UNIVERSITY OF CAPE COAST

OPTIMAL STRATEGY FOR EFFECTIVE CONTROL AND POSSIBLE ERADICATION OF MALARIA

PERPETUAL APPIAH

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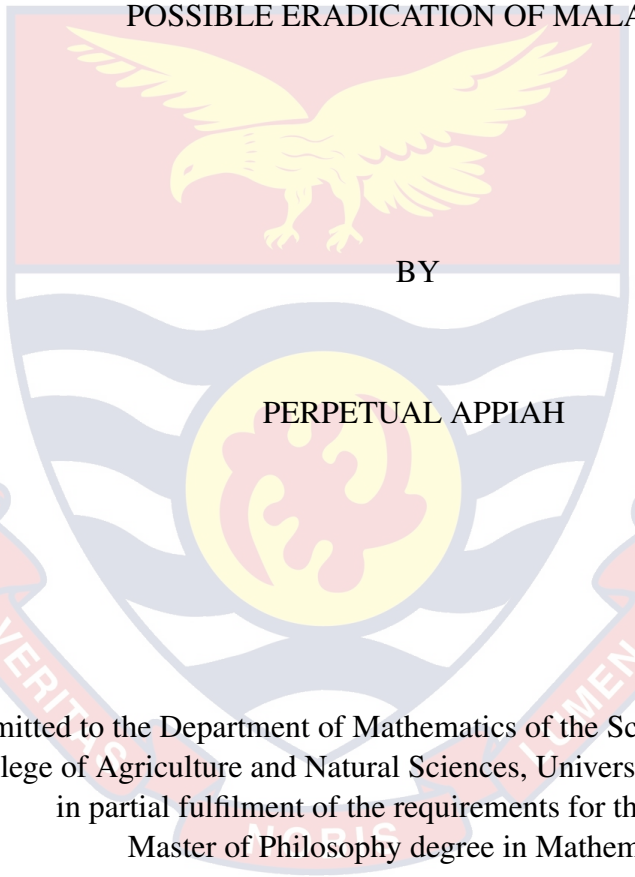

BY

PERPETUAL APPIAH

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in partial fulfilment of the requirements for the award of
Master of Philosophy degree in Mathematics

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DECLARATION

Candidate's Declaration

I hereby declare that this thesis is the result of my own original research and that no part of it has been presented for another degree in this university or elsewhere.

Candidate's signature ..... Date: .....

Name: Perpetual Appiah

Supervisor's Declaration

I hereby declare that the preparation and presentation of the thesis was supervised in accordance with the guidelines on supervision of thesis laid down by the University of Cape Coast.

Supervisor's Signature ..... Date: .....

Name: Dr Henry Amankwah

ABSTRACT

In this thesis, a deterministic mathematical model for the transmission and control of malaria, incorporating *prevention* and *treatment* as *control parameters* has being developed. A novel addition in our model is that, a proportion $c\alpha, (0 \leq c \leq 1)$, of the prevention effort (α), reduces the vector population. The model has two unique equilibrium points namely, a *disease-free* equilibrium point, which is locally and globally asymptotically stable when $\Re_0 < 1$; and an *endemic* equilibrium point which is locally and globally asymptotically stable when $\Re_0 > 1$. The parameters of the model were estimated using yearly malaria transmission data for Ghana, (from 2004 to 2017), obtained from the World Health Organization. Simulations of our model using various combinations of treatment and prevention, with increasing values of the constant c, show that, infected vector and human populations can be drastically reduced, thus effectively controlling the transmission of Malaria. To determine an optimal combination of prevention and treatment, we formulated an optimal control problem, with an appropriate *cost functional*, using $0 \leq u_1 \leq 1$ (prevention), and $0 \leq u_2 \leq 1$ (treatment) as *controls*. Pontryagin's Maximum Principle was used to determine the *optimality system*. Solutions of the optimality system, with $u_{1\max} = 0.5$, and $u_{2\max} = 0.2$, (representing maximum prevention effort and treatment rate respectively), show a dramatic reduction in both infected human and vector populations. Further simulations show that, malaria can be eradicated by increasing prevention efforts ($u_{1\max} > 0.5$), combined with treatment made accessible to everyone diagnosed with malaria.

KEY WORDS

Basic reproduction number

Malaria transmission model

Numerical simulations

Optimality system

Pontryain's Maximum Principle

Stability of equilibrium points

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DEDICATION

To my family

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LIST OF ABBREVIATIONS

ACT Artemisinin-based Combination Therapies

DFE Disease Free Equilibrium

EE Endemic Equilibrium

ITN Insecticide Treated Net

SEI Susceptible Exposed Infected

SEIR Susceptible Exposed Infected Recovered

SI Susceptible Infected

SIR Susceptible Infected Recovered

SIRS Susceptible Infected Recovered Susceptible

SSE Sum of Squares Error

WHO World Health Organization

CHAPTER ONE

INTRODUCTION

The application of epidemic models to investigate the spread of an infectious disease is widely used by mathematical biologist and epidemiologist. In addition, the application of optimal control methods in mathematical epidemiology has become an important area of research in applied mathematics. In this study, we will investigate various strategies for effectively containing the spread of, and possibly eradicating, malaria in Ghana. Several works in the literature have been used by researchers to understand the transmission characteristics of malaria, and this has lead to some improvements in controlling disease. In this study, we will use optimal control methods applied to an epidemic model, which incorporates *vector reduction* through prevention efforts. This chapter discusses background to the study, transmission process, treatment process, motivation, objectives and definition of terms.

Background to the Study

Malaria is a leading cause of mortality and morbidity in tropical and subtropical regions around globe, where an estimated two hundred million people are at constant risk of infection, with Africa being the most impacted. The World Health Organization reports that in Sub-Saharan Africa, malaria kills at least one million people annually and it has the potential to increase significantly due to continuous climate change. Thus, the role of rainfall and temperature in population dynamics and its mosquito vector. In underdeveloped countries, the disease persists and has become a severe public health and socio-economic challenge.

Plasmodium genus with four different species causes human malaria and transmitted via the bite from infected female anopheles mosquito. The following

species are the causative agents for malaria in humans:

1. *P.falciparum*, the much more deadly human parasites and most prevalent in tropics.
2. *P.vivax* is the common cause for clinical malaria, yet its rarely fatal.
3. *P.malariae*, particularly in Africa, a rare cause of clinical malaria. It can last for decades as low-grade *parasitaemia*.
4. *P.ovale* causes clinically relevant but not severe disease, however it can be discovered in infections with some other species.

Malaria transmission

Transmission of the parasite occurs when an infected adult female anopheles mosquito bites an individual (Putri & Jaharuddin, 2014). The bites usually occur between dusk and dawn, and its intensity depends on factors related to the vector, the human, the environment and whether it chooses to bite humans or animals (World Health Organization, 2019a). The vector becomes infected when it bites an infected human or animal. They never recover from infection; moreover, the infection is not harmful to them. Adult female mosquitoes have a life span of approximately 4-6 weeks; Female Anopheles mosquitoes cannot live without a human host since they depend on blood of human to develop their eggs (Tumwiine, Luboobi, & Mugisha, 2006). Infection of malaria to humans takes place when mosquitoes inject their saliva containing sporozoites into humans and they are carried to the liver within 30-60 minutes (Scientific American, 2019). They then penetrate the liver hepatocytes and undergo a phase of asexual multiplication that results in the production of approximately $8-6$ merozoites and these merozoites penetrates the red blood cells. This continuous activity is responsible for the cause of infection of the disease (Hempelmann & Krafts, 2013). Chills, fever, headache, diarrhoea, anaemia, liver and neurological dam-

age are the symptoms of malaria (Adamu, Ochigbo, Williams, & Okorie, 2017).

Malaria prevention

The primary line of defense against mosquito-borne disease is personal protection. The use of mosquito repellent is one technique pf personal protection. These are chemicals that are applied to exposed skin or clothing to keep mosquitoes away from humans. These deter mosquitoes but do not harm them. The use of an *Insecticide-Treated bed Nets* to protect individuals against malaria has been found to lessen childhood (below five years of age) morbidity by 50% and global child mortality by 20-30%. When used in big quantities, ITNs are considered to be efficient instrument for controlling malaria vectors. However, resistance to the insecticides used in impregnated nets is a limiting problem. Resistance of the most important African malaria vector Anopheles *gambiae* s.l. to *pyrethroid* is already widespread in several West African countries and most especially Ghana. Government intervention comes in many forms, some of which have already been mentioned. Other attempt on the governmental level includes mass spraying of endemic areas to reduce the biting rate of mosquitoes.

Malaria treatment

There have been several attempts against the transmission of malaria including residual spraying indoor, the usage of insecticide treated bed-nets, rapid diagnosis and appropriate treatment (World Health Organization, 2019b). Insecticide treated net provides a physical barrier that restrict face to face interactions between mosquitoes and humans. In 2018 malaria report, about half of the human population of the endemic African countries were protected by insecticide treated net (World Health Organization, 2018).

Moreover, Ghana initiated the process of using Artemisinin-based combination therapies following recommendations given by WHO for all countries ex-

periencing resistance to mono-therapies in the treatment of falciparum malaria in 2002 (Azu-Tungmah, 2012).

Statement of the Problem

According to the World Malaria Report (2018), Ghana is considered to be one of the malaria-endemic countries. It is also one of the eleven countries that accounts for 70% highly cases and deaths of malaria globally (World Health Organization, 2019a). It also recorded 219 million malaria cases and 435000 malaria related death (World Health Organization, 2019b). Children under 5 years accounted for 61% malaria related death worldwide in 2017 (World Health Organization, 2019b).

Therefore, it is imperative that more research be carried out in order to effectively control malaria transmission.

Purpose of the Study

The purpose of the study is to develop a deterministic epidemic model, with prevention and treatment as contols. Then, use the model to determine an optimal combination of these two controls that will effectively contain, possibly eradicate malaria transmission.

Research Objectives

The study's major goal is to use mathematical methods to analyze the dynamics of malaria transmission and the minimum cost for effective eradication of malaria. The objectives of the research are:

1. To develop a deterministic vector-host epidemic model that incorporates prevention and treatment strategies for malaria transmission. In particu-

lar, we assume that a proportion of the prevention effort can be directed towards reducing the vector population.

2. To obtain the equilibrium points of the model that incorporates treatment and prevention strategies for malaria transmission.
3. To find the basic reproduction number $\mathfrak{R}_0$, of the vector host epidemic model.
4. To determine the conditions for local and global stability of that model.
5. To validate the model from data, using the least-squares method.
6. To perform simulations of the model using various combinations of treatment and prevention to determine which combination that reduces the infectious population fastest.
7. To suggest an optimal combination of treatment and prevention for possible eradication of the disease at a certain proportion of preventive measures that reduce mosquitoes (c), where c is proportion of the preventive measures that reduces mosquitoes population.

Significance of the Study

The studies would be feasible in various approach. Thus, it would aid in eradicating malaria by :

1. Reducing the number of infected human and vector populations.
2. Suggesting an optimal combination of treatment and prevention for possible eradication of malaria.

Delimitation

This study is focused on a five state epidemic model. The dataset used for this study was focused on the number of infected cases of malaria in Ghana and it was obtained from World Health Organization. This would help to obtain effective strategy for prevention and treatment of malaria.

Limitations

The availability of data for mosquito population in Ghana was a major limitation for this study. Also, there was no daily data on malaria for infected human population from the World Health Organization.

Definition of Terms

This section reviews some basic definitions needed to understand the model.

Definition 1

A differential equation of the type

$$\frac{dy}{dt} = f(y), \tag{1.1}$$

in which f does not depend explicitly on the independent variable (t, in this case) is called an *autonomous differential equation*.

Definition 2

A system of first-order ordinary differential equations of the form

$$\frac{dx}{dt} = f(x), \qquad x \in \mathbb{R}^n,\ f \in \mathbb{R}^n,\ t \in \mathbb{R}, \tag{1.2}$$

where $x = (x_1,...,x_n)^T$, $f(x) = f_1(x_1,...,x_n)^T, f_2(x_1,...,x_n)^T, \cdots, f_n(x_1,...,x_n)^T$, in which the independent variable does not appear explicitly is called an *autonomous system*

Definition 3

An *equilibrium point* (*fixed-point,steady-state solution, critical point*) of the differential equation (1.2) is a constant solution $x^* \in \mathbb{R}^n$, satisfying

$$f(x^*) = 0. \tag{1.3}$$

Definition 4

An equilibrium point x^* is said to be locally stable provided that, for each $\varepsilon > 0$, there is $\delta > 0$ such that

$$\|x^0 - x^*\| < \delta \Rightarrow \|x(t) - x^*\| < \varepsilon \quad \text{for all} \quad t > 0. \tag{1.4}$$

Intuitively, an equilibrium point $x^* = (x_1^*, x_2^*, \cdots, x_n^*) \in \mathbb{R}^n$, of the autonomous system (1.2) is called *stable* provided that if the initial point $x_0 = (x_1^0, x_2^0, \cdots, x_n^0) \in \mathbb{R}^n$ is sufficiently close to x^*, then the trajectory $x(t) = (x_1(t), x_2(t), \cdots, x_n(t))$ remains close to x^* for all $t \geq 0$.

Definition 5

An equilibrium point x^* is locally asymptotically stable if the point x^* is locally stable, and all the solutions that starts near x^0, approaches x^* as $t \to \infty$. Mathematically, $\exists \ \ \delta > 0$ such that

$$\|x^0 - x^*\| < \delta \Rightarrow \lim_{t \to \infty} x(t) = x^*$$

Organization of the Study

This thesis is divided into five main chapters. Chapter One describes background of the study, transmission and treatment of malaria.

Chapter Two reviews researches that have been done in the dynamics of a malaria epidemic. This chapter constructs strategies and results used to eradi-

cate malaria. It also gives an overview of initiatives that have been done locally and globally.

Chapter Three discusses the methods used to perform analytic computation of the system. This chapter also presents the results of the analytic and numerical computations of the system. The analysis includes computation of the equilibrium points, basic reproduction number and performing local and global stability of the equilibrium points. This involves the use of data on the number of infectives, using the data to determine some parameters of the model. Also, analysis of the model using different combinations for prevention and treatment strategies are investigated in this chapter. The chapter also gives a presentation on how an optimal control problem is formulated. First, an objective functional is defined, and necessarily conditions for optimality is established using Pontryagin's Maximum Principle.

Chapter Four investigate numerically the solutions of the optimality system, using the *forward-backward sweep* method, based on the Runge-Kutta method approach.

Chapter Five presents the summary, conclusions and recommendations.

Chapter Summary

In this chapter, a brief introduction to the problem of study is presented. Then, background to the study, transmission and treatment of malaria is explored. The purpose of study, the main objectives of the research, terms definition and the organization of the research are stated.

CHAPTER TWO

LITERATURE REVIEW

Introduction

This section re-examines related research on mathematical model of malaria and the application of optimal control approach is presented. Mathematical models enable us to understand the dynamics of an epidemic, predict transmission rates, evaluate and compare control and prevention strategies. In addition, Hocking (1991) examined the effect of an epidemic on social, economical, biological and environmental activities.

Use of Mathematical Models in Controlling Epidemics

This application of mathematical models to understand the dynamics, prevention and eradication of malaria has been investigated by several researchers. One of the first researcher to publish a series of papers on malaria using mathematical model to study transmission process was Ross (1911). His research was on the formulation of a differential equation model using standard incidence and some biological factors such as the biting frequency of the mosquitoes. Analysis from Ross (1911) shows that malaria can only persist if the number of mosquitoes is above a certain threshold. Therefore, it is not necessarily to kill all mosquitoes in order to eradicate malaria. Several research on malaria was explored and examined after Ross (1911). For example, there was a review by Aron and May (1982) on dynamics of malaria population. In their study, the added some features like incubation period in the mosquitoes model.

Also, Anderson, Anderson, and May (1992) reviewed research by Aron and May (1982) by adding new characteristics such as the latent period, recovery

rate for humans, life expectancy of the mosquitoes Bacaër (2011).

Several models on malaria was developed after that. For instance, N. R. Chitnis (2005) developed and examined a mathematical model of malaria to understand its transmission process. They used their model to measure intervention strategies to control malaria for areas with low and high transmission rates. After computing the sensitivity indices to obtain baseline values for the endemic equilibrium and the $\Re_o$, they observed that an effective control of malaria requires the usage of an insecticide treated nets and early diagnosis with treatment of an infected individual.

Also, Tumwiine et al. (2006) considered a vector-host mathematical model for the spread of malaria that incorporates recruitment of the human population through continuous immigration and a portion of infective immigrants. In their model analysis, they found out that there is no DFE point in the presence of infective immigrant people. However, it exhibits a unique endemic equilibrium state if the fraction of the infective immigrant is positive. Therefore, the role of human migration and travel must be recognized in the spread and transmission of malaria and should receive equal attention as given to malaria and its parasite.

Recently, a paper by Mojeeb, Adu, and Yang (2017) on the dynamics of a four dimensional, $SEIR$ followed by seven dimensional $SEIR-SEI$ malaria transmission model between human and mosquitoes. Their model investigated and varied parameters for the endemic and disease free equilibrium points. Results from the sensitivity analysis depicts that the infection rates for humans and mosquitoes are the most effective parameters for the models. In addition, results obtained from the simulations shows that reducing contact and infection between human and mosquito can help to reduce malaria transmission.

Another researcher, Adamu et al. (2017) proposed a topic on "Local Stability Analysis of Host-Vector Malaria Disease Model." This study was modifi-

cation of the work of Fekaduet Kobe and Koya (2015). The model by Adamu et al. (2017) incorporated a vector reduction parameter and vaccination as a new control strategy. A lot of study for infectious disease incorporate treatment to reduce infected population and vaccination or sensitization for the reduction of susceptible populations but in their model they included a vector reduction parameter as an additional control feature. Thus, they proposed that susceptible as well as infected mosquitoes are reduced at the same rates and the vaccination parameters are included. They found out that treatment and vaccination as a way of protecting the menace of the infection in the human population was quite insufficient. Also combining the effect of treatment, vaccination and vector population reduction as an additional strategy, malaria may be eradicated as soon as possible.

Moreover, Wedajo, Bole, and Koya (2018) presented a paper that analysed the *SIR* model of malaria with the inclusion of infected immigrants. In their model, they considered *SIR* compartment for human population and *SI* compartment for mosquito population. Also, individuals who recovers in the human population develops permanent immunity. This means recovered individuals cannot be infected again. Numerical analysis from the model of Wedajo et al. (2018) reveals that the reproductive number will reduce to one if a focus is given to infected human immigrant. Therefore, they recommends that prevention of infected human immigrant have a strong influence of bringing the disease under control.

In a model by Bala and Gimba (2019), they investigated the effects of bed-nets, drug treatment, and their efficiency on two strains of malaria model where global uncertainty and analysis was also conducted. They found out that if 95% of malaria-related occurrences can be treated with 95% ITN usage and 5% failing of treatment in population, then malaria can be controlled. Similarly

Putri and Jaharuddin (2014) investigated on $SIRS - SI$ model of malaria disease with the implementation of anti-malaria drugs,vaccines and spraying. They discussed the frame work for transmission of malaria with treatments given to humans and mosquitoes. From their results, they proposed the Homotopy Analysis Method (HAM) to construct an approximate solution since from their model it was shows that treatments affect the dynamics of human and mosquito population.

For instance, a paper by Blayneh, Cao, and Kwon (2009) emphasized on the application of an optimal control on vector borne disease with prevention and treatment effort as their two main controls using two deterministic model. In the first case, they formulated a vector borne disease model with prevention and treatment as it controls at a reduced cost. A term which looks into the fitness of treated and susceptible host was added. In the second case, the application of their model is applied to malaria disease where the effect of treatment and prevention strategies is investigated at a minimum cost. Numerical results obtained depicts that preventive practices are very efficient in reducing the incidence of infectious hosts and vectors.

Again, Yusuf and Benyah (2012) investigated the vaccine and treatment control for an SIR epidemiologic model with a bilinear incidence. They considered recovered individual with a permanent immunity. They used vaccination and treatment as their control strategies in their formulation. Their main objective was to examine the best combination of vaccination and treatment strategies that would reduce the cost of implementing the control, as well as infected individuals. Numerical results from the model of the optimal system depicts that, whenever vaccination is more costly treatment, then resources ought to be channel to treating the disease till the prevalence of the disease falls. On the other hand, if treatment is more expensive than to vaccinate, then resources should be

invested in vaccination. In the case where the two controls are expensive, then it is better to use more of the vaccination and less of the treatment as control since there is a considerable decrease in the number of infectives. Therefore, results shows that achieving relative cost for each of the control mechanism will determine their goal.

Also, a paper by Nana-Kyere et al. (2017) proposed a research on the control of malaria transmission model with standard incidence rate. Their model assumed that individuals who recover from malaria develops a temporal immunity. This means they are susceptible again and are likely to be re-infected. Also, they assumed that susceptible mosquitoes can be infected when they bite infectious or recovered human. Their model elaborated on some of the control strategies such as prevention, treatment and application of insecticide spray on the vector. These was to evaluate the effectiveness of usage on sleeping under insecticide treated mosquito net in order to avoid bites and direct interactions with mosquitoes, the utilization of insecticides spray on bleeding grounds of mosquito and the rate at which infected individual are treated after being infection. Numerical results obtained from their plots shows that the proposed control strategies are effective and efficient in the decrease of number of exposed and infected human and mosquito as well.

According to Bakare and Abolarin (2018), rainfall and other environmental can either be an efficient hindrance or promote a vector borne disease. So they presented a paper that included the effect of seasonality of rainfall and four timely dependent measures of control, namely, usage of treated bed-nets, educational campaign, insecticides spray and treatment of human. They realized that epidemiological modeling focuses mainly on recognizing mechanisms that are responsible for the outbreak of epidemics but takes small account on economic constraints in examining control strategies. Also, for economic models they

give intuition on optimal control approach subject to constraints under limited control strategies. Therefore, their results indicates that combining economic and epidemiological factors is important.

Chapter Summary

In this chapter, we have presented a review of related research on mathematical epidemic models incorporating control strategies. Many of the reviews on mathematical models of malaria include intervention strategies such as prevention, treatment, using treated insecticide nets and insecticides spray. From an optimal control perspective, these strategies serves as controls. However, in all the reviews stated above, the models do not include the effects of prevention on the reduction of vector populations, an essential factor in containing the spread of the disease. Again, all the papers in the reviews assumed that treatment is readily available to every infected individual. This is far from the truth. In fact, there are many communities which do not have ready access to treatment; and there are individuals who simply cannot afford the cost.

CHAPTER THREE

RESEARCH METHODS

Introduction

This chapter develops mathematically, a deterministic model for the transmission and controlling of malaria, using a *saturation incidence*. A special feature of our model is that a proportion $c\alpha, (0 \leq c \leq 1)$ of the prevention effort α, contributes to a reduction of the vector population; for effectively controlling the spread of malaria. A mathematical analysis including the computation of an equilibrium points, and the basic reproduction number $\mathfrak{R}_0$, will be performed. We will also perform global and local stability analysis of the equilibrium points. We will use the *method of least-squares*, implemented in Python, to optimize the parameters for our model, using data on confirmed cases of malaria infection, obtained from WHO, from the year 2004 to the year 2017. Simulation of the model, using various combination of the controls α and γ will be performed, to determine their effect on the incidence and prevalence of malaria in Ghana. In order to determine the best treatment (γ) and prevention (α) technique for the control of spread of malaria, We will formulate an Optimal Control problem. Pontryagin's Maximum Principle will be utilized to obtain the optimality system. The resulting two-point boundary-value problem would be solved to determine the best strategy of preventive and treatment for effectively controlling the disease.

Mathematical Background

This section reviews some basic definitions and theorems needed to understand the model.

Definition 6

An *equilibrium point* (*fixed-point or critical point*) of a differential equation (1.2) , is a constant solution $x^* = (x_1^*, x_2^*, \cdots, x_n^*) \in \mathbb{R}^n$, satisfying

$$f(x^*) = 0. \tag{3.1}$$

Example 1

For $n = 1$, the 1-dimensional differential equation

$$\frac{dx}{dt} = kx(1 - \frac{x}{M}), \quad k > 0,\ M > 0 \tag{3.2}$$

has two points of equilibrium: $x_1^* = 0$, and $x_2^* = M$.

Example 2

For $n = 2$, the 2-dimensional SIS epidemic model

$$\begin{aligned} \frac{dS}{dt} &= \mu - \beta SI + \gamma I - \mu S, \\ \frac{dI}{dt} &= \beta SI - \gamma I - \mu I, \end{aligned} \tag{3.3}$$

has two equilibrium points:

1. *disease-free equilibrium point*: $(S_0, I_0) = (1,\ 0)$;
2. *endemic equilibrium point*: $(S_*, I_*) = \left(\frac{\gamma+\mu}{\beta},\ \frac{[\beta - (\gamma+\mu)]}{\beta} \right)$.

Local stability of an equilibrium point

Intuitively, an equilibrium point $x^* = (x_1^*, x_2^*, \cdots, x_n^*) \in \mathbb{R}^n$, of the autonomous system (1.2) is said to be *stable* provided that if the initial point $x_0 = (x_1^0, x_2^0, \cdots, x_n^0) \in \mathbb{R}^n$ is sufficiently close to x^*, then the trajectory $x(t) = (x_1(t), x_2(t), \cdots, x_n(t))$ remains close to $\mathbf{x}^*$ for all $t \geq 0$.

Lyapunov's indirect method for local stability

Lyapunov's indirect method enables us to determine the local stability of an equilibrium point through the linearization of a nonlinear system. This method is usually referred to as the *Lyapunov's first method*. Lyapunov's *indirect method* uses a linearization of a nonlinear system. Then, the eigenvalues of the Jacobian matrix would be used to determine the local stability at the equilibrium point x^*. This section investigates properties that makes an equilibrium state stable for a non linear linearized system.

Theorem 1

Let x^* be an equilibrium point for the nonlinear system

$$\dot{x} = f(x), \quad x(0) = x_0,$$

where $f : D \to \mathbb{R}^n$ is continuously differentiable and D is a neighbourhood of x^*. The Jacobian matrix J, evaluated at x^* is given by

$$J = \frac{\partial f}{\partial x}\Big|_{x=x^*}.$$

Then, the linearized system is

$$\dot{u} = Ju, \qquad u = x - x^*. \tag{3.4}$$

The stability of the equilibrium point x^* can then be determined as follows:

1. An equilibrium point (x^*) is stable asymptotically if the eigenvalues obtained from J satisfy $Re(\lambda_i(J)) < 0$, for $i = 1, ..., n$.

2. If the $Re(\lambda_i(J)) > 0$, for at least one i then equilibrium point (x^*) is unstable.

CASE 1: The equilibrium point is asymptotically stable if all the eigenvalues of J are negative or have negative real component.

CASE 2: If at least, one of the eigenvalues is equal to or greater than zero, then the equilibrium point is unstable.

The Routh-Hurwitz conditions for 2-dimensional nonlinear systems

The Routh-Hurwitz criteria give the necessary and sufficient conditions both roots of the characteristic polynomial to have negative parts, signifying local asymptotic stability. Let the equilibrium point, (x^*, y^*) be obtained from the nonlinear system

$$\begin{aligned} \frac{dx}{dt} &= u(x, y) \\ \frac{dy}{dt} &= v(x, y). \end{aligned} \tag{3.5}$$

Local stability of (x^*, y^*) can be determined from the following Theorem.

Theorem 2

Let

$$J = \begin{bmatrix} u_x(x^*, y^*) & u_y(x^*, y^*) \\ v_x(x^*, y^*) & v_y(x^*, y^*) \end{bmatrix}$$

be the Jacobian matrix of the linearized system given in (3.5) evaluated at the critical point (x^*, y^*). Then the equilibrium point (x^*, y^*) is asymptotically stable iff

$$\texttt{trace}(J) < 0 \quad \text{and} \quad \texttt{det}(J) > 0$$

Otherwise, it is unstable.

Proof. Let $a_1 = u_x(x^*, y^*), a_2 = u_y(x^*, y^*), a_3 = v_x(x^*, y^*), a_4 = v_y(x^*, y^*)$.

$$J = \begin{bmatrix} a_1 & a_2 \\ a_3 & a_4 \end{bmatrix} \tag{3.6}$$

The roots of the characteristics polynomial are eigenvalues of J

$$\lambda^2 - (a_1 + a_4)\lambda - (a_2a_3 - a_1a_4) = 0 \tag{3.7}$$

The expression for the roots are

$$\lambda_{1,2} = \frac{(a_1 + a_4)}{2} \pm \sqrt{\left(\frac{a_1 + a_4}{2}\right)^2 - (a_1a_4 - a_2a_3)}.$$

So

$$\lambda_1 = \frac{(a_1 + a_4)}{2} - \sqrt{\left(\frac{a_1 + a_4}{2}\right)^2 - (a_1 a_4 - a_2 a_3)}$$

and

$$\lambda_2 = \frac{(a_1 + a_4)}{2} + \sqrt{\left(\frac{a_1 + a_4}{2}\right)^2 - (a_1 a_4 - a_2 a_3)}$$

Suppose $(a_1 + a_4) < 0$ and $(a_1 a_4 - a_2 a_3) > 0$ then, λ_1, λ_2 are real when both are negative, or complex when they have negative real component.

The trace of A is $(a_1 + a_4)$ and the determinant is $(a_1 a_4 - a_2 a_3)$. □

For instance, the SIS epidemic model in Equation (3.3) has a *disease-free* equilibrium point at $E^0 = (S^0, I^0) = (1, 0)$. and a Jacobian matrix as

$$J = \begin{bmatrix} \beta I - \mu & -\beta S + \gamma \\ \beta I & \beta S - \mu - \gamma \end{bmatrix} \tag{3.8}$$

Evaluating the Jacobian matrix at the equilibrium point $E^0 = (S^0, I^0) = (1, 0)$, gives

$$J_0 = \begin{bmatrix} -\mu & -\beta + \gamma \\ 0 & \beta - \mu - \gamma \end{bmatrix} \tag{3.9}$$

The eigenvalues of J_0 are $\lambda_1 = -\mu, \lambda_2 = \beta - \mu - \gamma$. Since $\lambda_1 < 0$, the remaining condition for asymptotic stability is that $\lambda_2 = \beta - (\mu + \gamma) < 0$. That is, $\beta/(\mu + \gamma) < 1$. In other words, the condition for the equilibrium point $E_1^0 = (1, 0)$ to be asymptotically stable is that $\beta/(\mu + \gamma) < 1$.

The next generation matrix and the basic reproduction number

Mathematical epidemiology uses *next-generation matrix* procedure to obtain $\mathfrak{R}_o$ with the aid of a compartmental model of an infectious class of a dynamical system. This approach was derived by (Diekmann, Heesterbeek, & Metz, 1990) and (Van den Driessche & Watmough, 2002). Many of today's

most important emerging infectious diseases are multi-host infections by their very nature. As a result, they require a slightly more complex formalism for investigating epidemic thresholds, etc. The basic tool for examining epidemic thresholds in complex, structured models is the so-called *next generation matrix*.

Consider a population of individuals (or species) subdivided into n compartments, of which m are infected. Let x_i represent the proportion of the population in the ith compartment and let the vector of the proportions in all the compartments be x.

Distinguishing new infections from the all other changes in a population is an important feature that helps to compute $\mathcal{R}_0$. So we let

- $\mathcal{F}_i(x)$ represent the rate at which new infections appears in compartment i,
- $V_i^+(x)$ represent the rate at which individuals are transferred *into* compartment i, and
- $V_i^-(x)$ represent the rate at which individuals transferred *out of* compartment i.

Note that transmission model for a disease consists of nonnegative initial conditions together with the following system of equations:

$$\dot{x}_i = f_i(x) = \mathcal{F}_i(x) - \mathcal{V}_i(x), i = 1, \ldots, n, \tag{3.10}$$

where $\mathcal{V}_i = \mathcal{V}_i^- - \mathcal{V}_i^+$. We define the matrices,

$$F = \left[\frac{\partial F_i}{\partial x_j}(E^0)\right], \qquad V = \left[\frac{\partial V_i}{\partial x_j}(E^0)\right],$$

where E^0 denotes the DFE with indices $i, j = 1, \cdots, m$. The matrix G, given by

$$G = FV^{-1}$$

is called the *next generation matrix* (Diekmann et al., 1990). The entries of the matrix give the rate at which infected individuals of state j generate new infections of type i.

The *dominant eigenvalue* of G is the basic reproduction number $\Re_o$. That is

$$\Re_0 = \rho(G) = \rho\left(FV^{-1}\right). \tag{3.11}$$

For instance, the following SEIS epidemic model

$$\begin{aligned} S' &= \mu - cSI - \mu S + \delta I \\ E' &= cSI - (\mu+\kappa)E \\ I' &= \kappa E - (\mu+\delta)I \end{aligned} \tag{3.12}$$

has $E^0 = (1,0,0)$.

To compute $\Re_0$ for the model, we note the two disease states of the model namely, E and I. The vectors $\mathcal{V}_i$ and $\mathcal{F}_i$ are defined respectively as

$$\mathcal{F} = \begin{bmatrix} cSI \\ 0 \end{bmatrix}, \qquad \mathcal{V}_i^- - \mathcal{V}_i^+ = \mathcal{V} = \begin{bmatrix} (\mu+\kappa)E \\ (\mu+\delta)I - \kappa E \end{bmatrix}.$$

The matrices F and V are given respectively as

$$F = \begin{bmatrix} 0 & cS \\ 0 & 0 \end{bmatrix}, \qquad V = \begin{bmatrix} \mu+\kappa & 0 \\ -\kappa & \mu+\delta \end{bmatrix}.$$

Now,

$$V^{-1} = \begin{bmatrix} \frac{1}{\mu+\kappa} & 0 \\ \frac{\kappa}{(\mu+\kappa)(\mu+\delta)} & \frac{1}{\mu+\delta} \end{bmatrix}.$$

The matrix **G** is now given by

$$G = FV^{-1} = \begin{bmatrix} \frac{c\kappa}{(\mu+\kappa)(\mu+\delta)} & \frac{c}{\mu+\delta} \\ 0 & 0 \end{bmatrix}.$$

The basic reproduction number is given by the *spectral radius* of G, denoted by $\rho(G)$. That is,

$$\Re_0 = \rho(G) = \frac{c\kappa}{(\mu+\kappa)(\mu+\delta)}.$$

Global stability analysis

Generally, Lyapunov direct method is used to establish properties of an equilibrium point of a non-linear system globally. This is when scalar functions are selected carefully and studied how the system state evolves.

Theorem 3

Consider the system $\dot{x} = g(x), \quad x_* = 0$ where $g : \mathbb{D} \to \mathbb{R}^n$ is locally Lipschitz and $\mathbb{D} \subset \mathbb{R}^n$ a domain of origin. Let $V : \mathbb{D} \to \mathbb{R}$ be a continuous differentiable positive definite function in $\mathbb{D}$.

1. If $\dot{V}(x) = \dfrac{\partial V}{\partial x} \cdot g \leqslant 0$, then $x_* = 0$ is globally stable
2. If $\dot{V}(x) = \dfrac{\partial V}{\partial x} \cdot g < 0$, then $x_* = 0$ is globally asymptotically stable .

In both cases above, V is called a Lyapunov function. Moreover, if the conditions hold for all $x \in \mathbb{R}^n$ and $\|x\| \to \infty$ implies that $V(x) \to \infty$, then $x_* = 0$ is globally stable in (1), and globally asymptotically stable in (2).

We present the common Lyapunov candidate functions.

1. Logarithmic Lyapunov Function:

   $V(x_1, x_2, ..., x_n) = \sum_{i=1}^{n} c_i(x_i - x_i^* - x_i^* \ln \frac{x_i}{x_i^*})$,

2. Common Quadratic Lyapunov Function:

   $V(x_1, x_2, ..., x_n) = \sum_{n}^{i=1} \frac{c_i}{2}(x_i - x^*)^2$,

3. Composite Quadratic Lyapunov Function:

   $V(x_1, x_2, ..., x_n) = \frac{c}{2}\left[\sum_{n}^{i=1}(x_i - x^*)\right]^2$,

Parameter Estimation

This section presents the method used for estimating parameters. In mathematical modelling of epidemics, one of the relevant techniques is to relate the model output with observed data.

Definition 7

Curve-fitting also known as Curve Calibration is the process of determining the models parameters so that the solution best matches the data.

In order to calibrate a mathematical model, we require time series data that describe the temporal changes in one or more states of the system. The data sets available might be a *daily*, *weekly*, *monthly* or *yearly* data sets. Simulations of the models using different combinations of prevention and treatment will be performed to determine their effects on the incidence and prevalence of the disease. In addition, the simulations will help us to know the effects of the parameter c on the infected vector and human populations.

Least squares method

The *least-squares approach* fits the solution curve through the data points so that the *sum of squares error SSE*, of the vertical distances from the data points to the point on the curve is as small as possible.

Consider an epidemic model described by the initial value problem of a system of differential equations:

$$\frac{y(t)}{dt} = f(t, y; p), \qquad y(0) = y_0, \tag{3.13}$$

where $y \in \mathbb{R}^n, f \in \mathbb{R}^n$, and $p \in \mathbb{R}^m$, is some vector of parameters.

Suppose we have a collection of observed values of the *prevalence* $I(t)$, of the disease at k data points: $(t_1, Y_1), (t_2, Y_2), \cdots (t_k, Y_k)$. The *least squares method*

determines the optimal parameters, p, by minimizing the *Sum of Squares Error*

$$SSE(p) = \sum_{i=1}^{k} \|I(t_i) - Y_i\|_2^2, \tag{3.14}$$

where $I(t) = y^j(t;p)$, is the j^{th} component of the solution of the system in Equation (3.13), representing the infected population; and Y_i are the actual observed values of $I(t)$ at the points t_i.

Differential equations of epidemic models are often nonlinear and therefore, cannot be expressed explicitly. Also, the sum-of-squares error SSE, is a function of the parameters of the model. Hence, the minimization problem given in Equation (3.14) is also highly nonlinear. In general case, this problem is solved numerically using Computer Packages such as *Mathematica, Maple, Matlab/Octave, Python or R*.

The code requires two basic components: *a differential equation solver* and *a minimization routine*. Both routines are available in Python.

Optimal Control Formulation Methods

This section describes the general formulation of optimal control. These includes the the description of the state and costate equation and a general overview of the optimal formulations with definition of some basic terms. The state equation is as fellow:

$$\dot{X} = g(x,u,t), \qquad x(t_0) = x_0, \qquad 0 \leq t \leq t_f, \tag{3.15}$$

where

$$x(t) = x_1(t), x_2(t), \ldots, x_n(t) \tag{3.16}$$

are the state variables and

$$u(t) = u_1(t), u_2(t), \ldots, u_n(t) \tag{3.17}$$

are the control variables. The initial time t_0 is mostly given whiles the T is the terminal time and may be free or fixed.

Definition 8

The cost functional is denoted by

$$J(u) = \Phi(x(t_f)) + \int_0^{t_f} f(x(t), u(t), t)dt, \tag{3.18}$$

with $\Phi(x(T))$ as the terminal cost and the integrand depends the state of the system along the trajectory of the solution. The general form of optimal control problem can be defined as fellow

$$\min\{J(u) = \Phi(x(t_f)) + \int_0^{T} f(x(t), u(t), t)dt\} \tag{3.19}$$

subject to dynamics of

$$\dot{x} = g(x(t), u(t), t), \qquad x_0 = x(t_0), \tag{3.20}$$

where x_0 and t_0 are given. The domain of the controls is given as

$$U = \{u|u : [t_0, T]\} \qquad \forall\, t \in [t_0, t_f]. \tag{3.21}$$

Pontryagin's Maximum Principle

The Pontryagin's Maximum Principles uses necessarily conditions to obtain the optimality system (Panetta & Fister, 2000).

First Order Necessary Conditions

The first order necessary condition is obtained by adjoining the constraint to the objective function using the Lagrangian multiplier vector and is given as

$$\{J(u) = \Phi(x(t_f)) + \int_0^{t_f} f(x(t), u(t), t) + \lambda^T[f(x(t), u(t), t) - \dot{x}]dt\} \tag{3.22}$$

The Hamiltonian function is given as

$$H = f(x(t), u(t), t) + \lambda^T g(x(t), u(t), t). \tag{3.23}$$

The numerical approach for obtaining optimality system is as follows:

1. solving the state equation forward in time using

$$\left[\frac{\partial H}{\partial x}\right]^T = 0, \qquad x(t_0) = x_0 \tag{3.24}$$

2. solving the costate equation backward in time using

$$\left[\frac{\partial H}{\partial \lambda}\right]^T = 0, \qquad [\lambda_{t_f}]^T = \frac{\partial \phi(x(t_f))}{\partial x} \tag{3.25}$$

3. solving the optimal condition using

$$\left[\frac{\partial H}{\partial u}\right]^T = 0 \tag{3.26}$$

4. using the solutions u^* and x^* to evaluate the objective function numerically to obtain convergence.

A Mathematical Model for Malaria Transmission

Here, a *vector-host* epidemic model for malaria transmission would be formulated. We assume that movement from the susceptible classes to the infectious classes in both the host and the vector is dependent on the mosquitoes biting rate and their transmission probabilities. The biting rate b, is defined as the average number of bites per mosquitoes per day; while the transmission probabilities β_h, β_v, is the probability that an infectious bite will result in a new case in a susceptible population only. We also assume that the mosquitoes do not only feed on a human host, but have m alternative hosts available as blood sources.

Model Formulation

The total population sizes for the vector and host at a given time t is denoted as $N_v(t)$ and $N_h(t)$ respectively. The population for the host uses the *SIRS* epidemic model with three compartments, namely, the Susceptible S_h, Infected

I_h and Removed R_h with partial immunity at a given time. The total population for human is expressed as

$$N_h(t) = S_h(t) + I_h(t) + R_h(t).$$

At the susceptible stage, individuals are recruited at a rate Λ_h. This includes natural birth rate and migration. Individuals in this class move to the infectious class at a biting rate b and transmission rate β_h. The probability that an individual receive a bite from a mosquito per unit time is given as $\left(\frac{bN_v}{N_h}\right)\left(\frac{N_h}{N_h+m}\right)$ and the rate at which susceptible human is being infected is given as $\left(\frac{\beta_h b I_v}{N_h+m}\right)$. In addition, individuals in the susceptible class can be given preventive measures and they move to the removed class. Also, at the infection stage, an individual can die or receive treatment and recover with partial immunity. In addition, the recovered individual in the removed class returns back to the susceptible class with a higher chance of being infected again after loss immunity.

Similarly, for the vector population $N_v(t)$, it uses the SI epidemic model with two classes S_v, I_v representing the susceptible and infected class of the vector respectively. Thus, we have

$$N_v(t) = S_v(t) + I_v(t).$$

The susceptible population includes migration and natural birth. Mosquitoes become infected when they bite an infected human host at a biting rate b and transmission rate β_v. The probability that mosquitoes takes human blood meals per unit time is given as $\left(\frac{bN_h}{N_h+m}\right)$ and the rate at which susceptible vector is being infected is given as $\left(\frac{\beta_v b I_h}{N_h+m}\right)$. Susceptible mosquitoes progress to the infectious stage when they come into contact with an infected human. Note that at this stage, the vector partition does not incorporate immune class since mosquitoes never recover from infection. Mosquitoes infective period ends with death due

to its short life cycle (Hu, Lou, & Lu, 2009; Mojeeb et al., 2017; Putri & Jaharuddin, 2014).

In addition, we assume that some preventive measures α goes to reduce the vector population.

Parameters and state variables

Explanation of state variables for the system with respect to time are presented in Table 1.

Table 1: Description of State Variables

State Variables	Explanation
$S_h(t)$	Susceptible humans at a given time t.
$I_h(t)$	Infectious humans at a given time t.
$R_h(t)$	Recovered humans at a given time t.
$S_v(t)$	Susceptible mosquitoes at a given time t.
$I_v(t)$	Infectious mosquitoes at a given time t.

From Table 1 the state variables described presents the total number of the human and vector populations respectively at a given time. Taking into consideration the aforementioned of the explanation of state variables, the description of the SIRS-SI model is presented in Figure 1.

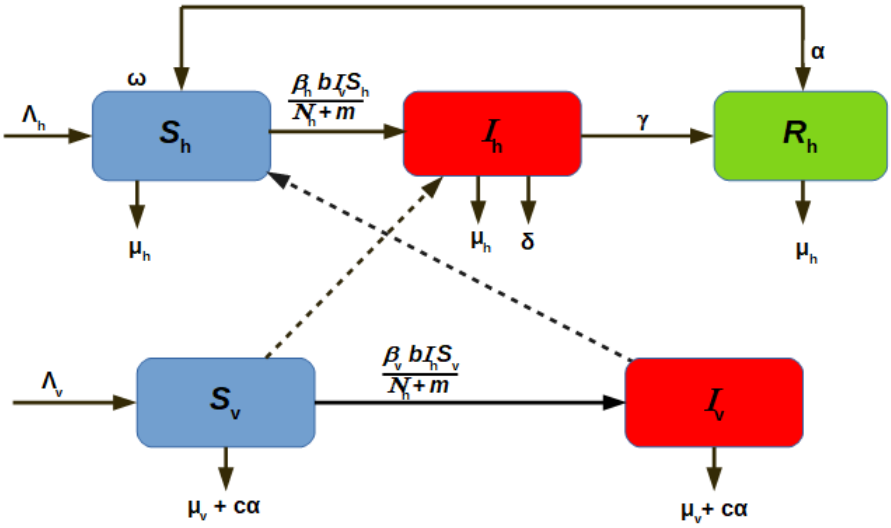

Figure 1: Schematic diagram for the dynamics of malaria epidemic model.

Diagrammatically, from Figure 1 the compartmental model moves an individual of the respective population from one class to the other with an appropriate rate and it is represented by the thick lines. From the figure, the dash lines from I_v to S_h show the transfer of the Plasmodium parasite from an infected mosquito to a susceptible human provided a contact has occurred whiles the dashed lines from S_v to I_h show that susceptible mosquitoes get infected when they bite infected human provided there is a contact. Thus, it shows an interaction between human and mosquito.

So the susceptible human S_h gets infected at a biting rate b and transmission probability rate β_v of an adult female Anopheles mosquitoes. After that, the susceptible human moves to infectious class I_h and then progresses to recovered with partial immunity at rate γ. In addition, individuals who are given prevention in S_h move to the removed class R_h at the rate α and recovered individuals can die naturally or move to the susceptible class at rate ω and μ_h respectively.

Also, for the vector populations, mosquito in susceptible class S_v become

infected due to biting rate and transmission probability and become infectious until its die naturally (Bedada, Lemma, & Koya, 2015).

Now, considering the assumptions made and the interactions from Figure 1, the system of non-linear ordinary differential equations with saturation incidence is given as:

$$\begin{cases} \dot{S}_h &= \Lambda_h - \frac{\beta_h b I_v S_h}{N_h+m} - \mu_h S_h - \alpha S_h + \omega R_h \\ \dot{I}_h &= \frac{\beta_h b I_v S_h}{N_h+m} - \mu_h I_h - \gamma I_h - \delta I_h \\ \dot{R}_h &= \gamma I_h - \mu_h R_h - \omega R_h + \alpha S_h \\ \dot{S}_v &= \Lambda_v - \frac{\beta_v b I_h S_v}{N_h+m} - (\mu_v + c\alpha) S_v \\ \dot{I}_v &= \frac{\beta_v b I_h S_v}{N_h+m} - (\mu_v + c\alpha) I_v, \end{cases} \tag{3.27}$$

where

$$N_v(t) = S_v(t) + I_v(t) \text{ and } N_h(t) = S_h(t) + I_h(t) + R_h(t).$$

The description of parameters in Equations (3.27) is shown in Table 2.

Table 2: Description of Parameters Used in the Model

Parameter	Detailed Explanation
Λ_h	Recruitment rate for humans.
Λ_v	Recruitment rate for mosquitoes.
β_h	Transmission rate from infectious vector to a susceptible human.
β_v	Transmission rate from an infectious human to a susceptible vector.
μ_h	Natural death rate for humans.
μ_v	Natural death rate for mosquitoes.
δ	Disease induced death rate.
γ	Recovery rate.
α	Prevention rate.
$c\alpha$	Prevention effort directed at reducing vector population.
ω	Rate of loss of immunity for recovered individuals.
b	Biting rate of the mosquitoes.
m	Number of alternative host.

From Table 2, we have the detailed explanation of the parameters used in the model respectively.

Model Analysis

In order for the model (3.27) to be well posed mathematically and epidemiologically, then all populations and sub-populations must be non-negative for $t > 0$ and all the parameters must be positive. This can be achieved by determining the positivity and feasible region for the model equation in (3.27).

Positivity of Solution

Here, the non-negativity for the solution system would be described. Thus, we will show that for each given non-empty initial conditions, results of the system remains positive. The following proposition would be used to investigate the positivity of the solutions of state variables for $t > 0$.

Proposition 1

Suppose that the initial conditions

$$\{(S_h(0),\ S_v(0)) > 0,\ \ (I_h(0),\ R_h(0),\ I_v(0)) \geq 0\} \in \Omega, \tag{3.28}$$

then the solution set $\{S_h(t), I_h(t), R_h(t), S_v(t), I_v(t)\}$ for Equation (3.27) is $\{S_h(t) > 0, I_h(t) > 0, R_h(t) > 0, S_v(t) > 0, I_v(t) > 0\}$ for all $t > 0$.

Proof. We assume that

$$\{(S_h(0),\ S_v(0)) > 0,\ \ (I_h(0),\ R_h(0),\ I_v(0)) \geq 0\} \in \Omega. \tag{3.29}$$

Then from Equation (3.27), the time derivative of the susceptible humans is given as

$$\frac{dS_h}{dt} = \Lambda_h - \frac{\beta_h b I_v S_h}{N_h + m} - (\mu_h + \alpha)S_h + \omega R_h \geq -(\mu_h + \alpha)S_h. \tag{3.30}$$

It follows that

$$\frac{dS_h}{dt} \geq -(\mu_h + \alpha)S_h. \tag{3.31}$$

Now, we have

$$\int \frac{dS_h}{dt} \geq -\int (\mu_h + \alpha)S_h. \tag{3.32}$$

This implies that

$$\int \frac{dS_h}{S_h} \geq -(\mu_h + \alpha)\int dt,$$

and

$$\ln|S_h| \geq -(\mu_h + \alpha)t + k, \tag{3.33}$$

where k is a constant. Note that Equation (3.33) simplifies to

$$S_h(t) \geq e^{-(\mu_h+\alpha)t+k} \tag{3.34}$$

and can also be expressed as

$$S_h(t) \geq A\, e^{-(\mu_h+\alpha)t}, \tag{3.35}$$

where $A = e^k$. Taking the given initial condition at $t = 0$, we have $S_h(0) \geq A$. This implies that

$$S_h(t) \geq S_h(0)\, e^{-(\mu_h+\alpha)t} \geq 0. \tag{3.36}$$

Again, the time derivative of an infectious human in Equation (3.27) is given as

$$\frac{dI_h}{dt} = \frac{\beta_h b I_v S_h}{N_h + m} - (\mu_h + \gamma + \delta)I_h \geq -(\mu_h + \gamma + \delta)I_h. \tag{3.37}$$

It follows that

$$\frac{dI_h}{dt} \geq -(\mu_h + \gamma + \delta)I_h. \tag{3.38}$$

So, this gives

$$\int \frac{dI_h}{dt} \geq -\int (\mu_h + \gamma + \delta)I_h \tag{3.39}$$

and it simplifies to

$$I_h(t) \geq e^{-(\mu_h+\gamma+\delta)t+k}, \tag{3.40}$$

where k is a constant. The expression can now be written as

$$I_h(t) \geq B\, e^{-(\mu_h+\gamma+\delta)t}, \tag{3.41}$$

where $B = e^k$. With the given initial condition and at $t = 0$, we have $I_h(0) \geq B$. Therefore,

$$I_h(t) \geq I_h(0)\, e^{-(\mu_h+\alpha)t} \geq 0. \tag{3.42}$$

Also, the time derivative of the recovered class in Equation (3.27) is given by

$$\begin{aligned} \frac{dR_h}{dt} &= \gamma I_h - (\mu_h+\omega)R_h + \alpha S_h \geq -(\mu_h+\omega)R_h \\ \frac{dR_h}{dt} &\geq -(\mu_h+\omega)R_h. \end{aligned} \tag{3.43}$$

This implies that

$$\int \frac{dR_h}{dt} \geq -\int (\mu_h+\omega)R_h \tag{3.44}$$

and can be simplified to

$$R_h(t) \geq e^{-(\mu_h+\omega)t+k}, \tag{3.45}$$

where k is a constant. The inequality is now written as

$$R_h(t) \geq C\, e^{-(\mu_h+\omega)t}, \tag{3.46}$$

where $C = e^k$. Using the given initial condition and at $t = 0$, we have that $R_h(0) \geq C$. Therefore,

$$R_h(t) \geq R_h(0)\, e^{-(\mu_h+\alpha)t} \geq 0. \tag{3.47}$$

Similarly, the time derivative of susceptible vector is given as

$$\frac{dS_v}{dt} = \Lambda_v - \frac{\beta_v b I_h S_v}{N_h+m} - (\mu_v+\alpha c)S_v \geq -(\mu_v+\alpha c)S_v. \tag{3.48}$$

This gives

$$\frac{dS_v}{dt} \geq -(\mu_v+\alpha c)S_v. \tag{3.49}$$

So it implies that

$$\int \frac{dS_v}{dt} \geq -\int (\mu_v+\alpha c)S_v, \tag{3.50}$$

and it simplifies to

$$S_v(t) \geq e^{-(\mu_v+\alpha c)t+k}. \tag{3.51}$$

Note that k is a constant. So we have that

$$S_v(t) \geq D\, e^{-(\mu_v+\alpha c)t}, \tag{3.52}$$

where $D = e^k$. Using the given initial condition and at $t = 0$, we have $S_v(0) \geq D$. Hence,

$$S_v(t) \geq S_v(0)\, e^{-(\mu_h+\alpha c)t} \geq 0. \tag{3.53}$$

Lastly, for the infectious class, the time derivative in Equation (3.27) is given as

$$\frac{dI_v}{dt} = \frac{\beta_v b I_h S_v}{N_h + m} - (\mu_v + \alpha c)I_v \geq -(\mu_v + \alpha c)I_v.$$

This is then rewritten as

$$\frac{dI_v}{dt} \geq -(\mu_v + \alpha c)I_v. \tag{3.54}$$

Integrating Equation (3.31) gives

$$\int \frac{dI_v}{dt} \geq -\int (\mu_v + \alpha c)I_v. \tag{3.55}$$

So, it simplifies to

$$I_v(t) \geq e^{-(\mu_v+\alpha c)t+k}, \tag{3.56}$$

where k is a constant. Now, we have

$$I_v(t) \geq E\, e^{-(\mu_v+\alpha c)t}, \tag{3.57}$$

where $E = e^k$. Also, using the given initial condition and at $t = 0$, we have that $I_v(0) \geq D$ and this gives

$$I_v(t) \geq I_v(0)\, e^{-(\mu_h+\alpha c)t} \geq 0. \tag{3.58}$$

□

Since the computation for feasible region and positivity for both the vector and the host population yields a positive results, we can therefore conclude that the feasible region denoted by Ω for the system of models in Equation (3.27) is defined as

$$\Omega := \left\{ (S_h, I_h, R_h, S_v, I_v) \in \mathbb{R}^5_+ : S_h + I_h + R_h \leq \frac{\Lambda_h}{\mu_h}, \ S_v + I_v \leq \frac{\Lambda_v}{(\mu_v + \alpha c)} \right\}. \tag{3.59}$$

The feasible region in Equation (3.59) implies that the ordinary differential equations for the epidemic model in Equation (3.27) is well-defined epidemiologically and positively invariant. Therefore the following proposition would be used to investigate the assumption for invariant.

Proposition 2

The region $\Pi = \Pi_h \times \Pi_v$ defined by

$$\begin{aligned} \Pi_h &:= \left\{ (S_h, I_h, R_h) \in \mathbb{R}^3_+ : S_h + I_h + R_h \leq \frac{\Lambda_h}{\mu_h}, \ S_h > 0, \ I_h > 0, \ R_h > 0 \right\} \\ \Pi_v &:= \left\{ (S_v, I_v) \in \mathbb{R}^2_+ : S_v + I_v \leq \frac{\Lambda_v}{(\mu_v + c\alpha)}, \ S_v > 0, \ I_v > 0 \right\} \end{aligned} \tag{3.60}$$

is the feasible region for the system.

Proof. Using the expression for total human population given as $N_h = S_h + I_h + R_h$, we have

$$\begin{aligned} \dot{N}_h &= \dot{S}_h + \dot{I}_h + \dot{R}_h \\ \dot{N}_h &= \Lambda_h - (S_h + I_h + R_h)\mu_h - \delta I_h \\ \dot{N}_h &= \Lambda_h - \mu_h N_h - \delta I_h. \end{aligned} \tag{3.61}$$

It follows directly from Equation (3.61) that

$$\dot{N}_h + \mu_h N_h = \Lambda_h - \delta I_h. \tag{3.62}$$

We then have

$$\dot{N}_h + \mu_h N_h \leq \Lambda_h. \tag{3.63}$$

Using integrating factor $e^{\mu_h t}$, the computation for solving Equation (3.63) is given as:

$$\begin{aligned} e^{\mu_h t}\dot{N}_h + e^{\mu_h t}\mu_h N_h &\leq e^{\mu_h t}\Lambda_h \\ \frac{d}{dt}\left(e^{\mu_h t}N_h\right) &\leq e^{\mu_h t}\Lambda_h \\ e^{\mu_h t}N_h(t) &\leq \Lambda_h \int e^{\mu_h t}\, dt \\ e^{\mu_h t}N_h(t) &\leq \frac{\Lambda_h}{\mu_h}e^{\mu_h t} + k_1, \end{aligned} \tag{3.64}$$

where k_1 is the constant of integration. Now, it follows that

$$N_h(t) \leq \frac{\Lambda_h}{\mu_h} + k_1 e^{-\mu_h t}. \tag{3.65}$$

With the use of the initial condition, $N_h(0) = N_0$, the constant k_1 is $N_0 - \frac{\Lambda_h}{\mu_v}$. So, Equation (3.65) now becomes

$$N_h(t) + \left(\frac{\Lambda_h}{\mu_h} - N_0\right) \leq \frac{\Lambda_h}{\mu_h}. \tag{3.66}$$

Taking the limit on both sides of Equation (3.66) gives

$$\lim_{t\to\infty}\left(N_h(t) + \left(\frac{\Lambda_h}{\mu_h} - N_0\right)\right) \leq \lim_{t\to\infty}\left(\frac{\Lambda_h}{\mu_h}\right), \tag{3.67}$$

which then simplifies to

$$\lim_{t\to\infty} N_h(t) \leq \frac{\Lambda_h}{\mu_h} = K_h. \tag{3.68}$$

Hence, the host population is bounded above by the carrying capacity $\frac{\Lambda_h}{\mu_h}$ and its feasible solution set can be defined as

$$\Pi_h = \left\{(S_h, I_h, R_h) \in \mathbb{R}^3_+ : N_h \leq \frac{\Lambda_h}{\mu_h} = K_h,\ \ S_h > 0,\ \ I_h \geq 0,\ \ R_h \geq 0\right\}. \tag{3.69}$$

Similarly, for total population of the vector, we have

$$\begin{aligned} \dot{N}_v &= \dot{S}_v + \dot{I}_v \\ \dot{N}_v &= \Lambda_v - (\mu_v + c\alpha)(S_v + I_v) \\ \dot{N}_v &= \Lambda_v - (\mu_v + c\alpha)N_v. \end{aligned} \tag{3.70}$$

This follows that

$$\dot{N}_v + (\mu_v + c\alpha)N_v \leq \Lambda_v. \tag{3.71}$$

The computation for solving Equation (3.71) using the integrating factor $e^{(\mu_v+c\alpha)t}$ is given as

$$\begin{aligned} e^{(\mu_v+c\alpha)t}\dot{N}_v + e^{(\mu_v+c\alpha)t}(\mu_v + c\alpha)N_v &\leq e^{(\mu_v+c\alpha)t}\Lambda_v \\ \frac{d}{dt}\left(e^{(\mu_v+c\alpha)t}N_v\right) &\leq e^{(\mu_v+c\alpha)t}\Lambda_v \\ \left(e^{(\mu_v+c\alpha)t}N_v(t)\right) &\leq \Lambda_v \int e^{(\mu_v+c\alpha)t}\, dt \\ e^{(\mu_v+c\alpha)t}N_v(t) &\leq \frac{\Lambda_v}{(\mu_v + c\alpha)}e^{(\mu_v+c\alpha)t} + k_2, \end{aligned} \tag{3.72}$$

where k_2 is the constant of integration. Now, we have

$$N_v(t) \leq \frac{\Lambda_v}{\mu_v} + k_2 e^{-(\mu_v+c\alpha)t}. \tag{3.73}$$

Using the initial condition, $N_v(0) = N_0,\ \ k_2 = N_0 - \frac{\Lambda_v}{N_v}$. So, Equation (3.73) now becomes

$$N_v(t) + \left(\frac{\Lambda_v}{(\mu_v + c\alpha)} - N_0\right)e^{(\mu_v+c\alpha)t} \leq \frac{\Lambda_v}{(\mu_v + c\alpha)}. \tag{3.74}$$

Hence taking the limits of Equation (3.74) gives us

$$\begin{aligned} \lim_{t\to\infty}\left(N_v(t) + \left(\frac{\Lambda_v}{(\mu_v + c\alpha)} - N_0\right)e^{\mu_v t}\right) & \\ \leq \lim_{t\to\infty}\left(\frac{\Lambda_v}{(\mu_v + c\alpha)}\right) &= \frac{\Lambda_v}{(\mu_v + c\alpha)}. \end{aligned} \tag{3.75}$$

Thus

$$\lim_{t\to\infty}(N_v) \leq \frac{\Lambda_v}{(\mu_v + c\alpha)} = K_v. \tag{3.76}$$

This is also positive and bounded above by its carrying capacity. So the feasible region is therefore defined as

$$\Pi_v := \left\{ (S_v, I_v) \in \mathbb{R}^2_+ : N_v \leq \frac{\Lambda_v}{(\mu_v + c\alpha)} = K_v,\ S_v > 0,\ I_v \geq 0 \right\}.$$

□

The system of non linear differential equation in Equation (3.27) is rewritten using N_h replaced by the carrying capacity K_h, as

$$\begin{cases} \dot{S_h} &= \Lambda_h - \frac{\beta_h b I_v S_h}{K_h + m} - \mu_h S_h - \alpha S_h + \omega R_h \\ \dot{I_h} &= \frac{\beta_h b I_v S_h}{K_h + m} - \mu_h I_h - \gamma I_h - \delta I_h \\ \dot{R_h} &= \gamma I_h - \mu_h R_h - \omega R_h + \alpha S_h \\ \dot{S_v} &= \Lambda_v - \frac{\beta_v b I_h S_v}{K_h + m} - (\mu_v + c\alpha) S_v \\ \dot{I_v} &= \frac{\beta_v b I_h S_v}{K_h + m} - (\mu_v + c\alpha) I_v, \end{cases} \tag{3.77}$$

Existence of Equilibrium Points

The equilibrium points are the solutions of

$$\dot{S_h} = \dot{I_h} = \dot{R_h} = \dot{S_v} = \dot{I_v} = 0. \tag{3.78}$$

The system has a unique DFE and EE point, denoted respectively by

$$\Theta^0 = \left(S_h^0, I_h^0, R_h^0, S_v^0, I_v^0\right)$$

and

$$\Theta^1 = \left(S_h^1, I_h^1, R_h^1, S_v^1, I_v^1\right).$$

The DFE is given by

$$\Theta^0 = \left[\frac{\Lambda_h(\mu_h + \omega)}{\mu_h(\alpha + \mu_h + \omega)},\ 0,\ \frac{\Lambda_h \alpha}{\mu_h(\alpha + \mu_h + \omega)}, \frac{\Lambda_v}{\alpha c + \mu_v}, 0 \right]. \tag{3.79}$$

The EE is given by

$$\Theta^1 = \left(S_h^1, I_h^1, R_h^1, S_v^1, I_v^1\right)$$

where

$$S_h^1 = \frac{W\left[\left(\Lambda_h \beta_v b + \mu_h\right)\left(\mu_h + \omega\right) + \left((\delta + \gamma)\mu_h + \delta\omega\right)\left(N_h + m\right)\left(\mu_v + \alpha c\right)\right]}{Y_h + Z_h}$$

$$I_h^1 = \frac{\Lambda_h \Lambda_v b^2 \beta_h \beta_v (\mu_h + \omega) X}{Y_h + Z_h}$$

$$R_h^1 = \frac{\Lambda_h \Lambda_v b^2 \beta_h \beta_v \gamma + W\left[\Lambda_h \beta_v \alpha b - (K_h + m)(\mu_v + \alpha c)\left(\mu_h(\delta - \alpha) - \delta\gamma\right)\right]}{Y_h + Z_h}$$

$$S_v^1 = \frac{(K_h + m)\left[\mu_h(\mu_h + \delta + \omega) + \delta\omega\right] + \left(W\mu_h(\mu_h + \alpha + \omega)\right)(K_h + m)}{Y_v + Z_v}$$

$$I_v^1 = \frac{\Lambda_h \Lambda_v b^2 \beta_h \beta_v (\omega + \mu_h) X}{Y_v + Z_v},$$

where

$$W = (\mu_h + \delta + \gamma)(\mu_v + \alpha c)(K_h + m)$$

$$X = \left[\left(\mu_h(\mu_h + \alpha + \omega)\right)(\mu_h + \gamma + \delta)(\mu_v + \alpha c)^2 (K_h + m)^2\right]$$

$$Y_h = \Lambda_v \beta_h \beta_v b^2 \left[(\mu_h + \delta + \gamma)(\mu_h + \omega) - \delta\omega\right]$$

$$Z_h = \beta_v b(\mu_h + \gamma + \delta)(\mu_v + \alpha c)\left[\mu_h(\mu_h + \omega + \alpha)\right]$$

$$Y_v = \Lambda_h \beta_h \beta_v b^2 (\mu_h + \omega)$$

$$Z_v = \left[\beta_h b(\mu_v + \alpha c)\left((\mu_h + \delta + \gamma)(\mu_h + \omega) - \gamma\omega\right)\right](K_h + m)$$

The Basic Reproduction Number

This section describes how the basic reproduction number $\Re_o$ was computed. One important aspect of $\Re_o$ is that, it determines whether a disease will

persist or die off if there is an outbreak or there is a small perturbation of the system. Therefore, using next generation matrix approach, the appearance of new cases of infections and the rate of transfer of infectious from one compartment to a different one in the systems of equations in Equation (3.77) is

$$F_i = \begin{bmatrix} \frac{\beta_h b I_v S_h}{K_h+m} \\ \\ \frac{\beta_v b I_h S_v}{K_h+m} \end{bmatrix} \quad \text{and} \quad V_i = \begin{bmatrix} I_h\delta + I_h\gamma + I_h u_h \\ \\ (u_v + c\alpha)I_v \end{bmatrix}.$$

So, we have F and V to be given as

$$F = \begin{bmatrix} 0 & \frac{S_h b\beta_h}{K_h+m} \\ \\ \frac{S_v b\beta_v}{K_h+m} & 0 \end{bmatrix} \quad \text{and} \quad V = \begin{bmatrix} \delta+\gamma+\mu_h & 0 \\ \\ 0 & \alpha c+\mu_v \end{bmatrix}.$$

The next generation matrix $G = FV^{-1}$, at DFE is given by

$$G = \begin{bmatrix} 0 & \frac{(\alpha c+\mu_v)(\Lambda_h\mu_h+\Lambda_h\omega)b\beta_h}{(\alpha\mu_h+\mu_h^2+\mu_h\omega)(K_h+m)} \\ \\ \frac{\Lambda_v b\beta_v(\delta+\gamma+\mu_h)}{(\alpha c+\mu_v)(K_h+m)} & 0 \end{bmatrix}.$$

The eigenvalues obtained from G are

$$\begin{aligned} \Re_1(\alpha) &= +\sqrt{\frac{\Lambda_h\Lambda_v b^2\beta_h\beta_v(\mu_h+\omega)}{(\alpha+\mu_h+\omega)(\delta+\gamma+\mu_h)\mu_h(\alpha c+\mu_v)^2(K_h+m)^2}} \\ \Re_2(\alpha) &= -\sqrt{\frac{\Lambda_h\Lambda_v b^2\beta_h\beta_v(\mu_h+\omega)}{(\alpha+\mu_h+\omega)(\delta+\gamma+\mu_h)\mu_h(\alpha c+\mu_v)^2(K_h+m)^2}}. \end{aligned} \tag{3.80}$$

The spectral radius is the dominant eigenvalues obtained in Equation (3.80). The basic reproduction number, with prevention at the rate α, denoted by $\Re_o(\alpha)$, is given by

$$\Re_o(\alpha) = \sqrt{\frac{\Lambda_h\Lambda_v b^2\beta_h\beta_v(\mu_h+\omega)}{\mu_h(\alpha+\mu_h+\omega)(\delta+\gamma+\mu_h)(\alpha c+\mu_v)^2(K_h+m)^2}}. \tag{3.81}$$

Without prevention $\alpha = 0$ the corresponding basic reproduction number

$$\Re_o(0) = \sqrt{\frac{\Lambda_h \Lambda_v b^2 \beta_h \beta_v}{\mu_h(\delta+\gamma+\mu_h)(\mu_v)^2(K_h+m)^2}} = \Re_o. \tag{3.82}$$

It is easy to see that

$$\Re_o(\alpha) \leq \Re_o. \tag{3.83}$$

Equation (3.83) indicates that it is easier to control the spread of an infectious disease when there is prevention than without prevention. **Remark 1**

From Equation (3.81), it can be estimated that higher values of $\Lambda_h, \Lambda_v, b, \beta_h, \beta_v, \mu_h$ and ω can lead to the outbreak of malaria and on the other hand, small values of $\Lambda_h, \Lambda_v, b, \beta_h, \beta_v, \mu_h$ and ω, the disease dies out.

From Equation (3.82), an infective human is initiated into the susceptible population bitten by $\frac{\Lambda_v b}{(\mu_v)(K_h+m)}$ mosquitoes per unit time during the infective period of $\frac{\Lambda_v b}{(\mu_v)(K_h+m)} \times \frac{1}{(\mu_h+\delta+\gamma)}$.
A proportion $\beta_v \left(\frac{\Lambda_v b}{(\mu_v)(K_h+m)} \times \frac{1}{(\mu_h+\delta+\gamma)} \right)$ of the mosquitoes become infectious. Similarly, an infective mosquito disseminates $\left(\frac{\Lambda_h b}{(\mu_v)(K_h+m)} \times \frac{1}{(\mu_h+\delta+\gamma)} \right)$ bites into human population during its entire life and a proportion
$\beta_h \left(\frac{\Lambda_h b}{(\mu_v)(K_h+m)} \times \frac{1}{(\mu_h+\delta+\gamma)} \right)$ of these bites becomes infectious in the human population. Therefore, the geometric mean of these quantities that is equal to $\Re_o$, produces secondary infections.

Endemic equilibrium points expressed in terms of basic reproduction number

The endemic equilibrium expressed in terms of $\Re_o$ is given as

$$S_h^1 = \frac{\frac{\Lambda_h \Lambda_v b^2 \beta_h \beta_v (\mu_h+\omega)(\mu_h(\mu_h+\gamma+\delta)+\omega(\mu_h+\delta)}{R_0^2(\alpha)(\mu_h(\mu_h+\alpha+\omega))} + \Lambda_h b \beta_v (\mu_h+\omega) W}{Y_h + Z_h}$$

$$I_h^1 = \frac{X(R_0^2(\alpha)-1)}{Y_h+Z_h}$$

$$R_h^1 = \frac{W\left[\frac{R_0^2(\alpha)\gamma(\mu_h(\mu_h+\alpha+\omega))}{\mu_h+\omega} + \mu_h(\alpha-\gamma)+\delta\alpha\right] + \Lambda_h\beta_v b\alpha}{Y_h+Z_h}$$

$$S_v^1 = \frac{\frac{\Lambda_h\Lambda_v b^2\beta_h\beta_v(\mu_h+\omega)}{R_0^2(\alpha)(\mu_v+c\alpha)} + (\Lambda_v b\beta_h(\mu_h(\mu_h+\delta+\gamma)+\omega(\mu_h+\delta))(K_h+m)}{Y_v+Z_v}$$

$$I_v^1 = \frac{X(R_0^2(\alpha)-1)}{Y_v+Z_v}.$$

Local Stability Analysis

This section will establish stability of EE and DFE locally and globally. The following theorems would be used to investigates the global and local stability of DFE and EE.

Local stability of disease free equilibrium point

To investigate the stability of DFE locally in Ω we use the following theorem.

Theorem 4

The disease free equilibrium point for the model in 3.27 is locally asymptotically stable in Ω if $\Re_o < 1$ and unstable if $\Re_o > 1$.

Proof. We will begin the proof by linearizing the system of differential equation in Equation 3.77 at the DFE. The Jacobian for the linearization denoted by J is

given as

$$J = \begin{bmatrix} -\frac{I_v b\beta_h}{K_h+m} - \alpha - \mu_h & 0 & \omega & 0 & -\frac{S_h b\beta_h}{K_h+m} \\ \frac{I_v b\beta_h}{K_h+m} & -\delta-\gamma-\mu_h & 0 & 0 & \frac{S_h b\beta_h}{K_h+m} \\ \alpha & \gamma & -\mu_h-\omega & 0 & 0 \\ 0 & -\frac{S_v b\beta_v}{K_h+m} & 0 & -\frac{I_h b\beta_v}{K_h+m} - \alpha c - \mu_v & 0 \\ 0 & \frac{S_v b\beta_v}{K_h+m} & 0 & \frac{I_h b\beta_v}{K_h+m} & -\alpha c - \mu_v \end{bmatrix}.$$

Evaluating at DFE gives $J(\Theta_0)$ as

$$\begin{bmatrix} -\alpha-\mu_h & 0 & \omega & 0 & -\frac{(\Lambda_h\mu_h+\Lambda_h\omega)b\beta_h}{(\alpha\mu_h+\mu_h^2+\mu_h\omega)(K_h+m)} \\ 0 & -\delta-\gamma-\mu_h & 0 & 0 & \frac{(\Lambda_h\mu_h+\Lambda_h\omega)b\beta_h}{(\alpha\mu_h+\mu_h^2+\mu_h\omega)(K_h+m)} \\ \alpha & \gamma & -\mu_h-\omega & 0 & 0 \\ 0 & -\frac{\Lambda_v b\beta_v}{(\alpha c+\mu_v)(K_h+m)} & 0 & -\alpha c-\mu_v & 0 \\ 0 & \frac{\Lambda_v b\beta_v}{(\alpha c+\mu_v)(K_h+m)} & 0 & 0 & -\alpha c-\mu_v \end{bmatrix}. \tag{3.84}$$

The eigenvalues obtained from the Jacobian matrix in Equation (3.84) would be used to examine the stability of DFE locally and it states that DFE will be locally stable if the eigenvalues are negative or has a negative real parts. The eigenvalues of the matrix $J(\Theta_0)$ are

$$\lambda_1 = -(\alpha+\omega+u_h),\ \lambda_2 = -\mu_h,\ \lambda_3 = -(\mu_v+\alpha c),$$
$$\lambda_4 = -K(B+\sqrt{C}), \lambda_5 = -K(B-\sqrt{C}).$$

Here,

$$\begin{cases} K &= \dfrac{1}{2(K_h+m)(\mu_v+\alpha c)(\alpha+\omega+\mu_h)\mu_h} \\ B &= (\mu_v+\alpha c)\,(K_h+m)\,[(\mu_h+\gamma+\delta+\mu_v+\alpha c)\,(\mu_h(\mu_h+\alpha+\omega))] \\ C &= \left[4\Lambda_h\Lambda_v b^2\beta_h\beta_v(\omega+\mu_h)(\mu_v+\alpha c)\,(\mu_h(\mu_h+\alpha+\omega))\right] \\ &\quad +(K_h+m)^2\,(\mu_v+\alpha c)^2\left[((\mu_h+\gamma+\delta)-(\mu_v+\alpha c))^2\,(\mu_h(\mu_h+\alpha+\omega))\right]. \end{cases}$$

It is clear that the eigenvalues $\lambda_1,\lambda_2,\lambda_3$ and λ_4 are all negatives. The eigenvalue λ_5 will be negative provided that

$$B-\sqrt{C}>0, \quad \text{or equivalently} \quad B^2>C.$$

Now, $B^2-C>0$ simplifies

$$\begin{aligned}(\mu_h+\alpha+\omega)(\mu_v+\alpha c)\left[-4\Lambda_h\Lambda_v b^2\beta_h\beta_v(\mu_h+\omega)\right] \\ +(\mu_h+\alpha+\omega)(\mu_v+\alpha c) \\ \left[4\mu_h(\alpha+\omega+\mu_h)(\mu_h+\gamma+\delta)(K_h+m)^2(\mu_v+\alpha c)^2\right]>0. \quad (3.85)\end{aligned}$$

Equation (3.85) simplifies to

$$\begin{aligned}-4\Lambda_h\Lambda_v b^2\beta_h\beta_v(\mu_h+\omega) \\ >-4\mu_h(\alpha+\omega+\mu_h)(\mu_h+\gamma+\delta)(K_h+m)^2(\mu_v+\alpha c)^2,\end{aligned}$$

and can further be written as

$$\frac{\Lambda_h\Lambda_v b^2\beta_h\beta_v(\mu_h+\omega)}{\mu_h(\alpha+\omega+\mu_h)(\mu_h+\gamma+\delta)(K_h+m)^2(\mu_v+\alpha c)^2}<1.$$

Hence,

$$\mathfrak{R}_o{}^2<1. \quad (3.86)$$

Since the threshold parameter is less than one(1), as in Equation (3.86), we have shown that the DFE is asymptotically stable. □

Local stability of endemic equilibrium point

The changes of the infectious class of the EE will be used to examine the local stability.

Theorem 5

The EE is asymptomatically stable if $\Re_o(\alpha) > 1$ and unstable if $\Re_o(\alpha) < 1$.

We will elaborate on the theorem by expressing the infectious classes of the EE in terms of $\Re_o(\alpha)$. So, we have the given as

$$I_h^1 = \frac{X(R_0^2(\alpha)-1)}{Y_h + Z_h}$$
$$I_v^1 = \frac{X(R_0^2(\alpha)-1)}{Y_v + Z_v}. \tag{3.87}$$

From I_v^1 and I_h^1, the endemic condition exists only when Equation (3.87) are positive. Thus, we have

$$\Re_o{}^2(\alpha) - 1 > 0, \tag{3.88}$$

since both the numerator and denominator is positive. Hence, EE is locally asymptotically stable if $\Re_o{}^2(\alpha) > 1$.

Global Stability Analysis

Here, we will investigate global stability analysis for DFE and the EE in the feasible region Ω.

Global stability of disease free equilibrium point

To ensure that DFE is independent of the primary size of the sub-population then it is essential to show that the DFE is globally asymptotically stable. One of the approach to study global asymptotic stability of DFE is the construction

of an appropriate Lyapunov function (Lazarus, 2018). The following theorem describes the global stability.

Theorem 6

The DFE is asymptotically stable globally in Ω provided $\Re_o \leq 1$.

Proof. Considering a Lyapunov function

$$V = k_1 I_h + k_2 I_v, \qquad \text{where} \qquad k_1 > 0\,, k_2 > 0.$$

The time derivative of the Lyapunov function V gives the following expression.

$$\dot{V} = k_1 \dot{I}_h + k_2 \dot{I}_v.$$

Substituting $\dot{I}_h$ and $\dot{I}_v$ into the equation above gives us

$$\dot{V} = k_1 \left[\frac{\beta_h b I_v S_h}{K_h + m} - (\mu_h + \gamma + \delta) I_h \right] + k_2 \left[\frac{\beta_v b I_h S_v}{K_h + m} - (\mu_v + \alpha c) I_v \right]. \tag{3.89}$$

Note that

$$S_h = \frac{\Lambda_h(\mu_h + \omega)}{\mu_h(\mu_h + \alpha + \omega)} \qquad \text{and} \qquad S_v = \frac{\Lambda_v}{\mu_v + \alpha c}. \tag{3.90}$$

Substituting Equation (3.90) into Equation (3.89) gives

$$\begin{aligned} \dot{V} = k_1 & \left[\frac{\beta_h b I_v \Lambda_h(\mu_h + \omega)}{\mu_h(\mu_h + \alpha + \omega)(K_h + m)} - (\mu_h + \gamma + \delta) I_h \right] \\ & + k_2 \left[\frac{\beta_v b I_h \Lambda_v}{(\mu_v + \alpha c)(K_h + m)} - (\mu_v + \alpha c) I_v \right]. \end{aligned} \tag{3.91}$$

Grouping Equation (3.91) into I_h and I_v gives

$$\begin{aligned} \dot{V} = & \left[k_2 \frac{\beta_v b \Lambda_v}{(\mu_v + \alpha c)(K_h + m)} - k_1(\mu_h + \gamma + \delta) \right] I_h \\ & + \left[k_1 \frac{\beta_h b \Lambda_h(\mu_h + \omega)}{\mu_h(\mu_h + \alpha + \omega)(K_h + m)} - k_2(\mu_v + \alpha c) \right] I_v. \end{aligned} \tag{3.92}$$

Further simplification gives

$$\begin{aligned} \dot{V} = & k_1(\mu_h + \gamma + \delta) \left[\frac{k_2 \beta_v b \Lambda_v}{k_1(\mu_h + \gamma + \delta)(\mu_v + \alpha c)(K_h + m)} - 1 \right] I_h \\ & + k_2(\mu_v + \alpha c) \left[\frac{k_1 \beta_h b \Lambda_h(\mu_h + \omega)}{k_2(\mu_v + \alpha c)\mu_h(\mu_h + \alpha + \omega)(K_h + m)} - 1 \right] I_v. \end{aligned} \tag{3.93}$$

Considering the coefficient of I_v in Equation (3.92), we choose the constant k_1, k_2 is respectively as

$$k_1 = (\mu_v + \alpha c) \qquad \text{and} \qquad k_2 = \frac{\beta_h b \Lambda_h (\mu_h + \omega)}{\mu_h (\mu_h + \alpha + \omega)(K_h + m)}.$$

Substituting k_1, k_2 into Equation (3.92) gives

$$\begin{aligned} \dot{V} = (\mu_v + \alpha c)(\mu_h + \gamma + \delta) & \left[\frac{\Lambda_h \Lambda_v \beta_h b^2 \beta_v (\mu_h + \omega)}{\mu_h (\mu_h + \alpha + \omega)(\mu_h + \gamma + \delta)(\mu_v + \alpha c)^2 (K_h + m)^2} - 1 \right] I_h \\ & + \frac{\beta_h b \Lambda_h (\mu_h + \omega)(\mu_v + \alpha c)}{\mu_h (\mu_h + \alpha + \omega)(K_h + m)} \left[\frac{\mu_h (\mu_h + \alpha + \omega)(K_h + m)(\mu_v + \alpha c) \beta_h b \Lambda_h (\mu_h + \omega)}{\beta_h b \Lambda_h (\mu_h + \omega)(\mu_v + \alpha c) \mu_h (\mu_h + \alpha + \omega)(K_h + m)} - 1 \right] I_v. \end{aligned} \tag{3.94}$$

Simplifying Equation (3.94) gives

$$\dot{V} = (\mu_v + \alpha c)(\mu_h + \gamma + \delta) \left[\frac{\Lambda_h \Lambda_v \beta_h b^2 \beta_v (\mu_h + \omega)}{\mu_h (\mu_h + \alpha + \omega)(\mu_h + \gamma + \delta)(\mu_v + \alpha c)^2 (K_h + m)^2} - 1 \right] I_h, \tag{3.95}$$

which can be expressed in terms of $\mathfrak{R}_o$ as

$$\dot{V} = (\mu_v + \alpha c)(\mu_h + \gamma + \delta) \left[{\mathfrak{R}_o}^2 - 1 \right] I_h. \tag{3.96}$$

Therefore,

$$\begin{cases} \dot{V} = 0 & \text{if} \quad {\mathfrak{R}_o}^2 = 1 \\ \dot{V} < 0 & \text{if} \quad {\mathfrak{R}_o}^2 < 1 \end{cases} \tag{3.97}$$

Hence, the DFE is globally asymptotically stable in Ω if ${\mathfrak{R}_o}^2 \leq 1$.

□

Global stability of endemic equilibrium point

The following theorem will be used to prove the stability of the EE globally.

Theorem 7

The EE is globally asymptotically stable in Ω if $\Re_o > 1$.

Proof. We will begin this proof by defining logarithmic Lyapunov function as

$$\begin{aligned} V = &\left(S_h - S_h^1 - S_h^1 \log \frac{S_h}{S_h^1}\right) + \left(I_h - I_h^1 - I_h^1 \log \frac{I_h}{I_h^1}\right) \\ &+ \left(R_h - R_h^1 - R_h^1 \log \frac{R_h}{R_h^1}\right) \\ &+ \left(S_v - S_v^1 - S_v^1 \log \frac{S_v}{S_v^1}\right) + \left(I_v - I_v^1 - I_v^1 \log \frac{I_v}{I_v^1}\right). \end{aligned}$$

The time derivative of V is represented as

$$\begin{aligned} \dot{V} = &\left(1 - \frac{S_h^1}{S_h}\right)\dot{S}_h + \left(1 - \frac{I_h^1}{I_h}\right)\dot{I}_h + \left(R_h - \frac{R_h^1}{R_h}\right)\dot{R}_h \\ &+ \left(S_v - S_v^1 - \frac{S_v^1}{S_v}\right)\dot{S}_v + \left(1 - \frac{I_v^1}{I_v}\right)\dot{I}_v. \end{aligned} \tag{3.98}$$

Substitute $\dot{S}_h, \dot{I}_h, \dot{R}_h, \dot{S}_v, \dot{I}_v$ into Equation (3.98) gives us

$$\begin{aligned} \dot{V} = &\left(\frac{S_h - S_h^1}{S_h}\right)\left[\Lambda_h - \frac{\beta_h b I_v S_h}{K_h + m} - (\mu_h + \alpha)S_h + \omega R_h\right] \\ &+ \left(\frac{I_h - I_h^1}{I_h}\right)\left[\frac{\beta_h b I_v S_h}{K_h + m} - (\mu_h + \gamma + \delta)I_h\right] \\ &+ \left(\frac{R_h - R_h^1}{R_h}\right)[\gamma I_h - (\mu_h + \alpha)R_h] \\ &+ \left(\frac{S_v - S_v^1}{S_v}\right)\left[\Lambda_v - \frac{\beta_v b I_h S_v}{K_h + m} - (\mu_v + \alpha c)S_v\right] \\ &+ \left(\frac{I_v - I_v^1}{I_v}\right)\left[\frac{\beta_v b I_h S_v}{K_h + m} - (\mu_v + \alpha c)I_v\right], \end{aligned} \tag{3.99}$$

which can be expressed as

$$\begin{aligned}
\dot{V} = & \left(\frac{S_h - S_h^1}{S_h}\right)\left[\left(\frac{\beta_h b I_v^1 S_h^1}{K_h^1 + m} + (\mu_h + \alpha)S_h^1 - \omega R_h^1\right)\right] \\
& - \left(\frac{S_h - S_h^1}{S_h}\right)\left[\left(\frac{\beta_h b I_v S_h}{K_h + m} + (\mu_h + \alpha)S_h - \omega R_h\right)\right] \\
& + \left(\frac{I_h - I_h^1}{I_h}\right)\left[(\mu_h + \gamma + \delta)I_h^1 - (\mu_h + \gamma + \delta)I_h\right] \\
& + \left(\frac{R_h - R_h^1}{R_h}\right)\left[(\mu_h + \alpha)R_h - (\mu_h + \alpha)R_h^1\right] \\
& + \left(\frac{S_v - S_v^1}{S_v}\right)\left[\left(\frac{\beta_v b I_h^1 S_v^1}{K_h^1 + m} + (\mu_v + \alpha c)S_v^1\right)\right] \\
& - \left(\frac{S_v - S_v^1}{S_v}\right)\left[\left(\frac{\beta_v b I_h S_v}{K_h + m} - (\mu_v + \alpha c)S_v\right)\right] \\
& + \left(\frac{I_v - I_v^1}{I_v}\right)\left[(\mu_v + \alpha c)(I_v - I_v^1)\right].
\end{aligned} \tag{3.100}$$

Further simplification of Equation (3.100) is of the form

$$\begin{aligned}
\dot{V} = & \left(\frac{S_h - S_h^1}{S_h}\right)\left[S_v^1\left(\frac{\beta_h b I_v^1}{K_h^1 + m} + \mu_h + \alpha\right)\right] \\
& - \left(\frac{S_h - S_h^1}{S_h}\right)\left[\left(S_h\frac{\beta_h b I_v}{K_h + m} + \mu_h + \alpha\right) + \omega(R_h - R_h^1)\right] \\
& + \left(\frac{I_h - I_h^1}{I_h}\right)\left[(\mu_h + \gamma + \delta)(I_h^1 - I_h)\right] \\
& + \left(\frac{R_h - R_h^1}{R_h}\right)\left[(\mu_h + \alpha)(R_h - R_h)\right] \\
& + \left(\frac{S_v - S_v^1}{S_v}\right)\left[S_v^1\left(\frac{\beta_v b I_h^1}{K_h^1 + m} + (\mu_v + \alpha c)\right)\right] \\
& - \left(\frac{S_v - S_v^1}{S_v}\right)\left[S_v\left(\frac{\beta_v b I_h}{K_h + m} - (\mu_v + \alpha c)\right)\right] \\
& + \left(\frac{I_v - I_v^1}{I_v}\right)\left[(\mu_v + \alpha c)(I_v - I_v^1)\right].
\end{aligned} \tag{3.101}$$

For $\dot{V} = 0$ and $\dot{V} > 0$ in Equation (3.101) then it must obey the following condition respectively.

- The expression $S_h = S_h^1, I_h = I_h^1, R_h = R_h^1, S_v = S_v^1$ and $I_v = I_v^1$.
- The expression $I_v < I_v^1, I_h < I_h^1, S_h < S_h^1$ and $S_v < S_v^1$ whiles $R_h = R_h^1$.

Note that S_h^1, I_h^1, R_h^1, S_v^1, I_v^1, are the EE states. Hence, the EE is globally asymptomatically stable if the condition above is true. □

Parameter Estimation using the Least Square Method

The main tool for estimating the parameters of the model given in Equation (3.77), is an implementation of the *least-squares* method in Python. The data is the daily confirmed cases in Ghana, obtained from W.H.O., from 2004 to 2017.

Demographic estimates

Here, we pre-estimates some demographic parameters such as Λ_h and μ_h using informations obtained from (FactBook, 2019) and (World Health Organization, 2019b) . The total population of Ghana as of 2016 was given as 28,207,000 and the life expectancy at birth was given as 64 years (World Health Organization, 2019b).

Hence, the estimated daily natural death μ_h rate is given as

$$\mu_h = \frac{1}{64 \times 365} = 0.000042808219.$$

We assume that the *birth rate* = *death rate* = μ_h.

The carrying capacity for humans K_h, is given as

$$K_h = \frac{\Lambda_h}{\mu_h},$$

so the recruitment rate is given by

$$\Lambda_h = K_h \times \mu_h.$$

Therefore, the estimated daily recruitment rate for human is computed as

$$\Lambda_h = K_h \times \mu_h = 28000000 \times 0.000042808219. \approx 1200.$$

The life expectancy for mosquito to live is 30 days (World Health Organization, 2018). Hence, the estimated death rate for mosquito was given as

$$\mu_v = \frac{1}{30} = 0.03$$

The remaining parameters $\Lambda_v, b, \beta_h, \beta_v, \gamma, \alpha, \omega, \delta$ and m were obtained from fitting the model solution to the observed infection data.

Observed data sets and the curve fitting process

Here, data for confirmed cases from Ghana were obtained from (World Health Organization, 2019a). The data range from the year 2004 to the year 2017, as shown in Table 3.

Table 3: Data on Confirmed Cases of Malaria in Ghana

Year	Confirmed Cases
2004	475441
2005	655093
2006	472255
2007	476484
2008	1094483
2009	1104370
2010	1071637
2011	1041260
2012	3755166
2013	1639451
2014	3415912
2015	4319919
2016	4535167
2017	4348694

Source: World Health Organization (2019a)

The data points in Table 3 is graphically represented in Figure 2.

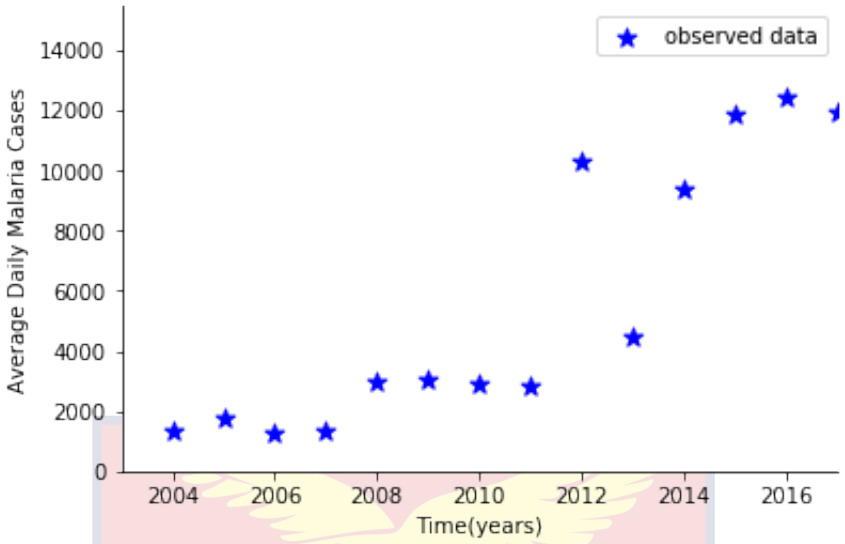

Figure 2: Observed infection cases from the World Health Organization.

From Figure 2, the blue star represents the data points. The *least-squares curve of best fit* is shown in Figure 3. The fit was obtained using an implementation of the *least-squares* method in Python.

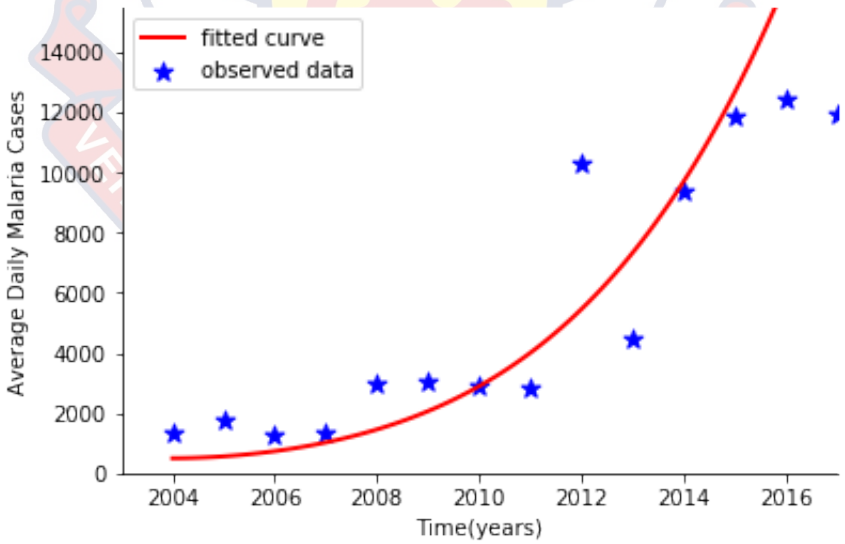

Figure 3: Model 3.27 fitted to the data in Table 1.

From Figure 3 the red solid coloured curve represents the *curve of best fit*. The corresponding estimated parameter obtained from the demographic point

of view were maintained. Graphically the best fit diagram is presented in Figure 3. The parameters attained from the best fit and demographic data are given in Table 4.

Table 4: Parameters obtained from the Best Fit and Demographics

Parameters	Units (day^{-1})	Values	Sources
Λ_h	day^{-1}	1200	Estimated from WHO
Λ_v	day^{-1}	13000	Estimated from data
β_h	day^{-1}	0.70000223	Estimated from data
β_v	day^{-1}	0.60000000	Estimated from data
μ_h	day^{-1}	$1/(64\times 365)$	WFB and WHO
μ_v	day^{-1}	0.03	Estimated from data
δ	day^{-1}	0.00900000	Estimated from data
γ	day^{-1}	$[0.05, 0.2]$	Control parameter
α	day^{-1}	$[0.05, 0.8]$	Control parameter
ω	day^{-1}	0.00100000	Estimated from data
b	day^{-1}	0.50223306	Estimated from data
c	day^{-1}	$[0, 1]$	Constant of proportionality
m	day^{-1}	5	Assumed

From Table 4 the estimated daily optimal parameters were obtained from the best fits.

Solution of the Model with Parameter Values in Table 4

With the parameters in Table (4) and the initial populations for the state variables given by $S_h(0) = 27500000$, $I_h(0) = 500000$, $R_h(0) = 0$, $S_v(0) = 138000000$, $I_v(0) = 2000000$, the plots of the graph for the human populations is presented in Figure 4.

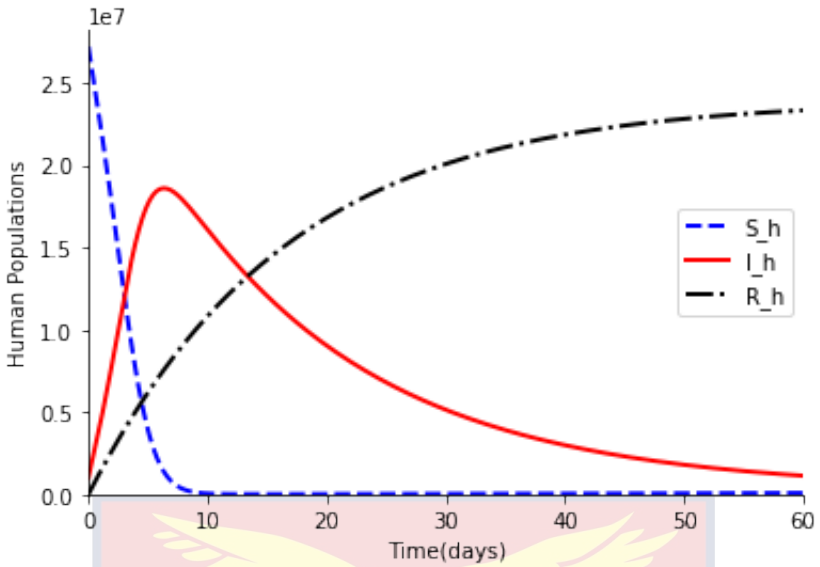

Figure 4: Plot of human populations.

From Figure 4, the infected human population I_h increases from its initial population to about 18 million, and then decreases steadily towards its endemic component. The susceptible human population S_h reduces from its initial population, while the recovered human population R_h, it increases, as expected. The corresponding vector populations are presented in Figure 5.

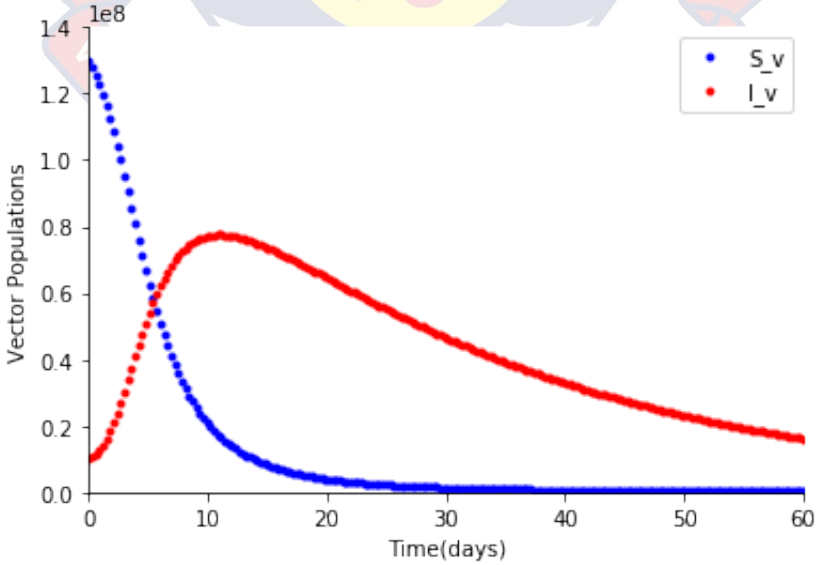

Figure 5: Plot of vector populations.

From Figure 5, we see that the susceptible vector population S_v decreases with time, while the infected vector population I_v increases initially and then decreases towards a non-zero component. The $\mathfrak{R}_o$, computed from the parameters in Table 1 gives

$$\mathfrak{R}_o = 1.0290549263859299 > 1.$$

This value of $\mathfrak{R}_o > 1$ explains why $I_h \neq 0$, and $I_v \neq 0$.

In the next section, we examine the effects on human and vector populations, with values of $c = 0.0, 0.1$ and $c = 0.2$. For each value of c, we use combination of increasing values of $\alpha = 0.2, 0.4, 0.60.8$, and $\gamma = 0.2, 0.4, 0.6, 0.8$.

Varying Prevention and Treatment Levels with $c = 0$

In this section, we investigate the effects on infection levels for both human and vector populations when $c = 0$, with a combination of different rates for treatment (γ) and prevention (α). The results are shown in Figure 6 for infected human populations, and in Figure 7 for infected vector populations.

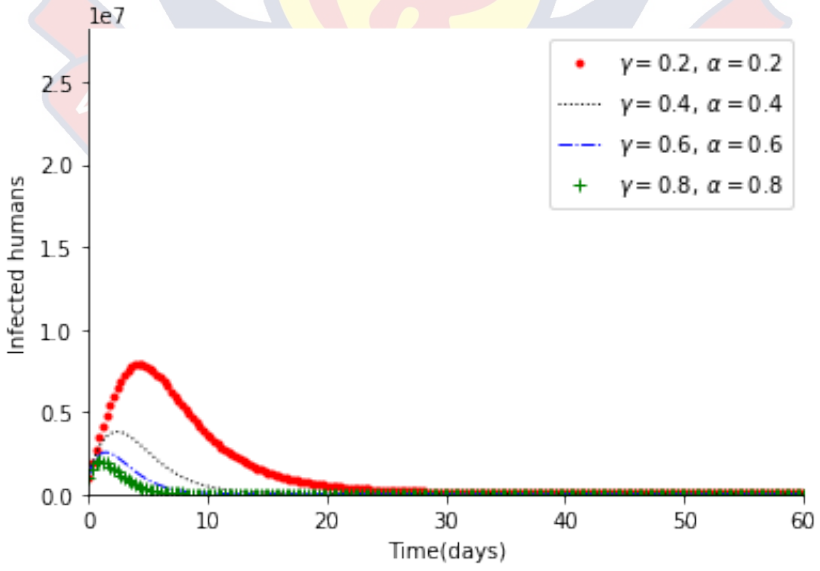

Figure 6: Infected human populations, with $c = 0$.

In Figure 6, we observe a reduction in the number of infected humans

with increasing prevention and treatment rates; but not much reduction in the infected vector population. The plots for the vector population is represented in Figure 7

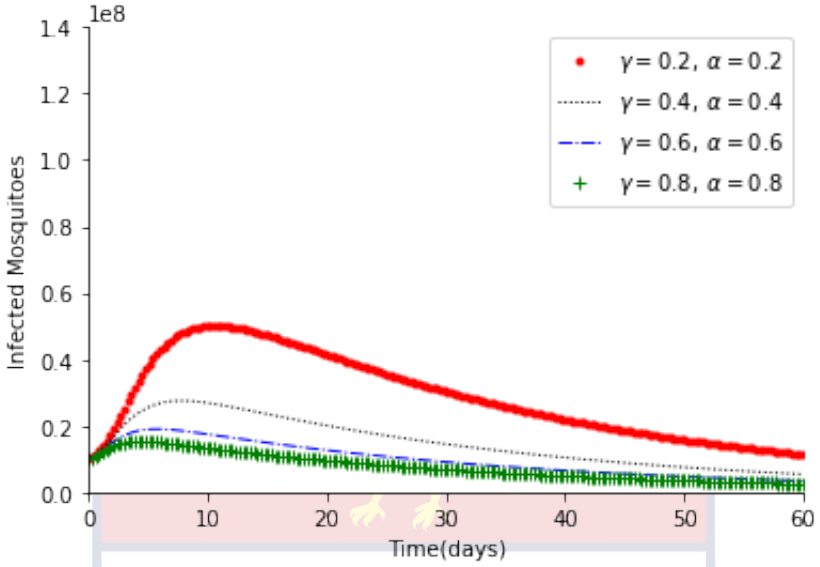

Figure 7: Infected vector populations, with $c = 0$.

In Figure 7, we observe a reduction in the number of infective human populations, but not much reduction in the infected vector population.

Varying Prevention and Treatment Levels with $c = 0.1$

The plots in Figure 8 show changes of the infected class for human populations when treatment (γ) and prevention (α) are varied at the same rates, with $c = 0.1$.

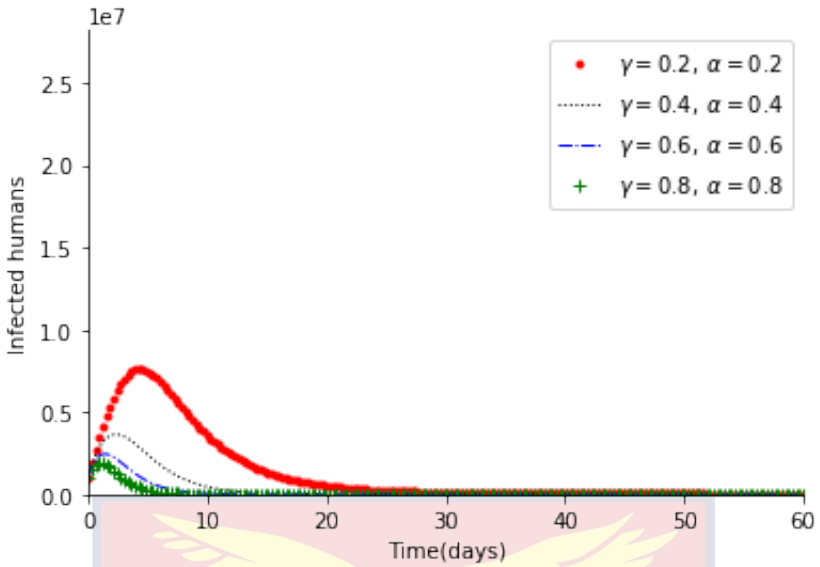

Figure 8: Infected human populations, with $c = 0.1$.

For Figure 8, we observed that increasing both prevention and treatment from 20% through to 80% decreases infected human population. The corresponding vector population is shown in Figure 9

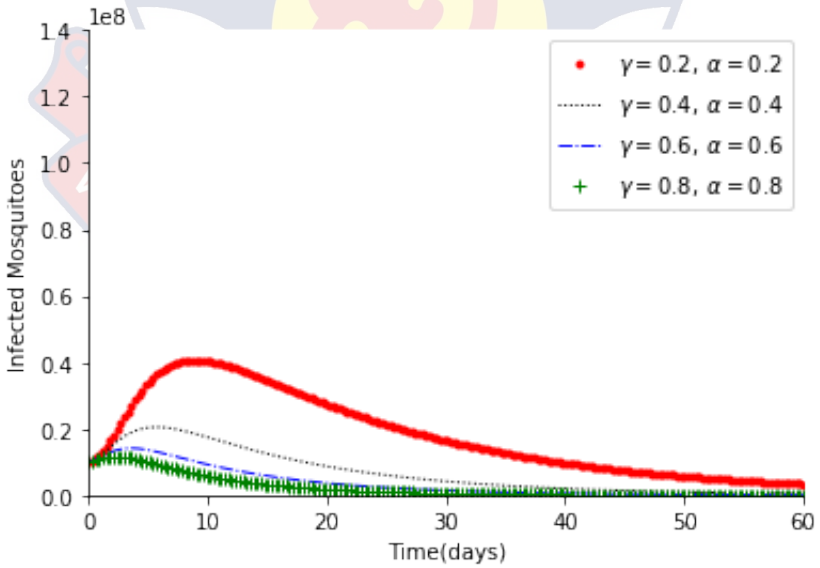

Figure 9: Infected vector populations, with $c = 0.1$.

Observation in Figure 9 shows that increasing both prevention and treatment from 20% through to 80% also decreases the infected vector population

rapidly.

Varying Prevention and Treatment Levels with $c = 0.20$

Varying treatment and prevention at the same rate, with $c = 0.20$, gives the results shown in Figures 10, and 11.

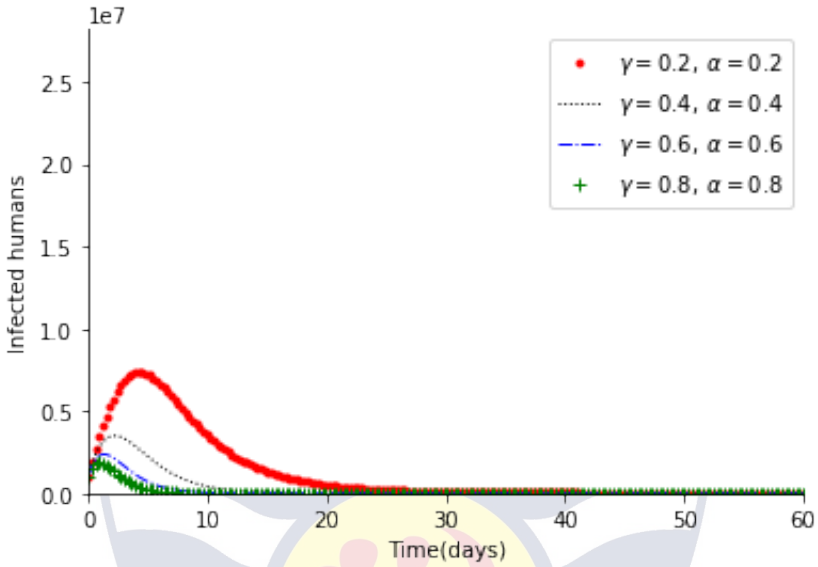

Figure 10: Infected human populations, with $c = 0.2$.

From Figure 10, it was observed that increasing both treatment and prevention from 20% through to 80% decreases infected human population to a disease free state much faster. The corresponding vector population is given in Figure 11.

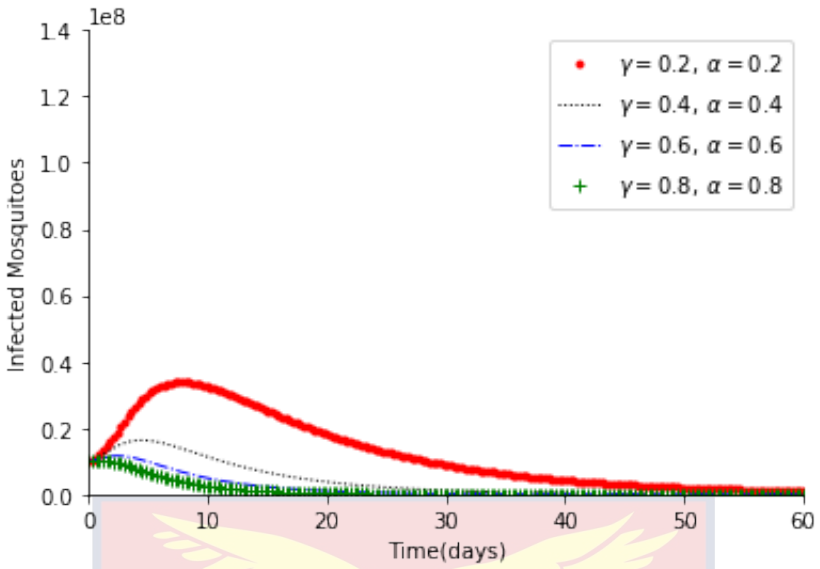

Figure 11: Infected vector populations, with $c = 0.2$.

From Figure 11, it was also observed that increasing both treatment and prevention from 20% through to 80% decreases effectively the infected vector population.

Observations

The following observation were made for effective treatment and prevention.

1. Increasing the constant c reduces the vector population.
2. With prevention effort at 0.2 and treatment effort at 0.2, the disease stays high and more people lives with the disease.
3. Increasing prevention and treatment rate to about 0.8 greatly reduces the prevalence of the disease.
4. The smaller the infected populations the less likelihood of transmission to a susceptible individual.

Remark 2

The cost of achieving the level of prevention and treatment needed to reduce both the incidence and prevalence has not been factored into the model. We will therefore, formulate and Optimal Control Problem, incorporating the cost of treatment and prevention.

Optimal Control Formulation

In this section, a strategy for effective control of malaria transmission as an optimal control problem will be formulated. The purpose of this formulation is to figure ou the best treatment and prevention strategy that minimizes the incidence and prevalence, while keeping the cost of prevention and treatment as low as possible. This will be done by first, defining an appropriate *cost functional*.

Then, Pontryagin's Maximum Principle will be used to determine an optimal combination of the *prevention* and *treatment* efforts needed to reduce the transmission. Numerical simulations will then be performed to determine the evolution of the disease, over a finite time horizon.

Formulating optimal control

Let $u_1(t)$ represent the rate of *prevention*, and $u_2(t)$, the rate at which infected individuals get treatment. Replacing α and γ in the model Equation (3.77) with the *controls* $u_1(t)$ and $u_2(t)$ respectively, gives

$$\begin{cases} \dot{S_h} = \Lambda_h - \dfrac{\beta_h b I_v S_h}{K_h + m} - \mu_h S_h - u_1(t) S_h + \omega R_h \\ \dot{I_h} = \dfrac{\beta_h b I_v S_h}{K_h + m} - \mu_h I_h - u_2(t) I_h - \delta I_h \\ \dot{R_h} = u_2(t) I_h - \mu_h R_h - \omega R_h + u_1(t) S_h \\ \dot{S_v} = \Lambda_v - \dfrac{\beta_v b I_h S_v}{K_h + m} - (\mu_v + u_1(t) c) S_v \\ \dot{I_v} = \dfrac{\beta_v b I_h S_v}{K_h + m} - (\mu_v + u_1(t) c) I_v, \end{cases} \tag{3.102}$$

The objective functional was defined as

$$J(u_1,u_2) = I_h(T) + I_v(T) + \frac{1}{2}\int_0^T \left(B_1u_1^2 + B_2u_2^2\right)\, dt, \tag{3.103}$$

with $u_1, u_2 \in \mathfrak{U}$, the set of admissible controls of Lebesgue measure defined as

$$\mathfrak{U} = \{u_1(t), u_2(t) \in L(0,T) | 0 \leq u_i \leq 1\}$$

The terms $\frac{1}{2}B_1u_1^2$ and $\frac{1}{2}B_2u_2^2$, $(B_1, B_2 > 0)$, gives the cost associated with implementing *prevention* and *treatment* respectively. The interval $[0,\ T]$ is the time horizon, and T is the *terminal time*. $I_h(T)$ and $I_v(T)$ represent the number of infected humans and vectors respectively, at the end of the terminal time. The maximum values for u_1 and u_2 are given by $u_{1\max}$ and $u_{2\max}$ respectively. The choice of the quadratic cost for the controls indicates that the cost of applying the controls is nonlinear.

The optimal control pair (u_1^*, u_2^*), is given by

$$J(u_1^*, u_2^*) = \min_{u_1,u_2}\{J(u_1,u_2) : (u_1,u_2) \in \mathfrak{U})\}. \tag{3.104}$$

Existence of the Optimal Control Pair

The necessarily condition for the existence of the optimal control pair proposed by (Flemming & Rishel, 1975) cited in (Panetta & Fister, 2000) and (Yusuf & Benyah, 2012) is established in this section. According to (Flemming & Rishel, 1975), the existence of an optimal control pair (u_1^*, u_2^*) is guaranteed by the compactness and the states, and the convexity of the problem. Therefore, the essential requirement cited in (Yusuf & Benyah, 2012) is given by

1. The set of all solutions to system (3.102) with corresponding admissible control functions in $\mathfrak{U}$ is non-empty.

2. The state system can be written as a linear function of the control variables $u_i's$, with coefficients depending on time and the state variables.

3. The integrand of $J(u_1,u_2)$ is convex on $\mathfrak{U}$ and is bounded above by

$$B_1\|(u_1,u_2)\|^2 - B_2$$

where, $B_1, B_2 > 0$.

First order necessary conditions

In this section, we establish conditions that will help us to determine the optimal control functions. Using Pontryagin's Maximum Principles the necessarily conditions is derived using the following theorem.

Theorem 8

Suppose (u_1^*, u_2^*) is a pair of optimal control, with corresponding optimal states, $S_h^*, I_h^*, R_h^*, S_v^*, I_v^*$ that minimizes the objective functional in Equation (3.103), then there is co-state variables $\lambda_1^*, \cdots, \lambda_5^*$ such that the following necessary conditions are satisfied:

1. State equations:

$$\frac{dS_h}{dt} = \frac{\partial H}{\partial \lambda_1}, \cdots, \frac{dI_v}{dt} = \frac{\partial H}{\partial \lambda_5},$$

where,

$$\begin{aligned}
\frac{dS_h}{dt} &= \Lambda_h - \frac{\beta_h b I_v S_h}{K_h + m} - \mu_h S_h - u_1(t) S_h + \omega R_h \\
\frac{dI_h}{dt} &= \frac{\beta_h b I_v S_h}{K_h + m} - \mu_h I_h - u_2(t) I_h - \delta I_h \\
\frac{dR_h}{dt} &= u_2(t) I_h - \mu_h R_h - \omega R_h + u_1(t) S_h \\
\frac{dS_v}{dt} &= \Lambda_v - \frac{\beta_v b I_h S_v}{K_h + m} - (\mu_v + u_1(t) c) S_v \\
\frac{dI_v}{dt} &= \frac{\beta_v b I_h S_v}{K_h + m} - I_v(\mu_v + u_1(t) c),
\end{aligned} \tag{3.105}$$

with

$$S_h(0) > 0,\ I_h(0) > 0,\ R_h(0) > 0,\ S_v(0) > 0,\ I_v(0) > 0$$

as the initial conditions.

2. Co-state equations:

$$\frac{d\lambda_1}{dt} = -\frac{\partial H}{\partial S_h}, \cdots, \frac{d\lambda_5}{dt} = -\frac{\partial H}{\partial I_v},$$

given by,

$$\begin{aligned}
\frac{d\lambda_1}{dt} &= -\left[\left(-\frac{\beta_h b I_v}{K_h+m} - \mu_h - u_1(t)\right)\lambda_1 + \frac{\beta_h b I_v \lambda_2}{K_h+m} + u_1(t)\lambda_3\right] \\
\frac{d\lambda_2}{dt} &= -\left[-\left(\mu_h + u_2(t) + \delta\right)\lambda_2 + u_2(t)\lambda_3 - \frac{\beta_v b S_v \lambda_4}{K_h+m} + \frac{\beta_v b S_v \lambda_5}{K_h+m}\right] \\
\frac{d\lambda_3}{dt} &= -\left[\omega\lambda_1 - (\omega+\mu_h)\lambda_3\right] \\
\frac{d\lambda_4}{dt} &= -\left[\left(-\frac{\beta_v b I_h}{K_h+m} - (\mu_v + u_1(t)c)\right)\lambda_4 + \frac{\beta_v b I_h \lambda_5}{K_h+m}\right] \\
\frac{d\lambda_5}{dt} &= -\left[-\frac{\beta_h b S_h \lambda_1}{K_h+m} + \frac{\beta_h b S_h \lambda_2}{K_h+m} - (\mu_v + u_1(t)c)\lambda_5\right],
\end{aligned} \tag{3.106}$$

with the transversality condition,

$$\lambda_1(T) = \lambda_3(T) = \lambda_4(T) = 0, \quad \text{and} \quad \lambda_2(T) = \lambda_5(T) = 1,$$

3. Optimality conditions,

$$\begin{aligned}
\frac{\partial H}{\partial u_1} &= B_1 u_1 + (\lambda_3 - \lambda_1)S_h - (\lambda_4 S_v + \lambda_5 I_v)c = 0 \\
\frac{\partial H}{\partial u_2} &= B_2 u_2 + (\lambda_3 - \lambda_2)I_h = 0.
\end{aligned} \tag{3.107}$$

where H is the Hamiltonian of the system given by

$$\begin{aligned}
H(S_h, I_h, R_h, S_v, I_v, u_1, u_2, \lambda_1, \lambda_2, \lambda_3, t) = {} & \frac{1}{2}\left(B_1 u_1^2 + B_2 u_2^2\right) \\
& + \lambda_1\left[\Lambda_h - \frac{\beta_h b I_v S_h}{K_h+m} - \mu_h S_h\right] \\
& - \lambda_1\left[u_1(t)S_h + \omega R_h\right] \\
& + \lambda_2\left[\frac{\beta_h b I_v S_h}{K_h+m} - \mu_h I_h - u_2(t)I_h - \delta I_h\right] \\
& + \lambda_3\left[u_2(t)I_h - \mu_h R_h - \omega R_h + u_1(t)S_h\right] \\
& + \lambda_4\left[\Lambda_v - \frac{\beta_v b I_h S_v}{K_h+m} - (\mu_v + u_1(t)c)S_v\right] \\
& + \lambda_5\left[\frac{\beta_v b I_h S_v}{K_h+m} - (\mu_v + u_1(t)c)I_v\right].
\end{aligned}$$

Solving Equations (3.107) and for u_1 and u_2 gives respectively, the optimal controls

$$\begin{aligned} u_1^* &= \frac{(\lambda_1 - \lambda_3)S_h^* + (\lambda_4 S_v^* + \lambda_5 I_v^*)c}{B_1} \\ u_2^* &= \frac{(\lambda_2 - \lambda_3)I_h^*}{B_2}. \end{aligned} \tag{3.108}$$

Since the controls are bounded, that is, $0 \leq u_1 \leq u_{1\max}$, $0 \leq u_2 \leq u_{2\max}$, the optimal controls in (3.108) are replaced by

$$\begin{aligned} u_1^* &= \min\left\{\max\left\{0, \frac{(\lambda_1 - \lambda_3)S_h^* + (\lambda_4 S_v^* + \lambda_5 I_v^*)c}{B_1}\right\}, u_{1\max}\right\} \\ u_2^* &= \min\left\{\max\left\{0, \frac{(\lambda_2 - \lambda_3)I_h^*}{B_2}\right\}, u_{2\max}\right\}. \end{aligned} \tag{3.109}$$

Numerical Solution of the Optimality System

The optimality system consists of the two-point boundary-value problem given in (3.105) and (3.106), and the optimality condition given in (3.107).

The constants B_1, and B_2 in the objective functional play a dual role. First, they are needed to balance the units in the cost functional; the controls u_1 and u_2 have values between 0 and 1, while the I_h and I_v have values in millions. Secondly, the values of B_1 and B_2 are chosen to indicate relative importance of *prevention* or *treatment* in the minimization of the infected populations.

We used the *forward-backward sweep method*, developed by (Lenhart S. and Workman J.T., 2007), based on the *Runge-Kutta method of order 4*, to solve the two-point boundary-value system.

The following procedure outlined, was implemented in *OCTAVE*, a *MATLAB*-like Public Domain Software.

1. Choose an initial guess for u_1^* and u_2^*.
2. Solve the state equations (3.105), with the given initial conditions *forward in time*,

3. Solve the costate equations (3.106), with the given transversality conditions *backward in time*,

4. Update the expression for u_1^* and u_2^* in (3.109) with the *new* values of the state and the cost ate variables

5. Repeat steps (2) - (4) until convergence criteria is met.

Chapter Summary

In this chapter we have developed mathematically a deterministic *S*IRS-SI *vector-host* model for the control and transmission of malaria, using *prevention* and *treatment* as the controls. We showed that the model has a unique (DFE) and EE points. The *next generation matrix* approach was used to derive the basic reproduction number, $\mathfrak{R}_0$, a threshold quantity that determines whether an infectious disease dies out or becomes endemic in a community. We showed that the DFE point is asymptotically stable globally and locally if $\mathfrak{R}_0 < 1$; and the EE point is globally and locally asymptotically stable if $\mathfrak{R}_0 > 1$. We used the least square method, implemented in Python, to derive the model parameters. Numerical simulations of the model were performed to determine the effects of prevention and treatment on the incidence and prevalence of the disease. We then, formulated an Optimal Control Problem, with *prevention* and *treatment* as controls. The existence of the optimal controls u_1^*, u_2^* was established. Pontryagin's Maximum Principle was applied to obtain the necessary conditions for optimality, and also characterize the optimal controls u_1^* and u_2^*. The *forward-backward sweep* method, implemented in OCTAVE, was used to solve numerically, the optimality system.

CHAPTER FOUR

RESULTS AND DISCUSSION

Introduction

This chapter discuss results of simulations obtained from using the optimal control functions $u_1^*(t)$ and $u_2^*(t)$. We recall that each of the control functions depends on its respective maximum, $0 \leq u_{1\max} \leq 1$, and $0 \leq u_{2\max} \leq 1$. We will discuss the results obtained from using various combinations of $u_{1\max}$ and $u_{2\max}$, with given values of the parameter c.

Simulations on the Effect of c on Infected Populations

We now investigate the effects of c, on infected vector and infected host population, with fixed values of maximum available controls: (i) $u_{1\max} = u_{2\max} = 0.2$; (ii) $u_{1\max} = u_{2\max} = 0.4$: and (iii) $u_{1\max} = u_{2\max} = 0.5$.

The effect of the parameter c, on vector populations are displayed in Figures 12, 13 and 14.

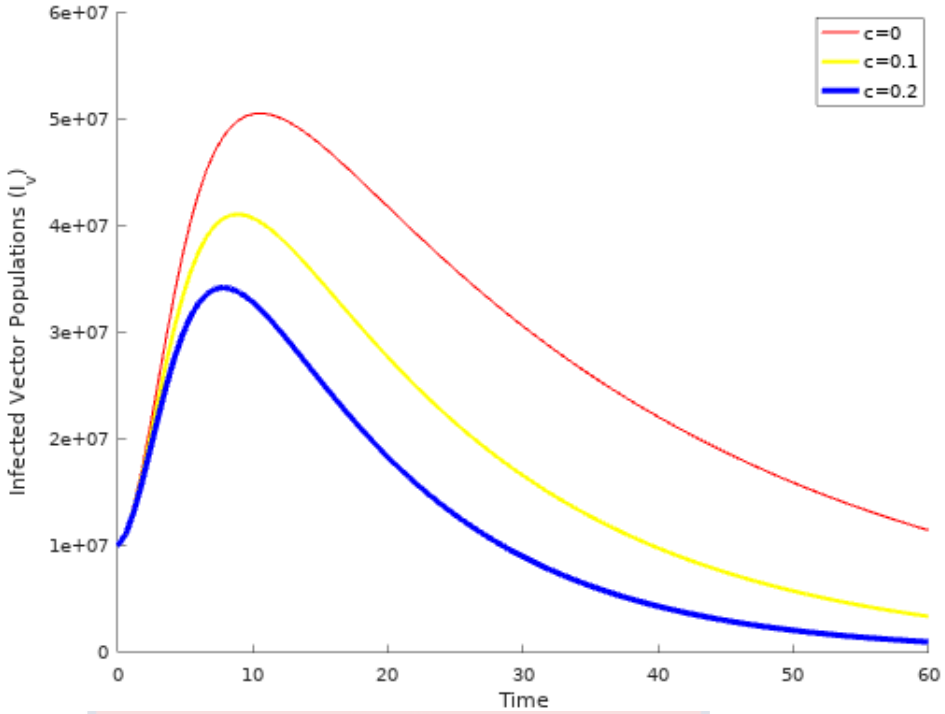

Figure 12: Infected vector populations with $u_{1\max} = u_{2\max} = 0.2$.

From Figure 12, increasing the constant ci, from 0.0 to 0.2 reduces the infected vector population from about 50×10^6 to about 30×10^6, when $u_{1\max} = u_{2\max} = 0.2$.

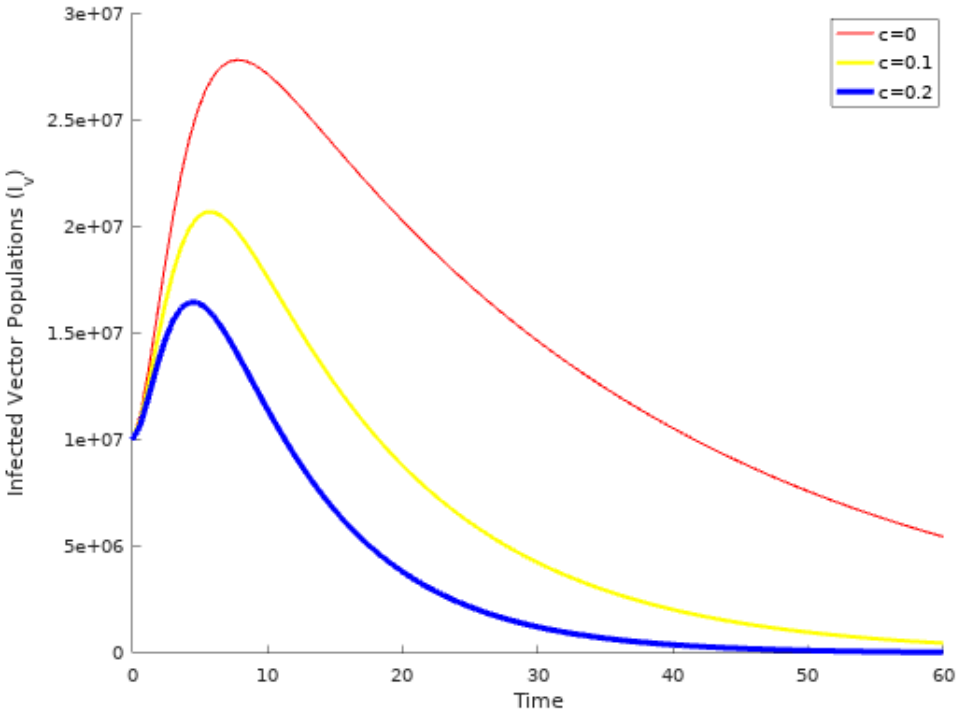

Figure 13: Infected vector populations with $u_{1\max} = u_{2\max} = 0.4$.

From Figure 13 the infected vector population reduces from about 26×10^6 to about 10×10^6, when $u_{1\max} = u_{2\max} = 0.4$.

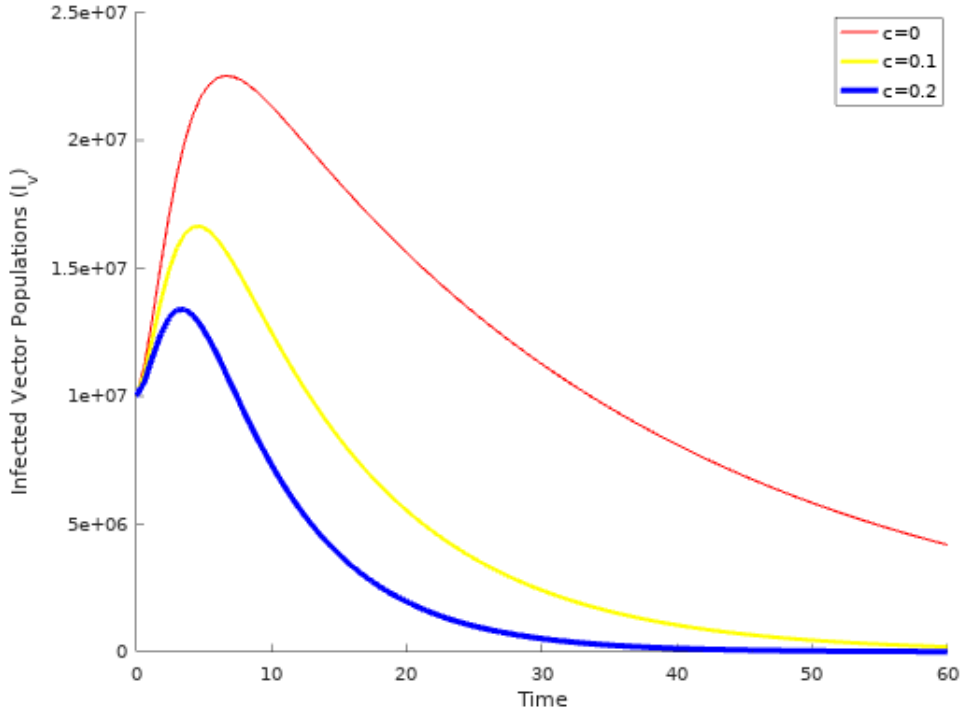

Figure 14: Infected vector populations with $u_{1\max} = u_{2\max} = 0.5$.

Also, from Figure 14 the infected vector population reduces from about 23×10^6 to about 8×10^6, when $u_{1\max} = u_{2\max} = 0.5$.

The effect of varying the parameter c, on human populations are displayed in Figures 15, 16 and 17.

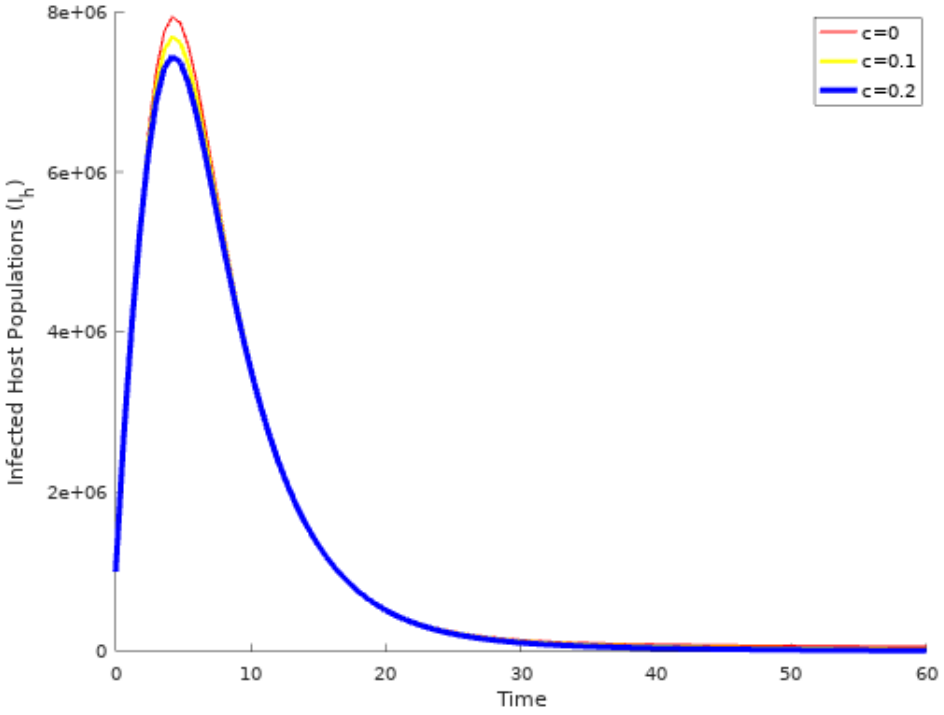

Figure 15: Infected human populations with $u_{1\max} = u_{2\max} = 0.2$.

Figure 15 shows that increasing the constant c from 0.0 to 0.2, reduces the infected human population from i about 8×10^6, to about 7.4×10^6, when $u_{1\max} = u_{2\max} = 0.2$.

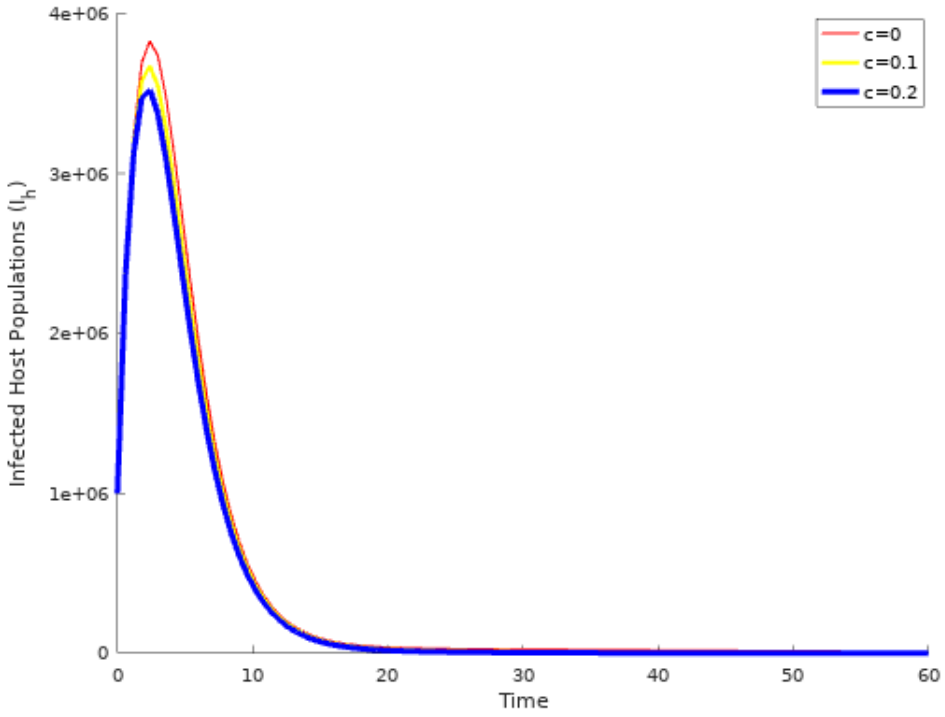

Figure 16: Infected human populations with $u_{1\max} = u_{2\max} = 0.4$.

Figure 16 shows that increasing the constant c from 0.0 to 0.2, reduces the infected human population from about 3.8×10^6, to 3.5×10^6, when $u_{1\max} = u_{2\max} = 0.4$.

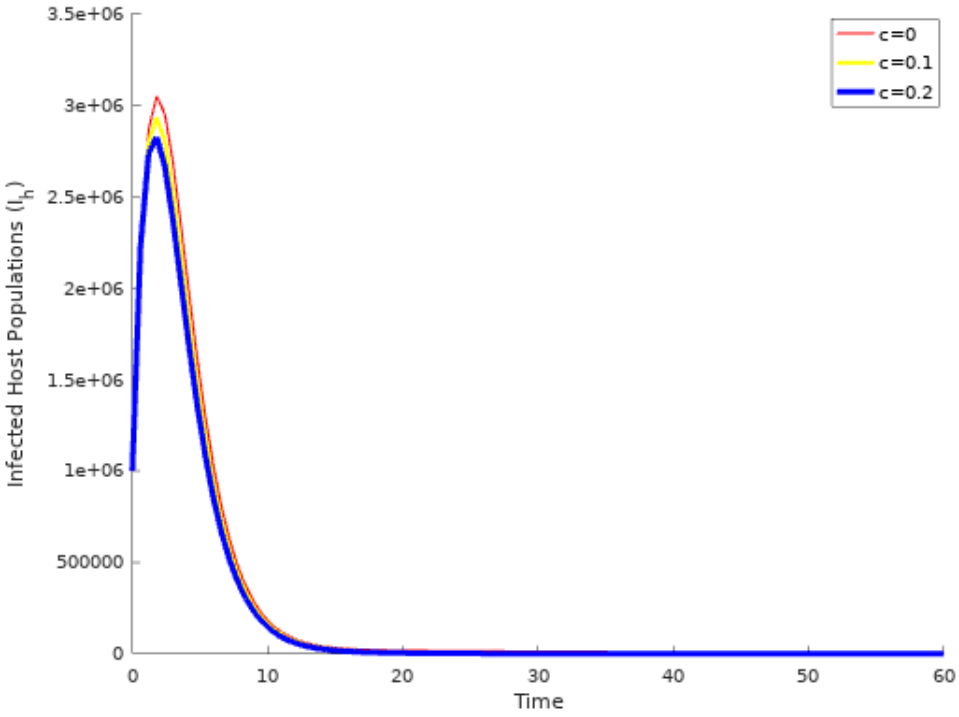

Figure 17: Infected human populations with $u_{1\max} = u_{2\max} = 0.5$.

Figure 17 shows that the infected human population reduces from about $u_{1\max} = u_{2\max} = 0.5$.

Simulations Using Various Combinations of $u_{1\max}, u_{2\max}$, with $c = 0$

The simulations consisted of using various combinations of the maximum available controls to investigate their effect on the infected human and vector populations. For example, the effect on the infected human populations, of choosing

$$u_{1\max} = \{0.2, 0.4, 0.6, 0.8\}, \quad u_{2\max} = \{0.2, 0.4, 0.6, 0.8\},$$

are shown in Figures 18, and 19.

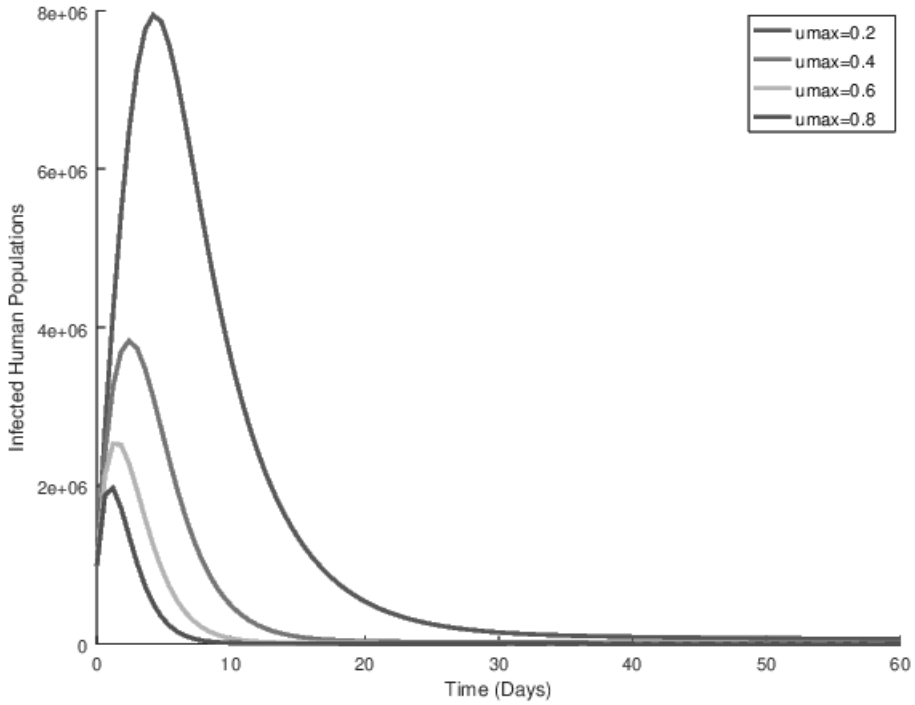

Figure 18: Infected human populations with $c = 0$.

Figure 18 shows that the infected human population reduces considerably, with increasing values of controls $u_{1\max}$ and $u_{2\max}$.

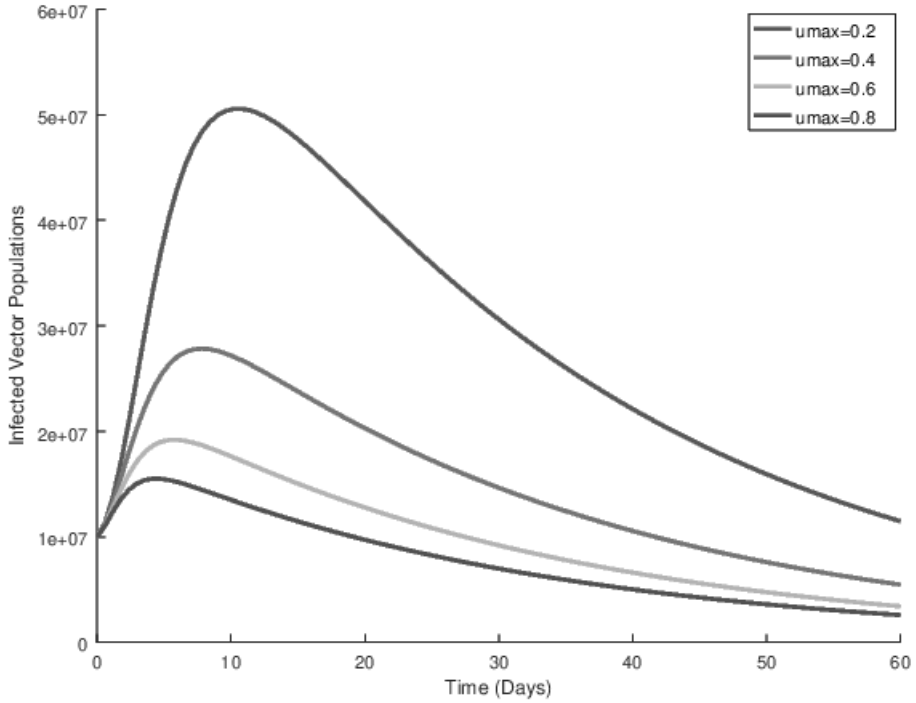

Figure 19: Infected vector populations with $c = 0$.

Once again, we see from Figure19 that the infected vector population reduces as the control maxima are increased.

Simulations with $u_{1\max} = 0.5, u_{2\max} = 0.2$

We now consider more realistic values for $u_{1\max}$ and $u_{2\max}$. Choosing $u_{1\max} = 0.5$, means that $u_1 S_h$ represents a maximum of 50% of the susceptible population. Choosing $u_{2\max} = 0.2$, corresponds a treatment period of about $1/0.2 = 5$ days.

The resulting host and vector populations are shown in Figures 20 and 21 respectively.

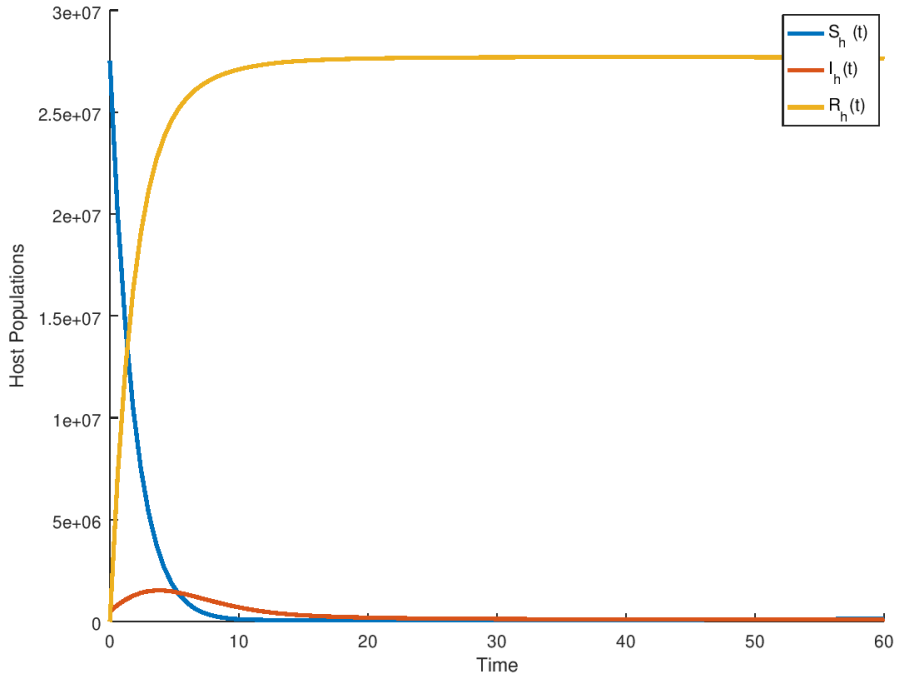

Figure 20: Human populations with $u_{1\max} = 0.5$, $u_{2\max} = 0.2$

From Figure 20, we see a considerable reduction in the infected Human population, with the above choices.

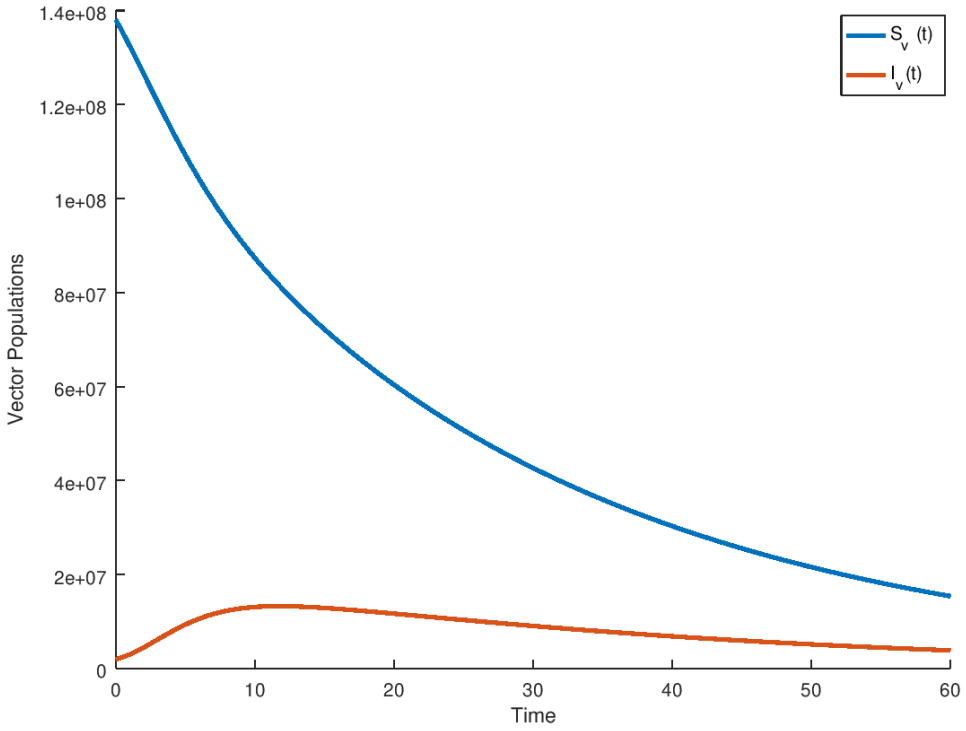

Figure 21: Vector populations with $u_{1\max} = 0.5$, $u_{2\max} = 0.2$.

Figure 21 shows a reduction in the infected vector population; however, the reduction is not as dramatic as in the human population.

The optimal control functions are displayed in Figures 22 and 23.

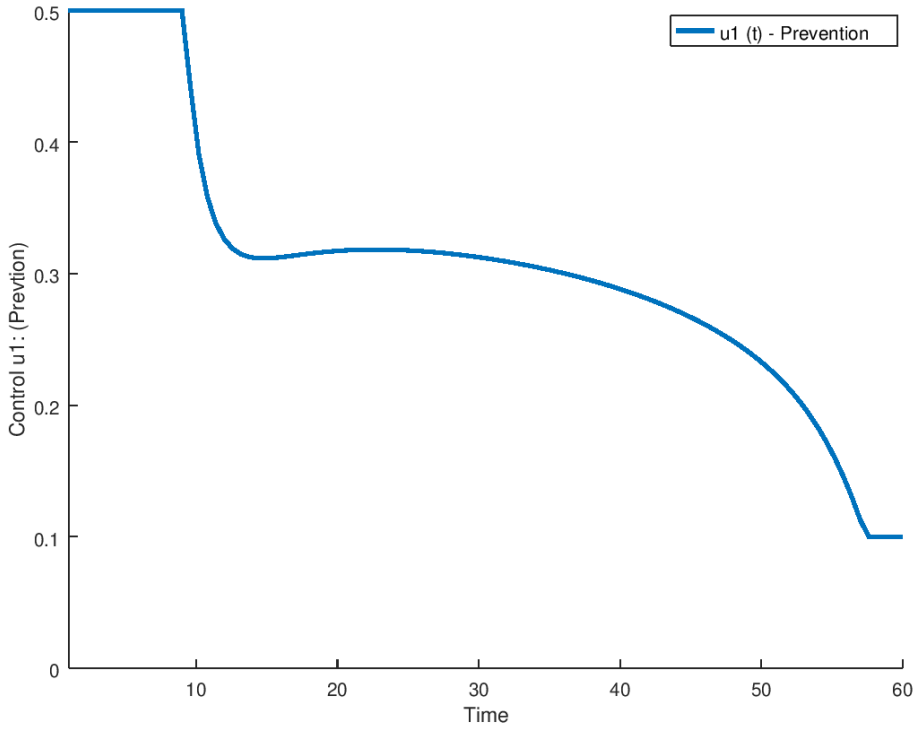

Figure 22: Optimal control function $u_1(t)$, with $u_{1\max} = 0.2$

Figure 22 shows that the control function $u_1^*(t)$ start from the maximum $u_{2\max} = 0.5$ and gradually decreases, as the susceptible population decreases.

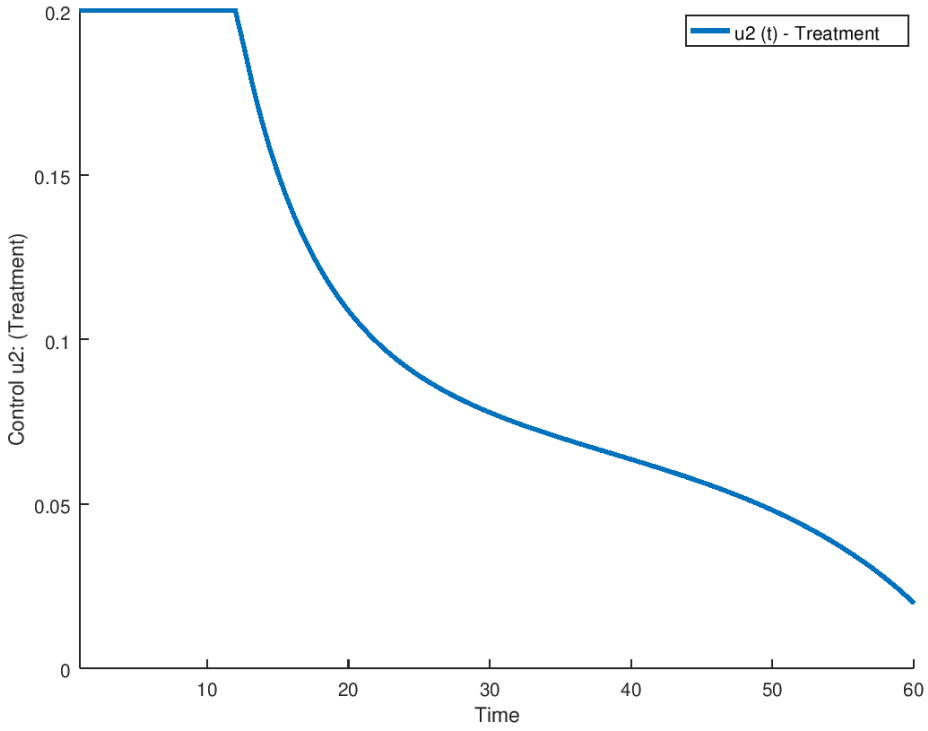

Figure 23: Optimal control functions $u_2(t)$, with $u_{2\max} = 0.2$.

Similarly, Figure 23 shows that the control function $u_2^*(t)$ start from the maximum $u_{2\max} = 0.2$ and gradually decreases, as the infected population decreases.

Simulations with Differential Treatment Regimes

Figure 24 displays the effect on the total infected human populations, when treatment is not readily available to everyone infected. This scenario happens for a variety of reasons including, lack of medical attention for for the infected individuals, as well as affordability for the cost of treatment. In Figure 24, the labels "p25Ih", "p50Ih" and "Ih" represents respectively, the total infected population, when 25%, 50% and the whole infected population receive treatment.

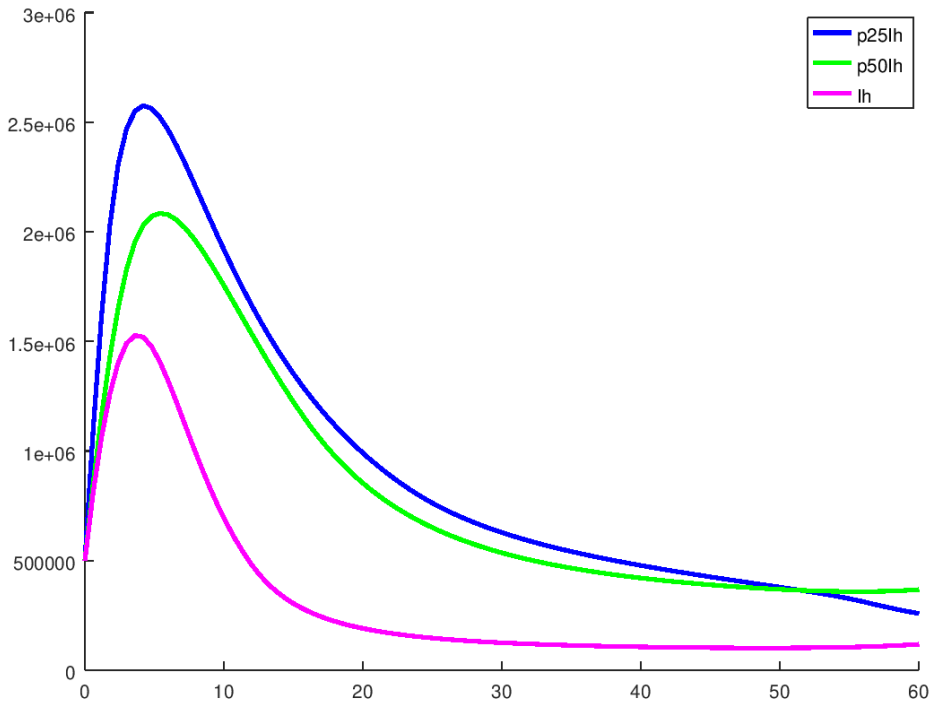

Figure 24: Infected human populations with differential treatment regimes.

Figure 24 shows that the total infected human populations decrease over time, when treatment is accessible to greater proportion of those infected.

Chapter Summary

This chapter presented results from simulation using combinations of different values of $u_{1\max}$ and $u_{2\max}$. Figures 12, 13 and 14 show that increasing the parameter c, with fixed maximum values both $u_{1\max}$ and $u_{2\max}$ drastically reduces the infected vector populations. From Figures 15, 16 and 17, we notice that increasing c, with fixed maximum values both $u_{1\max}$ and $u_{2\max}$ also reduces the infected human populations, but not as much as the vector populations. Figures 18 and 19 show that increasing $u_{1\max}$ and $u_{2\max}$ with a fixed value of c reduces both infected populations. In particular, choosing $u_{1\max} = 0.5$, means that $u_1 S_h$ represents a maximum of 50% of the susceptible population. Similarly,

choosing $u_{2\max} = 0.2$, corresponds a treatment period of $1/0.2 = 5$ days; so that $u_2 I_h$ represents treatment for all infected humans, (assuming an infectivity period of about 5 days). The plots in Figures 20 and 21; show a considerable reduction in both human and vector populations respectively. The control functions, *prevention* and *treatment* are shown in Figures 22 and 23 respectively. From the plots, we notice that each control function starts with the maximum available, and gradually reduces as the susceptible and infected population declines, respectively Figure 24 shows the effect of increasing accessibility of treatment for patients, to the overall reduction in infected human population.

Our simulations clearly show that,

1. increasing the parameter c reduces the vector population.
2. increasing $u_{1\max}$ reduces the susceptible human population,
3. ensuring the accessibility of treatment for diagnosed cases, reduces the overall infected human population,

We must remember that, every untreated case becomes a reservoir for mosquitoes to further transmit the disease.

CHAPTER FIVE

SUMMARY, CONCLUSIONS AND RECOMMENDATIONS

Overview

In this chapter, we present the summary, conclusion and recommendations, based on the findings of the thesis. Some recommendations based on the research is also presented.

Summary

In this thesis, we have developed mathematically a deterministic SIRS-SI *vector-host* model for the transference and control of malaria, using *prevention* and *treatment* as the controls. A unique and special feature of our model is that, it assumes that a proportion $c\alpha, (0 \leq c \leq 1)$ of the prevention efforts α, is directed to reduce the vector population. We established that the model has a unique *disease-free* (DFE) and *endemic* equilibrium points. The *next generation matrix* approach was used to derive the basic reproduction number, $\mathcal{R}_0$, a threshold quantity that determines whether an infectious disease dies out or becomes endemic in a community. We showed that the DFE point is asymptotically stable globally and locally if $\mathfrak{R}_0 < 1$; and the EE point is asymptotically stable globally and locally if $\mathfrak{R}_0 > 1$.

We used the *method of least-squares*, implemented in Python, to estimate the model parameters, using data on confirmed cases from 2004 to 2017, obtained from the W.H.O. Several simulations of the model, using various combination of prevention α, treatment γ, with increasing values of the parameter c, were performed to determine their effect on the incidence and prevalence of malaria in Ghana From the simulations we observed that, with prevention effort

at $\alpha = 0.5$, combined with treatment rate of $\gamma = 0.2$, and a value of the constant $c = 0.2$, reduced the vector population considerably. The smaller the infected vector populations, the less likelihood of a human becoming infected.

Obviously, increasing the values of α and γ will result in a more dramatic reduction in the vector populations, as well as infected human populations.

To determine an optimal combination of treatment and prevention, we formulated an optimal control problem, with an appropriate cost functional. Pontryagin's Maximum Principle was used to characterize the optimal controls functions, $u_1^*(t)$ and $u_2^*(t)$, and obtain the optimality system. We used the *forward-backward sweep method*, based on the *Runge-Kutta method of order 4*, to solve the optimality system.

Plots of solutions of the model, using different combinations of achievable rates for $u_{1\max}$, $u_{2\max}$ with values of the parameter c, were examined to determine the evolution of the disease in Ghana. In particular, we chose a fixed value of $u_{1\max} = 0.5$, so that $u_1 S_h$ represents about 50% prevention for the susceptible population. In addition, we chose $u_{2\max} = 0.2$, corresponding to an infectivity period of $1/0.2 = 5$ days; this is the average recovery period of infectivity, when there are no complications. We then examined the effect on the total infected human populations, over time, when treatment is available only to different proportion of the infected population. This scenario happens for a variety of reasons including, lack of medical facilities in some communities, as well as affordability for the cost of treatment.

Conclusions

The main objective for this research is the use of mathematical methods to investigate malaria transmission and the minimum cost effective approach to eradicate malaria. The key to successfully containing the spread of any infec-

tious disease, lies in prevention as well as effective treatment for those infected with the disease. The fewer the infected population, the smaller the transmission rate. Our simulations show that making treatment accessible to everyone infected, considerably reduces the overall transmission rate. Our simulations also show that if at least, 50% of the susceptible population follow proper prevention protocols, the reduction in transmission will be remarkable. In fact, proper prevention effort plays the role of a vaccine.

Recommendations

Our recommendations are based on the results of our simulation, together with the maxim that *the key to effectively controlling any infectious disease lies in rapid reduction in the susceptible population, through appropriate prevention efforts, plus a reduction in the infected population through effective treatment.*

Prevention methods that reduces vector populations include

1. Indoor spraying with residual insecticides. This is when the inside of house structures is prayed once or twice a year with insecticide spray. This activity should be regularly done since it reduces the proportion of the resident mosquitoes whether susceptible or infectious.
2. The use of insecticide treated mosquito nets (ITN). This reduces the contact rates.
3. Larval control. This activity may be implemented through environmental modification such as draining and killing or the use of larvacides.

Treatment strategies must include

1. The use of WHO-approved Anti-malarial medications including Coartem 80/480, Hydroxyl-Chloroquine and Fansidar (Sulfadoxine and Pyrimethamine).
2. Early diagnosis and effective treatment. Each untreated case becomes a

reservoir for mosquitoes to further transmit to other susceptibles.

In order to eradicate malaria, especially in the developing countries, where most people cannot afford the cost of treatment,

1. the medication must be free, or at least, highly subsidized in order to ensure a rapid reduction in the infected population.
2. the prevention methods listed above, must be enforced on all contiguous neighbourhoods.

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