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USING SEIR-SEI MATHEMATICAL MODEL TO ILLUSTRATE THE DYNAMICS OF MALARIA TRANSMISSION IN RWANDA

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Declaration

I, **HAKIZIMANA Emmanuel**, hereby confirm that, this research work entitled "*USING SEIR-SEI MATHEMATICAL MODEL TO ILLUSTRATE THE DYNAMICS OF MALARIA TRANSMISSION IN RWANDA*" is my own work and it was never being published elsewhere by any person to any University or another higher learning institution either for academic publication or award. It was conducted under the supervision of **Prof. NTAGANDA Jean Marie** from the University of Rwanda-College of Science and Technology.

Sign: ..... Date: .....

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Declaration by supervisor

I declare that this thesis was submitted under my supervision.

Sign: .....  ..... Date: **4th November 2020**

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Dedication

I dedicate the present work to the almighty God and relatives

Abstract

Malaria showcased to be a predominant root cause of mortality in many parts of the world in general and Africa in particular. As far as Rwanda is concerned, malaria is a serious issue in a number of regions and its incidence is found to be highly variable. This explains why researchers are still working on different intervention strategies meant to alleviate it. In this research, our work consisted in studying the dynamics of malaria transmission in Rwanda using the SEIR-SEI mathematical model. The formulation and analysis of the malaria transmission model dynamics is discussed. The impact of applying nonlinear forces of infection in the control form is also presented. The optimal control problems for malaria model found the control parameters which minimize the malaria contamination in Rwanda to prevent the prevalence of infection such as reducing of exposed and infected populations, then after, comes the mosquito population. The method of next generation matrix approach helped to get the basic reproduction number R_0. The presence of the endemic equilibrium was also identified under condition. The real data of malaria in Rwanda context were used to identify the parameters of our malaria model and the calculation were done using MATLAB. The numerical simulation showed that the number of exposed and infected people and mosquito population are decreased due to the control strategies. The findings show that the existence of an optimal control problem for the most effective intervention strategy in reduction of infected population and increasing the susceptible and recover human is the combination of two or more controls. Finally, this work found out that the transmission of malaria with special to Rwanda can be minimized by using the combination of controls like Insecticide Treated bed Nets (ITNs), Indoor Residual Spray (IRS) and Artemisinin based Combination Therapies (ACTs). This work points out some interesting directions for the future research such as mathematical model that focus many factors influencing the spread of malaria in Rwanda, mathematical model with considering four or more control measures strategies of malaria in Rwanda.

Keywords and phrases: Mathematical model, malaria, force of infection, reproduction number, fractional derivative, optimal control and numerical simulation.

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List of Acronyms

ACTs: Artemisinin based Combination Therapies

DDT: Dichloro Diphenyl Trichloroethane

DFE: Disease Free Equilibrium

DHS: Demographic and Health Survey

EE : Endemic Equilibrium

EEP: Endemic equilibrium point

FOCP: Fractional Optimal Control Problem

HMIS: Health Management Information System

IRS: Indoor Residual Spray

ITNs: Insecticide Treated bed Nets

LCFD: Left Caputo fractional derivatives

LLINs: Long Lasting Impregnated Nets

LLITNs:Long Lasting Insecticide Treated bed Nets

LRLFI:Left Riemann Liouville fractional integrals

MIS: Malaria Indicator Survey

PMI: Presidential Malaria Initiative

RCFD: Right Caputo fractional derivatives

RRLFI: Right Riemann Liouville fractional integrals

SEI: Susceptible Exposed Infected mosquitoes

SEIR: Susceptible Exposed Infected Recover human

US: United State

USAID: United States Agency for International Development

WHO: World Health Organization

Chapter 1

Introduction

This chapter includes the background, problem statement and objectives of the thesis; it includes also the motivation, scope and the context of the study and the structure of the thesis.

1.1 Background

Malaria is a contagious disease caused by Plasmodium. The transmission of disease is started when there is a bite of infectious female mosquito to the susceptible humans or susceptible mosquito to the infected human [26]. In the world, the disease is widespread in the most countries. [34].

The dynamics of malaria disease can be started from humans or mosquitoes. Firstly, the scenario starts by a bite of female mosquito to susceptible human and that infected mosquito is injecting her saliva in the human body. In the blood of the human individual the sporozoite will reproduce itself and form large quantities of the trophozoite the blood cells. The red blood cells is used by parasite as an incubator where the parasite reproduces into the merozoite form in a large quantity. This process is repeated more times until the merozoite stage of the parasite produces the gametocyte form of the parasite [2].

Secondly, an uninfected female mosquito gets infected by biting an infected human where its blood meal is infected. Then, when the sporozoites attack to the salivary glands of the newly infected mosquito, it becomes easy to transmit the germs to uninfected humans [28]. Plasmodium is classified in four types: Plasmodium malaria, falciparum,

vivax, oval and knowlesi. In Africa, plasmodium falciparum is the first one which causes the big number of mortality rate induced by the disease [2]. In the human body, the symptoms of malaria appear during the 10th to 14th day after a bite from an infectious mosquito [51].

In 2015, the World Health Organization (WHO) reported 214 million cases of malaria and about 438 thousands resulted into deaths [24]. In fact, the disease treatment cost is heavy to poor countries. On the other hand, the developed countries have reduced the disease owing to their treatment capacity [35]. Even if malaria has been investigated for many years, it is still one of the major public health problem in the most countries where in widespread regions, non-immune adults, pregnant women and children under five years old have a big number of malaria death [26].

In Rwanda, malaria is considered as a seasonal disease and environment related [11]. The children who are aged less than 5 years are easily attacked by malaria due to their lack of acquired immunity. Within six months of birth, the new born is protected by antibodies acquired from her mother in pregnancy but towards the end of this period, the baby starts getting his or her own immunity as the maternal immunity disappears [22]. In 2017, the Eastern and Southern Provinces were considered as the regions where malaria was most predominant. In these provinces, there are five districts, namely Bugesera, Gisagara, Gatsibo, Kirehe and Nyagatare, where malaria infection risk is highest [47].

In fact, the rate of malaria transmission increases during rainy seasons. Indeed, climate, altitude, population movement, population density, etc are the factors of malaria transmission. In a survey done in 2005, malaria was considered as first cause of morbidity in young people under five years but in 2008, malaria went to the third cause of morbidity, and by 2012 it had gone to the fourth place [47].

Between 2005 and 2011, Rwanda Health Management Information System (HMIS) reported that overall malaria incidence reduced by 86 %. However, between 2012 to 2016, malaria incidence increased every year in Rwanda from 4.8% in 2012 to 40.3% in 2016. As malaria increased, an increase in malaria-caused deaths was also reported. For instance, there occurred 419 deaths in 2013 and 715 in 2016. Among the children under five years of age, Malaria Indicator Survey (MIS) in 2017 reported that malaria increased with incidence rising to 7.2 % comparing to 2.2% reported by Demographic and Health

Survey (DHS) in 2014 to 2015 [47].

Thus, malaria is still one of the biggest health issues facing the society today and researchers should play their role to handle it in Rwanda [11]. Epidemiologists and others are still to put more effort in understanding and controlling the dynamics of malaria [26]. Some of mathematicians have developed an important tool of mathematical models of malaria to understand the interaction between the human and mosquito populations and malaria control until its eradication [25]. Mathematical models form an essential tool to find the impacts of malaria control strategies and the most effective strategies are also specified [5].

In its effort to fight malaria, the Government of Rwanda got, in 2005, a donation from the US-Presidential Malaria Initiative (PMI) to minimize malaria deaths by an integrated application of ITNs, prompt use of Artemisinin based Combination Therapies (ACTs) and IRS with insecticides. These involvements played a role in the reduction of malaria transmission [12].

In 2019, the goal of Rwanda Government was to further reduce the number of deaths and illness due to malaria, towards the goal of elimination in extend period [47]. The current aim of Rwanda National Malaria control strategic plan is to improve the healthiness of Rwandans by trying to eliminate malaria and thus contribute to the global national effort of poverty reduction. The purpose is to increase the interventions in order to get the malaria preelimination phase and near zero deaths in Rwanda by 2018 [21].

1.2 Motivation of the Study

This study will be able to evaluate the current intervention strategies in controlling malaria in Rwanda. The results from the study will be a model with special highlighting on Rwanda for malaria infection. Meanwhile no previous SEIR-SEI mathematical study has been carried out in Rwanda on malaria, the results on the effects of prevention and control measures will also help the policy makers, the stakeholders for malaria elimination and National Malaria Control Programs in intervention of malaria eradication to know the level of reduction. Specifically, the results from this thesis will guide us on how malaria can be eradicated in Rwanda. The results of this study will contribute on the further

research to the current literature on malaria transmission dynamics, optimal control in analysis of malaria intervention strategies. Students and academics wishing to carry out research in this area may use findings of this study for their further research.

1.3 Problem statement

The malaria is a controllable disease. Although the disease has been studied for many years, it is still a big health problem. In Rwanda, the mathematical models of malaria dynamics are not frequently used, thus some people are still at risk of malaria even if there are many measures that have been taken to control it such as using IRS, ITNs and others. The challenge facing Rwanda is to get reliable information through mathematical models about the factors which can be taken manipulated in order to control malaria infection until near zero case.

In this study, mathematical model for host and vector interactions with malaria control strategies was used to study the control of malaria transmission and eventually eliminating malaria infection. It has been used in determination of effectiveness and optimal allocation of different type of interventions against malaria. Thus, in the prevention of malaria in Rwanda, the mathematical model including control variables was investigated for minimizing the rate of malaria transmission by applying three control variables as follow;

$$\begin{cases} \frac{dS_h}{dt} = \lambda_h - (1-v_1)b\beta_h S_h S_{N_h} I_m - \mu_h S_h + \gamma_{k\tau} R_h, \\ \frac{dE_h}{dt} = (1-v_1)b\beta_h S_h S_{N_h} I_m - (\mu_h + \eta_h) E_h, \\ \frac{dI_h}{dt} = \eta_h E_h - (\mu_h + \delta_h + \rho_h + \phi_3 v_3) I_h, \\ \frac{dR_h}{dt} = (\rho_h + \phi_3 v_3) I_h - (\mu_h + \gamma_{k\tau}) R_h, \\ \frac{dS_m}{dt} = \lambda_m - (1-v_1)b\beta_m S_m S_{N_m} I_h - (\mu_m + \phi_1 v_1 + \phi_2 v_2) S_m, \\ \frac{dE_m}{dt} = (1-v_1)b\beta_m S_m S_{N_m} I_h - (\mu_m + \eta_m + \phi_1 v_1 + \phi_2 v_2) E_m \\ \frac{dI_m}{dt} = \eta_m E_m - (\mu_m + \phi_1 v_1 + \phi_2 v_2) I_m. \end{cases} , \quad (1.1)$$

where S_h is Susceptible humans, E_h is Exposed humans, I_h is Infectious humans, and R_h is Recovered humans, $S_m$is Susceptible mosquitoes, E_m is Exposed mosquitoes and I_m Infectious mosquitoes then those chosen controls are the control $v_1(t)$ which justify the use of ITNs and it reduces the contact of human and mosquito population on the bed, the control $v_2(t)$ which represent the use of IRS and it kills the mosquitoes in the house then

the control $v_3(t)$ which qualify the use of ACTs and it increases the number of recover human population.

1.4 Objectives of thesis

This study has a general objective and a number of specific objectives referring to the problem statement above.

1.4.1 General objective

Generally, the aim of this work is to study the malaria transmission using SEIR-SEI mathematical model including optimal control in Rwanda. Furthermore, the control measures are used to the mathematical model to analyze their effect on the dynamics of malaria in Rwanda.

1.4.2 Specific objectives

The following are the specific objectives for our research.

- To suggest a mathematical model that includes the forces of infection which is not linear in the form of controls in the human and mosquito populations.
- Find optimal control strategies that capable to minimize the spreading of malaria transmission in Rwanda.
- Provide research-drawn advice to policy makers about effective methods meant to decrease the spread of malaria in Rwanda.

1.5 Methodology

In this study, we find the data to estimate the model parameters; we set optimal control problem to study how the malaria dynamics can be controlled until near zero and we find the solution of the Controlled Malaria Model using Fractional Derivatives.

- The data have helped to estimate the parameter values of the malaria model. We use the secondary data from World report for Rwanda.

- The optimal control problem has been helped to analyze the efforts on preventing malaria.
- The chosen set of three control variables is the use of ITNs, the use of IRS and the use of ACTs and method of Caputo fractional derivatives has been used to solve the optimal control problem.
- Using MATLAB we have presented numerical tests without control measures and have then analyzed the effect of control strategies applied on the malaria transmission model dynamics in Rwanda

1.6 Scope and limitation of the study

Using the SEIR-SEI mathematical model and data collected in Rwanda and basing on the parameters of model, this work focuses only on the malaria transmission model dynamics in Rwandans and studies the ways of controlling it. This study deals with the dynamics of malaria transmission without basing on seasons.

1.7 Structure of thesis

The structure of the thesis is described hereafter. Chapter one consists in the introduction of the study. Chapter two focuses on the description of some mathematical models to illustrate the malaria transmission dynamics. Chapter three covers the setting of SEIR-SEI model and the solution of an optimal control problem. Chapter four presents the simulations of malaria model numerically with graphical illustrations to show the dynamical behavior of the results and their discussion. Conclusions and recommendations of the study are finally drawn in Chapter five.

Chapter 2

Description, analysis of some mathematical models and optimal control of malaria

This chapter presents the literature on malaria history, some mathematical models developed on malaria and some theoretical aspects related to quantitative study of epidemiological models and their control, that is, reproduction number and optimal control.

2.1 History of malaria transmission

The meaning of malaria originated from the middle-age Italian: mala-aria meaning bad air. Even it had no longer of persistence due to the advanced controls, the malaria once appeared in most of North America and Europe [14]. In 2018, the World Malaria Report showed that the malaria cases were 219 million in 87 countries. The most malaria cases in Africa were in the following countries: Mali, Burkina Faso, Niger, Cameroon, Uganda, Mozambique, Ghana, Nigeria, Democratic Republic of Congo and Tanzania [49]. In Rwanda, the districts of Eastern and Southern Provinces such as Bugesera, Gisagara, Gatsibo, Kirehe, and Nyagatare are considered as the regions where malaria is predominant [47].

In 1880, the parasites were found in the blood of malaria patients by Alphonse Laveran. In the 1890, Patrick Manson said that mosquitoes helped in transmission of malaria.

Ronald Ross, in 1897, showed that the avian malaria parasite Plasmodium relictum is transmitted by culicine mosquitoes and recommended that mosquitoes help in the transmission of human malaria parasites. He worked again on malaria control efforts in Panama, Egypt, Greece and Mauritius [14].

Peru is the country where the effort treatment of malaria started from the bark of Cinchona tree; that tree contains quinine. Quinine was the most used in the medication of malaria up to 1920 when other medications started emerging. In 1940, the results showed that quinine was replaced by chloroquine in the treatment until the density of malaria has been changed in South-East Asia so South America. Tu Youyou et al. in the 1970s, mentioned that for the treatment of Plasmodium falciparum malaria; the artemisinins from plant Artemisia annua are better to use. In killing mosquitoes; the Dichloro Diphenyl Trichloroethane (DDT) used for IRS [14].

In 2016, James Kant KAMUHANDA found that a malaria in Rwanda is one of the major health issues for researchers and Government [11]. He argued that malaria is a seasonal disease and environmental-related where Eastern province is more epidemic-prone than other provinces of Rwanda. Rwanda had adopted a strategy to realize malaria pre-eradication phase in 2017, with an ambitious target of reaching near zero deaths due to malaria [40]. In 2015, Domina Asingizwe et al described the main practices that can be used in eliminating malaria and they described the strategies helped to stop malaria in the population [7]. Rwanda took measures to control malaria, some of them are the following:

- Implement IRS in the districts which have the most case of malaria and the others.
- Ensure sustained universal coverage with LLINs for one net for two people.
- Put more effort in elimination of malaria.
- Collaborate with private partners in malaria prevention and control interventions.
- Emphasize malaria prevention and control in vulnerable.

2.2 Some mathematical models applied on malaria

In 1911, the malaria study using mathematical modeling was started by Ronald Ross. He found that within the transmission of malaria dynamics, the malaria can be eliminated due to the reduction of the mosquito population [39]. In 1957, Macdonald updated Ross's concept and used it to global malaria eradication programme. He said that the elimination of malaria; the effect of minimizing the number of mosquitoes was not enough in region where the rate of transmission is highest [18]. Ross model which described the malaria transmission is the following:

$$\begin{cases} \frac{dI_h}{dt} = abmI_m(1 - I_h) - \alpha I_h \\ \frac{dI_m}{dt} = acI_h(1 - I_m) - \beta I_m. \end{cases} \tag{2.1}$$

The model equations (2.1), I_h is infectious humans, I_m is infectious mosquitoes, a, b, c, m, α and β are the parameters where a be the rate of mosquito bites a human, b be a ratio of bites to the infectious human produced, c indicates a rate of bites that one susceptible mosquito becomes infected, m indicates the proportion of female mosquitoes to that of humans, α denotes human recovery rate of and mosquito mortality rate is written as β [14].

In 2017, Mojeeb AL et al. used SEIR model to investigate the reproduction number and the stability analysis of Disease Free Equilibrium (DFE)and Endemic Equilibrium (EE) by using LaSalle's invariance principle of Lyapunov function, and they found that the malaria can be well controlled by reduction of transmission rate among human and mosquito by using malaria drugs, insecticides and ITNs [26].

In 2018, Mojeeb AL et al., using SEIR-SEI epidemic model; they found that malaria can be transmitted among human and mosquito, they developed what they had done in their model in 2017 by including the optimal control strategies like the use of ITNs and treated infected individual. They found that an increasing of the ratio of antibodies has a major effect in the reduction of malaria transmission [24].

Mojeeb AL et al., in 2018, proposed another SEIR-SEI malaria model including optimal controls [23]. The suggested controls are using to prevent the infection within the country [23]. They found that the prevention using Long Lasting Impregnated Nets (LLITNs) and effort treatment are the best in minimizing the number of exposed and

infected individuals and the recovered individuals are also increased [23].

In 2019, Mojeeb AL et al. updated their SEIR-SEI model done in 2018 by including other optimal controls which are the insecticide spray on the breeds grounds, treated infected individual and ITNs [25]. By using these three optimal controls, they found that malaria will be reduced in coming years [25].

In 2016, Okello Gabriel Otieno [30], used four optimal control strategies which are ITNs, effort treatment, IRS and Intermittent Preventive Treatment for Pregnant women. He found that malaria control in endemic areas, the effective of IRS use and effort treatment is best to the society in control of malaria. In the epidemic prone areas, effort treatment and IRS reduce the infectious individuals and mosquito population. For seasonal areas, ITNs and effort treatment are enough to scale back infectious individuals and mosquito population [30].

The diagram below is a SEIR model description of 2017 by Mojeeb AL et al.

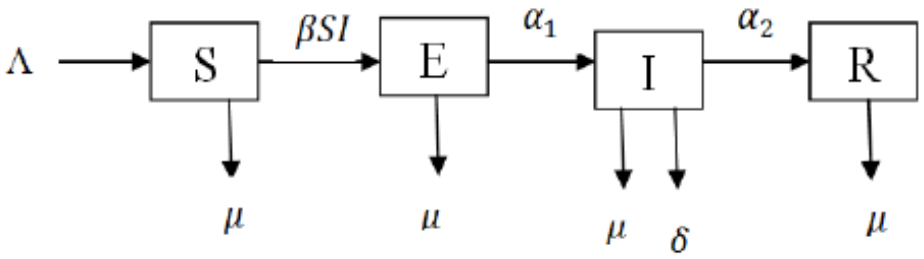

Figure 2.1: Diagram of Malaria transmission by Mojeeb AL.

Where S is Susceptible Humans, E indicates Exposed Humans, I denotes Infectious Humans and R is Removed Humans. Mojeeb AL described the malaria transmission model by using the system of ordinary differential equation as follow:

$$\begin{cases} \frac{dS}{dt} = \wedge - \beta SI - \mu S \\ \frac{dE}{dt} = \beta SI - (\alpha_1 + \mu)E \\ \frac{dI}{dt} = \alpha_1 E - (\alpha_2 + \mu + \delta)I \\ \frac{dR}{dt} = \alpha_2 I - \mu R \end{cases} \tag{2.2}$$

With $S(0) > 0, E(0) \geq 0, I(0) \geq 0$ and $R(0) \geq 0$ are the initial state variables. The Table

2.1 shows the description of parameters.

Table 2.1: Description of parameters from (2.2)

Name of parameter	**Description of parameter**
$\wedge$	Susceptible immigration rates .
β	The rate that Susceptible human become exposed human
α_1	Developing rate from exposed to infectious
α_2	Human recover rate
μ	Human natural death rate
δ	Death rate due to malaria

With the positive invariant in domain of the human population being given by

$$\perp = \left\{(S, E, I, R) : S + E + I + R \leq \frac{\wedge}{\mu}, S > 0, E \geq 0, I \geq 0, R \geq 0\right\}.$$

2.3 Determination of reproduction number

In 2007, C.E.G. Smith et al. defined a basic reproduction number as the number of secondary infections obtained from one primary infection into another susceptible population [43]. Mathematically, the new infections generated by a given infectious individual in a population at DFE is the basic reproduction number [3]. In 2015, E.A. Bakare and C.R. Nwozo used a mathematical model which demonstrated that when the basic reproduction number is more than one, then EE is globally asymptotically stable [4]. The basic reproductive number, R_0 is a key in epidemiological quantities as it provides a foundation for control and elimination [13]. The disease will continue in a population when R_0 is greater than one but if it is less than one, the disease will disappear in the population [20].

Determination of R_0 is done in some common methods such as the survival function method, the method of next generation matrix, existence of an endemic equilibrium point, final size equation, constant term of the characteristic polynomial, ... Most of them yield different values of R_0 for the same model, and many methods produce different values of R_0 based on what the modeler considers to be appropriate [20]. The method of next generation matrix is useful in determination of the basic reproduction number. In 2018,

Antoine considered the Figure 2.2 [3], to explain the notion of basic reproduction number.

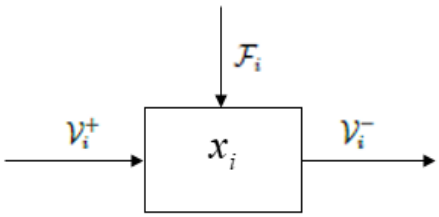

Figure 2.2: The variable coming in and out related to compartment i

From Figure 2.2, all diseases are defined as the set of
$X_d = \{x \geq 0 \ | x_i = 0, i = 1, 2, \ldots, n\}$, the new infections in compartments i are appeared at the rate $\mathcal{F}_i(x)$, the individuals come into compartment i by all other means are at the rate $\mathcal{V}_i^+(x)$ and the others are coming out the compartment i at the rate $\mathcal{V}_i^-(x)$, with considering that every function $\mathcal{F}_i(x)$, $\mathcal{V}_i^+$ and $\mathcal{V}_i^-$ is continuously differentiable with respect to each variable [17]. The initial conditions are non negative in the transmission model with the following system of equations

$$\frac{dx}{dt} = f_i(x) = \mathcal{F}_i(x) - \mathcal{V}_i(x)$$

with $i = 1, 2, \ldots, k$ and $\mathcal{V}_i = \mathcal{V}_i^+(x) - V_i^-(x)$ and the following conditions should be satisfied on the functions:

1. If $x \geq 0$, then $\mathcal{F}_i, \mathcal{V}_i^+, \mathcal{V}_i^- \geq 0$, , for $i = 1, 2, \ldots, k$ indicates that there is no individuals transfer out when the compartment empty.

2. If $x_i = 0$, then $\mathcal{V}_i^- = 0$ means that nobody leaves the compartment. Particularly, $\mathcal{V}_i^- = 0$ with $i = 1, 2, \ldots, n$ when $x \in X_d$.

3. $\mathcal{F}_i = 0$ with $i > n$ means that n is the number of infective class

4. If $x \in X_d$, then $\mathcal{F}_i = 0$, and $\mathcal{V}_i^- = 0$ for all $i = 1, 2, \ldots, n$

5. Every eigenvalue from $Df(x_0)$ has negative real parts when $\mathcal{F} = 0$.

Lemma 1. *If x_0 is a DFE of (2.2) and $f_i(x)$ satisfies the conditions (1) to (5), then $D\mathcal{F}(x_0)$ and $D\mathcal{V}(x_0)$ can be written as [20];*

$$D\mathcal{F}(x_0) = \begin{pmatrix} F & 0 \\ 0 & 0 \end{pmatrix}, \; D\mathcal{V}(x_0) = \begin{pmatrix} V & 0 \\ J_3 & J_4, \end{pmatrix}$$

with F and V are the $n \times n$ matrices can be written as

$$F = \frac{\partial \mathcal{F}(x_0)}{\partial x_j}, \; V = \frac{\partial \mathcal{V}(x_0)}{\partial x_j}. \tag{2.3}$$

with $1 \leq i \leq n$. F is positive matrix and V is invertible matrix. Then the inverse of matrix V is given as V^{-1} and then compute FV^{-1}. Find $A = (FV^{-1})$ and set $R_0 = \rho(A)$ where $\rho(A)$ is the spectral radius of the matrix A which is a maximum eigenvalue from matrix A. The proof of lemma (1) is in the thesis of Michael A. Mikucki [20].

In 2013, Olaniyi et al. studied mathematical model using a system of seven dimensional ODE'S [32]. They studied the analysis of DFE and found that when reproduction number R_0 is less than one, DFE is asymptotically stable, it is unstable when reproduction number R_0 is greater than one and for R_0 is equal to one, they said that there is a backward bifurcation [32]. They studied again the presence of the unique EE under definite conditions. Generally, the basic reproductive number R_0 helps in analyzing the stability of malaria; it can be taken as a measure of the intensity of transmission [41].

Example of computing a basic reproduction number

From equation (2.2) of malaria transmission model by Mojeeb AL, R_0 was calculated by using the next generation matrix method. From the system of equation (2.2), the DFE point is $X_0 = (\frac{\wedge}{\mu}, 0, 0)$. Deduce F and V from (2.2) where

$$\mathcal{F}(x) = \begin{pmatrix} \beta IS \\ 0 \\ 0 \end{pmatrix}, \; \mathcal{V}(x) = \begin{pmatrix} (\alpha_1 + \mu)E \\ -\alpha_1 E + (\alpha_2 + \mu + \delta)I \\ - \wedge + \beta SI + \mu S \end{pmatrix}. \tag{2.4}$$

Then, using (2.3), find F and V from (2.4)

$$F = \begin{pmatrix} 0 & \beta\frac{\wedge}{\mu} \\ 0 & 0 \end{pmatrix}, \; V = \begin{pmatrix} (\alpha_1 + \mu) & 0 \\ -\alpha_1 & (\alpha_2 + \mu + \delta) \end{pmatrix}.$$

The basic reproduction number is obtained by the spectral radius of FV^{-1} therefore

$$R_0 = \rho(FV^{-1}) = \begin{pmatrix} 0 & \beta\dfrac{\wedge}{\mu} \\ 0 & 0 \end{pmatrix} \times \begin{pmatrix} \dfrac{1}{(\alpha_1 + \mu)} & 0 \\ \dfrac{\alpha_1}{(\alpha_1 + \mu)(\alpha_2 + \mu + \delta)} & \frac{1}{(\alpha_2 + \mu + \delta)} \end{pmatrix} \tag{2.5}$$

After computing the calculation in (2.5), the reproduction number can be written as

$$R_0 = \frac{\alpha_1 \beta \wedge}{\mu(\alpha_1 + \mu)(\alpha_2 + \mu + \delta)}.$$

When R_0 is less than one, the DFE $X_0(\frac{\wedge}{\mu}, 0, 0)$ is asymptotically stable meaning that the disease will vanish and unstable if R_0 is greater than one, meaning the disease will continue in the population.

2.4 Optimal control problems and Caputo derivatives

Infectious diseases prevention and control strategies are the measures which can reduce the disease infection in a population. Optimal control theory is a useful part in the analysis of dynamical diseases in clarifying the available prevention and control measures. Optimal control model has been used to determine the effort control of vector borne diseases. [31]. Agrawal et al. developed optimal control problems using Caputo fractional derivatives and established a stable numerical scheme on the mathematical model in 2008 [1].

2.4.1 Caputo fractional derivative

The Caputo fraction derivative uses the fraction integral and Riemann Liouville fractional integrals as a prerequisite [19]. Before introducing the study of fractional control problem, it is necessary to define the basic fractional operator:

- Gamma function:

  Gamma function is notated as $\Gamma(u)$, it is given by

  $$\Gamma(u) = \int_0^\infty \left(t^{u-1} e^{-t}\right) dt,$$

  where $u > 0$ and $\Gamma(n) = (n-1)!$.

- Fractional operator

  $$J^q f(t) = \frac{1}{\Gamma(q)} \int_a^t (t-s)^{q-1} f(s) ds. \tag{2.6}$$

  For q=0 the equation (2.6) becomes

  $$J^0 f(t) = \frac{1}{\Gamma(0)} \int_a^t (t-s)^{-1} f(s) ds = f(t). \tag{2.7}$$

From the equation (2.7), by convention $J^0 = I$ which is the identity, thus $J^0 f(t) = f(t)$ [19].

- Riemann Liouville fractional integrals:

  The Left Riemann Liouville fractional integrals (LRLFI) can be written as

$$ {}_aI_t^q f(t) = \frac{1}{\Gamma(q)} \int_a^t (t-s)^{q-1} f(s) ds. \tag{2.8} $$

  For $q = 0$ the equation (2.8) becomes

$$ {}_aI_t^0 f(t) = \frac{1}{\Gamma(0)} \int_a^t (t-s)^{-1} f(s) ds. \tag{2.9} $$

  It is clear that the equation (2.9) has a second member which is similar to the second member of equation (2.7), thus

$$ {}_aI_t^0 f(t) = f(t). \tag{2.10} $$

  Similarly, the Right Riemann Liouville fractional integrals (RRLFI) can be written as

$$ {}_tI_b^q f(t) = \frac{1}{\Gamma(q)} \int_t^b (s-t)^{q-1} f(s) ds. \tag{2.11} $$

  For $q = 0$ the equation (2.11) becomes

$$ {}_tI_b^0 f(t) = \frac{1}{\Gamma(0)} \int_t^b (s-t)^{-1} f(s) ds = \frac{1}{\Gamma(0)} \int_b^t (t-s)^{-1} f(s) ds. \tag{2.12} $$

  It is clear that the second member of equation (2.12) looks like the second member of equation (2.7), thus ${}_tI_b^0 f(t) = f(t)$ [37].

Riemann Liouville fractional derivative and Caputo fractional derivative are commonly used in engineering applications and mathematical modeling [42]. In this study we prefer to use Caputo Fractional Derivative for solving the optimal control.

Consider that f be a function which is defined from $[a, b]$ to $\mathbb{R}$, and let $q > 0$ be a real number representing the order of Caputo derivative of f, $n - 1 < q < n$ if $q \notin \mathbb{N}$ and $n = q$ if $q \in \mathbb{N}$ where $n \in \mathbb{N}$.

- The LCFD is defined as

$$ {}_a^c D_t^q f(t) = {}_aI_t^{n-q} \frac{d^n}{dt^n} f(t) = \frac{1}{\Gamma(n-q)} \int_a^t (t-s)^{n-q-1} f^{(n)}(s) ds. \tag{2.13} $$

  When $q = n$ with using equation (2.10) then the equation (2.13) becomes

$$ {}_a^c D_t^q f(t) = {}_aI_t^0 \frac{d^n}{dt^n} f(t) = \frac{d^n}{dt^n} f(t). \tag{2.14} $$

- The RCFD can be written as

$$ {}_t^c D_b^q f(t) = (-1)^n \ {}_t I_b^{n-q} \frac{d^n}{dt^n} f(t) = \frac{(-1)^n}{\Gamma(n-q)} \int_t^b (s-t)^{n-q-1} f^{(n)}(s) ds. \tag{2.15} $$

When $q = n$ with using equation (2.12) then the equation (2.15) becomes

$$ {}_t^c D_b^q f(t) = (-1)^n \ {}_t I_b^0 \frac{d^n}{dt^n} f(t) = (-1)^n \frac{d^n}{dt^n} f(t). \tag{2.16} $$

2.4.2 General study of fractional control problem

Let v_i be a control vector with $i = 1, 2, 3, \ldots, n$ with n is the controls number and set $a = 0$ the lower bound. Define the objective function as follows,

$$ J(v) = \int_0^T L(x, v, t) dt, \tag{2.17} $$

subject to

$$ {}_0^c D_t^q x(t) = G(x, v, t), \tag{2.18} $$

with $x(t)$ is vector state, $\forall t \in [0, T]$, L is Lagrangian and G is a system of equations of given model including controls. Setting $n = q = 1$ in (2.14) then the equation (2.18) becomes

$$ {}_0^c D_t x(t) = \frac{d}{dt} x(t) = G(x, v, t), $$

To seek the optimal control, we first find a modified objective function $\overline{J}(v)$ by using the combination of the equation (2.17) and equation (2.18) by introducing the Lagrangian multiplier technique, and then we obtain

$$ \overline{J}(v) = \int_0^T \left[L(x, v, t) + k \left(G(x, v, t) - \ {}_0^c D_t^q x(t) \right) \right] dt, \tag{2.19} $$

with k is the Lagrange multiplier which is called again an adjoint variable. By considering the variation of equation (2.19) with respect to the variables x, v and k, (2.19) becomes

$$ \delta \overline{J}(v) = \int_0^T \left[\frac{\partial L}{\partial x} \delta x + \frac{\partial L}{\partial v} \delta v + \delta k \left(G - \ {}_0^c D_t^q x \right) + k \left(\frac{\partial G}{\partial x} \delta x + \frac{\partial G}{\partial v} \delta v - \delta \left({}_0^c D_t^q x \right) \right) \right] dt. \tag{2.20} $$

This variation is defined as a change of modified objective function and $\delta x, \delta v$ and δk are the variation of x, v, k respectively. From Fred Riewe, 1996 [38], the integration by parts gives;

$$ \int_a^b \frac{d^n f(t)}{d(t-a)^n} g(t) dt = (-1)^{-n} \int_a^b f(t) \frac{d^n g(t)}{d(t-b)^n} dt, \ \textit{and } n > 0. \tag{2.21} $$

Transform the equation (2.21) with $a = 0$ and $b = T$ can be written as [44];

$$\int_0^T \left({}_0^c D_t^q f(t)\right) g(t) dt = \int_0^T f(t) \left({}_t^c D_T^q g(t)\right) dt, \tag{2.22}$$

here the operator ${}_0^c D_t^q$ can be written as ${}_t^c D_T^q$ when the functions are interchanged. Thus after the substitution in (2.20), the last part is $\int_0^T k\delta \left({}_0^c D_t^q x\right) dt$, using equation (2.22), this last part can be transformed as follow;

$$\int_0^T k\delta \left({}_0^c D_t^q x\right) dt = \int_0^T \delta x \left({}_t^c D_T^q k\right) dt. \tag{2.23}$$

From equation (2.23), assume that the variation order and the fractional derivative are permuted. For initial time $a = 0$ and terminal time $b = T$, we have
$\delta x(0) = 0$ or $k(0) = 0$, and $\delta x(T) = 0$ or $k(T) = 0$ [33]. By using (2.23) in the relation (2.20), we get

$$\delta\overline{J}(v) = \int_0^T \left[\delta k \left(G - {}_0^c D_t^q x\right) + \delta x \left(\frac{\partial L}{\partial x} + k\frac{\partial G}{\partial x} - {}_t^c D_T^q k\right) + \delta v \left(\frac{\partial L}{\partial v} + k\frac{\partial G}{\partial v}\right)\right] dt. \tag{2.24}$$

Minimization of $\overline{J}(v)$ which leads to minimization of $J(v)$, exist when the coefficients of $\delta x, \delta u$ and δk in (2.24) are zero. It means that

$$\begin{cases} G - {}_0^c D_t^q x = 0 \\ \frac{\partial L}{\partial x} + k^T \frac{\partial G}{\partial x} - {}_t^c D_T^q k = 0 \\ \frac{\partial L}{\partial v} + k^T \frac{\partial G}{\partial v} = 0 \end{cases} \quad which \quad gives \begin{cases} {}_0^c D_t^q x = G(x, v, t) \\ {}_t^c D_T^q k = \frac{\partial L}{\partial x} + k^T \frac{\partial G}{\partial x} \\ \frac{\partial L}{\partial v} + k^T \frac{\partial G}{\partial v} = 0. \end{cases} \tag{2.25}$$

From (2.25)

$${}_0^c D_t^q x = G(x, v, t) \text{ and } {}_t^c D_T^q k = \frac{\partial L}{\partial x} + k^T \frac{\partial G}{\partial x},$$

is the Euler-Lagrange equations on the Fractional Optimal Control Problem (FOCP). From (2.25) gives the necessary conditions for the optimality of the FOCP [33]. In the system (2.25), the first relation contains the LCFD while second relation contains the RCFD. For $q = 1$, the system (2.25) reduce in standard methods in the following ways; the equation (2.14) gives

$${}_0^c D_t x(t) = \frac{d}{dt} x(t), \tag{2.26}$$

and the equation (2.16) gives

$${}_t^c D_T k(t) = (-1)\frac{d}{dt} k(t) = -\frac{d}{dt} k(t) \qquad [37]. \tag{2.27}$$

Chapter 3

Setting of SEIR-SEI model and solution of an optimal control problem

This chapter deals with the formulation of the SEIR-SEI model, conducting a qualitative study of the developed SEIR-SEI mathematical model, optimal control of the model and its application to malaria transmission dynamics between mosquitoes and humans in Rwanda.

3.1 Model framework

3.1.1 Formulation of the model

Let $N(t)$ is defined as the total population size at time t. Setting lower scripts h to stand for human and m to stand for mosquito, we want to set a mathematical model such that

$$N_h(t) = S_h(t) + E_h(t) + I_h(t) + R_h(t), \tag{3.1}$$

and

$$N_m(t) = S_m(t) + E_m(t) + I_m(t), \tag{3.2}$$

where S is susceptible; E refers to exposed; I denotes infectious and R is recovered. Furthermore, the human population is classified into four compartments: Susceptible humans (S_h), Exposed humans (E_h), Infectious humans (I_h), and Recovered humans (R_h); and

the mosquito population is divided in three compartments: Susceptible mosquitoes (S_m), Exposed mosquitoes (E_m), and Infectious mosquitoes (I_m), respectively. The variation of the nonlinear force of infection of malaria in human individual is modeled by the following logistic function

$$f_h(t) = \frac{N_h S_h(0)}{S_h(0) + (N_h - S_h(0))\, e^{-\alpha t}}, \tag{3.3}$$

where $S_h(0)$ is susceptible humans at initial time and α is a positive coefficient to be estimated. With simplicity we write the inverse of (3.3) as

$$S_{N_h} = \frac{1}{f_h(t)} = \frac{S_h(0) + (N_h - S_h(0))\, e^{-\alpha t}}{N_h S_h(0)},$$

where S_{N_h} is a nonlinear saturating feature that inhibits the force of infection coming from infected mosquitoes to susceptible humans. The logistic function increases with time, which shows the maximum rate of transmission of malaria. When $t \to \infty$, $f_h \to N_h$ meaning that $S_{N_h} = \frac{1}{N_h}$. This logistic function plays a role in variation of the rate at which the susceptible become infected human by infected mosquitoes in the model (3.5). Similarly, the following logistic function describes the infection of malaria in mosquito population

$$f_m(t) = \frac{N_m S_m(0)}{S_m(0) + (N_m - S_m(0))\, e^{-\upsilon t}}, \tag{3.4}$$

where $S_m(0)$ is susceptible mosquitoes and υ is positive coefficient to be estimated. We also find the inverse of (3.4) as

$$S_{N_m} = \frac{1}{f_m(t)} = \frac{S_m(0) + (N_m - S_m(0))\, e^{-\upsilon t}}{N_m S_m(0)},$$

where S_{N_m} refers to nonlinear saturating feature where the antibodies generate the antigens contacted from infected human at the rate. When $t \to \infty$, $f_m \to N_m$ meaning that $S_{N_m} = \frac{1}{N_m}$. Here, the logistic function plays a role in changing the rate at which the susceptible become infected mosquitoes by infected human in the system of model (3.5).

The bilinear function $b\beta_h S_h(t) I_m(t)$ indicates the incidence that shows the ratio at which the $S_h(t)$ becomes infected human due to infectious mosquitoes $I_m(t)$, with b is the mosquito biting rate and β_h refers to the probability of biting by an infectious mosquito. Since from 2012 to 2016, malaria incidence increased every year in Rwanda [50], we use a saturated force of infection from mosquito to the human of the form $b\beta_h S_h S_{N_h} I_m(t)$.

The mosquitoes develop antibodies against the malaria parasites because their DNA is like that of humans [29]. Considering a saturated force of infection from human to

mosquito of the form $b\beta_m S_m S_{N_m} I_h(t)$, the parasite is transmitted to a susceptible mosquito at probability of biting β_m. However, in the blood stream of recovered humans there is a low level of parasite. Thus, they lose their immunity at a certain time, then come back into susceptible compartment. To take into account the immunity in the mathematical model, we consider that it temporarily appears only for τ such that the new born individuals are susceptible and they can be infected at a rate k. The rate of loss immunity is given by $\gamma_{k\tau} = \frac{ke^{-k\tau}}{1-e^{-k\tau}}$.

It is assumed that the infection can be transferred to mosquitoes from recovered human with transmission rate, less than infected human transmission rate that is $\beta_m < \beta_h$. Through the birth or immigration rates (recruitment rate) λ_h and λ_m, human and mosquito enter the susceptible compartment, respectively. The parasite will be moved into human at an infection rate $b\beta_h S_h S_{N_h} I_m(t)$ and that human will shift to the exposed compartment. The infected humans will be passed into the recovered compartment at a rate ρ_h and will die at a rate δ_h due to malaria infection. The recovered individuals can again join the susceptible compartment after losing their temporary immunity at a rate $\gamma(k,\tau)$. Humans and mosquitoes can be died at the natural death rates μ_h and μ_m respectively. We consider η_h and η_m to be progression rates from E_h to I_h compartment and E_m to I_m compartment, respectively. The Figure 3.1 shows the schematic diagram of interaction between the seven compartments.

The following system of differential equations is obtained by applying all above assumptions.

$$\begin{cases} \frac{dS_h}{dt} = \lambda_h - b\beta_h S_h S_{N_h} I_m(t) - \mu_h S_h + \gamma_{k\tau} R_h, \\ \frac{dE_h}{dt} = b\beta_h S_h S_{N_h} I_m(t) - (\mu_h + \eta_h) E_h, \\ \frac{dI_h}{dt} = \eta_h E_h - (\mu_h + \delta_h + \rho_h) I_h, \\ \frac{dR_h}{dt} = \rho_h I_h - (\mu_h + \gamma_{k\tau}) R_h, \\ \frac{dS_m}{dt} = \lambda_m - b\beta_m S_m S_{N_m} I_h(t) - \mu_m S_m \\ \frac{dE_m}{dt} = b\beta_m S_m S_{N_m} I_h(t) - (\mu_m + \eta_m) E_m, \\ \frac{dI_m}{dt} = \eta_m E_m - \mu_m I_m, \end{cases} \tag{3.5}$$

with $S_h(0) > 0, E_h(0) \geq 0, I_h(0) \geq 0, R_h(0) \geq 0, S_m(0) > 0, E_m(0) \geq 0, I_m(0) \geq 0$ are the initial conditions.

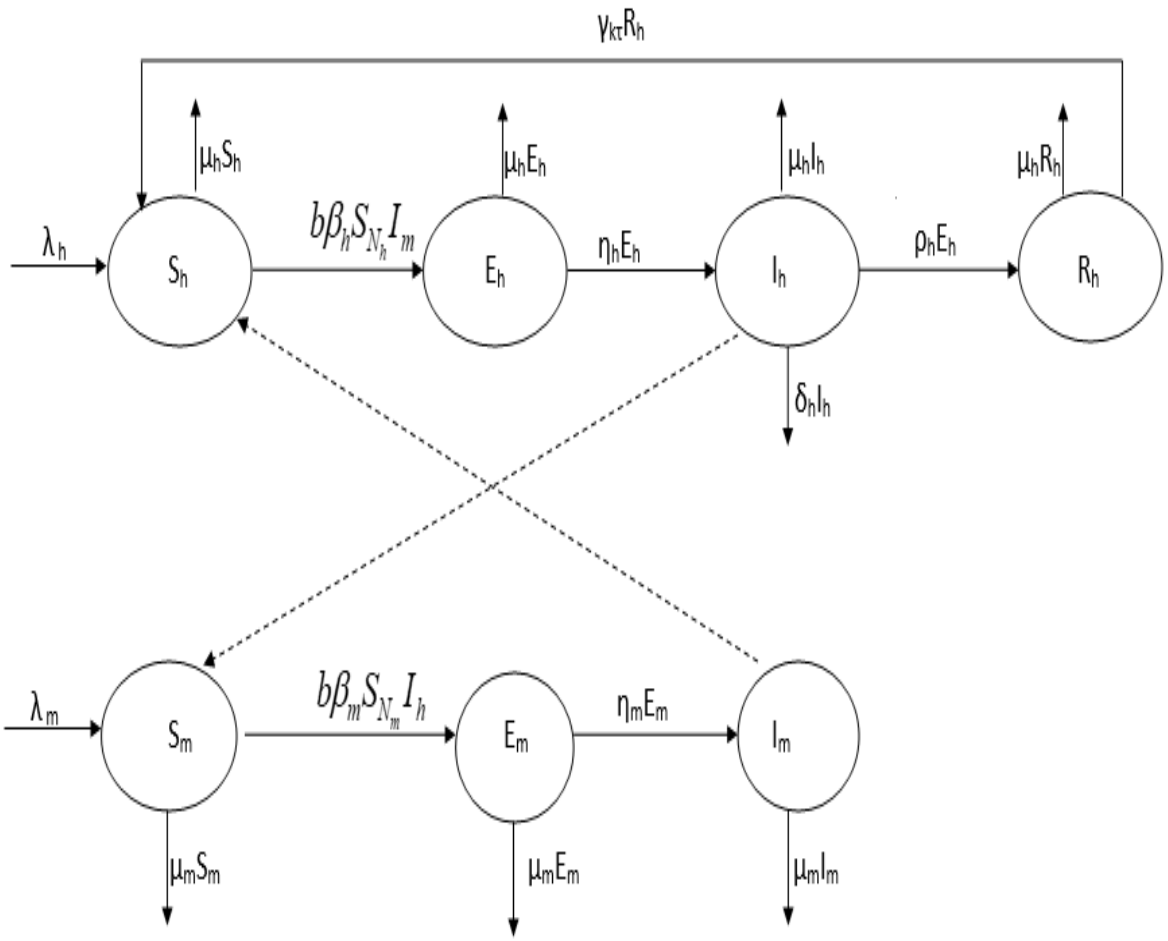

Figure 3.1: Schematic diagram of malaria transmission

3.2 Analysis of the model

3.2.1 Properties and positivity of solution

3.2.1.1 Invariant region

From the system of (3.5), the human population from all compartments is given by

$$N_h(t) = S_h(t) + E_h(t) + I_h(t) + R_h(t), \tag{3.6}$$

and the mosquito population from all compartments is given by

$$N_m(t) = S_m(t) + E_m(t) + I_m(t), \tag{3.7}$$

which are all constant. Thus, $\frac{dN_h}{dt} = 0$ and $\frac{dN_m}{dt} = 0$. Assume that we have a non negative parameters and the state variables for every $t \geq 0$. Therefore, the invariant region is

$$\perp = \left\{(S_h, E_h, I_h, R_h, S_m, E_m, I_m) \in \mathbb{R}^7_+\right\},$$

which is positive invariant. Each solution of the system of the model (3.5) with the initial condition is in the domain $\perp$ for all $t \geq 0$.

Moreover, in domain $\perp$; uniqueness, the presence, and continuation results hold in the system, implying that the system (3.5) is well posed epidemiologically and mathematically with considering the dynamics of system (3.5) in domain $\perp$ [9].

3.2.1.2 Positivity of solution

The system (3.5) at initial condition has a solution which is positive for every $t \geq 0$; it is then necessary to prove that all state variables of the system are non negative. For the human population, using the equation (3.6) we find the derivative of $N_h(t)$ with respect to t is given by:

$$\frac{dN_h}{dt} = \frac{d}{dt}\left(S_h(t) + E_h(t) + I_h(t) + R_h(t)\right),$$

which can be written

$$\frac{dN_h}{dt} = \lambda_h - \mu_h S_h - \mu_h E_h - \mu_h I_h - \mu_h R_h - \delta_h I_h.$$

Then,

$$\frac{dN_h}{dt} = \lambda_h - \mu_h(S_h + E_h + I_h + R_h) - \delta_h I_h.$$

Thus, we obtain that

$$\frac{dN_h}{dt} = \lambda_h - \mu_h N_h - \delta_h I_h.$$

In this model, N_h is constant, thus it gives that $\dfrac{dN_h}{dt} = 0$, meaning that

$$\lambda_h - \mu_h N_h - \delta_h I_h = 0.$$

Neglecting the term $\delta_h I_h$, we find that $\lambda_h - \mu_h N_h > 0$ which indicates that $N_h < \frac{\lambda_h}{\mu_h}$. Thus,

$$\lim_{t\to\infty} Sup(S_h + E_h + I_h + R_h) \leq \frac{\lambda_h}{\mu_h}.$$

Then, the domain of the system (3.5) for the individual population is given by

$$\perp_h = \left\{(S_h,\ E_h,\ I_h,\ R_h) : S_h + E_h + I_h + R_h \leq \frac{\lambda_h}{\mu_h},\ S_h > 0,\ E_h \geq 0,\ I_h \geq 0,\ R_h \geq 0\right\}.$$

It is clear that the state variables at any time are positive, implying that $\perp_h$ is a positive invariant.

For the mosquito population, we consider again the equation (3.7) and we seek the derivative of

$N_m(t)$ with respect to t as follow:

$$\frac{dN_m}{dt} = \frac{d}{dt}\left(S_m(t) + E_m(t) + I_m(t)\right),$$

which gives

$$\frac{dN_h}{dt} = \lambda_m - \mu_m S_m - \mu_m E_m - \mu_m I_m.$$

Then,

$$\frac{dN_h}{dt} = \lambda_m - \mu_m\left(S_m + E_m + I_m\right).$$

Thus, we obtain

$$\frac{dN_m}{dt} = \lambda_m - \mu_m N_m.$$

According to the model, N_m is constant or $\frac{dN_m}{dt} = 0$, meaning that $\lambda_m - \mu_m N_m = 0$. Therefore, $N_m = \frac{\lambda_m}{\mu_m}$. Thus,

$$\lim_{t\to\infty} Sup(S_m + E_m + I_m) \leq \frac{\lambda_m}{\mu_m}.$$

Then, the domain of the system (3.5) for the mosquito population can be expressed as

$$\perp_m = \left\{(S_m, E_m, I_m) : S_m + E_m + I_m \leq \frac{\lambda_m}{\mu_m}, S_m > 0, E_m \geq 0, I_m \geq 0\right\}.$$

Meanwhile the state variables are positive, $\perp_m$ is a positive invariant. Finally, we generalize that the domain of the system (3.5) can be written as

$$\perp = \left\{(S_h, E_h, I_h, R_h, S_m, E_m, I_m) \in \mathbb{R}^7_+ : 0 \leq N_h \leq \frac{\lambda_h}{\mu_h}, 0 \leq N_m \leq \frac{\lambda_m}{\mu_m}\right\}.$$

3.2.2 Analysis of equilibrium

The equilibrium points are obtained when the system (3.5) equal to zero.

3.2.2.1 The presence of the trivial equilibrium point

Since λ_h and λ_m stand on the rate of recruitment human and the rate of recruitment mosquito respectively are different to zero, the population cannot be zero. This indicates that trivial point doesn't exist in system of equations (3.5)
$(S_h^*, E_h^*, I_h^*, R_h^*, S_m^*, E_m^*, I_m^*) \neq (0, 0, 0, 0, 0, 0, 0)$.

3.2.2.2 The presence of disease free equilibrium

We define a DFE as a steady state solution where the malaria infections do not exist in the population. In absence of the disease, the system (3.5) of SEIR-SEI model has a DFE can be written as

$X_0 = (S_h^0, E_h^0, I_h^0, R_H^0, S_m^0, E_m^0, I_m^0)$ where $E_h^0, I_h^0, R_h^0, E_m^0, I_m^0$ are zeros, then the first and fifth equations of the system (3.5) give that

$$S_h^0 = \frac{\lambda_h}{\mu_h} \; and \; S_m^0 = \frac{\lambda_m}{\mu_m}.$$

Therefore, a DFE point of the malaria model (3.5) is expressed as $X_0 = (\frac{\lambda_h}{\mu_h}, 0, 0, 0, \frac{\lambda_m}{\mu_m}, 0, 0)$.

3.2.2.3 Calculation of basic reproduction number

The method of next generation matrix is used in computation of the basic reproductive number R_0. If R_0 is less than one, the disease will disappear in the population and it persists in the population when R_0 is greater than one. We arrange the system (3.5) firstly on infected compartments of humans and mosquitoes; the infected compartments are E_h, I_h, E_m and I_m lastly uninfected compartments are S_h, R_h and S_m. The system (3.5) becomes

$$\begin{cases} \frac{dE_h}{dt} = b\beta_h S_h S_{N_h} I_m(t) - (\mu_h + \eta_h) E_h, \\ \frac{dI_h}{dt} = \eta_h E_h - (\mu_h + \delta_h + \rho_h) I_h, \\ \frac{dE_m}{dt} = b\beta_m S_m S_{N_m} I_h(t) - (\mu_m + \eta_m) E_m, \\ \frac{dI_m}{dt} = \eta_m E_m - \mu_m I_m, \\ \frac{dS_h}{dt} = \lambda_h - b\beta_h S_h S_{N_h} I_m(t) - \mu_h S_h + \gamma_{k\tau} R_h, \\ \frac{dR_h}{dt} = \rho_h I_h - (\mu_h + \gamma_{k\tau}) R_h, \\ \frac{dS_m}{dt} = \lambda_m - b\beta_m S_m S_{N_m} I_h(t) - \mu_m S_m, \end{cases}$$

$\mathcal{F}_i$ and $\mathcal{V}_i$ are defined as;

$$\mathcal{F} = \begin{bmatrix} b\beta_h S_h S_{N_h} I_m \\ 0 \\ b\beta_m S_m S_{N_m} I_h \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \quad and \quad \mathcal{V} = \begin{bmatrix} (\mu_h + \eta_h) E_h \\ -\eta_h E_h + (\mu_h + \sigma_h + \rho_h) I_h \\ (\mu_m + \eta_m) E_m \\ -\eta_m E_m + \mu_m I_m \\ -\lambda_h + \mu_h S_h - \gamma_{k\tau} R_h \\ -\rho_h I_h + (\mu_h + \gamma_{k\tau}) R_h \\ -\lambda_m + \mu_m S_m \end{bmatrix}.$$

By taking the partial derivative of $\mathcal{F}$ and $\mathcal{V}$ with respect to the variables E_h, I_h, E_m and I_m we get the Jacobian matrices F and V at DFE point X_0 as follow

$$F = \begin{bmatrix} 0 & 0 & 0 & \frac{b\beta_h S_{N_h}\lambda_h}{\mu_h} \\ 0 & 0 & 0 & 0 \\ 0 & \frac{b\beta_m S_{N_m}\lambda_m}{\mu_m} & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}, \; V = \begin{bmatrix} \mu_h+\eta_h & 0 & 0 & 0 \\ -\eta_h & \mu_h+\sigma_h+\rho_h & 0 & 0 \\ 0 & 0 & \mu_m+\eta_m & 0 \\ 0 & 0 & -\eta_m & \mu_m \end{bmatrix}.$$

The reproduction number is given by a spectral radius of FV^{-1} where

$$FV^{-1} = \begin{bmatrix} 0 & 0 & \frac{b\beta_h\lambda_h S_{N_h}\eta_m}{\mu_h(\mu_m+\eta_m)\mu_m} & \frac{b\beta_h\lambda_h S_{N_h}}{\mu_h\mu_m} \\ 0 & 0 & 0 & 0 \\ \frac{b\beta_m\lambda_m\eta_h S_{N_m}}{\mu_m(\mu_h+\eta_h)(\mu_h+\delta_h+\rho_h)} & \frac{b\beta_m\lambda_m S_{N_m}}{\mu_m(\mu_h+\delta_h+\rho_h)} & 0 & 0 \\ 0 & 0 & 0 & \end{bmatrix}.$$

Then, the spectral radius of FV^{-1} is denoted by $\rho\left(FV^{-1}\right)$. We obtain that

$$R_0 = \rho\left(FV^{-1}\right) = \sqrt{\frac{b^2\beta_h\lambda_h S_{N_h}\eta_h\beta_m\lambda_m S_{N_m}\eta_m}{\mu_h\left(\mu_h+\eta_h\right)\left(\mu_h+\delta_h+\rho_h\right)\mu_m^2\left(\mu_m+\eta_m\right)}}. \tag{3.8}$$

From (3.8), $\frac{\eta_h}{\mu_h+\eta_h}$ indicates the probability that the exposed human survives to be infectious individual, $\frac{1}{\mu_h+\delta_h+\rho_h}$ refers to the average time of the infection period in the human, $\frac{\eta_m}{\mu_m+\eta_m}$ is defined as the probability that the mosquito in exposed state survives to be infectious mosquito and $\frac{1}{\mu_m}$ refers to the average time of the infection period in the mosquito.
Equation (3.8) can give $R_{0h} = \frac{b\beta_h\lambda_h S_{N_h}\eta_h}{\mu_h(\mu_h+\eta_h)(\mu_h+\delta_h+\rho_h)}$, which is defines as the number of susceptible humans that were infected by a single infectious mosquito during infection time and $R_{0m} = \frac{b\beta_m\lambda_m S_{N_m}\eta_m}{\mu_m^2(\mu_m+\eta_m)}$, refers to the number of susceptible mosquitoes that were infected by a single infectious human during infection time. Thus, the basic reproduction number R_0 can be written as

$$R_0 = \sqrt{R_{0h}R_{0m}}. \tag{3.9}$$

3.2.2.4 Stability analysis of disease free equilibrium

The stability of the DFE, E_0, is described using the Jacobian matrix of the system (3.5) at the point E_0.

Lemma 2. *When R_0 is less than one; DFE X_0 of system* (3.5) *is locally asymptotically stable and when R_0 is greater than one; it is unstable [32].*

Proof: To find the local stability of DFE point, we use the Jacobian matrix by applying the linearization of the system (3.5). The point X of the state variables from the system (3.5)

can be written as

$x_1 = S_h, x_2 = E_h, x_3 = I_h, x_4 = R_h, x_5 = S_m, x_6 = E_m$ and $x_7 = I_m$ and

$$f_1 = \frac{dS_h}{dt}, f_2 = \frac{dE_h}{dt}, f_3 = \frac{dI_h}{dt}, f_4 = \frac{dR_h}{dt}, f_5 = \frac{dS_m}{dt}, f_6 = \frac{dE_m}{dt} \text{ and } f_7 = \frac{dI_m}{dt},$$

thus

$$X = (x_1, x_2, x_3, x_4, x_5, x_6, x_7)^T, \tag{3.10}$$

and

$$F = (f_1, f_2, f_3, f_4, f_5, f_6, f_7)^T, \tag{3.11}$$

representing the matrices transpose respectively. Then, using (3.10) and (3.11), we find the Jacobian matrix as

$$J(X) = \frac{\partial F(X)}{\partial x_i} \text{ at the point } X, \tag{3.12}$$

where $F(X) = \frac{dX_i}{dt}$ be a function of the system (3.5). At DFE point X_0, we find the Jacobian matrix (3.12) as follows

$$J(X_0) = \begin{bmatrix} -\mu_h & 0 & 0 & \gamma_{k\tau} & 0 & 0 & -b\beta_h S_{N_h}\frac{\lambda_h}{\mu_h} \\ 0 & -(\mu_h+\eta_h) & 0 & 0 & 0 & 0 & b\beta_h S_{N_h}\frac{\lambda_h}{\mu_h} \\ 0 & \eta_h & -(\mu_h+\delta_h+\rho_h) & 0 & 0 & 0 & 0 \\ 0 & 0 & \rho_h & -(\mu_h+\gamma_{k\tau}) & 0 & 0 & 0 \\ 0 & 0 & -b\beta_m S_{N_m}\frac{\lambda_m}{\mu_m} & 0 & -\mu_m & 0 & 0 \\ 0 & 0 & b\beta_m S_{N_m}\frac{\lambda_m}{\mu_m} & 0 & 0 & -(\mu_m+\eta_m) & 0 \\ 0 & 0 & 0 & 0 & 0 & \eta_m & -\mu_m \end{bmatrix}. \tag{3.13}$$

The characteristic equation is $det(J(X_0) - \lambda) = 0$. By setting that

$$\begin{cases} m_1 = \mu_h + \eta_h, m_2 = b\beta_h S_{N_h}\frac{\lambda_h}{\mu_h}, \\ m_3 = \eta_h, m_4 = \mu_h + \delta_h + \rho_h, \\ m_5 = b\beta_m S_{N_m}\frac{\lambda_m}{\mu_m}, m_6 = \mu_m + \eta_m, \\ m_7 = \eta_m, m_8 = \mu_m, \end{cases} \tag{3.14}$$

It is clear that $m_i > 0$ with $i = 1, 2, \ldots, 8$. Using (3.13) and (3.14), after calculation we get eigenvalues $\lambda_1 = -\mu_h, \lambda_2 = -(\mu_h + \gamma_{k\tau})$ and $\lambda_3 = -\mu_m$ which are nonpositive and the rest characteristic equation is

$$\lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4, \tag{3.15}$$

where

$$a_1 = m_1 + m_4 + m_6 + m_8, a_2 = m_1m_4 + m_1m_6 + m_1m_8 + m_4m_6 + m_4m_8 + m_6m_8,$$

$$a_3 = m_1m_4m_6 + m_1m_4m_8 + m_1m_6m_8 + m_4m_6m_8, a_4 = m_1m_4m_6m_8 - m_2m_3m_5m_7.$$

It is clear that a_1, a_2, a_3 are strictly positive. We use (3.14) to find a_4 as

$$a_4 = (\mu_h + \eta_h)(\mu_h + \delta_h + \rho_h)(\mu_m + \eta_m)\mu_m - (b\beta_h S_{N_h}\frac{\lambda_h}{\mu_h})\eta_h(b\beta_m S_{N_m}\frac{\lambda_m}{\mu_m})\mu_m. \tag{3.16}$$

From equation (3.8), the second term of equation (3.16) can be written as

$$b\beta_h S_{N_h}\frac{\lambda_h}{\mu_h})\eta_h(b\beta_m S_{N_m}\frac{\lambda_m}{\mu_m})\mu_m = R_0^2(\mu_h + \eta_h)(\mu_h + \delta_h + \rho_h)(\mu_m + \eta_m)\mu_m. \tag{3.17}$$

Using (3.17) in (3.16), with simplification, we get

$$a_4 = (\mu_h + \eta_h)(\mu_h + \delta_h + \rho_h)(\mu_m + \eta_m)\mu_m(1 - R_0^2)$$

which will be positive if and only if $R_0 < 1$.

For any polynomial equation of the form

$$d_0x^n + d_1x^{n-1} + d_2x^{n-2} + \cdots + d_{n-2}x^2 + d_{n-1}x + d_n = 0,\ di > 0 \tag{3.18}$$

where $d_0 = 1$, $di, i = 1, 2, \ldots n$ are real coefficients, the Hurwitz matrix H_i is given by

$$H_i = \begin{bmatrix} d_1 & d_0 & 0 & 0 & 0 & 0 & \cdots & 0 \\ d_3 & d_2 & d_1 & d_0 & 0 & 0 & \cdots & 0 \\ d_5 & d_4 & d_3 & d_2 & d_1 & d_0 & \cdots & 0 \\ d_7 & d_6 & d_5 & d_4 & d_3 & d_2 & \cdots & 0 \\ d_9 & d_8 & d_7 & d_6 & d_5 & d_4 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ d_{2i-1} & d_{2i-2} & d_{2i-3} & d_{2i-4} & d_{2i-5} & d_{2i-6} & \cdots & d_i \end{bmatrix}.$$

Proposition 3. *By Peña [36], all zeros of the polynomial* (3.18) *have a negative real part if and only if* $d_i > 0$ *for all* $i = 0, 1, \ldots, n$ *and the determinant of the Hurwitz matrices* H_i *from the characteristic equation* (3.18)*,* $det(H_i) > 0$ *for all* $i = 0, 1, \ldots, n$.

Using the proposition 3, all eigenvalues of (3.15) have a negative real part if and only if

$$det(H_1) = a_1 > 0,\ a_2 > 0,\ a_3 > 0,\ a_4 > 0,\ det(H_2) = a_1a_2 - a_3 > 0;$$

$$det(H_3) = a_1a_2a_2a_3 - a_3^2 - a_1^2a_4 > 0,\ det(H_4) = a_4det(H_3).$$

Thus, every eigenvalue from the Jacobian matrix $J(X_0)$ has a negative real parts if R_0 is less than one and the DFE point is locally asymptotically stable. But $a_4 < 0$ if and only if R_0 is greater than one, thus the DFE point is unstable, meaning that there exists one eigenvalue with positive real part.

3.2.2.5 Presence of endemic equilibrium point

EE point is a positive steady state solution where the disease continues in the population [32]. Consider that all steady states are given by

$$X^* = (S_h^*, E_h^*, I_h^*, R_h^*, S_m^*, E_m^*, I_m^*).$$

Lemma 4. *For the model* (3.5)*, when* $R_0 \leq 1$ *there is negative EE point, but there exists a unique EE point when* R_0 *is greater than one.*

Using the system (3.5), we set the system of differential equations to zero

$$\begin{cases} \lambda_h - b\beta_h S_h^* S_{N_h} I_m^* - \mu_h S_h^* + \gamma_{k\tau} R_h^* = 0, \\ b\beta_h S_h^* S_{N_h} I_m^* - (\mu_h + \eta_h) E_h^* = 0, \\ \eta_h E_h^* - (\mu_h + \delta_h + \rho_h) I_h^* = 0, \\ \rho_h I_h^* - (\mu_h + \gamma_{k\tau}) R_h^* = 0, \\ \lambda_m - b\beta_m S_m^* S_{N_m} I_h^* - \mu_m S_m^* = 0, \\ b\beta_m S_m^* S_{N_m} I_h^* - (\mu_m + \eta_m) E_m^* = 0, \\ \eta_m E_m^* - \mu_m I_m^* = 0. \end{cases} \tag{3.19}$$

By solving this system of equations (3.19), we get all state variables as functions of I_h^*

$$\begin{cases} S_h^* = \lambda_h \frac{b\beta_m S_{N_m} I_h^* + \mu_m}{\mu_h \mu_m R_{0h} R_{0m}}, \\ E_h^* = \frac{\mu_h + \delta_h + \rho_h}{\eta_h} I_h^*, \\ R_h^* = \frac{\rho_h}{\mu_h + \gamma_{k\tau} I_h^*}, \\ S_m^* = \frac{\lambda_m}{b\beta_m S_{N_m} I_h^* + \mu_m}, \\ E_m^* = \frac{\mu_m^2 R_{0m} I_h^*}{\eta_m \left(b\beta_m S_{N_m} I_h^* + \mu_m\right)}, \\ I_m^* = \frac{\mu_m R_{0m} I_h^*}{b\beta_m S_{N_m} I_h^* + \mu_m}. \end{cases} \tag{3.20}$$

Using the first equation of the system (3.19), we get that

$$S_h^* = \frac{(\lambda_h(\mu_h + \gamma_{k\tau}) + \gamma_{k\tau}\rho_h I_h^*)\,(b\beta_m S_{N_m} I_h^* + \mu_m)}{[b\beta_h S_{N_h} \mu_m R_{0m} I_h^* + (\mu_h b\beta_m S_{N_m} I_h^* + \mu_m)](\mu_h + \gamma_{k\tau})}. \tag{3.21}$$

Comparing the first equation in the system (3.20) and equation (3.21) we get that

$$\frac{(\lambda_h(\mu_h + \gamma_{k\tau}) + \gamma_{k\tau}\rho_h I_h^*)\,(b\beta_m S_{N_m} I_h^* + \mu_m)}{[b\beta_h S_{N_h} \mu_m R_{0m} I_h^* + (\mu_h b\beta_m S_{N_m} I_h^* + \mu_m)](\mu_h + \gamma_{k\tau})} = \lambda_h \frac{b\beta_m S_{N_m} I_h^* + \mu_m}{\mu_h \mu_m R_{0h} R_{0m}}. \tag{3.22}$$

To solve (3.22), we set that

$$\begin{aligned} w_1 &= \mu_h b\beta_m S_{N_m}[\lambda_h b\beta_h S_{N_h} \mu_h(\mu_h + \gamma_{k\tau})(R_{0m} + 1) - R_0^2 \mu_m \gamma_{k\tau}\rho_h], \\ w_2 &= \mu_h \mu_m[\lambda_h b(\mu_h + \gamma_{k\tau})(\beta_h S_{N_h}(R_{0m} + 1) + \beta_m S_{N_m}) - R_0^2(\lambda_h b\beta_m S_{N_m} + \mu_h \gamma_{k\tau}\rho_h)], \\ w_3 &= \lambda_h \mu_h^2 \mu_m(1 - R_0^2). \end{aligned}$$

From (3.22), we get

$$w_1 \left(I_h^*\right)^2 + w_2 I_h^* + w_3 = 0, \tag{3.23}$$

We can now solve (3.23) for I_h^* and we get

$$I_h^* = \frac{-w_2 \pm \sqrt{w_2^2 - 4w_1 w_3}}{2w_1}.$$

The equation (3.23) has only one positive solution if $w_1 > 0$ that is $\lambda_h b \beta_h S_{N_h} \mu_h (\mu_h + \gamma_{k\tau})(R_{0m} + 1) > R_0^2 \mu_m \gamma_{k\tau} \rho_h$ and $w_3 < 0$ when $R_0 > 1$. For another side the roots of the equation (3.23) are defined in the following ways:

- When $w_2 > 0$ meaning that $\lambda_h b(\mu_h + \gamma_{k\tau})(\beta_h S_{N_h}(R_{0m} + 1) + \beta_m S_{N_m}) > R_0^2(\lambda_h b \beta_m S_{N_m} + \mu_h \gamma_{k\tau} \rho_h)$, with considering that $w_1 > 0$ the sum of solutions of the equation (3.23) is negative.
- When $w_3 > 0$ implies that $R_0 \leq 1$ with respecting that $w_1 > 0$ the equation (3.23) has two solution of the same sign.

By combining both $w_2 > 0$ and $w_3 > 0$, the equation (3.23) has negative solution which is not biologically realistic. The mathematical model (3.5) should have a negative solution, thus the DFE is the only equilibrium and the disease will vanish in given period.

3.2.2.6 Stability of endemic equilibrium point

The stability of EE is analyzed in different methods but Lyapunov method is more powerful for multidimensional systems [45].

Lemma 5. *The EE point X^* of the system of equations* (3.5) *is globally asymptotically stable in the domain $\perp$ if R_0 is greater than one.*

The obtained DFE is locally stable which imply the local stability on EE, thus we find a global stability of the EE point. The global stability of the EE point of the model (3.5) is found by using Lyapunov function [27].
Set the following nonlinear Lyapunov function $Z(S_h, E_h, I_h, R_h, S_m, E_m, I_m) > 0$ in domain $\perp$ which was obtained in the system (3.5) as follows

$$\begin{aligned} Z = &(S_h - S_h^* \ln S_h) + (E_h - E_h^* \ln E_h) + (I_h - I_h^* \ln I_h) + (R_h - R_h^* \ln R_h) \\ &+(S_m - S_m^* \ln S_m) + (E_m - E_m^* \ln E_m) + (I_m - I_m^* \ln I_m). \end{aligned}$$

Find Lyapunov derivative along solutions of the model (3.5),

$$\begin{aligned} \left.\frac{dZ}{dt}\right|_{X^*} = &(1 - \tfrac{S_h^*}{S_h})\tfrac{dS_h}{dt} + (1 - \tfrac{E_h^*}{E_h})\tfrac{dE_h}{dt} + (1 - \tfrac{I_h^*}{I_h})\tfrac{dI_h}{dt} + (1 - \tfrac{R_h^*}{R_h})\tfrac{dR_h}{dt} \\ &+(1 - \tfrac{S_m^*}{S_m})\tfrac{dS_m}{dt} + (1 - \tfrac{E_m^*}{E_m})\tfrac{dE_m}{dt} + (1 - \tfrac{I_m^*}{I_m})\tfrac{dI_m}{dt}; \end{aligned} \tag{3.24}$$

from the equation (3.24) replace $\frac{dS_h}{dt}, \frac{dE_h}{dt}, \frac{dI_h}{dt}, \frac{dR_h}{dt}, \frac{dS_m}{dt}, \frac{dE_m}{dt}, \frac{dI_m}{dt}$ with the results from the system (3.5). This leads to

$$\begin{aligned}\left.\frac{dZ}{dt}\right|_{X^*} &= (1-\tfrac{S_h^*}{S_h})(\lambda_h - b\beta_h S_h S_{N_h} I_m - \mu_h S_h + \gamma_{k\tau} R_h)\\ &+(1-\tfrac{E_h^*}{E_h})(b\beta_h S_h S_{N_h} I_m - (\mu_h+\eta_h)\,E_h) + (1-\tfrac{I_h^*}{I_h})(\eta_h E_h - (\mu_h+\delta_h+\rho_h)\,I_h)\\ &+(1-\tfrac{R_h^*}{R_h})(\rho_h I_h - (\mu_h+\gamma_{k\tau})\,R_h) + (1-\tfrac{S_m^*}{S_m})(\lambda_m - b\beta_m S_m S_{N_m} I_h - \mu_m S_m)\\ &+(1-\tfrac{E_m^*}{E_m})(b\beta_m S_m S_{N_m} I_h - (\mu_m+\eta_m)\,E_m) + (1-\tfrac{I_m^*}{I_m})(\eta_m E_m - \mu_m I_m).\end{aligned} \tag{3.25}$$

The system of equation (3.19) is rewritten as follows,

$$\begin{cases}\lambda_h = (b\beta_h S_{N_h} I_m^* + \mu_h) S_h^* - \gamma_{k\tau} R_h^*,\\ \mu_h + \eta_h = b\beta_h S_{N_h} \frac{I_m^*}{E_h^*} S_h^*,\\ \mu_h + \delta_h + \rho_h = \eta_h \frac{E_h^*}{I_h^*},\\ \mu_h + \gamma_{k\tau} = \rho_h \frac{I_h^*}{R_h^*},\\ \lambda_m = (b\beta_m S_{N_m} I_h^* + \mu_m) S_m^*,\\ \mu_m + \eta_m = \frac{b\beta_m S_{N_m} S_m^*}{E_m^*},\\ \mu_m = \eta_m \frac{E_m^*}{I_m^*}.\end{cases} \tag{3.26}$$

The relation (3.26) in (3.25) gives

$$\begin{aligned}\left.\frac{dZ}{dt}\right|_{X^*} &= (1-\tfrac{S_h^*}{S_h})\left[-(1-\tfrac{S_h^*}{S_h})\mu_h S_h + b\beta_h S_{N_h} S_h^* I_m^* (1-\tfrac{S_h}{S_h^*}\tfrac{I_m}{I_m^*}) + \gamma_{k\tau} R_h^* (1-\tfrac{R_h}{R_h^*})\right]\\ &+(1-\tfrac{E_h^*}{E_h})\left[b\beta_h S_{N_h} S_h^* I_m^* (\tfrac{S_h}{S_h^*}\tfrac{I_m}{I_m^*} - \tfrac{E_h}{E_h^*})\right]\\ &+(1-\tfrac{I_h^*}{I_h})\left[\eta_h E_h^* I_h^* (\tfrac{E_h}{E_h^*} - \tfrac{I_h}{I_h^*})\right] + (1-\tfrac{R_h^*}{R_h})\left[\rho_h I_h^* (\tfrac{I_h}{I_h^*} - \tfrac{R_h}{R_h^*})\right]\\ &+(1-\tfrac{S_m^*}{S_m})\left[-(1-\tfrac{S_m^*}{S_m}) S_m \mu_m + b\beta_m S_{N_m} S_m^* I_h^* (1-\tfrac{S_m}{S_m^*}\tfrac{I_h}{I_h^*})\right]\\ &+(1-\tfrac{E_m^*}{E_m})\left[b\beta_m S_m^* S_{N_m} I_h^* (\tfrac{S_m}{S_m^*}\tfrac{I_h}{I_h^*} - \tfrac{E_m}{E_m^*})\right] + (1-\tfrac{I_m^*}{I_m})\left[\eta_m E_m^* (\tfrac{E_m}{E_m^*} - \tfrac{I_m}{I_m^*})\right],\end{aligned} \tag{3.27}$$

with simplification, the equation (3.27) becomes

$$\begin{aligned}\left.\frac{dZ}{dt}\right|_{X^*} &= -(1-\tfrac{S_h^*}{S_h})^2 \mu_h S_h + (1-\tfrac{S_h^*}{S_h})(1-\tfrac{S_h}{S_h^*}\tfrac{I_m}{I_m^*}) b\beta_h S_{N_h} S_h^* I_m^*\\ &+(1-\tfrac{S_h^*}{S_h})(1-\tfrac{R_h}{R_h^*})\gamma_{k\tau} R_h^*) + (1-\tfrac{E_h^*}{E_h})(\tfrac{S_h}{S_h^*}\tfrac{I_m}{I_m^*} - \tfrac{E_h}{E_h^*}) b\beta_h S_{N_h} S_h^* I_m^*\\ &+(1-\tfrac{I_h^*}{I_h})(\tfrac{E_h}{E_h^*} - \tfrac{I_h}{I_h^*})\eta_h E_h^* + (1-\tfrac{R_h^*}{R_h})(\tfrac{I_h}{I_h^*} - \tfrac{R_h}{R_h^*})\rho_h I_h^*\\ &-(1-\tfrac{S_m^*}{S_m})^2 \mu_m S_m + (1-\tfrac{S_m^*}{S_m})(1-\tfrac{S_m}{S_m^*}\tfrac{I_h}{I_h^*}) b\beta_m S_{N_m} S_m^* I_h^*\\ &+(1-\tfrac{E_m^*}{E_m})(\tfrac{S_m}{S_m^*}\tfrac{I_h}{I_h^*} - \tfrac{E_m}{E_m^*}) b\beta_m S_m^* S_{N_m} I_h^* + (1-\tfrac{I_m^*}{I_m})(\tfrac{E_m}{E_m^*} - \tfrac{I_m}{I_m^*})\eta_m E_m^*.\end{aligned}$$

Finally, we get

$$\left.\frac{dZ}{dt}\right|_{X^*} = -(1-\frac{S_h^*}{S_h})^2 \mu_h S_h - (1-\frac{S_m^*}{S_m})^2 \mu_m S_m + H(S_h, E_h, I_h, R_h, S_m, E_m, I_m),$$

where we have set

$$\begin{aligned}H(S_h,E_h,I_h,R_h,S_m,E_m,I_m) &= (1-\tfrac{S_h^*}{S_h})(1-\tfrac{S_h}{S_h^*}\tfrac{I_m}{I_m^*})b\beta_h S_{N_h}S_h^*I_m^* + (1-\tfrac{S_h^*}{S_h})(1-\tfrac{R_h}{R_h^*})\gamma_{k\tau}R_h^*\\ &+(1-\tfrac{E_h^*}{E_h})(\tfrac{S_h}{S_h^*}\tfrac{I_m}{I_m^*}-\tfrac{E_h}{E_h^*})b\beta_h S_{N_h}S_h^*I_m^* + (1-\tfrac{I_h^*}{I_h})(\tfrac{E_h}{E_h^*}-\tfrac{I_h}{I_h^*})\eta_h E_h^*\\ &+(1-\tfrac{R_h^*}{R_h})(\tfrac{I_h}{I_h^*}-\tfrac{R_h}{R_h^*})\rho_h I_h^* + (1-\tfrac{S_m^*}{S_m})(1-\tfrac{S_m}{S_m^*}\tfrac{I_h}{I_h^*})b\beta_m S_{N_m}S_m^*I_h^*\\ &+(1-\tfrac{E_m^*}{E_m})(\tfrac{S_m}{S_m^*}\tfrac{I_h}{I_h^*}-\tfrac{E_m}{E_m^*})b\beta_m S_m^*S_{N_m}I_h^* + (1-\tfrac{I_m^*}{I_m})(\tfrac{E_m}{E_m^*}-\tfrac{I_m}{I_m^*})\eta_m E_m^*.\end{aligned}$$

In Mpeshe et al. [27], $H(S_h,E_h,I_h,R_h,S_m,E_m,I_m)\leq 0$ and consequently $\frac{dZ}{dt}\leq 0$ if

$$\begin{cases}(1-\frac{S_h^*}{S_h})(1-\frac{S_h}{S_h^*}\frac{I_m}{I_m^*})\leq 0,\\ (1-\frac{S_h^*}{S_h})(1-\frac{R_h}{R_h^*})\leq 0,\\ (1-\frac{E_h^*}{E_h})(\frac{S_h}{S_h^*}\frac{I_m}{I_m^*}-\frac{E_h}{E_h^*})\leq 0,\\ (1-\frac{I_h^*}{I_h})(\frac{E_h}{E_h^*}-\frac{I_h}{I_h^*})\leq 0,\\ (1-\frac{R_h^*}{R_h})(\frac{I_h}{I_h^*}-\frac{R_h}{R_h^*})\leq 0,\\ (1-\frac{S_m^*}{S_m})(1-\frac{S_m}{S_m^*}\frac{I_h}{I_h^*})\leq 0,\\ (1-\frac{E_m^*}{E_m})(\frac{S_m}{S_m^*}\frac{I_h}{I_h^*}-\frac{E_m}{E_m^*})\leq 0,\\ (1-\frac{I_m^*}{I_m})(\frac{E_m}{E_m^*}-\frac{I_m}{I_m^*})\leq 0,\end{cases}$$

that is,

$$\begin{cases}1+\frac{I_m}{I_m^*}-\frac{S_h^*}{S_h}-\frac{S_h}{S_h^*}\frac{I_m}{I_m^*}\leq 0,\\ 1+\frac{S_h^*}{S_h}\frac{R_h}{R_h^*}-\frac{R_h}{R_h^*}-\frac{S_h^*}{S_h}\leq 0,\\ 1+\frac{S_h}{S_h^*}\frac{I_m}{I_m^*}-\frac{E_h}{E_h^*}-\frac{E_h^*}{E_h}\frac{S_h}{S_h^*}\frac{I_m}{I_m^*}\leq 0,\\ 1+\frac{E_h}{E_h^*}-\frac{I_h}{I_h^*}-\frac{I_h^*}{I_h}\frac{E_h}{E_h^*}\leq 0,\\ 1+\frac{I_h}{I_h^*}-\frac{R_h}{R_h^*}-\frac{R_h^*}{R_h}\frac{I_h}{I_h^*}\leq 0,\\ 1+\frac{I_h}{I_h^*}-\frac{S_m^*}{S_m}-\frac{S_m}{S_m^*}\frac{I_h}{I_h^*}\leq 0,\\ 1+\frac{S_m}{S_m^*}\frac{I_h}{I_h^*}-\frac{E_m}{E_m^*}-\frac{E_m^*}{E_m}\frac{S_m}{S_m^*}\frac{I_h}{I_h^*}\leq 0,\\ 1+\frac{E_m}{E_m^*}-\frac{I_m}{I_m^*}-\frac{I_m^*}{I_m}\frac{E_m}{E^*}\leq 0.\end{cases}\tag{3.28}$$

The first row of (3.28) can be written as follow

$$\frac{I_m^*+I_m}{I_m^*}-\frac{(S_h^*)^2I_m^*+S_h^2I_m}{S_hS_h^*I_m^*}\leq 0,$$

then

$$I_m^*S_hS_h^*+I_mS_hS_h^*\leq (S_h^*)^2I_m^*+S_h^2I_m,$$

which becomes

$$I_m^*S_h^*(S_h-S_h^*)\leq I_mS_h(S_h-S_h^*).$$

Finally, we obtain that

$$I_m^*S_h^*\leq I_mS_h\Rightarrow\frac{I_mS_h}{I_m^*S_h^*}\geq 1.\tag{3.29}$$

Similarly, from the second up to seventh row of (3.28) we obtain respectively

$$\begin{cases} R_h^* \leq R_h, \frac{E_h}{E_h^*} \leq \frac{I_m S_h}{I_m^* S_h^*}, E_h \leq E_h^*, \\ \frac{E_h}{E_h^*} \leq \frac{I_h}{I_h^*}, I_h^* \leq I_h, \frac{I_h}{I_h^*} \leq \frac{R_h}{R_h^*}, \\ \frac{I_h S_m}{I_h^* S_m^*} \geq 1, S_m^* \leq S_m, \frac{E_m}{E_m^*} \leq \frac{I_h S_m}{I_h^* S_m^*}, \\ E_m \leq E_m^*, \frac{E_m}{E_m^*} \leq \frac{I_m}{I_m^*}, I_m^* \leq I_m, S_h^* \leq S_h. \end{cases} \tag{3.30}$$

By considering the calculation done in (3.29) and (3.30), it is implied that $\frac{dZ}{dt} \leq 0$, thus the point X^* is globally asymptotically stable. By La Salle invariance principle 1976 [15], for every solution of $\dfrac{dZ}{dt}$ with the initial condition in domain $\perp$ converges to EE as $t \to \infty$.

3.3 Solution of optimal control

3.3.1 Formulation of optimal control problem

In this study, the optimal control of malaria based on the main strategies taken by Rwanda have been considered in order to see how the malaria dynamics will be controlled until near zero. The optimal control problems are answered by using the method of Caputo fractional derivatives [31].

The optimal control strategy is explored by including the time dependent controls into the mathematical model (3.5). We define the set of controls as $v = (v_1, v_2, v_3)^T$ given that v_i is measurable and acceptable controls set with $0 \leq v_i(t) \leq 1$, $\forall t \in [0, T]$, where $i = 1, 2, 3$, shows the effort of controlling malaria by using ITNs, IRS and ACTs on malaria.

To prevent malaria, the control $v_1(t)$ justifies the use of ITNs, the control $v_2(t)$ represents the use of IRS while $v_3(t)$ qualifies the use of ACTs. When $v_i = 0$, there is no control but when $v_i = 1$, there is a control at 100% [16].

The factor $(1 - v_1(t))$ represents the coefficient that reduces the associated forces of infection of susceptible humans or mosquito population that becomes infected. The mortality of mosquitoes increases at the rate of $\phi_1 v_1$, and $\phi_2 v_2$. $\phi_3 v_3$ indicates increasing of human recovery [23].

The system of equations (1.1) define the dynamics of malaria. For the first equation, $(1 - v_1) b \beta_h S_h S_{N_h} I_m$ indicates the rate of susceptible that move into the exposed by getting malaria, when $v_1 = 1$ the proportion of nets usage is maximum.

In the second equation, the exposed humans transfer into the infectious compartment after developing the signs, at the given rate η_h. The third equation has the infectious individuals

Table 3.1: The table below shows the control vector

Symbol	Description
$v_1(t)$	It reduces the contact of human and mosquito population on the bed
$v_2(t)$	It kills the mosquitoes in the house.
$v_3(t)$	It increases the number of recover human population.
ϕ_1	Constant rate due to the use of ITNs
ϕ_2	Constant rate due to the use of IRS
ϕ_3	Constant rate due to the use of ACTs

recovered at the sum rate of ρ_h and $\phi_3 v_3$ when $v_3 = 1$ treatment of infected individuals' usage is maximum.

In the fifth equation, the susceptible mosquitoes die at the sum rate of μ_m, $\phi_1 v_1$ and $\phi_2 v_2$ or they can be passed onto the exposed compartment by getting malaria due to the contact of infected humans at the rate $(1 - v_1) b \beta_m S_m S_{N_m} I_h$ when $v_2 = 1$ the proportion of using Indoor Residual Spray is maximum.

In the sixth equation, the exposed mosquitoes move to the infectious compartment after developing the symptoms, at the rate η_m. Finally, in the seventh equation, the infectious mosquitoes die at the sum of rate μ_m, $\phi_1 v_1$ and $\phi_2 v_2$ [30].

Set the Lagrangian,

$$L(x, v, t) = AE_h + BI_h + CI_m + Dv_1^2 + Ev_2^2 + Fv_3^2, \tag{3.31}$$

where the constants A, B and C are weight of the exposed individual population, infected individual population and mosquito population, respectively; D, E and F are weighting constants in the prevention strategies; Dv_1^2 is the cost of protection with ITNs; Ev_2^2 is the cost prevention with IRS; Fv_3^2 is the cost of treatment of infected individual population [1].

The optimal control strategies of malaria with the reduction of cost is based on the formulation of an optimal control model for malaria [8]. Using (3.31) in (2.17), we find the optimal control v_i^* as the solution of

$$J(v_i^*) = \min_{v_i \in V} J(v_i) \tag{3.32}$$

subject to the system (1.1),

where we have the objective function $J(v_i) = \int_0^T L(x, v, t)dt$. Our objective is to reduce the cost function $J(v_i)$. Furthermore, using the optimal control strategies $v_i(t)$, we get a number which is minimum on exposed and infected human population and mosquito population while minimizing the cost of controls.

3.3.2 Solution of controlled malaria model with fractional derivatives

Consider that the vector state and vector state at initial point are given by

$$x(t) = (S_h, E_h, I_h, R_h, S_m, E_m, I_m)^T,$$

$$x(0) = (S_h(0), E_h(0), I_h(0), R_h(0), S_m(0), E_m(0), I_m(0))^T,$$

respectively. Adjoint variables are

$$k = (k_1, k_2, k_3, k_4, k_5, k_6, k_7)^T.$$

By using the necessary conditions stated in (2.25), the system of optimality for the fractional optimal control malaria model is discussed below;

3.3.2.1 Left Caputo fractional derivatives (LCFD)

Using the equation (2.26), the first relation of system (2.25) gives

$$ {}_0^c D_t x(t) = \frac{d}{dt}x(t) = G(x, v, t); \tag{3.33}$$

from (3.33), we get

$$\frac{d}{dt}x(t) = (\frac{d}{dt}S_h, \frac{d}{dt}E_h, \frac{d}{dt}I_h, \frac{d}{dt}R_h, \frac{d}{dt}S_m, \frac{d}{dt}E_m, \frac{d}{dt}I_m)^T.$$

The component $\frac{d}{dt}S_h$ should be equal to the first relation of the system of the equations (1.1), meaning that

$$\frac{d}{dt}S_h = \lambda_h - (1 - v_1)b\beta_h S_h S_{N_h} I_m - \mu_h S_h + \gamma_{k\tau} R_h,$$

Similarly, we can get the others from the relation (3.33) and we have

$$\begin{cases} \frac{d}{dt}S_h = \lambda_h - (1 - v_1)b\beta_h S_h S_{N_h} I_m - \mu_h S_h + \gamma_{k\tau} R_h, \\ \frac{d}{dt}E_h = (1 - v_1)b\beta_h S_h S_{N_h} I_m - (\mu_h + \eta_h)\, E_h, \\ \frac{d}{dt}I_h = \eta_h E_h - (\mu_h + \delta_h + \rho_h + \phi_3 v_3)\, I_h, \\ \frac{d}{dt}R_h = (\rho_h + \phi_3 v_3) I_h - (\mu_h + \gamma_{k\tau})\, R_h, \\ \frac{d}{dt}S_m = \lambda_m - (1 - v_1)b\beta_m S_m S_{N_m} I_h - (\mu_m + \phi_1 v_1 + \phi_2 v_2)\, S_m, \\ \frac{d}{dt}E_m = (1 - v_1)b\beta_m S_m S_{N_m} I_h - (\mu_m + \eta_m + \phi_1 v_1 + \phi_2 v_2)\, E_m \\ \frac{d}{dt}I_m = \eta_m E_m - (\mu_m + \phi_1 v_1 + \phi_2 v_2)\, I_m. \end{cases}$$

3.3.2.2 Right Caputo fractional derivatives (RCFD)

From (2.27), the second relation of (2.25) becomes

$$ {}_{t}^{c}D_{T}k = -\frac{d}{dt}k = \frac{\partial L}{\partial x} + k^{T}\frac{\partial G}{\partial x}. \tag{3.34} $$

Therefore, in (3.34) we have that

$$ \frac{d}{dt}k = (\frac{d}{dt}k_1, \frac{d}{dt}k_2, \frac{d}{dt}k_3, \frac{d}{dt}k_4, \frac{d}{dt}k_5, \frac{d}{dt}k_6, \frac{d}{dt}k_7)^{T}, $$

and $\dfrac{\partial L}{\partial x}$ gives that

$$ \begin{gathered} \frac{\partial L}{\partial S_h} = 0, \quad \frac{\partial L}{\partial E_h} = A, \quad \frac{\partial L}{\partial I_h} = B, \quad \frac{\partial L}{\partial R_h} = 0, \\ \frac{\partial L}{\partial S_m} = C, \quad \frac{\partial L}{\partial E_m} = C \quad and \quad \frac{\partial L}{\partial I_m} = C. \end{gathered} \tag{3.35} $$

In the same way, for $\dfrac{\partial G}{\partial x}$ we have to find the first component S_h:

$$ \frac{\partial G}{\partial S_h} = \begin{bmatrix} \dfrac{\partial \{\lambda_h - (1-v_1)b\beta_h S_h S_{N_h} I_m - \mu_h S_h + \gamma_{k\tau} R_h\}}{\partial S_h} \\ \dfrac{\partial \{(1-v_1)b\beta_h S_h S_{N_h} I_m - (\mu_h + \eta_h) E_h\}}{\partial S_h} \\ \dfrac{\partial \{\eta_h E_h - (\mu_h + \delta_h + \rho_h + \phi_3 v_3) I_h\}}{\partial S_h} \\ \dfrac{\partial \{(\rho_h + \phi_3 v_3) I_h - (\mu_h + \gamma_{k\tau}) R_h\}}{\partial S_h} \\ \dfrac{\partial \{\lambda_m - (1-v_1)b\beta_m S_m S_{N_m} I_h - (\mu_m + \phi_1 v_1 + \phi_2 v_2) S_m\}}{\partial S_h} \\ \dfrac{\partial \{(1-v_1)b\beta_m S_m S_{N_h} I_m - (\mu_m + \eta_m + \phi_1 v_1 + \phi_2 v_2) E_m\}}{\partial S_h} \\ \dfrac{\partial \{\eta_m E_m - (\mu_m + \phi_1 v_1 + \phi_2 v_2) I_m\}}{\partial S_h} \end{bmatrix} $$

which gives that

$$ \frac{\partial G}{\partial S_h} = \begin{bmatrix} -(1-v_1)b\beta_h S_h S_{N_h} I_m - \mu_h \\ (1-v_1)b\beta_h S_h S_{N_h} I_m \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}. \tag{3.36} $$

By using the system (3.36), we get

$$ k^{T}\frac{\partial G}{\partial S_h} = k_1\left(-(1-v_1)b\beta_h S_h S_{N_h} I_m - \mu_h\right) + k_2(1-v_1)b\beta_h S_h S_{N_h} I_m. \tag{3.37} $$

From (3.34), there are seven equations related to the adjoint variables. Thus, the first equation in (3.34) is obtained by using (3.35) and (3.37) in the following way:

$$-\frac{d}{dt}k_1 = \frac{\partial L}{\partial S_h} + k^T \frac{\partial G}{\partial S_h} = (k_2 - k_1)(1 - v_1)b\beta_h I_m - k_1\mu_h.$$

Similarly, from (3.34) we have

$$\begin{cases} -\frac{d}{dt}k_1 = (k_2 - k_1)(1 - v_1)b\beta_h S_{N_h} I_m - k_1\mu_h, \\ -\frac{d}{dt}k_2 = A + (k_3 - k_2)\eta_h - k_2\mu_h, \\ -\frac{d}{dt}k_3 = B + (k_4 - k_3)(\rho_h + \phi_3 v_3) + (k_6 - k_5)(1 - v_1)b\beta_m S_m \alpha_1 S_{N_m} S_m - k_3\left(\delta_h + \mu_h\right), \\ -\frac{d}{dt}k_4 = (k_1 - k_4)\gamma_{k\tau} - k_4\mu_h, \\ -\frac{d}{dt}k_5 = C + (k_6 - k_5)(1 - v_1)b\beta_m S_{N_m} I_h - k_5\left(\mu_m + \phi_1 v_1 + \phi_2 v_2\right), \\ -\frac{d}{dt}k_6 = C + (k_7 - k_6)\eta_m - k_6\left(\mu_m + \phi_1 v_1 + \phi_2 v_2\right), \\ -\frac{d}{dt}k_7 = C + (k_2 - k_1)(1 - v_1)b\beta_h S_h \alpha_1 S_{N_h} - k_7\left(\mu_m + \phi_1 v_1 + \phi_2 v_2\right). \end{cases}$$

Since for the control variable $\frac{\partial L}{\partial v} + k^T \frac{\partial G}{\partial v} = 0$, we obtain

$$\begin{bmatrix} \frac{\partial L}{\partial v_1} + k^T \frac{\partial G}{\partial v_1} \\ \frac{\partial L}{\partial v_2} + k^T \frac{\partial G}{\partial v_2} \\ \frac{\partial L}{\partial v_3} + k^T \frac{\partial G}{\partial v_3}. \end{bmatrix} = 0. \tag{3.38}$$

The terms of the first relation of (3.38) are

$$\frac{\partial L}{\partial v_1} = \frac{\partial AE_h + BI_h + CI_m + Dv_1^2 + Ev_2^2 + Fv_3^2}{\partial v_1} = Dv_1$$

and

$$\frac{\partial G}{\partial v_1} = \begin{bmatrix} \frac{\partial\left\{\lambda_h - (1 - v_1)b\beta_h S_h S_{N_h} I_m - \mu_h S_h + \gamma_{k\tau} R_h\right\}}{\partial v_1} \\ \frac{\partial\left\{(1 - v_1)b\beta_h S_h S_{N_h} I_m - (\mu_h + \eta_h) E_h\right\}}{\partial v_1} \\ \frac{\partial\left\{\eta_h E_h - (\mu_h + \delta_h + \rho_h + \phi_3 v_3) I_h\right\}}{\partial v_1} \\ \frac{\partial\left\{(\rho_h + \phi_3 v_3) I_h - (\mu_h + \gamma_{k\tau}) R_h\right\}}{\partial v_1} \\ \frac{\partial\left\{\lambda_m - (1 - v_1)b\beta_m S_{N_m} I_h S_m - (\mu_m + \phi_1 v_1 + \phi_2 v_2) S_m\right\}}{\partial v_1} \\ \frac{\partial\left\{(1 - v_1)b\beta_m S_{N_m} I_h S_m - (\mu_m + \eta_m + +\phi_1 v_1 \phi_2 v_2) E_m\right\}}{\partial v_1} \\ \frac{\partial\left\{\eta_m E_m - (\mu_m + \phi_1 v_1 + \phi_2 v_2) I_m\right\}}{\partial v_1} \end{bmatrix}$$

$$= \begin{bmatrix} b\beta_h S_h S_{N_h} I_m \\ -b\beta_h S_h S_{N_h} I_m \\ 0 \\ 0 \\ (b\beta_m S_{N_m} I_h - \phi_1) S_m \\ -b\beta_m S_m S_{N_m} I_h - \phi_1 E_m \\ -\phi_1 I_m \end{bmatrix}. \tag{3.39}$$

From (3.39) we have,

$$k^T \frac{\partial G}{\partial v_1} = (k_1 - k_2) b\beta_h S_h S_{N_h} I_m + (k_5 - k_6) b\beta_m S_m S_{N_m} I_h - k_5\phi_1 S_m - k_6\phi_1 E_m - k_7\phi_1 I_m.$$

Finally, we obtain

$$\begin{aligned} &\tfrac{\partial L}{\partial v_1} + K^T \tfrac{\partial G}{\partial v_1} \\ &= 2Dv_1 + (k_1 - k_2) b\beta_h S_h S_{N_h} I_m + (k_5 - k_6) b\beta_m S_m S_{N_m} I_h - (k_5 S_m + k_6 E_m + k_7 I_m)\, \phi_1 = 0. \end{aligned}$$

Similarly, the second and the third relations of (3.38) give

$$\begin{cases} 2Dv_1 + (k_1 - k_2) b\beta_h S_h S_{N_h} I_m + (k_5 - k_6) b\beta_m S_m S_{N_m} I_h - (k_5 S_m + k_6 E_m + k_7 I_m)\, \phi_1 = 0, \\ 2Ev_2 - k_5\lambda_m - k_5\phi_2 S_m - (k_6 E_m + k_7 I_m)\phi_2 = 0, \\ 2Fv_3 + (k_4 - k_3)\phi_3 I_h = 0. \end{cases} \tag{3.40}$$

Using (3.40), we get controls as

$$\begin{cases} v_1 = \dfrac{(k_2 - k_1) b\beta_h S_h S_{N_h} I_m + (k_6 - k_5) b\beta_m S_m S_{N_m} I_h + (k_5 S_m + k_6 E_m + k_7 I_m)\, \phi_1}{2D}, \\ v_2 = \dfrac{k_5\lambda_m + k_5\phi_2 S_m + (k_6 E_m + k_7 I_m)\phi_2}{2E}, \\ v_3 = \dfrac{(k_3 - k_4)\phi_3 I_h}{2F}. \end{cases} \tag{3.41}$$

The obtained values of v_1, v_2 and v_3 can be out of [0, 1], but by [48], the existence and continuity property of optimal controls are due to the convexity of L with respect to v_i where v_i is bounded, meaning that V is closed and $v_i \in V$. Therefore, the solution of optimal control v_i^* should be ranged in $[0, 1]$ because its control component v_i is bounded in $[0, 1]$. From (3.41), we deduce the optimal control v_i^* as follow;

$$v_i^* = \begin{cases} 0 & if \quad v_i \le 0, \\ v_i & if \quad 0 < v_i < 1, \\ 1 & if \quad v_i \ge 1, \end{cases} \qquad with\ i = \ 1,\ 2,\ 3.$$

Chapter 4

Numerical simulation

The real data of malaria in Rwanda context were used to identify the parameters of our malaria model and the calculation were done using MATLAB by solving an optimal control problem. We present numerical tests without control measures and we analyze the effect of control strategies applied on malaria dynamics in Rwanda.

4.1 Setting of data and computing model parameters

4.1.1 Setting of data

The data are helped to estimate the parameters of the malaria model. We use the secondary data of WHO as given in World malaria report for Rwanda [50]. These data are based on the human population. In [50] the susceptible human stands on population at risk, exposed human is suspected population and the infected human stands on the presumed and confirmed population. The recovered human population is determined by the difference of infected human population and death number of human population [6].

In the US-PMI [46], the hot region of Rwanda where the mosquitoes are predominant were considered, where the data of Anopheles mosquitoes were collected in some sectors of Nyagatare, Bugesera, Kirehe and Ngoma districts in 2016, 2017 and 2018. Referring to collected mosquitoes from these sectors, we estimated the number of susceptible, exposed and infected mosquitoes per district from that region. In [46] the rate of higher and lower burden districts in malaria transmission are established. The secondary data of mosquitoes and the results from a World malaria report [50] help to know the districts with lower and higher number of malaria cases. The Table 4.1 shows the data reported in [50] in Rwandan context.

Table 4.1: The secondary data in number of dynamic of malaria in Rwanda from 2010 to 2018

Years	2010	2011	2012	2013	2014	2015	2016	2017	2018
All population	10039338	10293331	10549678	10811545	11083635	11369071	11668818	11980937	12301939
All death	73287	69995	67518	65950	64285	63667	63012	63499	63970
Susceptible human	6696358	8483583	6973916	6813612	5303960	2784195	859919	32989	1904259
Exposed human	2070304	1393373	2611916	2125509	2567394	3587320	4177496	3144393	2023452
Infected human	638669	208898	483470	939076	1610812	2505794	3324678	4413473	4198029
Death due to malaria	670	380	459	409	496	516	715	376	345
Other death	72617	69615	67059	65541	63789	63151	62297	63123	63629
Recovered humans	634007	207477	480376	933348	1601469	2491762	3306725	4390082	4176199
Total mosquitoes	154262	404748	362179	305214	259097	235101	161756	98205	139667
Susceptible mosquitoes	78102	353382	290497	255438	198842	115975	35820	1374	76942
Exposed mosquitoes	75989	51143	71553	49519	59814	118364	124925	95489	61448
Infected mosquitoes	171	224	130	257	441	762	1011	1342	1277

For seeking a simplicity of the calculation, we set that the sum of variables is equal to 1. This does not change the results but numerical simulations and the solution of the optimal control problem (1.1)-(3.32) in MATLAB is quickly performed. From (3.1) and (3.2) we set

$$s_h(t) = \frac{S_h(t)}{N_h}, \quad e_h(t) = \frac{E_h(t)}{N_h}, \quad i_h(t) = \frac{I_h(t)}{N_h}, \quad r_h(t) = \frac{R_h(t)}{N_h} \tag{4.1}$$

and

$$s_m(t) = \frac{S_m(t)}{N_m}, \quad e_m(t) = \frac{E_m(t)}{N_m}, \quad i_m(t) = \frac{I_m(t)}{N_m}. \tag{4.2}$$

Therefore, we get

$$1 = s_h(t) + e_h(t) + i_h(t) + r_h(t), \tag{4.3}$$

and

$$1 = s_m(t) + e_m(t) + i_m(t). \tag{4.4}$$

From the Table 4.1 and using (4.3) and (4.4), the Table 4.2 describes the dynamics of malaria in Rwanda for each variable of the mathematical model.

Table 4.2: Number of dynamic of malaria in Rwanda using data given in Table 4.1 and taking into consideration the relations (4.3) and (4.4)

Years	2010	2011	2012	2013	2014	2015	2016	2017	2018
Susceptible human	0.6670	0.8242	0.6611	0.6302	0.4785	0.2449	0.0737	0.0028	0.1548
Exposed human	0.2062	0.1354	0.2476	0.1966	0.2316	0.3155	0.3580	0.2624	0.1645
Infected human	0.0636	0.0203	0.0458	0.0869	0.1453	0.2204	0.2849	0.3684	0.3412
Recovered humans	0.063	0.020	0.046	0.086	0.144	0.219	0.283	0.366	0.339
Susceptible mosquitoes	0.506	0.873	0.802	0.837	0.767	0.493	0.221	0.014	0.551
Exposed mosquitoes	0.493	0.126	0.198	0.162	0.231	0.503	0.772	0.972	0.440
Infected mosquitoes	0.001	0.001	0.0004	0.001	0.002	0.003	0.006	0.014	0.009

4.1.2 Computing model parameters

To find the parameter values, a lot of methods can be used. As long as they stay in a reasonable range, it seems that many different specific values are possible due to the variety of populations, regions, treatments and variables of the mathematical model. Using (4.1) and (4.2); the system (3.5) becomes,

$$\begin{cases} \frac{ds_h}{dt} = \lambda_h - b\beta_h s_h S_{N_h} i_m(t) - \mu_h s_h + \gamma_{k\tau} r_h, \\ \frac{de_h}{dt} = b\beta_h s_h S_{N_h} i_m(t) - (\mu_h + \eta_h)\, e_h, \\ \frac{di_h}{dt} = \eta_h e_h - (\mu_h + \delta_h + \rho_h)\, i_h, \\ \frac{dr_h}{dt} = \rho_h i_h - (\mu_h + \gamma_{k\tau})\, r_h, \\ \frac{ds_m}{dt} = \lambda_m - b\beta_m s_m S_{N_m} i_h(t) - \mu_m s_m \\ \frac{de_m}{dt} = b\beta_m s_m S_{N_m} i_h(t) - (\mu_m + \eta_m)\, e_m, \\ \frac{di_m}{dt} = \eta_m e_m - \mu_m i_m. \end{cases} \tag{4.5}$$

The discretization of the system (4.5) can be done through a wide choice of the methods. Euler method is one which is convergent alongside among others. The derivative of any variable $\frac{dx}{dt}$ is approximated by

$$\frac{dx}{dt} \approx \frac{x_j - x_{j-1}}{\Delta t}, \quad 0 \leq t \leq T_{\max},\ j = 1, ..., N$$

with considering that $x^j = x(t_j)$ and $\Delta t = \frac{T_{\max}}{N}$ with N indicates the total number of discretization intervals such that $x_j = x_{j-1} + \Delta t$. Therefore, the discrete system (4.5) becomes

$$\begin{cases} s_h^{n+1} = (1 - \Delta t\mu_h)s_h^n + \Delta t\left(\lambda_h - b\beta_h s_h^n S_{N_h} i_m^n + \gamma_{k\tau} r_h^n\right), \\ e_h^{n+1} = (1 - \Delta t\left(\mu_h + \eta_h\right))e_h^n + \Delta t b\beta_h s_h^n S_{N_h} i_m^n(t), \\ i_h^{n+1} = (1 - \Delta t\left(\mu_h + \delta_h + \rho_h\right))i_h^n + \Delta t e_h^n \eta_h e_h^n, \\ r_h^{n+1} = (1 - \Delta t\left(\mu_h + \gamma_{k\tau}\right))\, r_h^n + \Delta t\rho_h i_h^n, \\ s_m^{n+1} = (1 - \Delta t\mu_m)\, s_m^n + \Delta t\left(\lambda_m - b\beta_m s_m^n S_{N_m} i_h^n\right) \\ e_m^{n+1} = (1 - \Delta t\left(\mu_m + \eta_m\right))e_m^n + \Delta t b\beta_m s_m^n S_{N_m} i_h^n, \\ i_m^{n+1} = (1 - \Delta t\mu_m)i_m^n + \Delta t\eta_m e_m^n. \end{cases} \tag{4.6}$$

To estimate the model parameter, first let us focus on defining the cost function of an optimal control. We consider

$$\underline{i_h}^{\mu} = (i_h^{\mu}(t_1), ..., i_h^{\mu}(t_N))^T,$$
$$\underline{i_m}^{\mu} = (i_m^{\mu}(t_1), ..., i_m^{\mu}(t_N))^T,$$

where the measured data are $i_h^{\mu}(t_k)$ and $i_m^{\mu}(t_k)$ in given time $t_k = \frac{kT_{\max}}{N}$, expressing ideal values $i_h(t_k)$ and $i_m(t_k)$ respectively. The super script μ denotes the perturbation parameter which is caused by some imprecision on measured data. Mathematically, the problem can be identified and formulated as follows.

Find $\underline{u}= (\lambda_h, \beta_h, \mu_h, \eta_h, \delta_h, \rho_h, \lambda_m, \beta_m, \mu_m, \eta_m, \alpha, \upsilon, k, \tau)^t$, solution of the output least squares problem,

$$J(\underline{u}) = \min_{\underline{u}} J(\underline{u}) \tag{4.7}$$

subject to (4.6) where

$$J(\underline{u}) = \left\|\underline{i_h}^{\mu} - i_h^{\mu}\right\|^2 + \left\|\underline{i_m}^{\mu} - i_m^{\mu}\right\|^2.$$

Since $(\underline{i_h}, \underline{i_m})^t$ depend continuously on $\underline{u}$, the problem (4.7) is a nonlinear inverse problem which is ill-posed due to the aspect of data behavior. Therefore, small data perturbation enables solution to be different from the original one. The well posed problem from (4.7) is obtained using regularization techniques [10]. One of these regularization techniques is Tikhonov regularization [10] which considers the problem as follows. Find $\underline{\bar{u}}^{\eta}$ solution of

$$J(\underline{\bar{u}}^{\eta}) = \min_{\underline{u}} J^{\eta}(\underline{u}) \tag{4.8}$$

subject to (4.6) where we have set

$$J^{\eta}(\underline{u}) = \left\|\underline{i_h}^{\mu} - i_h^{\mu}\right\|^2 + \left\|\underline{i_m}^{\mu} - i_m^{\mu}\right\|^2 + \eta \left\|\mathcal{L}u\right\|^2$$

for a certain η such that $\underline{u}^{\eta}$ is converging toward the solution $\underline{u}$ as $\eta \to 0$. Here $\mathcal{L}$ is defined as an operator helped in stabilization (i.e., $\mathcal{L}$ is the identity, a differentiation operator, ...).

The fminicom is used in numerical simulation to identify the parameters in a model to the best fit data in solving the objective function subject to (4.5) . The observed data are those described in the Table 4.2. MATLAB packages enable to carry out numerical solutions for solving the optimization problem (4.6) - (4.8).

Table 4.3: Estimate value of the mathematical model

Parameter	Value	Parameter	Value	Parameter	Value	Parameter	Value	Parameter	Value
λ_h	29.3285	b	39.4232	β_h	0.9802	μ_h	0.8636	η_h	46.9972
δ_h	5.9195	ρ_h	6.0048	υ	14.0843	k	26.4648	τ	26.4639
λ_m	17.6182	β_m	0.9517	μ_m	44.9498	η_m	0.8227	α	28.6799

The Table 4.3 shows the estimate parameters whereas the trend of infectious humans (i_h) and infectious mosquitoes (i_m) foud from the model and their observed data are illustrated in Figures 4.1 and 4.2.

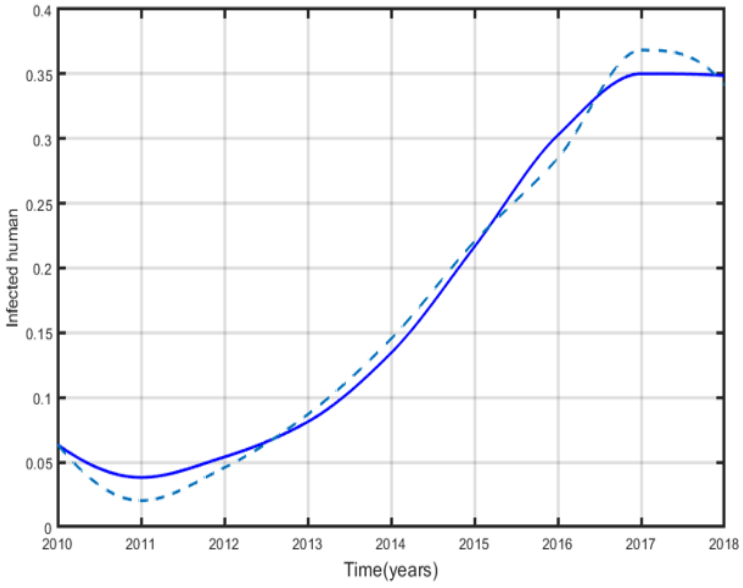

Figure 4.1: Trend of infectious humans. It shows that the solutions of the mathematical model (4.5) (Solid lines) are close to observed data (dashed lines) for infected human

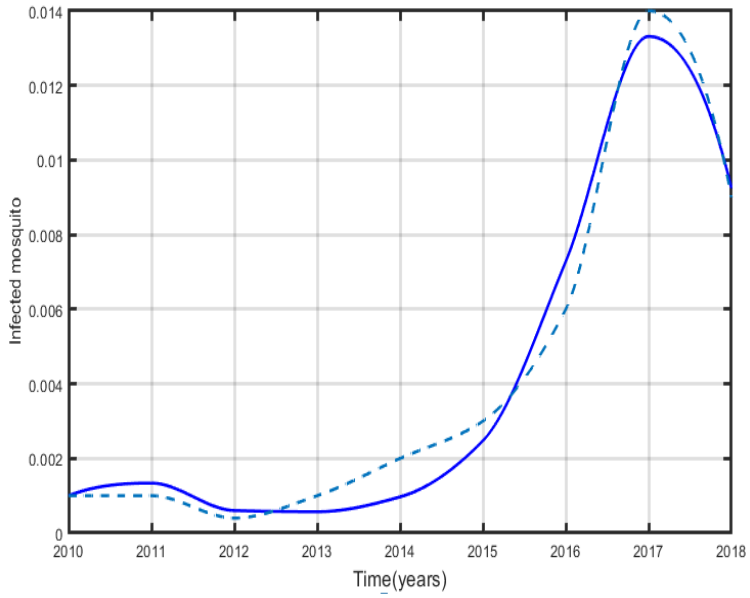

Figure 4.2: Trend of infectious mosquitoes. It shows that the solutions of the mathematical model (4.5) (Solid lines) are close to observed data (dashed lines) for infected mosquitoes

4.2 Numerical test and Discussion

4.2.1 Simulation of malaria model (3.5)

4.2.1.1 Computing the basic reproduction number of model (3.5)

As it is mentioned in chapter 3, the basic reproduction number is the most frequently used by epidemiologists in mathematical models. The result of the reproduction number is obtained by applying the formula that is

$$R_0 = \rho\left(FV^{-1}\right) = \sqrt{\frac{b^2\beta_h\lambda_h S_{N_h}\eta_h\beta_m\lambda_m S_{N_m}\eta_m}{\mu_h\left(\mu_h+\eta_h\right)\left(\mu_h+\delta_h+\rho_h\right)\mu_m^2\left(\mu_m+\eta_m\right)}}$$

and the parameters obtained in the Table 4.3. After calculation we get the reproduction number $R_0 = 1.3250$. This result shows that new infection population produced by one typical infective is greater than one and the size of infective class is increased. During any time, the disease will spread in the population of the country. Therefore, here the control is very needed to control the disease in the way of decreasing the size of infected population. Thereafter we focus on this issue.

4.2.1.2 Numerical simulation of malaria model (3.5)

This simulation of the model (3.5) was done without considering the intervention strategies on malaria transmission in Rwanda. Basing one the basic reproduction number, we calculated in relation (3.8)-(3.9) by using the value of parameters in the Table 4.3.

For Figures 4.3, the susceptible human was increased as the time increase. The exposed human decreased small bit and increased slowly until 2018. The infected human was increased and decreased within a half of year and then decreased with small rate until 2018. Humans recovered due to some existence treatments. For Figure 4.4, the mosquitoes were just increased around two years decreased in small bit then they were increased slowly until 2018.

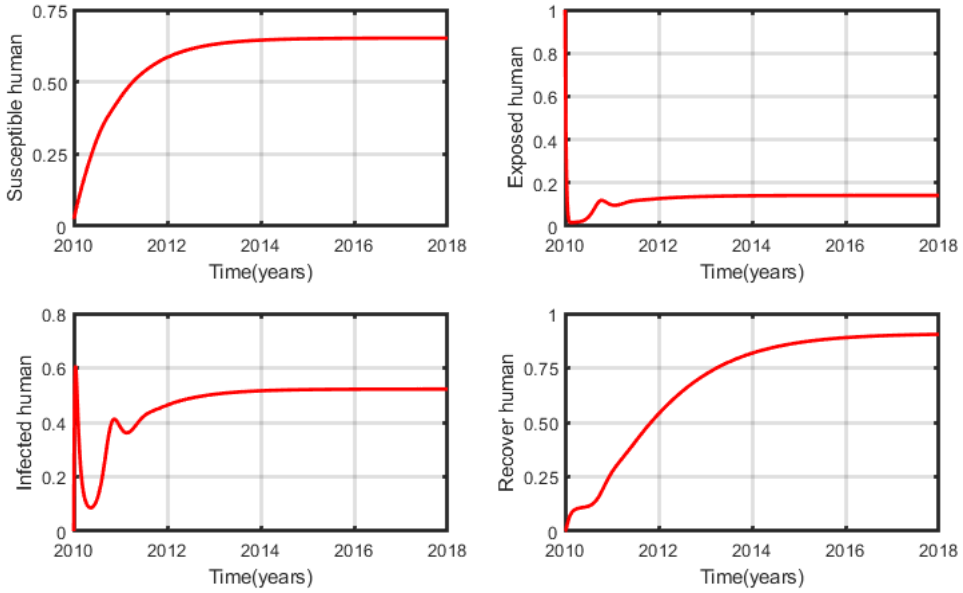

Figure 4.3: Trend of Susceptible, Exposed, Infected and Recover humans without intervention strategies

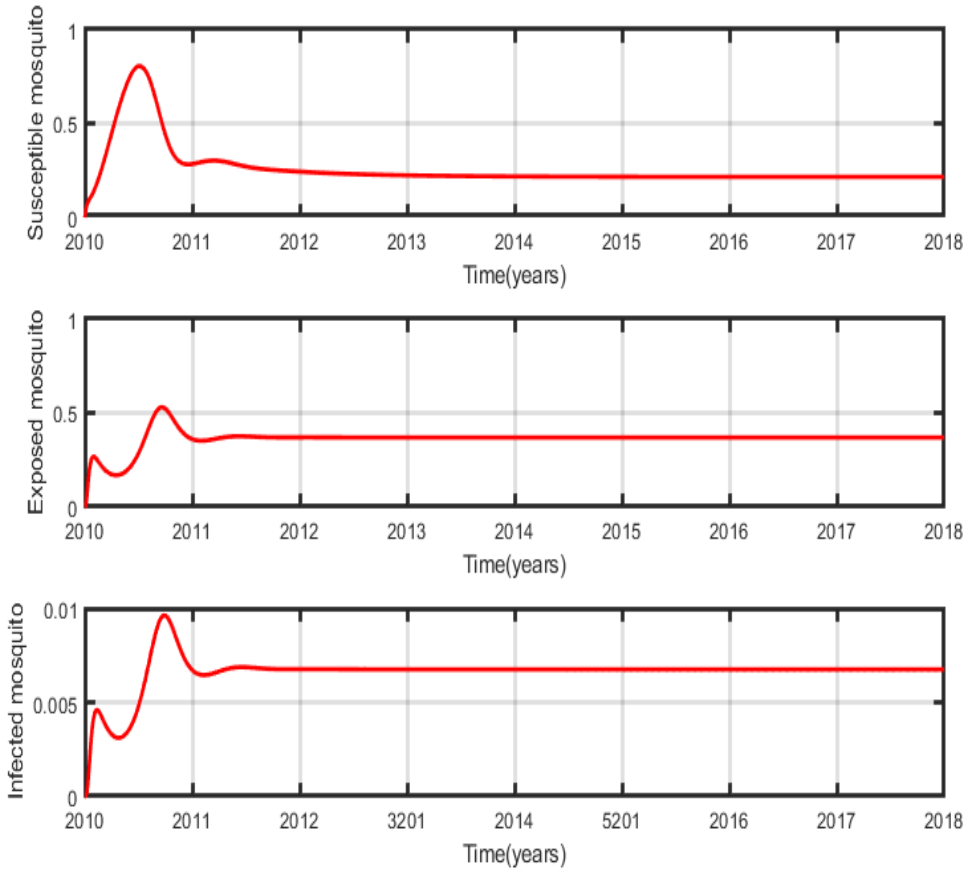

Figure 4.4: Trend of Susceptible, Exposed and Infected mosquitoes without intervention strategies

It is clear that without control; the calculation shows that the reproduction number $R_0 = 1.3250$. This result shows that a typical infected population produced more than one infected population.

4.2.2 Numerical simulation of optimal control problem (1.1)-(3.32)

Numerical simulations of malaria model can be done in two different ways: Sensitivity analysis of reproduction number R_0 by changing some parameters which intervene in its mathematical expression or exploration of optimal control strategy. Here we would like to solve the optimal control problem with cost function (3.32) subject to (1.1) by considering different cases of control impact. The numerical simulations are done using MATLAB packages. To clarify the crucial role of using control measures to prevent the malaria transmission in Rwanda population, the results are illustrated in figures where the dashed lines denote the use of controls while solid lines are related to not using control strategy.

4.2.2.1 Malaria prevention using insecticide treated bed nets

The strategy is to use treated bed net ($v_1(t) \neq 0$) and to consider ($v_2(t) = v_3(t) = 0$). The Figure 4.5 illustrate the results of numerical simulations.

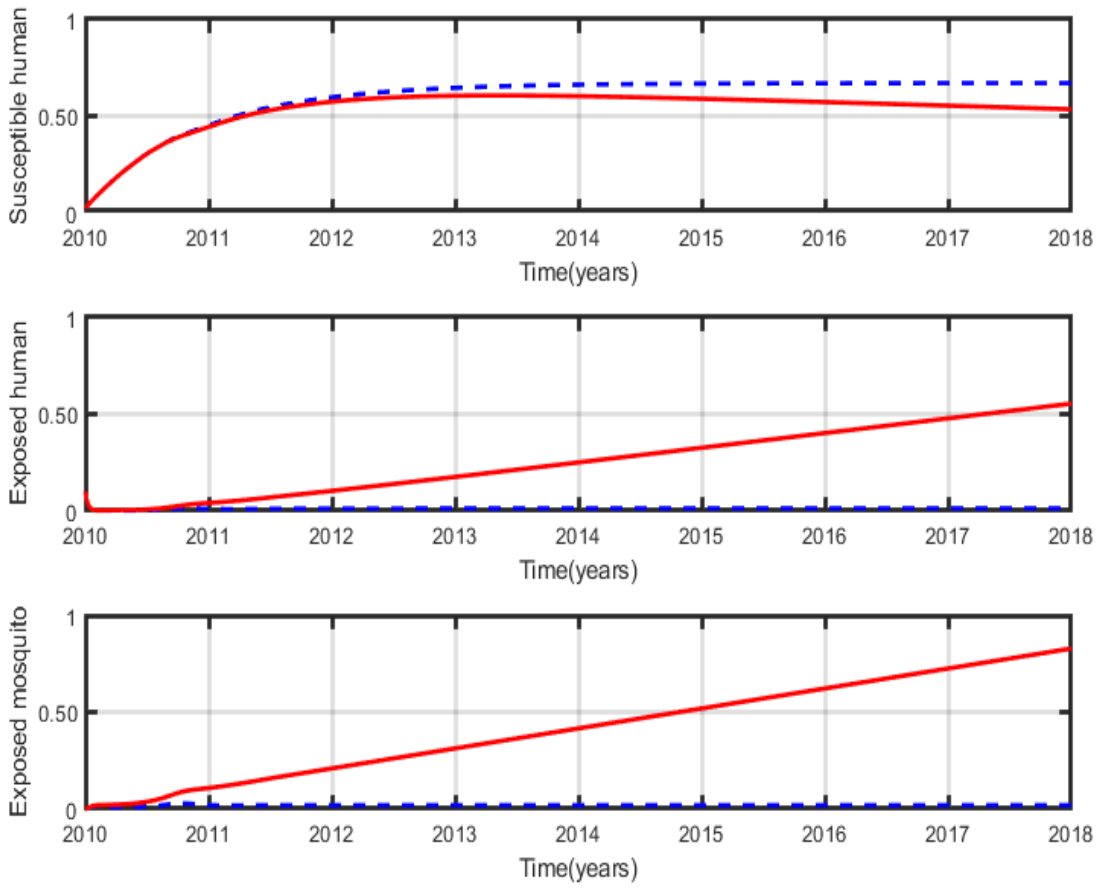

Figure 4.5: Impact of using treated bed net on the variation of susceptible, exposed human and exposed mosquito.

It is clear that with the use of ITNs; the calculation shows that the reproduction number $R_0 = 1.0769$. This result shows that a typical infected population produced more than one infected population.

4.2.2.2 Malaria prevention using indoor residual spray

The indoor residual spray ($v_2(t) \neq 0$) is used and to consider ($v_1(t) = v_3(t) = 0$). The results of numerical simulation are shown in the Figure 4.6.

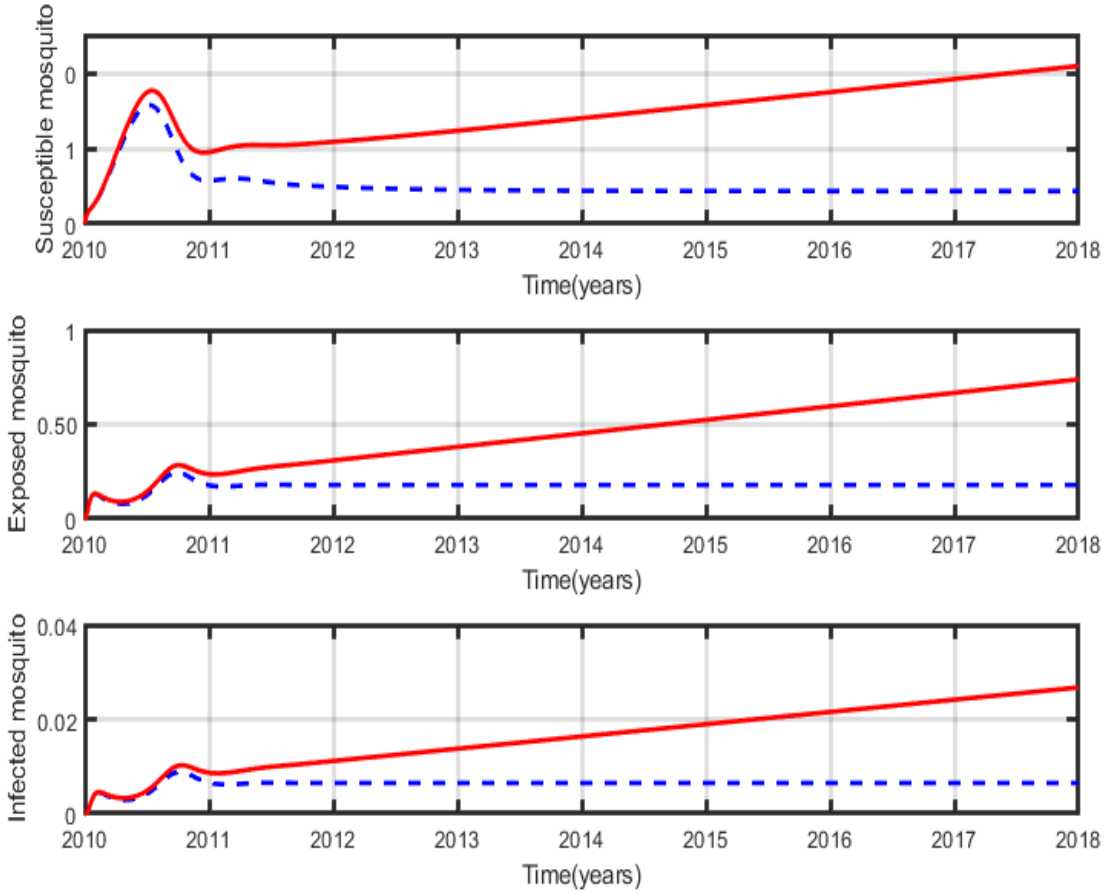

Figure 4.6: Impact of using indoor residual spray on the variation of susceptible, exposed and infected mosquitoes.

With the use of IRS; the calculation shows that the reproduction number $R_0 = 1.0781$. This result shows that a typical infected population produced more than one infected population.

4.2.2.3 Malaria prevention using Artemisinin based Combination Therapies

The Artemisinin based Combination Therapies ($v_3(t) \neq 0$) is used while the other controls are zero ($v_1(t) = v_2(t) = 0$). The Figure 4.7 shows the representation of numerical simulations.

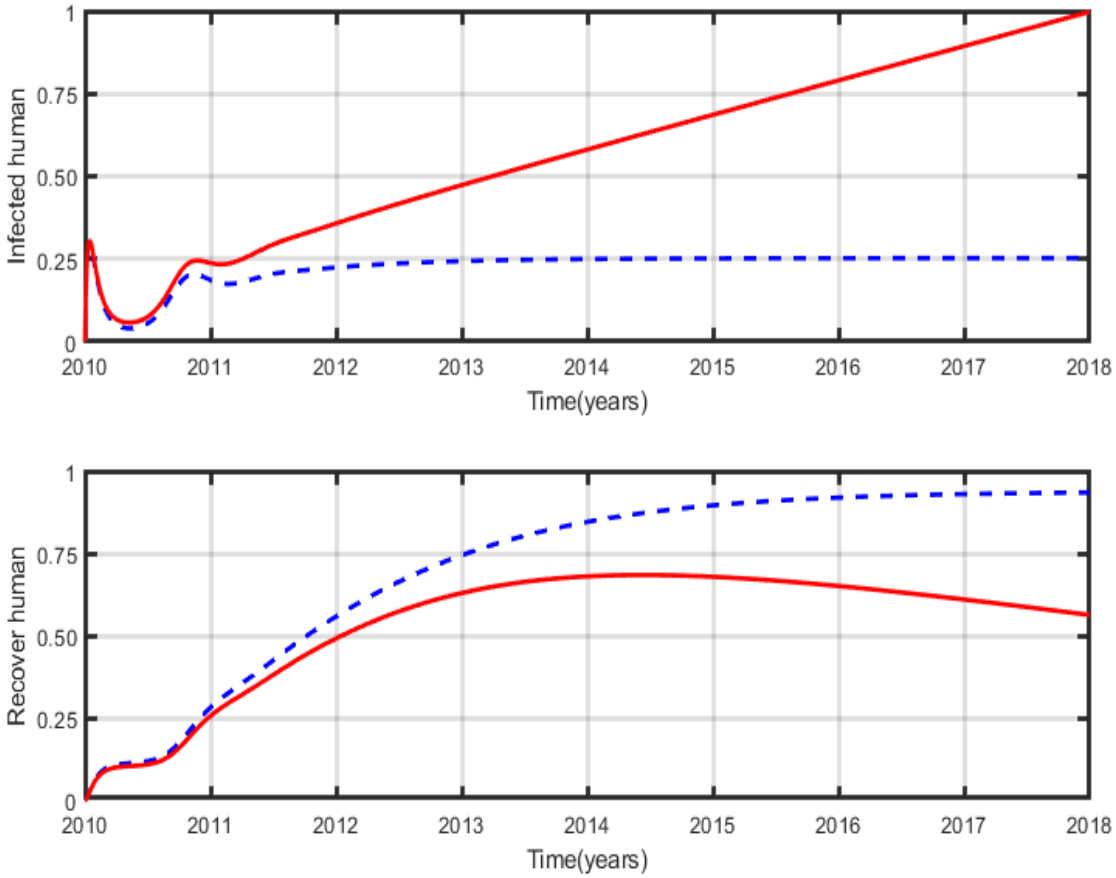

Figure 4.7: Impact of using Artemisinin based Combination Therapies on the variation of infected and recover human.

It is clear that with the use of ACTs; the calculation shows that the reproduction number $R_0 = 1.0780$. This result shows that a typical infected population produced more than one infected population.

4.2.2.4 Malaria prevention using insecticide treated bed nets and indoor residual spray

The combination of use insecticide treated bed nets ($v_1(t) \neq 0$) and indoor residual spray ($v_2(t) \neq 0$) are used and ($v_3(t) = 0$). The results of numerical simulations are given in the Figure 4.8.

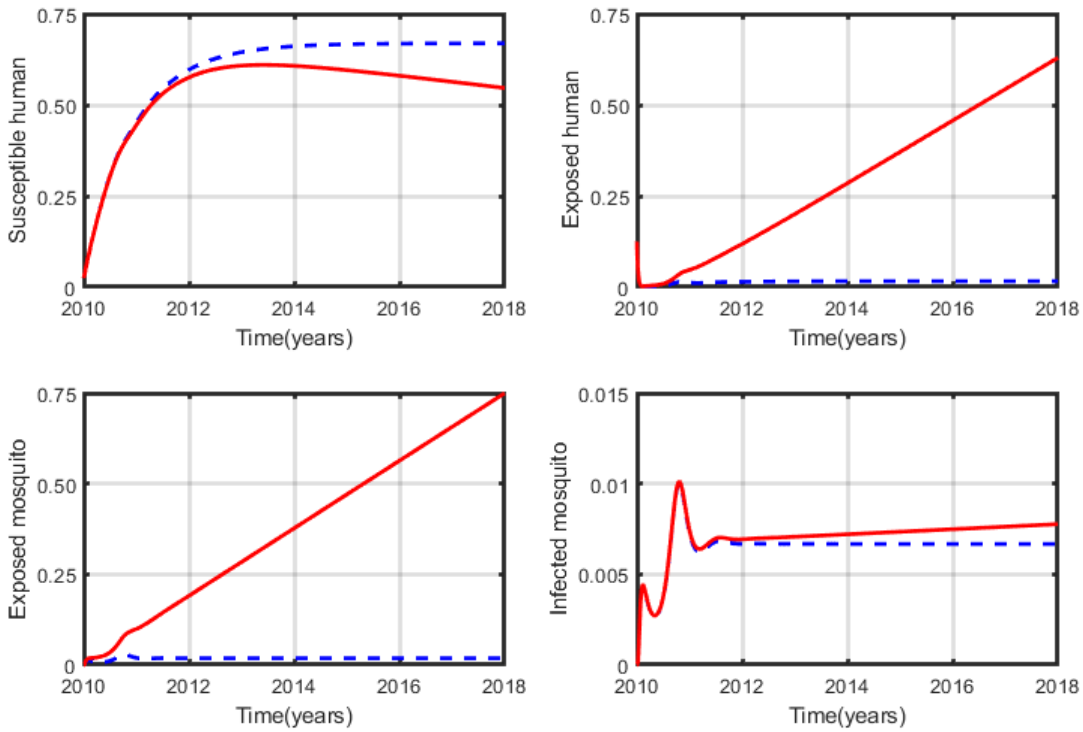

Figure 4.8: Impact of using ITNs and IRS on the variation of susceptible, exposed human, exposed and infected mosquitoes.

Using ITNs and IRS as controls; the calculation shows that the reproduction number $R_0 = 1.0333$. This result shows that a typical infected population produced more than one infected population.

4.2.2.5 Malaria prevention using insecticide treated bed nets and Artemisinin based Combination Therapies

The insecticide treated bed nets ($v_1(t) \neq 0$) together with Artemisinin based Combination Therapiest ($v_2(t) \neq 0$) are used and ($v_2(t) = 0$). numerical simulations results are shown in the Figures 4.9 and 4.10.

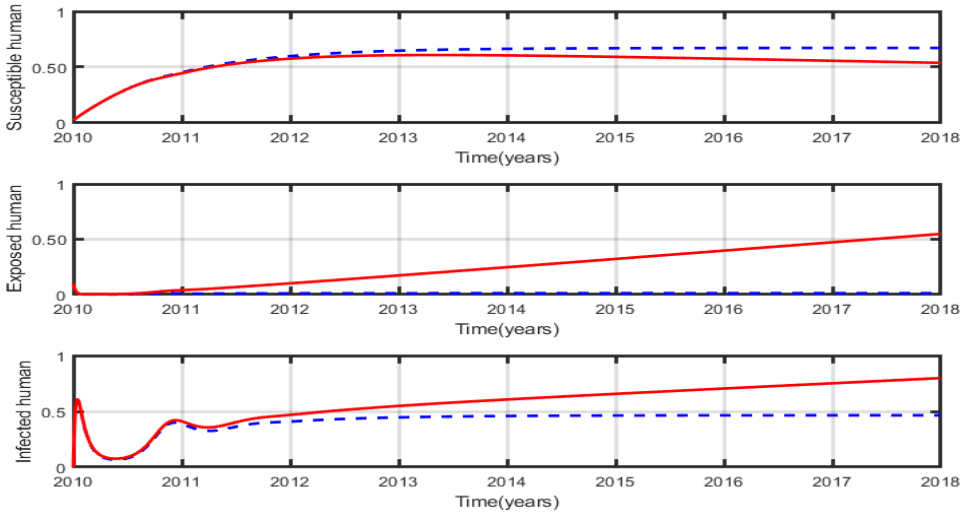

Figure 4.9: Impact of using insecticide treated bed nets and Artemisinin based Combination Therapies on the variation of susceptible, exposed and infected human.

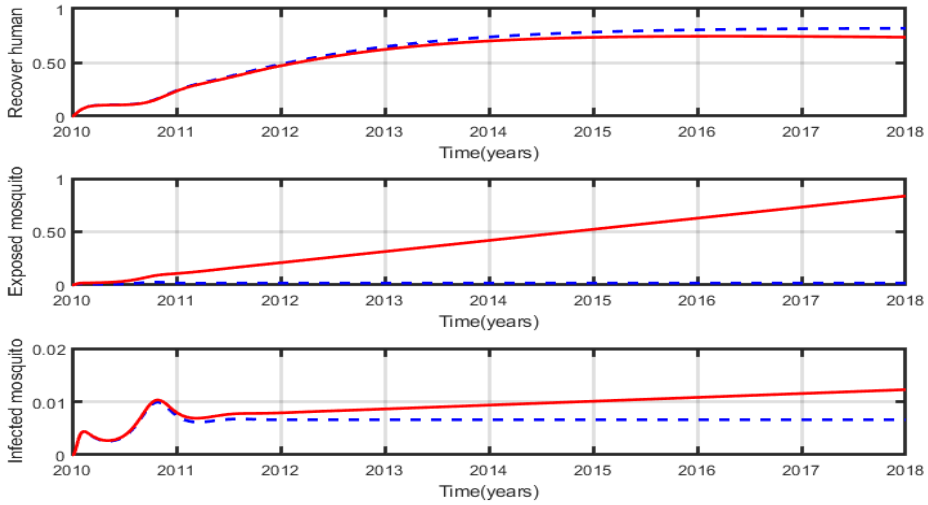

Figure 4.10: Impact of using insecticide treated bed nets and Artemisinin based Combination Therapies on the variation of recover human, exposed and infected mosquito.

Using ITNs and ACTs as controls; the calculation shows that the reproduction number $R_0 = 1.0299$. This result shows that a typical infected population produced around one infected population.

4.2.2.6 To prevent malaria Using the combination of indoor residual spray and Artemisinin based Combination Therapies

The indoor residual spray ($v_2(t) \neq 0$) and Artemisinin based Combination Therapies ($v_3(t) \neq 0$) are used. We obtain the results of numerical simulations plotted in the Figures 4.11.

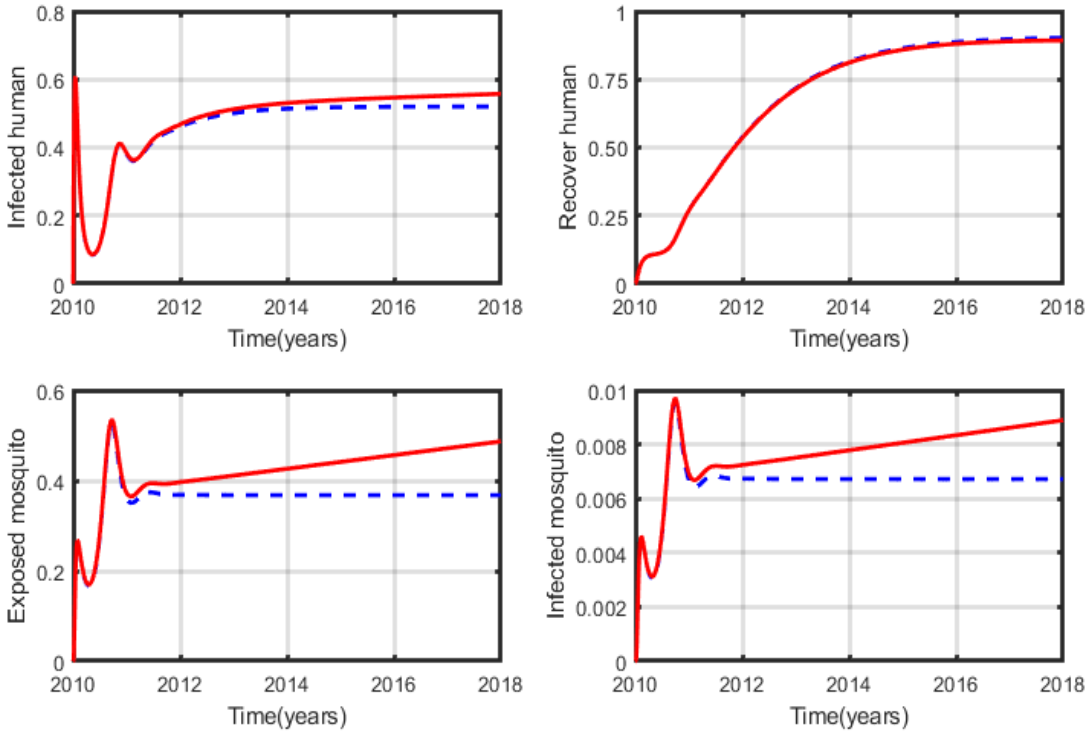

Figure 4.11: Impact of using IRS and ACTs on the variation of infected, recover human, exposed and infected mosquito.

Using the combination of IRS and ACTs as controls; the calculation shows that the reproduction number $R_0 = 1.0865$. This result shows that a typical infected population produced more than one infected population.

4.2.2.7 Using the combination of insecticide treated bed nets, indoor residual spray and Artemisinin based Combination Therapies to prevent malaria.

In this case, all controls; insecticide treated bed nets ($v_1(t) \neq 0$), indoor residual spray ($v_2(t) \neq 0$) and Artemisinin based Combination Therapies ($v_3(t) \neq 0$) as controls are used. We get the Figures 4.12 and 4.13 that illustrated the results of numerical simulations.

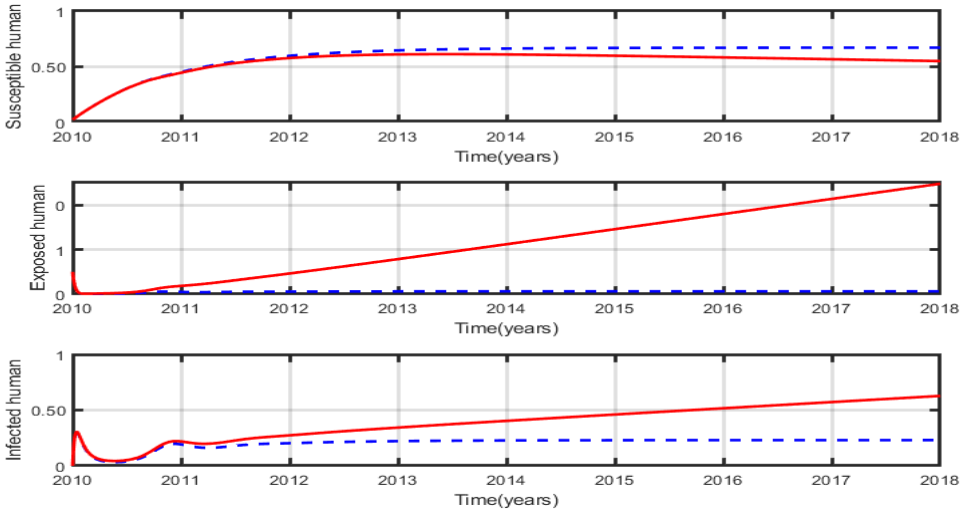

Figure 4.12: Impact of using ITNs, IRS and ACTs on the variation of susceptible, exposed and infected human.

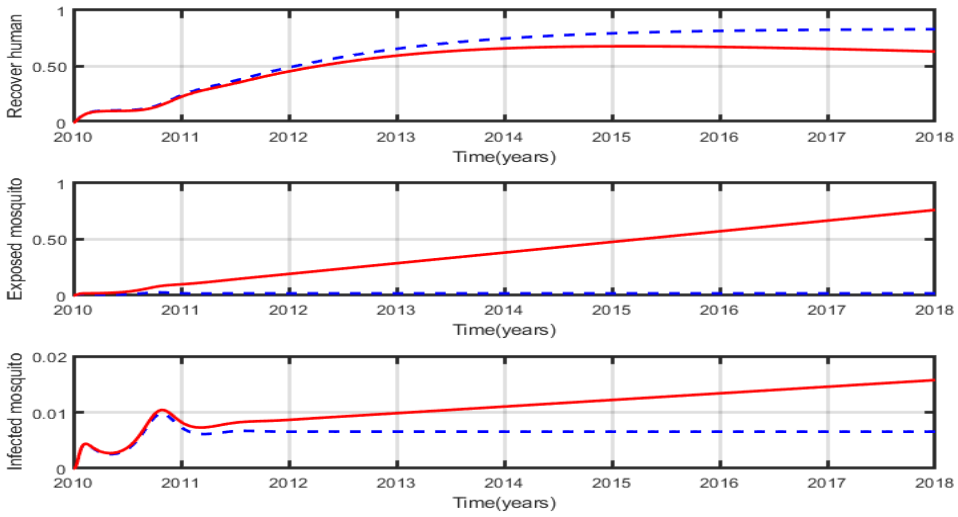

Figure 4.13: Impact of using ITNs, IRS and ACTs on the variation of mosquitoes.

Using the combination of ITNs, IRS and ACTs as controls; the calculation shows that the reproduction number $R_0 = 0.9699$. This result shows that a typical infected population produced less than one infected population. Therefore the disease will die out in the population.

4.2.3 Discussion

The results of reproduction number obtained using the parameters from the Table 4.3 shows that without intervention strategies, the malaria will spread in the population of country. The result of the optimal control problem helps to know which intervention or combination of controls that has the strong effect in the control of malaria. Basing on the results from numerical simulation, we show the highest impact for each control or combination of them.

- The expected impact of using ITNs is the reduction of the contact rate between humans and mosquitoes, killing some mosquitoes resulting in the reduction of mosquito population and exposed humans thus increasing susceptible humans. However, the Figure 4.5 shows that the highest impact of using ITNs is increasing susceptible humans and decreasing exposed humans and mosquitoes. Therefore, this control is not enough for eradicating the disease due to the persistence of infected population.

- The expected effect of using IRS in population is killing mosquitoes which reduces the rate of infections. As it is shown on the Figure 4.6, the highest impact of using IRS is lowering the mosquito population. The infected humans persist, which shows that this control is not enough in the control of malaria.

- The expected response of using ACTs in the population is the reduction of the morbidity and transmission rate of malaria. But, the Figure 4.7 shows that the highest impact of ACTs is a great reduction of infected humans and a high increase of human recovery. Since the mosquito population is not affected by this control, the disease cannot be eradicated.

- The expected result of using the ITNs and IRS at the same time is reducing the mosquitoes by killing them and the contact rate of human and mosquito. The Figure 4.8 shows that the highest impact of this combination is increasing susceptible human and decreasing exposed population. Then, this method is not effective due to persistence of infected population.

- The expected response of using the combination of ITNs and ACTs is increasing susceptible and human recovery, lowering the exposed and infected humans and mosquitoes. Therefore, the results from Figure 4.9 and Figure 4.10 show that the highest impact achieved is lowering exposed and infected population and increasing susceptible humans. This control can stabilize the disease.

- The expected effect of using the combination of IRS and ACTs is increasing the human recovery and decreasing the infected human and mosquito population. The Figure 4.11 shows that the highest impact is that the mosquitoes are highly decreased. However, all mosquitoes cannot be killed by IRS, thus the rate of malaria transmission cannot be zero.

- The expected impact of using the combination of ITNs, IRS and ACTs is increasing susceptible and human recovery, decreasing exposed and infected human then reducing mosquito population. The results from Figure 4.12 and 4.13 show that the highest impact of this combination is increasing the susceptible humans and human recovery and lowering the infected human and mosquitoes at a good level. Therefore, this method is the best as far as eradicating or lowering the disease in the country is concerned.

Our numerical findings indicate that the combination of ITNs, IRS and ACTs is best control strategies which is optimal for malaria in Rwanda. The combination of ITNs, IRS and ACTs in endemic region will be beneficial to the society for malaria control. Those who will follow these strategies can effectively minimize the rate of malaria transmission in Rwanda. Our findings are different from the results of OKELLO (2016) [30], who found that the best control of malaria is the use of IRS and ACTs both combined. The result of Gabriel (2016) [8], who found that to combine the use of ITNs and IRS is better in endemic region.

Chapter 5

Conclusion and Recommendation

5.1 Conclusion

In this work, we did the formulation and analysis of the SEIR-SEI mathematical model with seven ordinary differential equations describing the dynamics of malaria transmission in the host and vector populations, with incidence forces of infections which are nonlinear for human and mosquito populations. The formulation and analysis of the model were concluded by control strategies which are ITNs, IRS and ACTs.

The existence of DFE and EE, and reproduction number R_0 were investigated. The optimal control of this malaria model and the Caputo fraction derivative were also considered to find the optimal control parameters which minimize the spread of malaria in Rwanda. Using secondary data from malaria reports and basing on the impact of the optimal control strategies on malaria, Figures 4.12 and 4.13 show that the number of exposed and infected human with mosquito populations are highly lowered and the number of recovery individuals is greatly increased at the same time. Therefore, the combination of ITNs, IRS and ACTs is better in prevention compared with the others discussed.

Finally, our research has showed that the implementation of the best intervention strategies in Rwanda will eventually eliminate malaria.

5.2 Recommendation

From a report of WHO, the malaria transmission is still now a major health problem in the world. Moreover, epidemiological mathematical models make a reliable tool which provide the basic information to guide the policy makers about malaria control. The following recommendations should be considered.

1. All people in Rwanda, especially the people living in agglomeration have to sleep under ITNs or LLTNs.

2. Put more effort in the research on transmission of malaria mathematical models in Rwanda.

3. The combination of malaria controls strategies can be executed more effectively in Rwanda to minimize a rate of malaria transmission such as IRS, ITNs and ACTs.

4. Policy makers and Government should continue to sensitize the general public about the best practices meant to reduce the dynamics of malaria transmission in Rwanda.

5.2.1 Future Work

This proposed model has limited scope; the future work should be focused on the following points.

1. Propose a mathematical model that consider on many factors influencing the transmission of malaria in Rwanda including seasons, climate change, environment, temperature and rain season or humidity. Those inclusions should give more information than what we have obtained.

2. Propose the mathematical model and consider more control measure strategies of malaria such as IRS, ITNs or LLITNs, Treatment for Pregnant Women, ACTs, ... These will help to get more information about malaria elimination.

3. From the mathematical model developed, study a stochastic mathematical model or statistical mathematical model to understand the malaria dynamics.

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