, f_2, f_3, f_4, f_5, f_6, f_7)^T$, as shown below:

$$\begin{cases} \frac{dx_1}{dt} = \Lambda_h + \kappa x_4 - \beta_m x_1 - \mu_h x_1, \\ \frac{dx_2}{dt} = \beta_m x_1 - (\alpha_1 + \mu_h) x_2, \\ \frac{dx_3}{dt} = \alpha_1 x_2 - (r + \psi + \mu_h) x_3, \\ \frac{dx_4}{dt} = r x_3 - (\kappa + \mu_h) x_4, \\ \frac{dx_5}{dt} = \Lambda_v - \lambda_v x_5 - \mu_v x_5, \\ \frac{dx_6}{dt} = \lambda_v x_5 - (\alpha_2 + \mu_v) x_6, \\ \frac{dx_7}{dt} = \alpha_2 x_6 - \mu_v x_7, \end{cases} \tag{4.2.26}$$

with

$$\beta_m = \frac{\beta^* \epsilon \phi x_7}{x_1 + x_2 + x_3 + x_4}, \ \lambda_v = \frac{\lambda \epsilon \phi x_3}{x_1 + x_2 + x_3 + x_4}.$$

The Jacobian matrix of (4.2.26) is given by

$$J(\mathcal{E}_0) = \begin{bmatrix} -\mu_h & 0 & 0 & \kappa & 0 & 0 & -J_1 \\ 0 & -J_5 & 0 & 0 & 0 & 0 & J_1 \\ 0 & \alpha_1 & -J_2 & 0 & 0 & 0 & 0 \\ 0 & 0 & r & -J_6 & 0 & 0 & 0 \\ 0 & 0 & -J_4 & 0 & -\mu_v & 0 & 0 \\ 0 & 0 & J_4 & 0 & 0 & -J_8 & 0 \\ 0 & 0 & 0 & 0 & 0 & \alpha_2 & -\mu_v \end{bmatrix},$$

where

$$J_1 = \beta^* \epsilon \phi, \;\; J_2 = \psi + \mu_h + r,$$

$$J_4 = \frac{\lambda \epsilon \phi \Lambda_v \mu_h}{\Lambda_h \mu_v}, \;\; J_5 = \alpha_1 + \mu_h,$$

$$J_6 = \kappa + \mu_h, \;\; J_8 = \alpha_2 + \mu_v.$$

$J(\mathcal{E}_0)$ has a simple zero eigenvalue, with other eigenvalues having negative real part. Hence, the Center Manifold Theorem (4.1.2) can be applied. For this we need to calculate a and b.

We first start by calculating a right and a left eigenvector of $J(\mathcal{E}_0)$ denoted respectively by $\mathbf{w} = [w_1, w_2, w_3, w_4, w_5, w_6, w_7]^T$, and $\mathbf{v} = [v_1, v_2, v_3, v_4, v_5, v_6, v_7]$. We obtain

$$w_1 = \frac{\kappa w_4 - w_2(\alpha_1 + \mu_h)}{\mu_h}, \quad w_2 = \frac{\beta^* \epsilon \phi}{\alpha_1 + \mu_h},$$

$$w_3 = \frac{\alpha_1 w_2}{r + \psi + \mu_h}, \quad w_4 = \frac{r w_3}{\kappa + \mu_h},$$

$$w_5 = -\frac{\lambda \epsilon \phi \Lambda_v \mu_h (\kappa + \mu_h) w_4}{r \Lambda_h \mu_v^2}, \quad w_6 = \frac{\mu_v}{\alpha_2}, \quad w_7 = 1,$$

and

$$v_1 = v_4 = v_5 = 0$$

$$v_2 = \frac{v_3 \alpha_1}{\alpha_1 + \mu_h}, \quad v_3 = \frac{\mu_v(\alpha_1 + \mu_h)}{\beta^* \epsilon \phi \alpha_1},$$

$$v_6 = \frac{\alpha_2}{\alpha_2 + \mu_v}, v_7 = v_7.$$

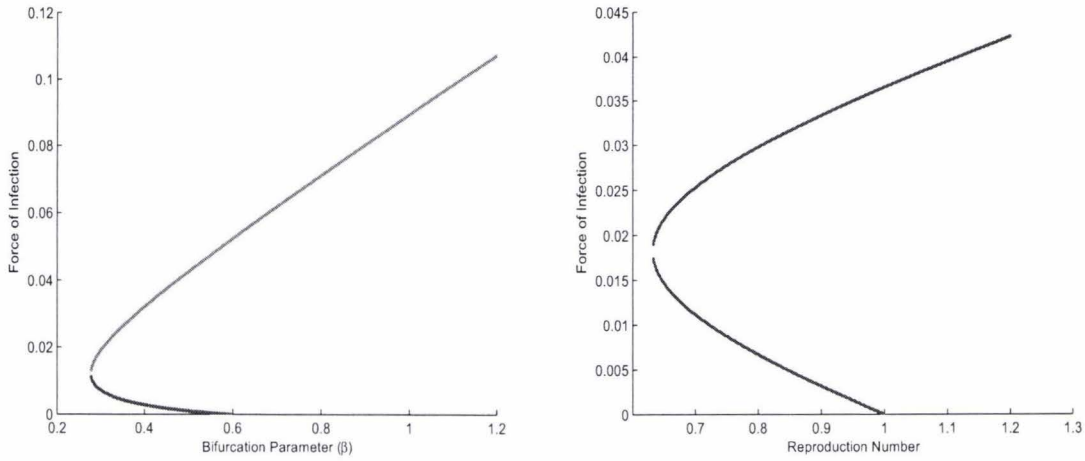
After rigorous computations, it can be shown that

$$\begin{aligned} a &= 2 v_6 w_3 \lambda \epsilon \phi \frac{\mu_h}{\Lambda_h} \left(w_5 - w_1 \frac{\Lambda_v \mu_h}{\Lambda_h \mu_v} \right), \\ b &= v_2 w_7 \epsilon \phi > 0. \end{aligned} \tag{4.2.27}$$

Clearly $b > 0$. Using Mathematica we obtained that if $R_{s\#} < 1$ then $a > 0$ implying that the SEI malaria model exhibits a backward bifurcation and that the endemic one of steady states is unstable.

The backward bifurcation phenomenon is illustrated in (Figure 4.2.).

In this chapter, we calculated the basic reproduction number, $\widehat{R}_T$. We also investigated the existence and stability of equilibria. The mass action force of infection model is found to exhibits transcritical bifurcation, the DFE will be globally stable whenever $\widehat{R}_T < 1$, while the standard incidence form of infection exhibits backward bifurcation. This has



(a) (b)

Figure 4.3: Diagram depicting the bifurcation diagram using the following set of parameter values $\Lambda_h = 0.00099$, $\Lambda_v = 0.0089$, $\beta = 0.07833$, $\lambda = 0.00572333$, $\epsilon\phi = 0.58$, $\alpha_1 = 100$, $\alpha_2 = 0.981$, $\mu_h = 0.00049139$, $\mu_v = 0.009$, $r = 0.00656$, $\psi = 0.0013945392$, $\kappa = 0.7902$. it follows that $\widehat{\mathcal{R}}_T = 0.526826$ and $a = 0.172524$ with $b = 0.114899$ so that (4.2.27) is satisfied.

epidemiological implication, it means that for effective eradication and control of malaria, bringing $\widehat{R}_T$, is no longer sufficient, but rather, that $\widehat{R}_T$. Moreover, to achieve this may be too costly, because it means that for constant controls, one needs to keep implementing all controls for infinite time.

In determining how best to reduce human mortality and morbidity due to malaria, it is necessary to know the relative importance of the different factors responsible for its transmission. Hence, in the next section we compute sensitivity indices of the reproduction numbers which measures initial disease transmission. This enables us to single out parameters that have a high impact on the reproductive number, $\widehat{R}_T$ and which should be targeted by intervention strategies.

4.3 Sensitivity analysis of model parameters

We carried out the sensitivity analysis to determine the model robustness to parameter values. That is to help us know the parameters that have a high impact on the disease transmission, that is, reproductive number ($\widehat{R}$). In carrying out the sensitivity analysis, we use the normalised forward sensitivity index of a variable to a parameter approach described in [68], this is defined as the ratio of the relative change in the variable to the relative change in the parameter. The sensitivity index may also be defined using partial derivatives when the variable is a differentiable function of the parameter.

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

$$\Upsilon_l^h := \frac{\partial h}{\partial l} \times \frac{l}{h}.$$

Sensitivity indices of $\widehat{R}$

We therefore derive the sensitivity of $\widehat{\mathcal{R}}$ to each of the twelve (12) different parameters described in Table (6.1). The sensitivity index of $\widehat{R}$ with respect to each of the following parameters, β, λ, Λ_h, Λ_v, ϕ and ϵ for example, is 0.5 and are independent of any parameter values. This is shown below,

$$\begin{aligned}
\Upsilon_\beta^{\widehat{\mathcal{R}}} &:= \frac{\partial \widehat{\mathcal{R}}}{\partial \beta} \times \frac{\beta}{\widehat{\mathcal{R}}}, \\
\Upsilon_\lambda^{\widehat{\mathcal{R}}} &:= \frac{\partial \widehat{\mathcal{R}}}{\partial \lambda} \times \frac{\lambda}{\widehat{\mathcal{R}}}, \\
\Upsilon_{\Lambda_h}^{\widehat{\mathcal{R}}} &:= \frac{\partial \widehat{\mathcal{R}}}{\partial \Lambda_h} \times \frac{\Lambda_h}{\widehat{\mathcal{R}}}, \\
\Upsilon_{\Lambda_v}^{\widehat{\mathcal{R}}} &:= \frac{\partial \widehat{\mathcal{R}}}{\partial \Lambda_v} \times \frac{\Lambda_v}{\widehat{\mathcal{R}}}, \\
\Upsilon_\phi^{\widehat{\mathcal{R}}} &:= \frac{\partial \widehat{\mathcal{R}}}{\partial \phi} \times \frac{\phi}{\widehat{\mathcal{R}}}, \\
\Upsilon_\epsilon^{\widehat{\mathcal{R}}} &:= \frac{\partial \widehat{\mathcal{R}}}{\partial \epsilon} \times \frac{\epsilon}{\widehat{\mathcal{R}}},
\end{aligned} \tag{4.3.28}$$

The implication of this, is that by increasing (or decreasing) any of these parameter values by 10%, increases (or decreases the reproductive number $\widehat{R}$ by 5%. Other detail evaluation of the sensitivity indices of $\widehat{\mathcal{R}}$ resulting from the other different parameters,

having obvious expressions, are shown below.

$$\begin{aligned}
\frac{\partial \widehat{\mathcal{R}}}{\partial \alpha_2} \ \mathbf{x} \ \frac{\alpha_2}{\widehat{\mathcal{R}}} &= \frac{\mu_v}{2(\alpha_2+\mu_v)}, \\
\frac{\partial \widehat{\mathcal{R}}}{\partial \alpha_1} \ \mathbf{x} \ \frac{\alpha_1}{\widehat{\mathcal{R}}} &= \frac{\mu_h}{2(\alpha_1+\mu_h)}, \\
\frac{\partial \widehat{\mathcal{R}}}{\partial \mu_v} \ \mathbf{x} \ \frac{\mu_v}{\widehat{\mathcal{R}}} &= \frac{-2\alpha_2+3\mu_v}{2(\alpha_2+\mu_v)}, \\
\frac{\partial \widehat{\mathcal{R}}}{\partial r} \ \mathbf{x} \ \frac{r}{\widehat{\mathcal{R}}} &= \frac{-r}{2(r+\psi+\mu_h)}, \\
\frac{\partial \widehat{\mathcal{R}}}{\partial \psi} \ \mathbf{x} \ \frac{\psi}{\widehat{\mathcal{R}}} &= \frac{-\psi}{2(r+\psi+\mu_h)}
\end{aligned} \tag{4.3.29}$$

Sensitivity indices of $\widehat{R}$

	Parameter	Parameter description	Sensitivity index
1	μ_v	Natural death rate in mosquitoes	-1.00455
2	μ_h	Natural death rate in humans	-0.554092
3	β	probability of human getting infected	+0.5
4	λ	probability of a mosquito getting infected	+0.5
5	Λ_v	mosquitoes birth rate	+0.5
6	Λ_h	human birth rate	+0.5
7	ϕ	mosquito contact rate with human	+0.5
8	ϵ	mosquito biting rate	+0.5
9	ψ	disease induced death	-0.45614
10	r	recovery rate	-0.45614
11	α_2	progression rate from exposed to infected mosquito	+0.00454545
12	α_1	progression rate from exposed to infected human	+0.00000245696

However, the expression for sensitivity indices for human natural death μ_h is complex. Hence we evaluate the sensitivity indices at the baseline parameter values given in Table (6.1). The parameters are arranged from the most sensitive to the least. The most sensitive parameter is the natural death rate in mosquitoes, μ_v, followed by probability of human getting infected, β. Other important parameters include, mosquito contact rate with human, ϕ, mosquito biting rate, ϵ and probability of a mosquito getting infected, λ. The least sensitive parameter is the progression rate from exposed to infected human, α_1.

The sensitivity index of $\widehat{R}$ with respect to the transmission probability (β) is +0.5, implying that decreasing (or increasing) the β by 10%, decreases (or increases) $\widehat{R}$ by 5%. Since $\Upsilon_{\mu_v}^{\widehat{R}} = -1.0045$, increasing (or decreasing) μ_v by 10%, decreases (or increases) the

$\widehat{R}$ by 10.05%, similarly increasing (or decreasing) the contact rate, ϕ, by 10%, increases (or decreases) the $\widehat{R}$ by 5%. In the same way, increasing (or decreasing) the mosquitoes biting rates ϵ, increases (or decreases) $\widehat{R}$, by 5%.

Reducing the number of contacts between humans and mosquitoes, through a reduction in either or both, the frequency of mosquito contact and the mosquitoes biting rate, would have the largest effect on disease transmission. Shortening the lifespan of the mosquitoes reduces the basic reproductive number because more infected mosquitoes die before they become infectious.

Therefore, any changes in N_v have two opposite effects on one hand, decreasing N_v, decreases the number of mosquitoes which tend to increase $\widehat{R}$. On the other hand, increasing μ_v also decreases the mosquito lifespan which tend to reduce $\widehat{R}$. For all the parameters, the sign of the sensitivity indices of $\widehat{R}$ agrees with intuitive expectation, that is, whether $\widehat{R}$ increases or decreases when the parameter increases. In the next section we proceed to study the optimal control and analysis of the model, putting into consideration the important model parameters.

We incorporate into the model time dependent control measures for preventive interventions such as use of treated bednets, treatment of infective individuals and spray of insecticides. Then we apply optimal control method using Pontryagin's Maximum Principle to determine the necessary conditions for the optimal control of the malaria disease.

Chapter 5

Optimal control analysis of SEIR model with treatment and preventions

5.1 Model description

In order to investigate the optimal control strategy for the control of disease, we incorporate into the model time dependent control parameters for the use of treated bednets, treatment of infective individuals and insecticide spray. The modified model description is given below.

Susceptible individuals acquire malaria infection following contact with infectious mosquitoes at a rate $(1 - v_1)\beta\iota\phi$, and v_1 $(0 \leq v_1 \leq 1)$ is the control on the use of mosquitoes treated bednet. Individuals with malaria symptoms are effectively treated at a rate τv_2 where $0 \leq \tau \leq 1, 0 \leq v_2 \leq 1$, v_2 is the control on treatment to ensure compliance and τ are proportion of individuals effectively treated. Human spontaneous recovery rate is given by b, where $0 \leq b < \tau$. Susceptible mosquitoes (S_v) acquire malaria infection (following effective contacts with humans infected with malaria) at a rate $(1 - v_1)\lambda\epsilon\phi$. Each mosquitoes group is reduced at the rate $v_3(1 - p)$, where $(1 - p)$ is the fraction of mosquitoes population reduced and $0 \leq v_3 \leq 1$, is the control function representing spray of insecticide aimed at reducing the mosquitoes sub-populations. We assumed also that the disease transmission is further subject to the cost of preventions and treatments, where C_T is total cost of malaria control, c_1, per unit cost of bednets and c_2 is per unit cost of

malaria treatment, c_3, per unit area cost of insecticides and σ is discount rate (3% to 5%). Thus, putting the above formulations and assumptions together gives the following human-vector model, given by system of ordinary differential equations below as

$$\begin{aligned}
\frac{dS_h}{dt} &= \Lambda_h + \kappa R_h - (1-v_1)\beta\epsilon\phi I_v S_h - \mu_h S_h, \\
\frac{dE_h}{dt} &= (1-v_1)\beta\epsilon\phi I_v S_h - (\alpha_1 + \mu_h)E_h, \\
\frac{dI_h}{dt} &= \alpha_1 E_h - (b + \tau v_2)I_h - (\psi + \mu_h)I_h, \\
\frac{dR_h}{dt} &= (b + \tau v_2)I_h - (\kappa + \mu_h)R_h, \\
\frac{dS_v}{dt} &= \Lambda_v - (1-v_1)\lambda\epsilon\phi I_h S_v - v_3(1-p)S_v - \mu_v S_v, \\
\frac{dE_v}{dt} &= (1-v_1)\lambda\epsilon\phi I_h S_v - v_3(1-p)E_v - (\alpha_2 + \mu_v)E_v, \\
\frac{dI_v}{dt} &= \alpha_2 E_v - v_3(1-p)I_v - \mu_v I_v.
\end{aligned} \tag{5.1.1}$$

We define the cost associated with preventive measures by the following function

$$C_T = \int_0^{t_f} [c_1 v_1 S_h + c_2 v_2 I_h + c_3 v_3 (S_v + E_v + I_v)] e^{-\sigma t} dt \tag{5.1.2}$$

where t_f is the final time. In the case of constant controls the stability and bifurcation analysis is the same as for the model with treatment (4.2.12) as the preventive interventions introduced in the model result only in modifications of the parameters of the model and not the model itself.

5.2 Economic analysis

Specifically, carrying out a comparative analysis, knowing costs and outcomes of alternative control strategies is important to decision makers who are often faced with the challenge of resources allocation. The resources are scarce and so must be judiciously allocated. Hence, in the next section, we consider the economic evaluation involved in these strategies, the use of treated bednets, treatment of infective individuals and spray of insecticides. To consider the economic analysis of the control strategies, we use the

objective function W. The goal is to compare the costs of these interventions and their effectiveness in the control of malaria.

$$W = \max_{v_1,v_2,v_3} \int_0^{t_f} [-c_1 v_1(t) S_h(t) - c_2 v_2(t) \tau I_h(t) - c_3 p v_3(t)(S_v(t) + E_v(t) + I_v(t))] e^{-\sigma t} dt \tag{5.2.3}$$

The Hamiltonian associated with (5.1.1) is given by

$$\begin{aligned} H_c &= -c_b v_1(t) S(t) - c_t v_2(t) \tau I_h(t) - c_v p v_3(t)(S_v(t) + E_v(t) + I_v(t)) \\ &+\lambda_{S_h} \{\Lambda_h + \kappa R_h - (1 - v_1)\beta \epsilon \phi I_v S_h - \mu_h S_h\} \\ &+\lambda_{E_h} \{(1 - v_1)\beta \epsilon \phi I_v S_h - (\alpha_1 + \mu_h) E_h\} \\ &+\lambda_{I_h} \{\alpha_1 E_h - (b + \tau v_2) I_h - (\psi + \mu_h) I_h\} \\ &+\lambda_{R_h} \{(b + \tau v_2) I_h - (\kappa + \mu_h) R_h\} \\ &+\lambda_{S_v} \{\Lambda_v - (1 - v_1)\lambda \epsilon \phi I_h S_v - v_3(1 - p) S_v - \mu_v S_v\} \\ &+\lambda_{E_v} \{(1 - v_1)\lambda \epsilon \phi I_h S_v - v_3(1 - p) E_v - (\alpha_2 + \mu_v) E_v\} \\ &+\lambda_{I_v} \{\alpha_2 E_v - v_3(1 - p) I_v - \mu_v I_v\} \end{aligned} \tag{5.2.4}$$

where $\lambda_{S_h}, \lambda_{E_h}, \lambda_{I_h}, \lambda_{R_h}, \lambda_{S_v}, \lambda_{E_v}, \lambda_{I_v}$ represent the shadow prices associated with their respective classes. By the Pontryagin's Maximum Principle we have

$$\frac{d\lambda_{S_h}}{dt} = \frac{\partial H_c}{\partial S_h}, \frac{d\lambda_{E_h}}{dt} = \frac{\partial H_c}{\partial E_h}, \frac{d\lambda_{I_h}}{dt} = \frac{\partial H_c}{\partial I_h}$$

,

$$\frac{d\lambda_{R_h}}{dt} =, \frac{d\lambda_{S_v}}{dt} = \frac{\partial H_c}{\partial S_v}, \frac{d\lambda_{E_v}}{dt} = \frac{\partial H_c}{\partial E_v}, \frac{d\lambda_{I_v}}{dt} = \frac{\partial H_c}{\partial I_v}.$$

Therefore, in all cases, optimal policy occurs where the marginal benefit for a further reduction in disease prevalence is equal to the marginal cost to achieving it.

5.2.1 Economic evaluation of treated bednets

Differentiating the H_c with respect to the use of bednet $v_1(t)$, we obtain

$$\frac{\partial H_c}{\partial v_1} = -c_b S_h(t) + \beta S_h(t) I_v(t)(\lambda_{S_h} - \lambda_{E_h}) + \lambda S_v(t) I_h(t)(\lambda_{S_v} - \lambda_{E_v}) = 0. \tag{5.2.5}$$

The associated shadow prices with the use of treated bednets are given by the following equations

$$\begin{aligned}
-\frac{d\lambda_{S_h}}{dt} &= [((1-v_1)(\beta\epsilon\phi I_v)+\mu_h+\sigma)]\lambda_{S_h} - (1-v_1)(\beta\epsilon\phi I_v)\lambda_{E_h} + c_1 v_1 \\
-\frac{d\lambda_{E_h}}{dt} &= (\mu_h+\alpha_1)\lambda_{E_h} - \alpha_1\lambda_{I_h} \\
-\frac{d\lambda_{S_v}}{dt} &= [((1-v_1)\lambda\epsilon\phi I_h + v_3(1-p)+\mu_v+\sigma)]\lambda_{S_v} + (1-v_1)\lambda\epsilon\phi I_h\lambda_{E_v} + c_3 v_3 \\
-\frac{d\lambda_{E_v}}{dt} &= [(v_3(1-p)+\alpha_2+\mu_v+\sigma)]\lambda_{E_v} - \alpha_2\lambda_{I_v} + c_3 v_3
\end{aligned} \tag{5.2.6}$$

The optimal policy is achieved when the marginal cost of treated bednets is equal to the marginal benefit.

$$v_1(t) = 0 \; if \; c_1 S_h(t) > \beta S_h I_v(\lambda_{S_h} - \lambda_{E_h}) + \lambda S_v I_h(\lambda_{S_v} - \lambda_{E_v})$$

$$v_1(t) \in (0,1) \; if \; c_1 S_h(t) = \beta S_h I_v(\lambda_{S_h} - \lambda_{E_h}) + \lambda S_v I_h(\lambda_{S_v} - \lambda_{E_v})$$

$$v_1(t) = 1 \; if \; c_1 S_h(t) < \beta S_h I_v(\lambda_{S_h} - \lambda_{E_h}) + \lambda S_v I_h(\lambda_{S_v} - \lambda_{E_v})$$

This optimal policy indicates that increase in the use of treated bednets has two effects. Firstly, it reduces the number of exposed humans and exposed mosquitoes, and secondly, it increases the numbers of susceptible (uninfected) humans and susceptible (uninfected) mosquitoes.

The expression

$$\beta S_h I_v(\lambda_{S_h} - \lambda_{E_h}) + \lambda S_v I_h(\lambda_{S_v} - \lambda_{E_v})$$

is the total marginal benefits of the use of treated bednets and $c_1 S_h(t)$ is the marginal cost. The interpretation is that malaria prevention through the use of bednets will be optimal only when the expected marginal benefit $\beta S_h I_v(\lambda_{S_h} - \lambda_{E_h}) + \lambda S_v I_h(\lambda_{S_v} - \lambda_{E_v})$ is larger than the marginal cost of using treated bednets, $c_1 S_h(t)$. Then the best strategy is for all susceptibles to use treated bednets. However, if the marginal benefit is less than the marginal cost, then no susceptible humans will use treated bednets.

5.2.2 Economic evaluation of treatment

Differentiating H_c with respect to optimal treatment of infective individuals, we get

$$\frac{\partial H_c}{\partial v_2} = -c_t \tau I_h(t) - I_h(t)\tau(\lambda_{I_h} - \lambda_{R_h}) = 0,$$

where $c_2\tau I_h(t)$ is the marginal cost for being treated and $I_h(t)\tau(\lambda_{I_h} - \lambda_{R_h})$ is the marginal benefits for being treated.

The associated shadow prices with being treated are given by the following equations

$$\begin{aligned} -\frac{d\lambda_{I_h}}{dt} &= ((\sigma + b + \tau v_2) + (\mu_h + \psi))\lambda_{I_h} - (b + \tau v_2)\lambda_{R_h} \\ &\quad +(1 - v_1)\lambda\epsilon\phi S_v\lambda_{S_v} - (1 - v_1)\lambda\epsilon\phi S_v\lambda_{E_v}, \\ -\frac{d\lambda_{R_h}}{dt} &= -\kappa\lambda_{S_h} + (\mu_h + \kappa)\lambda_{R_h}. \end{aligned} \tag{5.2.7}$$

The optimal policy is to ensure that the marginal benefits for being treated is equal to the marginal costs for being treated.

$$\begin{aligned} v_2(t) &= 0 \qquad if\ c_2\tau I_h(t) > (\lambda_{R_h} - \lambda_{I_h}), \\ v_2(t) &\in (0,1) \quad if\ c_2\tau I_h(t) = (\lambda_{R_h} - \lambda_{I_h}), \\ v_2(t) &= 1 \qquad if\ c_2\tau I_h(t) < (\lambda_{R_h} - \lambda_{I_h}). \end{aligned}$$

The higher the marginal benefit for being treated, $(\lambda_{R_h} - \lambda_{I_h})$, than the marginal cost for being treated, $c_2\tau I_h(t)$, the more treatment is appreciated, then all infected humans will seek full treatment. However, if the marginal benefit $(\lambda_{R_h} - \lambda_{I_h})$ is less than the marginal cost for being treated, $c_2\tau I_h(t)$, then no infected human seeks treatment.

5.2.3 Economic evaluation of insecticide spray

Differentiating H_c with respect to the spray of insecticides v_3, we have,

$$\frac{\partial H_c}{\partial v_3} = -c_3p(S_v(t) + E_v(t) + I_v(t)) - (1 - p)(S_v(t)\lambda_{S_v} + E_v(t)\lambda_{E_v} + I_v(t)\lambda_{I_v}) = 0 \tag{5.2.8}$$

where $c_3p(S_v(t) + E_v(t) + I_v(t))$ is the marginal cost for spray of insecticides against mosquitoes and $(1 - p)(S_v(t)\lambda_{S_v} + E_v(t)\lambda_{E_v} + I_v(t)\lambda_{I_v})$ is the marginal benefits.

The associated shadow prices with spray of insecticides are given by the following equations

$$\begin{aligned} -\frac{d\lambda_{S_v}}{dt} &= ((1 - v_1)\lambda\epsilon\phi I_h + v_3(1 - p) + \mu_v + \sigma)\lambda_{S_v} + (1 - v_1)\lambda\epsilon\phi I_h\lambda_{E_v} + c_3pv_3, \\ -\frac{d\lambda_{E_v}}{dt} &= (v_3(1 - p) + \alpha_2 + \mu_v + \sigma)\lambda_{E_v} - \alpha_2\lambda_{I_v} + c_3pv_3, \\ -\frac{d\lambda_{I_v}}{dt} &= (1 - v_1)\beta\epsilon\phi S_h\lambda_{S_h} - (1 - v_1)\beta\epsilon\phi S_h\lambda_{E_h} + (v_3(1 - p) + \mu_v + \sigma)\lambda_{I_v} + c_3pu_3. \end{aligned} \tag{5.2.9}$$

The optimal policy is,

$$v_3(t) = 0 \; if \; c_3 p(S_v(t) + E_v(t) + I_v(t)) > (p-1)(S_v(t)\lambda_{S_v} + E_v(t)\lambda_{E_v} + I_v(t)\lambda_{I_v}),$$

$$v_3(t) \in (0,1) \; if \; c_3 p(S_v(t) + E_v(t) + I_v(t)) = (p-1)(S_v(t)\lambda_{S_v} + E_v(t)\lambda_{E_v} + I_v(t)\lambda_{I_v}),$$

$$v_3(t) = 1 \; if \; c_3 p(S_v(t) + E_v(t) + I_v(t)) < (p-1)(S_v(t)\lambda_{S_v} + E_v(t)\lambda_{E_v} + I_v(t)\lambda_{I_v}).$$

If marginal benefits for optimal spray of insecticides against mosquitoes

$$(p-1)(S_v(t)\lambda_{S_v} + E_v(t)\lambda_{E_v} + I_v(t)\lambda_{I_v}).$$

is less than the marginal cost of spray of insecticides,

$$c_3 p(S_v(t) + E_v(t) + I_v(t)),$$

the spray of insecticides is optimal. If the marginal cost of spray of insecticides is less than the marginal benefits, then it is optimal to spray insecticides against mosquitoes for malaria control.

Next we investigate the impact of the shadow prices and marginal benefits numerically, by evaluating the shadow price at the start of malaria epidemic as a function of the numbers of recovered or protected at the time of outbreak. This is shown in Figures 5.1, 5.2 and 5.3 respectively. Shadow price is the change in the objective value of the optimal solution of an optimization problem obtained by relaxing the constraint by one (1) unit. In other words, this tells us by how much the objective function would increase, since we could protect or treat few more additional persons.

We observed in Fig 5.1 that the marginal value (shadow price) of S_h is much less damaging than the marginal value of I_h. This is economically reasonable as susceptible human only represents disutility as potentially infected human. This further established that an infected human represents a welfare cost in its self and also a source of infection for susceptibles. The shadow price on infected drops negatively before increasing again, indicating an initial negative impact on the cost and again rises in response to the positive impact achieved which stabilizes at time $t = 75$.

Figure 5.2 has an economic interpretation, an indication that as more individuals are protected or recovered from the disease, the consequences of the diseases becomes negligible. Also an indication that the shadow price on S_h tends to zero as the numbers of protected and recovered susceptibles approaches zero. Then it increases (although still

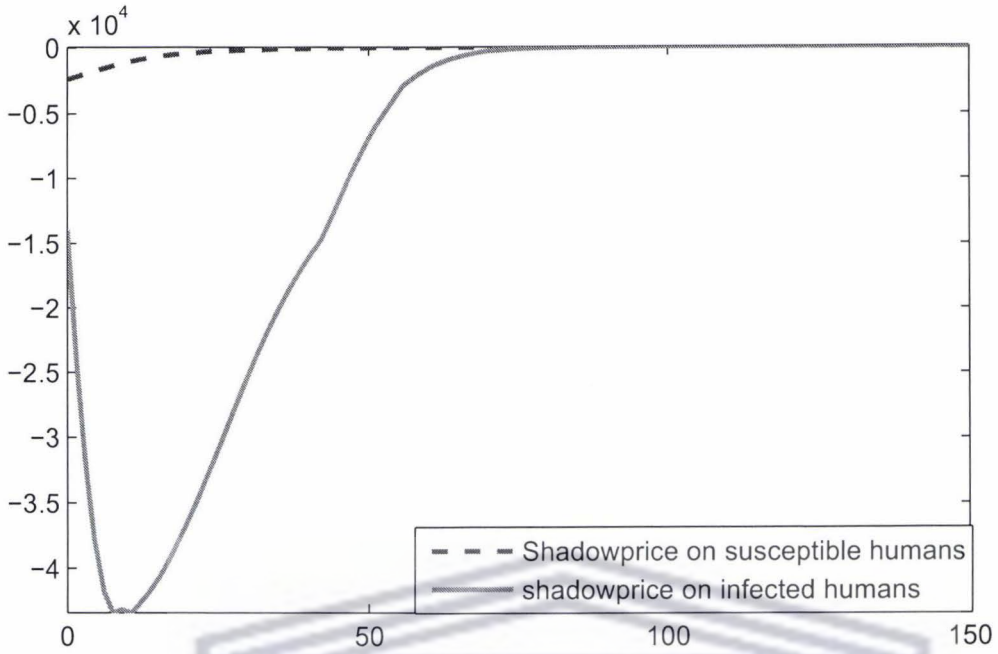


Figure 5.1: The Figure shows shadow price against time

negative) as the numbers of recovered and protected susceptibles increases to ultimately stabilize at zero.

Figure 5.3 indicates that the marginal benefit for further reduction in disease prevalence falls as disease prevalence itself falls. The Figure further shows that a smaller amount of efforts on spray of insecticides is needed to eliminate the disease, compared to treated bednets. For example in time $t = 10$, with the spray of insecticides, elimination of malaria will be optimal. While with the use of treated bednets, it will be eliminated in $t = 32$.

5.3 Analysis of optimal control

In case the elimination of malaria is not affordable whether due to costs, social or environmental reasons, we need to investigate the optimal level of efforts that would be needed to control the disease. For this to be achieved, we give the objective functional J, which is to minimize the number of human infectives and the cost of applying the controls v_1, v_2, v_3.

$$J = \min_{v_1,v_2,v_3} \int_0^{t_f} [m_d I_h + n v_1^2 + c v_2^2 + d v_3^2] e^{-\sigma t} dt \tag{5.3.10}$$

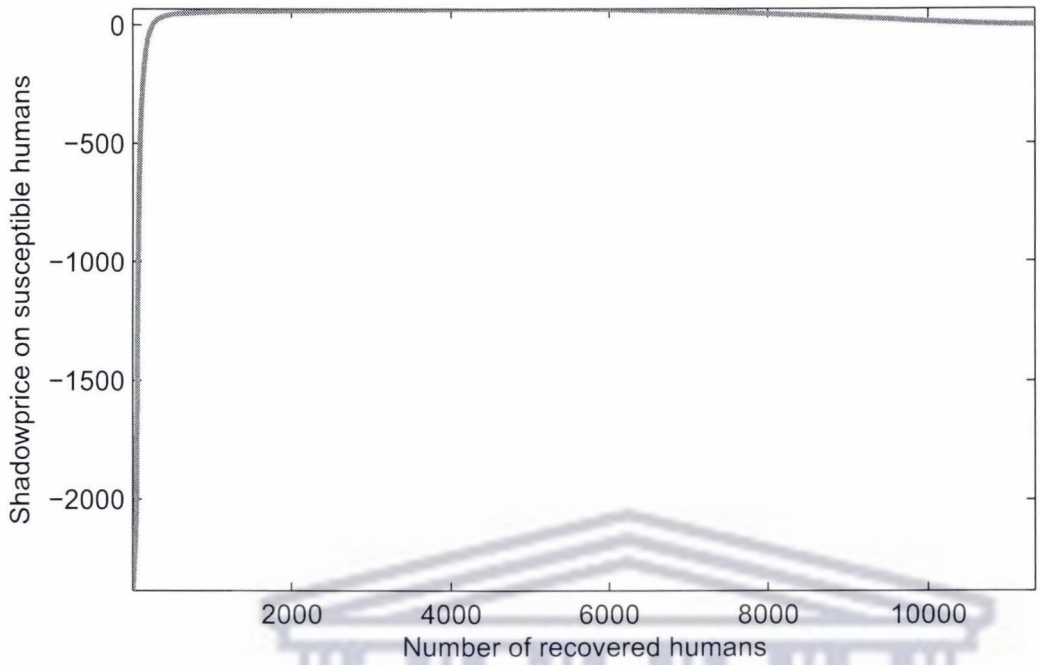


Figure 5.2: The shadow price on S_h is close to zero for small numbers of recovered susceptibles at time t^*, the shadow price is increasing, although still negative.

where m_d, n, c, d are positive weights. With the given objective function $J(u)$; our goal is to minimize the number of infected humans $I_h(t)$, while minimizing the cost of control $v_1(t), v_2(t), v_3(t)$. We seek an optimal control v_1^*, v_2^*, v_3^* such that

$$J(v_1^*, v_2^*, v_3^*) = \min\{J(v_1, v_2, v_3) | v_1, v_2, v_3 \in \mathcal{U}\} \tag{5.3.11}$$

where $\mathcal{U} = \{(v_1, v_2, v_3)$ such that v_1, v_2, v_3 measurable with $0 \leq v_1 \leq 1, 0 \leq v_2 \leq 1, 0 \leq v_3 \leq 1$ for $t \in [0, t_f]\}$ is the control set. The necessary conditions that an optimal control must satisfy come from the Pontryagin's Maximum Principle [75]. This principle converts (5.2.4)-(5.3.10) into a problem of minimizing pointwise a Hamiltonian H, with respect to

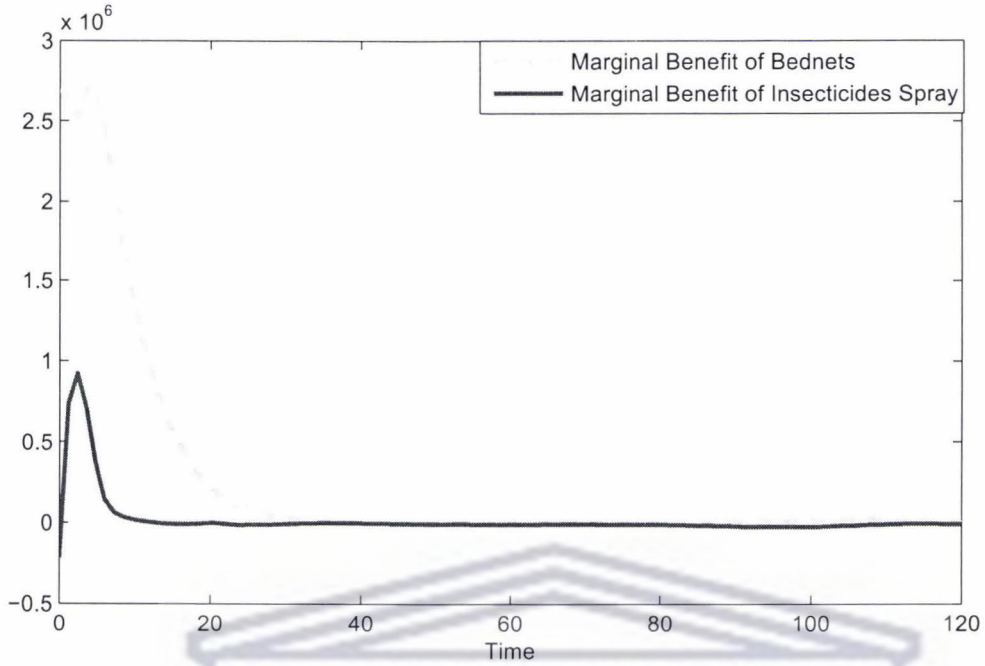


Figure 5.3: The marginal benefit of use of insecticides is much smaller than the marginal benefit of treated bednets.

(v_1, v_2, v_3).

$$
\begin{aligned}
H \quad &= mI_h + nv_1^2 + cv_2^2 + dv_3^2 + \lambda_{S_h}\{\Lambda_h + \kappa R_h - (1-v_1)\beta\epsilon\phi I_v S_h - \mu_h S_h\} \\
&+\lambda_{E_h}\{(1-v_1)\beta\epsilon\phi I_v S_h - (\alpha_1 + \mu_h)E_h\} \\
&+\lambda_{I_h}\{\alpha_1 E_h - (b + \tau v_2)I_h - (\psi + \mu_h)I_h\} \\
&+\lambda_{R_h}\{(b + \tau v_2)I_h - (\kappa + \mu_h)R_h\} \\
&+\lambda_{S_v}\{\Lambda_v - (1-v_1)\lambda\epsilon\phi I_h S_v - v_3(1-p)S_v - \mu_v S_v\} \\
&+\lambda_{E_v}\{(1-v_1)\lambda\epsilon\phi I_h S_v - v_3(1-p)E_v - (\alpha_2 + \mu_v)E_v\} \\
&+\lambda_{I_v}\{\alpha_2 E_v - v_3(1-p)I_v - \mu_v I_v\} \\
&+\lambda_{C_T}\{(c_1 v_1 S_h + c_2 v_2 I_h + c_3 v_3(S_v + E_v + I_v)),\}
\end{aligned}
\tag{5.3.12}
$$

where the $\lambda_{S_h}, \lambda_{E_h}, \lambda_{I_h}, \lambda_{R_h}, \lambda_{S_v}, \lambda_{E_v}$ and λ_{I_v} are the adjoint variables or co-state variables. By applying Pontryagin's Maximum Principle [75] and the existence result for the optimal control from [25], we obtain

Proposition 4. *For the optimal control tripple v_1^*, v_2^*, v_3^* that minimizes $J(u)$ over $\mathcal{U}$,*

there exist adjoint variables $\lambda_{S_h}, \lambda_{E_h}, \lambda_{I_h}, \lambda_{R_h}, \lambda_{S_v}, \lambda_{E_v}, \lambda_{I_v}$ *satisfying*

$$\begin{aligned}
-\frac{d\lambda_{S_h}}{dt} &= ((1-v_1)(\beta\epsilon\phi I_v) + \mu_h)\lambda_{S_h} - (1-v_1)(\beta\epsilon\phi I_v)\lambda_{E_h} - c_1\lambda_{C_T}v_1, \\
-\frac{d\lambda_{E_h}}{dt} &= (\mu_h + \alpha_1)\lambda_{E_h} - \alpha_1\lambda_{I_h}, \\
-\frac{d\lambda_{I_h}}{dt} &= -m + ((b+\tau v_2) + (\mu_h + \psi))\lambda_{I_h} - (b+\tau v_2)\lambda_{R_h}, \\
&\quad +(1-v_1)\lambda\epsilon\phi S_v\lambda_{S_v} - (1-v_1)\lambda\epsilon\phi S_v\lambda_{E_v} - c_2\lambda_{C_T}v_2, \\
-\frac{d\lambda_{R_h}}{dt} &= -\kappa\lambda_{S_h} + (\mu_h + \kappa)\lambda_{R_h}, \\
-\frac{d\lambda_{S_v}}{dt} &= ((1-v_1)\lambda\epsilon\phi I_h + v_3(1-p) + \mu_v)\lambda_{S_v} + (1-v_1)\lambda\epsilon\phi I_h\lambda_{E_v} - c_3\lambda_{C_T}v_3, \\
-\frac{d\lambda_{E_v}}{dt} &= (v_3(1-p) + \alpha_2 + \mu_v)\lambda_{E_v} - \alpha_2\lambda_{I_v} - c_3\lambda_{C_T}v_3, \\
-\frac{d\lambda_{I_v}}{dt} &= (1-v_1)\beta\epsilon\phi S_h\lambda_{S_h} - (1-v_1)\beta\epsilon\phi S_h\lambda_{E_h} + (v_3(1-p) + \mu_v)\lambda_{I_v} - c_3\lambda_{C_T}v_3, \\
-\frac{d\lambda_{C_T}}{dt} &= 0,
\end{aligned} \tag{5.3.13}$$

and with transversality conditions

$$\lambda_{S_h}(t_f) = \lambda_{E_h}(t_f) = \lambda_{I_h}(t_f) = \lambda_{R_h}(t_f) = \lambda_{S_v}(t_f) = \lambda_{E_v}(t_f) = \lambda_{I_v}(t_f) = \lambda_{C_T} = 0, \tag{5.3.14}$$

$$\begin{aligned}
v_1^* &= \max\left\{0, \min\left(1, \frac{(\beta\epsilon\phi I_v^*(\lambda_{E_h} - \lambda_{S_h})S_h^* + \lambda\epsilon\phi I_h^*(\lambda_{E_v} - \lambda_{S_v})S_v^* - c_1\lambda_{C_T}S_h^*)e^{\sigma t}}{2n}\right)\right\}, \\
v_2^* &= \max\left\{0, \min\left(1, \frac{(\tau(\lambda_{I_h} - \lambda_{R_h})I_h^*) - c_2\lambda_{C_T}I_h^*)e^{\sigma t}}{2c}\right)\right\}, \\
v_3^* &= \max\left\{0, \min\left(1, \frac{(S_h^*\lambda_{S_h} + (1-p)(S_v^*\lambda_{S_v} + E_v^*\lambda_{E_v} + I_v^*\lambda_{I_v}) - c_3\lambda_{C_T}(S_v^* + E_v^* + I_v^*))e^{\sigma t}}{2d}\right)\right\}.
\end{aligned} \tag{5.3.15}$$

Proof: Corollary 4.1 of [25] gives the existence of an optimal control due to the convexity of the integrand of J with respect to v_1, v_2 and v_3, a *priori* boundedness of the state solutions, and the *Lipschitz* property of the state system with respect to the state variables. The differential equations governing the adjoint variables are obtained by the differentiation of the Hamiltonian function and evaluated at the optimal control.

$$
\begin{aligned}
-\frac{d\lambda_{S_h}}{dt} &= \frac{\partial H}{\partial S_h} = ((1-v_1)\beta\epsilon\phi I_v + \mu_h)\lambda_{S_h} - (1-v_1)\beta\epsilon\phi I_v\lambda_{E_h} - c_1\lambda_{C_T}v_1,\\
-\frac{d\lambda_{E_h}}{dt} &= \frac{\partial H}{\partial E_h} = (\mu_h+\alpha_1)\lambda_{E_h} - \alpha_1\lambda_{I_h},\\
-\frac{d\lambda_{I_h}}{dt} &= \frac{\partial H}{\partial I_h} = -m + (b+\tau v_2+\mu_h+\psi)\lambda_{I_h} - (b+\tau(1+v_2))\lambda_{R_h},\\
&\quad +(1-v_1)\lambda\epsilon\phi S_v\lambda_{S_v} - (1-v_1)\lambda\epsilon\phi S_v\lambda_{E_v} - c_2\lambda_{C_T}v_2,\\
-\frac{d\lambda_{R_h}}{dt} &= \frac{\partial H}{\partial R_h} = -\kappa\lambda_{S_h} + (\mu_h+\kappa)\lambda_{R_h},\\
-\frac{d\lambda_{S_v}}{dt} &= \frac{\partial H}{\partial S_v} = ((1-v_1)\lambda\epsilon\phi I_h) + v_3(1-p) + \mu_v)\lambda_{S_v} + (1-v_1)\lambda\epsilon\phi I_h\lambda_{E_v} - c_3\lambda_{C_T}v_3,\\
-\frac{d\lambda_{E_v}}{dt} &= \frac{\partial H}{\partial E_v} = (v_3(1-p)+\alpha_2+\mu_v)\lambda_{E_v} - \alpha_2\lambda_{I_v} - c_3\lambda_{C_T}v_3,\\
-\frac{d\lambda_{I_v}}{dt} &= \frac{\partial H}{\partial I_v} = (1-v_1)\beta\epsilon\phi S_h\lambda_{S_h} - (1-v_1)\beta\epsilon\phi S_h\lambda_{E_h} + (v_3(1-p)+\mu_v)\lambda_{I_v} - c_3\lambda_{C_T}v_3,\\
-\frac{d\lambda_{C_T}}{dt} &= \frac{\partial H}{\partial C_T} = 0,\\
\\
0 &= \frac{\partial H}{\partial v_1} = v_1^*2n + \beta\epsilon\phi I_v^*(\lambda_{S_h}-\lambda_{E_h})S_h^* + \lambda\epsilon\phi I_h^*(\lambda_{S_v}-\lambda_{E_v})S_v^* + c_1\lambda_{C_T}S_h^*,\\
0 &= \frac{\partial H}{\partial v_2} = v_2^*2c - \tau(\lambda_{I_h}-\lambda_{R_h})I_h^* + c_2\lambda_{C_T}I_h^*,\\
0 &= \frac{\partial H}{\partial v_3} = v_3^*2d - S_h^*\lambda_{S_h} - (1-p)(S_v^*\lambda_{S_v} + E_v^*\lambda_{E_v} + I_v^*\lambda_{I_v})\\
&\quad +c_3\lambda_{C_T}(S_v^* + E_v^* + I_v^*).
\end{aligned}
\tag{5.3.16}
$$

which in a more explicit form becomes,

$$
\begin{aligned}
-\frac{d\lambda_{S_h}}{dt} &= ((1-v_1)\beta\epsilon\phi I_v + \mu_h)\lambda_{S_h} - (1-v_1)\beta\epsilon\phi I_v\lambda_{E_h} + c_1\lambda_{C_T}v_1,\\
-\frac{d\lambda_{E_h}}{dt} &= (\mu_h+\alpha_1)\lambda_{E_h} - \alpha_1\lambda_{I_h},\\
-\frac{d\lambda_{I_h}}{dt} &= -m + ((b+\tau v_2)+(\mu_h+\psi))\lambda_{I_h} - (b+\tau v_2)\lambda_{R_h}\\
&\quad +(1-v_1)\lambda\epsilon\phi S_v\lambda_{S_v} - (1-v_1)\lambda\epsilon\phi S_v\lambda_{E_v} + c_2\lambda_{C_T}v_2,\\
-\frac{d\lambda_{R_h}}{dt} &= -\kappa\lambda_{S_h} + (\mu_h+\kappa)\lambda_{R_h},\\
-\frac{d\lambda_{S_v}}{dt} &= ((1-v_1)\lambda\epsilon\phi I_h + v_3(1-p) + \mu_v)\lambda_{S_v} + (1-v_1)\lambda\epsilon\phi I_h\lambda_{E_v} + c_3\lambda_{C_T}v_3,\\
-\frac{d\lambda_{E_v}}{dt} &= (v_3(1-p)+\alpha_2+\mu_v)\lambda_{E_v} - \alpha_2\lambda_{I_v} + c_3\lambda_{C_T}v_3,\\
-\frac{d\lambda_{I_v}}{dt} &= (1-v_1)\beta\epsilon\phi S_h\lambda S_h - (1-v_1)\beta\epsilon\phi S_h\lambda E_h + (v_3(1-p)+\mu_v)\lambda_{I_v} + c_3\lambda_{C_T}v_3.
\end{aligned}
$$

Hence, we obtain

$$\begin{aligned} v_1^* &= \frac{(\beta\epsilon\phi I_v^*(\lambda_{E_h}-\lambda_{S_h})S_h^* + \lambda\epsilon\phi I_h^*(\lambda_{E_v}-\lambda_{S_v})S_v^* - c_1\lambda_{C_T}S_h^*)e^{\sigma t}}{2n} \\ v_2^* &= \frac{(\tau(\lambda_{I_h}-\lambda_{R_h})I_h^* - c_2\lambda_{C_T}I_h^*)e^{\sigma t}}{2c} \\ v_3^* &= \frac{(S_h^*\lambda_{S_h} + (1-p)(S_v^*\lambda_{S_v} + E_v^*\lambda_{E_v} + I_v^*\lambda_{I_v}) - c_3\lambda_{C_T}(S_v^* + E_v^* + I_v^*))e^{\sigma t}}{2d}. \end{aligned}$$

By standard control arguments involving the bounds on the controls, we conclude

$$v_1^* = \begin{cases} 0 & if w_1^* \le 0 \\ w_1^* & if 0 < w_1^* < 1 \\ 1 & if w_1^* \ge 1 \end{cases}$$

$$v_2^* = \begin{cases} 0 & \text{if } w_2^* \le 0 \\ w_2^* & \text{if } 0 < w_2^* < 1 \\ 1 & \text{if } w_2^* \ge 1 \end{cases}$$

$$v_3^* = \begin{cases} 0 & \text{if } w_3^* \le 0 \\ w_3^* & \text{if } 0 < w_3^* < 1 \\ 1 & \text{if } w_3^* \ge 1 \end{cases}$$

where

$$\begin{aligned} w_1^* &= \frac{FZ + \lambda\epsilon\phi I_h^*(\lambda_{E_v}-\lambda_{S_v})S_v^* + c_1\lambda_{C_T}S_h^*}{2ne^{-\sigma t}} \\ w_2^* &= \frac{(\tau(\lambda_{I_h}-\lambda_{R_h})I_h^* + c_2\lambda_{C_T}I_h^*)e^{\sigma t}}{2c} \\ w_3^* &= \frac{S_h^*\lambda_{S_h} + GZ + c_3\lambda_{C_T}(S_v^* + E_v^* + I_v^*)}{2de^{-\sigma t}} \end{aligned}$$

$$v_1^* = \min\{1, w_1^*\},\ v_2^* = \min\{1, w_2^*\}\ ,v_3^* = \min\{1, w_3^*\}.$$

where $FZ = \beta\epsilon\phi I_v^*(\lambda_{E_h}-\lambda_{S_h})S_h^*$, $GZ = (1-p)(S_v^*\lambda_{S_v} + E_v^*\lambda_{E_v} + I_v^*\lambda_{I_v})$

For the standard incidence form of infection, we give the necessary conditions for the

disease control below.

$$
\begin{aligned}
-\frac{d\lambda_{S_h}}{dt} = \quad & \frac{\partial H}{\partial S_h} = \left(\frac{(1-v_1)\beta\epsilon\phi I_v}{N_h} + \mu_h - \frac{(1-v_1)\beta\epsilon\phi I_v S_h}{N_h^2}\right)\lambda_{S_h} \\
& -\frac{(1-v_1)\beta\epsilon\phi I_v}{N_h}(1 - \frac{S_h}{N_h}\lambda_{E_h} - c_1\lambda_{C_T}v_1 - \frac{(1-v_1)\beta\epsilon\phi I_v S_h}{N_h^2}(\lambda_{S_v} - \lambda_{E_v}), \\
-\frac{d\lambda_{E_h}}{dt} \quad & = \frac{\partial H}{\partial E_h} = (\mu_h + \alpha_1 + \frac{(1-v_1)\beta\epsilon\phi I_v S_h}{N_h^2})\lambda_{E_h} - \alpha_1\lambda_{I_h} \\
& -\frac{(1-v_1)\beta\epsilon\phi I_v S_h}{N_h^2}\lambda_{S_h} - \frac{(1-v_1)\lambda\epsilon\phi I_h S_v}{N_h^2}(\lambda_{S_v} - \lambda_{E_v}), \\
-\frac{d\lambda_{I_h}}{dt} = \quad & \frac{\partial H}{\partial I_h} = -m + (b + \tau v_2 + \mu_h + \psi)\lambda_{I_h} - (b + \tau(1+v_2))\lambda_{R_h} \\
& +(\frac{(1-v_1)\lambda\epsilon\phi S_v}{N_h} - \frac{(1-v_1)\lambda\epsilon\phi I_h S_v}{N_h^2})(\lambda_{S_v} - \lambda_{E_v}) - c_2\lambda_{C_T}v_2, \\
-\frac{d\lambda_{R_h}}{dt} = \quad & \frac{\partial H}{\partial R_h} = (-\frac{(1-v_1)\beta\epsilon\phi I_v S_h}{N_h^2} - \kappa)\lambda_{S_h} + (\mu_h + \kappa)\lambda_{R_h} + \frac{(1-v_1)\beta\epsilon\phi I_v S_h}{N_h^2}\lambda_{E_h} \\
& -\frac{(1-v_1)\lambda\epsilon\phi I_h S_v}{N_h^2}(\lambda_{S_v} - \lambda_{E_v}), \\
-\frac{d\lambda_{S_v}}{dt} = \quad & \frac{\partial H}{\partial S_v} = (\frac{(1-v_1)\lambda\epsilon\phi I_h)}{N_h} + v_3(1-p) + \mu_v)\lambda_{S_v} \\
& +\frac{(1-v_1)\lambda\epsilon\phi I_h}{N_h}\lambda_{E_v} - c_3\lambda_{C_T}v_3 \\
-\frac{d\lambda_{E_v}}{dt} = \quad & \frac{\partial H}{\partial E_v} = (v_3(1-p) + \alpha_2 + \mu_v)\lambda_{E_v} - \alpha_2\lambda_{I_v} - c_3\lambda_{C_T}v_3, \\
-\frac{d\lambda_{I_v}}{dt} = \quad & \frac{\partial H}{\partial I_v} = \frac{(1-v_1)\beta\epsilon\phi S_h}{N_h}(\lambda_{S_h} - \lambda_{E_h}) \\
& +(v_3(1-p) + \mu_v)\lambda_{I_v} - c_3\lambda_{C_T}v_3, \\
-\frac{d\lambda_{C_T}}{dt} = \quad & \frac{\partial H}{\partial C_T} = 0,
\end{aligned}
$$

and with transversality conditions

$$\lambda_{S_h}(t_f) = \lambda_{E_h}(t_f) = \lambda_{I_h}(t_f) = \lambda_{R_h}(t_f) = \lambda_{S_v}(t_f) = \lambda_{E_v}(t_f) = \lambda_{I_v}(t_f) = \lambda_{C_T} = 0. \tag{5.3.17}$$

$$
\begin{aligned}
v_1^* &= \max\left\{0, \min\left(1, \frac{FZ + \frac{\lambda\epsilon\phi I_h^*}{N_h}(\lambda_{S_v} - \lambda_{E_v}) + c_1\lambda_{C_T}S_h^*}{2ne^{-\sigma t}}\right)\right\}, \\
v_2^* &= \max\left\{0, \min\left(1, \frac{(\tau(\lambda_{I_h} - \lambda_{R_h})I_h^* + c_2\lambda_{C_T}I_h^*)e^{\sigma t}}{2c}\right)\right\} \\
v_3^* &= \max\left\{0, \min\left(1, \frac{((1-p)(S_v^*\lambda_{S_v} + E_v^*\lambda_{E_v} + I_v^*\lambda_{I_v}) + c_3\lambda_{C_T}(S_v^* + E_v^* + I_v^*))e^{\sigma t}}{2d}\right)\right\}.
\end{aligned} \tag{5.3.18}
$$

where $FZ = \frac{\beta\epsilon\phi I_v^*}{N_h}(\lambda_{S_h} - \lambda_{E_h})S_h^*$